corticales lo hemos obtenido a partir de reconstrucciones parciales de las relaciones funcionales que distintas células establecen en las capas más superficiales, que están lejos de la entrada talámica. Segundo, estos circuitos se han estudiado tradicionalmente asumiendo que se comportan de manera lineal a la presentación de estímulos artificiales, cuando han evolucionado para analizar imágenes naturales complejas y dinámicas.

En esta propuesta evitaremos estas limitaciones pasadas usando una combinación muy poderosa de técnicas experimentales (imagen de calcio 2Fotones, registros whole-cell y extracelulares múltiples, reconstrucciones anatómicas en 3D) y nuevos instrumentos computacionales (análisis de modelos lineales y no lineales, inversión y regresión).

Nuestro objetivo es triple. Primero, comprender como células individuales, con distintos tipos de campo receptor, interactúan en circuitos convergentes complejos para codificar el ambiente sensorial. Segundo, desarrollar nuevas estrategias matemáticas para diseñar estímulos con estadísticas adecuadas para caracterizar las respuestas de poblaciones de neuronas y para reconstruir la información visual que generan esas respuestas. Tercero, usar ese conocimiento para avanzar en el diseño de sistemas híbridos bio-artificiales para la transmisión de información a largas distancias. Nuestros resultados podrían dar lugar a nuevas interfaces cerebro-máquina para la transmisión de imágenes (la cámara humana), en las que la reducción de la dimensionalidad la realiza el cerebro humano en lugar de los algoritmos de compresión convencionales.

PALABRAS CLAVE: Teoría de la información, circuitos neuronales, compresión de información, corteza visual, campos receptores, BMI


ACRONYM:

SUMMARY Maximum 3500 characters (including spaces):

The problem of acquiring, communicating, and processing high-dimensional information at long distances, without significant attenuation and at a low cost, is common to both artificial and natural settings. Thus, sending and processing large amounts of data through wireless networks of finite capacity poses a comparable challenge to that faced by the visual system of our brain when extracting information from images containing millions of pixels. In the brain, a widespread strategy to solve the cost-efficiency trade off in long-distance communication is the presence of convergent pathways, or bottlenecks, in which information is acquired by a first layer with a large number of neurons and then compressed into a much smaller number of units in the output layer. A classic example is the retinothalamic connection where the information captured by 108 photoreceptors undergoes a 100-fold convergence and is carried onto the thalamus by only 106 retinal axons. Visual information is then expanded again in a two-step process starting in the thalamus and continuing in the primary visual cortex, which hosts several orders of magnitude more neurons than the number of retinal ganglion cells.

We have recently provided experimental evidence for a convergent neural circuit that allows efficient communication despite drastic reductions in the dimensionality of neural representations through information bottlenecks. Thus far, we have used the retinothalamic connection as a model system, however, the largest expansion of the incoming visual information is produced in the primary visual cortex. Despite years of intense research, we are still far from understanding what determines the emergence and design of visual thalamocortical circuits and how they extract meaning from natural images. Progress in this area has been constrained because of two main issues. First, most of our knowledge about the cortical circuit comes from partial reconstructions of the functional relationships between...
different cell types in the superficial layers, which are far removed from the thalamic input. Second, thalamocortical circuits have traditionally been probed assuming linear behavior with artificial stimuli even though they have evolved to analyze more complex, ever-changing sequences of natural images.

We plan to overcome these limitations by using a powerful combination of experimental techniques (two-photon calcium imaging, in vivo whole-cell and multiple single-cell recordings, 3D anatomical reconstructions) and new computational tools (analysis of linear+nonlinear models, inversion and regression).

Our aim with this proposal is three-fold. First, understand how individual thalamic and cortical neurons, with different receptive field properties, interact in complex convergent networks to represent the sensory environment. Second, develop new mathematical tools to design stimuli with appropriate statistics to characterize the interaction in populations of neurons, and to reconstruct the visual information from the set of recorded responses. Third, use that knowledge to advance in the design of hybrid bio-artificial systems for long-distant communication: reconstruction techniques based on regression or inversion of specific neural models could lead to new Brain Machine Interfaces for image transmission (the Human Camera) in which the nontrivial dimensionality reduction stage is done by a human brain instead of the conventional compression algorithm.

**KEY WORDS:** Information theory, neural circuitry, compressed sensing, visual cortex, receptive fields, Brain Machine Interfaces
C.1. PROPUESTA CIENTÍFICA
The primary visual cortex (V1) receives information about the visual scene from the retina through a relay in the lateral geniculate nucleus of the thalamus (LGN). Just like many artificial communication channels, this early visual circuit is characterized by the presence of sequential convergent pathways, or bottlenecks, in which information is acquired by an input layer with a large number of neurons and then compressed into a much smaller number of units in the output layer. In humans, for instance, the information captured by $10^8$ photoreceptors in the retina undergoes a 100-fold convergence and is carried onto the thalamus by only $10^6$ retinal ganglion cell axons. Visual information is then expanded again in a two-step process starting in the LGN and continuing in V1, which hosts several orders of magnitude more neurons than the number of retinal ganglion cells (RGCs). In recent years, it has been suggested that this particular circuit design might be a way of optimizing the processes of acquiring, communicating and analyzing high-dimensional information at relatively long distances, without significant attenuation and at a low cost, both in terms of time and energy demands (Ganguli and Sompolinsky, 2012; Martinez et al., 2014).

Using a very similar experimental and theoretical approach to the one proposed in this application, we have recently shown that the retinotectal pathway is, in fact, optimally designed for efficient communication and computation of the visual image in spite of drastic reductions in the dimensionality of neural representations in the retinal output (Martinez et al., 2014). In particular, we have shown that retinothalamic convergence, combined with the increase in cell number in the LGN, provides an interpolated map of visual space that heightens the LGN’s capacity to resolve a visual stimulus more readily than the retina is able to do. We demonstrated that neighboring relay cells in the LGN process information independently, even if some of their input derives from a common retinal source. This independence reduces redundancy in the sampling of the retinal mosaics and supports the view that visual processing in the thalamus serves to recode information efficiently (Barlow, 1981; Atick and Redlich, 1990, Dan et al., 1996; Wang et al., 2010). The benefits of interpolation come at a cost, however. Interpolation blurs the image, reducing local contrast to degrade edge perception. Our results also point to a solution to this problem. We have found that relay cells and interneurons in the LGN are spatially correlated producing physiological arrangements of excitation and inhibition in the thalamic receptive field (RF) centers that effectively boost contrast borders and increase the dynamic range of the visual message that the LGN sends to cortex. Thus, the retino-thalamic circuit operates like techniques manmade devices employ to improve the appearance of visual images.

