Learning More Effective Cell Representations Efficiently

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Abstract

Capturing similarity among cells is the core of many tasks in single-cell transcriptomics, such as the identification of cell types and cell states. This problem can be formulated in a paradigm called metric learning. Metric learning aims to learn data embeddings (feature vectors) in a way that reduces the distance between feature vectors corresponding to cells belonging to the same cell type and increases the distance between the feature vectors corresponding to different cell types. Deep metric learning on the other hand uses neural networks to automatically learn discriminative features from the cells and then compute the metric. The (deep) metric learning approaches have been successfully applied to computational biology tasks like similar cell identification and synthesis of heterogeneous single-cell modalities. We identify two computational challenges: precise distance measurement between cells and scalability over a large amount of data in the applications of (deep) metric learning. And then we propose our solutions: optimal transport and coreset optimization. Optimal transport has the potential to measure cell similarity more effectively and coreset optimization is promising to train representation learning models more efficiently. Empirical studies in image retrieval and clustering tasks show the promise of the proposed approaches. We propose to further explore the applicability of our methods to cell representation learning.

1 Introduction

The success of machine learning algorithms largely depends on data representation. Metric learning learns data embeddings and feature vectors in a way that reduces the distance between feature vectors corresponding to objects belonging to the same class and increases the distance between the feature vectors corresponding to different classes. Deep metric learning, on the other hand, uses neural networks to automatically learn discriminative features from the objects and then compute the metric. (Deep) metric learning falls into the broad umbrella of representation learning, whose quest for representation learning is motivating the design of more powerful representation [3, 10].

These representation learning methods have achieved great successes in biology applications [31, 33**?** , 15, 17**?** , 27, 40, 17, 37, 1]. For example, Schema [31] uses a principled metric learning strategy to

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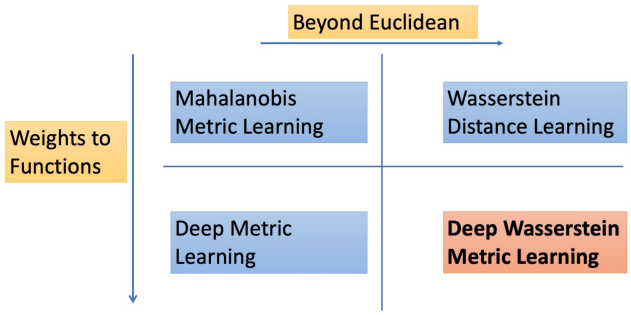

Figure 1: Overview of the Deep Wasserstein Metric Learning Framework

identify informative features in a modality to synthesize disparate modalities into a single coherent interpretation. It is used to infer cell types by integrating gene expression and chromatin accessibility data. The deep metric learning framework SCimilarity (Invited Talk "Design for Inference in Drug Discovery and Development" by Aviv Regev, ICML 2022), which employs a standard triplet loss design, has achieved impressive performance in identifying similar cells in a massive collection of scRNA-Seq datasets. The results can help answer questions like in which tissues and diseases we find fibrotic macrophage-like cells.

[11] proposes the Deep Wasserstein Metric Learning Framework, as shown in Figure 1, which conducts multiple steps of adjustments over the original metric learning framework and achieves improved performance in image retrieval and clustering tasks. In the rest of the proposal, we introduce the adjustments accordingly and design empirical studies for single-cell applications.

2 Methods

2.1 Representation Learning: Metric Learning and Deep Metric Learning

Representation learning is a class of machine learning approaches that allow a system to discover the representations required for feature detection or classification from raw data [14, 18, 13, 19, 9, 39] The requirement for manual feature engineering is reduced by allowing a machine to learn the features and apply them to a given activity. Metric learning and deep metric learning, specifically, focus on similarity-based approaches to learning the representations. Thus the similarity measurement becomes very important. Metric learning has only limited capability to capture non-linearity in the data, while deep metric learning captures non-linear features better by learning the non-linear transformation. In the following, we present two adjustments that can improve metric learning's performances, one is optimal transport [8], and one is coreset optimization [23].

2.2 Optimal Transport

The most widely used loss functions for deep metric learning are the contrastive loss and the triplet loss, both use euclidean distance to measure the distance between objects. A more comprehensive illustration of so-called "ranking-based" loss functions are summarized in Figure 2. Optimal transport (OT) is the general problem of moving one distribution of mass to another as efficiently as possible [32, 11, 26, 36]. Optimal transport has been used tremendously in computational biology [30, 29, 34, 35]. For example, [30] uses scRNA-seq data collected across a time course to infer how these probability distributions evolve over time, by using the mathematical approach of optimal transport.

