Becoming what you smell

Adaptive sensing in the olfactory system

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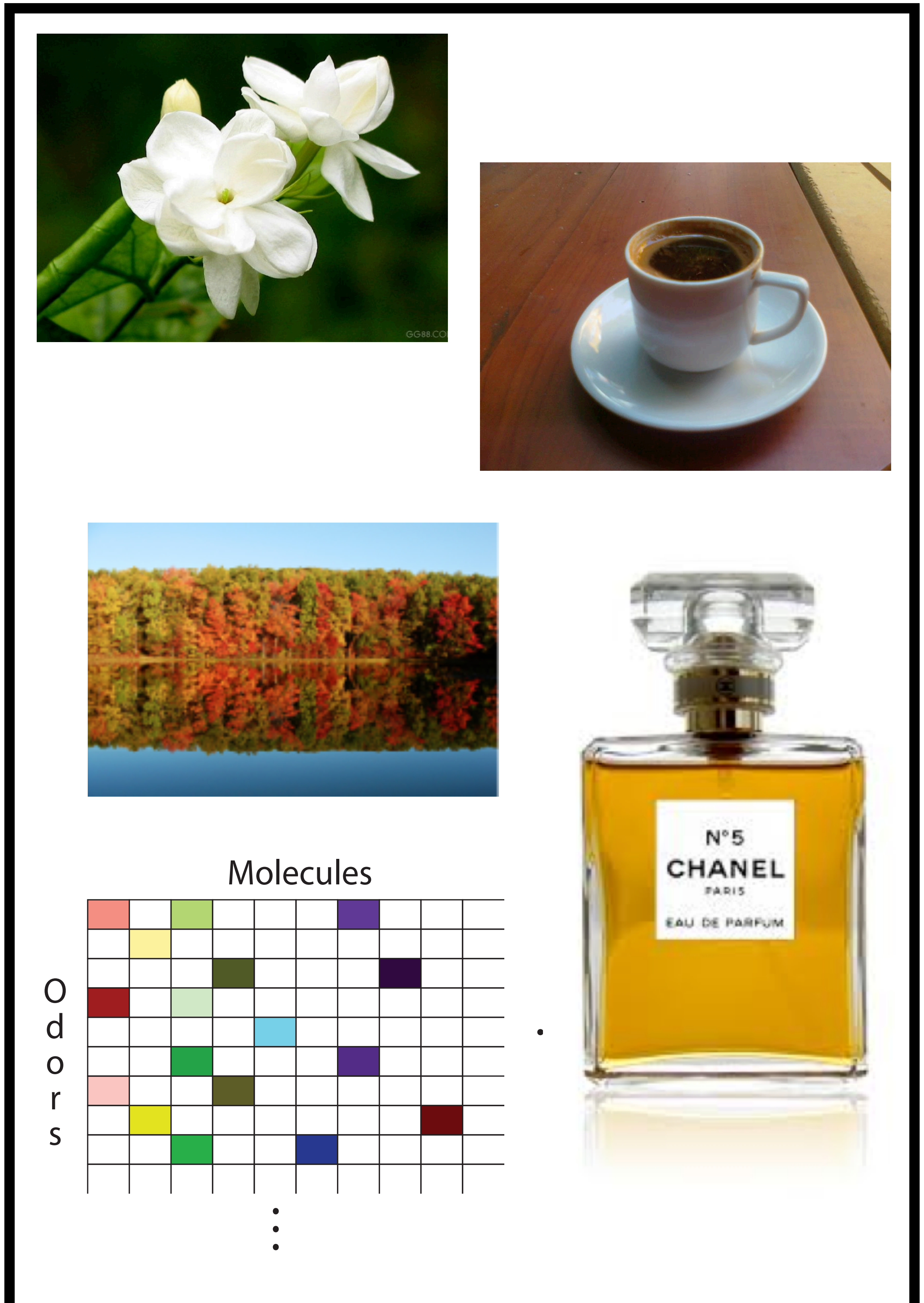
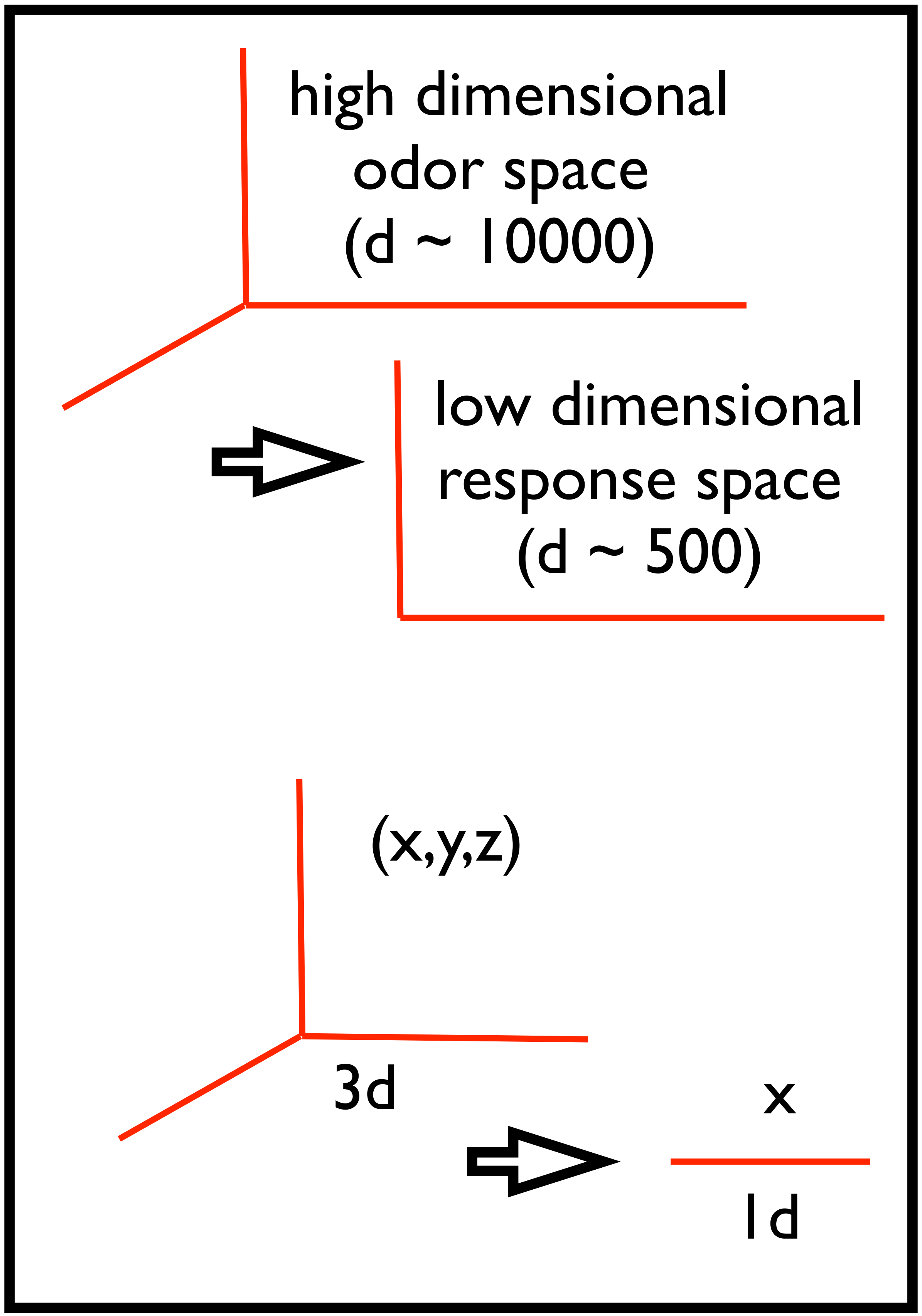
The intimidatingly diverse space of smells



- There are many volatile molecules, more than 10,000 at least
- Typical natural odors are mixtures of ~50 molecular species, so that there are $\sim(10{,}000)^{50}$ natural smells
- The odor environment changes, reflecting changing seasons and circumstances, new opportunities, and new threats
- Olfaction = a system for feeling the shape of molecules

