SensX: Model-Agnostic Local Feature Attribution via Calibrated Global Sensitivity Analysis

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Abstract

Local feature attribution is a standard tool for auditing and debugging deep learning predictions, but existing attribution methods are not designed for systems that chain pretrained, frozen, or API-only modules. Gradient-based methods such as Integrated Gradients require an end-to-end computational graph that may be unavailable. Perturbation-based methods such as KernelSHAP require a reference input or background distribution that composite pipelines cannot reliably provide. We present SensX, a local attribution method that treats the model as a black box and replaces arbitrary design choices with interpretable, application-grounded parameters. SensX adapts Morris-style coordinate walks from global sensitivity analysis to local attribution. It requires no access to model internals, training data, or arbitrary reference inputs. We validate SensX across four case studies, each targeting a distinct limitation of existing methods. On a synthetic benchmark where ground-truth relevant features vary per input, SensX reaches 95% top-2 attribution accuracy versus 58% for the best KernelSHAP/Integrated Gradients variant. On a ViT with $> 150{,}000$ pixel-channel features, SensX produces spatially coherent maps and exposes systematic intra-patch bias where KernelSHAP is infeasible and Integrated Gradients yields task-irrelevant attributions. On single-cell classifiers with unstructured gene-expression features, SensX attains the lowest top-k perturbation AUC. On a composite spatial transcriptomics system where neither method is applicable, SensX reveals reliance on preprocessing grid artifacts and a bias toward low-staining regions.

1 Introduction

Local feature attribution aims to identify which input features influence a predictive system's output on a given input, particularly for modern deep learning models. Explanations are typically presented as feature-importance scores, e.g., pixel-level heatmaps in vision and ranked feature lists in tabular settings. Such high-resolution explanations are a practical tool for debugging models, auditing shortcut learning, and assessing whether a system's behavior aligns with domain knowledge. This is especially important in clinical and biomedical settings where model predictions inform diagnoses, treatment decisions, and biological hypotheses. For example, DeGrave et al. (2021) showed that a high-performing COVID-19 detector relied on dataset-specific artifacts rather than clinically relevant features.

In many AI deployments today, the predictor to be explained is not a single end-to-end network but a composite system built from heterogeneous pretrained, frozen, or API-only components (Wang et al., 2025; Li et al., 2025; Hoang et al., 2024; Nonchev et al., 2025). This breaks two common assumptions behind existing local explainers—(i) access to an end-to-end computational graph for gradients, and (ii) the availability of a defensible reference input or background distribution for perturbation-based methods.

In particular, gradient-based methods such as Integrated Gradients (Sundararajan et al., 2017) require access to the computational graph, which may be unavailable when individual modules are frozen or served behind an API. Even when gradients are available, they can be numerically unstable in some deep networks (Balduzzi et al., 2017) and flow through frozen encoders whose representations were shaped by pretraining objectives unrelated to the downstream task. The resulting attributions further depend on the

choice of integration reference input (Sturmfels et al., 2020), accumulate at irrelevant locations along the integration path (Kapishnikov et al., 2021; Miglani et al., 2020), and can reflect input structure rather than learned model parameters (Adebayo et al., 2018). Attention-based methods (Vaswani et al., 2017; Jain and Wallace, 2019) are architecture-specific and produce attributions at the model's internal resolution rather than at input-feature resolution. KernelSHAP (Lundberg and Lee, 2017) and LIME (Ribeiro et al., 2016) are model-agnostic but require a perturbation distribution or background dataset that may not exist for composite pipelines, and can be computationally prohibitive (e.g., KernelSHAP triggered a memory allocation request of ~ 33 TB for the vision transformer analyzed here). KernelSHAP additionally discards interaction structure (Kumar et al., 2021), and LIME's linear surrogate guarantees hold only for linear functions (Garreau and Luxburg, 2020). For reference-input- or background-based explainers, the same arbitrariness that affects attribution computation also affects evaluation: validating a ranking requires specifying how to replace feature values, and common choices reintroduce the same reference assumptions.

Each method depends on access to model internals, a reference distribution, or a surrogate functional form—requirements that composite systems can deny or invalidate. Global sensitivity analysis offers an alternative, quantifying how input variations affect model output without requiring model internals (Van Stein et al., 2022). However, existing global sensitivity methods rely on arbitrary perturbation regimes. For example, Fel et al. (2021) applied Sobol indices (Sobol, 2001) to neural network explainability by decomposing output variance over perturbation masks applied to image regions. The perturbation masks interpolate each region toward a chosen reference value (e.g., black, grey, or blurred), reintroducing the dependence on an arbitrary reference that limits IG and KernelSHAP. The approach uses a fixed perturbation scale and requires grouping features into spatial regions to remain tractable, making it inapplicable to domains where features lack spatial or hierarchical structure—as in single-cell transcriptomics, where each gene must be attributed individually.

We introduce SensX, a local attribution framework that requires only forward evaluations and admissible feature bounds. SensX identifies an input-specific perturbation scale at which the model response saturates, yielding a neighborhood calibrated to the model's sensitivity rather than chosen ad hoc. Within this neighborhood, it adapts the coordinate-walk strategy of Morris (1991) to local attribution by anchoring trajectories at the input being explained. SensX does not require reference inputs, background datasets, or access to the training distribution. Its hyperparameters are interpretable and grounded in the application.

We validate and demonstrate generality of SensX using four settings, each targeting a distinct limitation of existing methods. The settings span synthetic benchmarks with input-dependent ground truth, a vision transformer with over 150,000 features, single-cell transcriptomics with $\sim$ 27,000 genes per cell, and a composite spatial transcriptomics pipeline where gradients are not exposed and background datasets are not available.

2 SensX

SensX treats the model as a black box that maps input $\mathbf{x} = (x_1, \ldots, x_n)$ to output $\mathbf{y} = m(\mathbf{x})$. The quantity of interest (QOI) is any continuous scalar function $q(\mathbf{y})$. SensX measures the sensitivity of $q(\mathbf{y})$ to each input feature x_j (Figure 1A). For notational convenience, we write $q(\mathbf{x}) \equiv q(m(\mathbf{x}))$.

Local neighborhood and characteristic perturbation scale. Let $\Omega^g = \prod_j [f_j^-, f_j^+]$ be a global domain bounding the input space where f_j^- and f_j^+ are lower and upper bounds of the j-th input feature. SensX defines a local neighborhood of $\mathbf{x}$ parameterized by a perturbation factor $\delta \in [0, 1]$ as

$$\Omega(\mathbf{x}, \delta) = \prod_{1 \le j \le n} \big[\max\{f_j^-,\, x_j - \delta\, r_j\},\ \min\{f_j^+,\, x_j + \delta\, r_j\}\big], \quad r_j = f_j^+ - f_j^-. \tag{1}$$

At $\delta = 0$ this reduces to $\{\mathbf{x}\}$; at $\delta = 1$ it equals Ω^g (Figure 1B). For each δ in a user-defined discrete set Δ, we draw n_s inputs uniformly at random from $\Omega(\mathbf{x}, \delta)$ and form the distribution of QOIs, $D(\mathbf{x}, \delta, n_s)$. Let $\underline{D}(\mathbf{x}, \delta, n_s)$ and $\overline{D}(\mathbf{x}, \delta, n_s)$ denote the 1st and 99th percentiles of this distribution, which define the prediction envelope (Figure 1C). These percentiles provide a robust measure of the prediction range that mitigates the influence of extreme outliers.

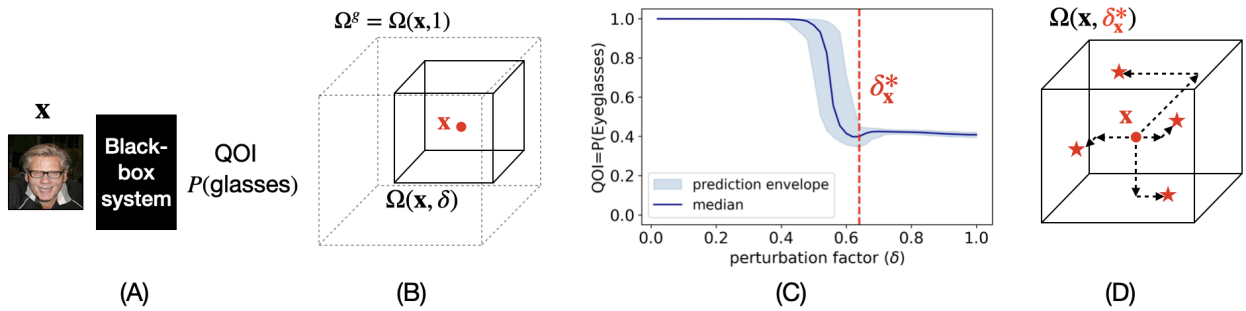


Figure 1: **Overview of SensX.** (A) An input image $\mathbf{x}$ is passed through a black-box system that predicts the probability of wearing eyeglasses (the quantity of interest, QOI). (B) $\Omega(\mathbf{x}, \delta)$ is a local neighborhood parameterized by perturbation factor $0 < \delta \leq 1$ within the global domain $\Omega^g = \Omega(\mathbf{x}, 1)$. (C) The prediction envelope is the variation in QOI (shaded blue). The characteristic perturbation scale $\delta^*_{\mathbf{x}}$ (dashed vertical line) is the smallest δ beyond which the prediction envelope remains within a user-defined threshold for all larger scales. (D) Within $\Omega(\mathbf{x}, \delta^*_{\mathbf{x}})$, SensX samples coordinate-wise walks (dashed arrows) from $\mathbf{x}$ to random endpoints (stars) in a random feature order. Changes in QOI along these walks contribute to feature attribution. Algorithm 1 summarizes the main steps of the full framework.

The characteristic perturbation scale $\delta^*_{\mathbf{x}}$ is the smallest $\delta' \in \Delta$ such that the prediction envelope remains within a user-defined threshold τ_a for all subsequent scales,

$$\delta^*_{\mathbf{x}} = \min_{\delta' \in \Delta} \Big\{ \max_{\delta \in \Delta:\, \delta > \delta'} \overline{D}(\mathbf{x}, \delta, n_s) \; - \; \min_{\delta \in \Delta:\, \delta > \delta'} \underline{D}(\mathbf{x}, \delta, n_s) \; < \; \tau_a \Big\}. \tag{2}$$

This condition is stricter than requiring the envelope width to be small at each individual δ. It ensures the prediction range has globally saturated beyond $\delta^*_{\mathbf{x}}$, not merely at isolated scales (Appendix A.3).

Grounded trajectories and elementary effects. Within the local neighborhood $\Omega(\mathbf{x}, \delta^*_{\mathbf{x}})$, SensX samples n_w coordinate-wise walks from $\mathbf{x}$ to random endpoints $\mathbf{e}$ uniformly drawn from $\Omega(\mathbf{x}, \delta^*_{\mathbf{x}})$ (Figure 1D). Each walk is a *grounded trajectory*: a sequence of $n+1$ points $T_{\mathbf{x},\mathbf{e}} = (\mathbf{t}_0 = \mathbf{x}, \mathbf{t}_1, \ldots, \mathbf{t}_n = \mathbf{e})$ where a random permutation $(i_1, \ldots, i_n)$ determines the order in which features are changed, and $\mathbf{t}_k$ differs from $\mathbf{t}_{k-1}$ only in feature i_k, which is set to e_{i_k}. This design adapts the Morris method (Morris, 1991) for local attribution by anchoring all trajectories at the input being explained rather than at random points in the input space.

The elementary effect of feature i_k along trajectory $T_{\mathbf{x},\mathbf{e}}$ is the normalized output change at step k:

$$d_{i_k}^{T_{\mathbf{x},\mathbf{e}}} = \frac{q(\mathbf{t}_k) - q(\mathbf{t}_{k-1})}{e_{i_k} - x_{i_k}}. \tag{3}$$

The feature order is randomized across trajectories, so each elementary effect is measured against a different configuration of the remaining features.

Anchored μ^* (SensX values). Following Campolongo et al. (2007), we use the mean absolute elementary effect μ^* to avoid sign cancellation when averaging effects across trajectories. In SensX, μ^* is computed on grounded trajectories anchored at the input $\mathbf{x}$ and confined to the calibrated local neighborhood $\Omega(\mathbf{x}, \delta^*_{\mathbf{x}})$. We refer to these anchored-μ^* attributions as *SensX values*. The SensX value of feature j is

$$\widehat{s}_{\mathbf{x},j} = \frac{1}{n_w} \sum_{T_{\mathbf{x},\mathbf{e}} \in \mathcal{T}_{\mathbf{x}}} \left| d_j^{T_{\mathbf{x},\mathbf{e}}} \right|. \tag{4}$$

Our implementation evaluates multiple feature updates per forward pass by batching features. Batch size trades off GPU throughput and memory. SensX also supports grouped attribution where features are perturbed as a single unit with L_2-normalized effects (Appendix A.6).

Algorithm 1 SensX($\mathbf{x}$)

Require: Scalar QOI $q(\cdot)$, input $\mathbf{x} \in \mathbb{R}^n$, global bounds $\Omega^g = \prod_j [f_j^-, f_j^+]$, sweep set Δ, samples n_s, walks n_w, threshold τ_a
Ensure: SensX values $\widehat{\mathbf{s}}_{\mathbf{x}} \in \mathbb{R}^n$

Define local neighborhoods $\Omega(\mathbf{x}, \delta)$ ▷ equation 1
Stability profile / envelope:
for all $\delta \in \Delta$ **do**
  Sample n_s perturbations $\sim \mathrm{Unif}(\Omega(\mathbf{x}, \delta))$
  Evaluate QOI values and record the 1st/99th percentiles
end for
Select characteristic scale:
Compute $\delta^*_{\mathbf{x}}$ from the envelope and handle edge cases ▷ equation 2
Grounded coordinate-walk attribution (anchored μ^*):
Initialize $S_j \leftarrow 0$ for all $j = 1, \ldots, n$
for $w = 1, \ldots, n_w$ **do**
  Sample endpoint $\mathbf{e} \sim \mathrm{Unif}(\Omega(\mathbf{x}, \delta^*_{\mathbf{x}}))$
  Sample a random permutation π of $\{1, \ldots, n\}$
  Set $\mathbf{t} \leftarrow \mathbf{x}$
  for $k = 1, \ldots, n$ **do** ▷ Batched (GPU-parallelism)
    $i \leftarrow \pi(k)$
    Update $t_i \leftarrow e_i$ (change one feature at a time)
    Compute elementary effect for feature i and accumulate magnitude: ▷ equation 3
      $S_i \leftarrow S_i + |d_i|$
  end for
end for
SensX values:
for $j = 1, \ldots, n$ **do**
  $\widehat{s}_{\mathbf{x},j} \leftarrow \frac{1}{n_w} S_j$ ▷ equation 4
end for
return $\widehat{\mathbf{s}}_{\mathbf{x}}$

Hyperparameters. The global domain Ω^g is specified by the practitioner based on domain knowledge of admissible feature ranges. The parameters n_s and n_w control convergence of the stability profile and attribution estimate, respectively, and the discretization of the δ sweep controls the resolution of the stability profile. The primary context-dependent choice is the stability threshold τ_a, which specifies what magnitude of output change is considered meaningful. For classification tasks, $\tau_a = 0.1$ corresponds to a 10% change in predicted probability. For gene expression prediction, $\tau_a = 0.5$ corresponds to a half-unit change in log expression. These choices are transparent, auditable, and grounded in the application. Algorithm 1 summarizes the main steps of the full framework.

