Introduction to Optimal Transport and its Applications to Computational Biology

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Outline

Relevant Materials

- **Theoretical and Computational Optimal Transport**:
  - "**Optimal transport for single-cell and spatial omics**" by Charlotte Bunne, Geoffrey Schiebinger, Andreas Krause, Aviv Regev and Marco Cuturi. [1]
  - "**Computational Optimal Transport**" by Gabriel Peyré and Marco Cuturi. [5]
  - "**Optimal Transport for Applied Mathematicians**" by Filippo Santambrogio. [6]
- **Software Packages**:
  - `transport` [7]
  - `POT` [3]
  - `scDiagnostics` [2]

Basics of Optimal Transport

- Optimal Transport (OT) focuses on the most efficient way to move mass between distributions.
- Connections to diverse fields: probability, statistics, optimization, functional analysis, and many more.

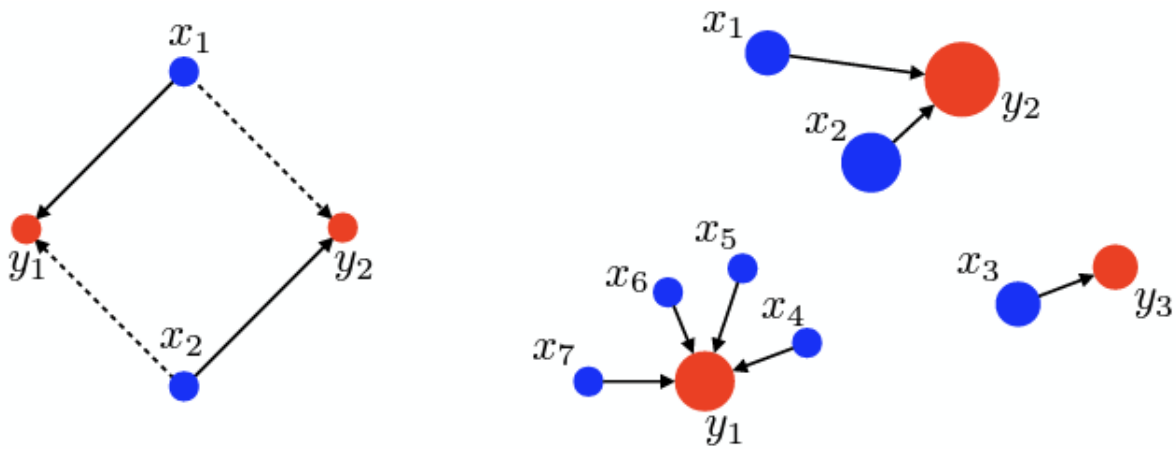
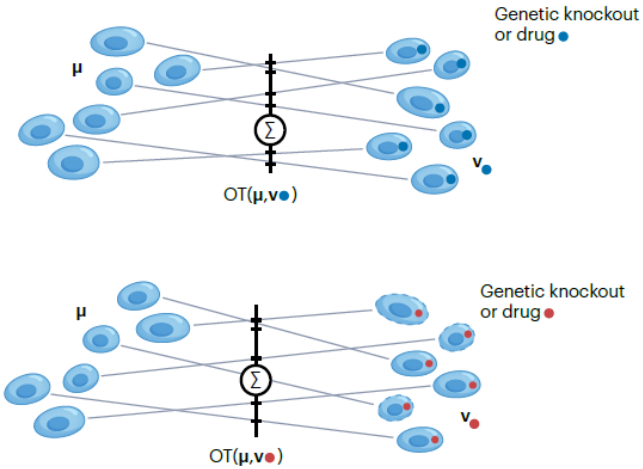


Figure: Example discrete OT problem solutions. [5]