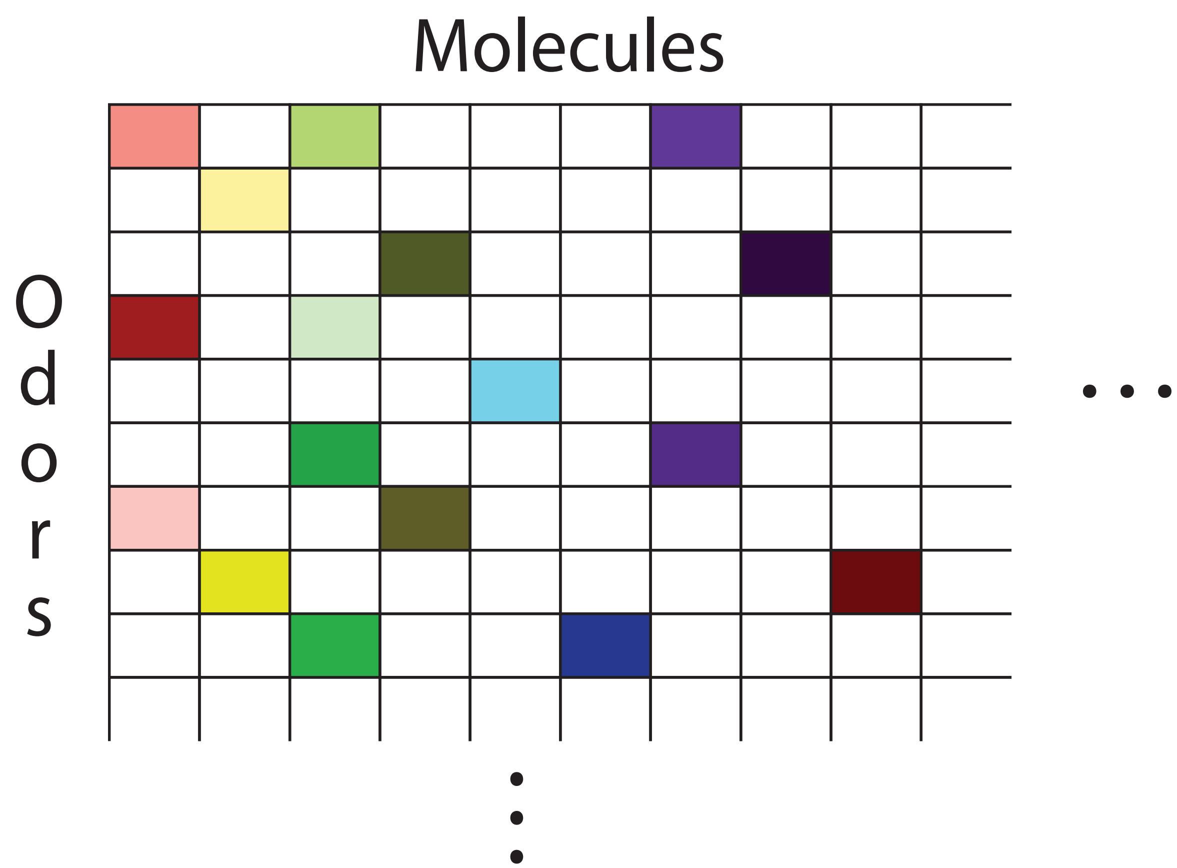
Encoding and decoding smells



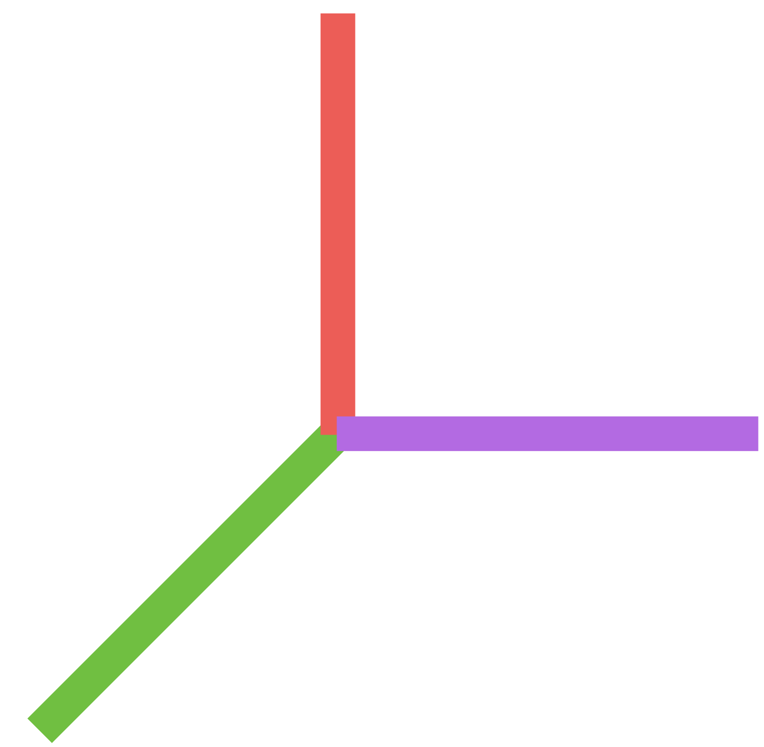
- Odors are sensed when molecules bind to olfactory receptors in the nose
- Every receptor has a separate gene: O(100) in fly, O(300) in human, O(1000) in mouse and dog, O(2000) in elephant.
- How can you possibly represent such a vast odor space with so few responses?
- Required invariance: distance between odors

Strategy: adaptation to the environment to commit limited resources effectively.

Geometry of olfactory mixture space

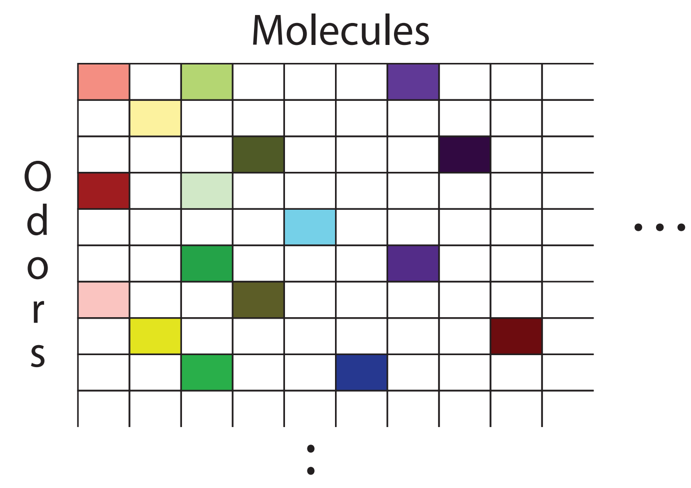


Natural odors are sparse in "chemotopic" space

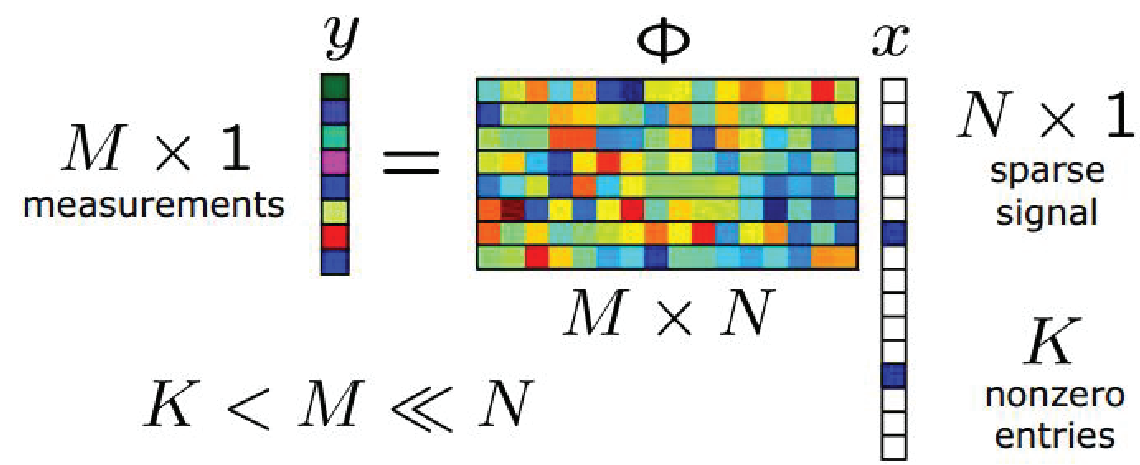


A union of K-dimensional hyperplanes in an N-dimensional space of volatile molecules. Odors are complex ($1 \ll K$) but sparse ($K \ll N$).

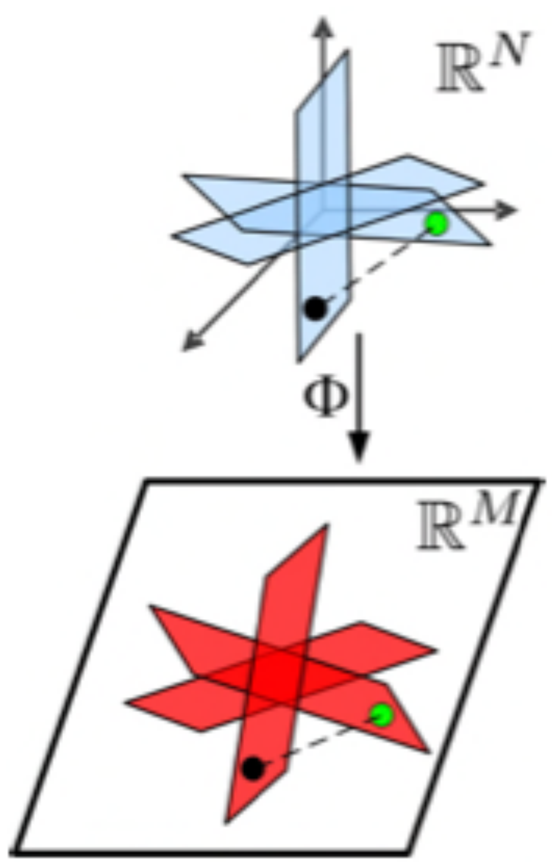
Compressive sensing of sparse mixtures



Natural odours are sparse in “chemotopic” space



Can recover x from y as long as x is known to be sparse



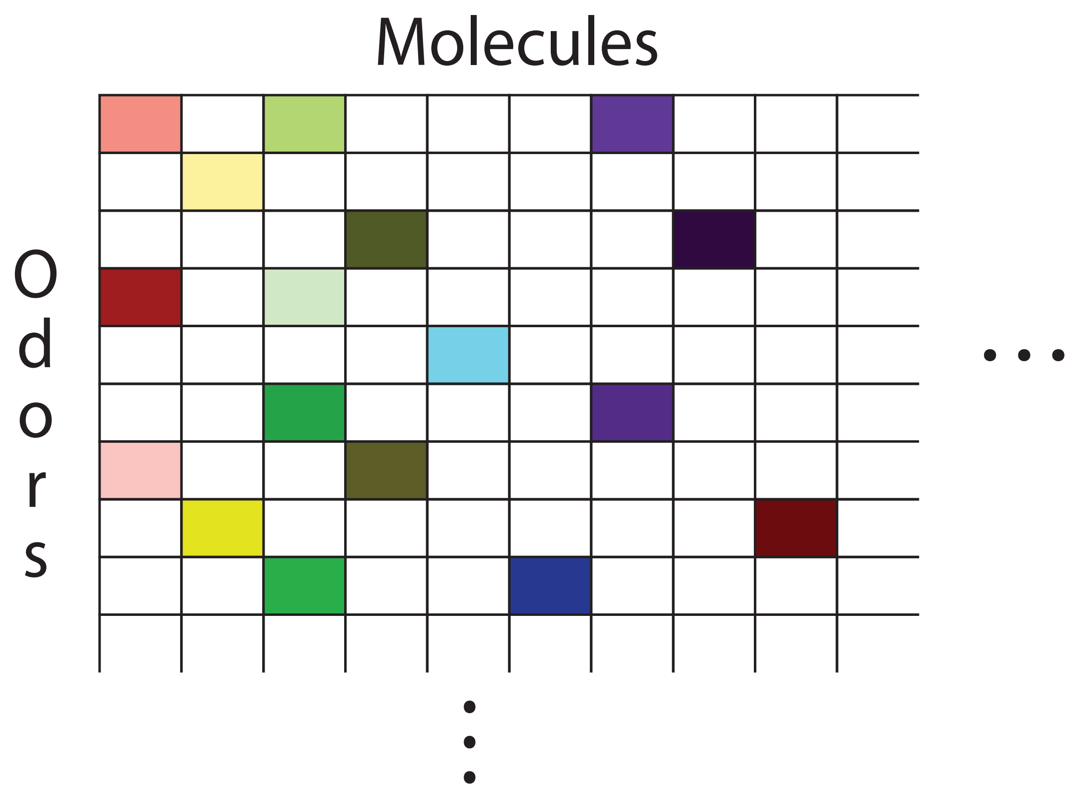
Distances in the odor space will be preserved in the neural space

Decoding

Find a vector **x** such that **y**= A **x** (where **y** is the measured output), and x minimizes the L1 norm.

$$||\mathbf{x}||_1 = \sum_{i=1}^{N} |x_i|$$

Olfaction & Compressive Sensing?