Computational cost. Each grounded trajectory requires evaluating the QOI at n points, one per feature update. With batch size B, these n evaluations are grouped into $\lceil n/B \rceil$ forward passes, since the endpoint $\mathbf{e}$ is reached at step n and is therefore included in the final batch. Across n_w independent walks, the total number of forward evaluations is $n_w \cdot \lceil n/B \rceil$, and the total wall-clock time is $\mathcal{C} \approx n_w \cdot \lceil n/B \rceil \cdot T$, where T is the time to complete one forward pass over a batch of B feature updates. Increasing B reduces $\lceil n/B \rceil$ and therefore $\mathcal{C}$, at the cost of higher peak memory. The batch size thus controls the throughput–memory tradeoff. The walks are fully independent and trivially parallelizable across devices, reducing wall-clock time proportionally to the number of devices.

Grouped attribution. SensX also supports grouped attribution, where features are partitioned into G disjoint groups and all features in a group are perturbed simultaneously in one trajectory step. This reduces trajectory length from n steps (per-feature) to G steps (per-group) while still sampling independent perturbation targets for each feature within the group. Grouped elementary effects are normalized by the L_2

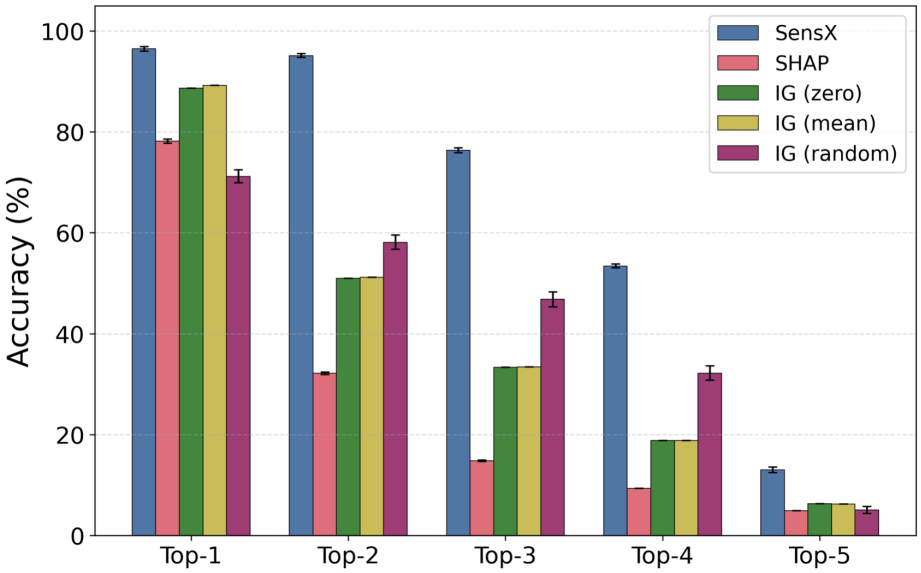


Figure 2: **SensX recovers local feature attributions that reference-dependent methods miss.** Fraction of samples in which the top-k ranked features all belong to the ground-truth set, averaged over 100 independent runs (± 1 standard deviation), at the best-performing hyperparameter for each method on the Switch dataset. SensX outperforms KernelSHAP and all three IG reference-input variants across all k values.

magnitude of the group perturbation to keep sensitivities comparable across groups (see Appendix A.6 for details). Our current implementation restricts grouping to equal-sized groups. Extending to unequal group sizes with appropriate normalization is left to future work.

Perturbation validation. To validate that a ranking concentrates model sensitivity into its highest-ranked features, we perform a top-k/bottom-k perturbation analysis. The k highest-ranked (or lowest-ranked) features are perturbed within the local neighborhood while the rest are held fixed, and the change in QOI is recorded. If the ranking is effective, top-k perturbation produces a rapid change in QOI at small k, while bottom-k perturbation has little effect until the majority of features are perturbed (Appendix A.7).

3 Results

3.1 SensX recovers local feature attributions that reference-based methods miss

We benchmark SensX against KernelSHAP and Integrated Gradients (IG) with three reference-input choices—zero vector, training-set mean, and random training samples—on four established synthetic datasets with known relevant features (Chen et al., 2018) (Appendix F.1).

Figure 2 shows results on the Switch dataset, where relevant features vary dynamically per input. SensX outperforms all alternatives at every k. At top-2, SensX (95%) exceeds the best alternative, IG (random), by 37 percentage points. At top-5, accuracy drops below 13% for all methods, reflecting the difficulty of identifying all five relevant features simultaneously. Results are robust to hyperparameter choice, with accuracy varying by fewer than 5 percentage points across the full hyperparameter range for all methods (Supplementary Figures D1 and D2). On the remaining datasets, both SensX and KernelSHAP achieve perfect accuracy on XOR (Supplementary Figure D1A). On Orange Skin and Nonlinear Additive, the methods diverge only at the highest k, where SensX converges to near-perfect accuracy while KernelSHAP plateaus below (Supplementary Figures D1B and D1C).

The characteristic perturbation scale δ^* converges to 1 for nearly all inputs across three of the four datasets (Supplementary Figure D3B). On the Orange Skin dataset, δ^* shows non-trivial variance at low sample

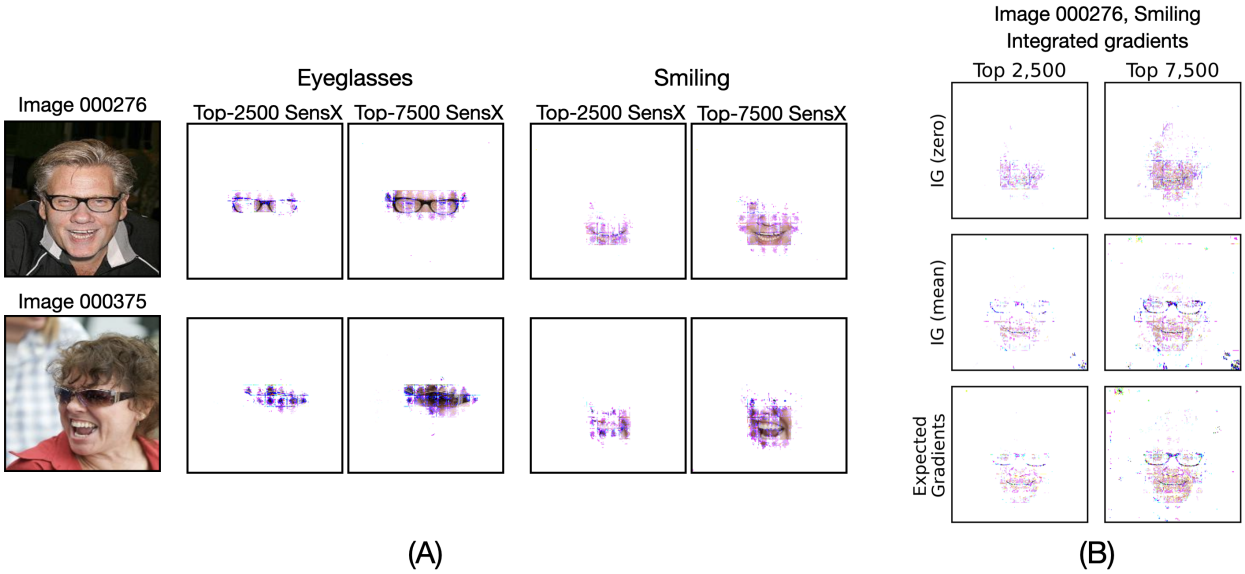


Figure 3: **SensX produces spatially coherent attributions at over 150,000 features.** (A) Top-k SensX masks for two input images under the eyeglasses and smiling models. Top-ranked features concentrate on class-relevant regions and expand coherently as k increases from 2,500 to 7,500. Features outside the top-k are set to white; each feature is an individual color channel at a pixel location. (B) IG masks for image 000276 under the smiling model with three reference-input choices. Two of the three reference inputs attribute to the eyeglass frames rather than the mouth, despite the smiling model being fine-tuned independently. All masks are shown in Supplementary Figure D5.

budgets before stabilizing near 1 (Supplementary Figure D3A). In the higher-dimensional case studies that follow, δ^* takes values below 1.

3.2 Feature-level attribution of a vision transformer reveals architectural bias

We finetuned two pretrained ViT models (Dosovitskiy et al., 2020) on the CelebFaces Attributes dataset (Liu et al., 2015) for smile detection and eyeglass detection (Appendix F.2). Input images are 224×224 pixels across three color channels, totaling 150,528 features, where each feature is an individual color channel at a pixel location. The characteristic perturbation scale ranges from $\delta^* = 0.54$ to 0.70 across the four (image, model) combinations. KernelSHAP required 33 TB of memory at this scale, whereas SensX required less than 10 GB. Gradient access is available for these models, so we also computed IG with zero vector, training-set mean, and expected gradients (Erion et al., 2021) reference inputs as a non-model-agnostic comparison.

Supplementary Fig. E shows how the SensX feature ranking stabilizes with the number of walks. The Spearman correlation between rankings computed with n_w and $n_w - 20$ walks exceeds 0.99 by $n_w \approx 200$ across all (image, model) pairs. Each walk takes $\sim$5 minutes with batch-size of 1000 on a single NVIDIA A100 GPU at 32-bit precision for the ViT forward evaluation. The following results in this section are based on $n_w = 600$.

Figure 3A shows masks of the top-k ranked SensX features. For the eyeglasses model, the top 2,500 features localize tightly to the eyeglass frames and for the smiling model, they localize to the mouth. IG attributions are reference-input-dependent and mislocalize to task-irrelevant regions (Figure 3B). On the smiling model, the mean reference input and expected gradients (Erion et al., 2021) attribute to high-contrast eyeglass frames rather than the mouth, consistent with the input-structure dependence identified by Adebayo et al. (2018). All IG reference-input variants lack the spatial coherence of SensX attributions (Supplementary Figure D5).

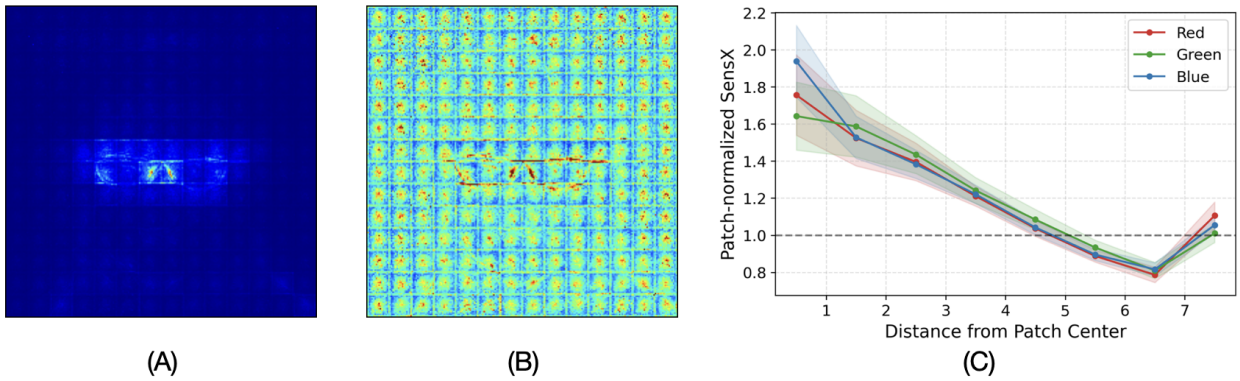


Figure 4: **Precise attribution exposes intra-patch spatial bias in ViT tokenization.** (A) SensX attribution heatmap (green channel, Eyeglasses model, image 000276). (B) The same heatmap after normalizing each 16×16 patch by its median, revealing a consistent intra-patch pattern. (C) Patch-normalized SensX averaged across all patches as a function of distance from the patch center. Shaded regions denote ± 1 standard deviation.

We validated the SensX ranking with two complementary checks. First, perturbing features from highest to lowest SensX rank produces a rapid QOI decline, while perturbing over 130,000 bottom-ranked features has no measurable effect (Supplementary Figure D6A). Second, the cascading randomization test of Adebayo et al. (2018) confirms that attributions depend on learned weights rather than input structure. Progressively randomizing transformer blocks destroys the SensX ranking, and at deeper randomization levels the characteristic perturbation scale δ^* drops to zero, indicating that the model output becomes insensitive to input perturbations (Supplementary Figure D6B,C).

The SensX heatmaps reveal grid artifacts aligned with the 16×16 pixel patches defining the ViT tokenization. Patch-normalized SensX is consistently highest at the patch center, decays toward the interior boundary, and rebounds at the edge (Figure 4). This profile holds across all color channels and all image–model combinations (Supplementary Figure D8), indicating a systematic architectural bias rather than image-specific structure. IG attributions analyzed with the same patch-normalization methodology show a coarse center bias in the distance profiles, but the pattern is not apparent in the normalized IG heatmaps (Supplementary Figure D9), suggesting that the intra-patch structure is below the effective resolution of IG at this scale.

3.3 SensX rankings concentrate model sensitivity into fewer genes than DeepSHAP and Integrated Gradients in single-cell classification

We trained 14 binary classifiers, one per cell type, on the core human lung cell atlas (Sikkema et al., 2023) (Appendix F.3). The characteristic perturbation scale δ^* varies by up to two orders of magnitude across cell types (Supplementary Figure D10). Lower values indicate that the classifier's predictions are determined by finer differences in expression. The within-cell-type spread shows that SensX adapts δ^* independently for each cell.

The global domain Ω^g was set to the feature-wise minimum and maximum of the training data. For log-normalized gene expression data, however, biologically grounded bounds are also available independently of any specific dataset: the lower bound is exactly zero for all genes, since a gene that is not expressed has zero counts and $\log(1+0) = 0$ is a true biological state, and the upper bound is constrained by the normalization scheme itself—for log1p-normalized counts-per-10k, the theoretical maximum is $\log(1 + 10{,}000) \approx 9.2$. A practitioner without access to training data could therefore define $\Omega^g = [0, 10]^n$ for all genes, which is biologically defensible and would yield the same practical result.

For a rank-convergence analysis, we computed SensX rankings cumulatively and measured the Spearman correlation between rankings obtained with n_w and $n_w - 20$ walks (in increments of 20). Mean correlations

across 1000 cells per cell type rise quickly toward 1, while the across-cell standard deviation decreases with additional walks, indicating that rankings stabilize both on average and across cells (Supplementary Figure E2). The following results use $n_w = 600$ walks. The computational cost for single-cell attribution is significantly lower as compared to the ViT. SensX processes 20 coordinate-walks per second for a single cell ($27,399$ features) using a batch size of $8,192$. This represents a throughput nearly three orders of magnitude higher than the ViT case study.

We compared SensX with DeepSHAP (Lundberg and Lee, 2017) and Integrated Gradients (Sundararajan et al., 2017) with three reference-input variants. KernelSHAP required over 230 GB of memory and was excluded. For each cell, genes are ranked by the absolute value of their attribution. All methods attribute the same quantity of interest (predicted probability).

Figure 5A shows perturbation curves for natural killer cells at δ^*. The predicted probability drops fastest with the fraction of top-ranked genes perturbed for SensX, and requires the largest fraction of bottom-ranked genes perturbed before changing. Figure 5B summarizes the normalized AUC across all cell types. SensX achieves the lowest top-k AUC (0.53–0.83) and the highest bottom-k AUC (0.98–1.00) across all cell types.

The perturbation validation at δ^* uses a scale derived from SensX's own stability analysis. We repeated the analysis at $\delta = 1$ using the same SensX rankings (Supplementary Figure D11). SensX top-k AUC is zero (rounded to two decimal places) for all cell types, showing that the rankings transfer to global perturbation.

