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Figures and figure supplements

Expanding the olfactory code by in silico decoding of odor-receptor chemical space

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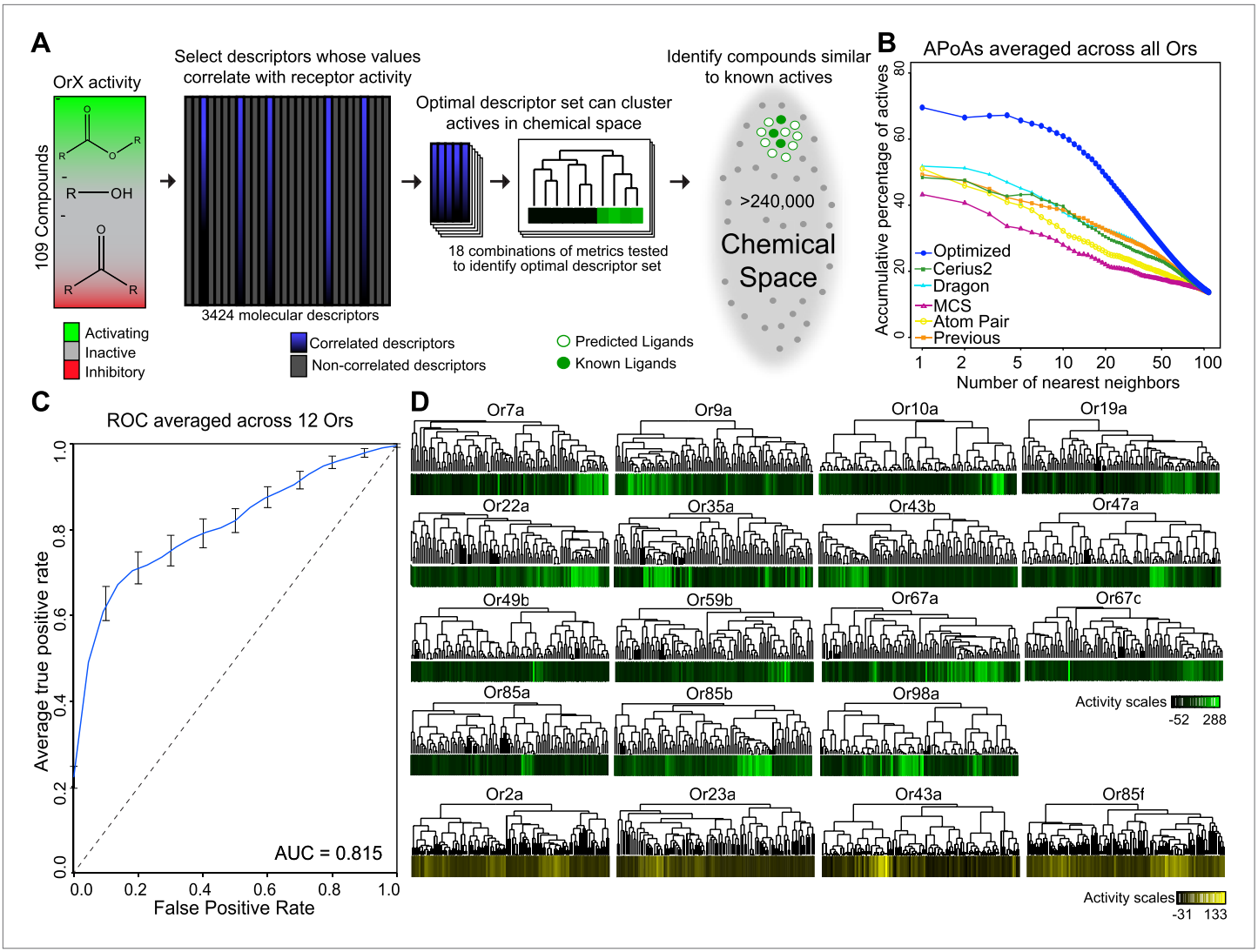

Figure 1. A receptor-optimized molecular descriptor approach has strong predictive power to find new ligands. (**A**) Schematic of the cheminfomatics pipeline used to identify novel ligands from a larger chemical space. (**B**) Plot of mean APoA values for 19 Drosophila Ors calculated using various methods including a previously identified set (***Haddad et al., 2008***). (**C**) Receiver-operating-characteristic curve (ROC) representing computational validation of ligand predictive ability of the Or-optimization approach. (**D**) Hierarchical cluster analysis of the 109 odorants of the training set using Or-specific optimized descriptor sets to calculate distances in chemical space for odorant receptors with strong activators (green), and odorant receptors with no strong activators (yellow).

