A Computational Model of the Signals in Optical Imaging with Voltage-Sensitive Dyes

Yiu Fai Sit and Risto Miikkulainen

Department of Computer Sciences
The University of Texas at Austin
Austin, TX 78712, U.S.A.

Abstract

Optical imaging with voltage-sensitive dyes (VSD imaging) can record neural activity over an area of several square centimeters with high spatiotemporal resolution. The relative contributions of subthreshold and suprathreshold activity to the VSD signal are, however, poorly understood, making it difficult to interpret the imaging result. This paper shows how the activity in a computational model of V1 can be related to the VSD signal. The orientation tuning curve and the response time course in the model match those observed in VSD imaging, suggesting that the model represents VSD signal accurately and can be used to link neural activity to it.

Key words: Optical Imaging, Voltage-Sensitive Dyes, Computational Model

1 Introduction

Optical imaging measures neural activity through the reflectance of cortical surface. Its main advantage is that it provides high spatial resolution over an area of several square centimeters. Intrinsic optical imaging measures the change of reflectance due to metabolic and hemodynamic responses to the underlying electrical activity; it has been used to e.g. identify the layout of the orientation map in V1 [1]. However, such intrinsic signals have limited temporal resolution. Optical imaging with voltage-sensitive dyes (VSD) is a new technique that solves this problem, thus providing high resolution in both time and space [2]. Voltage-sensitive dyes measure electrical signals directly and the dye signal therefore has temporal resolution in the millisecond range. With careful monitoring and maintenance procedures, optical recording from the cortex of alert cats or monkeys can be performed for many months [2]. It can therefore be used to study brain activity even in complex behavioral tasks.

When voltage-sensitive dye solution is applied topically to the brain, dye molecules penetrate the tissue and bind to cellular membranes. These molecules transduce changes in membrane voltage into changes in fluorescence. Early in vitro studies showed that the dye signal is proportional to membrane voltage [3, 4]. However, it is also proportional to the surface area of the stained elements. Because the surface area of dendrites is much larger than that of cell bodies, dye signal is likely to emphasize subthreshold synaptic activity in dendritic arborizations. The relative contributions of the subthreshold population activity and suprathreshold spiking activity to the dye signal are unknown, making it difficult to interpret the signal.

This paper shows how the activity in a computational model of V1 can be related to the VSD signal. In particular, the orientation tuning curve and the response time course in the model match those measured in VSD imaging, suggesting that the model represents VSD signal accurately and can be used to link neural activity to it.

2 Computational Model

The computational model is based on the LISSOM model (Laterally Interconnected Synergetically Self-Organizing Map; [5, 6]), extended to include propagation delays in the cortical connections and to output VSD signal.

LISSOM has been used extensively to understand how the organization of the visual cortex emerges during development through self-organization. In this model, V1 is a 2-dimensional sheet of units representing vertical columns of cells through the six layers of the biological cortex. Each unit receives inputs from lower level units, as well as lateral inputs from the units on the same sheet (Figure 1).

Email address: {yfsit, risto}@cs.utexas.edu (Yiu Fai Sit and Risto Miikkulainen).

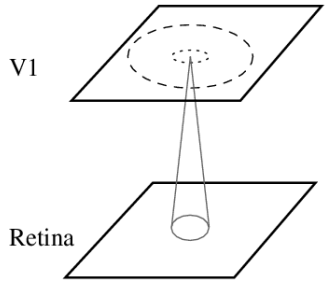

Fig. 1. **Architecture of the simplified LISSOM model.** The model is a hierarchy of sheets of neural units that represent the retina and V1. Sample connections are indicated for a unit in V1. The feedforward connections to a V1 unit form a local receptive field on the retina. V1 units also have short-range lateral excitatory (small dotted circle) and long-range lateral inhibitory (large dashed circle) connections.

For each input, the initial response or firing rate $\eta_a(0)$ for the V1 unit a is

$$\eta_a(0) = \sigma\left(\sum_r \chi_r A_{r,a}\right),$$

where σ is a piecewise linear sigmoid activation function for the V1 map, χ_r is the activation of the retinal unit r, and $A_{r,a}$ is the afferent weight value that connects unit r to unit a.

After the initial activation, V1 activity settles through short-range excitatory and long-range inhibitory lateral interactions:

$$\eta_a(t) = \sigma\left(\sum_r \chi_r A_{r,a} + \sum_\rho \gamma_\rho \sum_{\hat{a}} \eta_{\hat{a}}(t - d(a,\hat{a}))L_{\rho\hat{a},a}\right),$$

where the first term is the weighted sum of the activations from the retina and the second term is the sum of lateral signals arriving at unit a at time t. The label ρ in the second term identifies the type of lateral connection weight L (E for excitatory and I for inhibitory), and γ_ρ is a constant scaling factor for each ρ (negative for inhibitory connections). The index $\hat{a}$ spans the whole V1 map. The delay function $d(a,\hat{a})$ models the propagation delay between V1 units a and $\hat{a}$.