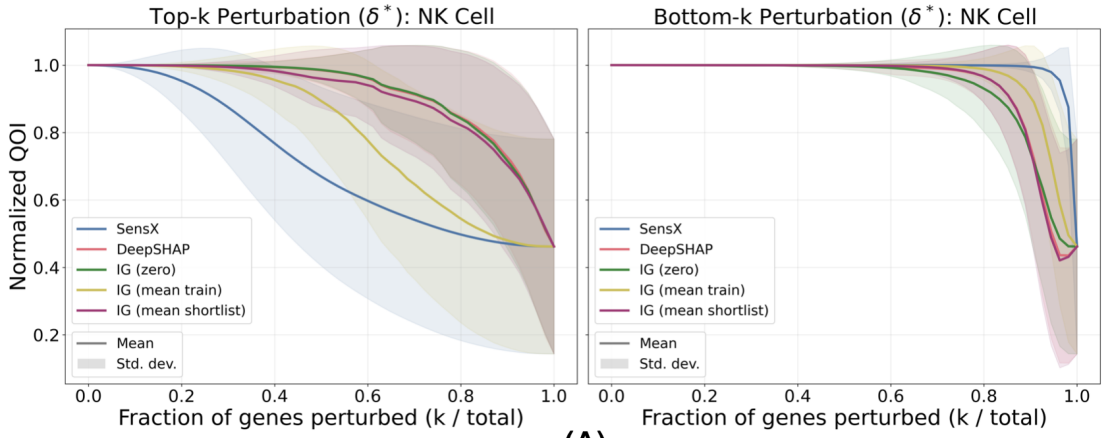
The comparison across IG reference-input variants shows that reference-input choice has a substantial effect on attribution quality. IG with a training-data mean reference input outperforms IG with the mean of the high-confidence cells in every cell type (Figure 5B), despite the latter being closer to the inputs being explained—an instance of the reference-input sensitivity discussed in Section 3.2 and examined further in the Discussion.

3.4 Pixel-level attribution of a composite spatial transcriptomics model

DeepSpot (Nonchev et al., 2025) is a composite framework that predicts expression of 5,000 genes from H&E histology images. For a given spot (100×100 pixel tile), DeepSpot integrates the tile and its eight neighbors through the UNI pathology foundation model (Chen et al., 2024) and secondary architectures (Figure 6A, Appendix F.4). We show results only for SensX. IG is not applicable because UNI is frozen (no exposed computational graph or gradients). KernelSHAP is also not applicable in a principled way because the training sets of the system and its modules are not known. We applied SensX to 745 spots from a whole-slide H&E colon tissue image, analyzing four genes selected for high mean and high variance of predicted log-expression.

We first attributed at the tile level by grouping 270,000 input features into 9 tiles. The center tile's SensX value exceeds that of the strongest neighbor by more than an order of magnitude in 98.4% of spot-gene pairs, confirmed by independent center-tile perturbation validation (Supplementary Figure D12). We then computed pixel-level SensX values within the center tile. The characteristic perturbation scale ranges from $\delta^* = 0.1$ to 0.6 across spots and genes (Supplementary Figure D13). Perturbation validation confirms that the pixel-level ranking is effective (Supplementary Figure D15).

The pixel-level attributions reveal two systematic patterns (Figure 6). First, high-attribution pixels concentrate near the boundaries of the 3×3 subspot grid used in DeepSpot preprocessing: 61.9% of spot-gene pairs show significant grid proximity at $p < 0.025$, ranging from 60.8% (*LGALS4*) to 63.6% (*MUC5B*) (Supplementary Figure D14A), confirming that the subspot partitioning introduces spatial bias. Second, among spot-gene pairs without significant grid bias, 73.9% show significantly lower staining saturation in the top-ranked pixels at $p < 0.025$, ranging from 71.0% (*LGALS4*) to 80.8% (*TFF3*) (Supplementary Figure D14B), indicating that the model preferentially attends to lighter-stained regions. These low-saturation regions are visually consistent with colonic crypts (Figure 6B).



(A)

	Top-k AUC (↓ lower is better) (δ^*)					Bottom-k AUC (↑ higher is better) (δ^*)				
	SensX	DeepSHAP	IG (zero)	IG (mean train)	IG (mean shortlist)	SensX	DeepSHAP	IG (zero)	IG (mean train)	IG (mean shortlist)
Basal Cell	**0.53**	0.90	0.88	0.74	0.88	**0.99**	0.79	0.83	0.92	0.80
AT2 Cell	**0.63**	0.93	0.91	0.78	0.94	**0.99**	0.90	0.91	0.96	0.90
CD8⁺ T Cell	**0.64**	0.91	0.91	0.79	0.90	**0.98**	0.86	0.89	0.91	0.86
Elicited Macrophage	**0.64**	0.93	0.93	0.81	0.92	**0.99**	0.84	0.87	0.91	0.84
CD4⁺ T Cell	**0.67**	0.89	0.90	0.73	0.88	**0.99**	0.94	0.93	0.97	0.95
Classical Monocyte	**0.68**	0.93	0.93	0.80	0.90	**0.99**	0.91	0.92	0.94	0.91
NK Cell	**0.71**	0.92	0.92	0.80	0.91	**0.99**	0.94	0.94	0.96	0.94
Goblet Cell	**0.72**	0.96	0.95	0.87	0.95	**0.99**	0.88	0.91	0.94	0.88
Club Cell	**0.76**	0.96	0.96	0.88	0.95	**0.99**	0.90	0.92	0.94	0.90
Alveolar Macrophage	**0.77**	0.95	0.96	0.82	0.95	**1.00**	0.95	0.94	0.97	0.95
Adventitial Fibroblast	**0.79**	0.96	0.96	0.87	0.95	**0.99**	0.94	0.92	0.97	0.95
Capillary EC	**0.81**	0.96	0.96	0.86	0.96	**1.00**	0.96	0.96	0.98	0.98
Multiciliated Cell	**0.83**	0.99	0.98	0.94	0.98	**1.00**	0.95	0.96	0.98	0.97
Venous EC	**0.83**	0.97	0.97	0.90	0.97	**1.00**	0.95	0.96	0.98	0.97

(B)

Figure 5: **Perturbation validation of per-cell feature rankings across 14 cell types.** (A) Top-k (left) and bottom-k (right) perturbation curves for natural killer cells. Curves show the mean across 1,000 cells; shaded regions denote ± 1 standard deviation. (B) Normalized AUC of the perturbation curves for all 14 cell types. For top-k, lower is better; for bottom-k, higher is better. SensX achieves the best value (bold) in every cell type for both metrics.

4 Discussion

The case studies collectively show that the granularity of attribution determines what can be discovered about a model's behavior. The ViT patch-boundary bias and the DeepSpot subspot grid effects are invisible to any method that attributes at the token or region level; they become visible only when attribution is resolved to individual pixel-channels and pixels, respectively. In single-cell transcriptomics, where genes lack spatial or hierarchical structure, feature-level attribution is the only option—and finer resolution directly translated into rankings that concentrated model sensitivity into fewer genes than all alternatives tested. These artifacts would go undetected by coarser methods regardless of their theoretical properties.

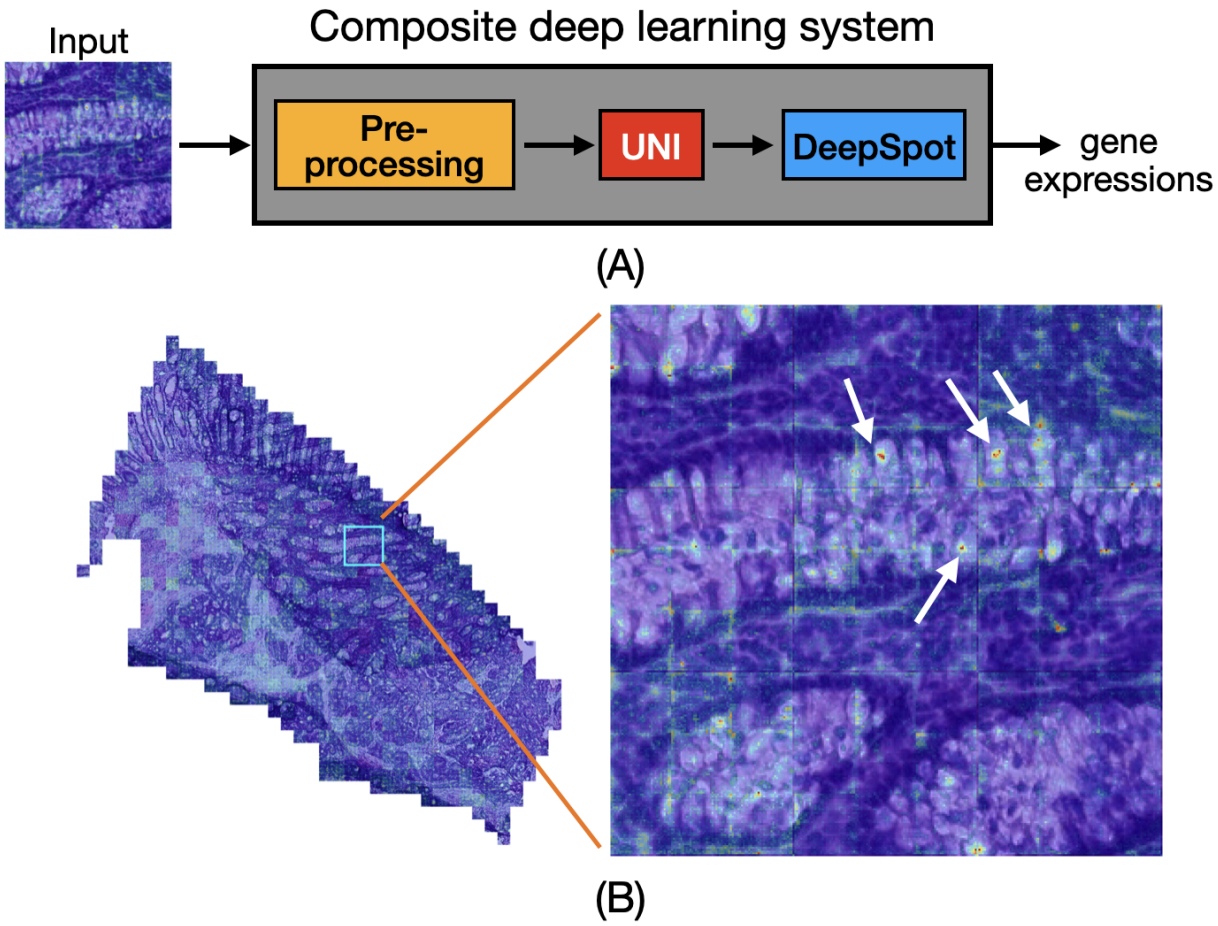


Figure 6: **Pixel-level SensX attributions for gene expression predictions of a composite spatial transcriptomics model.** (A) The composite system chains three modules—preprocessing to get subspots, frozen pretrained foundation model UNI to get morphological features, and custom deep neural network (DeepSpot) to predict gene expression. (B) Whole-slide view SensX attribution overlay for *MUC4* expression in a colon tissue section. The cyan box is zoomed in to show boundary effects that align with the 3×3 subspot grid that is created during preprocessing. White arrows indicate regions of lighter staining where high-attribution pixels concentrate.

An objection to independent feature perturbation is that it produces unrealistic feature combinations off the data manifold (Frye et al., 2020). This concern conflates two distinct objectives—explaining predictions under the data distribution and identifying which features the model depends on. Data-aware methods such as conditional SHAP (Aas et al., 2021) spread attribution across correlated features, reflecting the dataset's covariance structure rather than the model's learned dependencies. Independent perturbation isolates whether the model has learned to rely on one feature over another. SensX mitigates the manifold concern not by conditioning on the data distribution but by calibrating perturbation scale to the model's local response.

The three user-specified inputs to SensX—the stability threshold τ_a, the perturbation factor grid Δ, and the global domain Ω^g—are interpretable and have predictable effects, which distinguishes them from the arbitrary choices embedded in competing methods. τ_a encodes a domain-meaningful tolerance: a stricter threshold yields a smaller neighborhood and a more permissive one yields a larger neighborhood, a monotonic relationship with no analogue in reference-input selection. By contrast, substituting one IG reference input for another can redirect attributions to entirely different features with no a priori way to anticipate the effect (Figure 3B), and the same sensitivity was observed across all cell types in single-cell transcriptomics

(Figure 5B)—a zero reference input is not a biologically meaningful state (Sturmfels et al., 2020), and Expected Gradients (Erion et al., 2021) embeds the training distribution's class structure into the attribution. No principled criterion exists for choosing among reference inputs. For Δ, an initial uniform grid sufficed in most settings. We used a log-spaced grid for the single-cell case since δ^* clustered near zero (Appendix B). The resolution can similarly always be refined in the neighborhood of the first estimate of δ^* by a secondary stability sweep. For Ω^g, the gene expression case study (Section 3.3) illustrates that admissible feature ranges can be grounded in domain knowledge independently of any training set—in contrast to the background datasets required by KernelSHAP and Expected Gradients, which embed the training distribution's structure and are unavailable when data are proprietary or distributed across heterogeneous sources.

The δ^* protocol additionally serves as a diagnostic. $\delta^*_{\mathbf{x}} = 0$ flags inputs where model output variation is below threshold under any neighborhood size, warranting investigation rather than producing misleading attributions. Models with sharp non-smooth regions pose a challenge, as narrow sensitivity spikes could fall between grid points in Δ. However, such regimes are at least as problematic for gradient-based methods, where gradient shattering and saturation can degrade attributions (Balduzzi et al., 2017; Miglani et al., 2020). When $\delta^* \ll 1$, restricting trajectories to the calibrated neighborhood also improves sampling efficiency. Trajectories at $\delta = 1$ would otherwise sample predominantly from the saturated regime where the model's output has already plateaued.

The coordinate-wise walks in SensX differ structurally from path-based methods such as IG. IG interpolates all features simultaneously along a straight path from a reference input, accumulating gradients that can vanish in saturated regions. SensX changes one feature at a time in random order and measures finite output differences, averaging interaction effects across multiple walks. This structural difference, together with the δ^* calibration, is what allows SensX to resolve the intra-patch bias in the ViT and the subspot grid effects in DeepSpot—both patterns require perturbations confined to the sensitivity regime and resolved at the level of individual features.

We compared SensX against the most widely used model-agnostic and gradient-based attribution methods where applicable—KernelSHAP, Integrated Gradients variants, and DeepSHAP. We did not pursue an exhaustive evaluation of architecture- and modality-specific methods such as Grad-CAM (Selvaraju et al., 2017), which rely on intermediate spatial feature maps and are incompatible with forward-only composite systems. LIME (Ribeiro et al., 2016) was not benchmarked because its linear surrogate guarantees hold only for linear functions (Garreau and Luxburg, 2020) and, under specific kernel choices, LIME reduces to KernelSHAP (Lundberg and Lee, 2017). Other model-agnostic methods including permutation feature importance (Breiman, 2001), counterfactual explanations (Wachter et al., 2017), and randomized saliency methods (Petsiuk et al., 2018) share one or more of the limitations identified in the Introduction.

As composite deep learning systems grow in architectural complexity, attribution methods must treat them as black boxes. SensX provides this capability through a principled framework with interpretable hyperparameters, requiring only forward evaluations and admissible feature bounds. The results here suggest that the precision gains from feature-level attribution are not merely quantitative—they expose qualitatively different model behaviors that coarser or reference-dependent methods cannot reach.

Code and data availability

The source code for our implementation, including the training scripts, hyperparameter configurations, data simulation or data acquisition details for our case studies, is provided in the supplementary material.

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A SensX Framework: Formal Definitions

A.1 Terminology

A trained model is a mathematical function that maps an input to an output. $\mathbf{x} = (x_1, ..., x_n)$ is a model input of n features (all real numbers) and $\mathbf{y} = m(\mathbf{x})$ is the corresponding model output. The quantity of interest (QOI) for GSA is a scalar function (a single real number) of the model output, which is a function of the input,

$$q(\mathbf{x}) \equiv q(m(\mathbf{x})) \equiv q(\mathbf{y}). \tag{A1}$$

A.2 Global Domain and Parameterized Local Neighborhood

We define the global domain as

$$\Omega^g = \prod_{1 \leq j \leq n} [f_j^-, f_j^+] \tag{A2}$$

where f_j^- and f_j^+ are lower and upper bounds of the j-th feature. The framework accepts any user-defined Ω^g that may be contextually relevant based on expert advice. For the case studies in this work, Ω^g was chosen as the smallest hypercube containing the training set.