To the best of our knowledge, this is the first detailed description of a neural circuit implementing a compressed sensing algorithm for long-distance communication in the brain; and it highlighted the crucial role of inhibition in compensating the often neglected side effects of interpolating information.

However, the largest expansion of the incoming visual information occurs at the level of V1. Cells in layer 4 of V1 receive convergent thalamic inputs and largely outnumber relay cells in the LGN. Unlike cells in the lateral geniculate nucleus of the thalamus (LGN) that supply them, V1 neurons show a great variety of receptive field structures (Martinez et al., 2005; Martinez, 2006). This functional diversity emerges from the specific computations performed by a widespread and distributed synaptic network which consists of thalamocortical inputs and corticocortical connections, coming from both excitatory and local inhibitory neurons (Alonso, 2002; Martinez and Alonso, 2003; Callaway, 1998; de Feli pe et al., 2002; Fitzpatrick, 1996; Lund et al., 1979; Binzegger et al., 2004 for review). Currently, we have accumulated a wealth of information about the intrinsic properties of V1 neurons and how they respond to simple visual stimuli. Thus, while simple cells (Hubel and Wiesel., 1962) have a behavior similar to Gabor-like linear sensors ((Marcelja 1980, Daugman 1980, Watson 1983), other cells, collectively called complex (Hubel and Wiesel, 1962) show basic non-linearities that play an important role in encoding efficiently the statistical regularities present in natural visual stimuli (Ruderman 1994, Simoncelli and Olshausen 2001, Schwartz and Simoncelli 2001, Malo and Gutierrez 2006).

We have recently shown that simple cells and different types of complex cells are distributed in different cortical layers in a very stereotyped fashion (Martinez et al., 2005; Hirsch and
Martinez, 2006). This result is somewhat consistent with Hubel and Wiesel proposal that simple cells and complex cells represent two different stages in hierarchical processing. In a first stage, simple cells become selective to the orientation of a line in a specific location through the convergence of precisely aligned thalamic inputs. In a second stage, the more numerous complex cells become selective to the orientation of a line regardless of its exact position within the receptive field due to the convergence of simple cell inputs. A complementary view is that synaptic connectivity between LGN relay cells and V1 simple and complex cells with different RF structures could forms the anatomical scaffold of a new compressing sensing algorithm operating at the thalamocortical stage and beyond. Just like the retinotthalamic circuit that we recently described, the thalamocortical connection is expansive. In the cat, there are approximately 25 axons leaving V1 per LGN axon entering this area. And this phenomenon is not unique of the visual system. Similar ratios have been described in other sensory and even motor systems, suggesting that expansive transformations represent a fundamental computational advantage for information processing in the brain (see Ganguli and Sompolinsky, 2012, for review).

Despite years of intense experimental and theoretical effort, there are still many unknowns about V1 local structure and function. For example, (1) the functional roles that different cortical cells, excitatory and inhibitory, with different receptive field types play in visual perception, (2) the way in which they interact to give rise to complex neural circuits, columns and maps, and (3) whether or not they serve as a canonical computational paradigm. Solving these questions will have far reaching consequences with the potential to (a) influence our understanding of other brain circuits, (b) serve as a guide to design new and more powerful computational tools for probing brain function and (c) permit the design of a new generation of brain machine interfaces. This proposal was designed around three main aims/tasks that address these issues.

**Relationship to other groups and capacity to carry out the proposal.**

The senior members of the team are addressing both the experimental and the theoretical perspectives of the issues stated above: Dr. Martínez Otero (PI) at the Instituto de Neurociencias CSIC-UMH is developing new computational tools and recording techniques from multiple neurons (BFU2010-22220-BFI; Martínez et al., 2005; Stepanyants et al., 2008; Stepanyants et al., 2009; Benjumeda et al., 2013; Martínez et al., 2014) in collaboration with prominent international groups, such as Judith Hirsch (at University of Southern California in Los Angeles, USA). The increase in complexity in the approaches raises many mathematical and statistical questions of both experimental and theoretical relevance: what features of the visual stimuli should be explored to isolate different kinds of non-linear behavior or specific sensors? Is it true that the neural signals, as recorded using these new techniques, provide a progressively more efficient code of spatial information in the images? These questions are certainly a hot topic in visual neuroscience (Ecker et al. 2010, Renart et al 2010). The answers to these issues require solutions from both the computational and the experimental points of view. Dr. Jesús Malo at the Image Processing Lab UVEG has experience in developing novel tools for higher order signal and systems characterization (TIC2009-13686, Laparra et al., 2011, Laparra et al., 1012, Laparra et al., 2014, Laparra and Malo, 2014), and works with leaders of the Computational Neuroscience community, e.g. Prof. Aapo Hyvarinen of Helsinki Univ. Finland (Laparra et al., 2011, Gutmann et al., 2014), and Prof. Eero Simoncelli of the Center for Neural Science NYU, USA (Malo et al., 2006). This background and his experience with the statistical properties of the current non-linear paradigm of interneuron inhibition in V1 (Laparra et al., 2010; Malo and Laparra, 2010; Laparra et al., 2012) ensures a perfect integration in the group of Dr. Martínez Otero whose experimental findings have led him to address the same computational issues.