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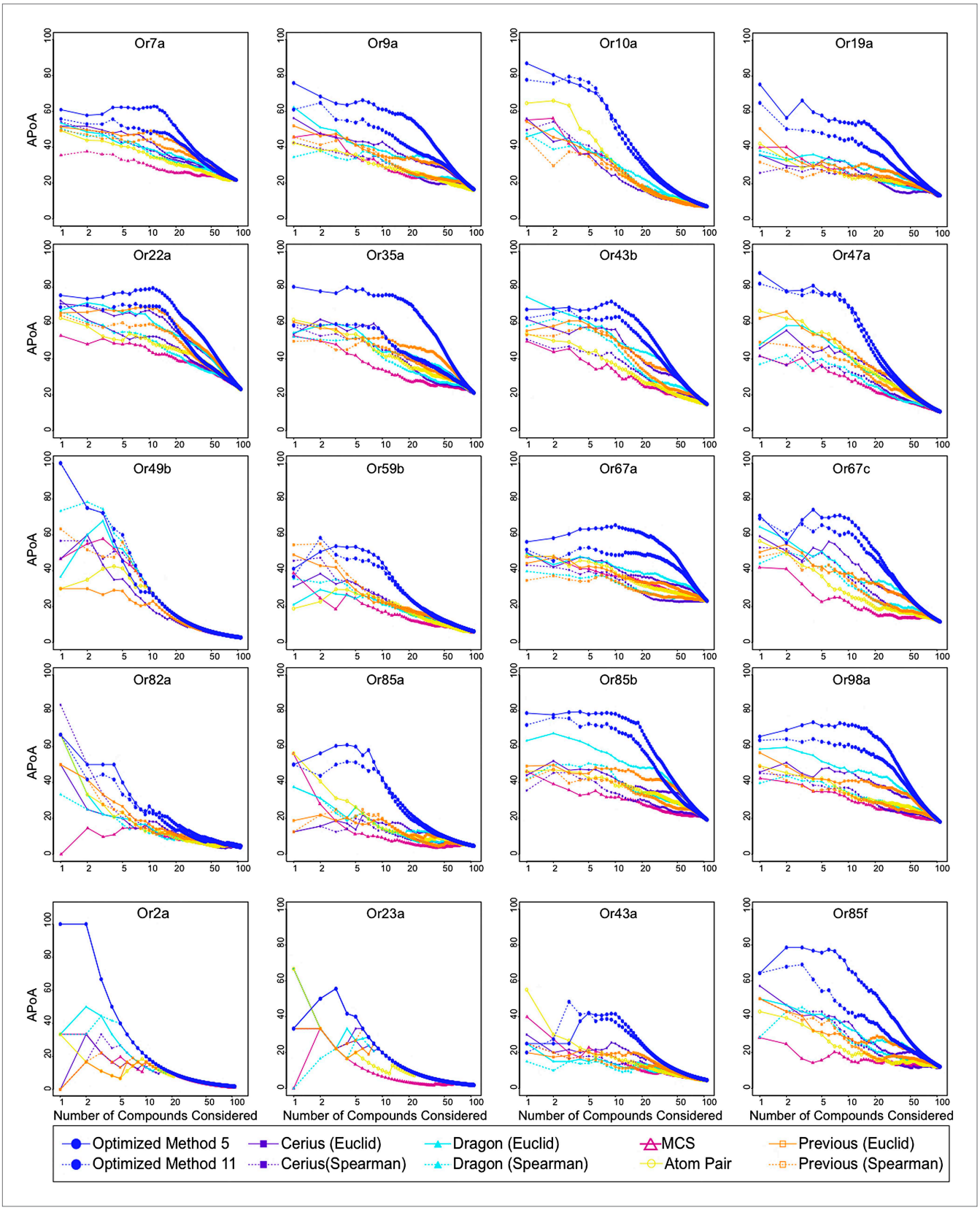