We define a local neighborhood of $\mathbf{x} \in \Omega^g$ parameterized by perturbation factor $\delta \in [0, 1]$ as

$$\Omega(\mathbf{x}, \delta) = \prod_{1 \leq j \leq n} [\max\{f_j^-, x_j - \delta r_j\}, \min\{f_j^+, x_j + \delta r_j\}], \text{where } r_j = f_j^+ - f_j^-. \tag{A3}$$

From Equation A3,

$$\Omega(\mathbf{x}, 0) = \{\mathbf{x}\}, \tag{A4}$$

$$\Omega(\mathbf{x}, 1) = \Omega^g, \text{ and} \tag{A5}$$

$$\Omega(\mathbf{x}, \delta_1) \subseteq \Omega(\mathbf{x}, \delta_2) \text{ if } \delta_1 < \delta_2. \tag{A6}$$

A.3 Identifying Input-Specific Characteristic Perturbation Scale

To avoid arbitrary selection of a perturbation scale, SensX identifies a characteristic perturbation factor $\delta_{\mathbf{x}}^*$ for each input $\mathbf{x}$. Let $D(\mathbf{x}, \delta, n_s)$ be the distribution of QOIs at n_s uniformly random samples within $\Omega(\mathbf{x}, \delta)$. We compute this distribution for all δ in a user-defined discrete set of perturbation factors Δ. By default, $n_s = 1000$ and $\Delta = \text{linspace}(0.02, 1, \text{num} = 50)$. Let $\underline{D}(\mathbf{x}, \delta, n_s)$ and $\overline{D}(\mathbf{x}, \delta, n_s)$ be the 1st and 99th percentiles of $D(\mathbf{x}, \delta, n_s)$, respectively.

We define the characteristic perturbation factor $\delta_{\mathbf{x}}^*$ as the smallest scale beyond which the prediction envelope remains within a user-defined threshold τ_a for all subsequent scales:

$$\delta_{\mathbf{x}}^* = \min_{\delta' \in \Delta} \{\max_{\delta > \delta'} \{\overline{D}(\mathbf{x}, \delta, n_s)\} - \min_{\delta > \delta'} \{\underline{D}(\mathbf{x}, \delta, n_s)\} < \tau_a\} \tag{A7}$$

Intuitively, $\delta_{\mathbf{x}}^*$ is the smallest neighborhood size at which the model's response to perturbations reaches a steady state. The region $\Omega_{\mathbf{x}}^* = \Omega(\mathbf{x}, \delta_{\mathbf{x}}^*)$ constitutes the input-specific neighborhood where the model remains sensitive to feature variations.

A.4 Adapting the Morris Method for Local Attribution Through Grounded Trajectories

In the standard Morris method, trajectories begin at random points in the input space, producing global sensitivity measures. SensX adapts this design for local feature attribution by anchoring all trajectories at the input $\mathbf{x}$ being explained.

For each of n_w perturbation endpoints $\mathbf{e} = (e_1, \ldots, e_n)$ uniformly sampled from $\Omega^*_{\mathbf{x}}$, we define a grounded trajectory as a sequence of points starting at $\mathbf{x}$ and ending at $\mathbf{e}$, where one feature value in $\mathbf{x}$ is replaced by its value in $\mathbf{e}$ at each step. The order in which features are perturbed is randomly selected. Formally, a grounded trajectory $T_{\mathbf{x},\mathbf{e}}$ is a sequence of $n+1$ points

$$T_{\mathbf{x},\mathbf{e}} = (\mathbf{t}_0 = \mathbf{x}, \mathbf{t}_1, \ldots, \mathbf{t}_n = \mathbf{e}), \tag{A8}$$

where $(i_1, \ldots, i_n)$ is a random permutation of feature indices and $\mathbf{t}_k = (t_{k1}, \ldots, t_{kn})$ such that

$$t_{kj} = \begin{cases} e_j & \text{if } j \in \{i_1, i_2, \ldots, i_k\} \\ x_j & \text{otherwise.} \end{cases} \tag{A9}$$

The set of n_w grounded trajectories originating at $\mathbf{x}$ is denoted $\mathcal{T}_{\mathbf{x}}$.

A.5 SensX Values and SensX Vector

The elementary effect of feature i_k along a grounded trajectory $T_{\mathbf{x},\mathbf{e}} \in \mathcal{T}_{\mathbf{x}}$ is defined as

$$s_{i_k}^{T_{\mathbf{x},\mathbf{e}}} = \left| \frac{q(\mathbf{t}_k) - q(\mathbf{t}_{k-1})}{e_{i_k} - x_{i_k}} \right|. \tag{A10}$$

The absolute value follows Campolongo et al. (2007), whose revised measure μ^* prevents cancellation of elementary effects with opposite signs in non-monotonic models. This captures the total sensitivity of each feature, including interaction effects, rather than the net directional effect.

We define the SensX value of feature i_k with respect to input $\mathbf{x}$ as the mean absolute elementary effect over all grounded trajectories,

$$\widehat{s}_{\mathbf{x},i_k} = \frac{1}{n_w} \sum_{T_{\mathbf{x},\mathbf{e}} \in \mathcal{T}_{\mathbf{x}}} s_{i_k}^{T_{\mathbf{x},\mathbf{e}}}. \tag{A11}$$

The SensX vector with respect to input $\mathbf{x}$ is

$$\mathbf{s}_{\mathbf{x}} = (\widehat{s}_{\mathbf{x},1}, \ldots, \widehat{s}_{\mathbf{x},n}). \tag{A12}$$

The SensX rank vector is

$$\mathbf{r}_{\mathbf{x}} = (r_{\mathbf{x},1}, \ldots, r_{\mathbf{x},n}) \tag{A13}$$

where $r_{\mathbf{x},k}$ is the rank of $\widehat{s}_{\mathbf{x},k}$ in $\mathbf{s}_{\mathbf{x}}$, with $r_{\mathbf{x},k} = 1$ assigned to the largest SensX value. Ties are broken by feature index.

A.6 Grouped Sensitivity Analysis

We extend SensX to allow grouping of features. This reduces the trajectory length from the number of features D to the number of groups of features G, while preserving independent perturbations for each feature.

Let $\{I_1, \ldots, I_G\}$ be a partition of the D input features into G non-overlapping groups of equal size. Each feature is assigned an independent perturbation target drawn uniformly within its local perturbation bounds, but all features within a group are perturbed simultaneously in a single trajectory step. For an input $\mathbf{x}$

and its corresponding perturbation target $\mathbf{e}$, a step at group m replaces all feature values in I_m with their perturbed counterparts. The grouped elementary effect is defined as:

$$s_m^{T_{\mathbf{x},\tilde{\mathbf{e}}}} = \left| \frac{q(\mathbf{t}_m) - q(\mathbf{t}_{m-1})}{\|\mathbf{e}_{I_m} - \mathbf{x}_{I_m}\|_2} \right| \tag{A14}$$

where the L_2 norm normalizes by the magnitude of the perturbation in the subspace of the m-th group. As with the standard analysis, the group ordering is randomized across trajectories, and the final grouped SensX value is the mean absolute finite difference over n_w trajectories.

The current implementation restricts grouped attribution to equal-sized groups because the expected L_2 norm of a random perturbation grows as $O(\sqrt{d})$ with group size d, making sensitivities across groups of different sizes incomparable. Extending the framework to unequal group sizes with appropriate normalization factors is left to future work.

A.7 Perturbation Validation Protocol

To validate that a feature ranking concentrates model sensitivity into its highest-ranked features, we perform a top-k/bottom-k perturbation analysis. Given a ranking of n features, for each value of k in a specified set, the k highest-ranked (top-k) or k lowest-ranked (bottom-k) features are perturbed: each selected feature is replaced by a value drawn uniformly at random within the local perturbation bounds defined by δ^*, while all remaining features are held fixed. For each k, N_p independent perturbations are generated and the QOI is recorded. If the ranking is effective, top-k perturbation produces a rapid change in QOI at small k, while bottom-k perturbation has little effect until the majority of features are perturbed.

To summarize each perturbation curve, we compute the normalized area under the curve (AUC). The k-axis is normalized to $[0, 1]$ by dividing by the total number of features, and the QOI at each k (median over N_p perturbations) is divided by the unperturbed baseline prediction. For top-k, lower AUC indicates that the method's highest-ranked features reduce the prediction faster. For bottom-k, higher AUC indicates that the method's lowest-ranked features can be perturbed with less effect.

B Perturbation Factor Grid Selection

For synthetic benchmarks, δ^* was close to 1 for all inputs, so a uniform partition of $[0, 1]$ provided sufficient resolution and grid refinement did not change the result. For the image-based tasks of vision transformers and spatial transcriptomics, a uniform grid was likewise adequate, as δ^* fell well above the minimum grid spacing.

For single-cell transcriptomics, the prediction envelope changed rapidly at small perturbation magnitudes. Replacing the uniform grid with a log-spaced Δ ($\delta \in [10^{-4}, 1]$) concentrated resolution at the fine scales where the model's sensitivity was steepest and yielded stable estimates of δ^*.

In general, we recommend starting with a uniform grid and switching to log-spaced Δ if δ^* clusters near the grid's lower bound across inputs. The perturbation validation protocol (Appendix A.7) provides the ultimate check on whether the resulting rankings are meaningful regardless of grid choice.

C Future Extensions

The uniform random sampling in the current implementation could be replaced by precomputed low-discrepancy quasi-random sequences (e.g., Sobol sequences) to improve convergence rates without additional computational overhead. This would connect SensX's sampling strategy to the quasi-Monte Carlo literature used in classical sensitivity analysis and in the Sobol-based attribution method of Fel et al. (2021).

The current implementation restricts grouped attribution to equal-sized groups (Appendix A.6). Extending the framework to unequal group sizes with appropriate normalization factors would enable hierarchical attribution across natural grouping structures of varying granularity.

D Supplementary Figures

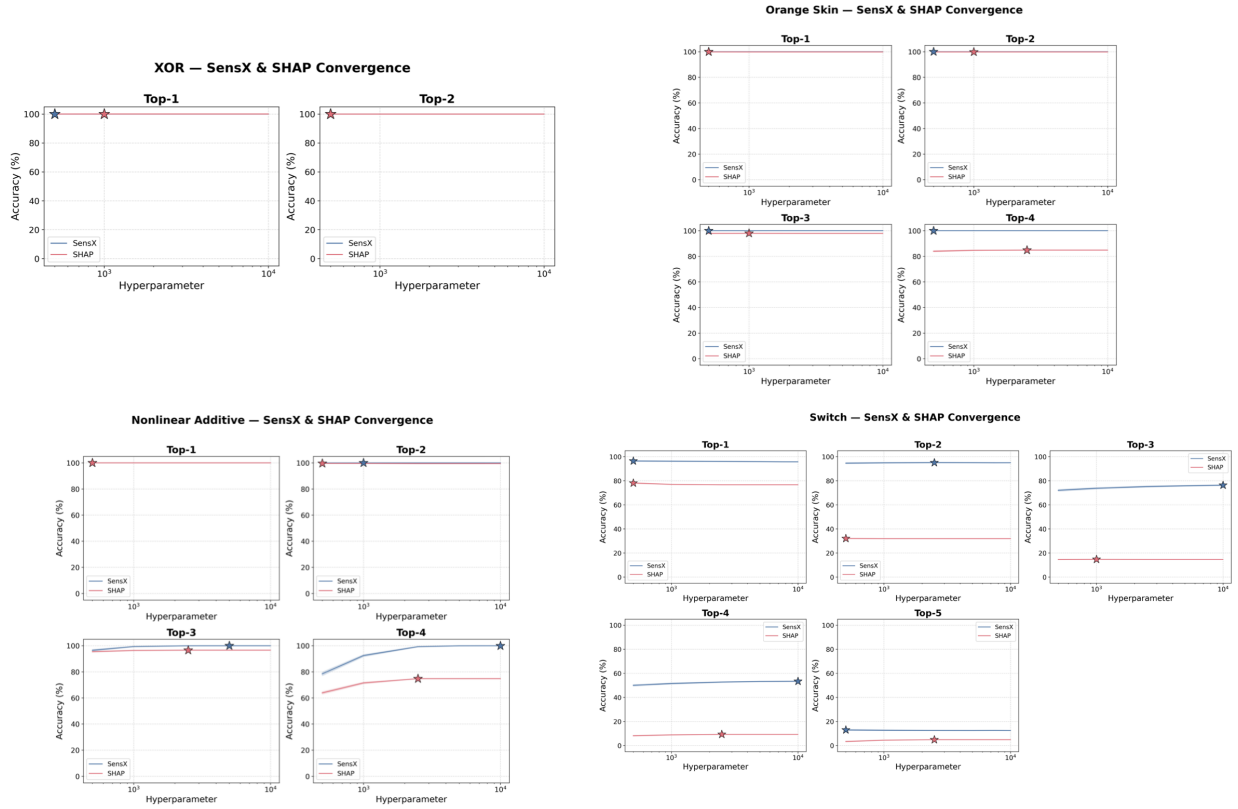


Figure D1: **SensX and KernelSHAP convergence across hyperparameters on synthetic benchmarks.** Mean top-k accuracy $\pm$ 1 standard deviation (100 repetitions per configuration) as a function of each method's hyperparameter for **(A)** XOR ($k = 1, 2$), **(B)** Orange Skin (k = 1–4), **(C)** Nonlinear Additive (k = 1–4), and **(D)** Switch (k = 1–5). Stars mark the best-performing hyperparameter for each method, corresponding to the values reported in the bar plots. Both methods are largely insensitive to hyperparameter choice: accuracy curves are flat across the range tested, with the exception of SensX on Nonlinear Additive at top-4, where accuracy increases with the number of walks.

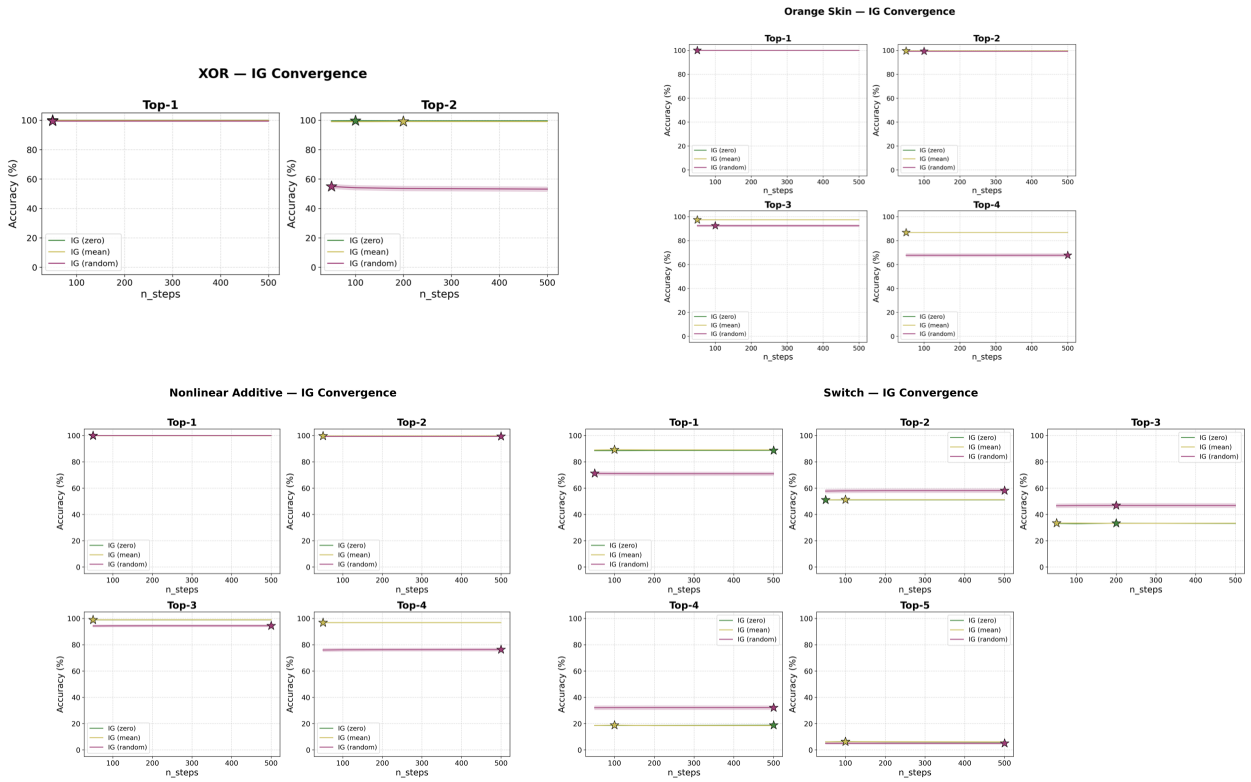


Figure D2: **Integrated gradients convergence across integration steps on synthetic benchmarks.** Mean top-k accuracy as a function of the number of integration steps n_{steps} for three baseline choices—zero vector (green), training-set mean (yellow), and random training sample (pink)—on **(A)** XOR ($k = 1, 2$), **(B)** Orange Skin (k = 1–4), **(C)** Nonlinear Additive (k = 1–4), and **(D)** Switch (k = 1–5). Stars mark the best-performing configuration for each baseline type. Accuracy is largely insensitive to n_{steps} across all datasets, indicating that the path integral is well-approximated even at 50 steps. Performance differences are driven by baseline choice rather than integration resolution, with the random baseline consistently matching or exceeding the deterministic baselines on the Switch dataset. Error bands for the random baseline show $\pm$ 1 standard deviation across 100 runs; zero and mean baselines are deterministic.

