Supplemental information

How inhibitory neurons increase information transmission under threshold modulation

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Methods S1. Related to STAR Methods.
Appendix on information calculations

Here we provide additional details for computing the mutual information, the total spiking probabilities for either single or a group of (binary) neurons, and descriptions for generating the main text figures.

A1 Neural responses and mutual information

This section focus on the mathematical formalism for the neural encoding model and information transmission. Firstly, we defined the model of neural response for one or a group of neurons \((N \geq 1)\) that jointly encode the same stimulus (Sec. A1.1). Our choice of the modeling framework was motivated in part by the experimental setup that used full-field temporally varying stimuli to probe responses of the retinal ganglion cells (RGCs) (Kastner and Baccus, 2011). Specifically, we were interested in characterizing how multiple fast-Off neuronal types jointly encode the temporal fluctuations in light intensity.

Given the neural response that depends on the neural threshold \((\mu_i)\) and noise level \((\nu_i)\) of each cell, we then defined the total spiking probability (Sec. A1.2) and mutual information (Sec. A1.3) as a function of \((\mu_i, \nu_i)\), either without or with threshold modulation.

A1.1 Joint response of for a group of neurons

If we consider a group of \(N\) binary neurons jointly encoding the same filtered stimulus \((x \in X)\), given the assumption that their responses are “conditionally independent” without significant correlations, the probability of yielding the joint response \(r\) for a given filtered stimulus \(x\) is

\[
p(r|x) = \prod_{i=1}^{N} p(r_i|x),
\]  

\((A1)\)

where the vector \(r = (r_1, r_2, ..., r_N)\) denotes \(N\)-neurons’ responses with \(r_i \in \{0, 1\}\), and \(p(r_i|x) = p(r_i|x, \mu_i, \nu_i)\) is the response function of individual neuron \(i\) (main text Eq. (4)),

\[
p(r_i = 1|x) = \frac{1}{2} \left[ 1 + \text{erf} \left( \frac{x - \mu_i}{\sqrt{2} \nu_i} \right) \right],
\]  

\((A2)\)

\[
p(r_i = 0|x) = 1 - p(r_i = 1|x).
\]  

\((A3)\)

For a binary neuron, its response function is modeled as the probability of threshold crossing event, with a threshold \((\mu)\) and a noise level \((\nu)\). The neural response above illustrate the nonlinearity of the primary pathway (without threshold modulation) as it considers the “primary” noise \(\nu_i\). Yet, by replacing the noise value \(\nu_i\) with \(\nu_{i, \text{eff}}\) (c.f. main text Eq. (5)), we get the neural response joint affected via both primary and secondary/modulatory pathway.
A1.2 Averaged neural responses and total spiking probability

The joint neural response $p(r|x)$ averaged across the stimulus distribution $p(x)$ gives the averaged probability of neural response $r$,

$$p(r) = \int dx \, p(x) \, p(r|x),$$  

(A4)

$$= \int dx \, p(x) \prod_{i=1}^{N} p(r_i|x).$$  

(A5)

where $p(x)$ is the probability density function of filtered stimulus ($x$). The averaged total spiking probability $p_{\text{spike}}$ of $N$ neurons is to sum over the $2^N$ possible responses ($r \in \mathbf{R}$) as follows,

$$p_{\text{spike}} = \sum_{r \in \mathbf{R}} \|r\|_1 \, p(r) = \sum_{i=1}^{N} p(r_i = 1),$$  

(A6)

where $p(r_i = 1) = \int_{-\infty}^{\infty} dx \, p(r_i = 1|x) \, p(x)$ is the spiking probability of $i$-th neuron. Note that the above equation is a general form whose noise level has not been explicitly specified. By plugging in the value of noise level, either $\nu_{i,\text{eff}}$ or $\nu_i$, Eq. (A6) can be the total spiking probability with or without threshold modulation.

**Examples** Taking $N = 1$ and 2 as examples, all the possible response $r \in \mathbf{R}$ and the total spiking probability are summarized as follows:

| $N$ | $r$       | $\mathbf{R}$                  | $p_{\text{spike}}$ |
|-----|-----------|--------------------------------|-------------------|
| 1   | $r_1$     | $\{1, 0\}$                    | $p(r_1 = 1)$      |
| 2   | $(r_1, r_2)$ | $\{(1, 1), (1, 0), (0, 1), (0, 0)\}$ | $p(r_1 = 1) + p(r_2 = 1)$ |

For $N = 2$, the total spiking probability is the linear sum of individual

$$p_{\text{spike}} = \sum_{r \in \mathbf{R}} \|r\|_1 \, p(r),$$

$$= \sum_{r \in \mathbf{R}} \|(r_1, r_2)\|_1 \, p(r_1, r_2)$$

$$= 2p(1,1) + p(1,0) + p(0,1),$$

$$= [p(1,1) + p(1,0)] + [p(1,1) + p(0,1)],$$

$$= p(r_1 = 1) + p(r_2 = 1).$$

This applies to arbitrary number of $N$, as given by Eq. (A6).

