Computing Bi-Clusters for Microarray Analysis

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General Bi-clustering Problem

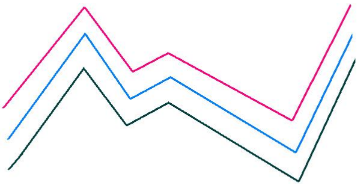
- Input: a $n \times m$ matrix A.
- Output: a sub-matrix $A_{P,Q}$ of A such that the rows of $A_{P,Q}$ are *similar*. That is, all the rows are identical.
  Why sub-matrix?
  A subset of *genes* are co-regulated and co-expressed under specific *conditions*. It is interesting to find the subsets of genes and conditions.

Similarity of Rows (1-5)

- 1. All rows are identical
  1 1 2 3 2 3 3 2
  1 1 2 3 2 3 3 2
  1 1 2 3 2 3 3 2
- 2. All the elements in a row are identical
  1 1 1 1 1 1 1 1
  2 2 2 2 2 2 2 2
  5 5 5 5 5 5 5 5
  (the same as 1 if we treat columns as rows)

Similarity of Rows (1-5)

- 3. The curves for all rows are similar (additive) $a_{i,j} - a_{i,k} = c(j,k)$ for $i = 1, 2, \ldots, m$. Case 3 is equivalent to case 2 (thus also case 1) if we construct a new matrix $a^*_{i,j} = a_{i,j} - a_{i,p}$ for a fixed p indicate a row.



Similarity of Rows (1-5)

- 4. The curves for all rows are similar (multiplicative)

$$\begin{array}{ccccc}
a_{1,1} & a_{1,2} & a_{1,3} & \dots & a_{1,m} \\
c_1 a_{1,1} & c_1 a_{1,2} & c_1 a_{1,3} & \dots & c_1 a_{1,m} \\
c_2 a_{1,1} & c_2 a_{1,2} & c_2 a_{1,3} & \dots & c_2 a_{1,m} \\
\dots & & & & \\
c_n a_{1,1} & c_n a_{1,2} & c_n a_{1,3} & \dots & c_n a_{1,m}
\end{array}$$

Transfer to case 2 (thus case 1) by taking log and subtraction.
Case 3 and Case 4 are called bi-clusters with coherent values.

Similarity of Rows (1-5)

- 5. The curves for all rows are similar (multiplicative and additive)

  $$a_{i,j} = c_i a_{k,j} + d_i$$

  Transfer to case 2 (thus case 1) by subtraction of a fixed row (row i), taking log and subtraction of row i again.
  The basic model: All the rows in the sub-matrix are identical.

Cheng and Churchs model

The model introduced a similarity score called the mean squared residue score H to measure the coherence of the rows and columns in the submatrix.

$$H(P,Q) = \frac{1}{|P||Q|} \sum_{i \in P, j \in Q} (a_{i,j} - a_{i,Q} - a_{P,j} + a_{P,Q})^2$$

where

$$a_{i,Q} = \frac{1}{|Q|} \sum_{j \in Q} a_{i,j}, \quad a_{P,j} = \frac{1}{|P|} \sum_{i \in P} a_{i,j}, a_{P,Q} = \frac{1}{|P||Q|} \sum_{i \in P, j \in Q} a_{i,j}.$$

If there is no error, H(P, Q)=0 for case 1, 2 and 3. A lot of heuristics (programs) have been produced.

Our Problem Definition

- Consensus Sub-matrix Problem
- Bottleneck Sub-matrix Problem

Consensus Sub-matrix Problem

- Input: a $n \times m$ matrix A, integers l and k.
- Output: a sub-matrix $A_{P,Q}$ of A with l rows and k columns and a consensus row z (of k elements) such that

  $\sum_{r_i \in P} d(r_i|^Q, z)$ is minimized.

  Here $d(\ ,\ )$ is the Hamming distance.

Bottleneck Sub-matrix Problem

- Input: a $n \times m$ matrix A, integers l and k.
- Output: a sub-matrix $A_{P,Q}$ of A with l rows and k columns and a consensus row z (of k elements) such that for any r_i in P

  $d(r_i|^Q, z) \leq d$ and d is minimized

  Here $d(\ ,\ )$ is the Hamming distance.

NP-Hardness Results

- Theorem 1: Both consensus sub-matrix and bottleneck sub-matrix problems are NP-hard.

  Proof: We use a reduction from maximum edge bipartite problem.

Approximation Algorithm for Consensus Sub-matrix Problem

- Input: a $n \times m$ matrix A, integers l and k.
- Output: a sub-matrix $A_{P,Q}$ of A with l rows and k columns and a consensus row z (of k elements) such that

  $\sum_{r_i \in P} d(r_i|^Q, z)$ is minimized.

  Here $d(\ ,\ )$ is the Hamming distance.