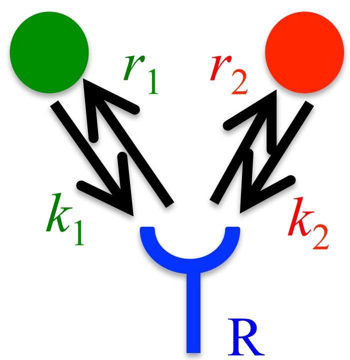
The typical odor contains maybe ~50 of the tens of thousands of possible molecules

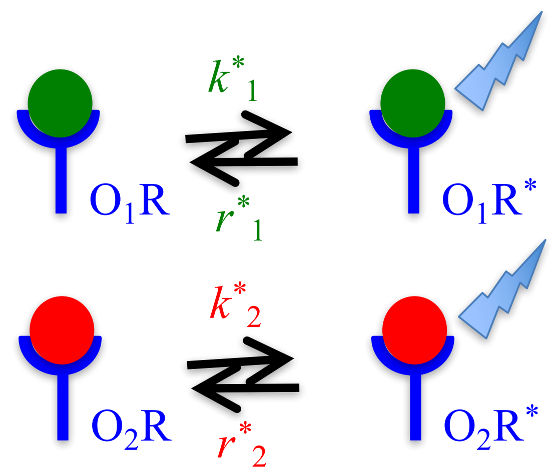
If each receptor binds with "random" affinities to volatile molecules then you only need ~O(100) sensors to represent all odors.

Does the olfactory system use this approach?

Krishnamurthy, Hermundstad, Walczak, Mora, VB

Nonlinear receptor responses from competitive binding





$$O_1 + R \underset{r_1}{\overset{k_1}{\rightleftharpoons}} O_1R \underset{r_1^*}{\overset{k_1^*}{\rightleftharpoons}} O_1R^*$$

$$O_2 + R \underset{r_2}{\overset{k_2}{\rightleftharpoons}} O_2R \underset{r_2^*}{\overset{k_2^*}{\rightleftharpoons}} O_2R^*$$

Binary Mixtures

$$\boxed{F(\{c_1, c_2\}) = \frac{e_1 \frac{c_1}{\mathrm{EC50}_1} + e_2 \frac{c_2}{\mathrm{EC50}_2}}{\left(1 + \frac{c_1}{\mathrm{EC50}_1} + \frac{c_2}{\mathrm{EC50}_2}\right)}}$$

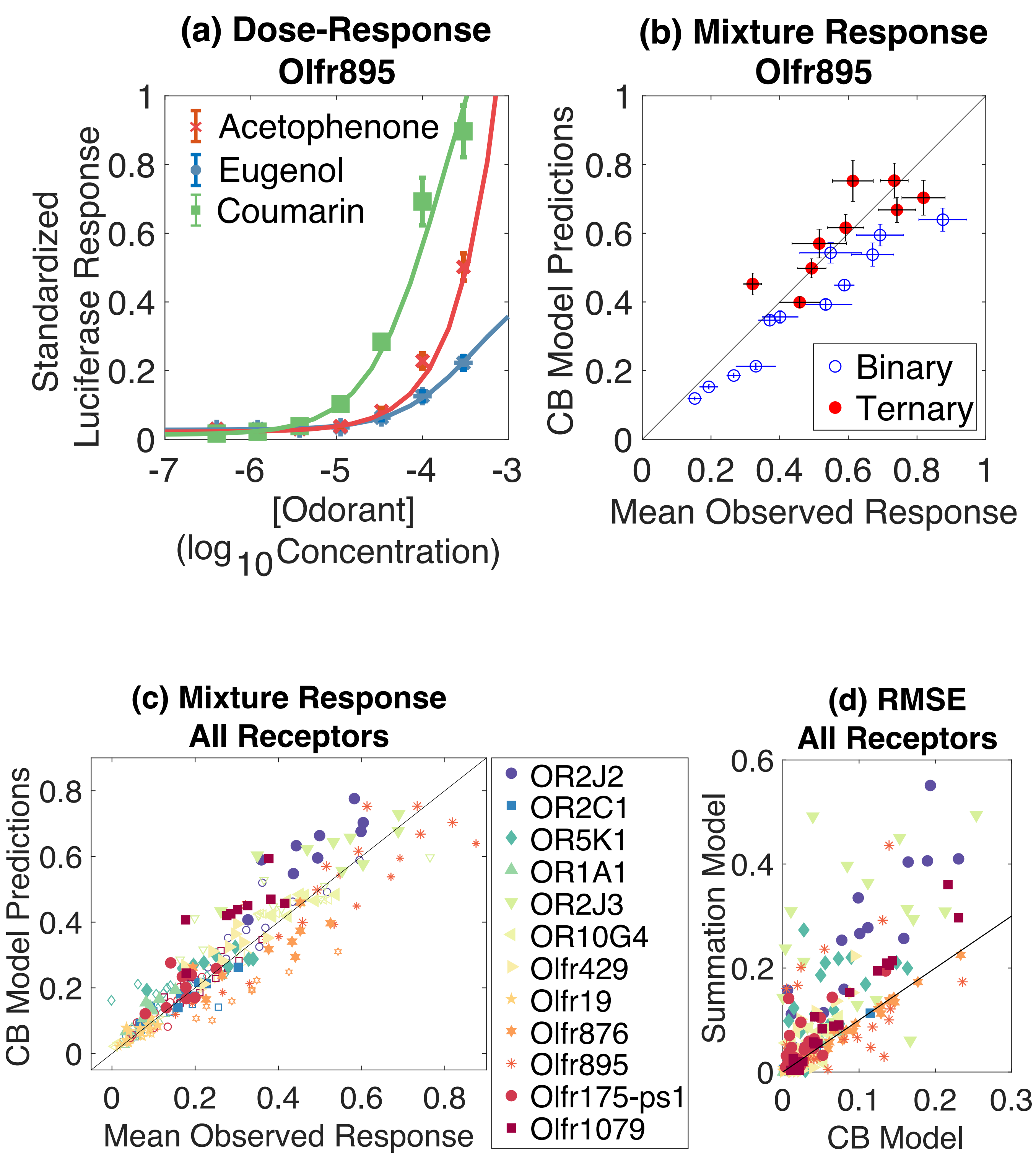
N component Mixtures

$$\boxed{F(\{c_i\}_1^N) = \frac{F_{\max} \sum_{i=1}^{N} \left(e_i \frac{c_i}{\mathrm{EC50}_i}\right)}{\left(1 + \sum_{i=1}^{N} \frac{c_i}{\mathrm{EC50}_i}\right)}}$$

$$\mathrm{EC50}_i = \frac{r_i r_i^*}{k_i(k_i^* + r_i^*)}$$

$$e_i = \frac{k_i^*}{(k_i^* + r_i^*)}$$

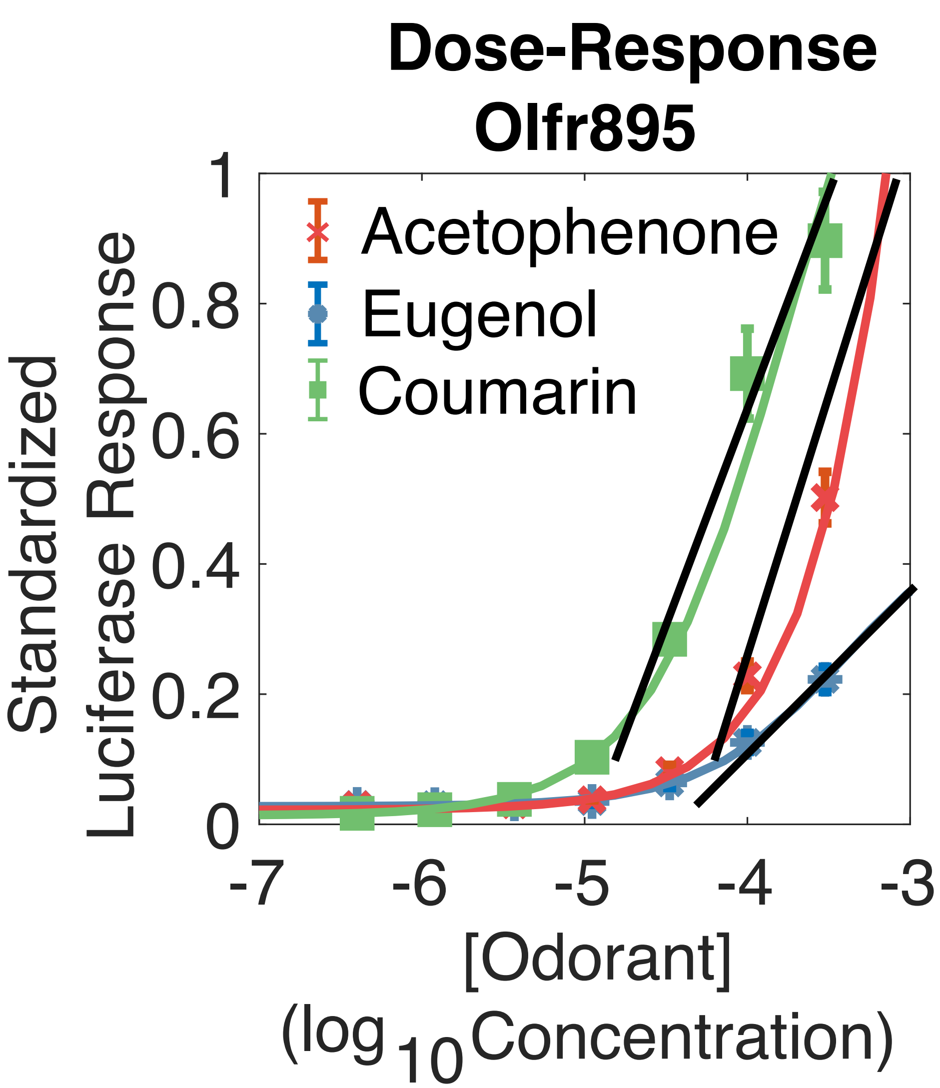
Competitive model predicts measurements



- Measure dose response curves and fit the CB model
- Predict responses to mixtures
- Predictions match data for most receptors
- CB model is better than a linear (summation) model

