If mitral cells are the answer, what is the question?

Summary: Why does the olfactory bulb contain two projection neuron populations? Called mitral and tufted cells (MCs and TCs), both sample receptor input at glomeruli but lie in different bulb layers [1], project to different regions of piriform cortex [2] and form parallel circuits wherein TCs interact mainly with the anterior olfactory nucleus (AON), and MCs with piriform cortex (PC) proper [3,4]. Experiments have revealed that (1) MCs are primarily driven by TCs [5], perhaps why (2) MC responses come later in the sniff cycle than TCs [6]; (3) MCs receive excitatory cortical feedback from the AON [7]; and (4) MC responses are harder to decode for odour properties than TCs [3]. We connect these observations and propose that parallel TC-AON and MC-PC circuits provide parallel explanations of glomerular input as caused by high dimensional latent odour features and implemented in AON/PC pyramidal activity. However, the more peripheral TC-AON circuit uses a simple prior to quickly sketch the olfactory environment, while the deeper MC-PC circuit uses a more complex prior to construct a more accurate explanation of the odour input. Steady-state MC/TC activity reflects the error between glomerular input and its explanations, so the better explanation by the MC-PC circuit yields lower activity, potentially explaining observation (4) above. The similarity of the two computations makes it natural to express MC drive in terms of TC activity, and doing so in circuitry readily reproduces observations (1–3). Thus we suggest MCs are the answer to how the olfactory system can explain glomerular inputs using a more complex prior than that of the TC-driven circuitry, while still using that drive to avoid unnecessary computation.

Additional Details: Inspired by [3] we model the olfactory system as two parallel circuits (Fig 1A). The first consists of TCs ($\mathbf{t}$) sampling odour input ($\mathbf{y}$) at the glomeruli, projecting to AON pyramidals ($\mathbf{s}$) and receiving disynaptic feedback inhibition via olfactory bulb granule cells. The second parallel circuit consists of MCs ($\mathbf{m}$) also sampling odour input at the glomeruli, but projecting to PC pyramidals ($\mathbf{x}$) and receiving disynaptic feedback inhibition from them via granule cells. Each circuit computes the maximum *a posteriori* (MAP) estimate of odour features most likely to have caused the glomerular activations $\mathbf{y}$, but using two different probabilistic models (Fig 1B). The TC-AON circuit models odours as high-dimensional vectors $\mathbf{s}$ of independent, non-negative, sparse features s_i, neurally implemented in the activity of individual AON pyramidals. Glomerular activations are assumed to be the sum of linear excitation by odour features and Gaussian noise of variance σ^2. Thus $p(\mathbf{y}|\mathbf{s}) = \mathcal{N}(\mathbf{y}; \mathbf{A}\mathbf{s}, \sigma^2)$; the affinity matrix $\mathbf{A}$ determines the strength of excitation of each glomerulus by each feature. The MC-PC circuit also models glomerular activity as due to linear excitation by its own copy $\mathbf{x}$ of the odour features implemented in the activity of its pyramidals, so $p(\mathbf{y}|\mathbf{x}) = \mathcal{N}(\mathbf{y}; \mathbf{A}\mathbf{x}, \sigma^2)$. However, it uses a more complex prior on odour features than the AON, by including, in addition to the sparsity prior, an auto-associative component to encourages coactivation of features that have been previously observed together. The two circuits interact in that each views the latents of the other as noisy versions of its own. The negative log posterior being minimized by the TC-AON circuit is then $\mathcal{L}_{\text{TC-AON}}(\mathbf{s}) = \beta\|\mathbf{s}\|_1 + \frac{\gamma}{2}\|\mathbf{s}\|_2^2 + \frac{1}{2\eta^2}\|\mathbf{x}-\mathbf{s}\|_2^2 + \frac{1}{2\sigma^2}\|\mathbf{y}-\mathbf{A}\mathbf{s}\|_2^2$. The objective for the MC-PC circuit adds an auto-associative term $\mathcal{L}_{\text{MC-PC}}(\mathbf{x}) = \beta\|\mathbf{x}\|_1 + \frac{\gamma}{2}\|\mathbf{x}\|_2^2 + \frac{1}{2\eta^2}\|\mathbf{x}-\mathbf{s}\|_2^2 + \frac{1}{2\sigma^2}\|\mathbf{y}-\mathbf{A}\mathbf{x}\|_2^2 - \frac{\rho}{2}\mathbf{x}^T\mathbf{W}\mathbf{x}$. Applying the approach in [8], dynamics that optimize the TC-AON objective are (see Fig 1A) $\tau_{\text{TC}}\dot{\mathbf{t}} \propto -\mathbf{t} + \sigma^{-2}(\mathbf{y} - \mathbf{A}\mathbf{s})$ for the TC activations, $\tau_{\text{AON}}\dot{\mathbf{u}} \propto -\mathbf{u} + \eta^{-2}\mathbf{x} + \mathbf{A}^T\mathbf{t}$ for the AON pyramidal voltages and $\mathbf{s} = \kappa[\mathbf{u} - \beta]_+$ for their firing rates. Dynamics to maximize the MC-PC objective are: $\tau_{\text{MC}}\dot{\mathbf{m}} = -\mathbf{m} + \sigma^{-2}(\mathbf{y} - \mathbf{A}\mathbf{x})$ for the MC activations, $\tau_{\text{PC}}\dot{\mathbf{v}} = -\mathbf{v} + \eta^{-2}\mathbf{s} + \mathbf{A}^T\mathbf{m} + \rho\mathbf{W}\mathbf{x}$ for the PC pyramidal cell voltages (notice the auto-associative term), and $\mathbf{x} = \min(\kappa[\mathbf{v} - \beta]_+, 1)$ for the firing rates. We often expect the MC drive $\mathbf{y} - \mathbf{A}\mathbf{x}$ to be similar to the TC drive, so instead of both computing a very similar quantity we express the former in terms of the latter (see Fig 1C) and arrive at $\tau_{\text{MC}}\dot{\mathbf{m}} = -\mathbf{m} + \mathbf{t} + \sigma^{-2}(\mathbf{A}\mathbf{s} - \mathbf{A}\mathbf{x})$, exhibiting MC drive by the TCs, and excitatory input from the AON. See Fig 2 for example dynamics.