Basic Ideas

- Assumptions: $H_{opt} = \sum_{p_i \in P_{opt}} d(x_{p_i}|^{Q_{opt}}, z_{opt}) = O(kl)$, $H_{opt} \times c' = kl$ and $|Q_{opt}| = k = O(n)$, $k \times c = n$.
- Basic Ideas: We use a random sampling technique to randomly select O(log$m$) columns in Q_{opt}, enumerate all possible vectors of length O(log$m$) for those columns. At some moment, we know O(log$m$) bits of r_{opt} and we can use the partial z_{opt} to select the l rows which are closest to z_{opt} in those O(log$m$) bits. After that we can construct a consensus vector r as follows: for each column, choose the (majority) letter that appears the most in each of the l letters in the l selected rows. Then for each of the n columns, we can calculate the number of mismatches between the majority letter and the l letters in the l selected rows. By selecting the best k columns, we can get a good solution.

Basic Ideas

- How to randomly select O(log$m$) columns in Q_{opt} while Q_{opt} is unknown?
- Our new idea is to randomly select a set B of $(c+1)\log m$ columns from A and enumerate all size $\log m$ subsets of B in time $O(m^{c+1})$ which is polynomial in terms of the input size $O(mn)$. We can show that with high probability, we can get a set of $\log m$ columns randomly selected from Q_{opt}.

Algorithm 1 for The Consensus Submatrix Problem

Input: one $m \times n$ matrix A, integers l and k, and $\epsilon > 0$

Output: a size l subset P of rows, a size k subset Q of columns and a length k consensus vector z

Step 1: randomly select a set B of $\lceil (c+1)(\frac{4\log m}{\epsilon^2}+1)\rceil$ columns from A.

(1.1) **for** every size $\lceil \frac{4\log m}{\epsilon^2} \rceil$ subset R of B **do**

(1.2) **for** every $z|^R \in \Sigma^{|R|}$ **do**

(a) Select the best l rows $P = \{p_1, ..., p_l\}$ that minimize $d(z|^R, x_i|^R)$.

(b) **for** each column j **do**

Compute $f(j) = \sum_{i=1}^{l} d(s_j, a_{p_i,j})$, where s_j is the majority element of the l rows in P in column j. Select the best k columns $Q = \{q_1, ..., q_k\}$ with minimum value $f(j)$ and let $z(Q) = s_{q_1} s_{q_2} \dots s_{q_k}$.

(c) Calculate $H = \sum_{i=1}^{l} d(x_{p_i}|^Q, z)$ of this solution.

Step 2: Output P, Q and z with minimum H.

Proofs

- Lemma 1: With probability at most $m^{-\frac{2}{\epsilon^2 c^2 (c+1)}}$, no subset R of size $\lceil \frac{4 \log m}{\epsilon^2} \rceil$ used in Step 1 of Algorithm 1 satisfies $R \subseteq Q_{opt}$.
- Lemma 2: Assume $|R| = \lceil \frac{4 \log m}{\epsilon^2} \rceil$ and $R \subseteq Q_{opt}$. Let $\rho = \frac{k}{|R|}$. With probability at most m^{-1}, there is a row x_i in X satisfying

$$\frac{d(z_{opt}, x_i|^{Q_{opt}}) - \epsilon k}{\rho} > d(z_{opt}|^R, x_i|^R).$$

With probability at most $m^{-\frac{1}{3}}$, there is a row x_i in X satisfying

$$d(z_{opt}|^R, x_i|^R) > \frac{d(z_{opt}, x_i|^{Q_{opt}}) + \epsilon k}{\rho}.$$

Proofs

- Lemma 3: When $R \subseteq Q_{opt}$ and $z|^R = z_{opt}|^R$, with probability at most $2m^{-\frac{1}{3}}$, the set of rows $P = \{p_1, \ldots, p_l\}$ selected in Step 1 (a) of Algorithm 1 satisfies $\sum_{i=1}^{l} d(z_{opt}, x_{p_i}|^{Q_{opt}}) > H_{opt} + 2\epsilon kl$.
- Theorem 2: For any $\delta > 0$, with probability at least $1 - m^{-\frac{8c'^2}{\delta^2 c^2 (c+1)}} - 2m^{-\frac{1}{3}}$, Algorithm 1 will output a solution with consensus score at most $(1+\delta)H_{opt}$ in $O(nm^{O(\frac{1}{\delta^2})})$ time.

Approximation Algorithm for Bottleneck Sub-matrix Problem

- Input: a $n \times m$ matrix A, integers l and k.
- Output: a sub-matrix $A_{P,Q}$ of A with l rows and k columns and a consensus row z (of k elements) such that for any r_i in P

  $d(r_i|^Q, z) \leq d$ and d is minimized

  Here $d(\ ,\ )$ is the Hamming distance.

Basic Ideas

- Assumptions: $d_{opt} = MAX_{p_i \in P_{opt}} d(x_{p_i}|^{Q_{opt}}, z_{opt}) = O(k)$, $d_{opt} \times c'' = k$ and $|Q_{opt}| = k = O(n)$, $k \times c = n$.
- Basic Ideas:
  (1) Use random sampling technique to know O(log$m$) bits of z_{opt} and select l best rows like Algorithm 1.
  (2) Use linear programming and randomized rounding technique to select k columns in the matrix.