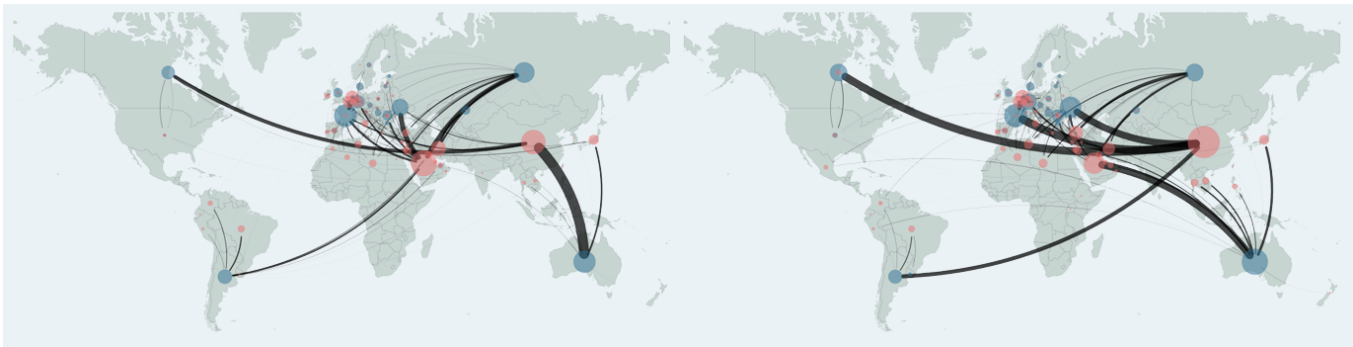
Basics of Optimal Transport

- Areas of applications: **computational biology**, image processing, economics, and many more.



(a) Computational Biology [1]

(b) Image Processing [6]



(c) Economics [4]

Basics of Optimal Transport

- Fundamental problem: Moving mass from one distribution to another at minimal cost.

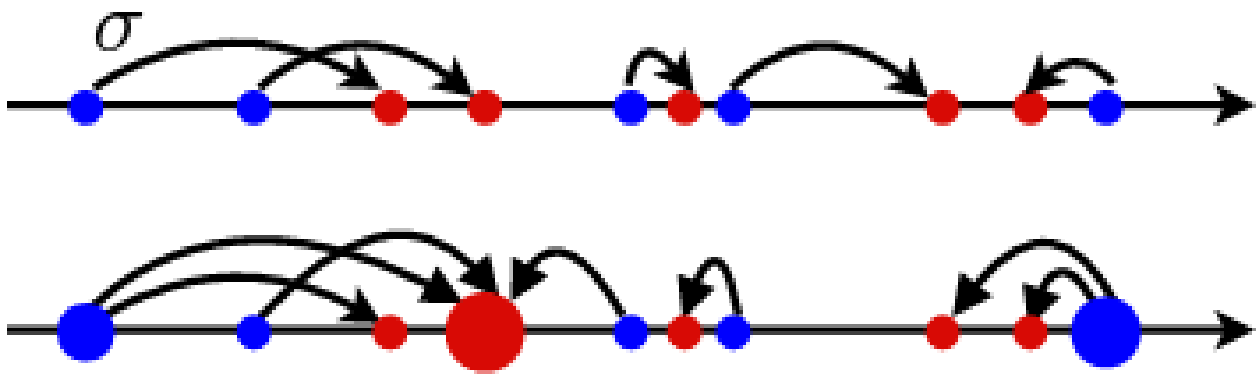


Figure: Fundamental problem in OT. [5]

Discrete OT: Mathematical Background

- **Source Distribution** (μ): $\mu = \sum_{i=1}^{n} a_i \delta_{x_i}$
  - a_i: Mass or probability at source point x_i.
  - δ_{x_i}: Dirac delta function, representing mass concentrated at x_i.
- **Target Distribution** (ν): $\nu = \sum_{j=1}^{m} b_j \delta_{y_j}$
  - b_j: Mass or probability at target point y_j.
  - δ_{y_j}: Dirac delta function, representing mass concentrated at y_j.
- **Dirac Delta Function** (δ_{x_i}):
  - Models an idealized point mass.
- **Measure Theory**:
  - Studies objects like μ and ν, defines how mass is distributed.

