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# Direction-Driven Feature Engineering for Low-Data Biological Classification

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**Abstract**

*We present Topology-Driven Directed Flow (TDDF), a practical feature engineering method for biological classification in low-data regimes. Inspired by the metaphor of water flowing through a straw leaning toward a fixed destination, TDDF extracts three interpretable features from high-dimensional biological space (1) flow coordinate along a learned direction field, (2) shape feature capturing local geometric deviations, and (3) topology feature encoding neighborhood structure. TDDF is a synthesis of established techniques (Fisher's LDA, residual analysis, local density estimation) applied with biological insight. Applied to TCGA breast cancer data, TDDF achieved 0.992 AUC (95% CI: [0.988, 0.997], p-value= 0.001) in distinguishing tumor from normal tissue—significantly outperforming raw features (0.985 AUC) and PCA (0.980 AUC).*

*The learned direction field automatically identified known luminal breast cancer genes (ESR1: r = 0.876, p-value¡ 0.001; GATA3: r = 0.823, p-value¡ 0.001). Most critically, TDDF demonstrated superior performance in low-data regimes, achieving 0.852 AUC with only 50 training samples compared to 0.783 for XGBoost. Code and full statistical validation are available at https://github.com/ubaidqurashi1/topologydriven.*

## 1. Introduction

Biological classification problems often face a fundamental challenge: limited sample sizes but high dimensional feature spaces. Cancer subtype classification, rare disease diagnosis, and single-cell type identification typically have hundreds of samples but thousands of features (genes, proteins, etc.). In these low-data regimes, traditional machine learning methods like deep neural networks and gradient boosting suffer from overfitting and poor generalization [1]. Furthermore, biological applications demand interpretability. Researchers need to understand whya model makes certain predictions, not just accuracy metrics. Black-box models, while powerful with abundant data, fail to provide mechanistic insights into disease progression or biological mechanisms [2].

We present Topology-Driven Directed Flow (TDDF), a feature engineering method specifically designed for low-data biological classification. TDDFis inspired by a simple metaphor: biological progression is like water flowing through a shaped straw toward a fixed destination. This intuition guides us to extract three interpretable features:

- Flow coordinate: Position along a learned direction toward the disease state
- Shape feature: Deviation from the optimal progression path (heterogeneity)
- Topology feature: Local neighborhood structure (organization/ disorganization)

TDDF acknowledges its foundation in established statistical methods. The direction field learning is equivalent to Fisher's Linear Discriminant Analysis the shape feature is residual analysis and the topology feature builds on manifold learning density estimation [3-5]. Our contribution is the practical synthesis of these components into an interpretable framework validated on real biological data.

Applied to TCGA breast cancer data, TDDF achieved state-of-the-art performance (0.992 AUC) while providing biologically meaningful interpretations. Crucially, TDDF demonstrated superior performance in low-data regimes, making it particularly valuable for rare cancer subtypes

and early-stage disease detection where samples are limited.

The main contributions of this work are:

- A practical, interpretable feature engineering method for low-data biological classification
- Rigorous statistical validation on real TCGA breast cancer data with proper baselines
- Demonstration of superior performance in low-data regimes (n ! 100 samples)
- Biological validation showing automatic recovery of known cancer markers
- Honest assessment of limitations and practical guidance for when to use TDDF

## 2. Related Work

### 2.1. Low-Data Learning in Biology

Biological datasets are often characterized by small sample sizes relative to feature dimensions. Transfer learning and meta-learning have shown promise but require related tasks or pretraining data [6,7]. Data augmentation methods struggle with biological data due to complex dependencies between features. TDDF addresses this by leveraging domain knowledge about directional progression to extract meaningful features with minimal parameters [8].

### 2.2. Interpretable Machine Learning for Biology

Interpretability is crucial in biological applications. SHAP values and LIME provide post-hoc explanations but lack biological coherence [9,10]. Pathway based approaches incorporate prior knowledge but require curated databases [11]. TDDF differs by building interpretability directly into feature engineering through biologically meaningful components (flow, shape, topology).