A1.3 Mutual information

For the two-pathway model, we compute the mutual information in two steps (c.f. main text Fig. 1). Here, we want to emphasize that the information for each step has a different dependence on ($\mu_i$, $\nu_i$, $\sigma_{\mu,i}$), as described below.
A) Information without modulation

For $N$ neurons ($r \in \mathbb{R}$) joint encoding the same filtered stimulus, mutual information between their responses ($r \in \mathbb{R}$) and the stimulus values ($x \in X$) at a set of fixed thresholds $\mu = \{\mu_i\}$ is given by (Cover and Thomas, 1991):

$$I_{\text{without modulation}} = I(X; R|M = \mu) = \int dx p(x) \sum_{r \in \mathbb{R}} p(r|x) \log_2 \frac{p(r|x)}{p(r)},$$

(A7)

where $p(r|x)$ is given by Eq. (A1) and $p(x)$ is the probability density function of filtered stimulus. Given the neural response $p(r|x)$ that depends on the neural threshold ($\mu_i$) and primary noise ($\nu_i$) of each cell, one can compute the total spiking probability ($p_{\text{spike}}$) and $I_{\text{without modulation}}$ as a function of ($\mu_i, \nu_i$).

B) Long-term information

On longer time scales, we average the mutual information over the varying threshold $\tilde{\mu}$:

$$I_{\text{long-term}} = \int d\tilde{\mu} I(X; R|M = \tilde{\mu}) p(\tilde{\mu}),$$

(A8)

$$= \int d\delta\mu I(X; R|M = \mu + \delta\mu) p(\delta\mu),$$

(A9)

Here, $p(\tilde{\mu})$ describes the multivariate normal distribution with mean $\mu = \{\mu_i\}$ and s.d. $\sigma_{\mu} = \{\sigma_{\mu,i}\}$. The total spiking probability with modulation ($p_{\text{spike, eff}}$) and long-term information ($I_{\text{long-term}}$) are functions of ($\mu_i, \nu_i, \sigma_{\mu,i}$).

A2 Information transmission of a single neuron

A2.1 Information without modulation

Given the neural response function (Eq. A2) and that the stimulus $p(x)$ is a Gaussian distribution with mean $x_0$ and standard deviation $\sigma_x$, we can compute the mutual information, $I_{\text{without modulation}}$, between the stimulus and the neural responses (Eq. A7) and the average spike probability, $p_{\text{spike}}$ (Eq. A6) (Fig. S5 (A)(B)). Note that both $I_{\text{without modulation}}$ and $p_{\text{spike}}$ shown in Fig. S5 are straightforwardly represented in the space of the neural threshold ($\mu$) and primary noise level ($\nu$), both of which are parameters of the neural response (Eq. A2). To better illustrate how the information depends on neural noise and average spike probability, we remap the information from the space of ($\mu, \nu$) to that of ($p_{\text{spike}}$, $\nu$) (Fig. S6 (A)) based on Fig. S5 (A)(B).

Figure S6 (A) to (C) summarize two main observations: (1) the average spike probability ($p_{\text{spike}}$) considered by itself increases information until $p_{\text{spike}}$ reaches the half of its maximal value (Fig. S6 (B)); (2) similarly, the noise ($\nu$) when considered separately from other parameters decreases information transmission (Fig. S6 (C)). Both of these effects are well established in the literature (Brenner et al., 2000).

A2.2 Long-term information

Information ($I_{\text{long-term}}$) and total spiking probability ($p_{\text{spike, eff}}$) with threshold modulation depend on ($\mu, \nu$) and the modulation strength ($\sigma_{\mu}$) (Eq. A8, A6). Each series of colored dots (filled/open) shown in Fig. 4(B) (main text) are computed with a fixed set of ($\mu, \nu$) but with different values of $\sigma_{\mu}$.