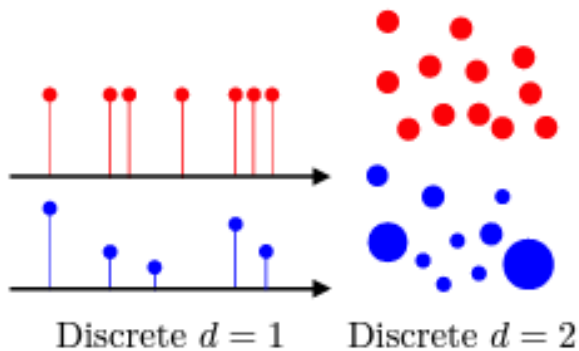


Figure: Example of probability mass functions. [5]

Discrete OT: Transport Plan and Objective

- **Transport Plan** (π): Matrix π_{ij} representing mass flow from x_i to y_j.
- **Objective**:

$$\min \sum_{i=1}^{n} \sum_{j=1}^{m} \pi_{ij} c(x_i, y_j)$$

- **Constraints**:

$$\sum_{j=1}^{m} \pi_{ij} = a_i, \quad \forall i$$

$$\sum_{i=1}^{n} \pi_{ij} = b_j, \quad \forall j$$

$$\pi_{ij} \geq 0, \quad \forall i, j$$

- Cost function $c(x_i, y_j)$ is often the squared distance $\|x_i - y_j\|^2$.

Entropy Regularization in Discrete OT

- **Objective with Entropy Regularization**: Enhances computational efficiency and stability.

$$\min_{\pi} \left(\sum_{i=1}^{n} \sum_{j=1}^{m} \pi_{ij} c(x_i, y_j) + \epsilon \sum_{i=1}^{n} \sum_{j=1}^{m} \pi_{ij} (\log \pi_{ij} - 1) \right)$$

  - ϵ: Regularization tuning parameter.
- **Benefits of Regularization**:
  - Induces sparsity in π.
  - Improves numerical stability in high-dimensional problems.
  - Faster convergence in optimization problems.
- **Optimization Methods**:
  - Sinkhorn-Knopp Algorithm
  - Other Methods: iterative Bregman projections, stochastic optimization, augmented lagrangian methods

Discrete OT: Dual Formulation

- The dual formulation involves maximizing:

$$\sum_{i=1}^{n} u_i a_i + \sum_{j=1}^{m} v_j b_j$$

- Subject to:

$$u_i + v_j \leq c(x_i, y_j) \quad \forall i, j$$

- Provides a complementary perspective on the transport problem.

Monge vs. Kantorovich in OT

- **Monge Problem**: Seeks a deterministic map T with $T_{\#}\mu = \nu$, i.e. a bijective mapping with no splitting (so it has more constraints than the traditional/Kantorovich OT).
- **Kantorovich Problem**: Uses a transport plan π allowing mass splitting.
- Kantorovich is more flexible and widely applicable, handling broader cases where direct mappings (as in Monge) aren't possible.
- Monge required more computationally intensive methods from combinatorics.

Monge Problem Example

- **Source Points**: $\{x_1, x_2, x_3, x_4, x_5\}$
- **Target Points**: $\{y_1, y_2, y_3, y_4, y_5\}$
- **Complex Cost Function**:

$$\text{Cost}(x_i, y_j) = (i - j)^2 + 2i + 3j$$

- **Objective**: Find a mapping $T : X \to Y$ minimizing the cost.