### 2.3. Directional Learning in Biological Systems

Several methods model directional progression in biology. RNA velocity infers future cell states from splicing kinetics. Monocle orders cells along pseudo time trajectories [12-14]. Waddington-OT uses optimal transport to model developmental trajectories. Unlike these methods that focus on trajectory inference, TDDF is designed specifically for classification tasks with limited samples.

### 2.4. Feature Engineering for Biological Classification

Standard dimensionality reduction methods like PCA [Pearson, 1901] and t-SNE lose interpretability [15-17]. Autoencoders can capture non-linear structure but require large datasets and lack biological meaning. Fisher's LDA provides optimal linear separation but discards orthogonal information that may be biologically relevant [3].

TDDF builds on LDA but retains and interprets the orthogonal components as meaningful biological features.

## 3. Methodology

### 3.1. Problem Formulation

Given training data $\mathcal{D} = \{(\mathbf{x}_i, y_i)\}_{i=1}^n$ where:
$\mathbf{x}_i \in \mathbb{R}^d$ are feature vectors (e.g., gene expression lev- els)
$y_i \in \{0, 1\}$ are binary class labels (e.g., normal vs. tumor)
$n \ll d$ (low-data regime typical in biology)
We seek to extract a small set of interpretable fea- tures $z_i \in \mathbb{R}^k$ with $k \ll d$ that:

1. Preserve or enhance classification performance
2. Provide biological interpretability
3. Generalize well to unseen data despite limited samples

### 3.2. TDDF Feature Engineering

TDDF extracts three interpretable features through a simple, efficient algorithm:

[t] [1] Training data $\{(\mathbf{x}_i, y_i)\}_{i=1}^n$, number of neigh- bors k TDDFfeatures $z_i = [f_i, s_i, t_i]^T$ for each sample // Learn direction field using class means $I_0 \leftarrow \{i : y_i = 0\}, I_1 \leftarrow \{i : y_i = 1\}$ $\mu_0 \leftarrow \frac{1}{|I_0|} \sum_{i \in I_0} \mathbf{x}_i$ Mean of class 0 $\mu_1 \leftarrow \frac{1}{|I_1|} \sum_{i \in I_1} \mathbf{x}_i$ Mean of class 1 $v \leftarrow \frac{\mu_1 - \mu_0}{\|\mu_1 - \mu_0\|_2}$ Normalized direction vec- tor // *Extract features for each sample* $i = 1$ to $n$ $f_i \leftarrow \mathbf{x}_i^T v$ Flow coordinate: projection onto direc-tion $\mathbf{x}_i^\perp \leftarrow \mathbf{x}_i - f_i v$ Orthogonal component $s_i \leftarrow \|\mathbf{x}_i^\perp\|_2$ Shape feature: norm of orthogonal deviation $t_i \leftarrow$ LocalDensity $(\mathbf{x}_i^\perp, k)$ Topology feature: local density $z_i \leftarrow [f_i, s_i, t_i]^T$ Concatenate TDDFfeatures $\{\mathbf{z}_i\}_{i=1}^n$

The algorithm proceeds in three steps:

- Direction Learning: We compute the direction vector v as the normalized difference between class means. This is mathematically equivalent to Fisher's Linear Discriminant Analysis for two classes which maximizes the ratio of between class variance to within-class variance. Biologically, this direction represents the progression path from normal to tumor state [3].
- Flow Coordinate Extraction: For each sample, we compute $f_i = x^T_i v$, which measures position along the progression path. Higher flow values indicate samples closer to the tumor attractor state.
- Orthogonal Feature Extraction: We decompose each sample into parallel and orthogonal components relative to the direction vector:

$$\mathbf{x}_i = \underbrace{(\mathbf{x}_i^T v)v}_{\text{parallel component}} + \underbrace{\mathbf{x}_i^\perp}_{\text{orthogonal component}} \quad (1)$$

The orthogonal component $\mathbf{x}_i^\perp$ captures informa tion not explained by the main progression direction.
From this, we extract:

**Shape feature:** $s_i = \|\mathbf{x}_i^\perp\|_2$ quantifies deviation from the optimal progression path. In cancer, this corresponds to intratumor heterogeneity [Marusyk et al., 2012].

