

Introduction to Optimal Transport and its Applications to Computational Biology

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January 23, 2025



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Outline

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Applications to Computational Biology

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- Applications to Spatial Omics

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References

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.

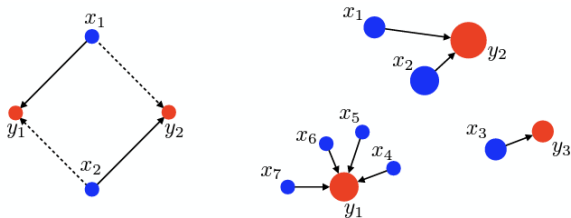
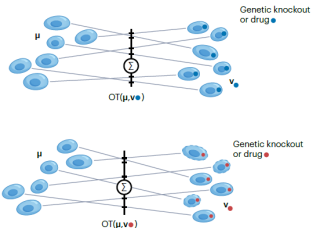


Figure: Example discrete OT problem solutions. [5]

Basics of Optimal Transport

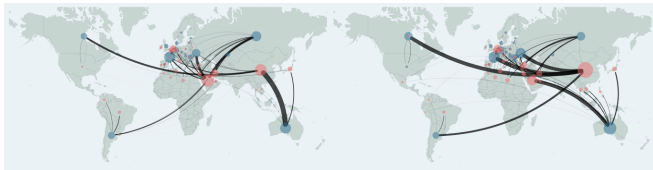
- Areas of applications: **computational biology**, image processing, economics, and many more.



(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.

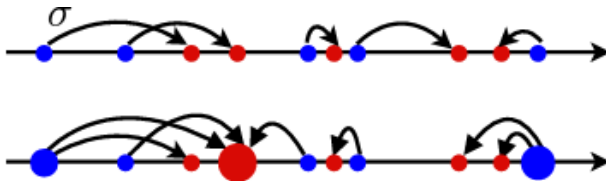


Figure: Fundamental problem in OT. [5]

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.

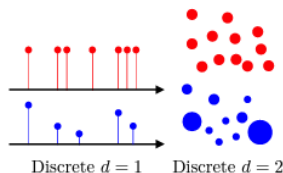


Figure: Example of probability mass functions. [5]

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 $T : X \rightarrow Y$ minimizing the cost.

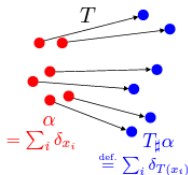


Figure: Bijective mapping example. [5]

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.

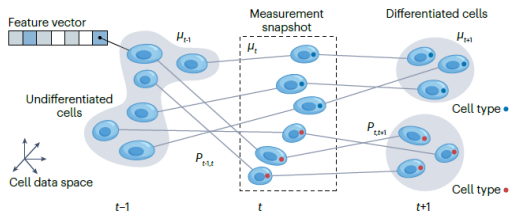


Figure: Cell differentiation relationship. [1]

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.

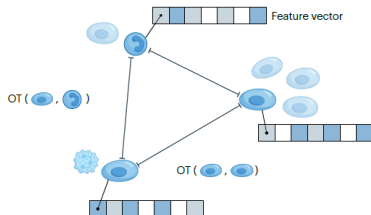


Figure: OT distances for cells. [1]

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.

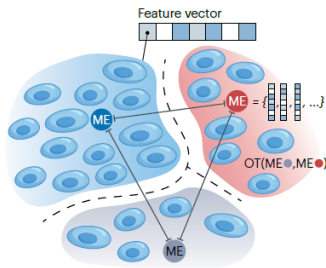


Figure: OT distances of MEs. [1]

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.

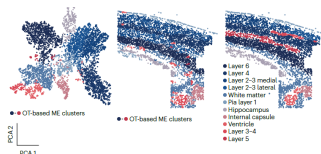


Figure: Clustering visualization of MEs. [1]

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.

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- [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>.
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