In the basic LISSOM model, $d(a,\hat{a}) = 1$, which means that all lateral signals from the previous time step reach unit a at the same time. Although this is a valid abstraction at a larger time scale, propagation delay actually affects how these signals modulate the response at the destination. For example, modulations due to neighboring neurons are effective in the early response and will continue to influence it, while neurons that are further away have a later influence on the already modulated response. As a result, the approximation that all lateral signals arrive at once is not accurate if high temporal resolution is needed, as it is when modeling VSD data.

Since the VSD signal is likely to emphasize subthreshold synaptic activity, in order to account for VSD imaging data, such activity needs to be measured in LISSOM as well. Inputs smaller than the lower threshold of the sigmoid function can be treated naturally as subthreshold activity; hence, the weighted sum of presynaptic activity can be used to model the VSD signal $V_a(t)$ of the activation $\eta_a(t)$:

$$V_a(t) = \sum_r \chi_r A_{r,a} + \sum_\rho \gamma_\rho \sum_{\hat{a}} \eta_{\hat{a}}(t - d(a,\hat{a}))L_{\rho\hat{a},a}.$$

After the activity has settled, the connection weights of each cortical unit are modified. Both the afferent and lateral weights adapt according to the same biologically motivated mechanism: the Hebb rule [7] with divisive postsynaptic normalization:

$$w'_{r,a} = \frac{w_{r,a} + \alpha X_r \eta_a}{\sum_u (w_{u,a} + \alpha X_u \eta_a)},$$

where $w_{r,a}$ is the current afferent or lateral connection weight (A, L_E, or L_I) from r to a, $w'_{r,a}$ is the new weight, α is the learning rate for each type of connection (α_A for afferent weights, α_E for excitatory, and α_I for inhibitory), X_r is the presynaptic activity after settling (χ for afferent, η for lateral), and η_a stands for the activity of unit a after settling. Afferent inputs, lateral excitatory inputs, and lateral inhibitory inputs are normalized separately.

The LISSOM model extended with delayed lateral connections and subthreshold signal can be used to account for VSD imaging data, as will be described next.

3 Experiment

A simulation was carried out to show that after self-organization, the simulated VSD signal matched the biological data.

The retina had 36×36 units, and V1 had 108×108 units. The receptive field radius of V1 was 6 and the excitatory and inhibitory lateral connections radii were 4 and 13, respectively. The weights of each connection types to a V1 unit were initialized randomly and normalized to 1. The propagation delay d between units a and $\hat{a}$ was made proportional to the Euclidean distance on the map, i.e. $d(a,\hat{a}) = \frac{1}{2}\sqrt{(a_x - \hat{a}_x)^2 + (a_y - \hat{a}_y)^2}$, where (a_x, a_y) and $(\hat{a}_x, \hat{a}_y)$ are the coordinates of units a and $\hat{a}$, respectively. Using a smaller proportional factor, and hence a smaller delay, yields similar results.

After $40,000$ presentations of elongated Gaussians (edges), the model V1 self-organized to form a realistic orientation map (Figure 2).

In order to verify that the temporal properties of this map are valid, its behavior was compared with the optical imaging data of Sharon and Grinvald [8]. In their experiment, the

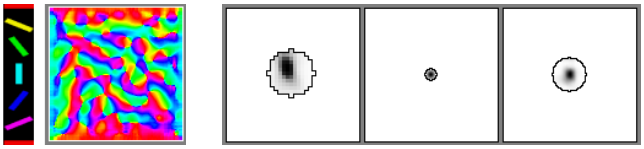

Fig. 2. **Orientation map and sample connections after self-organization.** The left plot shows the orientation preference map of the model V1 after training, with color keys representing orientations on the left. The right plot contains, from left to right, the receptive field on the retina, excitatory lateral connections, and inhibitory lateral connections of a sample V1 unit. The response of this unit is used to compute the data in Figure 4. The results in the above figures show that realistic orientation map can emerge from the LISSOM model extended with propagation delays.

time course and the orientation tuning curve of the cat V2 in response to grating input were measured. Similarly with the extended LISSOM model, long edges of different orientations were presented in the receptive fields of a particular group of nine neighboring V1 units that had similar orientation preference and their simulated VSD signals $V(t)$ were recorded over time. One major finding by Sharon and Grinvald was that the width of the tuning curve does not change over the response period. The tuning curves of the model V1 unit are plotted in Figure 3 at different time steps; they show similar property.

