Generative Models for scRNA

Jackson Loper

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Status Succesfully trained the new "iterative model," evaluated it to some extent

Todo Compare clusters against Allen, consider linear model, do more layers

1 Overview

The Allen Institute has developed a method for clustering, one that has apparently allowed them to distinguish 116 unique cell types using single cell RNA data. The method follows the following iterative procedure:

Algorithm 1: itclust

Data: RNA expression for a collection of cells

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Run PCA on the data (e.g. take first 16 components);
Run T-SNE on the resulting low-d representation;
Circle things that look like clusters;
if there is more than one cluster then
    for each cluster c do
        run itclust on the cells inside c;
    end
end
```

This method is nice because the important low-dimensional representations *within* a cluster may be quite different from the ones that help you distinguish *between* two subclusters within that cluster. This is what allows them to achieve the level of granularity that they have.

Unfortunately, it is a bit difficult to grasp the uncertainty involved in the process. There is certainly noise in the data, and different practitioners of this basic procedure may have different understandings of what this noise is. The result is that when Bosilijka Tasic (one of the lead experimentalists at Allen) gives two data scientists the same data, they each come back with different answers. And they have no way to compare or evaluate these two different answers. One essential question is "what level of granularity does the signal-to-noise ratio support?" The algorithm above, as stated, runs iteratively until subclusters cannot be distinguished via T-SNE. But this is obviously a very subjective matter. What to do?

We propose to help clarify some of these issues by building a fully generative model of gene expression, one that rigorously measures some kinds of uncertainty in every step of the process. To be most useful to the Allen Institute, however, we also want this generative model to fit into the scientific paradigm under which they are operating. In particular, the treatment of clusters should be hierarchical in nature, and it is desirable that the model

have latent representations that roughly correspond to the low-dimensional representations found in the Allen algorithm.

2 Model

Towards this end, we propose the following generative model for gene expression of a single cell. Let H denote a tree of cell types.

1. $T \sim \text{Categorical}(\pi)$, one of the leaves of H. Let $t_0, t_1(T), t_2(T), \cdots, t_\ell(T)$, indicate the nodes in the unique path in H which leads from the root to the leaf T. Here t_0 is the root of the tree, ℓ is the depth of the leaf T, and $t_\ell(T) = T$. To consolidate notation, we take $T_i \triangleq t_i(T)$.
2. For each $i < \ell$ let $Z_{T_i} \sim \mathcal{N}(\mu_{T_{i+1}}, \Sigma_{T_{i+1}})$, and take $Z_{T_\ell} \sim \mathcal{N}(0, I)$
3. For each gene g, let $\lambda_g \in \mathbb{R}^p$ denote a set of parameters. These will be a deterministic function of the Zs:
$$\lambda_g = f_g\left(\sum_{i=0}^{\ell} h_{T_i} Z_{T_i}\right)$$
4. Conditioned on Z, the gth gene of the cell be distributed according to some $p(x_g; \lambda_g)$.

Let us unpack some of this:

- The latent representation Z_i corresponds to features of that cell which are specific to all the cells which are descendents of T_i.
- The the cell's subcluster T_{i+1} effects the distribution of its latent features at the ith level, Z_i. That is, the latent distribution on the ith latent representation is governed by what subcluster it is part of within T_i.
- The distribution of the final latent representation, Z_T, is simply a standard normal.
- The functions h_{T_i} indicates how these cell-type-specific features alter the distribution on the gene expressions for cells in that branch of the tree.