Figure 1—figure supplement 1. Analysis of APoA curves for individual odor receptors. Plots of the mean APoA values obtained from various molecular descriptor methods demonstrates that optimized descriptor subsets generate highest values. Previous = 32 Dragon descriptors selected in ***Haddad et al. (2008)***. Molecular descriptor methods were compared using the 109 compounds that were previously tested in (***Hallem and Carlson, 2006***).

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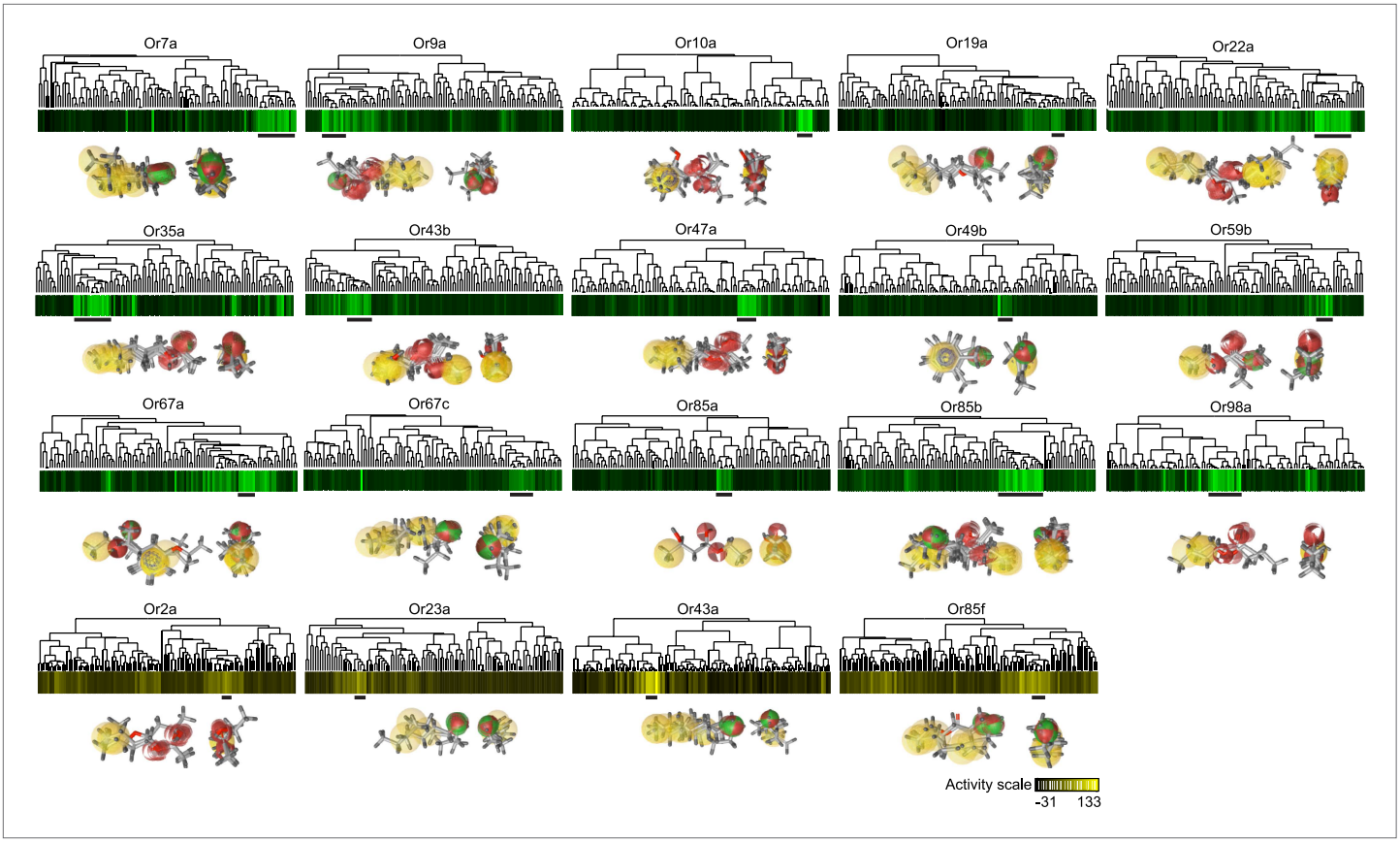

