'Silent' olfactory bulb mitral cells emerge from common feature subtraction.

Summary: Recordings from neural populations can be biased towards cells that are spontaneously active, and it is often implicitly assumed that stimulus responses will be unrelated to spontaneous activity. To avoid such biases [1] performed blind whole-cell patch clamp recordings of olfactory bulb mitral cells. Intriguingly, these recordings revealed an inverse relationship between spontaneous and odor-evoked activity: cells that were highly active at baseline were often quiet during odor presentation, while conversely, 'silent' cells, quiet at baseline, dominated odor responses. In this study we use a probabilistic model of early olfactory processing to show how such an inverse relationship between baseline and odor-evoked activity can emerge through an odor-triggered variant of olfactory background subtraction we call 'common feature subtraction.' In this computation, the olfactory system subtracts features common to recently encountered odors to preferentially infer the features unique to each odor. We suggest that the common features are not modeled directly, but are accounted for through the *negative* of their expected effects on receptor inputs. In a neural implementation of our probabilistic model we show that adjusting the background activation of mitral cells towards the *negative* of their recent activity results in their background rates reflecting the negative of the expected effect of the common features on receptor inputs. This negative expectation cancels the contribution of common features when odors are present, allowing preferential inference of odor-specific features by downstream neurons. Our model qualitatively reproduces the experimentally observed relationship between baseline and odor-evoked responses of mitral cells in [1] and provides a normative explanation for them. It is also readily testable through the direct link it predicts between baseline responses and the common features of recent odors.