Figure 2 (A) shows the percentage changes in information ($\Delta I/I_0 = I/I_0 - 1$) when the variability increases either in modulation (blue lines) $I = I_{\text{long-term}}(\nu = 0.2, \sigma_{\mu} = \sqrt{\text{Var}})$, or in the primary noise (black lines) $I = I_{\text{without modu.}}(\nu = \sqrt{0.2^2 + \text{Var}})$, relative to $I_0 = I_{\text{without modu.}}(\nu = 0.2)$. 
Figure 2 (B) shows mutual information $I_{\text{long-term}}(\nu, \sigma_{\mu})$ given that the primary and modulatory noises are constrained to the sum $\nu_{\text{eff}} = \sqrt{\nu^2 + \sigma^2_{\mu}} = 0.3$.

Figure 4 (C) presents the percentage change in total spiking probability, $\Delta p_{\text{spike}} / p_{\text{spike}} = p_{\text{spike, eff}} / p_{\text{spike}} - 1$, where $p_{\text{spike}}$ of each curve corresponds to a set of fixed $(\mu, \nu = 0.2)$.

### A3 Information transmission for a pair neurons

#### A3.1 Information without modulation

For the case of a group neurons ($N > 1$), both mutual information and total spiking probability depend on $4N$ parameters, i.e., the neural threshold $(\mu_i)$ and the neural noise $(\nu_i)$ of each cell. Via maximizing information transmission, one can find the optimal thresholds $(\mu_i)$ subject to the given constraints: the neural noises $(\nu_i)$ and the spiking probabilities $(p_{\text{spike}})$. This optimization problem can be formulated as follows,

$$\{\mu_{\text{opt.}}^i\} = \arg \max_{\{\mu_i\}} I_{\text{without modu.}}(\{\nu_i\}, \{\mu_i\})$$  \hspace{1cm} (A10)

subject to : $p_{\text{spike}}(\{\nu_i\}, \{\mu_i\}) \leq p_{\text{spike}}^{\text{max}}$,

$$\nu_i = \nu_i^{\text{const.}}.$$  

Figure S7 shows the examples of optimal thresholds and the individual spiking probability for the two and three neurons cases. The black line in Fig. 3 (A)(C) shows the information versus the constrained total spiking probability ($p_{\text{spike}}^{\text{max}}$) when their thresholds are set to the optimal values. In the main text, we also recapped the result (McDonnell et al., 2006; Kastner et al., 2015) that the mean noise level of a cell pair ($N = 2$) controls their optimal thresholds and that it becomes optimal to encode stimulus with different thresholds when the mean noise level is lower than a critical value (Fig. S1).

#### A3.2 Long-term information

The optimization for finding the optimal thresholds does not change much when it comes to include the threshold modulation $(\sigma_{\mu})$,

$$\{\mu_{\text{opt.}}^i\} = \arg \max_{\{\mu_i\}} I_{\text{long-term}}(\{\nu_i\}, \{\mu_i\}, \{\sigma_{\mu,i}\})$$  \hspace{1cm} (A11)

subject to : $p_{\text{spike}}(\{\nu_i\}, \{\mu_i\}) \leq p_{\text{spike}}^{\text{max}}$,

$$\sqrt{\nu^2_i + \sigma^2_{\mu,i}} = \nu_i^{\text{const.}}.$$  

The constraint on the total spiking probability is independent of the modulation because of our assumption that the primary pathway sets the ideal total spike rate ($p_{\text{spike}}$) in the absence of modulation. In contrast, the secondary pathway perturbs the thresholds independent of the primary one and brings the actual spike rate to a higher value, $p_{\text{spike, eff}}$. Besides, the primary and modulatory noises are constrained to match the given effective noise level (Eq. (5)).

Each colored curve in Fig. 3 (A)(C) shows $I_{\text{long-term}}$ versus $p_{\text{spike, eff}}$ at the optimal thresholds solved with Eq. (A11) but under different modulation combinations $(\sigma_{\mu,i})$. Figure 3 (B)(D) shows the percentage change in information, $\Delta I / I_{\text{without modu.}} = I_{\text{long-term}} / I_{\text{without modu.}} - 1$. 
Table S1: Estimated noise components in the primary $\nu$ and modulatory $\sigma_\mu$ pathways for each cell pair. Related to Results and STAR Methods. The dependence of noise components upon the contrast are fitted by cell pair, across the nine contrasts ($\sigma = 12\%$ to $36\%$ in $3\%$ intervals). All the fitting parameters are in the unit of critical noise value, $\nu_c$.