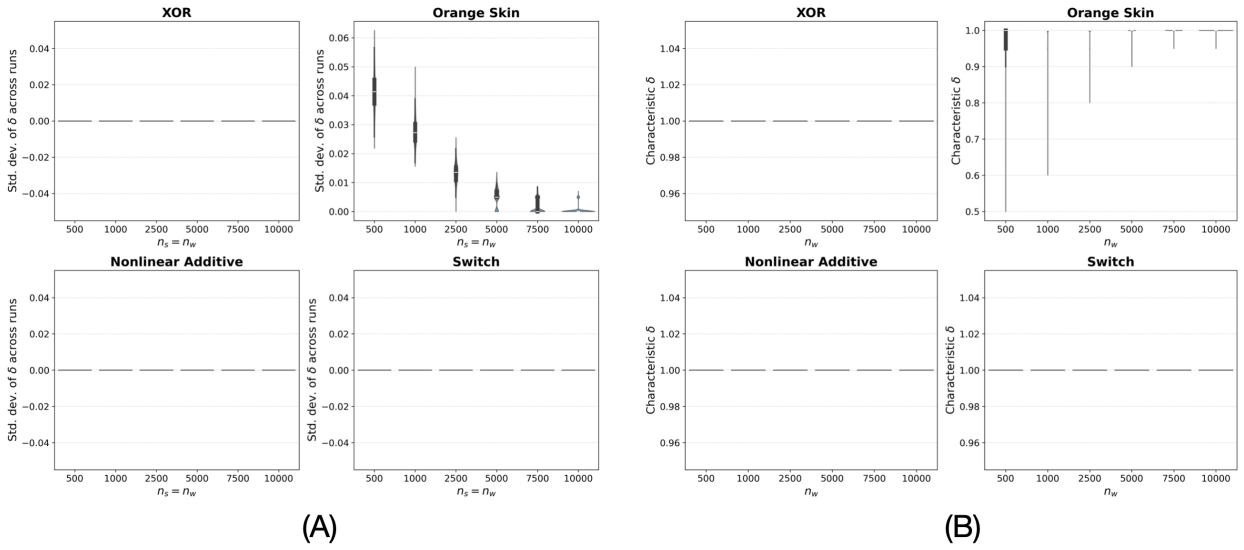


Figure D3: **Characteristic perturbation scale across synthetic datasets.** (A) Per-sample standard deviation of δ^* across 100 independent runs as a function of the number of samples ($n_s = n_w$). Only the Orange Skin dataset exhibits non-trivial variability, which decreases with increasing n_w. (B) Distribution of δ^* values across all samples and runs at each n_w. On the XOR, Nonlinear Additive, and Switch datasets, δ^* equals 1 for all inputs regardless of n_w. On the Orange Skin dataset, δ^* is concentrated near 1 but shows a tail of lower values that narrows as n_w increases.

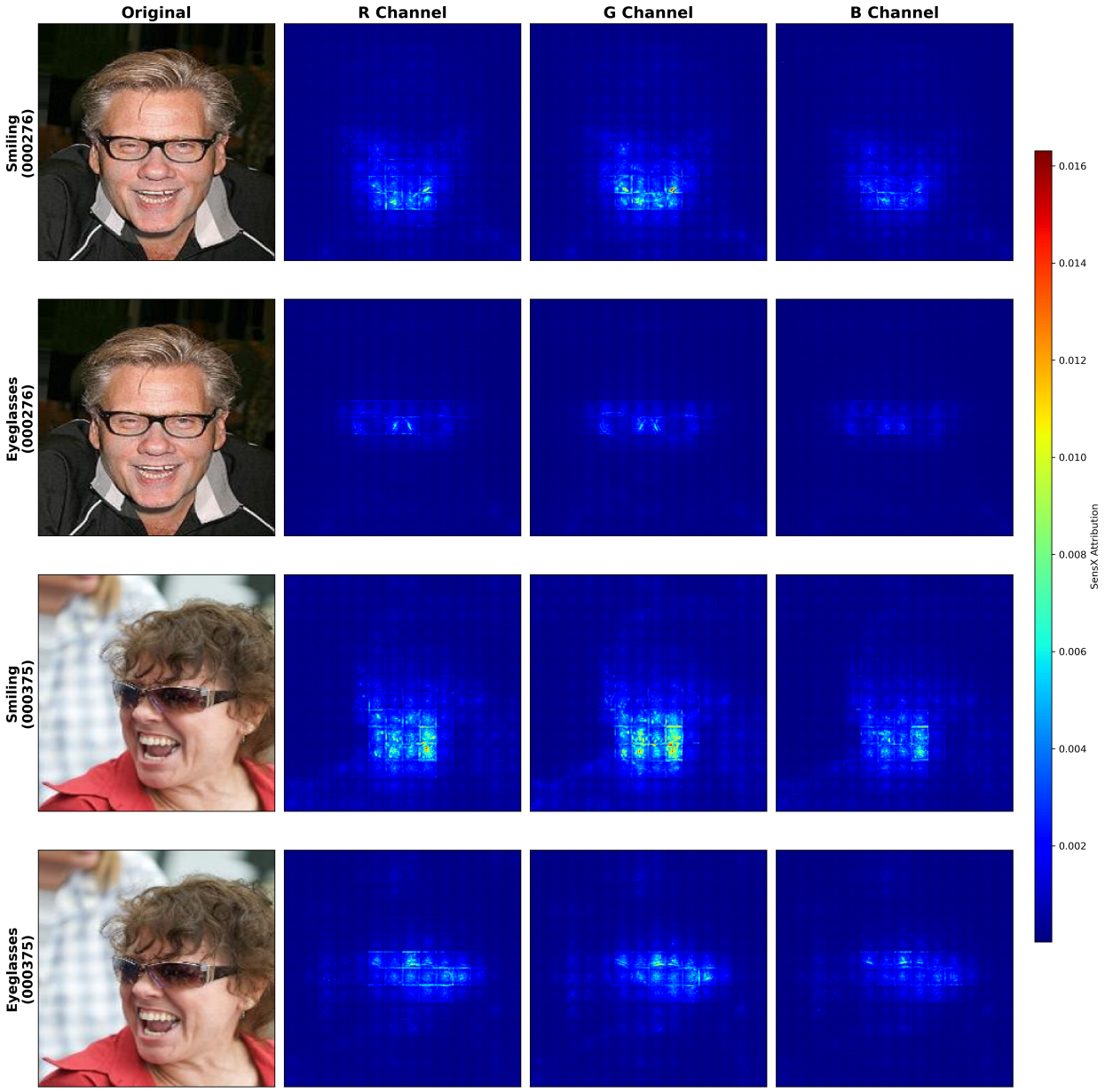


Figure D4: **Per-channel SensX attribution heatmaps for ViT models.** Each row corresponds to one (image, model) pair. Columns show the original image followed by SensX attribution values for the red, green, and blue channels independently. All heatmaps share a common color scale. Attribution patterns are consistent across color channels, confirming that the three channels at a given pixel location tend to receive similar attribution values. Grid artifacts aligned with the ViT's 16×16 patch tokenization are visible across all panels.

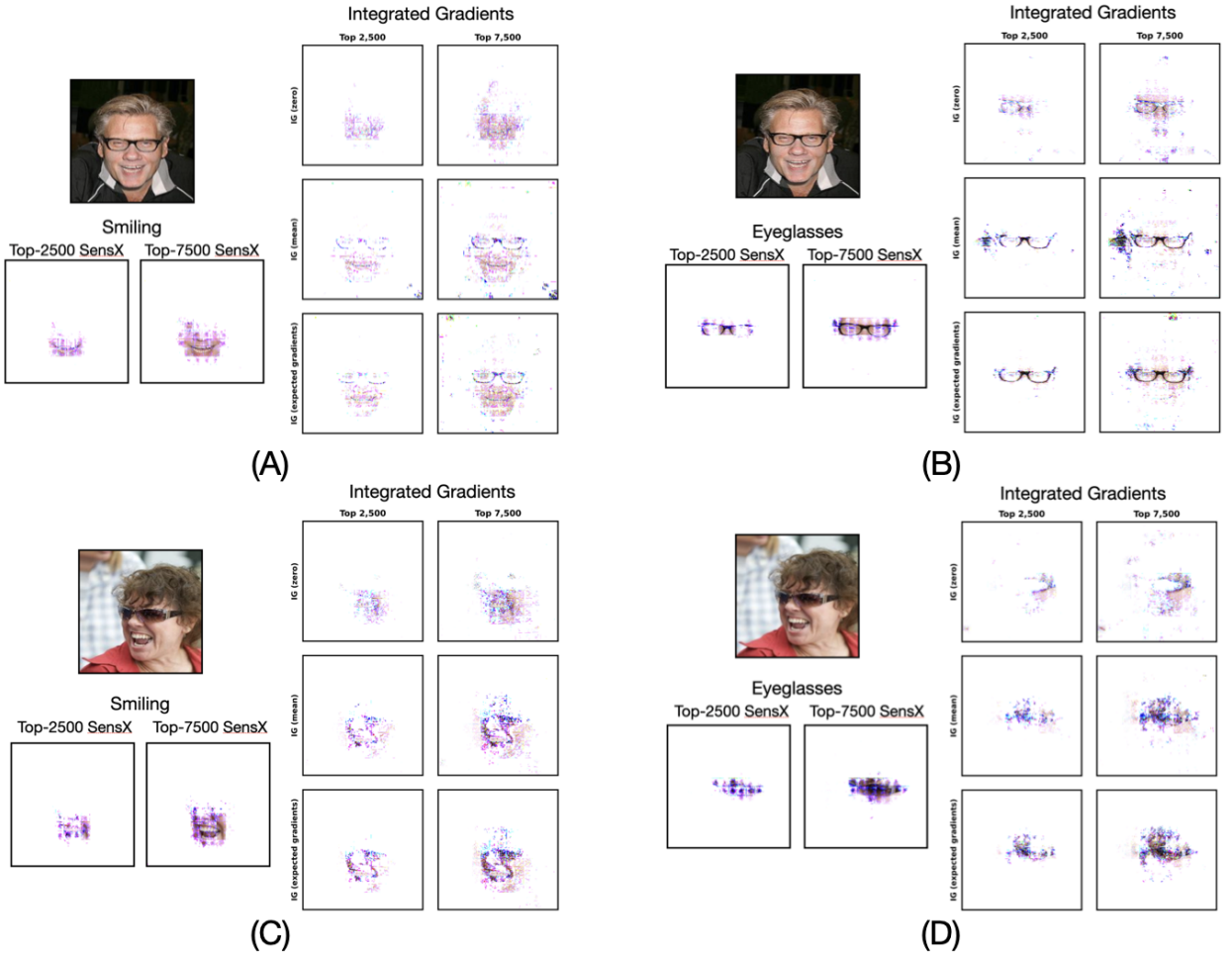


Figure D5: **SensX and IG top-k masks for all (image, model) combinations.** Each quadrant shows one (image, model) combination with SensX masks (left) and IG masks under three baseline choices (right). **(A)** Image 000276, Smiling. **(B)** Image 000276, Eyeglasses. **(C)** Image 000375, Smiling. **(D)** Image 000375, Eyeglasses. SensX consistently localizes to task-relevant regions across all combinations. IG attributions vary with baseline choice and are less spatially coherent than SensX. On the smiling model (A, C), the mean baseline and expected gradients attribute to the eyeglass frames despite this model being fine-tuned independently from the eyeglasses model.

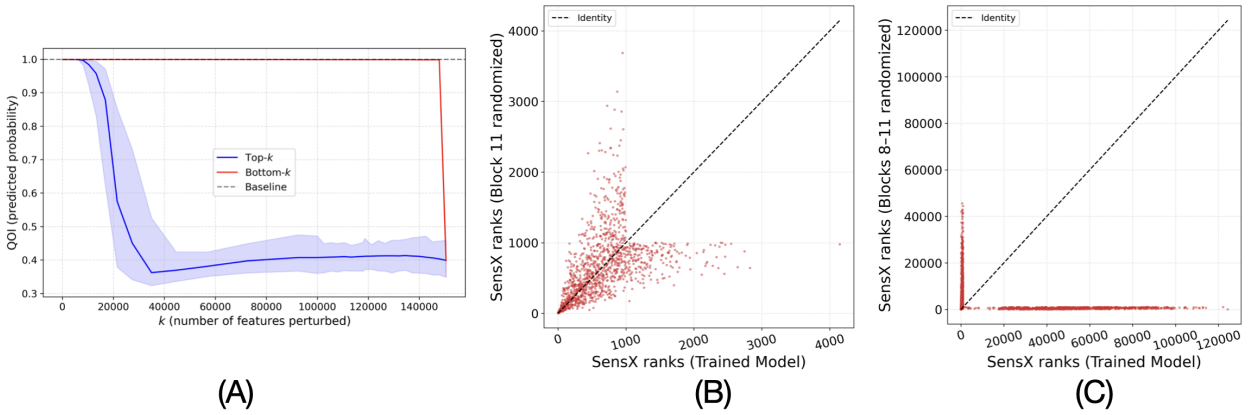


Figure D6: **Perturbation analysis and model randomization confirm SensX feature ranking.** All panels show results for the Eyeglasses model on image 000276. (A) Features are perturbed within the characteristic perturbation scale from highest to lowest (top-k, blue) and lowest to highest (bottom-k, red) SensX rank. Perturbing top-ranked features produces a rapid decline in QOI, while perturbing over 130,000 bottom-ranked features has no measurable effect. Shaded regions denote the 1st–99th percentile over 1,000 random perturbations. (B,C) Rank comparison between the trained model and models with progressively randomized weights. Each point represents a feature in the top 1,000 of either map. (B) Randomizing block 11 produces moderate rank disruption. (C) Randomizing blocks 8–11 destroys the ranking: top-ranked features in the trained model scatter to ranks above 20,000. Equivalent perturbation analyses for all four (image, model) combinations are shown in Supplementary Figure D7.