Figure 1—figure supplement 2. Pharmacophores of active compounds for individual Ors. Hierarchical cluster identical to ***Figure 1D***. Known odorant activity scale is indicated using independent color gradient scales. Horizontal black bars underneath cluster indicate part of active cluster, a subset of which were used to generate pharmacophores using the Ligand Scout program (shown underneath each Or in two orientations). Yellow = hydrophobic region, red = Hydrogen-bond acceptor, green/red = Hydrogen-bond donor or acceptor depending upon pH.

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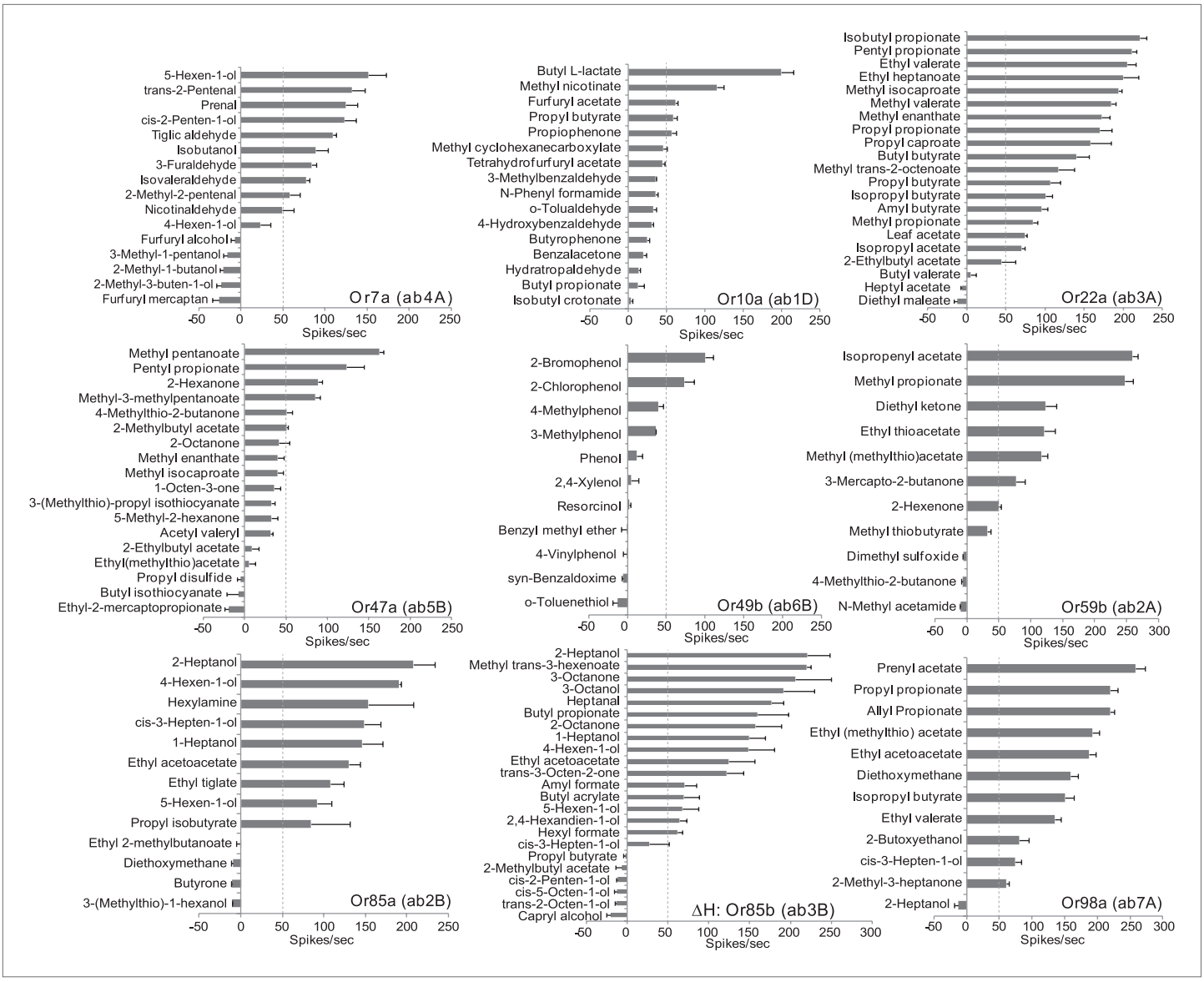