Wasserstein distance provides a mathematical tool to measure distances between functions, histograms, or more general objects in the optimal transport problem. Wasserstein distance is also called Earth Mover's Distance, which is employed to develop PhEMD (Phenotypic Earth Mover's Distance) [6], which is used to embed the space of drug perturbations on the basis of the drugs' effects on cell populations. Wasserstein distance-based loss functions have shown superior performance in learning tasks [16]. Thus a new set of loss functions are proposed to replace the Euclidean distance with Wasserstein distance in original contrastive loss and triplet loss by defining $d_w(x, y) = W_1(x, y)$. The new Wasserstein-contrastive (wcontrastive) loss and Wasserstein-triplet (wtriplet) loss can be

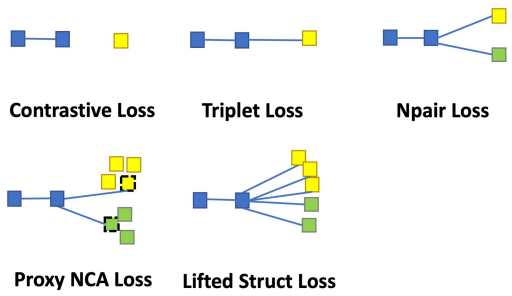

Figure 2: Illustration of different ranking-based loss functions. Different colors (blue, yellow, green) represent different classes. For simplicity, only 3 classes are shown. The left-most blue square is an anchor (query). In Contrastive loss, the anchor is compared with only one positive example. In Triplet loss, the anchor is compared with only one negative example and one positive example. In Npair, ProxyNCA, and Lifted Struct losses, one positive example and multiple negative classes are incorporated. Npair loss randomly selects one example per negative class. ProxyNCA loss pushes the anchor away from negative proxies instead of negative examples. The proxy is class-level and can represent any instance in the corresponding class. Lifted Struct loss uses all examples from all negative classes [12, 20].

formulated as the following [11]:

$$\mathcal{L}_{\text{wcontrastive}} = \frac{1}{b} \sum_{(i,j)\in\mathcal{P}}^{b} \mathbb{I}_{y_i=y_j} d_w\left(\phi_i, \phi_j\right) + \mathbb{I}_{y_i\neq y_j}\left[\gamma - d_w\left(\phi_i, \phi_j\right)\right]_+ , \tag{1}$$

$$\mathcal{L}_{\text{wtriplet}} = \frac{1}{b} \sum_{\substack{(a,p,n)\in\mathcal{T} \\ y_a=y_p\neq y_n}}^{b} \left[d_w\left(\phi_a, \phi_p\right) - d_w\left(\phi_a, \phi_n\right) + \gamma\right]_+ . \tag{2}$$

We propose to apply the two new loss functions to similar cell identification and synthesis of heterogeneous modalities applications.

2.3 Coreset Optimization

Coreset optimization is about data-efficient methods to find subsets of massive data that can generalize to the full data when trained on. In other words, a coreset is a subset of the original training set that is representative to train machine learning models [11, 38, 24, 21]. More specifically, Wasserstein measure coreset [7], is an extension of coresets that takes into account continuous data distribution and generalization. Recently coreset has been successfully applied to the purification of single-cell transcriptomics data [25]. It focuses on alleviating potential replicate specific biases within single-cell datasets. The key is to select a "representative" subset (coreset) of cells from areas of the single-cell landscape where multiple replicates are represented. [31] processes data from a Slide-seq replicate (three modalities with 20823 transcriptomes * 17607 genes) in 34 mins. [23] demonstrates a specific coreset optimization algorithm CRAIG can achieve the average speedup of 3x for similar loss residual and error rate. So we expect for the single cell synthesis task in [31], we can reduce data processing time from 34 mins to 11 mins. For future work, We refer the interested reader to [1, 2] for feature-efficient methods that remove irrelevant variables during the training.

3 Experiments Design

The experiments conducted on various datasets have demonstrated that optimal transport and coreset optimization can achieve superior performance on image retrieval and clustering tasks [11, 12]. We plan to follow the setup in [22] to apply the methods on multiple single-cell datasets including sci-CAR cell line [4], SNARE-seq cell line [5], and 10X Multiome T-cell depleted bone marrow [28] to validate the methods' effectiveness and develop new computational and biological insights from the downstream tasks.

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