Additional Details: We derive inference dynamics by discretizing time into consecutive $O(1$ sec.) bouts $1 \dots n$, where each bout i contains air at some fixed probability, so $\text{air}_i \sim \text{Ber}(p_0)$, or odors: sparse high-dimensional vectors summing unique features $\mathbf{x}_i \sim e^{-\beta\|\mathbf{x}_i\|_1 - \frac{\gamma}{2}\|\mathbf{x}_i\|_2^2}$ generated independently per bout, and common features $\mathbf{c}_i$ shared with recent bouts. Odors linearly excite receptors $\mathbf{y}_i$ via a matrix $\mathbf{A}$ assumed known to the animal. The animal is interested in $\mathbf{x}_i$ and accounts for $\mathbf{c}_i$ only via the *negative* of its expected receptor activations $\mathbf{b}_i = -\mathbf{A}\mathbf{c}_i$, thus $\mathbf{y}_i \sim \mathcal{N}(\mathbf{y}_i; (\mathbf{A}\mathbf{x}_i - \mathbf{b}_i)\overline{\text{air}}_i, \sigma^2)$, where $\overline{\text{air}}_i$ indicates an odor bout. Though $\mathbf{c}_i$ is a slowly varying high-dimensional sparse vector we assume its low-dimensional projection to receptor space $\mathbf{b}_i$ is approximately isotropic Gaussian: $\mathbf{b}_0 \sim \mathcal{N}(\mathbf{b}_0; \mathbf{0}, \eta_0^2)$, $\mathbf{b}_i|\mathbf{b}_{i-1} \sim \mathcal{N}(\mathbf{b}_i; \alpha\mathbf{b}_{i-1}, \eta^2)$. We assume further that $\mathbf{b}_i|\mathbf{Y}_i$, where $\mathbf{Y}_i = \{\mathbf{y}_1 \dots \mathbf{y}_i\}$ is the receptor history, is also in this family, with mean $\boldsymbol{\mu}_i$. We assume the olfactory system solves $\mathbf{x}_n^* = \text{argmax}_{\mathbf{x}_n}\, p(\mathbf{x}_n|\mathbf{Y}_n, \overline{\text{air}}_n) \propto p(\mathbf{x}_n)\, \mathcal{N}(\mathbf{y}_n; \mathbf{A}\mathbf{x}_n - \alpha\boldsymbol{\mu}_{n-1}, \alpha^2\eta_{n-1}^2 + \eta^2 + \sigma^2)$. We use neural dynamics based on [2] to maximize this posterior, yielding $\mathbf{x}_n^*$ in olfactory bulb granule cell activations, and mitral cell activations $\boldsymbol{\lambda}_n = \frac{\mathbf{y}_n - \mathbf{A}\mathbf{x}_n^* + \alpha\boldsymbol{\mu}_{n-1}}{\alpha^2\eta_{n-1}^2 + \eta^2 + \sigma^2}$, at the end of the bout. Updating $p(\mathbf{b}_n|\mathbf{Y}_n)$ requires updating its mean (we keep the variance fixed at η_∞^2, see below). If air is present then $\mathbf{y}_n$ gives no information about $\mathbf{b}_n$ so $p(\mathbf{b}_n|\text{air}_n, \mathbf{Y}_n) = \int p(\mathbf{b}_n|\mathbf{b}_{n-1}) p(\mathbf{b}_{n-1}|\mathbf{Y}_{n-1})\, \text{d}\mathbf{b}_{n-1}$ which we call $\mathcal{N}^+(\mathbf{b}_n)$, yielding $\boldsymbol{\mu}_n = \alpha\boldsymbol{\mu}_{n-1}$. If odor is present $p(\mathbf{b}_n|\overline{\text{air}}_n, \mathbf{Y}_n) \propto \mathcal{N}^+(\mathbf{b}_n) \int p(\mathbf{y}_n|\mathbf{x}_n, \mathbf{b}_n, \overline{\text{air}}_n) p(\mathbf{x}_n) \text{d}\mathbf{x}_n$ which we approximate using $\mathbf{x}_n^*$ computed above as $p(\mathbf{y}_n|\mathbf{x}_n^*, \mathbf{b}_n, \overline{\text{air}}_n)\mathcal{N}^+(\mathbf{b}_n) = \mathcal{N}(\mathbf{b}_n\ \mathbf{A}\mathbf{x}_n^* - \mathbf{y}_n, \sigma^2\mathbf{I})\mathcal{N}^+(\mathbf{b}_n)$. This is a Gaussian with variance $\eta_n^2 = \frac{\sigma^2(\alpha^2\eta_{n-1}^2 + \eta^2)}{\alpha^2\eta_{n-1}^2 + \eta^2 + \sigma^2}$ whose limiting value as $n \to \infty$ is η_∞^2. For the mean update when odor is present, we use $\boldsymbol{\lambda}_n$ above with η_{n-1}^2 replaced by η_∞^2 to get $\boldsymbol{\mu}_n = \alpha\boldsymbol{\mu}_{n-1} - (\eta^2 + \alpha^2\eta_\infty^2)\boldsymbol{\lambda}_n$. We must next average over the odor and air cases, since $p(\mathbf{b}_n|\mathbf{Y}_n) = p(\mathbf{b}_n|\overline{\text{air}}_n, \mathbf{Y}_n) p(\overline{\text{air}}_n|\mathbf{Y}_n) + p(\mathbf{b}_n|\text{air}_n, \mathbf{Y}_n) p(\text{air}_n|\mathbf{Y}_n)$. We assume that odors are presented at sufficiently high concentration to make $p(\text{air}_n|\mathbf{Y}_n)$ available to the animal as the binary indicator $\mathbb{1}_n^{\text{odor}}$. The mean updates can then be combined as $\boldsymbol{\mu}_n = \alpha\boldsymbol{\mu}_{n-1} - (\eta^2 + \alpha^2\eta_\infty^2)\boldsymbol{\lambda}_n \mathbb{1}_n^{\text{odor}}$. We convert these updates to continuous time by considering the response of a scalar $x(t)$ to step input of amplitude c, $\tau\dot{x}(t) = -x(t) + cu(t)$, mapping $x(0^-)$ to $\boldsymbol{\mu}_{n-1}$ and $x(T)$ to $\boldsymbol{\mu}_n$, where T is the average bout duration, to get $-\frac{T}{\log\alpha}\dot{\boldsymbol{\mu}} = -\boldsymbol{\mu} - \frac{\eta^2 - \alpha^2\eta_\infty^2}{1-\alpha}\boldsymbol{\lambda}\mathbb{1}^{\text{odor}}$. The remaining neural dynamics are as in [2] but with mitral cell dynamics modified to $\tau_\lambda\dot{\boldsymbol{\lambda}} = -\boldsymbol{\lambda} + \frac{\mathbf{y} - \mathbf{A}\mathbf{x} + \alpha\boldsymbol{\mu}}{\alpha^2\eta_\infty^2 + \eta^2 + \sigma^2}$, and now containing baselines $\propto \boldsymbol{\mu}$.