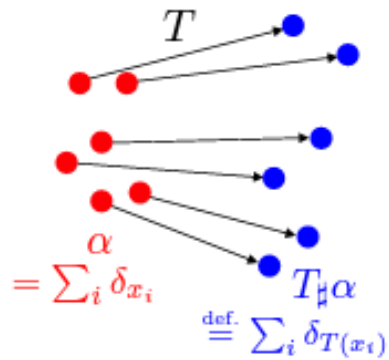


Figure: Bijective mapping example. [5]

Comparison of Solutions

Solution 1:

$$T(x_1) = y_3, T(x_2) = y_4, T(x_3) = y_5, T(x_4) = y_1, T(x_5) = y_2$$

Total Cost for Solution 1:

- Cost = 102

Solution 2:

$$T(x_1) = y_2, T(x_2) = y_3, T(x_3) = y_4, T(x_4) = y_5, T(x_5) = y_1$$

Total Cost for Solution 2:

- Cost = 98

Conclusion:

- Solution 2 has lower cost (98) compared to Solution 1 (102).
- Finding the optimal solution is very computationally expensive.

Kantorovich Problem Example

- **Source Points** with masses:
  - $x_1 : 0.2$, $x_2 : 0.1$, $x_3 : 0.3$, $x_4 : 0.2$, $x_5 : 0.2$
- **Target Points** with masses:
  - $y_1 : 0.15$, $y_2 : 0.25$, $y_3 : 0.25$, $y_4 : 0.15$, $y_5 : 0.2$
- **Cost Function**:

$$\text{Cost}(x_i, y_j) = \begin{cases} 1, & \text{if } i = j \\ 4, & \text{if } i \neq j \end{cases}$$

- **Objective**: Minimize cost with transport plan allowing splits.

Kantorovich Problem Solution

Transport Plan (π):

$$\pi = \begin{bmatrix} 0.15 & 0.05 & 0 & 0 & 0 \\ 0 & 0.05 & 0.05 & 0 & 0 \\ 0 & 0.2 & 0.1 & 0 & 0 \\ 0 & 0 & 0.1 & 0.1 & 0 \\ 0 & 0 & 0 & 0.05 & 0.15 \end{bmatrix}$$

- Reflects optimal mass distribution.
- Allows splitting for more flexibility and lower cost.
- Calculation involves sum of $\pi_{ij} \cdot \text{Cost}(x_i, y_j)$.

Discrete OT: Code Applications

- State-of-the-art solvers in R/CRAN package `transport`.
- See accompanying `R` script.
- Also available in Python via package POT.

Continuous OT: Introduction

- **Extension from Discrete to Continuous**:
  - Generalizes optimal transport to manage continuous probability distributions.
  - Useful for modeling and analyzing scenarios where data is naturally continuous.
- **Source and Target Measures**:
  - μ: Source measure, representing the initial "mass" distribution over space X.
  - ν: Target measure, representing the desired mass distribution over space Y.

Continuous OT: Mathematical Formulation

- **Transport Plan Set**:
  - $\Pi(\mu, \nu)$: Collection of all feasible transport plans π that shift μ into ν while conserving mass.
- **Cost Function**:
  - $c(x, y)$: Represents the cost of moving a unit of mass from $x \in X$ to $y \in Y$.
- **Objective**:
  - Minimize total transport cost:

$$\inf_{\pi \in \Pi(\mu,\nu)} \int_{X \times Y} c(x, y)\, d\pi(x, y)$$

  - inf: Infimum, denotes the greatest lower bound of the total cost.
  - $\int_{X \times Y} c(x, y)\, d\pi(x, y)$: Integral, representing expected transport cost under plan π.

Solving Continuous OT Problems

- **Problem Setup**:
  - Minimize integral-based cost:

$$\inf_{\pi \in \Pi(\mu,\nu)} \int_{X \times Y} c(x,y)\, d\pi(x,y)$$

- **Numerical Methods**:
  - **Discretization**: Transform continuous measures into discrete approximations, linking directly to discrete OT techniques.
  - **Sinkhorn-Knopp Algorithm**:
    - Extends discrete OT regularization for efficiency.
  - **Gradient-Based Approaches**: Leverages derivatives to iteratively approach solutions.
- **Theoretical Tools**:
  - **Kantorovich Duality**: Bridges discrete and continuous OT solutions, using dual variables.
- **Applications**: Extends discrete OT use cases in data science and ML.