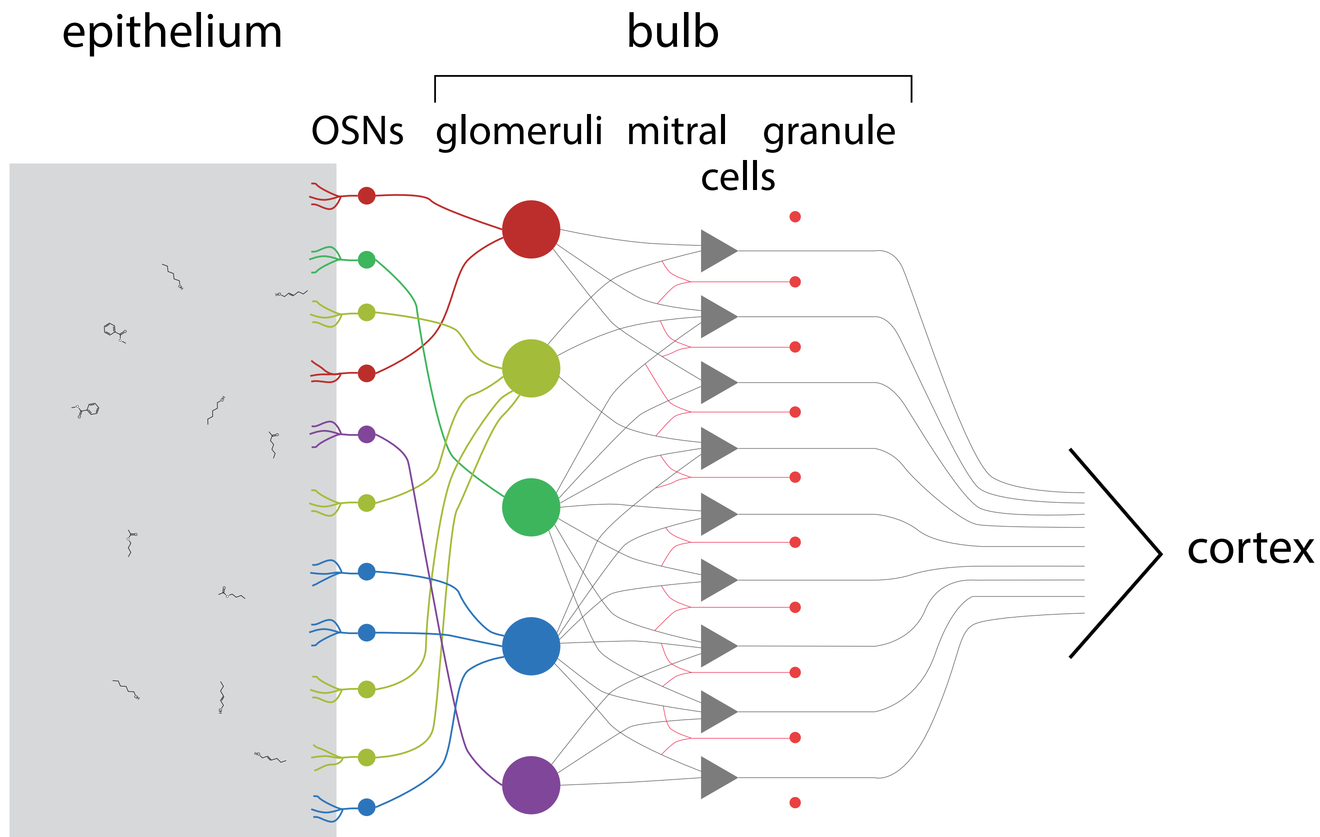
Singh, Murphy, Mainland, Balasubramanian
PNAS 2019

Linearized model of responses

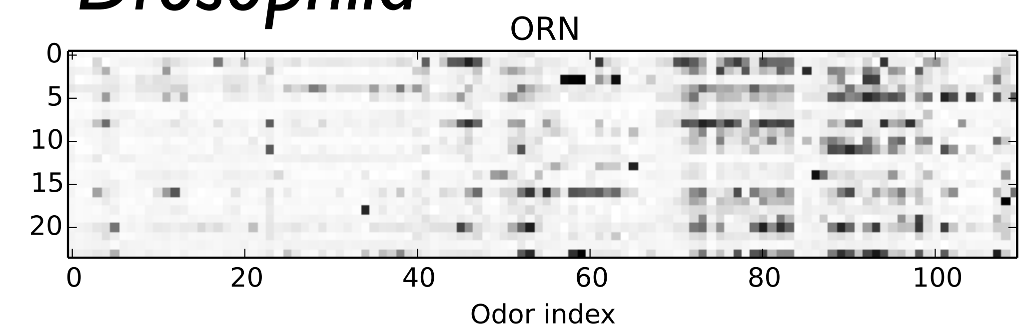


- Receptor dose-response curves are nonlinear
- Responses to mixtures can show nonlinear effects (e.g. synergy, overshadowing, suppression)
- We will linearize around an operating point