- Linear programming
  Given a set of rows $P = \{p_1, \ldots, p_l\}$, we want to find a set of k columns Q and vector z such that bottleneck score is minimized.

$$\min d;$$
$$\sum_{i=1}^{n} \sum_{j=1}^{|\Sigma|} y_{i,j} = k,$$
$$\sum_{j=1}^{|\Sigma|} y_{i,j} \leq 1, i = 1, 2, \ldots, n,$$
$$\sum_{i=1}^{n} \sum_{j=1}^{|\Sigma|} \chi(\pi_j, x_{p_s,i}) y_{i,j} \leq d, s = 1, 2, \ldots, l.$$

$y_{i,j} = 1$ if and only if column i is in Q and the corresponding bit in z is π_j.
Here, for any $a, b \in \Sigma$, $\chi(a, b) = 0$ if $a = b$ and $\chi(a, b) = 1$ if $a \neq b$.

- Randomized rounding
  To achieve two goals:
  (1) Select k' columns, where $k' \geq k - \delta d_{opt}$.
  (2) Get integers values for $y_{i,j}$ such that the distance (restricted on the k' selected columns) between any row in P and the center vector thus obtained is at most $(1+\gamma)d_{opt}$.
  Here $\delta > 0$ and $\gamma > 0$ are two parameters used to control the errors.

- Lemma 4: When $\frac{n\gamma^2}{3(cc'')^2} \geq 2\log m$, for any $\gamma, \delta > 0$, with probability at most $exp(-\frac{n\delta^2}{2(cc'')^2}) + m^{-1}$, the rounding result $y' = \{y'_{1,1}, \ldots, y'_{1,|\Sigma|}, \ldots, y'_{n,1}, \ldots, y'_{n,|\Sigma|}\}$ does not satisfy at least one of the following inequalities,

$$\sum_{i=1}^{n}(\sum_{j=1}^{|\Sigma|} y'_{i,j}) > k - \delta d_{opt},$$

and for every row $x_{p_s}(s = 1, 2, \ldots, l)$,

$$\sum_{i=1}^{n}(\sum_{j=1}^{|\Sigma|} \chi(\pi_j, x_{p_s,i}) y'_{i,j}) < \overline{d} + \gamma d_{opt}.$$

Algorithm 2 for The bottleneck Sub-matrix Problem

Input: one matrix $A \in \Sigma^{m \times n}$, integer l, k, a row $z \in \Sigma^n$ and small numbers $\epsilon > 0$, $\gamma > 0$ and $\delta > 0$.

Output: a size l subset P of rows, a size k subset Q of columns and a length k consensus vector z.

if $\frac{n\gamma^2}{3(cc'')^2} \leq 2\log m$ **then** try all size k subset Q of the n columns and all z of length k to solve the problem.

if $\frac{n\gamma^2}{3(cc'')^2} > 2\log m$ **then**

Step 1: randomly select a set B of $\lceil \frac{4(c+1)\log m}{\epsilon^2} \rceil$ columns from A. **for** every $\lceil \frac{4\log m}{\epsilon^2} \rceil$ size subset R of B **do**

for every $z|^R \in \Sigma^{|R|}$ **do**

(a) Select the best l rows $P = \{p_1, ..., p_l\}$ that minimize $d(z|^R, x_i|^R)$.

(b)Solve the optimization problem by linear programming and randomized rounding to get Q and z.

Step 2: Output P,Q and z with minimum bottleneck score d.

Proofs

- Lemma 5: When $R \subseteq Q_{opt}$ and $z|^R = z_{opt}|^R$, with probability at most $2m^{-\frac{1}{3}}$, the set of rows $P = \{p_1, \ldots, p_l\}$ obtained in Step 1(a) of Algorithm 2 satisfies $d(z_{opt}, x_{p_i}|^{Q_{opt}}) > d_{opt} + 2\epsilon k$ for some row $x_{p_i}(1 \le i \le l)$.
- Theorem 3: With probability at least $1 - m^{-\frac{2}{\epsilon^2 c^2 (c+1)}} - 2m^{-\frac{1}{3}} - exp(-\frac{n\delta^2}{2(cc'')^2}) - m^{-1}$, Algorithm 2 runs in time $O(n^{O(1)} m^{O(\frac{1}{\epsilon^2} + \frac{1}{\gamma^2})})$ and obtains a solution with bottleneck score at most $(1 + 2c''\epsilon + \gamma + \delta)d_{opt}$ for any fixed $\epsilon,\ \gamma,\ \delta > 0$.

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Let $X_1, X_2, \ldots, X_n$ be n independent random 0-1 variables, where X_i takes 1 with probability p_i, $0 < p_i < 1$. Let $X = \sum_{i=1}^{n} X_i$, and $\mu = E[X]$. Then for any $0 < \epsilon \leq 1$,

$$\begin{aligned} \mathbf{Pr}(X > \mu + \epsilon\, n) &< e^{-\frac{1}{3} n\epsilon^2}, \\ \mathbf{Pr}(X < \mu - \epsilon\, n) &\leq e^{-\frac{1}{2} n\epsilon^2}. \end{aligned}$$