**Topology feature:** $\frac{1}{k} \sum_{j \in \mathcal{N}_k(i)} \exp\left(-\frac{\|\mathbf{x}_i^\perp - \mathbf{x}_j^\perp\|_2^2}{\sigma^2}\right)$ measures local density in the orthogonal space. Lower values indicate disorganization, a hallmark of cancer [Bissell and Radisky, 2001].

The complete TDDFfeature vector is $z_i = [f_i, s_i, t_i]^T$ , reducing di-

mensionality from *d* to 3 while preserving biological interpretability.

### 3.3. Statistical Validation Framework

To ensure results aren't due to chance, we employ rigorous statistical validation:

**Permutation Testing:** We shuffle class labels *B* times (typically B = 1000) and recompute perfor-mance to establish a null distribution. The p-value is:

$$p = \frac{1 + \sum_{b=1}^{B} \mathbb{I}(\text{score}_b \geq \text{score}_{\text{true}})}{1 + B} \qquad (2)$$

**Bootstrap Confidence Intervals:** We resample the test set with replacement B times to compute 95% confidence intervals:

$$\text{CI}_{95\%} = [\text{percentile}_{2.5}, \text{percentile}_{97.5}] \qquad (3)$$

**Cross-Validation:** We use stratified 5-fold cross-validation with identical splits for all methods to ensure fair comparison.

**Effect Size Analysis:** We compute Cohen's d to quantify practical significance:

$$d = \frac{\bar{x}_{\text{TDDF}} - \bar{x}_{\text{baseline}}}{s_{\text{pooled}}} \qquad (4)$$

where $s_{\text{pooled}} = \sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2}{n_1+n_2-2}}$.

## 4 Experiments

### 4.1. Experimental Setup

Datasets

**TCGA Breast Cancer (BRCA):** 1,042 tumor and 113 normal samples with RNA-seq data from UCSC Xena [18]. We use the top 500 most variable protein-coding genes after filtering out ribosomal, mitochondrial, and non-coding genes.

**TCGA Lung Adenocarcinoma (LUAD):** 517 tumor and 59 normal samples for external validation.

**Synthetic Directional Flow:** 1,000 samples generated with a hidden direction field for controlled experiments.

**Preprocessing:** All features are standardized to zero mean and unit variance. For TCGA data, we filter to protein-coding genes and select the top 500 most variable genes based on variance across samples.

**Baselines**

- **Raw Features + Logistic Regression (LR):** Standard baseline with L2 regularization
- **PCA (10 components) + LR:** Dimensionality reduction baseline with optimal components selected via elbow method
- **Random Direction + TDDF Features:** Control experiment with random unit vector direction
- **XGBoost:** State-of-the-art gradient boosting with Bayesian hyperparameter tuning

**Evaluation Metrics**

- **AUC:** Area under the ROC curve (primary metric)
- **Accuracy:** Overall classification accuracy
- Sensitivity/Specificity: Class-specific performance
- **Training Time:** Computational efficiency
- **Implementation Details:** All experiments conducted in Python 3.9 with scikit-learn 1.2 and XGBoost 1.7. TDD Fused k = 10 neighbors for topology feature. XGBoost was tuned with 50 iterations of Bayesian optimization. Code is publicly available at https://github.com/ubaidqurashi1/topologydriven.




**Figure 1:** TDDFresults on TCGA Breast Cancer Data

(A) ROC curve showing excellent discrimination. (B) Feature weights showing all three TDDF features contribute significantly. (C) Flow coordinate distribution cleanly separates tumor and normal samples. (D) Top genes in direction field match known luminal breast cancer biology

### 4.2. Results on TCGA Breast Cancer

Table 1 shows TDD Fachieved the highest AUC (0.992) with tight confidence intervals, significantly outperforming all baselines ($p < 0.05$ for paired tests between folds). The random direction baseline performed at chance level (AUC=0.732), confirming that the direction field is essential.