Continuous OT Example: Problem Setup

- **Source Distribution (μ)**:
  - Gaussian centered at $(0, 0)$ with variance $\Sigma_1 = I$ (identity matrix).
- **Target Distribution (ν)**:
  - Gaussian centered at $(1, 1)$ with variance $\Sigma_2 = I$.
- **Cost Function**:
  - Squared Euclidean distance: $c(x, y) = \|x - y\|^2$.
- **Objective**:
  - Find transport map $T(x)$ that minimizes:

$$\inf_T \int_{\mathbb{R}^2} \|x - T(x)\|^2 \, d\mu(x)$$

  - Subject to mapping μ to ν.

Continuous OT Example: Solution

- **Optimal Transport Map via Brenier's Theorem**:
  - For Gaussian distributions with quadratic cost, the map is affine:
$$T(x) = Ax + b$$
  - Given $\Sigma_1 = \Sigma_2 = I$, set $A = I$.
- **Translation Vector (b)**:
  - Shift from source to target mean:
$$b = (1, 1) - (0, 0) = (1, 1)$$
- **Result**:
  - Optimal map:
$$T(x) = x + (1, 1)$$
  - Each point is shifted right and up by 1 to align with ν.
- **Explanation**:
  - Map $T(x)$ realigns means without variance adjustment, ideal for equal covariance identity matrices.

Continuous OT: Code Application

- See accompanying `R` script.
- In the continuous code example, we verify our intuition via simulation.
- See plot produced at the end of this example.

Comparing Single-Cell Expressions: Traditional Metrics

- **Limitations of Euclidean Distance**:
  - Sensitive to magnitude differences; lacks gene context scaling.
  - Overlooks functional relationships between genes.
- **Limitations of Correlation Metrics (Pearson/Spearman)**:
  - Emphasizes linear or monotonic relationships.
  - Misses complex interaction and shifts between differing gene profiles.

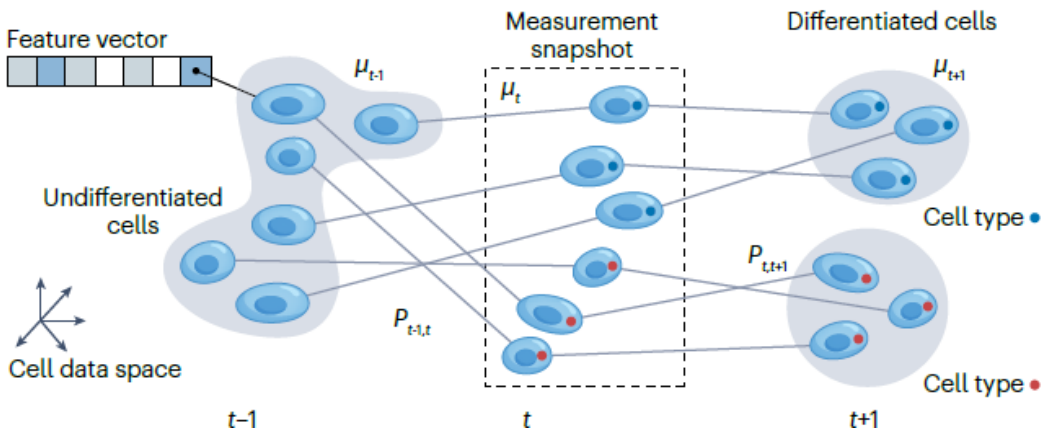


Figure: Cell differentiation relationship. [1]

Optimal Transport: A Flexible Alternative

- **Why Use OT for Single-Cell Comparison?**
  - Flexible cost functions to transition between cell expression profiles.
  - Models biologically relevant transitions in gene pathways and cellular dynamics.
- **Context**:
  - Interested in the evolution of cell populations.
  - OT allows adjustments to the cost matrix, aligning transformation likelihood with gene expression changes.