Figure 2. Electrophysiology validates that odorant receptor-optimized molecular descriptors can successfully identify new ligands for Drosophila. Mean increase in response of neurons to 0.5-s stimulus of indicated odors (10^{-2} dilution) predicted for each associated Or. Dashed lines indicate the activator threshold (50 spikes/s). *Δ*H: Or85b (ab3B) = flies lack expression of Or22a in neighboring neuron, thus all observed neuron activation is unambiguously caused by Or85b. N = 3, error bars = s.e.m.

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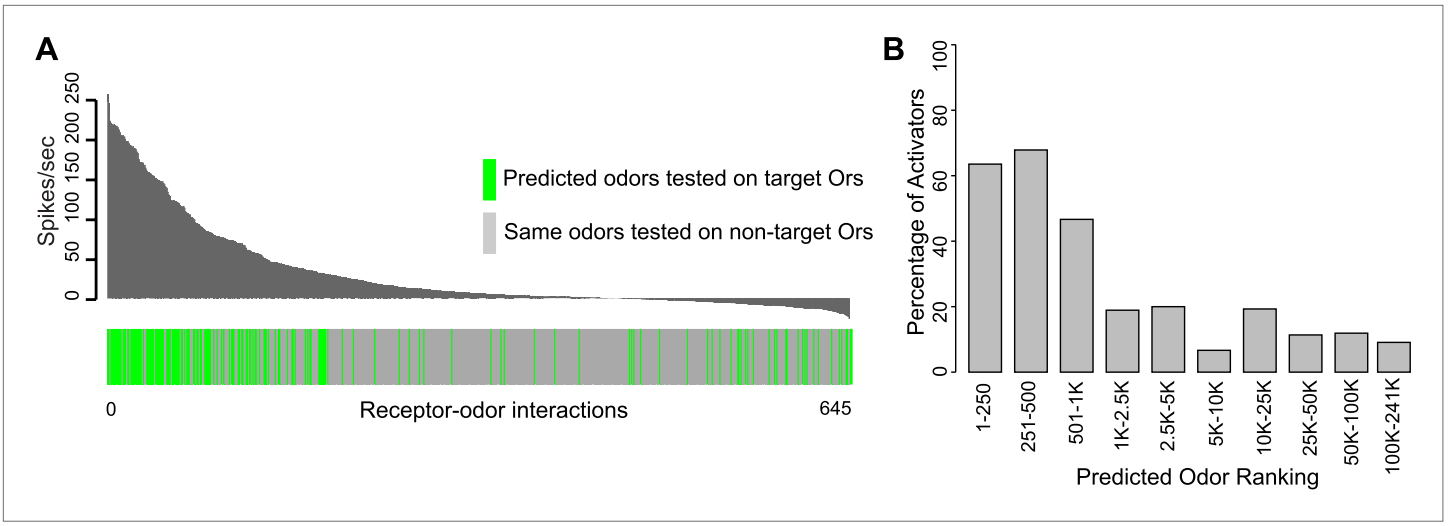

Figure 3. Predicted receptor–odor interactions are highly specific. (**A**) Plot of activity (Top) for electrophysiologically tested receptor-odor interactions. (Bottom) Plot indicating locations of predicted receptor-odor combinations (green) and same odorants tested in non-target receptor-odor combinations (gray). (**B**) Plot of percentage of activating odors (>50 spikes/s) considering all activating or inactive odors (>0 spikes/s) across ranking bins for all odors tested using electrophysiology.