Second, Sharon and Grinvald found that there is a deceleration of the response shortly after response onset followed by an acceleration. The deceleration is larger with the stimulus that is orthogonal to the cell's preferred orientation. The model again produces similar result (Figure 4).

The biological origin of such change in acceleration is poorly understood. A possible explanation suggested by the model is that the initial response is due to the afferent input and the deceleration and the subsequent acceleration result from the interaction of excitatory and inhibitory lateral connections. Since the two lateral connection types are normalized separately, individual short-range excitatory connections usually have larger weights than long-range inhibitory connections. The net effect of the lateral inputs within the radius of excitatory connections is therefore positive. Immediately after the initial response, only a few such excitatory lateral inputs arrive. The response therefore increases only a little, which gives rise to the deceleration.

The initial suprathreshold response to the orthogonal orientation is much smaller than the response to the preferred orientation. Since the responses of the nearby units are similar, the excitatory inputs are also smaller, resulting in the observed larger deceleration with orthogonal inputs.

The acceleration afterward is due to two effects. First, within the radius of excitatory connections, positive feedback loops are formed between interconnected units. Second, as time progresses, the area covered by lateral connections, and therefore the number of excitatory inputs, increases quadratically. These two factors together accelerate the VSD signal.

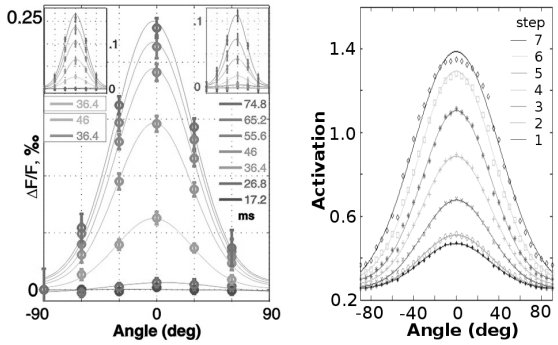

Fig. 3. **Average orientation tuning curve in VSD imaging and the model.** The left plot shows how the average orientation tuning curve (i.e. response to different orientations) changes over time as observed in VSD imaging, and the right plot shows the same data for the model (average of nine units). The width of the tuning curve does not change over time, suggesting that the VSD signal is represented accurately for different orientations and times in the model. (Left plot adapted from [8], with permission.)

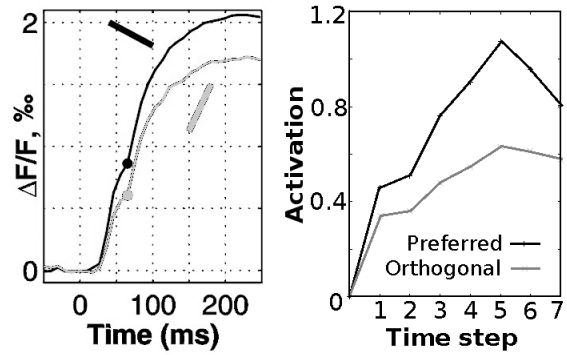

Fig. 4. **Time course of the response in VSD imaging and the model.** The left plot shows the time course of the optical signal to a grating with preferred orientation (black) and the orthogonal orientation (gray); the circles mark the deceleration-acceleration notch. The right plot is the same time course of a model unit when a long edge is presented, which also has the notch in the early response. The reason for such a change in acceleration is unknown; the model predicts that it arises because different numbers of lateral inputs arrive at different times. (Left plot adapted from [8], with permission.)

The response eventually saturates in the model because it is bounded by the sigmoid function.

The acceleration in the orthogonal orientation is again smaller than that of the preferred orientation, for two reasons. First, as in the deceleration, the suprathreshold response to the orthogonal orientation in the surrounding units is small. The effects of the positive feedback loops are therefore smaller. Second, lateral connections usually link units that prefer the same orientation. The units that are highly activated in this case (by the orthogonal orientation) thus have a smaller influence on the response of the unit.

Lateral inhibition also becomes stronger over time because of the increase in the area that it covers. The effect is slower, however, because individual lateral inhibitory connections

are usually longer and have smaller weights than those of the lateral excitatory connections. Lateral inhibition therefore takes a longer time to deliver in the model. In the late response, the inhibitory signals become strong enough to counteract lateral excitation and the VSD signal decreases.

These results match the VSD data well, showing that the model represents VSD signal accurately.

4 Conclusions

Optical imaging with VSD is an important neural recording technique that offers high resolution both spatially and temporally. There is, however, no direct relationship between spiking activity and the VSD signal. This paper shows how the activity in the computational model can be related to the VSD signal. The orientation tuning curve and the response time course in the model match those measured with VSD imaging, suggesting that the model represents VSD signal accurately and can be used to link neural activity to it. It also gives a possible computational explanation for the acceleration and deceleration observed in the time course of the VSD signal.

Acknowledgments

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