How not to get caught

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How much computation can one neuron do? A paper in *Nature* provides direct evidence that multiplication of two sensory variables may be instantiated at the single-cell level.

Why is it so hard to swat some insects? For many species, the answer lies in a visual neuron that responds best to approaching (looming) versus receding objects. For instance, the lobular giant motion detector (LGMD) neuron of the locust responds more strongly to looming objects than to receding ones. Furthermore, its peak firing time provides a reliable estimate of the target's angular size, which is likely to be key for initiating escape behavior. In new work just published in *Nature*[1], Gabbiani, Krapp, Koch and Laurent describe electrophysiological measurements of the LGMD looming response that provide direct evidence for the biophysical mechanisms underlying this computation.

Image processing of the visual scene is first expressed as simple stimulus selectivities in neurons of the early visual system. In insects, lower vertebrates and some mammals, the retina already shows an impressive range of selective responses. The LGMD response represents directional selectivity for a sort of 'to and fro' motion, just a few synapses from the photoreceptors. In contrast, for higher species, including humans, the 'heavy lifting' of extracting fundamental image features is generally shifted downstream to primary visual cortex. The explicit neuronal circuitry and mechanisms underlying such functional processing—selectivity for motion, edge orientation, contrast changes and so forth—have been the focus of many experimental and theoretical studies.

Gabbiani and colleagues previously[2] developed a phenomenological model for the spiking dynamics of the LGMD looming response as a product of an excitatory function of the stimulus angular velocity, $\dot{\theta}(t)$, and an inhibitory function of the angular size, $\theta(t)$ (**Math Box**). But what is the biophysical substrate for this computation? The LGMD neuron receives two main types of input, a retinotopic excitatory input that impinges on its large dendritic fan, and wide-field inhibitory inputs to two smaller dendritic trees adjacent to the fan (**Fig. 1**). In turn, the excitatory input arises from terminals that are thought to be a presynaptic substrate for lateral inhibition from nearby points in the image. How could these three signals—retinotopic excitation, feedforward inhibition and lateral inhibition—account for the computation? Are crucial steps in the computation of motion already expressed in the inputs themselves, thus accomplished presynaptically with respect to the LGMD, or are they apparent only in LGMD itself, thus postsynaptically?

To address these questions, Gabbiani *et al.* noted that the original multiplication could be recast as an addition by using logarithms (**Math Box**). The underlying biophysical hypothesis was that the LGMD excitatory and inhibitory inputs may be described as $\log(\dot{\theta}(t))$ and $\theta(t)$, respectively, that these inputs subtract from each other within the LGMD, and that a subsequent exponentiation completed the calculation.

In their new work[1], Gabbiani *et al.* used intracellular and extracellular recordings to show that the synaptic inputs and the intrinsic properties of the LGMD are indeed consistent with this relationship. Classical work showed that different moving backgrounds can selectively upregulate two inhibitory pathways[3]. When Gabbiani *et al.* used this approach to activate the presynaptic lateral inhibitory pathway during presentation of a looming object, the normal response was strongly attenuated, but only at the beginning of the response—well before the peak firing rate was achieved. When the postsynaptic feedforward pathway was facilitated by the background stimulus (confirmed directly by intracellular recordings of evoked hyperpolarizing postsynaptic potentials), the normal looming response was again strongly inhibited. However, in this case, the peak firing time—the essential functional variable—was also strongly affected.

$GABA_A$ receptors are involved in feedforward inhibition, whereas muscarinic acetylcholine receptors are involved in presynaptic lateral inhibition. Gabbiani *et al.* therefore blocked $GABA_A$ receptors with PCTX, which increased the LGMD spike response to the looming target. This suggested that the feedforward path was effective during the normal response. As a final step, the authors compared responses with and without the sodium channel blocker tetrodotoxin to evaluate the contributions from sodium channels. At the subthreshold level, sodium channels sped up the response. More relevant to the model, the average spike rate had a nonlinear relationship with the average (estimated) subthreshold voltage response, in some cases reminiscent of an exponential operation.

Taken together, the results are consistent with the authors' model: inhibition related to object angle acts postsynaptically on the LGMD, suppressing an excitatory input related to object angular velocity; sodium channel spike generation completes the multiplication through an expansive nonlinearity. These new data offer significant insight into how the LGMD works at the biophysical level; importantly, the new results also pose several new questions.

For example, what is the nature and mechanism of the hypothetical logarithmic transformation of the excitatory input? Because these inputs are retinotopic, any given excitatory synapse contributes only a local estimate of $\dot{\theta}(t)$, even when large stimuli are presented. As one proceeds toward the axon from any of these inputs, it seems likely that at some point the membrane voltage will roughly reflect the algebraic sum of all the excitatory inputs. This implies that at least some

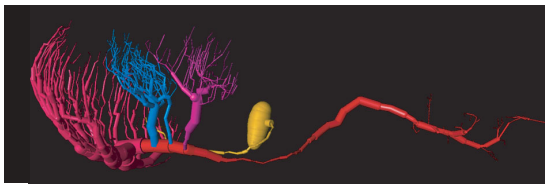

Fig. 1. The lobular giant motion detector neuron (LGMD) of the locust receives two main types of input: a retinotopic excitatory input that impinges on its large dendritic fan (left), and wide-field inhibitory inputs to two smaller dendritic trees (blue and purple). Image reprinted with permission from ref. 8.