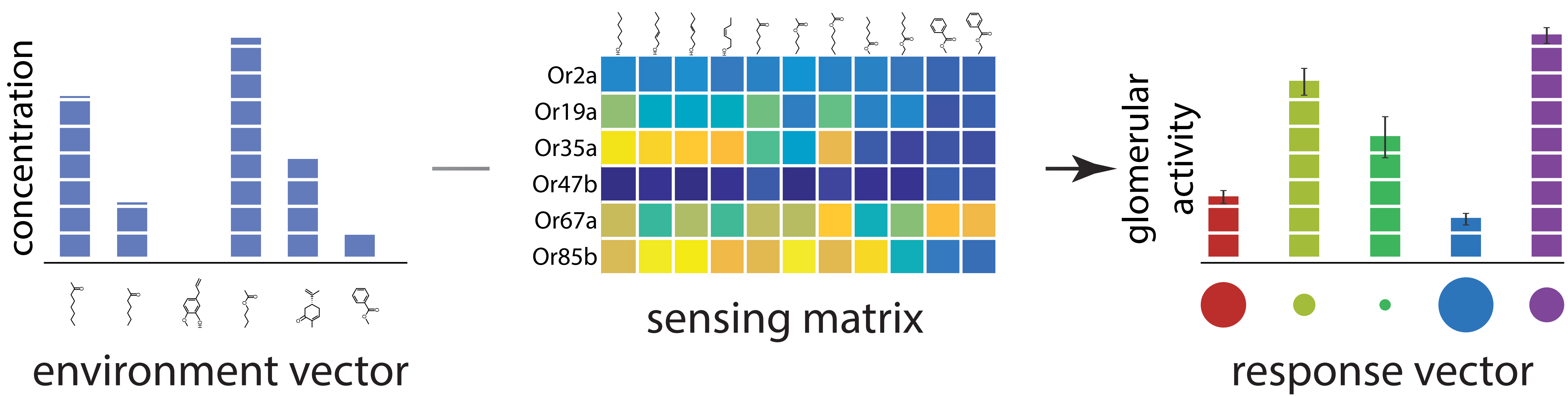
Schematic of sensing model

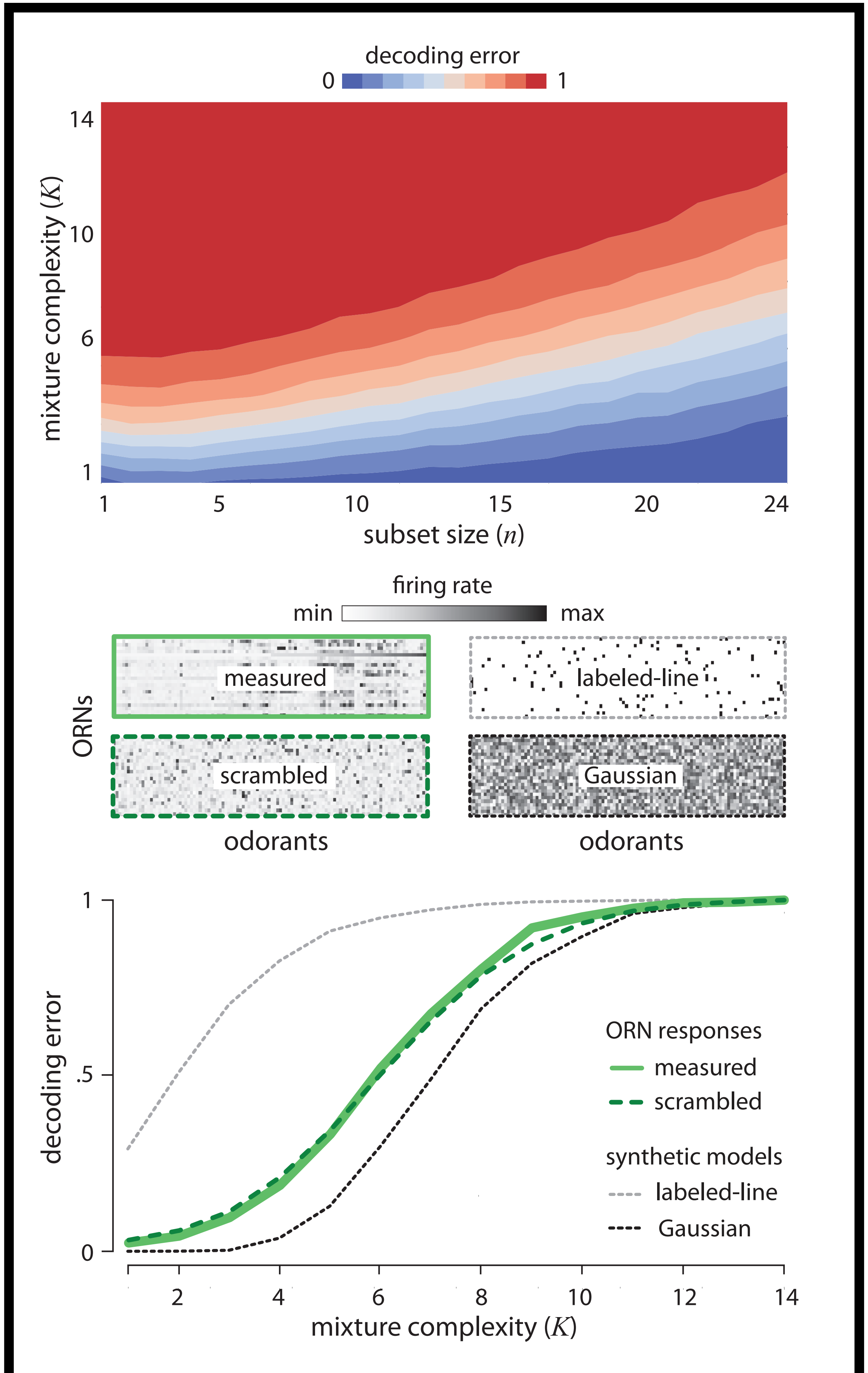


Drosophila



Hallem & Carlson

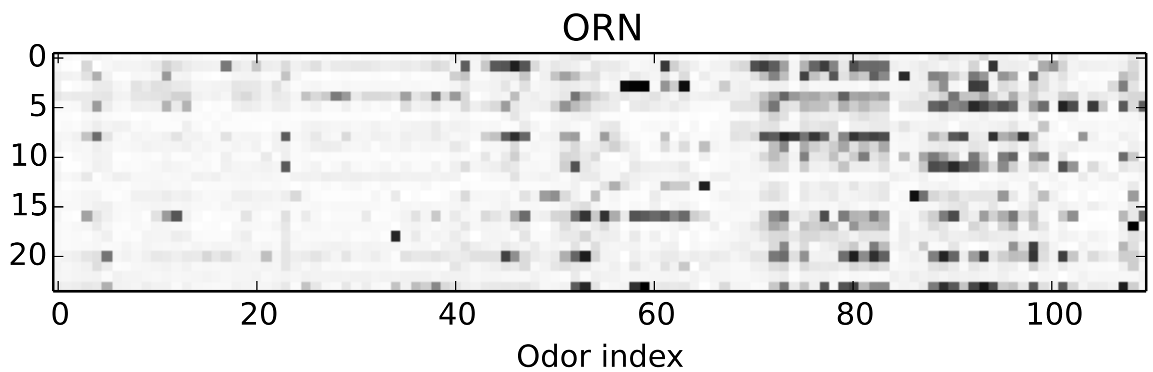




Compressive decoding

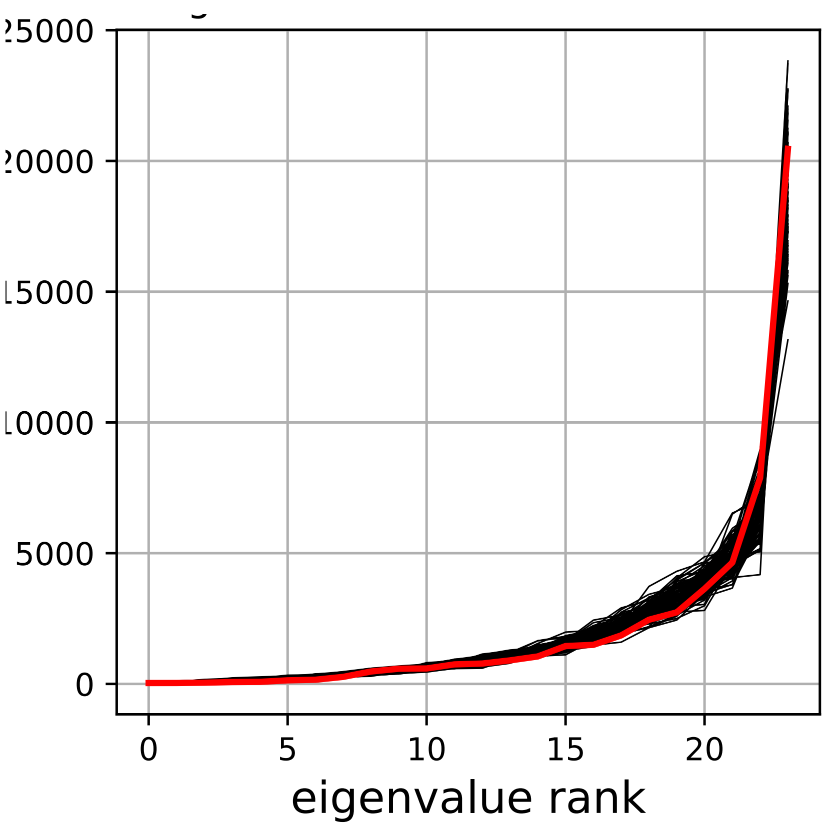
- Linearize the sensing, assuming odors have K components
- Generate responses and decode using the "L1 decoding" of compressive sensing
- Performance comes close to an ideal random sensor
- A labeled line encoder does worse; a scrambled encoder does the same

Extending the sensing matrix

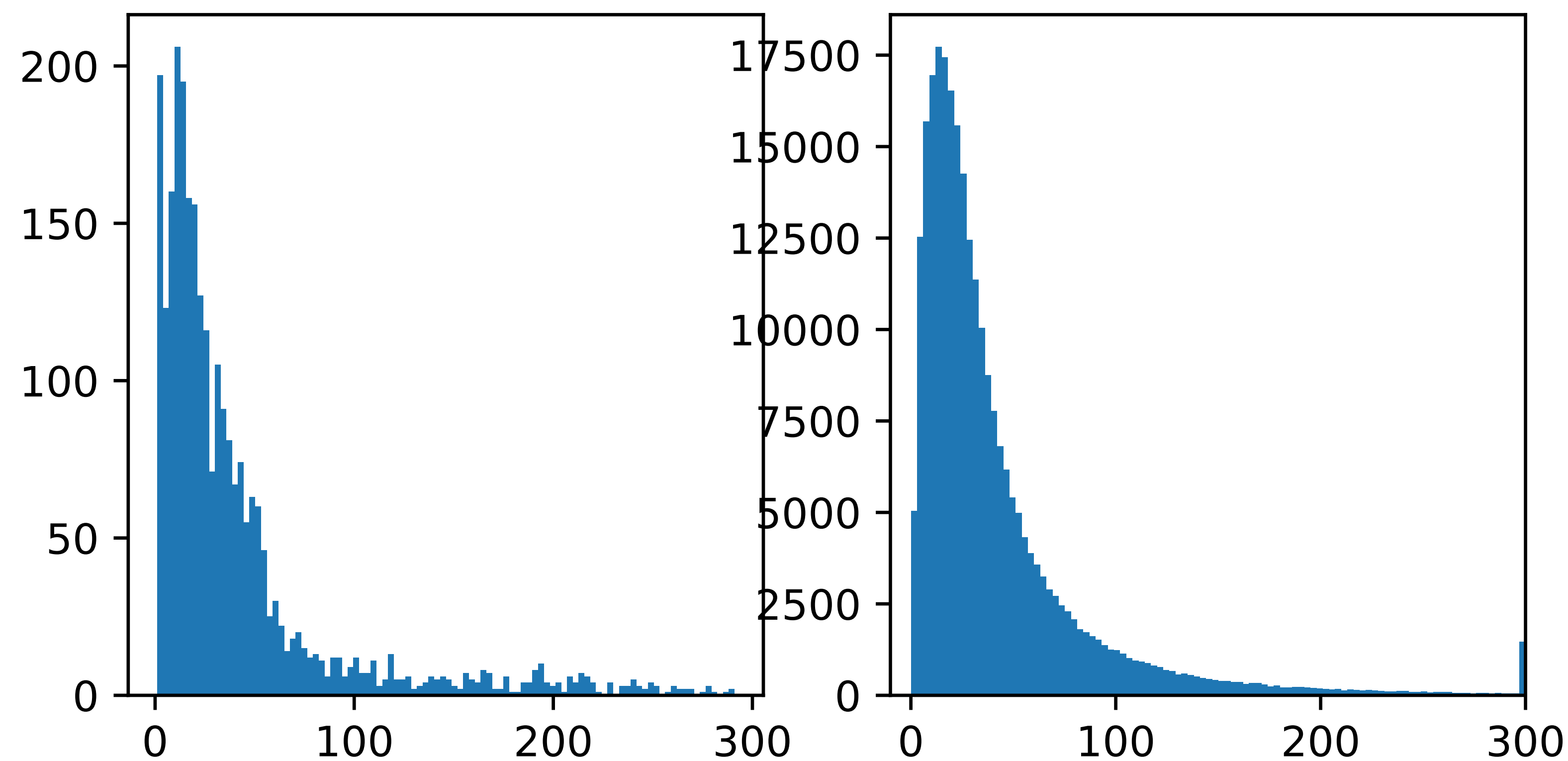


Statistically extend the measured sensing matrix to have more receptors responding to more odors