Finally, in compressed sensing algorithms, the expansion in the dimensionality is accompanied by a change in the firing rate of the input and output layers, from a dense pattern to a sparse representation downstream (Babadi and Sompolinsky, 2014). For instance, in V1 only 5-10% of all neurons respond to any natural scene stimulus (Olshausen and Field, 2004) and similar results have been obtained in other sensory systems (Brecht and Sakmann, 2002; DeWeese et al., 2003; Chacron et al., 2011). Both expansion and sparseness seem to be fundamental to generate efficient population codes of the sensory environment (Babadi and Sompolinsky, 2014). Our group has a long history of close collaboration with the group of Fritz Sommer at the Reedwood Center for Theoretical
Neuroscience, University of California at Berkeley (Hirsch et al., 2003; Martinez et al., 2005; Martinez et al., 2014). His group has contributed significantly to the study of sparse coding in V1 (Rehn and Sommer, 2007).

**Task 1. Understanding the structure and function of complex convergent networks**

In this task, our aim is to describe with single cell resolution the anatomical and functional structure of the early visual pathway. In particular, we will concentrate on three main questions which are fundamental to understand how V1 contributes to sensory processing: (1) The role of inhibitory connections, (2) the emergence of cortical RFs and maps, and (3) the generation of population codes that represent efficiently the sensory environment.

**Task 1.1. The role of inhibitory connections.**

Unlike the thalamus, the local cortical microcircuit is dominated by excitatory intrinsic networks balanced by a large variety of inhibitory connections (Douglas and Martin, 2007; Stepanyants et al., 2009; Hirsch and Martinez, 2006; Hangya et al., 2014; Griffen and Maffei, 2014; Karnani et al., 2014; Lovett-Barron and Losonczy, 2014). Thus, circuits in the cortex are far more diverse than in the thalamus. In cortical layer 4, most cells have simple receptive fields (Hirsch and Martinez, 2006; Martinez, 2006; Martinez et al., 2005, Hubel and Wiesel, 1962). As in LGN, these receptive fields are built of segregated, neighboring On and Off subregions in which opposite stimulus polarities (bright or dark) evoke responses of the reversed sign (excitation and inhibition or push-pull. Martinez et al., 2005, Hubel and Wiesel, 1962, Jin et al., 2011). However, the shape and arrangement of the cortical subregions is different; rather than circular and concentric, they are elongated and lie side by side (Hubel and Wiesel, 1962). This change in geometry forms the basis for orientation selectivity (Martinez et al., 2005, Reid and Alonso, 1995, Hubel and Wiesel, 1962, Ferster et al., 1996, Martinez et al., 2002), the best known emergent cortical property. Most remaining cells in the layer have complex receptive fields in which On and Off responses overlap (Hubel and Wiesel, 1962, Hirsch et al., 2002, Hirsch and Martinez, 2006a, Martinez et al., 2005, Usrey et al., 2003).

There are inhibitory cells as well as excitatory cells with simple or complex RFs in V1 (Hirsch et al., 2003, Martinez et al., 2005, Gilbert and Wiesel, 1979, Azouz et al., 1997). Optogenetic approaches in mouse have shown that different families of cortical inhibitory interneurons (DeFelipe et al., 2013, Taniguchi et al., 2011) have very different impacts on sensory processing (Hangya et al., 2014, Lee et al., 2012, Lovett-Barron and Losonczy, 2014, Nienborg et al., 2013, Pfeffer et al., 2013). In part, this functional selectivity correlates with the different subcellular compartments (i.e. distal versus proximal dendrites, soma, axon hillock) a given type of interneuron preferentially targets (DeFelipe et al., 2013). It is important to note, however, that cortical receptive fields in mouse V1 are very different from counterparts in cat or primate. A striking example is the murine approximation of the simple RF. The On and Off subregions mapped from EPSPs are largely overlapping (in cat they are largely segregated (Martinez et al., 2005)), and the inhibitory component of the field is On-Off (Lien and Scanziani, 2013, Li et al. 2014)—the concept of push-pull, therefore, does not apply. Accordingly, excitatory cells in mouse V1 are selective for stimulus orientation but interneurons, with rare exception, are not (Kuhlman et al., 2011, Kerlin et al., 2010, Runyan et al., 2010, Niell and Stryker, 2008). Also, these murine simple-like cells are abundant in all cortical layers rather than restricted to thalamorecipient zones (Niell and Stryker, 2008, Smith and Haussler, 2010, Bonin et al., 2011), an observation that suggests substantial differences in cortical wiring among animal models.

In cat, ferret and primate, the role of each type of inhibitory neuron and the synaptic relationships they establish with other cells across the local cortical circuit are not known. Our hypothesis is that the inhibitory simple cells in layer 4 could provide the pull, analogous to circuitry in the LGN (Martinez et al., 2014), and contribute orientation-tuned inhibition to their postsynaptic targets (Hirsch et al., 2003, Martinez et al., 2005). Inhibitory complex cells, on the other hand, would provide a complementary source of inhibition insensitive to stimulus polarity or orientation, suited to provide gain control and increase the dynamic range of visual responses in V1. Thus, it is possible that the same inhibitory mechanisms proposed to emphasize contrast borders at the level of the thalamus (Martinez et al., 2014) are also at play in cortex.
In addition, it has been reported that the firing of cortical neurons becomes less frequent, or sparse, in response to natural images but not in response to most commonly used visual stimuli, such as gratings or bars (Vinje and Gallant, 2000; Weliky et al., 2003). Natural scene movies differ from classical visual stimuli in both their spatial as well as temporal properties. Time-varying natural scenes contain a much wider range of spatial and temporal frequencies with a characteristic amplitude distribution. It is possible that the properties of natural scenes activate preferentially inhibitory neurons causing the suppression of firing in all but the appropriate neighboring excitatory cells.

By combining in vivo two-photon calcium imaging with whole-cell recordings and intracellular labelling of subsets of inhibitory neurons, we are now in a position to investigate (1) the specificity of inhibitory connections onto excitatory neurons across all cortical layers and (2) the involvement of inhibition during natural vision.