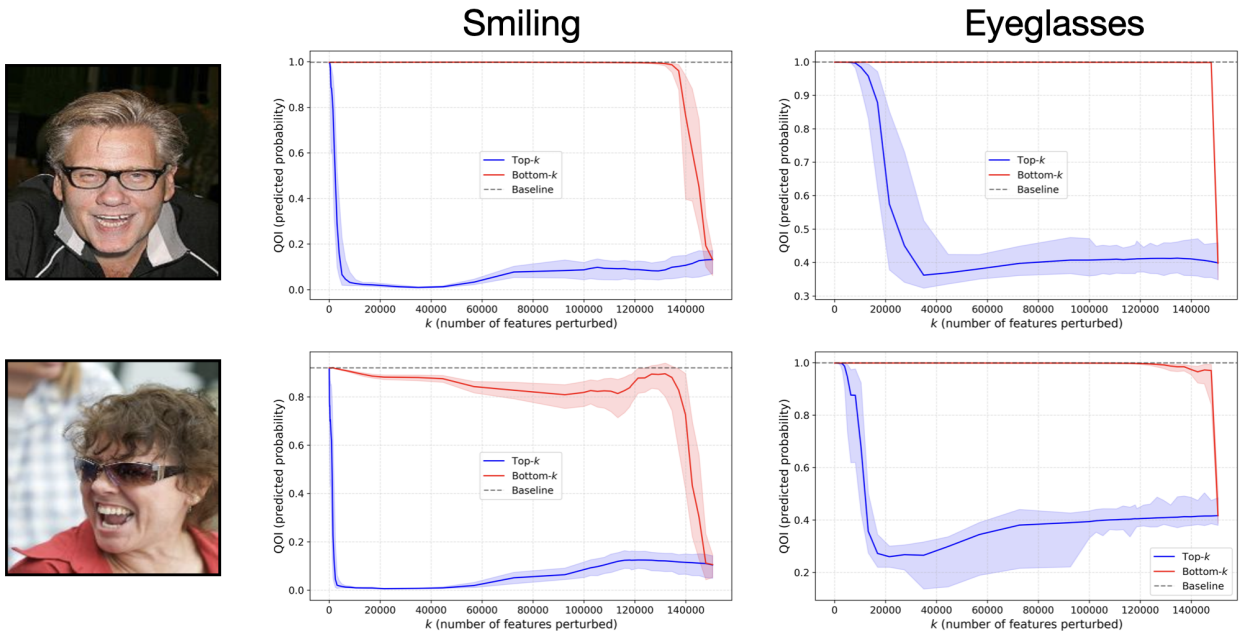


Figure D7: **Perturbation analysis confirms SensX feature ranking across all (image, model) combinations.** Each panel shows the QOI (predicted probability) as a function of the number of features perturbed within the characteristic perturbation scale, from highest to lowest (top-k, blue) and lowest to highest (bottom-k, red) SensX rank. Shaded regions denote the 1st–99th percentile over 1,000 random perturbations. Dashed line indicates the unperturbed baseline. Across all four cases, perturbing top-ranked features produces a rapid decline in QOI, while perturbing the majority of bottom-ranked features has no measurable effect. Both curves converge when all 150,528 features are perturbed.

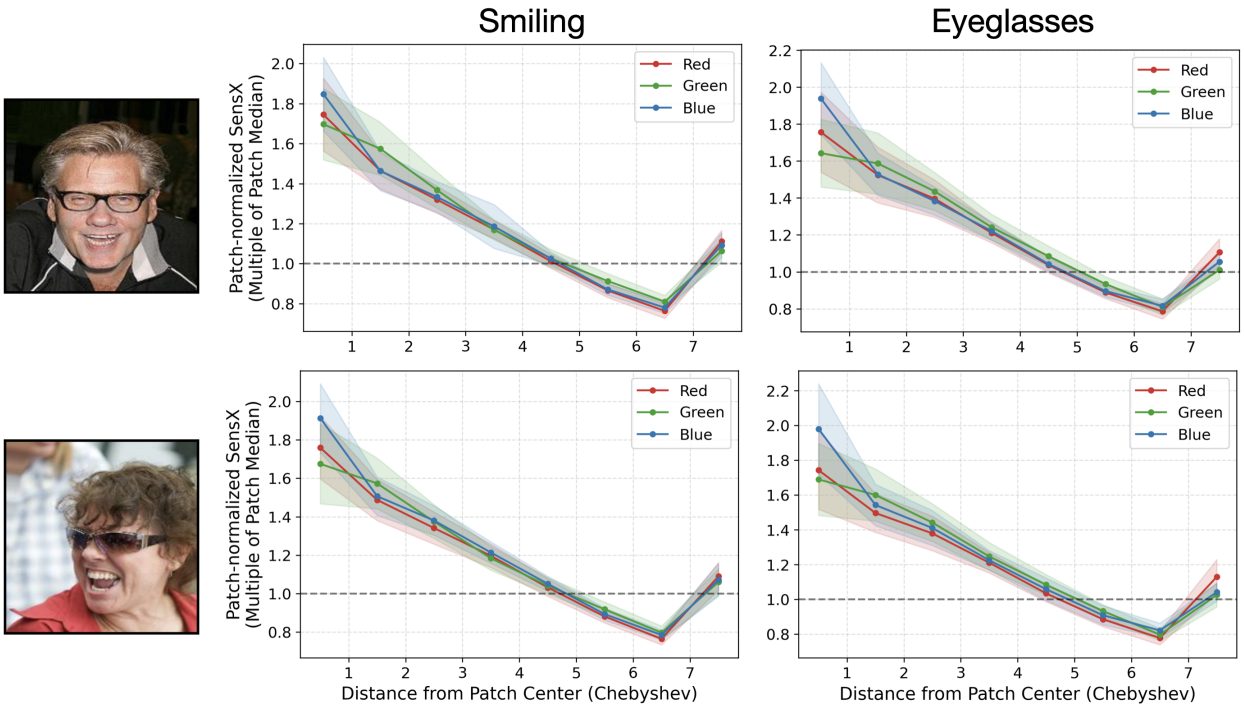


Figure D8: **Intra-patch spatial bias is consistent across images and models.** Patch-normalized SensX averaged across all 196 patches as a function of Chebyshev distance from the patch center, shown for both images (rows) and both models (columns). Shaded regions denote ±1 standard deviation. The profile shape — peak at center, decay to a minimum near distance 6, rebound at the patch boundary — is consistent across all four (image, model) combinations and all three color channels.

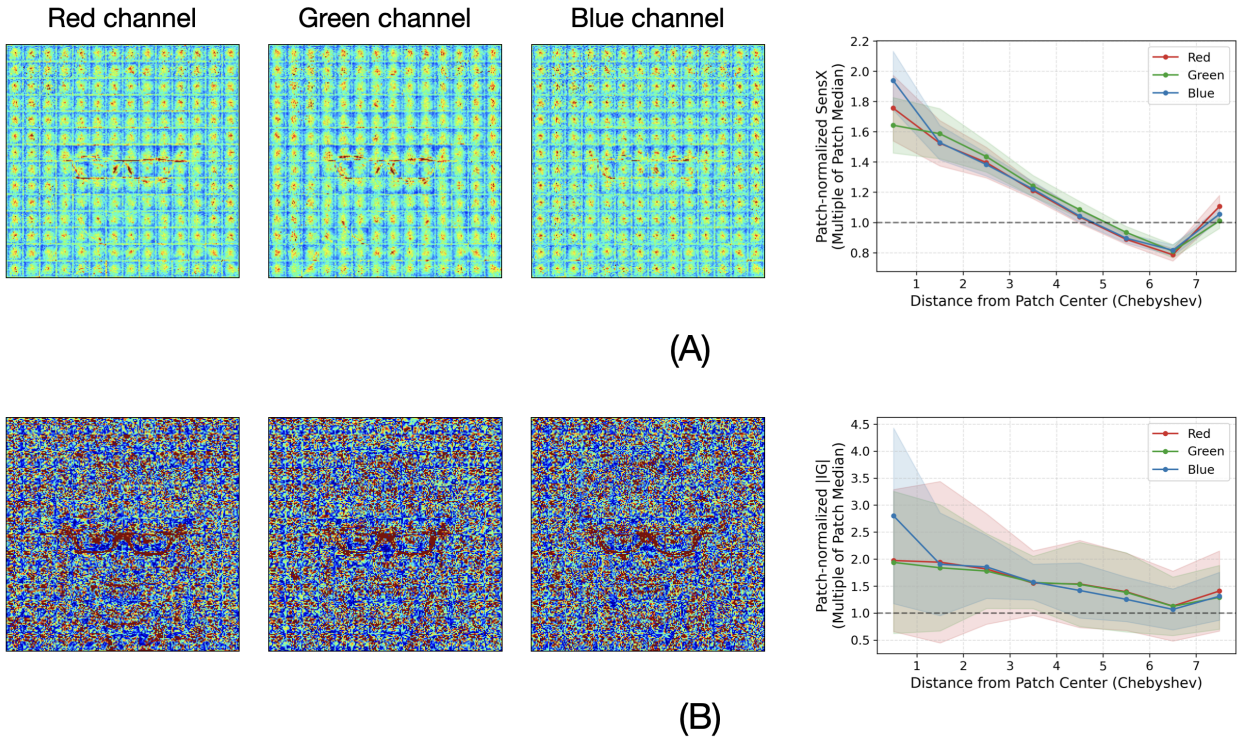


Figure D9: **IG does not resolve the intra-patch bias identified by SensX.** (A) SensX and (B) IG (expected gradients) for image 000276 under the Eyeglasses model. Left three columns: patch-median-normalized attribution heatmaps per color channel. Right column: patch-normalized attribution averaged across all 196 patches as a function of Chebyshev distance from the patch center; shaded regions denote ± 1 standard deviation. SensX reveals a systematic intra-patch pattern—center peak, decay to a minimum near distance 6, rebound at the patch boundary—with narrow cross-patch variance. The IG heatmaps show no visible grid structure, and the IG distance profile exhibits a coarse center bias with substantially wider variance that obscures the non-monotonic pattern resolved by SensX.

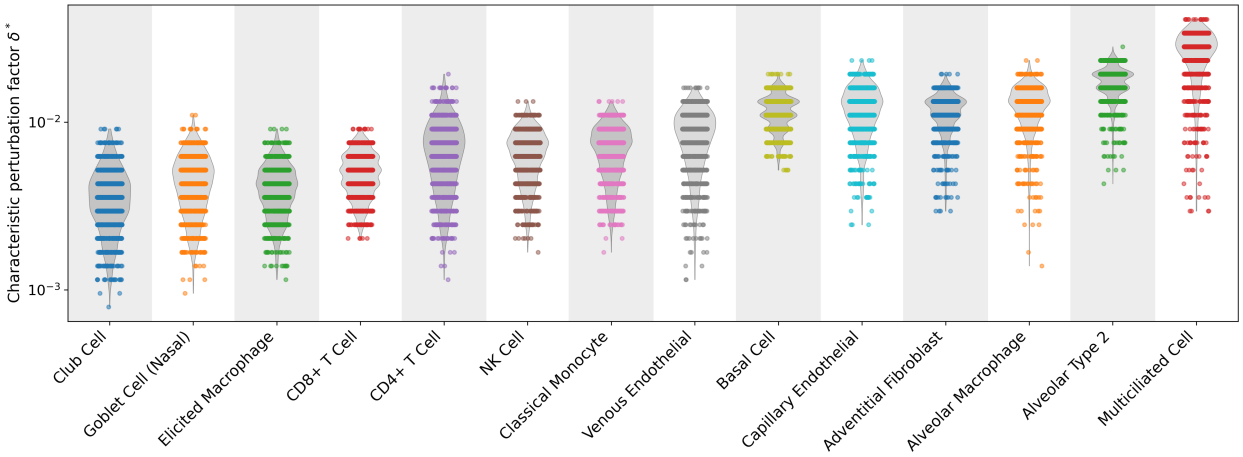
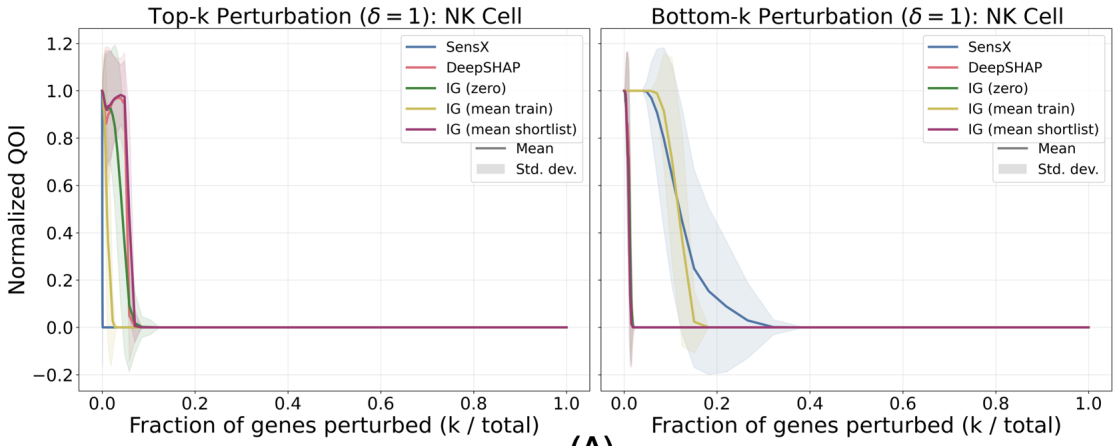


Figure D10: **Characteristic perturbation scale δ^* varies across and within cell types.** Distribution of δ^* for 1,000 high-confidence test cells (predicted probability ≥ 0.99) per cell type, shown as violin plots with overlaid individual cells on a logarithmic scale. δ^* spans approximately two orders of magnitude (10^{-3} to 10^{-1}), with medians varying across cell types. The within-cell-type spread confirms that a fixed perturbation scale would be a poor approximation. SensX adapts δ^* per cell, capturing the local sensitivity structure learned by each classifier. Cell types are ordered by median δ^*.



(A)

	Top-k AUC (↓ lower is better) ($\delta = 1$)					Bottom-k AUC (↑ higher is better) ($\delta = 1$)				
	SensX	DeepSHAP	IG (zero)	IG (mean train)	IG (mean shortlist)	SensX	DeepSHAP	IG (zero)	IG (mean train)	IG (mean shortlist)
Elicited Macrophage	**0.00**	0.09	0.06	0.00	0.10	0.06	0.00	0.00	**0.06**	0.00
CD4⁺ T Cell	**0.00**	0.05	0.04	0.00	0.02	0.47	0.01	0.01	**0.48**	0.01
NK Cell	**0.00**	0.05	0.04	0.01	0.06	**0.13**	0.01	0.01	0.12	0.01
Goblet Cell	**0.00**	0.11	0.06	0.02	0.12	**0.08**	0.00	0.00	0.06	0.00
Basal Cell	**0.00**	0.10	0.07	0.00	0.11	**0.23**	0.01	0.01	0.14	0.01
Club Cell	**0.00**	0.09	0.05	0.01	0.09	**0.08**	0.00	0.00	0.06	0.00
Capillary EC	**0.00**	0.06	0.05	0.01	0.01	**0.24**	0.02	0.02	0.16	0.02
Classical Monocyte	**0.00**	0.07	0.05	0.04	0.08	0.07	0.01	0.01	**0.11**	0.01
AT2 Cell	**0.00**	0.07	0.08	0.01	0.07	0.09	0.02	0.02	**0.10**	0.02
Venous EC	**0.00**	0.08	0.05	0.02	0.02	**0.18**	0.01	0.01	0.11	0.01
CD8⁺ T Cell	**0.00**	0.10	0.04	0.02	0.11	0.05	0.00	0.00	**0.07**	0.00
Adventitial Fibroblast	**0.00**	0.04	0.06	0.01	0.02	**0.23**	0.01	0.01	0.13	0.01
Alveolar Macrophage	**0.00**	0.06	0.07	0.04	0.06	**0.16**	0.02	0.02	0.14	0.02
Multiciliated Cell	**0.00**	0.05	0.09	0.04	0.03	**0.16**	0.02	0.03	0.12	0.03

(B)

Figure D11: **Perturbation validation at $\delta = 1$ (global perturbation range).** (A) Top-k (left) and bottom-k (right) perturbation curves for natural killer cells, with each gene perturbed across its full global expression range. For each cell, the median predicted probability across 1,000 perturbations is recorded, normalized by the unperturbed baseline. Curves show the mean across 1,000 cells; shaded regions denote $\pm$ one standard deviation. (B) Normalized AUC of the perturbation curves for all 14 cell types. The best value per cell type is shown in bold. Cell types are sorted by SensX top-k AUC. SensX top-k AUC is 0.00 for all cell types, confirming that its gene rankings remain valid under global perturbation.