Eigenvalues of covariance matrix



Histograms of firing rates

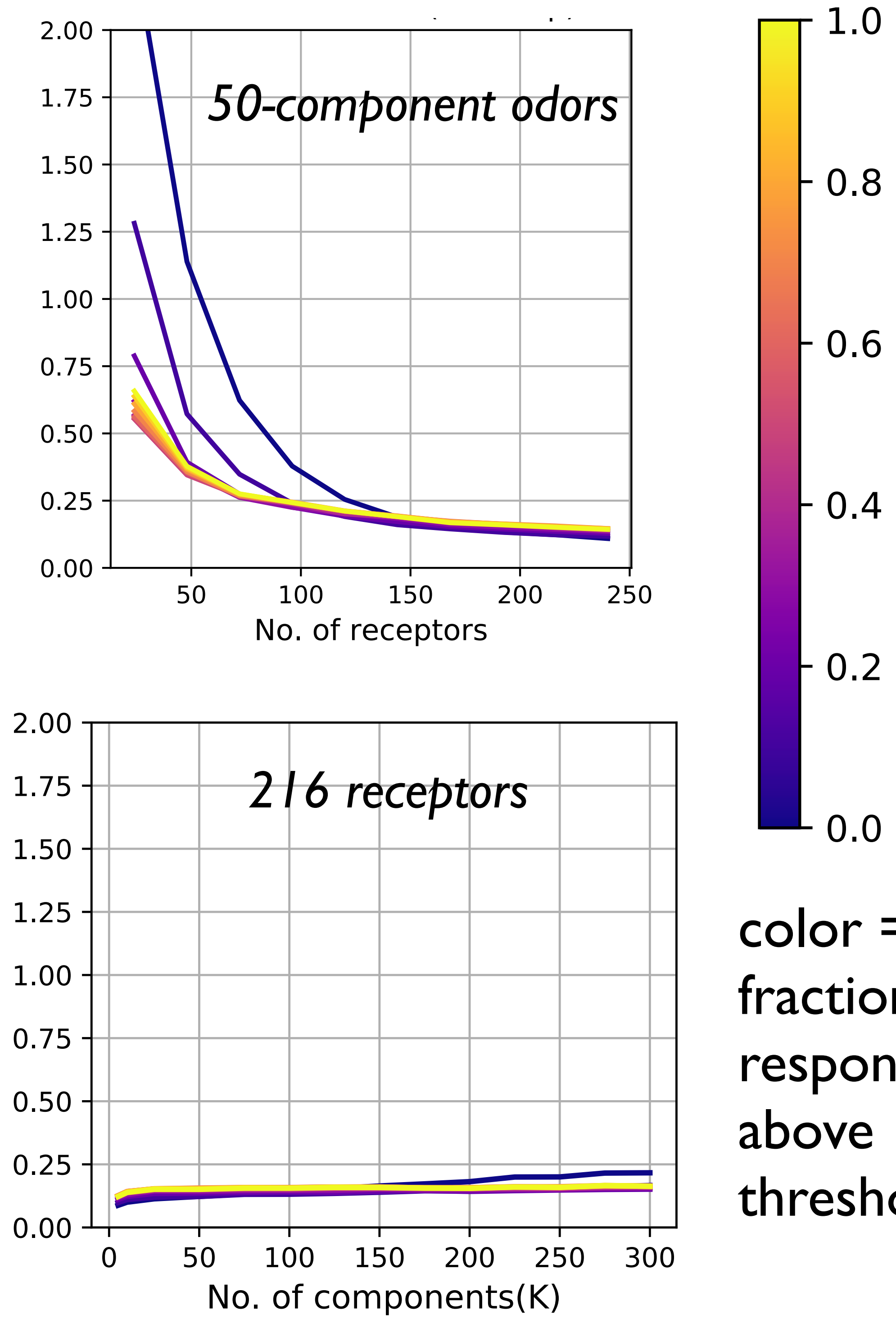


Data

Synthetic

Distances between odors are preserved

Distortion

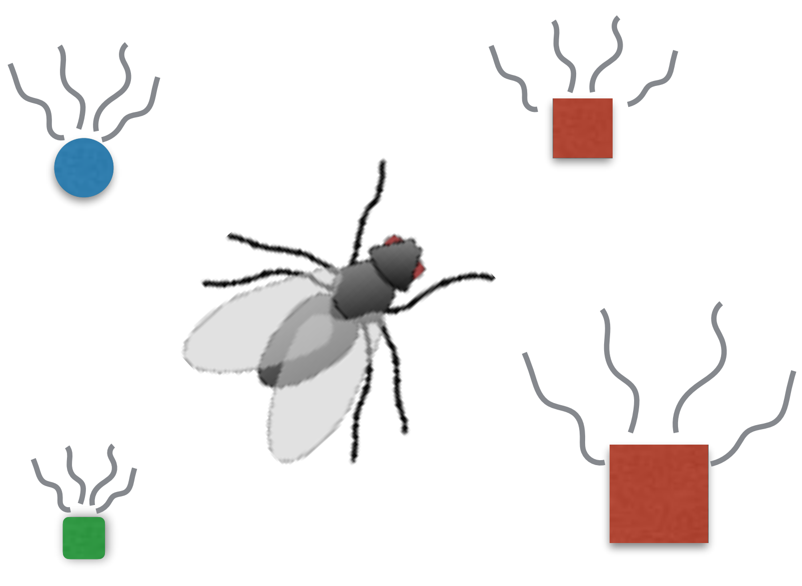


color = fraction of responses above threshold

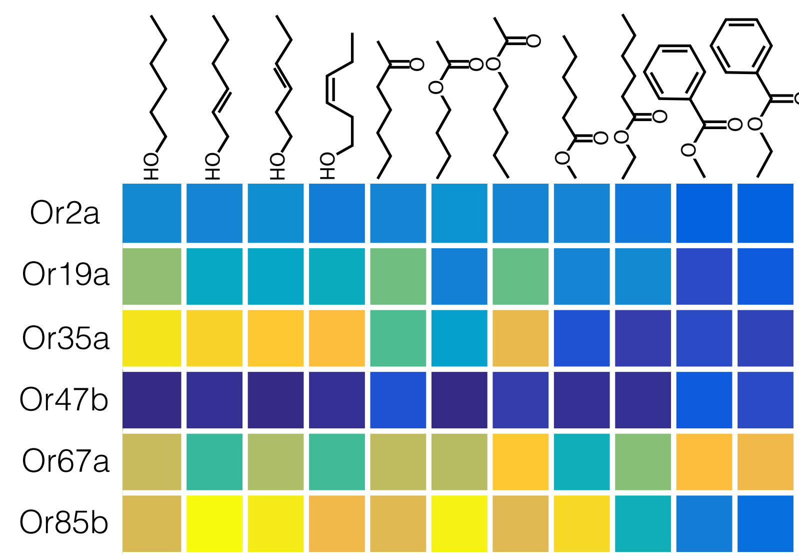
- Distortion = fractional change in distance
- With ~200 receptors distortion is low even for complex odors and a sparse sensing matrix
- *Perhaps this explains the "operating point" for all animals: a few hundred diffusely binding receptor types.*
- **Hypothesis**: the number of olfactory receptor types in animals is adapted to the sparse structure of natural odors.

Well-adapted receptor repertoire

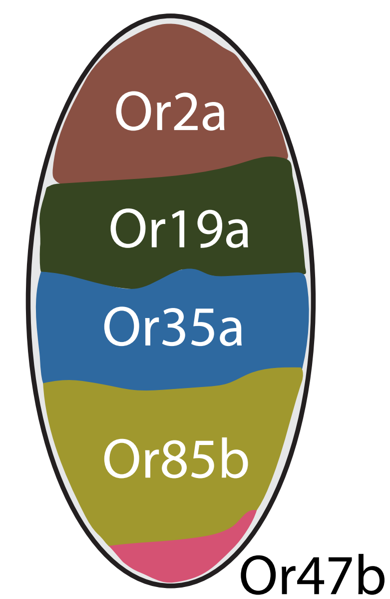
If the number of receptor *types* is adapted to the sparse structure of natural odors, what about the fraction of receptors of *each* type?



natural odor distribution



sensing matrix



distribution of receptor neurons

Tesileanu, Cocco, Monasson, VB, eLife 2019

Theory: Well-adapted receptor distribution

- **Framework**: maximize information about odor environment from olfactory receptor response

- **Simple model**: Gaussian distribution of odorant concentrations, linear receptor response