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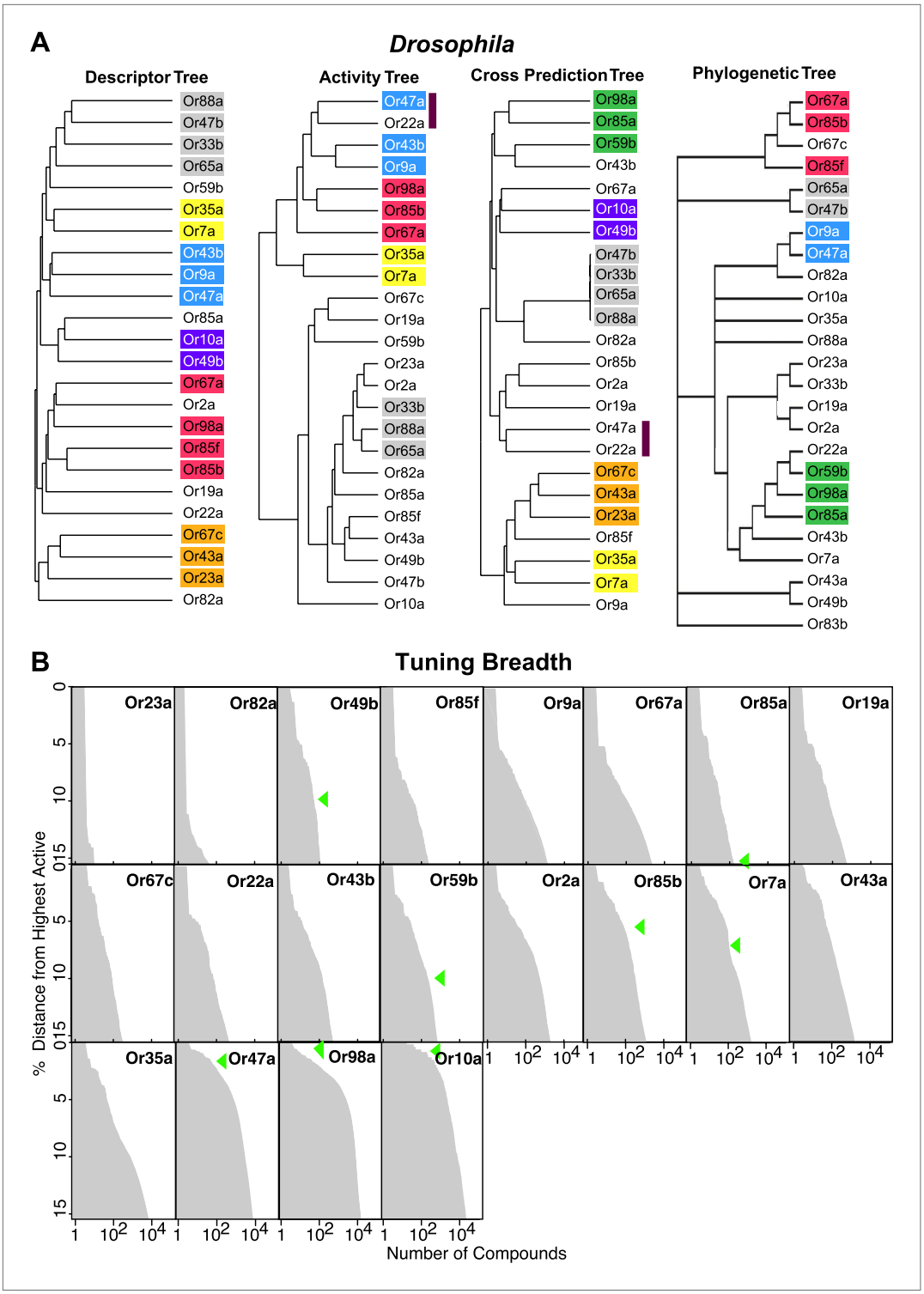