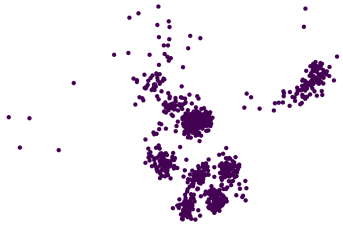
For inference, we use amortized variational inference. In particular, we take the variational family that T and all the Z_{T_i} are independent, T is some categorical, and Zs are isotropic gaussians. We build a neural network to estimate the variational parameters from gene expressions. Note that this network must estimate the parameters for a gaussian at *each node* in the tree H.

3 Empirical results

At the current moment, we have only actually implemented this model in the case the H is a tree with depth 1, i.e. the hierarchy is trivial. We take the data model to be a zero-inflated negative binomial. It looks fairly promising. For a simple qualitative assessment, consider the following.

Scatterplot of the aggregate posterior distribution of Z_{T_0}, colored by posterior mean of the cluster assigment:

Notice that there are only so many clusters that are really clearly distinct in this latent space. However, let's focus on that cluster on the right-hand side. What happens if we look at the Z_{T_1} variables for those cells? We get substantial subclustering apparent in the Z_{T_2} space:



3.1 Held out log likelihood

To quantitatively analyse our method, we used a held out log likelihood:

- Train the method on 75% of the cells
- For each of the remaining 25% of the cells, select 75% of the genes ("observed"):
  - Compute the posterior mode of Z given the expression of those genes
  - Compute the log probability of the observed genes given the posterior mode
  - Compute the log probability of the unobserved genes given the posterior mode
- Average values over those 25% of the cells

Here are the results for this "Posterior mode predictive (PMP)" approach:

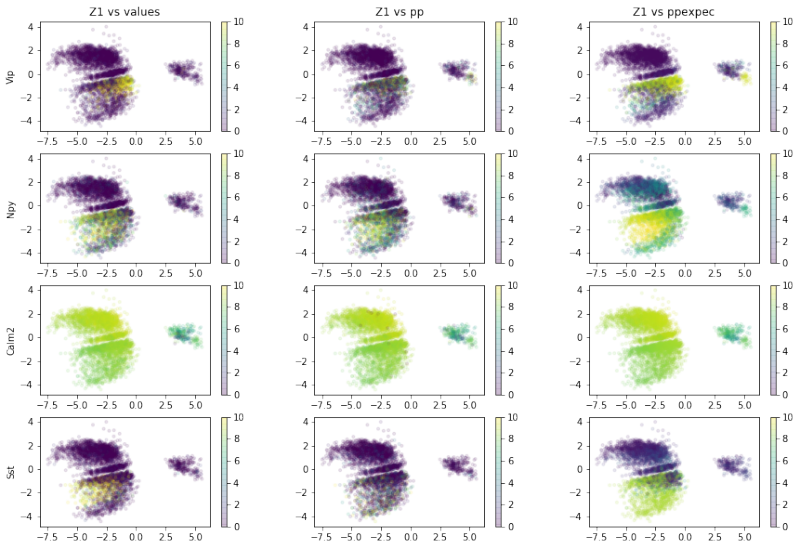
Method	PMP, observed	PMP, unobserved
Factor analysis $k = 16$	-4.2	-4.2
Factor analysis $k = 64$	-4.1	-4.3
HNBPF $k = 2$	-5.7	-5.7
HNBPF $k = 16$	-3.8	-3.9
HNBPF $k = 64$	-3.8	-5.7
ZINB-Vae $k = 2$	-3.6	-3.6
Smooth ZINB-Vae $k = 2$	-3.6	-3.6
Smooth Hierarchical ZINB $k = 2 + 2$	-3.5	-3.5

Here HNBPF is a negative-binomial-poisson-factorization approach, ZINB-Vae is based on a Michael Jordan paper, k is the number of latent dimensions. The results are certainly not mind-blowing, but its nice to see that we're at least not doing worse.

To do posterior inference on held out likelihood, our approach is to first set all of the "unobserved" entries to the average value for the corresponding genes, and apply our inference network unchanged to get estimates for the variational parameters. We then refine these estimates with gradient descent. We note that if we use completely random guesses to initialize the gradient descent, we often converge to inferior local minima; this shows the benefit of the amortized inference.

3.2 Posterior predictive samples

One limitation of the method as we have implemented it is that the posterior predictive distribution seems to be substantially underfitting. To see what we mean, consider the following figure:



Here we four rows and three columns of plots. Each row corresponds to a different gene. Each dot in each plot corresponds to a cell. The position of the dot indicates the latent representation of the cell, as inferred by posterior inference. The color indicates the amount of expression for the particular gene for that cell, measured three ways:

1. The first column shows the true expression of the appropriate gene for each cell (i.e the color of each dot is the gene expression for that cell)
2. The second column shows a posterior predictive sample of the gene expression for each cell
3. The third column shows the mean of such samples for each cell

We see that the true expression doesn't look much like the posterior predictive expression for the Vip and Sst genes. Something better is needed. Possibly more layers. Possibly more training. Worth thinking about.