

Notebook

2016/04/06

- init repo, wiki page
- set an hour for investigating the questions
- what are the primary human cell lineages?
- where can we get data for them?
- look into hematopoietic cell lineage
- some questions for the future
- how many cell lineages represented in COdat?
- how to separate cell lineages in COdat?
- there is The Human Cell Lineage Flagship Initiative
- has not been updated since 2010
- fertilized egg as root, extant cells as leaves, branches as cell divisions
- cell lineage of *C. elegans* known
- structure+dynamics of cell lineage in **development, growth, renewal, aging, disease**
- diseases such as **cancer, auto-immune diseases, diabetes, neuro-degenerative, cardiovascular, rare inherited**
- cells with similar **signatures** should reside close to each other in the cell lineage tree
- if it is \$1000 for whole genome sequencing, will be \$100 000 000 000 000 000 for the entire cell lineage
- but fraction of each genome is enough
- Presentation
- TEDxTelAviv - Ehud Shapiro - Uncovering the Human Cell lineage tree
- Reconstruction of Cell Lineage Trees in Mice
- more papers
- people - from UofT, John Dick working on 'Hematopoietic and immune system'
- looked for more recent papers on cell lineages from Shapiro
 - Comparing Algorithms That Reconstruct Cell Lineage Trees Utilizing Information on Microsatellite Mutations
- Stem cell lineage database
- Cell Lineage Analysis in Human Brain Using Endogenous Retroelements
- KEGG - Hematopoietic cell lineage

TODOs for next session: - look more into hematopoietic research, recent papers by John Dick? - does KEGG have other cell lineages? - which are the most studied human cell lineages? - read Comparing Algs. That Reconstruct Cell Lineage Trees paper

2016/04/07

- [x] read Comparing Algs. That Reconstruct Cell Lineage Trees paper

2016/04/08

- [x] nothing

2016/04/09

Comparing Algorithms That Reconstruct Cell Lineage Trees Utilizing Information on Microsatellite Mutations

- compared algs. and metrics on cluster and distance based methods
- vertices are cells, directed edges are progeny relationships
- examining only mutations in highly variable MS regions (also called STR)
- most algs. good if biological scenario to test for is *simple*
- best was neighbour joining with normalized abs. dist.

- idea: *distance* between genomic *signatures* can be used to reconstruct cell lineage tree
- slippage mutations @ 10^{-5} per locus per cell division vs. 10^{-10} for SNPs. also used mismatch-repair (MMR) deficient mice to get 10^{-2}
- “best method is not the one that gives the most accurate estimates of the mean distance, but rather the one with the lowest variance”
- differences b/w cell lineage reconstruction and population genetics:
 - stem cells can influence shape of tree
 - sometimes very shallow tree
 - large variation in numbers of divisions the cells have undergone since the zygote (vs. species with different evolutionary paces)
 - cells have undergone binary cell divisions
- two aspects of the lineage were examined:
 - clustering of biologically distinct cell groups
 - distinguishing b/w two groups of cells that are known to have different *depths*
- tree reconstruction algorithms
 - **NJ** Neighbour Joining
 - **UPGMA** Unweighted Pair Group Method with Arithmetic Mean alg.
 - **QMC** Quartet Max Cut
- distance measures
 - A_i^l and A_j^l are the number of repeats in the l 'th single allele of the i 'th and j 'th sampled cells
 - $\{L\}$ is the set of L alleles which were amplified for both samples i and j
 - abs. genetic distance
 1. regular

$$D(i, j) = \frac{1}{L} \sum_{l \in \{L\}} |A_i^l - A_j^l|$$

2. normalized

$$D(i, j) = \frac{1}{L} \sum_{l \in \{L\}} \left| \frac{A_i^l}{\sum_{l \in \{L\}} |A_i^l|} - \frac{A_j^l}{\sum_{l \in \{L\}} |A_j^l|} \right|$$

- Euclidean distance

$$D(i, j) = \sqrt{\sum_{l \in \{L\}} (A_i^l - A_j^l)^2}$$

- Equal or Not distance

$$D(i, j) = \frac{1}{L} \sum_{l \in \{L\}} 1\{(A_i^l - A_j^l) \neq 0\}$$

- six versions of **ML** Maximum Likelihood distances (ML estimate of the number of divisions separating the two cells):
 1. assuming equal mutation rates for all loci
 2. assuming two-different mutation rates for mono-nucleotide (1/22) and di-nucleotide (1/32) repeats
 3. assuming length dependent mutation rates
 4. three models with **SMM** Stepwise Mutation Model (equal prob. of addition/deletion of one repeat given that a mutation happens) and **MMM** Multistep Mutation Model (multiple additions/deletions of repeat unit possible according to a symmetrical dist.)
- clustered cells of individuals separately, but distinct clustering unlikely in some cases, esp. if individuals related
- three metrics to quantify clustering quality of distinct groups
 1. **QLC** Quality of the Largest Cluster

for each cell type i

for each internal node

count number of leaves of the i 'th type that are descendants of this node

- degree of node is defined as $p \cdot q$ where

- p is the percentage of cells from the i 'th type that are descendants of this node out of all cells of type i
- q is the percentage of cells from type i that are descendants of this node among all the cells that are descendants of this node
- $q < 0.6 \Rightarrow$ degree is 0
- score of each cell type i

$$QLC_i = \max(p \cdot q)$$

- and QLC of whole tree is avg. of QLC on all cell types

$$QLC = \frac{1}{I} \sum_{i \in \{I\}} QLC_i$$

2. **TE** Tree Entropy

- assesses the amount of mixing on the tree b/w each pair of cell groups
- affected only by number of clusters, not size
- number of clusters of cell types i and j is obtained
- equivalent state of the system is all the cases that will have the same number of clusters of each type. number of states:

$$\Omega(i, j) = \frac{(n_i - 1)!}{(n_i - c_i)!(c_i - 1)!} c_i! \frac{(n_j - 1)!}{(n_j - c_j)!(c_j - 1)!} c_j!$$

where n_i and n_j are the number of cells of type i and j , and c_i and c_j are the number of clusters of type i and j

$$\text{Entropy}(i, j) = \ln(\Omega)$$

- entropy of tree is a half diagonal matrix (not scalar), scalar entropy is avg. over all pairs i, j :

$$\text{Entropy} = \frac{1}{P} \sum_i \sum_{j=i+1} \text{Entropy}(i, j)$$

where P is the number of all pairs i, j

3. **HS** Hyper geometric Sampling

- test null hypothesis (no association b/w sub-tree and classification tree) with a hypergeometric test
- given sub-tree of n cells in which x cells are of type A , the branch's p-value is the probability to see x or more cells of type A given that the n cells are random samples from N :

$$p = f(n, N, s, x) = \frac{\binom{s}{n} \binom{N-s}{x-s}}{\binom{N}{x}}$$

- with 20% FDR. score for whole tree is

$$HS = \frac{1}{I} \sum_{i \in \{I\}} HS_i$$

- issue: only a limited amount of MS available
- NJ-Normalized absolute was best at inferring clustering of distinct groups: demonstrates clear-cluster separation not necessarily correlated with precise description of mutational process
- depth measures
 - Kolmogorov Smirnov **KS** test
 - **ND** Normalized Distance

$$ND = \frac{|\mu_1 - \mu_2|}{\frac{\sigma_1 + \sigma_2}{2}}$$

- overlap percentage

$$\text{Overlap} = \frac{\sum_{i=1}^{n_X} \sum_{j=1}^{n_Y} 1 \cdot \{\text{Dist}_Y(j) < \text{Dist}_X(i)\}}{n_X \cdot n_Y}$$