$$\vec{c} \sim \mathcal{N}(\vec{c}_0, \Gamma)$$

$$r_j = \sum_i S_{ji} c_i + \frac{\sigma}{\sqrt{K_j}} \eta_j$$

noise

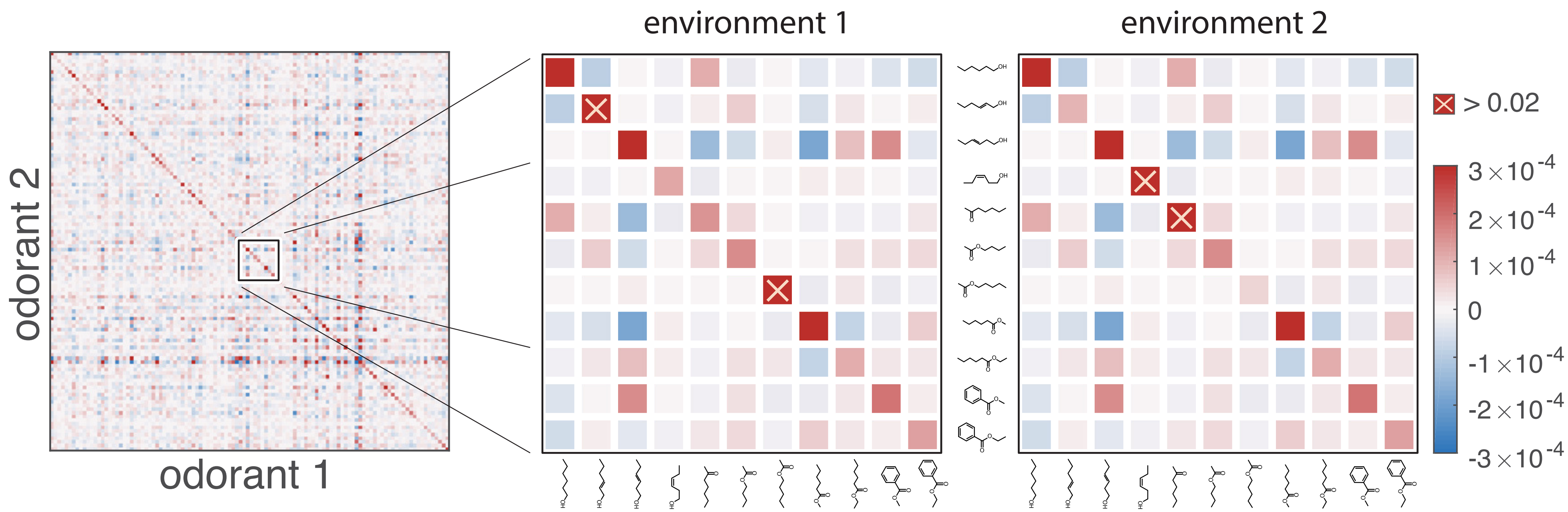
sensing matrix

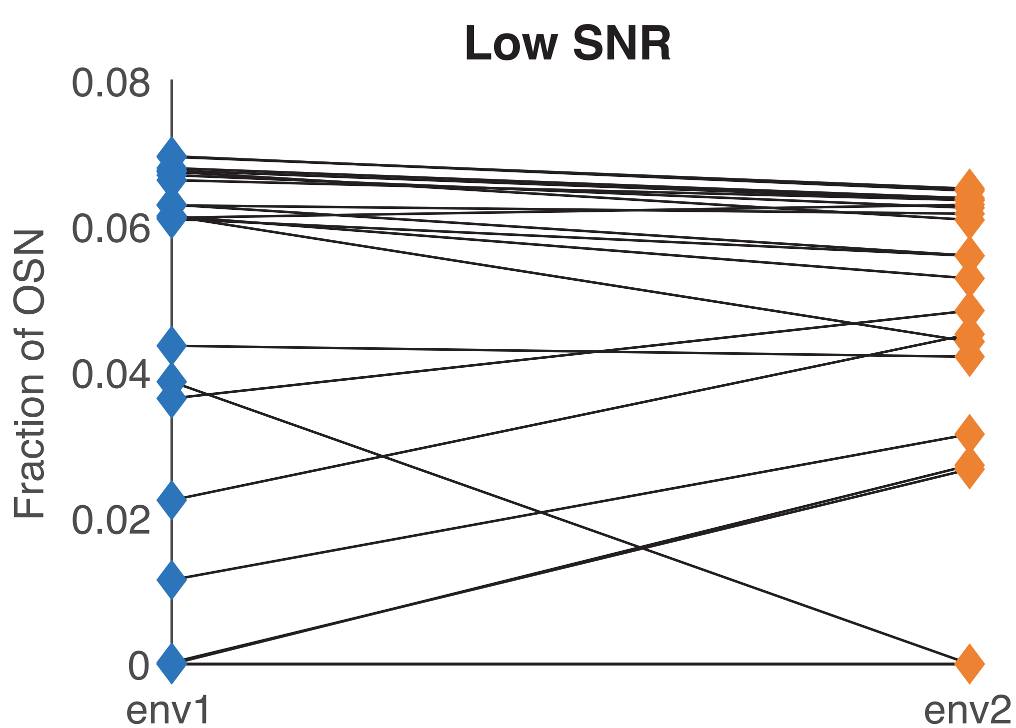
number of receptors of type *j*

Maximize mutual information between responses and odor distribution

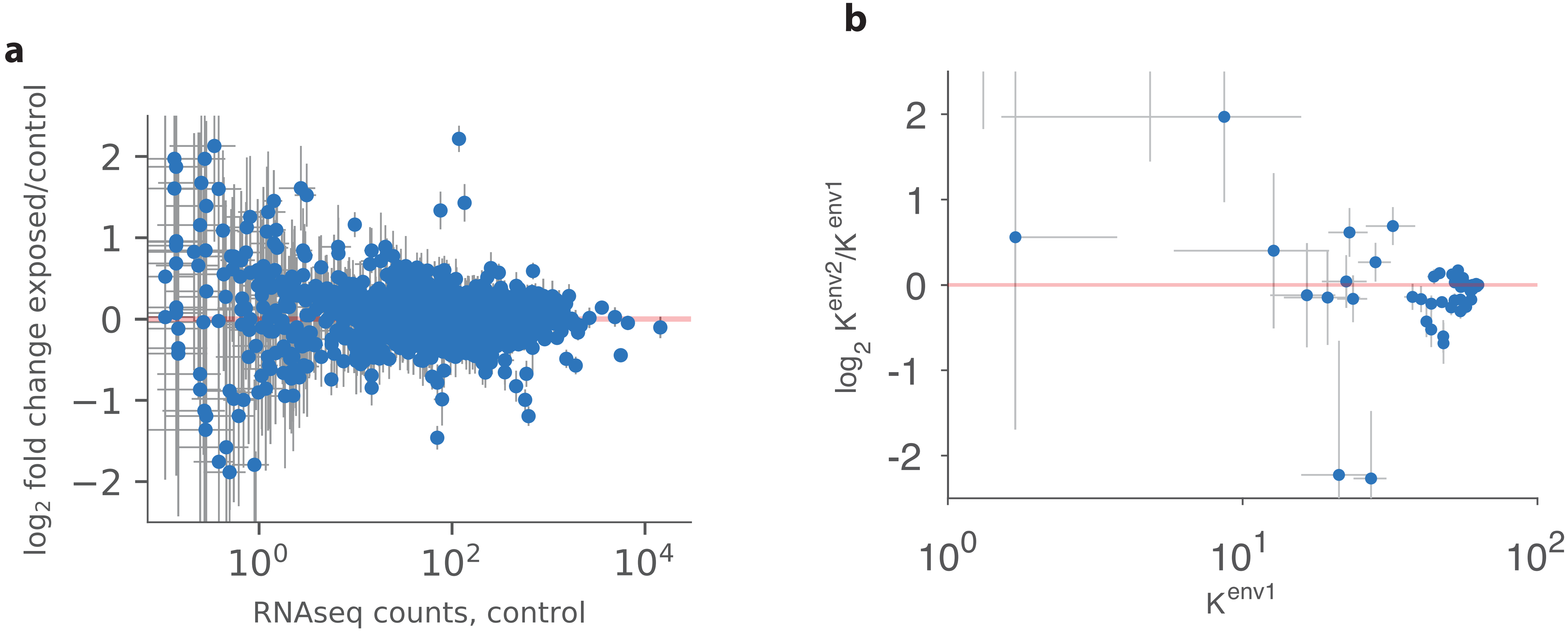
Effects of the olfactory environment on a well-adapted repertoire

odor environments with different covariance structure





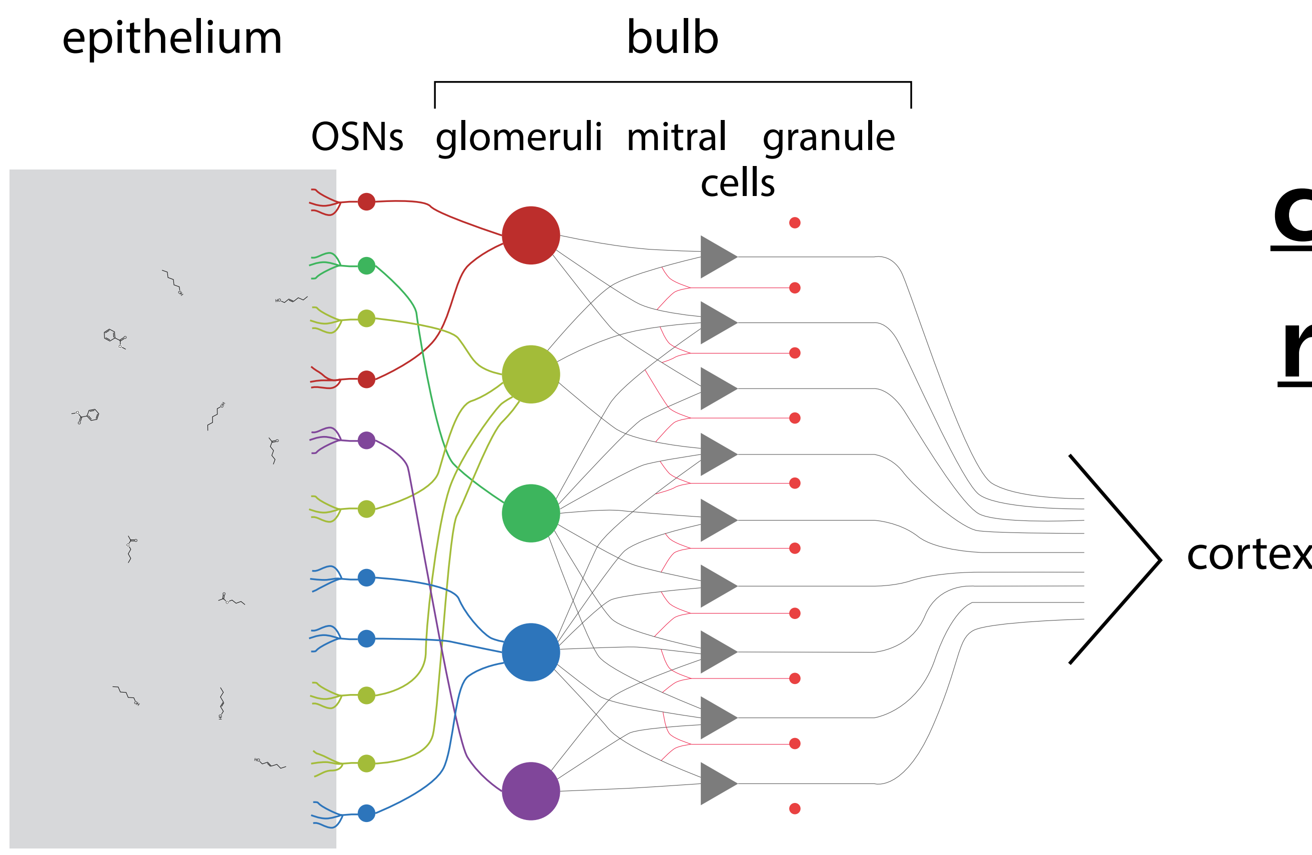
A first test



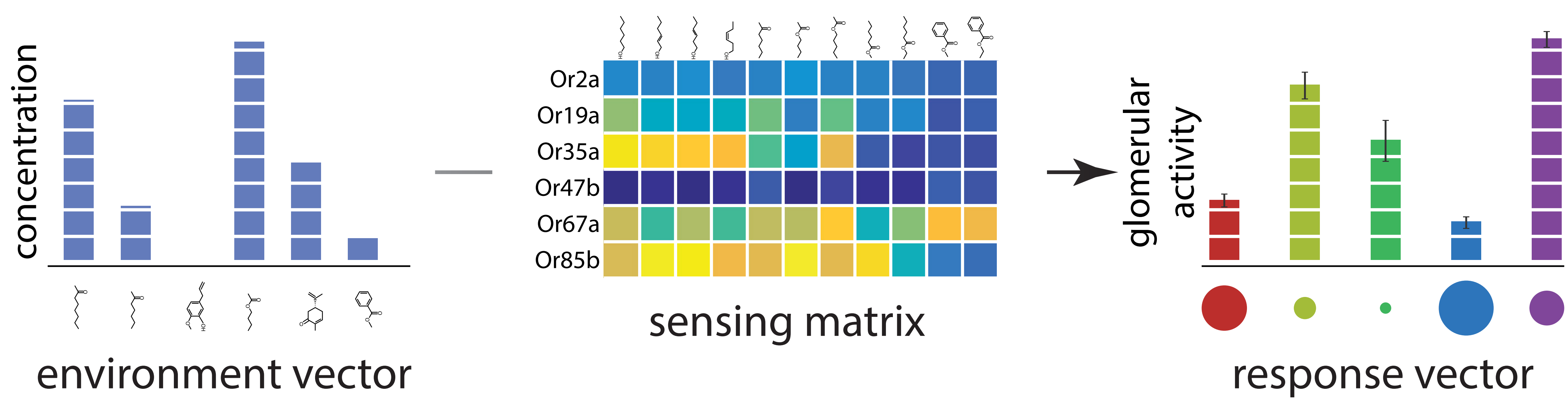
Ibarra-Soria et al., 2016; receptor abundances in mice exposed to two different odor environments

Our theory: 60 mouse receptors, and a model of the olfactory environment

Theory reproduces the qualitative structure of experimental results.

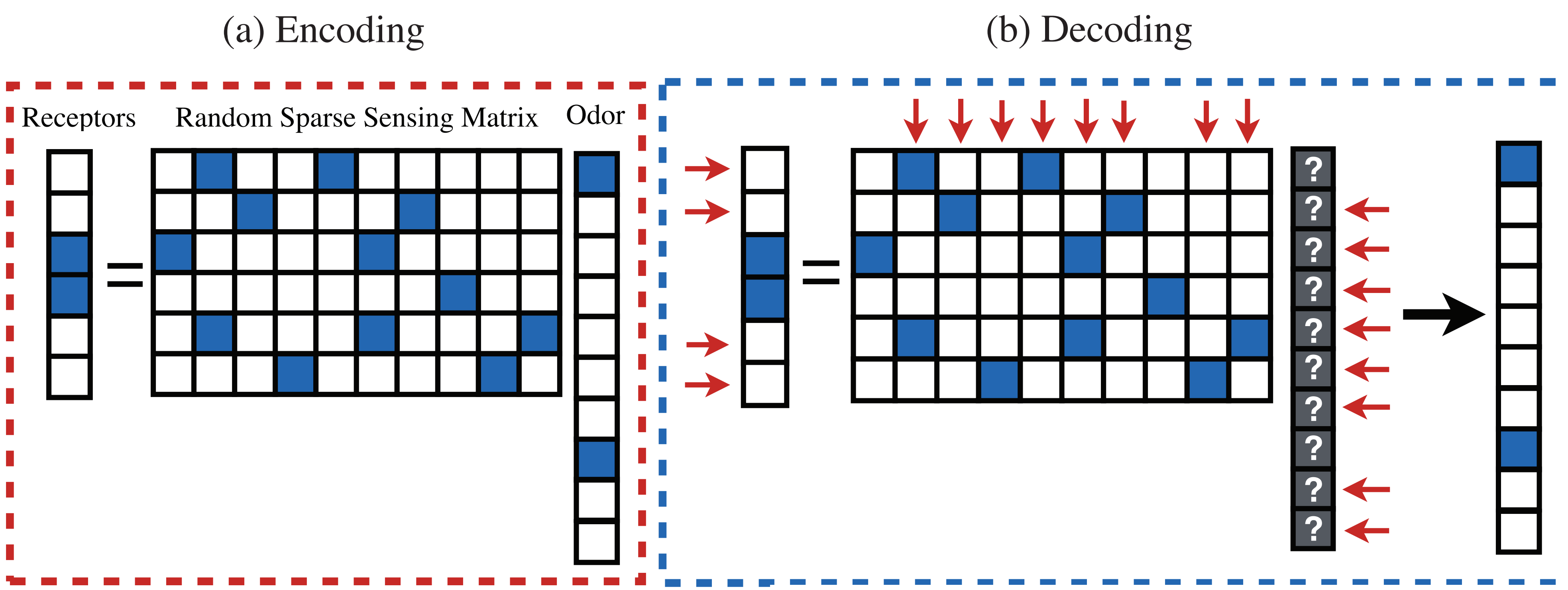


How can the combinatorial receptor responses be decoded?