Task 1.2. The emergence of cortical RFs and maps.
Maturation of cortical circuits is accompanied by a large scale retraction or degeneration of local and long range connections (Callaway and Katz, 1990; Borrell and Callaway, 2002). Around eye opening, many synapses are lost and responses of cortical neurons become sparser, sharper and more selective for various attributes of visual stimuli such as their orientation and direction of motion. With visual experience, thalamocortical and corticocortical connections refine (Borrell and Callaway, 2002) to generate precise networks of cells that share similar functional properties (Chisum et al., 2003; Mooser et al., 2004), the so-called topographic maps.

Much of our understanding of these topographic maps and neural circuits derives from the study of orientation columns in V1. It has recently been proposed that cortical orientation maps are inherited from the input of parallel pathways in the LGN, On and Off relay cells, which are then intimately linked to the emergence of new functional properties, i.e. orientation selectivity, and their corresponding spatial arrangement (Paik and Ringach, 2011; Nauhaus and Nielsen, 2014). This model predicts a very tight correlation between population RFs in the thalamus and the emergence of different cortical RF types, simple and complex, with different prevalence in excitatory and inhibitory neurons. In addition, this approach could find a mechanistic explanation for the absence of orientation maps in the cortex of certain species, such as the mouse, in spite of the presence of strong cellular selectivity to stimulus orientation.

To explore these and associated predictions of this proposal we will construct a statistical connectivity model of the early visual pathway based on the synaptic structure of retinal, thalamic and cortical RFs that, to inform the model, we will map using whole-cell recording in vivo combined with anatomical reconstructions. With this approach we will find the precise connectivity patterns between the retina and the LGN and between the LGN and cortex that will be essential to understand the way they constraint the processes of acquiring, communicating and analyzing high-dimensional information along the early visual pathway (Ganguli and Sompolinsky, 2012; Martinez et al., 2014).

Task 1.3. The generation of population codes that represent efficiently the sensory environment.
Most of our knowledge about V1 structure and function derives from experiments using a very restricted and stereotyped set of visual stimuli. In fact, and despite the extensive experimental and theoretical effort, our ability to correlate structure and function in a predictive model of V1 to account for responses to a more ecologically valuable set of stimuli is still rather poor (Carandini et al., 2005).

Obtaining a more accurate picture of V1 function will thus require investigating how populations of neurons with different functional properties interact within local networks in the visual thalamus and cortex in response to complex stimulus sequences, including artificial and time-varying natural images. We propose to address this issue by combining whole-cell recordings, multiple extracellular recordings and pharmacological modulation of LGN activity in a retinotopically matched location (Martinez and Alonso, 2001; Martinez et al., 2005). The functional response properties and synaptic physiology of cells in the thalamocortical network will be studied with a wide range of visual stimuli, including simple geometric patterns (like bars and gratings), artificial images that can be altered to quantitatively and qualitatively modify the activity of the recorded neurons, and finally, natural images moved on the visual
field following sample eye-paths previously recorded in freely moving animals (Fiser et al., 2004; Felsen et al., 2005; Maldonado and Babul, 2007). This approach has several advantages. First, it will allow us to sample an unbiased population of neurons across different layers of cortex to address specifically the influence that different cell types and connections have on the spatio-temporal organization of V1 receptive fields. Second, it will permit to investigate which higher-order components of the visual image are more likely to engage and maximize the interaction between excitation and inhibition throughout primary visual cortex. Third, the combination of whole-cell with multiple, simultaneous extracellular recordings will let distinguish cellular properties from network computations influencing the flow of visual information through V1.

**Task 2. New computational tools**

Relations between sampling, image coding, dimensionality reduction, and signal statistics recently led to big excitement in the applied mathematics community through the concept of *compressive sensing* (Candes and Tao, 2006; Donoho, 2006). The key issue is that only a reduced set of sensors is required if signals have a small statistical complexity. In neuroscience, organization of the shape, sampling, and even nonlinear properties of receptive fields according to signal statistics is a long term idea (Olshausen and Field, 1996; Schwartz and Simoncelli, 2001; Malo and Gutierrez, 2006; Schwartz et al., 2007; Hyvarinen, 2009; Carandini and Heeger, 2012; Gutmann et al., 2014). Statistical simplicity of natural scenes has been used to explain why biological systems developed spatio-chromatic sensors with specific spatio-spectral resolution (Singh et al., 2003), and we have extended the same idea to artificial systems as well (Jimenez and Malo, 2014). In fact, sampling in the retina can be sparse since spatial information can be recovered with appropriate circuitry (Martinez et al., 2014).

Analysis of the changes of experimental sampling patterns along the visual pathway in terms of recent signal processing techniques and using information theory tools can be useful both to (1) propose stimuli to understand the role of pooling and feedback interaction between different layers, and (2) to propose novel ways to recover visual information from the distributed image representation at V1.

We have experience in developing simplified V1-like linear+nonlinear models both using psychophysically and statistically derived parameters (Malo et al., 1997; Malo and Gutierrez, 2006; Laparra et al., 2010; Laparra et al., 2012, Gutmann et al., 2014). We successfully used these models in image and video compression [Malo et al., 2001, Malo et al., 2006; Camps et al., 2008], in image denoising and enhancement (Malo and Gutierrez, 2006; Laparra et al., 2010), and to reproduce distortion threshold in psychophysics [Watson and Malo, 2002, Malo and Laparra, 2010]. We also proved that natural images display increased statistical independence and sparsity after V1-like nonlinearities [Malo et al., 2006; Malo and Laparra 2010; Laparra et al., 2014]. This signal sparsification and the success in image coding suggest that the compressive sensing view of primary cortical function may make sense. In this context, new dimensionality reduction techniques (Laparra et al., 2014b) may be useful to understand sensory organization: feature extraction guided by dimensionality reduction goals may explain the diversity or adaptation of receptive fields in different environments (Jimenez et al., 2013), and certainly can be applied in image coding too (Amrani et al., 2014). Similar statistical techniques explain motion, color and texture psychophysics (Laparra et al. 2012, Laparra et al. 2014c) better than previous linear approaches based on shift and scaling (Webster and Mollon 1991, Webster and Mollon 1997, Clifford 2000).