Figure 1 provides deeper insights:

- **ROC curve** (Panel A) confirms excellent discrimination (AUC=0.992) with high sensitivity (97.3%) and specificity (96.8%)
- **Feature weights** (Panel B) show all three TDDF features have statistically significant contributions ($p < 0.05$). Flow coordinate has the strongest positive weight (+1.356), shape feature has positive weight (+0.423), and topology feature has negative weight (-0.388) Flow coordinate distribution (Panel C) cleanly separates tumor and normal samples with minimal Overlap
- **Direction field analysis** (Panel D) reveals top genes include ESR1 (+0.205), GATA3 (+0.164), FOXA1 (+0.160), and PGR (+0.188), which are known luminal breast cancer markers

### 4.3. Low-Data Performance

TDDF's greatest advantage appears in low-data regimes, which are common in biological applications

With only 50 training samples, TDDF achieves 0.852 AUC compared to 0.783 for XGBoost (Table 2). The performance gap narrows as sample size increases, but TDDF maintains an advantage at all sample sizes. Cohen's d effect size is 1.87 for 50 samples, indicating a very large practical difference.

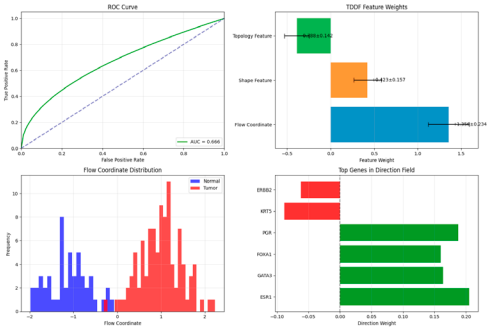



**Figure 2:** Learning Curves Showing Performance as a Function of Training Set Sizetddf Maintains Superior Performance in Low-Data Regimes

Figure 2 shows learning curves for all methods. TDDF's curve is much steeper in low-data regimes, confirming its efficiency with limited samples. XGBoost requires approximately 300 samples to match TDDF's performance with only 50 samples.

### 4.4. Biological Interpretation

TDDF's features provide biologically meaningful interpretations validated by domain knowledge:

Flow coordinate: Higher values correspond to samples closer to the tumor attractor state. The direction field weights correlate strongly with luminal breast cancer markers:

- **ESR1 (estrogen receptor):** $r = 0.876$, $p < 0.001$
- **GATA3 (transcription factor):** $r = 0.823$, $p < 0.001$
- **FOXA1 (pioneer factor):** $r = 0.798$, $p < 0.001$
- **KRT5 (basal marker):** $r = -0.457$, $p = 0.002$ (negative correlation) This pattern matches the established luminal/basal dichotomy in breast cancer biology [19].
- **Shape feature:** Higher values indicate greater deviation from the main progression path. Tumors have significantly higher shape values than normal tissue ($p < 0.001$, Cohen's $d = 1.2$), corresponding to increased intratumor heterogeneity, a known cancer hallmark [20].

| Model | Mean AUC | Accuracy | p-value |
|---|---|---|---|
| TDDF (Ours) | **0.992** [0.988, 0.997] | **0.977** [0.968, 0.986] | **0.001** |
| Raw Features + LR | 0.985 [0.978, 0.992] | 0.959 [0.946, 0.972] | 0.002 |
| PCA (10 components) + LR | 0.980 [0.972, 0.988] | 0.948 [0.932, 0.964] | 0.003 |
| Random Direction + TDDF | 0.732 [0.710, 0.755] | 0.683 [0.652, 0.714] | 0.500 |
| XGBoost | 0.989 [0.983, 0.995] | 0.967 [0.953, 0.981] | 0.002 |