Motivating Example: Gene Interaction in Immune Response

- **Gene A (Cytokine Receptor)**:
  - Essential for receiving environmental signals—low cost in transitions.
- **Gene B (Transcription Factor)**:
  - Works closely with Gene A to activate immune response genes—low joint transformation cost with Gene A.
- **Gene C (Cell Surface Marker)**:
  - Expression increases in activated cells but costly to adjust in conjunction with B or A independently.
  - Higher transformation cost with both A and B reflects its distinct biological role.
- **Biological Insight**:
  - Shows how OT can prioritize coupled transformations within a pathway (A & B) while maintaining overall functional coherence by recognizing C's selective role.

Interpreting OT in Single-Cell Context

- **OT Advantages**:
  - Enables comparisons considering gene-specific contexts and evolutionary pathways.
  - Cost matrix adjustments reflect biological transformation costs, aligning with cellular evolution likelihood.

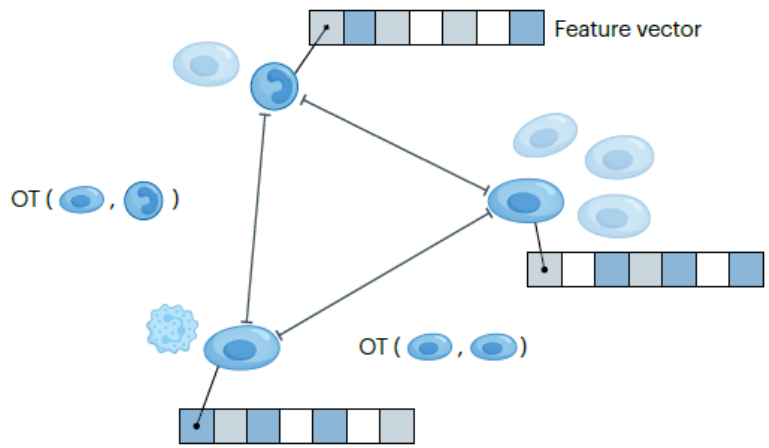


Figure: OT distances for cells. [1]

Spatial Omics: Research Questions

- **Key Biological Questions**:
  - Understanding cell–cell communication and spatial distribution of molecules.
  - Identifying key structural and functional units like microenvironments (MEs) and niches.

Optimal Transport in Spatial Omics

- **Using OT for Analyzing Microenvironments**:
  - OT distance for analysis of multicellular communities.
  - Models the microenvironment (ME) around each cell by aggregating spatial neighbor features into histograms.
- **Computational Approach**:
  - Compute OT distance between MEs: $OT(ME_i, ME_j)$.
  - Forms a pairwise distance matrix for all cellular MEs.

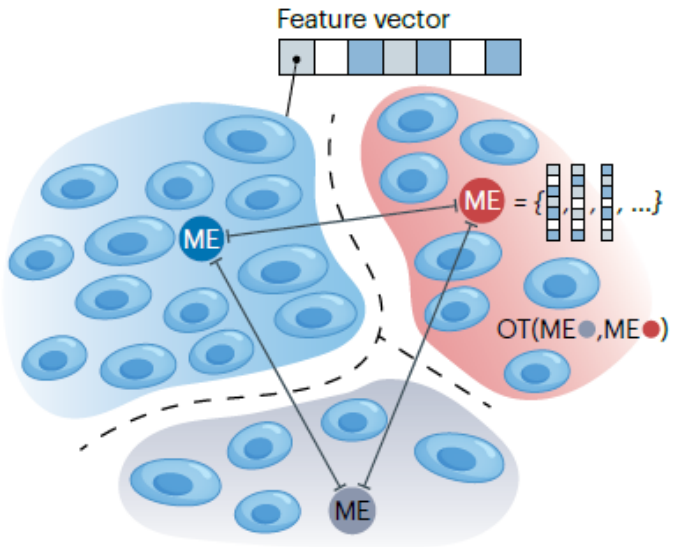


Figure: OT distances of MEs. [1]

Applications and Biological Insights

- **Clustering of Microenvironments**:
  - Apply clustering on the OT-derived distance matrix to identify cellular niches.
- **Real-World Findings**:
  - Studies by Yuan et al. and Mani et al. exemplify the use of OT in spatial omics.
  - OT-based MEs resemble known tissue structures when using multiplex fluorescence data.
- **Visual Confirmation**:
  - Detected microenvironments align with ground-truth tissue sections, corroborating OT's efficacy in characterizing spatial structures.