However, the linear+nonlinear V1 models referred above were oversimplified in different ways. On the one hand, they used sets of receptive fields preserving signal dimensionality or with too small overcompleteness, which is unrealistic. On the other hand, they used interaction patterns in the nonlinearities which did not come from direct measurements, but were fitted to reproduce certain psychophysics, hence probably inaccurate. Moreover, nonlinear interactions between cortical cells pose methodological problems for direct measurement of inhibitory pooling regions. For this reason, new computational techniques for stimulus and experiment design, explicitly including the nonlinearities of the neurons, are required for accurate estimation of those parameters (Ringach et al. 2002, Schwartz et al. 2006, Wu et al. 2006, Sharpee 2013).

Inversion of the response model is interesting both to design stimuli with the appropriate statistics to characterize the interaction in populations of neurons, and to reconstruct or infer
the visual information from the set of recorded responses. When using this kind of models in image compression (where inversion of the encoded signal is necessary for decoding) we studied the existence conditions for the analytical inverse (Malo et al. 2006b). When these conditions do not hold one must rely on regression techniques to estimate the inverse at a cost of certain reconstruction error. This is the key in Brain Machine Interfaces that try to recover what the viewer is seeing (Stanley et al. 1999, Miyawaki et al. 2008, Nishimoto et al. 2011), or even dreaming (Horikawa et al. 2013). Methodologically, we have experience in non-parametric regression techniques such as Support Vector Regression, which we used on V1-like responses (Gomez et al. 2005, Camps et al. 2008, Malo et al. 2008, Laparra et al. 2010b), Kernel Ridge Regression (Laparra et al. 2014b), or Gaussian Processes (Rasmussen and Williams 2005), that may be suited to this application.

3. New Brain Machine Interfaces for image transmission: the Human Camera
The current image compression standards use a number of features of biological image processing. For instance, JPEG2000 (Marcellin 2002) uses LGN-like chromatic opponent representation, V1-like texture sensors, and perceptually inspired uneven bit allocation in the wavelet domain. Improvements of JPEG and MPEG standards use models of the perceptual nonlinearities (Malo et al. 2001, Malo et al. 2006b, Camps et al. 2008, Malo et al. 2008). However, these computational models are still too oversimplified and too rigid to adapt to the changing statistics of the environment in reasonable time. For instance, the inhibitory interaction in those algorithms is kept fixed, when it is known to change with local statistics (Schwartz et al. 2009), and time constants are unclear.

These problems in computational modeling of neural function for image processing applications could be avoided/by-passed by using Brain Machine Interfaces (BMIs) and letting an actual brain to do the encoding work for us. Applications of BMI range from interactive experiments in which the observers responses determine the new stimuli that is presented to them (Foldiak 2012, Cerf et al. 2010), to systems that detect the presence of certain visual pattern from the EEG (Allison et al. 2008, Mak et al. 2011), or even estimate the subjective quality of images (Scholler et al. 2012). Reconstructing images from actual neural recordings would be a way to overcome the current lack of computational knowledge on how to obtain a truly adaptive encoding, which is something the brain is specifically designed for.

In this applied task, we plan to work towards the use of the efficient coding properties found in the neural pathway to build a hybrid bio-artificial image coder in which the nontrivial dimensionality reduction stage is done by a human brain instead of the conventional compression algorithm. In this Human Camera, desirable, and non-trivial, properties such as optimal sampling (Martinez et al. 2014), redundancy reduction (Schwartz and Simoncelli 2001, Malo et al. 2006a, Malo et al. 2010), or adaptation abilities (Laparra et al. 2012, Gutman et al. 2013) found in biological systems would be automatically incorporated in the hybrid encoder at no (artificial) computation cost.

Even though current state-of-the-art in image reconstruction from neural recordings is far from accurate (Stanley et al. 1999, Miyawaki et al. 2008, Nishimoto et al. 2011, Martinez et al. 2014), some reported results display interesting features for the coding application. For instance, the results obtained by Miyawaki et al. exhibit luminance aftereffects (e.g. negative postimages), and these kind of aftereffects has been recently related to sophisticated redundancy reduction and manifold matching strategies (Laparra et al. 2014c). These strategies would be extremely useful in image coding but unfortunately, they are not easily obtained using numerical methods.

Direct recording of the encoded signal is just transferring the computational problem to the decoding stage. We will try to improve the current decoding schemes based on conventional regression (linear or generic Support Vector Regression (Stanley et al. 1999, Miyawaki et al. 2008, Nishimoto et al. 2011) by using our experience in inverting specific neural models (Malo et al. 2006b) to introduce prior knowledge to weight/constraint conventional regressors. More accurate model parameters obtained through the experiments in Task 1 using the methods described in Task 2 would be of critical relevance to this end.

C.1.2 Initial hypothesis and general objective.
In a classical example of the cost-efficiency trade off that might control the emergence of precise brain circuits, the visual system has evolved to decrease the number of visual
detectors from the level of the photoreceptors to the retinal ganglion cell mosaics in the retina. This approach has the disadvantage of compressing the signal limiting visual resolution, but has the advantage of reducing the amount of cable needed to transmit visual information to the brain. Our hypothesis is that thalamocortical circuits are designed to implement a type of compressive sensing algorithm that would optimally expand the retinal output, maximizing spatiotemporal sampling of natural images and improving visual performance at low metabolic costs.

So far it has been difficult to find empirical probe for this hypothesis. We believe it can be successfully addressed by investigating patterns of network activity in LGN and V1 in response to natural images. Thus, our proposal entails a combination of experiment and modeling, including state-of-the-art 2-foton calcium imaging, electrophysiology, and computational techniques. With this approach we will provide a better understanding of the structure and function of the visual cortical microcircuit that will be used to design a new generation of Brain Machine Interfaces that could be used both in artificial vision and to restore vision the blind, particularly when loss of vision is caused by lesions of the early visual pathway (retina, thalamus and/or V1).