Figure 4. Analysis of receptor–odor relationships and breadth of tuning. (**A**) Hierarchical clusters created from Euclidean distance values between Drosophila Ors calculated using: (left to right) shared optimized descriptors; known activity to training set odors (***Hallem and Carlson, 2006***); overlap across top 500 predicted ligands; and Phylogenic tree of receptors (***Hallem and Carlson, 2006***). Sub clusters shaded with colors or bars. (**B**) Frequency distribution of compounds from the >240K library within the top 15% distance from highest active plotted to generate predicted breadth of tuning curves. Green arrows indicate relative distance of the furthest known activating compound determined by electrophysiology.

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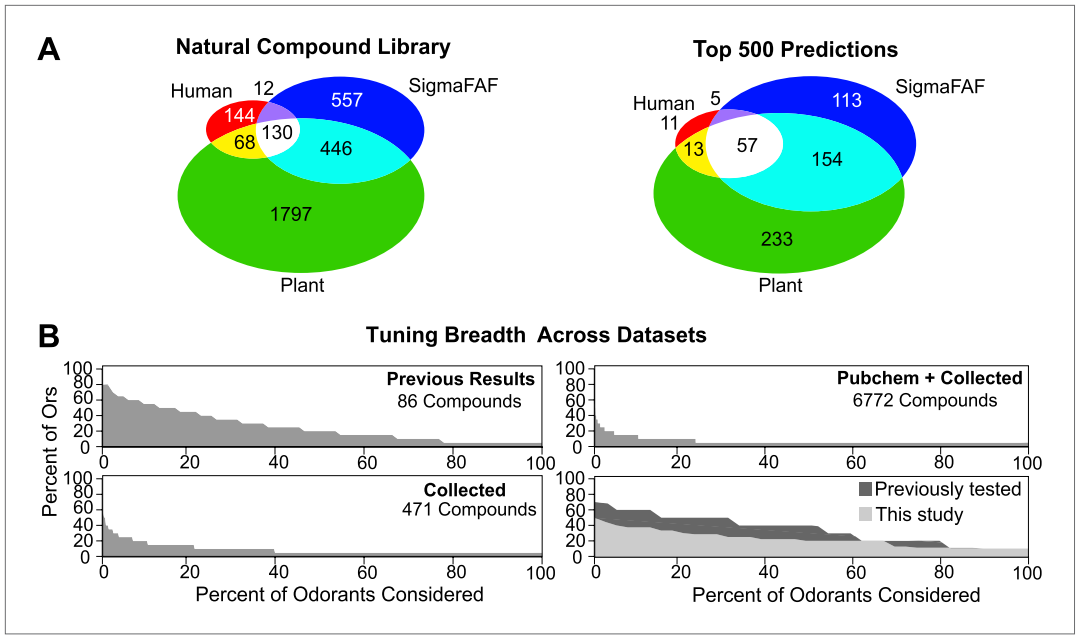

Figure 5. Analysis of predicted natural odor sources and cross activation. (**A**) (Left) The numbers of compounds present in the collected volatile library according to source. (Right) The numbers and sources of predicted ligands for the 19 Drosophila odor receptors/neurons within the top 500 predicted compounds. (**B**) Comparison of plots for percentage of receptors that are: (top left) activated by percentage of known odors from training set (***Hallem and Carlson, 2006***); (bottom left) predicted to be activated by Natural compound library; (top right) predicted to be activated from >240K library; and (bottom right) activated by ligands for 10 shared *Ors* in this study vs activated by comparable actives previously tested (***Hallem and Carlson, 2006***).