| Cell pair # | Adapting $\nu_1 (\sigma)$ | Sensitizing $\sigma_{\mu,1} (\sigma)$ | Adapting $\nu_2 (\sigma)$ | Sensitizing $\sigma_{\mu,2} (\sigma)$ |
|-------------|-----------------------------|----------------------------------------|-----------------------------|----------------------------------------|
| A           | 0.819$\sigma$               | 0.281$\sigma$                         | 0.784$\sigma$              | 0.0                                    |
| B           | 0.671$\sigma$               | 0.546$\sigma$                         | 0.749$\sigma$              | 0.049                                  |
| C           | 0.713$\sigma$               | 0.448$\sigma$                         | 0.801$\sigma$              | 0.025                                  |
| D           | 0.413$\sigma$               | 0.618$\sigma$                         | 0.545$\sigma$              | 0.051                                  |
| E           | 0.670$\sigma$               | 0.598$\sigma$                         | 0.758$\sigma$              | 0.010                                  |
| F           | 0.604$\sigma$               | 0.528$\sigma$                         | 0.622$\sigma$              | 0.033                                  |
| G           | 0.482$\sigma$               | 0.751$\sigma$                         | 0.594$\sigma$              | 0.013                                  |
| Combined fit| 0.597$\sigma$               | 0.563$\sigma$                         | 0.685$\sigma$              | 0.033                                  |
Supplemental figures

Figure S1: Information predicts the optimal thresholds for a pair of neurons given the values of noise level. Related to Figure 6 and STAR Methods. (A) and (B) shows the information transmitted by a pair of neurons at different values of noise and thresholds. The noise level is the same for the two neurons in (A) and different in (B), $\Delta \nu / \nu_c = -0.02$, between neurons. Black and dark-green dots mark global and local information maxima, respectively. Local maxima appear when noise levels differ across neurons (B); otherwise the maxima are equivalent as in (A). Gray dots mark the inflection points, the so-called spinodal lines that delineate the regions where local maxima can be found.
Figure S2: The maximally informative spike rates among neurons were similar for models with and without threshold modulation. Related to Figure 3. The results shown here correspond to the analyses of the impact of threshold modulation shown in Fig. 3.
Figure S3: **Optimal ways to apply modulation for neurons with identical spike rates depend on their rates.** Related to STAR Methods. For neurons with low spike rates, the negative impact of threshold modulation is minimized when modulation is applied equally to both neurons (gray line). For neuron with large response rates, selective application of modulation to one of the neurons is preferred. The neuron receiving modulation shifts its threshold to decrease its response rate (red line). Curves are shown as dashed in the regimes when they become sub-optimal in terms of information transmission in the presence of threshold modulation.
Figure S4: **Long-term information surface.** Related to STAR Methods. The threshold modulation effectively smooths the information surface (thin lines, gray dots mark maxima) to give rise to the long-term information surface (thick lines, red dots mark maxima).
Figure S5: Mutual information and the averaged spiking probability of a single neuron. Related to STAR Methods (Methods S1). (A) Information contours (bits) as a function of threshold ($\mu$) and neural noise level ($\nu$). Here, the threshold ($\nu$) is relative to the mean of the filtered input and both $\nu$ and $\mu$ are in the unit of stimulus standard deviation. (B) Information always peaks at $\mu = 0$ where spiking probability ($p_{\text{spike}}$) is 0.5 for any constant noise levels ($\nu$). (C) The global maximum of information is at $\nu = 0$ for a given threshold ($\mu$). (D) The spiking probability contours with the same axes as (A). (E) Spiking probability is asymptotic to one (zero) as the threshold ($\mu$) moves further below (above) the input mean. (F) Spiking probability increases (decreases) with neural noise ($\nu$) when the threshold ($\mu$) is below (above) the mean of the input, and stays as constant 0.5 as the threshold equals to the input mean ($\mu = x_0 = 0$).
Figure S6: Mutual information without modulation for single cell. Related to STAR Methods (Methods S1). (A) Information ($I_{\text{without modulation}}$) contours as a function of primary noise level ($\nu$) and spiking probability ($p_{\text{spike}}$). (B) Information as a function of $p_{\text{spike}}$ for various constant $\nu$. The first two lines ($\nu = 0, 0.2$) corresponds to the thick solid lines shown in the Fig. 3 in the main text. (C) Primary noise decreases information for any constant $p_{\text{spike}}$. 
Figure S7: Maximally informative solutions for a groups of neurons. Related to STAR Methods (Methods S1). (A) The distribution of thresholds are plotted as a function of noise level ($\nu = \nu_1 = \nu_2$), but subject to a constant total spiking probability ($p_{\text{spike}} = 0.2$), for the two (solid-line) and three neurons (dashed-line). (B) is the same as (A) but shown as a function of total spiking probability ($p_{\text{spike}}$) subject to constant neural noise ($\nu_i = 0.2$). (C, D) are similar to (A, B) but shows the distribution of individual spiking probability in groups of neurons.