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Math Box.
Gabbiani and colleagues[1] fit the LGMD neuron spiking response to looming objects, $R(t)$, to the product (or ratio, the distinction resting on an arbitrary sign assignment) of two functions of the visual input's angular velocity, $\dot{\theta}(t)$, and angular size, $\theta(t)$:

$$R(t) = \dot{\theta}(t) \times \exp(-\theta(t))$$

By exploiting the additive properties of logarithms, (different) functions of the inputs were subtracted, instead of multiplied, yielding an equivalent expression that more directly reflected the underlying biophysics:

$$R(t) = \exp\left[\log(\dot{\theta}(t)) - \theta(t)\right]$$

if not all the nonlinear transformation must occur within the LGMD. (It cannot be done before on each separate input, either pre- or postsynaptically, as the log of a sum is not the same as the sum of the log.) Taken together with the claim by Gabbiani *et al.* that the exponentiation must also occur within the LGMD, this raises the interesting possibility of a single neuron calculating first a function and then its inverse.

Another intriguing question arises because the feedforward inhibition is mediated by $GABA_A$ receptors, well known for their theoretical role of implementing synaptic division directly via membrane shunting. Because a division (or multiplication) of the inputs was called for by the original model equation, $GABA_A$ receptors would seem to be ideal. However, the rewritten form of the equation relies on the interaction being subtractive. Indeed, the action of 'shunting inhibition' tends to be subtractive vis-à-vis the spike output, because of the interaction with spiking conductances[4]. The present study[1] argues that the subtraction is manifested at the LGMD's subthreshold membrane potentials—before the spike membrane currents are invoked. Nevertheless, significant voltage-dependent currents are likely to be involved.

These sorts of questions should be addressable by more direct measurement of the inputs, as provided by conductance measurements of evoked synaptic responses. The large size of the LGMD and its electrotonic compactness makes it well suited to such protocols. This problem is also ideal for the development of a biophysically detailed compartmental model, to see if plausible membrane nonlinearities and synaptic input distributions on the LGMD dendritic/axonal skeleton can reconcile the data and the phenomenological model.

Finally, it remains to be shown how the particular hypothetical stimulus representations are generated by neurons presynaptic to the LGMD. That is, how do the inputs become related to angular size and velocity? Although the authors' electrodes did not reach that far back, the kinetic details of the postsynaptic signatures reported in this work should provide strong constraints on subsequent studies.

Certainly the model by itself does not describe the whole story; perhaps most obviously, it ignores integration over the visual field. In contrast, electrophysiological and imaging studies[5,6] of the well-known 'back and forth' direction selectivity of some retinal neurons to motion across the visual plane are starting to zero in on the crucial biophysical mechanisms at play here. A likely candidate is nonlinear synaptic integration along single extended dendritic cables. Both back-and-forth directional select ivity and to-and-fro direction selectivity require temporal computations over visual space, but with important differences. Back-and-forth selectivity requires retinotopic order of the inputs over a range of spatial scales, whereas to-and-fro detection requires only local order in the inputs. This latter point was well illustrated in an integrate-and-fire perceptron-like network model[7]. This isotropic network included local center–surround excitatory–inhibitory interactions (lateral inhibition), combined with a wide support inhibitory pathway (feedforward inhibition), to give translation-independent to-fro discrimination. In other words, the cell can detect a looming target coming from different angles toward the locust.

The present work[1] and the model of Rind and Bramwell[7] include both complementary and alternative points. The latter model[7] focuses more on to-and-fro directionality of the LGMD, showing that presynaptic lateral inhibition is important for suppressing the receding response. Similar to the work of Gabbiani *et al.*[1], this model[7] postulates a crucial postsynaptic role for feedforward inhibition during the looming response, which eventually shuts the response down. Gabbiani *et al.* go further with the proposal that this occurs at a critical moment to give the correct peak firing signal, allowing downstream neurons to derive an escape response.

Importantly, Rind and Bramwell[7] proposed that the local interaction of retinotopic excitation and lateral inhibition was nonlinear, implemented in their model by a phenomenological threshold that followed linear summation. As explained above, the current results argue for a postsynaptic nonlinear transformation of the excitation within the LGMD dendrites, for example by synaptic conductance interactions or voltage-dependent channels. The model of Rind and Bramwell also assumes that linear postsynaptic interactions are sufficient to predict the output of the LGMD, whereas Gabbiani *et al.* suggest that Na^+ channels are essential, especially to provide a supralinear spike function.

Typically several classes of models can account for some functional property. The work by Gabbiani *et al.*[1] provides a clearer picture of what is plausible at the level of single-cell computation. That is, it sheds light on the type of computation that we can expect from a single neuron compared with computations that emerge from properties of the network. In this way, learning why certain insects are awfully hard to catch may provide insights into the division of labor between neuron and network in our own cortex.

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