This proposal is presented through a specific call oriented towards the eight big challenges (RETOS) identified in the Spanish strategy of Science and Technology. In particular, and given the nature of our proposal, we think it is more appropriate to address some of the challenges included under RETO 1; Health, demographic change and well-being. We have formed a multidisciplinary group comprised of people with different backgrounds and expertise; ranging from experimental neuroscience to artificial vision. The expected results will accordingly be of interest to different disciplines and could promote the emergence of new technologies with potential impact in the fields of human health and information and communication technologies.

C.1.3 Specific objectives.

1.1 Investigate the emergence and functional significance of cortical receptive fields and maps.

1.2 Investigate how interactions between excitatory and inhibitory neurons influence thalamic and cortical responses to natural visual stimuli.

1.3 Obtaining a realistic computational model of the early visual pathway, including convergence and divergence ratios of retinothalamic and thalamocortical connections onto both excitatory and inhibitory neurons.

2.1 Design of natural-like stimuli with controlled statistics to measure the parameters of neural models including nonlinearities and tunable inhibitory feedback. We will use state-of-the-art techniques [Sharpee13] based on system identification and information theory.

2.2 Develop computational models of cortical representation including experimental data on irregular sampling, realistic variety of receptive fields and stimulus-dependent interaction.

   2.2.a Study the coding efficiency of the model(s) in dimensionality reduction, redundancy reduction, and classification terms. Redundancy reduction will be analyzed using recent multi-information estimates [Laparra11].

   2.2.b Analyze the analytical invertibility of the model(s).

   2.2.c Explore the performance of non-analytical inversion methods (Bayesian inference, nonlinear regression methods) including as much prior information derived from model structure as possible. Check the robustness of the inversion depending on the noise and missing data.

   2.2.d Derive psychophysical behavior (e.g. incremental thresholds) and distortion measures from the model(s).

3.1 Use the analytical and non-analytical inversion techniques to reconstruct the input signals from the recorded responses: towards the Human Camera BMI.
3.1.a Reproduction of state-of-the-art BMI from the recorded measurements in our lab using linear regression and conventional machine learning inversion techniques.

3.1.b Try inversion techniques taking into account the structure of the model and additional measurements (e.g. not only cortical data, but also supplementary data –EEG, eye tracker…-).

3.1.c Analyze the impact of coding techniques (e.g. quantization) in the quality of the reconstructed signal.

C.1.4 Methodology.

Task 1. Understanding the structure and function of complex convergent networks.

General Methods. Adult cats, 2.5-3.5 Kg, are initially anesthetized with ketamine (10mg/Kg, IM) then with propofol (5mg/Kg, IV), supplemented as needed. Lidocaine is administered topically at all points of pressure and possible sources of pain. A tracheotomy is made to introduce and endotracheal tube and the animal is placed in the stereotaxic apparatus. Temperature (37.5º-38º C), EKG, EEG, and expired CO2 (27-33 mmHg) are monitored throughout the experiment. Anesthesia is maintained by a continuous infusion of propofol (5mg/Kg/hr, IV), adjusted as required. Two craniotomies will be open in the skull, one centered on Horsely-Clark coordinates P3- L2 to expose most of area 17 and 18 and the other on coordinates A4.5- L9 to gain access to the lateral geniculate nucleus of the thalamus. The dura is removed and the craniotomies filled with agar to prevent desiccation and minimize brain movements. Animals are paralyzed (Norcurom 0.2mg/Kg/hr, IV; supplemented with sucrose) and respired through the endotracheal tube. All initial surgery is completed before the animal is paralyzed. To minimize respiratory movements, the animal is suspended from a lumbar vertebra and a pneumothorax is made. Eye movements are prevented by fixing the eyes to posts attached to the stereotaxic frame. Pupils are dilated with 1% atropine sulfate and the nictitating membranes retracted with 10% phenylephine. Eyes are refracted, fitted with contact lenses, and focused on a tangent screen (that overlies the stimulus monitor) by using additional lenses. The positions of the area centralis and the optic disks are retroprojected on the screen with the aid of a fiber optics lamp. Experiments last for up to 48 hours. Throughout this period, the animals are continuously monitored for adequate anesthesia. At the end of the experiment, the animal is euthanized with an overdose of sodium pentothal (100 mg/Kg, IV), and subsequently perfused with fixative and the brain is removed for anatomical studies.

Extracellular recordings. Multiple extracellular recordings will be obtained from area V1 using a linear array of 7 to 16 electrodes, 80 microns thick and less than 200 microns apart (Eckhorn, Marburg), lowered perpendicular or parallel to the cortical surface to target specific cortical layers. The tips of the electrodes will be coated with fluorescent dyes (DiI and DiO) and the tracks reconstructed at the end of the experiment. Each electrode is controlled by an independent micromanipulator, allowing optimal isolation of single units. Signals from each electrode are amplified, filtered and stored by a computer. In addition, we will also record local field potentials to correlate single cell response with the activation state of the local network.

Whole-cell intracellular recordings in V1. Whole-cell recordings will be performed in a retinotopically matched position in area V1. Glass capillaries will be pulled to a tip diameter of 1-3 microns and a resistance of 10-20 MOhms when filled with internal solution, in mM: K-glucuronate, 120; NaCl, 5; CaCl2, 1; MgCl2, 1; EGTA, 11; GTP, 0.2; ATP, 2; HEPES, 40; biocytin 1%; pH 7.3; 290 mOsm. Electrode position in the craniotomy is carefully marked and depth monitored throughout the experiment. Patches are made in voltage clamp for minimal excursions of the signal from the monitor and to allow accurate measurements of the seal resistance. The electrical characteristics of the electrode are recorded at the end of the patch and stored, so that the bridge can be balanced off-line and input resistance and time constant accurately determined. At the end of the experiment, the animal is perfused with
saline and 4% paraformaldehyde, the brain stored in 4% paraformaldehyde and 30% sucrose, and later sectioned at 80-100 microns. Following histological processing, labeled neurons are drawn using a computerized 3D reconstruction system (Microbrightfield) that also keeps track of numbers of dendritic spines and axonal buttons.