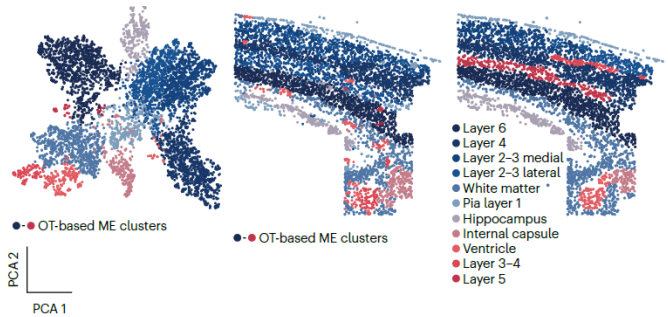


Figure: Clustering visualization of MEs. [1]

Optimal Transport in `scDiagnostics`

- **Purpose**:
  - Calculates Wasserstein distances (another name for Kantorovich distances) between query and reference single-cell datasets.
- **Process Overview**:
  - Projects query data into PCA space defined by the reference dataset.
  - Computes Wasserstein distances within the reference dataset to establish a null distribution.
  - Assesses differences by calculating distances between the query and reference datasets.
- **Biological Context**:
  - Identifies variations in cell populations or expression profiles.

Optimal Transport in `scDiagnostics`

- **Biological Context**:
  - Identifies variations in cell populations or expression profiles.
  - Provides insights into cell type differentiation and evolutionary pathways.
- **Key Outputs**:
  - `null_dist`: A numeric vector of distances from resampled reference dataset pairs.
  - `query_dist`: Mean distance between the query and reference datasets.
  - `cell_type`: Lists unique cell types identified in the reference dataset.

Optimal Transport in `scDiagnostics` Example

- **Data Preparation**:
  - Load `reference_data` and `query_data`.
  - Select CD4 cells from both datasets.
- **Gene Selection**:
  - Extract top 500 highly variable genes and find common genes.
- **Dimensionality Reduction**:
  - Perform PCA on reference data for feature reduction.
- **OT Distance Calculation**:
  - Compute Wasserstein distances and evaluate differences.
- **Visualization**:
  - Plot to compare datasets.
- **Output**:
  - See code example in `R` script.

Conclusion

- **Optimal Transport (OT)**:
  - Provides a versatile framework for comparing complex biological data.
- **Single-Cell Analysis**:
  - Offers a flexible approach to understand cell-type differences and evolutionary dynamics.
- **Spatial Omics**:
  - Enables characterization of microenvironments, revealing key tissue structures.
- **Broader Impact**:
  - OT bridges gaps between computational methods and biological insights, driving advances in multi-omics research.

References

[1] Charlotte Bunne et al. "Optimal transport for single-cell and spatial omics". In: *Nature Reviews Methods Primers* 4.1 (2024), p. 58.

[2] Anthony Christidis et al. *scDiagnostics: Cell type annotation diagnostics*. R package version 1.1.0. 2025. URL: https://github.com/ccb-hms/scDiagnostics.

[3] Rémi Flamary et al. "POT: Python Optimal Transport". In: *Journal of Machine Learning Research* 22.78 (2021), pp. 1–8. URL: http://jmlr.org/papers/v22/20-451.html.

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[6] Filippo Santambrogio. "Optimal transport for applied mathematicians". In: *Birkäuser, NY* 55.58-63 (2015), p. 94.