References: [1] Shepherd 2004 [2] Igarashi et al. 2012 [3] Chae et al. 2022 [4] Chen et al. 2022 [5] Gire et al. 2012 [6] Fukunaga et al. 2012 [7] Markopolous et al. 2012 [8] Author et al. 2022.

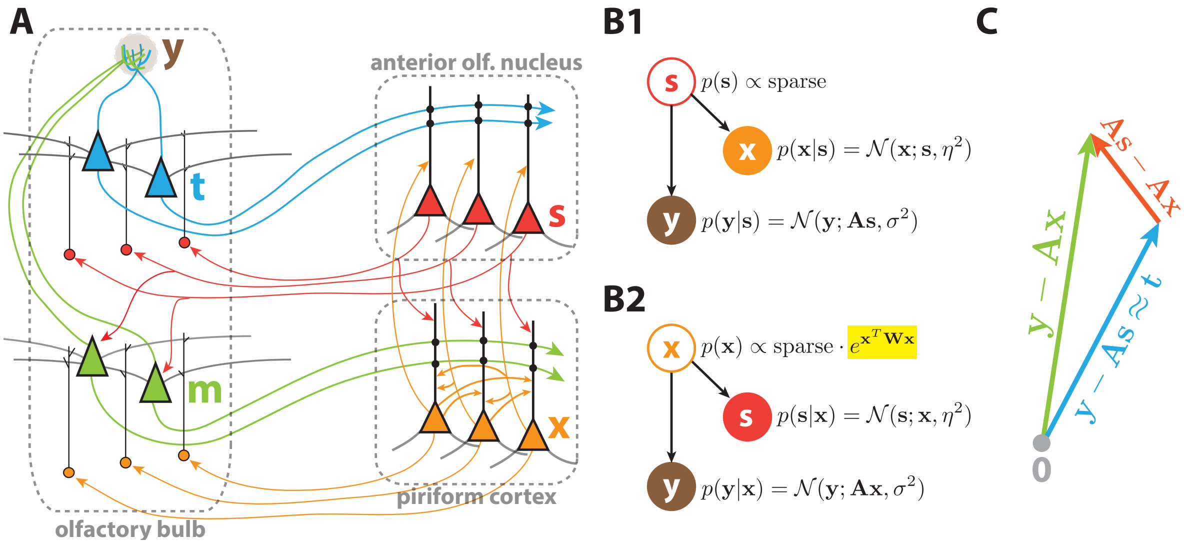

Figure 1. **(A)** Olfactory system schematic. TCs (**t**, blue) and MCs (**m**, green) sample olfactory receptor input (**y**) at glomeruli, project to AON (**s**, red), and PC pyramidals (**x**, orange), respectively, and receive disynaptic feedback inhibition via granule cells (red, orange circles). MCs also receive excitatory feedback from AON. AON pyramidals receive mutual excitation from PC pyramidals. Finally, PC pyramidals form excitatory auto-associative connections. **(B)** Probabilistic models. (B1) The TC-AON circuit infers the sparse odour features (**s**) responsible for glomerular (**y**) and PC pyramidal activations **x**, and reports these in AON pyramidals. (B2) The MC-PC circuit infers the odour features **x** responsible for glomerular **y** and AON pyramidal activations **s**, and reports these in PC pyramidals. Its more complex prior on odour features includes an auto-associative term (highlighted) that promotes joint recall of frequently coactive features. **(C)** MC