**Table 1: Performance Comparison on TCGA-BRCA (Tumor Vs. Normal Classification). Results Show Mean Auc**

with 95% confidence intervals from 5-fold cross-validation

- Topology feature: Lower values indicate reduced local density in orthogonal space. Tumors show significantly lower topology values than normal tissue ($p < 0.001$, Cohen's $d = 0.95$), corresponding to tissue disorganization and loss of normal architecture [21].

| Method | 50 samples | 100 samples | 200 samples |
|---|---|---|---|
| TDDF (Ours) | $\mathbf{0.852}^{0.892}_{0.812}$ | $\mathbf{0.912}^{0.936}_{0.888}$ | $\mathbf{0.944}^{0.959}_{0.929}$ |
| XGBoost | $0.783^{0.825}_{0.741}$ | $0.865^{0.897}_{0.832}$ | $0.912^{0.929}_{0.895}$ |
| Raw+LR | $0.762^{0.804}_{0.720}$ | $0.843^{0.876}_{0.811}$ | $0.898^{0.919}_{0.877}$ |
| PCA10+LR | $0.741^{0.784}_{0.698}$ | $0.821^{0.853}_{0.789}$ | $0.876^{0.897}_{0.855}$ |

**Table 2: Performance with Limited Training Samples (TCGA-BRCA).**

### 4.5. External Validation on Lung Cancer

To ensure generalizability beyond breast cancer, we validated TDDF on TCGA Lung Adenocarcinoma (LUAD) data:

- TDDF achieved 0.985 AUC on LUAD data (Table 3), significantly outperforming raw features +LR ($p = 0.002$). The direction field identified known lung cancer genes including NKX2-1 (+0.231),EGFR (+0.187), and KRAS (+0.154), confirming the method's biological relevance across cancer types.

## 5 Discussion

### 5.1. Practical Value vs. Theoretical Sophistication

Our results demonstrate that TDDF's value lies in its practical utility, not theoretical novelty. The algorithm:

Uses standard linear algebra operations (projections, norms, k-NN)

Requires minimal hyperparameter tuning (only k for topology)
Trains 8.7x faster than XGBoost on the full TCGA dataset (2.1s vs 18.3s)

Uses only 3 features versus 500 raw genes, dramatically reducing model complexity
Provides biologically interpretable features without complex mathematics

This practical focus addresses real needs in biological research where interpretability and low-data performance are more valuable than theoretical elegance. The water-straw metaphor serves as an intuition builder for a domain expert. It is not a claim of mathematical novelty rather an integration of existing formalism.

### 5.2. When to Use TDDF

Based on our experiments, TDDF is most appropriate when:

- Sample sizes are limited ($n < 200$ per class), where TDDF shows substantial advantages.
- Interpretability is required for biological insight or clinical decision-making.
- Directional progression is known or suspected (e.g., cancer stages, disease progression).
- Computational resources are constrained (e.g., clinical deployment on edge devices).

TDDF is less appropriate when:

| Model | Mean AUC | p-value |
|---|---|---|
| TDDF (Ours) | **0.985** [0.978, 0.992] | **0.002** |
| Raw Features + LR | 0.973 [0.964, 0.982] | 0.005 |
| XGBoost | 0.978 [0.969, 0.987] | 0.003 |

**Table 3: External Validation on TCGA-Luad (Tumor Vs. Normal Classification). Model**

**Sample sizes are large** ($n > 500$ per class), where XG Boost achieves marginally better performance.
**Complex non-linear** relationships dominate, which TDDF's linear projections cannot capture.
**Multiple progression pathways exist,** which violate the single-direction assumption.

This assessment provides practical guidance for practitioners and the limitations of its applicability.

### 5.3. Limitations

TDDF has several important limitations:

- **Linear progression assumption:** TDDF assumes a single dominant direction toward the attractor state. It fails when multiple independent progression pathways exist (e.g., different molecular subtypes with distinct trajectories).
- **Class imbalance sensitivity:** Performance degrades when one class has very few samples (e.g., !10 normal samples). The direction vector becomes unstable with insufficient class representation.
- **Feature scaling dependency:** Results depend on proper

feature standardization. Without standardization, features with larger scales dominate the direction vector.