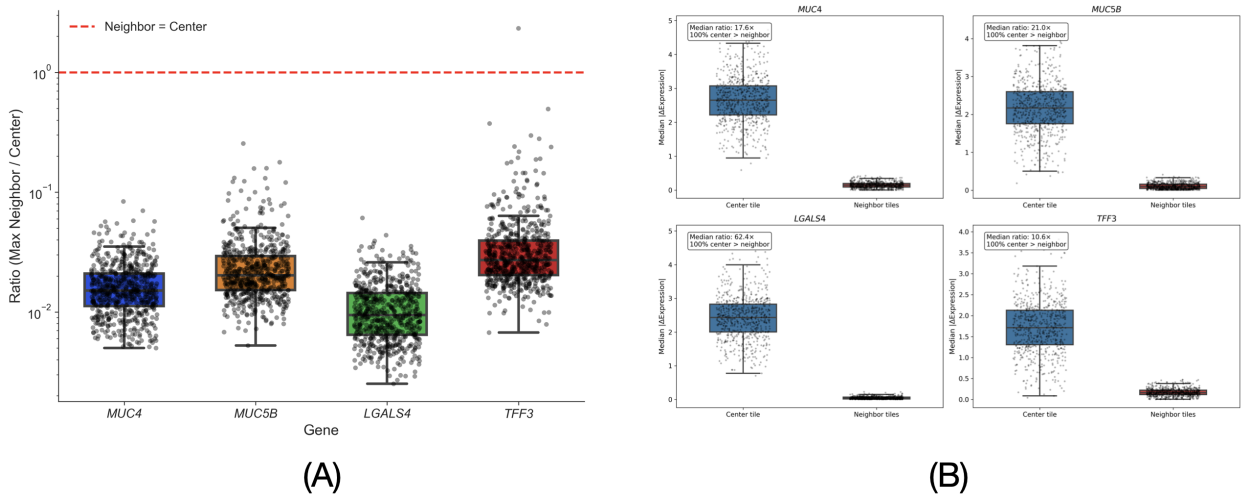


Figure D12: **Center-tile dominance in DeepSpot predictions.** (A) Ratio of the maximum neighboring-tile SensX to the center-tile SensX. The dashed red line indicates equal sensitivity. Nearly all ratios fall well below 1, with a median of 0.018. (B) Independent perturbation validation. For each spot-gene pair, the center tile or all eight neighbor tiles are perturbed within the characteristic perturbation scale (1,000 perturbations per condition), and the median absolute change in predicted log-expression is recorded. Perturbing the center tile produces substantially larger prediction changes than perturbing all neighbors across all four genes, with a median ratio of 20× and center-tile perturbation exceeding neighbor perturbation in 99.9% of spot-gene pairs.

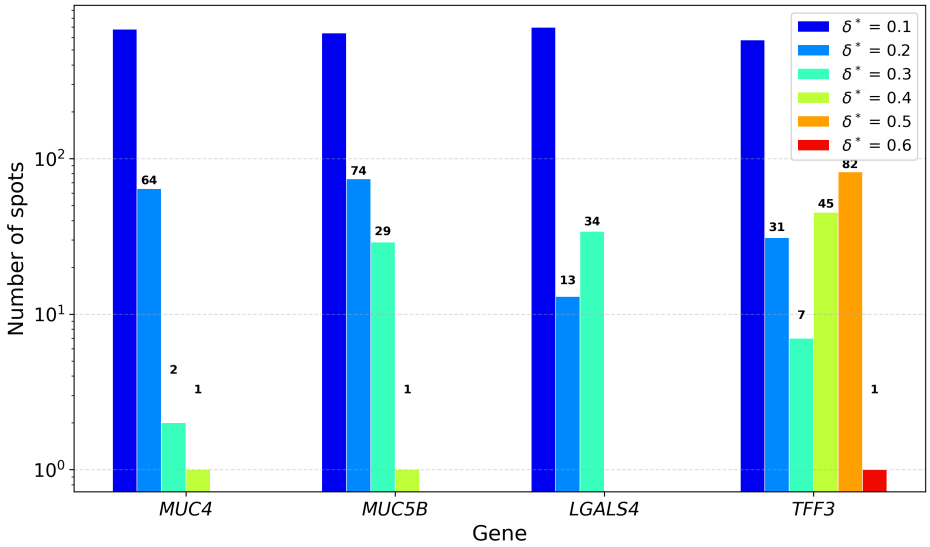


Figure D13: **Characteristic perturbation scale across spots in the histopathology case study.** Number of spots at each discrete δ^* value for four genes. The majority of spots have $\delta^* = 0.1$, the minimum value evaluated, across all genes. *TFF3* shows the broadest distribution, with 82 spots at $\delta^* = 0.5$.

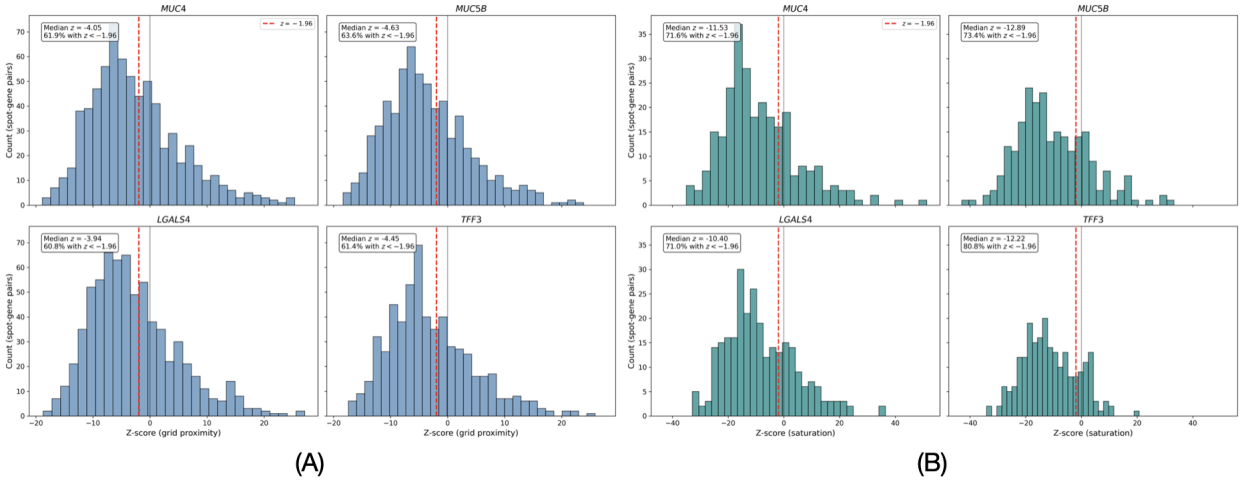


Figure D14: **Per-gene statistical confirmation of subspot grid bias and staining-saturation dependence.** (A) Distribution of z-scores from the subspot grid proximity test, shown separately for each gene. For each spot-gene pair, the mean distance from the top-500 SensX pixels to the nearest internal grid line is compared to a permutation null of 500 randomly selected pixels. Negative z-scores indicate that high-attribution pixels are significantly closer to grid boundaries than expected by chance ($z < -1.96$ corresponds to $p < 0.025$, one-tailed). (B) Distribution of z-scores from the saturation test, restricted to spot-gene pairs without significant grid bias. For each spot, the mean HSV saturation of the top-500 SensX pixels is compared to a permutation null of 500 randomly selected pixels. Negative z-scores indicate that high-attribution pixels have significantly lower saturation (lighter staining) than expected by chance. Dashed red line: $z = -1.96$ ($p = 0.025$). Both effects are consistent across all four genes.

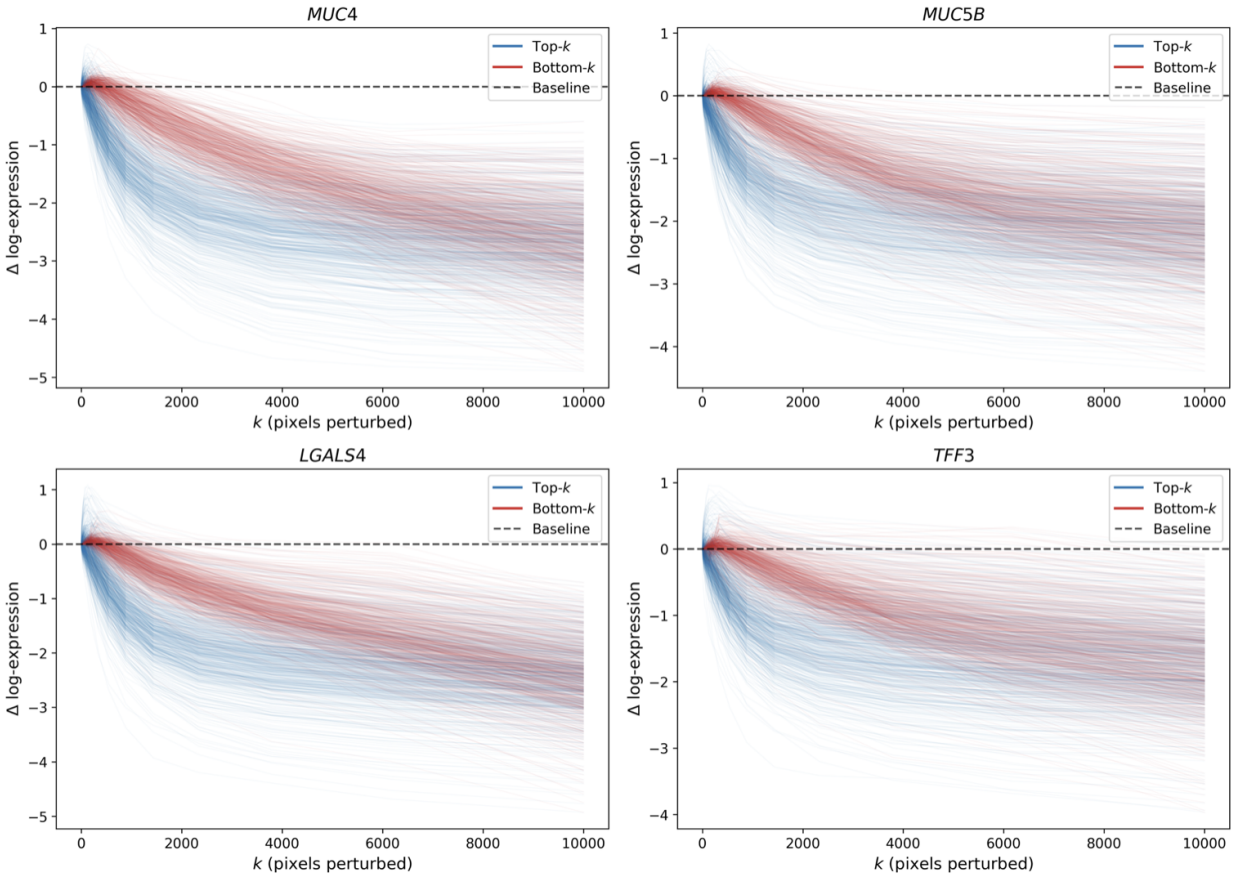


Figure D15: **Pixel-level perturbation validation of SensX ranking.** Change in predicted log-expression (Δ) when perturbing the top-k (blue) or bottom-k (red) SensX-ranked pixels within the characteristic perturbation scale, for 20 log-spaced values of k from 1 to 10,000 (100 perturbations per k). Each curve represents one spot. Perturbing a small number of top-ranked pixels produces large prediction changes, while perturbing thousands of bottom-ranked pixels has minimal effect, confirming that the pixel-level SensX ranking concentrates predictive importance into a small subset of pixels. Dashed black line: baseline (no perturbation).

E Ranking Convergence Analysis

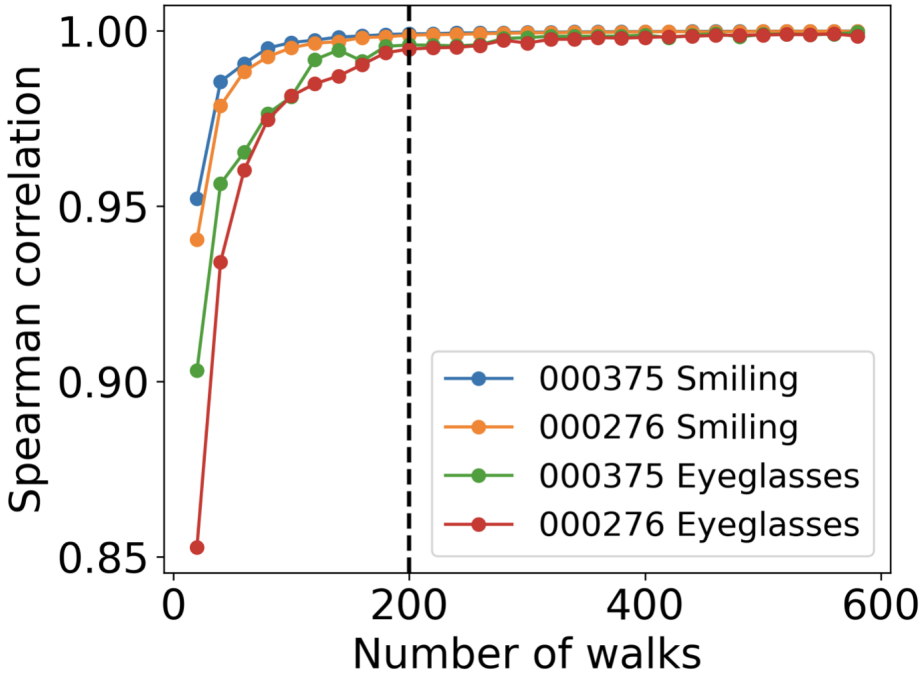


Figure E1: **SensX ranking convergence for the ViT case study.** We estimate SensX values cumulatively in batches of 20 coordinate-walks. At each cumulative walk count n_w, we compute the Spearman rank correlation between the feature rankings (higher SensX value gets a larger rank) obtained with n_w walks and with $n_w - 20$ walks (i.e., after adding one additional batch). Curves are shown for the four (image, model) combinations. Rankings stabilize rapidly. Correlations exceed 0.99 by ≈ 200 walks (dashed line), indicating diminishing returns from additional walks.