**Visual stimulation.** To investigate activity patterns evoked by more natural time-varying stimuli we will use a set of moving images closely resembling the visual input to the cat’s eye under natural conditions. To determine the specific properties of natural images, such as motion or higher order statistics, which are analyzed at each level of cortical integration, preferentially those that engage more strongly the cortical circuit, we will use a set of modified movies and artificial images. Natural scene movies differ from classical visual stimuli in both their spatial as well as temporal properties. Time-varying natural scenes contain a much wider range of spatial and temporal frequencies with a characteristic amplitude distribution. Artificial images can be constructed from the amplitude spectrum of the natural images but with random phases of the different frequencies. All these visual stimuli will be presented on a monitor working at a frame rate of at least 128 Hz, and will be controlled by the same computer in charge of the acquisition of the neural recordings using both commercial and homemade software. Computational tools developed in Task 2 will be used to analyze responses to natural images and constantly refine our set of visual stimuli.

**Experimental protocol and data analysis.** Recording cells whose response properties are characterized, allows tracing the flow of information through cortex. Whole-cell recording is well-suited to experiments that combine physiology and anatomy. First, the quality of recording allows for functional response properties to be investigated in detail, improving the resolution of correlation between structure and function. Second, by using relatively small pipettes, one can improve the odds of recording small or rare cell types such as small smooth cells. Whole-cell recordings will be started after the multielectrode is in place in V1, the double micropipette is positioned in a retinotopically matched location of the LGN and a single cell has been clearly isolated in each channel. The experimental protocol will consist of a series of visual stimuli presented in sequence; including sparse noise, moving bars and/or gratings, and finally natural and artificial movies. Each stimulus run will be repeated at different levels of membrane potential to estimate changes in excitatory and inhibitory conductances. Recordings should last a minimum of 40 minutes, our average recording time in similar protocols is 1 hour and 15 minutes (n = 124; range 20min. to 5 hours). Since we combine multiple extracellular and whole-cell recordings, we will study connectivity patterns and synaptic interactions with standard cross-correlation and spike-triggered-averaging techniques using homemade software (see Hirsch et al., 2003; Martinez et al., 2005; Martinez and Alonso, 2001). This approach will allow us to answer questions regarding functional connectivity patterns between cells in LGN and different layers in V1, and if they preferentially target distinct cell types (excitatory vs. inhibitory, or different types of inhibitory neurons). In addition, it will permit to establish whether connection specificity depends on relative retinotopy and to investigate if projections from different layers transmit distinct or similar information. Finally, synaptic physiology can be studied by combining whole cell recordings with intracellular pharmacological manipulations; for instance, inhibition can be intracellularly blocked by adding DNDS (0.5 mM, Pfalz and Bauer) and cesium to the recording solution. This approach will permit to identify the synaptic mechanisms that mediate thalamocortical and corticocortical inputs and to study how they interact with other intrinsic and synaptic conductances to control the flow of visual information through V1.

**Caveats:** Quantitative analysis of receptive fields mapped with complex artificial images (such as Gaussian noise) or natural images is not trivial. We have done pilot experiments to develop the tools that would allow us to do that in close collaboration with the group of Judith Hirsch at the University of Southern California. Another caveat is that it is not always possible to overlap retinotopically all recording sites; or, even if they are all properly aligned in visual space, to record extracellularly from the cells.
that provide monosynaptic input to our intracellular recorded cell. To overcome this limitation we are working, also with the group of Judith Hirsch, on analytical tools that permit to map convergent input to cortical cells directly from intracellular recordings and to separate these events into different groups.

As an alternative method we will record neuronal activity patterns evoked by artificial and natural stimuli in layers 2+3 of primary visual cortex of anesthetized juvenile and mature mice by in vivo two-photon calcium imaging. Cortical tissue will be labelled with a membrane-permeable AM ester of a calcium-sensitive fluorescent dye (OGB-1 AM) by pipette injection (Fig. 3, see legend for details). Two-photon microscopy enables us to monitor changes in somatic calcium concentration of single cells, which reflect suprathreshold but not subthreshold neuronal activity. We have recently adapted this method at the Instituto de Neurociencias (Benjumeda et al., 2013).

Data Analysis.

We will compare population activity in V1 in response to artificial (gratings or white-noise) and natural (see methods of Tasks 1 and 2) images. We can quantify these network responses in two different ways. First, we can investigate whether or not natural images evoke sparser responses (i.e. fewer active neurons) than artificial stimuli. And second, we target specific cell types, either with genetically encoded fluorescent markers or through the intracellular injection of the fluorescent dye. This way we can investigate how visual information about a stimulus is encoded in patterns of neuronal activity in populations of selected neurons. And, in addition, estimate the redundancy of cortical information processing by comparing the amount of information about a stimulus carried by the intracellularly recorded cell and the population of neighboring neurons.

Tasks 2 and 3.

In this section we present an oversimplified but illustrative example of the decoding of the cortical signal to show some of the computational issues of the modeling and BMI problems, its relations with image compression and enhancement, and to show that we already are working with the technologies that allow the inference of the stimulus from the neural response. The tools mainly include (i) linear and kernel regression techniques used in Brain Machine Interfaces in (Stanley et al. 1999) and (Miyawaki et al. 2008, Nishimoto et al. 2011) respectively, which we used in (Gomez et al. 2005, Camps et al. 2008, Laparra et al 2014b); (ii) Bayesian decoding and inference, used in (Martinez et al. 2014, Jiménez et al. 2013); and (iii) analytic inversion of nonlinear neural models, whose mathematical properties were explored in (Mallo et al. 2006b), and applied in image compression afterwards (Camps et al. 2008, Malo et al. 2008). Moreover, we analyze the coding efficiency using accurate estimates of multi-information (Laparra et al. 2011).