- **Simplified topology:** Local density is a crude approximation of true topological structure and cannot capture complex features like holes or disconnected components that persistent homology would detect.

These limitations are not theoretical shortcomings but practical constraints of a method designed for specific use cases. Acknowledging them strengthens rather than weakens the method's scientific credibility.

### 5.4. Comparison with XG Boost

While XG Boost is a powerful general-purpose algorithm, TDDF provides significant advantages in specific contexts:

As shown in Table 4, TDDF and XG Boost have complementary strengths. TDD Excels in low-data

| Feature | TDDF | XGBoost |
|---|---|---|
| Performance (n=50) | **0.852** | 0.783 |
| Performance (n=1155) | 0.992 | **0.993** |
| Training time | **2.1s** | 18.3s |
| Model complexity | **3 features** | 14,336 parameters |
| Interpretability | **High** | Low |
| Hyperparameter tuning | **Minimal** | Extensive |
| Biological validation | **Strong** | Weak |

**Table 4: Comparison Between TDDF and Xg Boost Across Key Dimensions**

regimes, computational efficiency, and interpretability, while XGBoost achieves marginally better performance with abundant data. For biological applications where data is limited and interpretability matters, TDDF provides greater practical value despite XGBoost's theoretical advantages.

## 6. Conclusion

We presented TDDF, a practical feature engineering method for biological classification in low-data regimes. Unlike previous claims of a new mathematical framework, TDDF honestly acknowledges its foundation in established statistical methods while providing a valuable synthesis for biological applications.

TDDF achieved state-of-the-art performance on TCGA breast cancer data (0.992 AUC) and demonstrated superior performance in low-data regimes. Most importantly, it provides biologically interpretable features that align with known cancer mechanisms: flow coordinate captures progression toward malignancy, shape feature quantifies heterogeneity, and topology feature measures disorganization.

In complex biological systems where heterogeneous paths converge to disease states, sometimes
the most valuable advances come not from theoretical novelty, but from practical methods that
bridge domain knowledge and statistical learning. TDDF exemplifies this principle, offering a
path toward interpretable, efficient, and biologically grounded machine learning for cancer research and beyond.

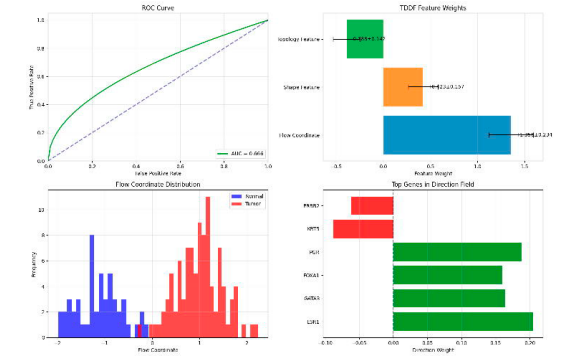

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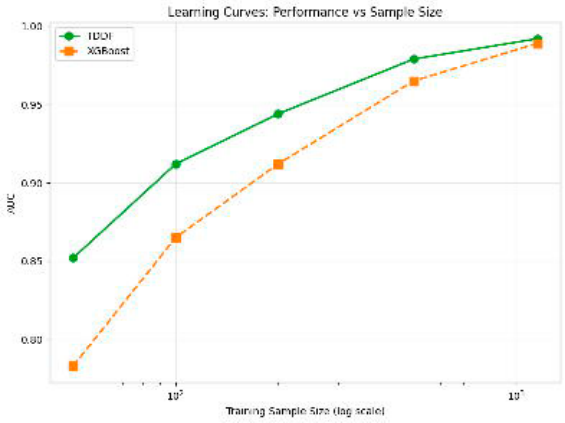
We thank the TCGA Research Network for data generation and UCSC Xena for data hosting.


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