drive $\mathbf{y} - \mathbf{A}\mathbf{x}$ can be decomposed into a component approximately equal to TC drive (exactly equal at steady-state) and a component that includes excitatory input $\mathbf{A}\mathbf{s}$ from AON pyramidals.

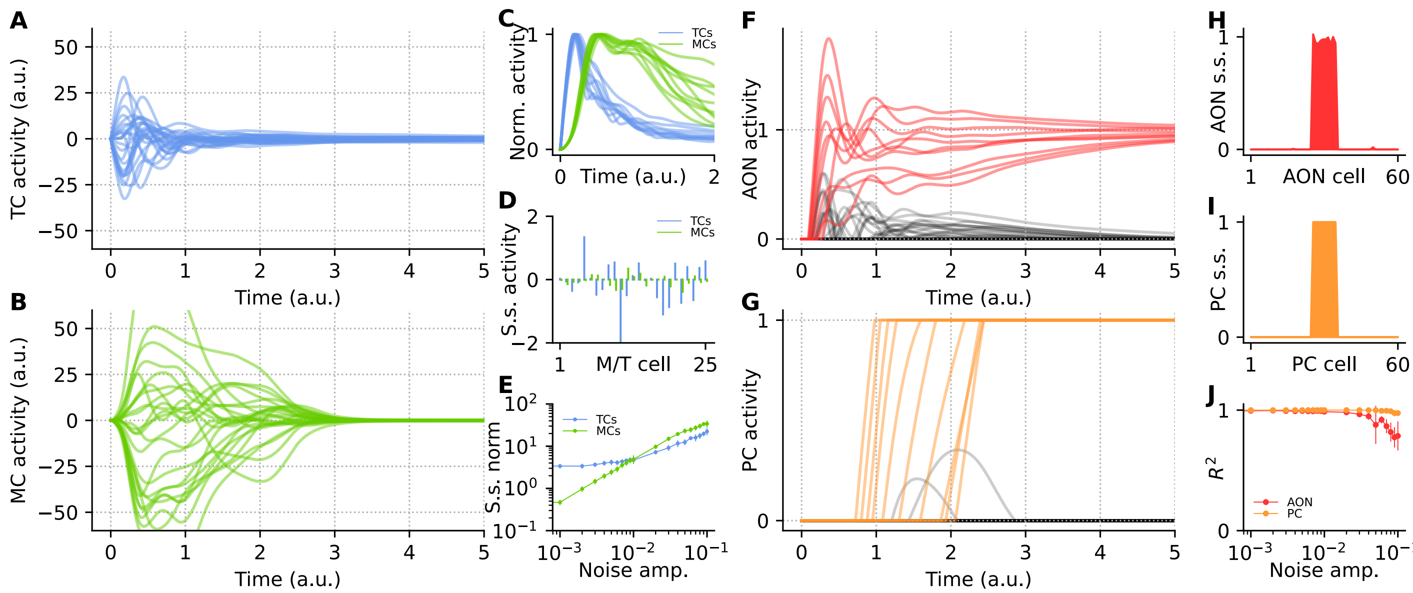

Figure 2. Dynamics. **(A)** Responses of 25 TCs and **(B)** 25 MCs to an example odour. **(C)** Time-course of norms of MC (green) and TC (blue) responses to 10 odours normalized to their peaks, demonstrating MC responses arriving later than TCs. **(D)** Activity of cells in panels (A) and (B) at convergence, demonstrating smaller MC steady-state (s.s.) responses. **(E)** Mean +/- S.D. of norms of s.s. MC and TC responses to 10 odours for increasing glomerular input noise. MC s.s. responses are smaller than TCs in the low noise setting, potentially contributing to easier TC decodability. **(F)** Time-course of 60 AON and **(G)** 60 PC pyramidal responses to an example odour. Cells presenting odour features actually present are coloured, others are gray. **(H)** S.s. response of AON and **(I)** PC pyramidals from panels F and G. PC recovers the odour perfectly. **(J)** Mean +/- S.D. of R^2 of inferred odours as input noise is increased.