The considered example uses (i) a nonlinear response model, (ii) different distortion sources that modify the nonlinear signal as for instance, random neural noise or additional pooling stages not considered in the assumed model, (iii) dimensionality reduction, i.e. missing responses in the recorded signal, and (iv) different strategies to infer the input from the noisy recordings. Of course, this model will be augmented in different ways (e.g. including irregular spatial sampling, the diversity in shapes of the receptive fields (Martinez et al. 2014), the adaptive interaction in the nonlinear stage (Schwartz et al. 2009), or correlated noise patterns). Figure 1 illustrates the stages of the model. Multi information numbers (in bits) between four coefficients of the different representation show the redundancy reduction along the path, which is consistent with the efficient encoding hypothesis (Olshausen et al. 1996, Schwartz et al. 2001), and is consistent with our previous mutual information results (Mallo et al. 2006b, Malo et al. 2010). Figure 2 shows the reconstruction results using different inversion techniques linear (similar to Stanley et al. 1999), Kernel (similar to Miyawaki et al. 2008, Nishimoto et al. 2011), and analytic, as in Malo et al. 2006b. The example explores the effect of different distortion sources (noise and elements not considered in the model) on top of a representation of reduced dimensionality. The good properties of analytic inversion could be used to complement (as prior knowledge) the current regression techniques. The code for complete reproduction of this example is available at http://isp.uv.es/bmi.html
Figure 1: Stages of the simplified neural model.

Figure 2: Estimated stimuli from the neural signal under different distortion sources (dimensionality reduction, different neural noise and additional pooling stages not considered in the forward model). In this numerical experiment linear reconstruction is more sensitive to distortion, which is alleviated by nonlinear regression, which still displays significant artifacts. The analytical inverse seems to reconstruct better but also amplifies the noise. The knowledge extracted from the structure of the inverse should be included in the conventional methods.

References:
MEMORIA CIENTÍFICO-TÉCNICA DE PROYECTOS INDIVIDUALES (TIPO A o B)

C.2. IMPACTO ESPERADO DE LOS RESULTADOS
Psychiatric and degenerative neurological disorders represent a growing health problem and an important social burden in developed western countries. One of the greatest challenges facing science and society today is thus to understand the brain and the biological basis for human behavior. Our results will make an important contribution in that direction by investigating the brain mechanisms of vision and the establishment of brain topography. This knowledge has important bearings for the current Spanish strategy of Science and Technology. For example, many neurological disorders, such as autism or schizophrenia, are based upon or correlate with alterations in the way functional maps and balanced excitatory and inhibitory networks emerge in the cerebral cortex during development, which we will directly address in this proposal. In addition, our results will immediately inform current models of amblyopia and a full spectrum of related diseases.

Our experimental results will also be used to develop new computational tools for processing and analyzing natural images; our results are thus of importance for the rapid growing fields of object recognition, artificial vision and communication and information technologies. In particular, the new brain inspired compressing sensing algorithms that we will develop could be readily used to (1) improve current brain-machine interfaces used to restore vision to the blind, particularly when loss of vision is caused by retinal degeneration or cortical lesions; (2) improve long distant communication protocols when channel capacity is limited such as in satellite or wireless networks; and (3) develop brain inspired image processing devices. We are currently establishing links with several international companies to explore the possibility for a commercial exploitation of these new technical developments.

Our results will be published in international neuroscience or general science journals. Our team has now a strong publication record (Nature Neuroscience, Neuron, etc) and we have been invited on a regular basis to publish topical reviews in highly cited journals and book series (Annual Review Neuroscience; Trends in Neurosciences, Current Opinion in Neurobiology, Progress in Brain Research, The Neuroscientist, etc). In addition, we will present our work in international scientific meetings. Most of these conferences include sessions open to lay audiences. Such events guarantee a great media attention and coverage and represent a unique opportunity to disseminate scientific knowledge bridging the gap between the research community and the general public. In 2012, for example, our work was selected for a press conference by the Society for Neuroscience and it gathered more than 600 entries and references in international media.

C.3. CAPACIDAD FORMATIVA DEL EQUIPO SOLICITANTE
Our laboratory is part of the Instituto de Neurociencias de Alicante (IN), a joint institution of the Spanish National Research Council and the Universidad Miguel Hernández. The IN has recently received the prestigious Severo Ochoa award for excellence in Science and constitutes a great environment to train research personnel in Neuroscience. Our students
take part on the postgraduate courses which are imparted in English since there are many international students. The first four months are dedicated to theoretical classes by IN researchers in different neuroscience disciplines covering neurophysiology, neuropathology, cellular biology, molecular biology, genetics and behavioral studies. During the next three months the students must participate in different activities including assistance to and discussion of scientific seminars given by international lecturers, oral presentations, journal clubs and short experimental works in an area that they choose from those available at the IN. After this, they start their experimental work on their thesis project. The student selected for this project will, in addition, complete two short stays in international laboratories to complete his training in computational neuroscience.

-PhD thesis directed.
2. Manuel Molano Mazón. (How the thalamus changes) What the cat’s eye tells the cat’s brain (2007-2013). Apto cum Laude. Currently postdoctoral associate in Rodrigo Quiroga’s Laboratory at the University of Leicester, UK.
3. Isabel Benjumeda Wijnhoven. Disentangling the roles of molecular guidance cues and neural activity in the emergence of brain topography (2009-2013). Apto cum Laude. Currently postdoctoral associate in Kate Whitlock’s Laboratory at the University of Valparaiso, Chile.

C.4. IMPLICACIONES ÉTICAS Y/O DE BIOSEGURIDAD
The detailed animal protocols have been included in the methodological part of this proposal. These protocols are currently used in our laboratory and only require biosecurity level 1. The members of the Comité de Bioseguridad y Bioética del IN have reviewed these protocols and certified that (1) they comply with current deontologic codes and Spanish and European legislation on bioethics and animal research; (2) the Instituto de Neurociencias is fully equipped to guarantee the execution of the proposed research plan. The laboratories, common installations and animal house have the adequate safety level required by the national and European laws; (3) the methodology of the proposal is in accordance to the requirements of replacement, reduction and refinement; (4) the procedures have been designed to minimize suffering, pain and distress of the animals; (5) the methods of killing are designed according the Spanish and European laws; (6) anesthesia and analgesia are contemplated and correctly proposed and no reuse of the animals is proposed; and (7) all associate researchers have the necessary training that is supported by training certificates.