Singh, Tchernookov, VB
bioRxiv 568626, submitted

Estimation by elimination: binary receptors

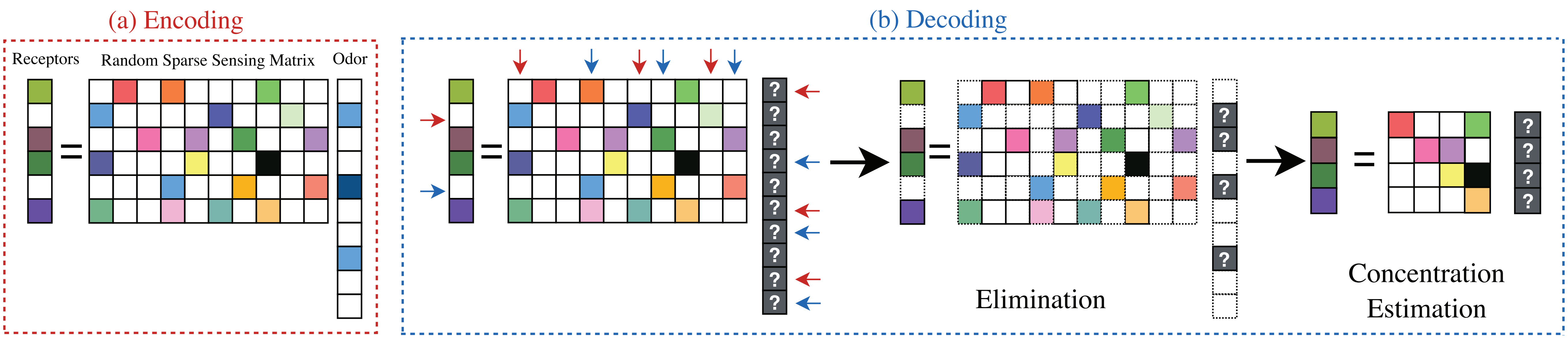


- At high noise, receptors are binary: above or below threshold
- Identify inactive receptors. Eliminate odors that bind to them. All other odors are present.
- Approximate theory:

$$P(\hat{c}_i = 1 | c_i = 0) \approx e^{-sN_\mathrm{R} e^{-sK}} \qquad P(\hat{\boldsymbol{c}} = \boldsymbol{c}) \approx \left(1 - N_\mathrm{L} e^{-sN_\mathrm{R} e^{-sK}}\right)$$

s = sparsity; N_R = no. of receptors; N_L = no. of odorants;
K = no. of odorants in an odor mixture

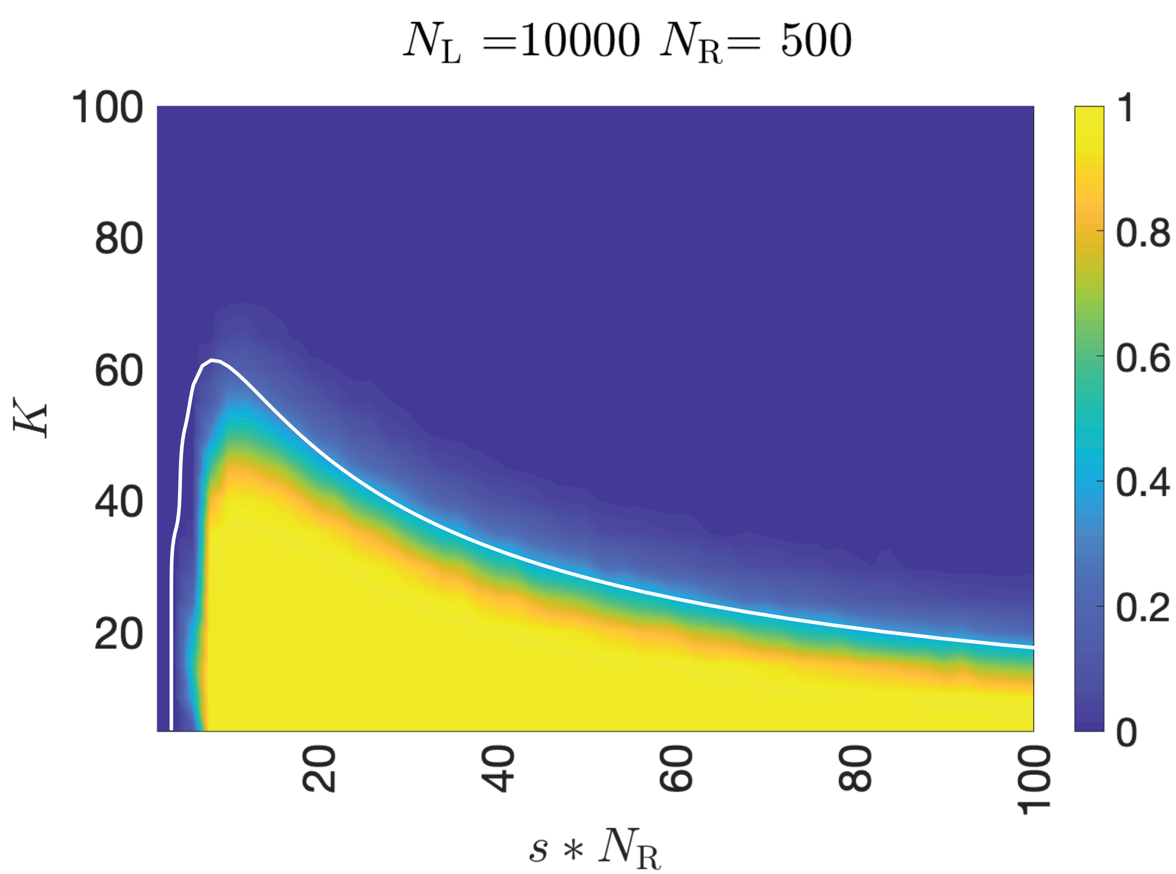
Estimation by elimination: continuous receptors



- At low noise, receptors have continuous response rates
- Identify inactive receptors. Eliminate odors that bind to them. All other odors are present.
- Invert the now (over)-determined nonlinear response function equations to determine the concentrations of odorants:

$$R = \frac{\sum_{j=1}^{N_{\mathrm{L}}} x_j}{\left(1 + d * \sum_{j=1}^{N_{\mathrm{L}}} x_j\right)}.$$

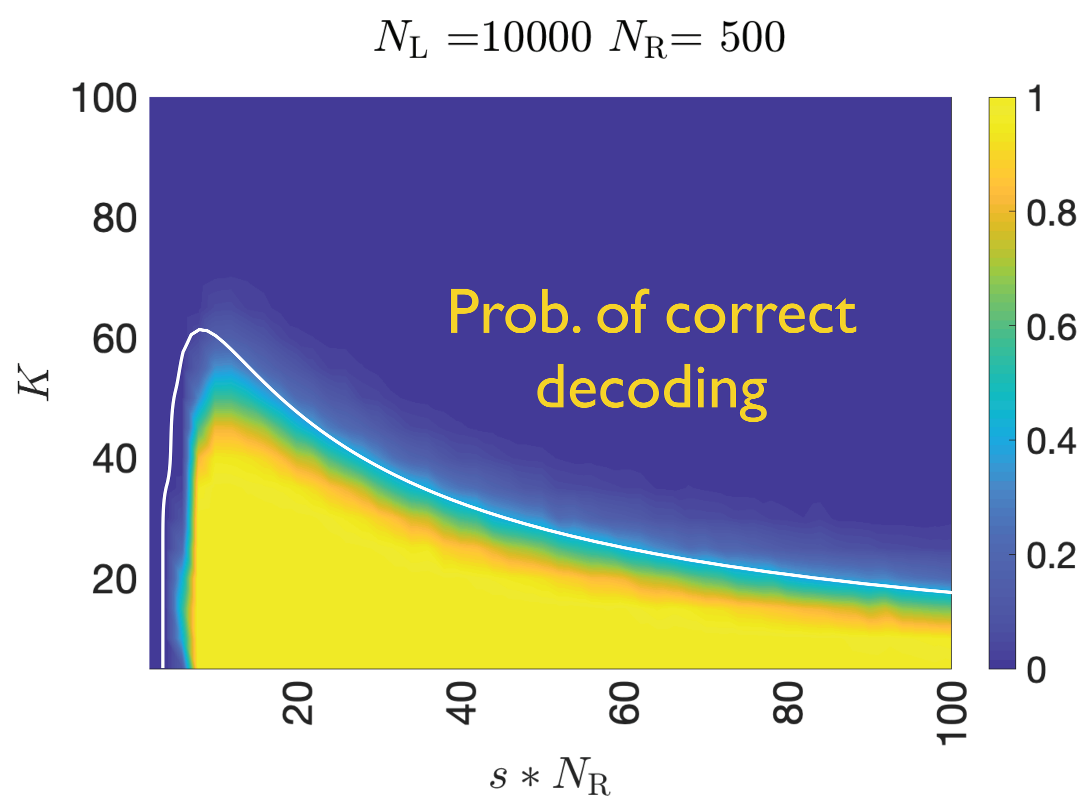
Estimation by elimination: continuous receptors



K = odor complexity
sN_R = number of active receptors

- Excellent decoding with a realistic number of receptors and sparsity
- Analytical theory is a good approximation
- Optimal sN_R is ~10 (humans 0.04 x 300 ~ 12; *Drosophila* 0.15 x 60 ~ 9)
- There is a sharp transition from excellent to poor decoding at around the complexity of natural odors (~50 components)
- *Perhaps this explains the "operating point" for all animals: a few hundred receptor types; sparsity in the 5-15% reange*

Experimental tests?



K = odor complexity
sN_R = number of active receptors

- Insight: A receptor that *does not* respond carries a lot more information than one that does.
- Prediction: an inactive receptor should eliminate all odors that bind to it.
- Test: optogenetic or pharmacological suppression of glomeruli. Animal should behave as if some odorants are absent even if they bind to other receptors.
- Prediction: how max complexity of decodable odors depends on number of receptors and sparsity
- Test: compare behavior across species

Becoming what you smell

- The nose becomes a representation of the world
- Compressive combinatorial sensing
- Adaptive changes in the olfactory receptor repertoire
- Decoding complex odors

The End