# Generative Models for scRNA

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

**Todo** Compare clusters against Allen, try unamortized inference

## 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, $\ell$ 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 $Z$s:
$$\lambda_g = f_g\left(\sum_{i=0}^{\ell} h_{T_i} Z_{T_i}\right)$$
4. Conditioned on $Z$, the $g$th 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 $i$th level, $Z_i$. That is, the latent distribution on the $i$th 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.

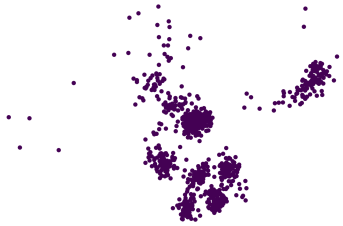
For inference, we use amortized variational inference. In particular, we take the variational family that $T$ and all the $Z_{T_i}$ are independent, $T$ is some categorical, and $Z$s are isotropic gaussians. We build a neural network to estimate the variational parameters from gene expressions. Note 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 heading in a reasonable direction. There may be an upper limit on the PMP, due to very real technical noise in the system, so it is hard to evaluate whether this is a trivial improvement or not.

To arrive at our figures for our model, we use a truly ridiculous method of variational inference. In particular, we simply *zero out* all of the "unobserved" entries, and apply our inference network unchanged to get estimates for the variational parameters. This is not "cheating" in the sense that it is a practical method for imputation in the case where certain genes are unobserved. However, it might well do less than optimally. I was talking to Scott, and it sounds like the question of amortized inference with unpredictably missing data is a big deal right now. Worth thinking about more.

### 3.2 Denoising