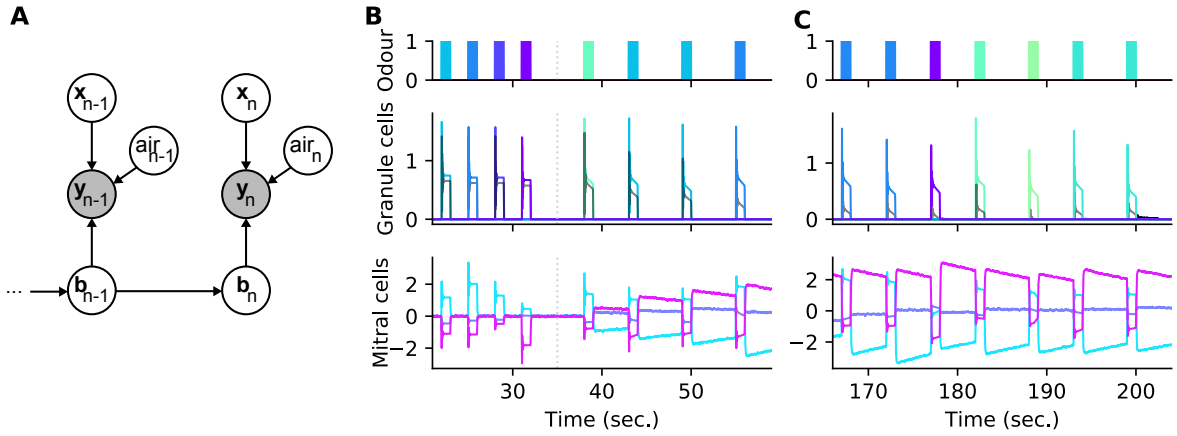

Figure 1. Probabilistic model and neural implementation. **(A)** Air and unique odor features $\mathbf{x}_n$ appear independently per bout, the effect $\mathbf{b}_n$ of common odor features on receptor activity has bout dependence. The animal uses the full history of receptor responses $\{\mathbf{y}_1 \dots \mathbf{y}_n\}$ to infer $\mathbf{x}_n$. **(B)** Neural implementation. Top row: Odors each consisting of a unique feature (colors) and a common feature, are presented in sequence, separated by air. Middle/bottom rows: Before common feature subtraction is enabled (dotted line) both the unique feature (colors) and the common feature (gray) are inferred in granule cell activations (middle), and mitral cell baselines are zero (bottom row, three cells shown). **(C)** Later, when adaptation has stabilized (note elevated mitral cell baseline rates, bottom row) the common feature (gray trace, middle row) has been greatly reduced relative to unique odor features (colors).

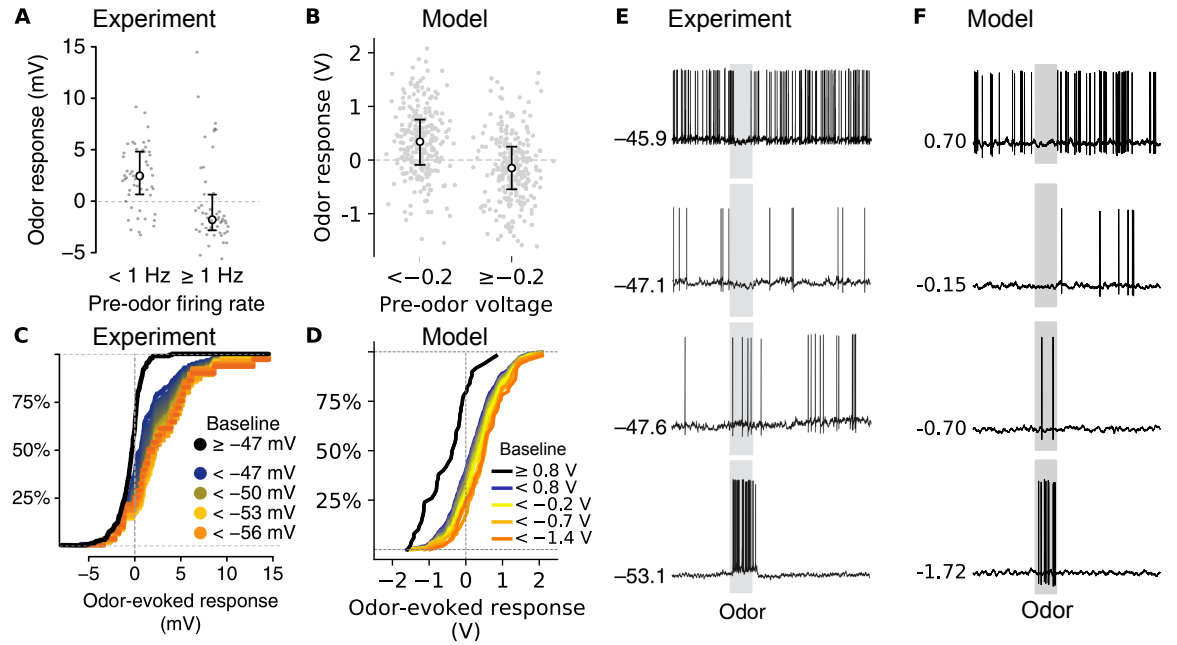

Figure 2. Comparing the data from [1] to the model. **(A)** Data from [1] showing distribution of M/TC odor responses split on pre-odor activity. Gray dots are individual cell-odor pairs, circle is the group mean, whiskers extend from 25th to 75th percentiles. **(B)** As in (A) but for model mitral cells, split on the median of baseline voltage. **(C)** Data from [1] showing the distribution of odor-evoked responses split according to the baseline voltage. **(D)** As in (C) but for model cells. **(E)** Data from [1] showing odor responses of four cells having different baseline voltages (numbers to the left of each trace). **(F)** As in (E) but for four model mitral cells. We generated spikes by converting mitral cell voltages to rates of inhomogeneous Poisson processes using a fixed multiplier. Spike heights and additive noise are purely cosmetic.

References: [1] Author et al. *Silent mitral cells dominate odor responses in the olfactory bulb of awake mice.* Nature Neuroscience 2014. [2] Author et al. *Sparse connectivity for MAP inference in linear models using sister mitral cells.* bioRxiv 2021.