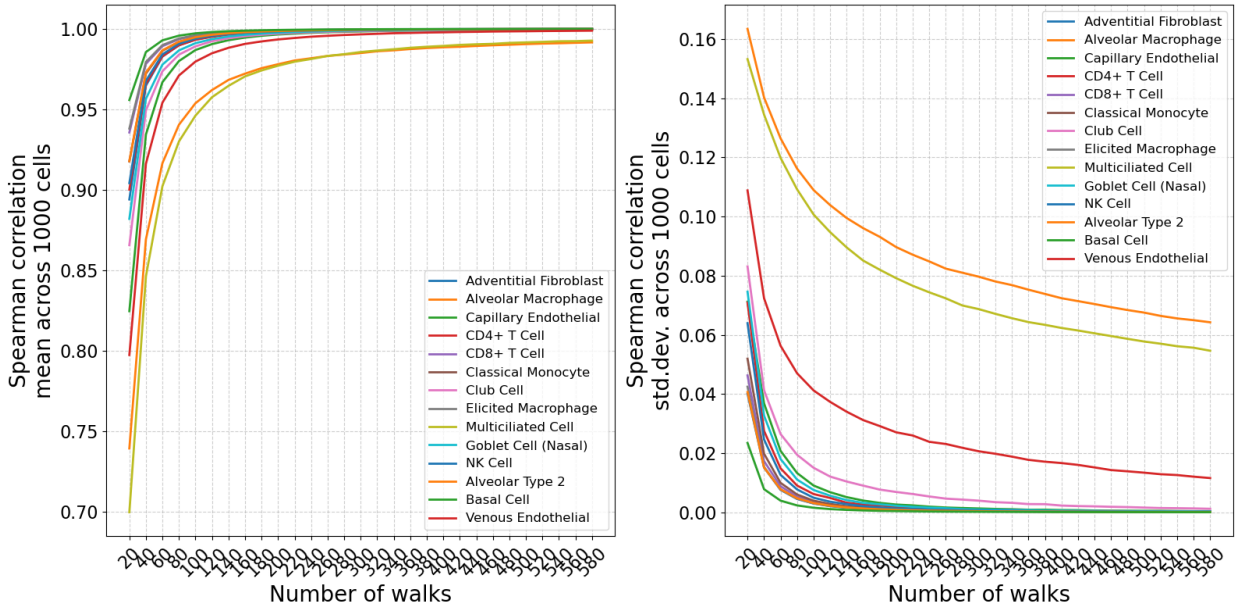


Figure E2: **Convergence of SensX gene rankings in single-cell classification.** SensX values are estimated cumulatively in batches of 20 coordinate-walks. At each cumulative walk count n_w, we compute the Spearman rank correlation between the gene rankings obtained with n_w walks and with $n_w - 20$ walks (i.e., after adding one additional batch). Curves summarize 1,000 cells per cell type. (A) Mean correlation across cells. (B) Standard deviation across cells. Rankings stabilize rapidly for most cell types and continue to tighten with additional walks.

F Case Study Details

F.1 Synthetic Datasets

Samples are generated from a ten-dimensional standard Gaussian distribution. Each sample, $\mathbf{x} = (x_1, \ldots, x_{10})$, is labeled $b \in \{0, 1\}$ based on the following criteria for three of the four synthetic datasets Chen et al. (2018):

- XOR: $P(b = 1) \propto x_1 x_2 \quad (k = 2$ important features$)$
- Orange skin: $P(b = 1) \propto \sum_{1 \le i \le 4} x_i^2 - 4 \quad (k = 4$ important features$)$
- Nonlinear additive: $P(b = 1) \propto -100 \sin(0.2\, x_1) + |x_2| + x_3 + e^{-x_4} - 2.4 \quad (k = 4$ important features$)$

The switch dataset is a mixture of data samples from two different generative processes. x_{10} is generated from a mixture of two Gaussians centered at ± 3 with equal probability. If x_{10} is generated from the Gaussian centered at $+3$, then x_1 to x_4 are used to label the sample based on the orange skin model. Otherwise, x_5 to x_8 are used to label the sample based on the nonlinear additive model.

For all datasets, $N = 100{,}000$ samples were generated and split into 80% training and 20% test sets. The test set was further divided equally into validation and held-out test subsets.

Model Architecture and Training. A feedforward neural network with three hidden layers (200, 100, and 50 units) and ReLU activations was trained independently on each dataset. The output layer produces a single logit, and binary cross-entropy with logits was used as the loss function. Models were trained for 50 epochs using the AdamW optimizer with a learning rate of 10^{-3}, weight decay of 10^{-4}, and a batch size of 64. The model with the highest validation F1 score was selected for downstream analysis. Feature attributions were computed on a subset of up to 1,000 test samples for which the trained model predicted class 1 with greater than 99% confidence.

SensX Configuration. Sensitivity was computed using $n_w = n_s \in \{500, 1000, 2500, 5000, 7500, 10{,}000\}$ perturbation samples. The stability profile was evaluated over 20 equally spaced perturbation magnitudes $\delta \in [0.05, 1.0]$, and the characteristic δ was selected using a stability threshold of $\tau_a = 0.1$. Perturbation bounds were set to the feature-wise minimum and maximum across the full dataset.

KernelSHAP Configuration. KernelSHAP was computed using a background dataset of $n_{\text{background}} = 100$ training samples summarized via K-means clustering, with coalition sample budgets of $n_{\text{samples}} \in \{500, 1000, 2500, 5000, 7500, 10{,}000\}$. Feature importance was taken as the absolute value of SHAP values.

Integrated Gradients Configuration. Integrated gradients (IG) (Sundararajan et al., 2017) were computed using the Captum library (Kokhlikyan et al., 2020) with Gauss–Legendre quadrature and $n_{\text{steps}} \in \{50, 100, 200, 500\}$ integration steps. Three baseline choices were evaluated: the zero vector, the training-set mean, and a random training sample drawn independently per input. The zero and mean baselines are deterministic and were run once per configuration. The random baseline was repeated over 100 independent runs to match the evaluation protocol of SensX and KernelSHAP. Feature importance was taken as the absolute value of IG attributions.

Evaluation. For SensX and KernelSHAP, each configuration was repeated over 100 independent runs to assess variability. Attribution accuracy was evaluated using a top-k criterion. Prediction is scored as correct at rank k only if the k highest-ranked features all belong to the ground-truth set $\mathcal{S}$,

$$\text{Acc@}k = \frac{1}{N} \sum_{i=1}^{N} \mathbf{1}\Big[\Big\{\hat{f}_1^{(i)}, \ldots, \hat{f}_k^{(i)}\Big\} \subseteq \mathcal{S}\Big]. \tag{F1}$$

This metric is order-invariant. It requires the correct set of features to appear in the top k but does not penalize their relative ranking. For the Switch dataset, accuracy was computed separately for each subpopulation

against its respective ground-truth set ($\mathcal{S}_{\text{orange}} = \{1, 2, 3, 4, 10\}$ and $\mathcal{S}_{\text{additive}} = \{5, 6, 7, 8, 10\}$), then combined across all samples. Bar plots report the mean accuracy at the best-performing hyperparameter for each method and convergence across hyperparameters is shown in Supplementary Figures 1 and 2.

F.2 Vision Transformer (ViT)

A pretrained ViT-Base model (Dosovitskiy et al., 2020) was downloaded from `google/vit-base-patch16-224-in21k` and fine-tuned to identify smiling and eyeglasses (two separate binary classifiers) using the Large-scale CelebFaces Attributes (CelebA) dataset (Liu et al., 2015) of 202,599 images. Details of model fine-tuning are available at the SensX code repository. Input images are 224×224 pixels across three color channels (RGB). Each feature is an individual color channel at a pixel location. The QOI is the predicted probability of belonging to the class.

SensX Configuration. Global perturbation bounds were set to $[0, 1]$, corresponding to the normalized pixel intensity range. The stability profile was evaluated over 50 equally spaced perturbation magnitudes $\delta \in [0.02, 1.0]$ with $n_s = 1{,}000$ samples. The characteristic δ was selected using a stability threshold of $\tau_a = 0.1$. Sensitivity was computed using $n_w = 600$ and batch-size 1000.

Integrated Gradients Configuration. IG was computed using the Captum library (Kokhlikyan et al., 2020) with Gauss–Legendre quadrature. Integration steps of $n_{\text{steps}} \in \{100, 200, 500\}$ were evaluated. The convergence delta (difference between the sum of attributions and the predicted output difference) was small at $n_{\text{steps}} = 500$, which was used for all reported results. Three baseline choices were evaluated. The zero baseline was set to the preprocessed zero image (accounting for ImageNet normalization). The mean baseline was computed as the pixel-wise mean of the training set after preprocessing. Expected gradients (Erion et al., 2021) averaged IG attributions over 100 random training images, each drawn independently as a per-input baseline. Feature importance was taken as the absolute value of IG attributions. The same top-k mask visualization and intra-patch bias analysis applied to SensX were repeated identically for all three IG baselines.

Perturbation Validation. We performed perturbation validation (Appendix A.7) using 50 log-spaced values of k from 1 to 150,528 with additional linear spacing between 100,000 and 150,528, and $N_p = 1{,}000$ perturbations per k.

Model Randomization Check. Following Adebayo et al. (2018), we progressively randomized ViT transformer blocks and recomputed SensX to verify that attributions depend on learned weights. Five cascading levels were tested: level 1 randomized block 11, level 2 randomized blocks 8–11, and levels 3–5 randomized progressively deeper blocks. For levels 3–5, the characteristic perturbation scale δ^* dropped to zero, indicating that the model output became insensitive to input perturbations. SensX was recomputed for levels 1 and 2 using the same configuration as the trained model.

Intra-Patch Bias Analysis. To quantify spatial bias introduced by the ViT's 16×16 patch tokenization, each patch in the attribution map was normalized by its median value. The normalized attribution was then computed as a function of Chebyshev distance from the patch center, averaged across all 196 patches per image. This analysis was applied to both SensX and all three IG baselines.

F.3 Single-Cell Transcriptomics

Dataset. The core human lung cell atlas (HLCA) (Sikkema et al., 2023) was downloaded from the Human Cell Atlas data portal (`https://data.humancellatlas.org/hca-bio-networks/lung/atlases/lung-v1-0`), comprising $\sim$ 584k cells. Cell type labels were taken from the `cell_type` field that maps HLCA cell populations to the standardized cell ontology terms and in some cases aggregates atlas-native subtypes. Genes with near-zero variance ($< 10^{-6}$) across all cells were removed, leaving 27,399 genes. Cell types with fewer than 10,000 cells were excluded, yielding 14 cell types for analysis.

Model architecture and training. For each cell type, a binary feedforward neural network with hidden layers $[250, 50]$, ReLU activations, and a single logit output was trained. The loss function was binary cross-entropy with logits, with class-specific positive weight equal to the ratio of negative to positive training samples. Models were trained for 10 epochs using AdamW (learning rate 10^{-4}, weight decay 10^{-4}) with a batch size of 64. The dataset was split into 70% training, 15% validation, and 15% test sets via stratified sampling. The model with the highest validation F1 score was selected. Details of model training are available at the SensX code repository.

Global domain. Per-gene minimum and maximum values were computed across the full dataset after applying the gene filter, defining the global domain Ω^g as the smallest hypercube containing the training data.

High-confidence cell selection. To determine which genes the trained models are using to predict cell types with high confidence, we sampled 1000 cells with predicted probability at least 0.99.

SensX configuration. The stability profile was evaluated over 50 log-spaced perturbation magnitudes $\delta \in [10^{-4}, 1]$ with $n_s = 1{,}000$ samples per δ. The characteristic perturbation scale δ^* was selected using a stability threshold of $\tau_a = 0.1$. SensX was computed with $n_w = 600$ and batch-size 8192.

DeepSHAP configuration. DeepSHAP (Lundberg and Lee, 2017) was computed using a background dataset of 100 samples drawn from the high-confidence cells of each cell type. SHAP values were computed in batches of 32 with additivity verification enabled. For each cell, genes were ranked by the absolute SHAP values.

Integrated Gradients configuration. Integrated Gradients (IG) (Sundararajan et al., 2017) was computed using Captum with $n_{\text{steps}} = 200$ and Gauss-Legendre quadrature. Three baseline variants were tested—(i) zero vector, (ii) mean of the training data, and (iii) mean of the high-confidence cells. For deterministic baselines (i–iii), a single baseline was shared across all cells. For each cell, genes were ranked by the absolute IG attribution. Convergence was verified via the completeness error returned by Captum.

Perturbation validation. We performed perturbation validation (Appendix A.7) for each method independently. For each cell, genes were ranked by SensX value, absolute DeepSHAP value, or absolute IG attribution. The top-k and bottom-k perturbation analyses were applied to each cell independently. We used 55 linearly spaced values of k from 1 to 27,399 and $N_p = 1{,}000$ perturbations per k. For each cell, all methods were evaluated under the same perturbation protocol and the cell's δ^*. All methods attribute the same quantity of interest (predicted probability via sigmoid).

F.4 Spatial Transcriptomics (DeepSpot)

DeepSpot (Nonchev et al., 2025) predicts spatially resolved gene expression from H&E histology images. For each spot, defined as a 100×100 pixel tile, the model integrates visual information from the center tile and its eight neighboring tiles. The center tile is additionally partitioned into a 3×3 grid of subspots. The UNI pathology foundation model (Chen et al., 2024) extracts morphological features from all 18 regions (9 tiles + 9 subspots), which secondary architectures integrate to predict gene expression at the center tile. A pretrained DeepSpot model for colon tissue (Colon_HEST1K) was applied to a whole-slide H&E image (sample ZEN38) from the DeepSpot repository, yielding 745 spots with eight neighbors each.

Gene Selection. Four genes were selected for analysis based on high mean and high variance of predicted log-expression across spots: *MUC4*, *MUC5B*, *LGALS4*, and *TFF3*. Each QOI is the predicted log-expression of a single gene.

Tile-Level SensX. The RGB values of the center and neighboring tile pixels total to 270,000 features ($(1 + 8) \times 100 \times 100 \times 3$). Subspots are derived from the perturbed center tile. The entire DeepSpot pipeline, including UNI foundation model feature extraction, is treated as a black box from raw pixels to predicted

expression. The 270,000 features were grouped into 9 tiles of 30,000 features each, yielding one SensX value per tile. Global perturbation bounds were set to $[0, 255]$. Sensitivity was computed using $n_w = 500$ walks with a batch size of 128.

Center-Tile Perturbation Validation. To independently validate center-tile dominance, we perturbed either the center tile (30,000 features) or all eight neighbor tiles (240,000 features) uniformly within the local perturbation bounds, holding the other fixed. For each condition, $N_p = 1{,}000$ perturbations were drawn and the median absolute change in predicted log-expression was compared across conditions for each spot-gene pair.

Pixel-Level SensX. Following the tile-level finding that the center tile dominates, pixel-level analysis was restricted to the center tile with neighboring tiles held fixed. The three color channels at each spatial coordinate were grouped, yielding 10,000 feature groups per spot. SensX was computed using $n_w = 300$ walks.

Pixel-Level Perturbation Validation. We performed perturbation validation (Appendix A.7) on the 10,000 pixels within each center tile using 20 log-spaced values of k and $N_p = 100$ perturbations per k. Because the SensX ranking differs across genes, perturbations were performed independently for each gene. Tasks sharing the same δ^* at a given spot were grouped to reduce redundant model evaluations.

Subspot Grid Bias Test. To test whether high-attribution pixels concentrate near the internal boundaries of DeepSpot's 3×3 subspot grid, we computed the minimum distance from each pixel to the nearest internal grid line (at pixel coordinates $33.\overline{3}$ and $66.\overline{6}$ in each dimension). For each spot-gene pair, we compared the mean grid-line distance of the top-500 SensX pixels to a null distribution of mean distances from 500 pixels sampled uniformly at random (10,000 permutations). The null distribution is independent of spot or gene identity and was computed once. Significance was assessed via a one-tailed permutation test at $p < 0.025$.

Staining Saturation Bias Test. To test whether high-attribution pixels are biased toward regions of lower staining intensity, we restricted the analysis to spot-gene pairs without significant grid bias ($p \geq 0.025$ in the grid proximity test). For each spot, the center tile was converted from RGB to HSV color space, and the saturation channel was extracted. We compared the mean saturation of the top-500 SensX pixels to a null distribution of mean saturations from 500 pixels sampled uniformly at random (10,000 permutations per spot). The null was computed once per spot and shared across genes, as saturation depends only on the tile image. Significance was assessed via a one-tailed permutation test at $p < 0.025$.