A Bayesian model for gene expression on MERFISH data
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Introduction

Multiplexed error-robust fluorescence in-situ hybridization (MERFISH, Chen et al. (2015)) is a new approach to measure RNA molecules of hundreds of different genes in single cells in parallel, while retaining spatial information. MERFISH uses the following strategy to label hundreds of RNA species in parallel with a limited set of colors (see Fig. 1):
- RNA molecules are labeled with multiple probes
- \( N \) hybridization rounds are performed
- in each round, different probes are marked fluorescently, generating a binary pattern for each RNA molecule
- RNA species are identified by comparing the pattern against the designed probsets
- a modified 4-bit distance hamming code is used for robustness

We present a Bayesian model to reliably estimate gene expression and differential gene expression on MERFISH data for any number of cells. The presented approach will be available soon as a set of fast, parallelized command line utilities, implemented on top of Rust-Bio (Köster 2015).

Estimating gene expression

The obtained binary words for each RNA molecule are assigned to RNA species (i.e., genes). Thereby, single bit errors can be corrected, obtaining an exact and a corrected count for each gene. Chen et al. (2015) report prior probabilities for making \( 1 \to 0 \) or \( 0 \to 1 \) errors, which can be used to derive the probability of an exact or corrected call or miscall and the probability to miss a molecule.

Let \( D \) be the given data, i.e., the binary words obtained assigned to a particular RNA species. We obtain the likelihood of an expression \( x \) by summing over all possibilities to have \( x \), correct calls, \( x_e \), miscalls, and \( x - x_e \) misses as

\[
Pr(D|X = x) = \sum_{x_e} \Pr(x|D) \sum_{i=0}^{\min(|D|,|x|)} \binom{|D|}{i} \binom{|D| - |D_e|}{i} (1 - \alpha)^i \alpha^{D - i}
\]

Using Bayes theorem, we can calculate the posterior probability \( Pr(X = x|D) \) for an expression \( x \) (see Fig. 2 and 3). For a set of \( n \) cells with data \( D \), the posterior probability for a mean expression \( \bar{X} = x \) in all cells is

\[
Pr(\bar{X} = x|D) = \sum_{x_e} \prod_{i=1}^{n} Pr(X = x_i|D_i)
\]

The probability mass function can be calculated in pseudo-polynomial time with dynamic programming.

Estimating differential gene expression

The posterior probability for a given fold change \( f \) between the sets of cells \( D \) and \( D' \) can then be calculated as

\[
Pr(F = f|D, D') = \sum_{\bar{X}} Pr(\bar{X} = x|D) Pr(\bar{X} = fx|D')
\]

On top of this probability, we can calculate the conditional expectation for the fold change and the corresponding standard deviation (see Fig. 4). We can further obtain the posterior error probability (PEP) for differential expression as \( Pr(|F| \leq \text{ferr}|D, D') \) and use it to control the false discovery rate (FDR) in a Bayesian way as described by Muller, Parmigiani, and Rice (2006).

References