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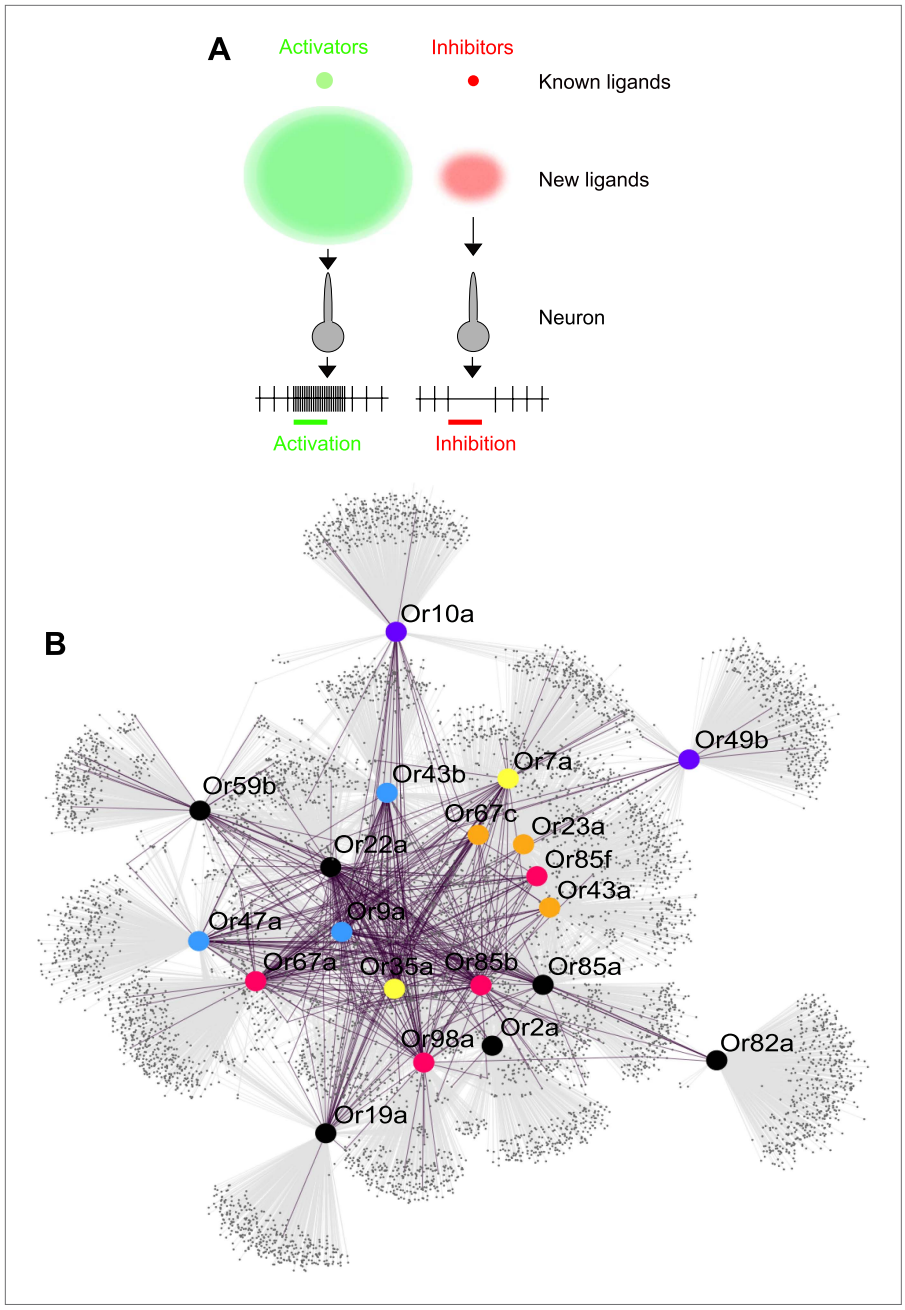

Figure 6. Predicted odor space and network view of odor coding. (**A**) Expansion of the peripheral olfactory code in this study: large increase in numbers of identified activators and inhibitors. The different sized circles represent the approximate ratio of numbers of previously known ligands (top circles), predicted ligands based on a cutoff of the top 500 predicted compounds per receptor and corrected to the validation success rate (lower, diffuse circles). (**B**) *Drosophila* receptor–odor network. Each known interaction (>50 spikes/s) from this and previous studies (***Hallem and Carlson, 2006***) is linked by a purple edge. Predicted receptor–odor network (top 500 hits) are linked by light-grey edges. All compounds are represented as small black circles and Ors are represented as large colored circles matching the colors used in (***Figure 4A***).

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