Supplementary Materials

0.1 Preprocessing expression data

We removed the gene expression profiles with overall small absolute values less than a percentile cutoff (60% is used here). Further, we removed the gene expression profiles with a variance less than the percentile specified by another cutoff (30% is used here). The procedure was done using the standard functions (genelowvalfilter(Data, ‘Percentile’, .60) and genevarfilter(Data, ‘Percentile’, .30)) in the Matlab software.

0.2 The SNMNMF algorithm and the discussion of its convergence

The SNMNMF algorithm minimizes the following objective function:

\[ F(W, H_1, H_2) = \sum_{i=1}^{I} \| X_i - W H_1 \|_F^2 \]

\[ - \lambda_1 Tr(H_2 A H_2^T) - \lambda_2 Tr(H_1 B H_2^T) \]

\[ + \gamma_1 \| W \|_F^2 + \gamma_2 \| \sum_j h_{ij} \|_1^2 + \sum_{j'} \| h_{ij} \|_2^2 \]

with the constraints \( W \geq 0, H_1 \geq 0 \) and \( I = 1, 2 \), where \( h_{ij} \) and \( h_{ij}' \) are the \( j \)th and \( j' \)th column of \( H_1 \) and \( H_2 \) respectively.

We expand the popular multiplicative updating algorithm developed for NMF and its variants to SNMNMF. For the NMF problem, although the objective function of NMF is convex in \( W \) only or \( H \) only, it is not convex in both variables together. Therefore it is unrealistic to expect an algorithm to find the global minimum. The same applies to the SNMNMF problem. Below we detail the multiplicative updating algorithm for SNMNMF to identify the local minimum of \( F \).

Based on the simple knowledge of linear algebra, the objective function \( F \) can be reformulated as follows:

\[ F = \sum_{I=1}^{2} \left[ Tr(X_i X_i^T) - 2Tr(X_i H_1^T W^T) + Tr(W H_1 H_1^T W^T) \right] \]

\[ - \lambda_1 Tr(H_2 A H_2^T) - \lambda_2 Tr(H_1 B H_2^T) \]

\[ + \gamma_1 Tr(W^T W) + \gamma_2 \sum_{I=1}^{2} e_{1 \times k} H_1 H_1^T e_{1 \times k} \]

(2)

Let \( \psi_{ij} \) and \( \phi_{ij} \) be the Lagrange multipliers for the constraints \( W_{ij} \geq 0 \) and \( (H_1)_{ij} \geq 0 \), respectively. The Lagrange \( \mathcal{L} \) is

\[ \mathcal{L}(W, H_1) = F + Tr(\Psi W^T) + \sum_{I=1}^{2} Tr(\Phi_I H_I^T) \]

where \( \Psi = [\psi_{ij}] \) and \( \Phi_I = [\phi_{ij}] \). The partial derivatives of \( \mathcal{L} \) with respect to \( W \) and \( H_1 \) are:

\[ \frac{\partial \mathcal{L}}{\partial W} = -2W^T X_1 + 2W^T W H_1 - \lambda_2 H_2 B^T + \gamma_2 e_{k \times k} H_1 + \Phi_1 \]

\[ \frac{\partial \mathcal{L}}{\partial H_1} = -2W^T X_1 + 2W^T W H_1 - \lambda_2 H_2 B^T + \gamma_2 e_{k \times k} H_1 + \Phi_1 \]

\[ \frac{\partial \mathcal{L}}{\partial H_2} = -2W^T X_2 + 2W^T W H_2 - \lambda_1 H_2 A - \lambda_2 H_1 B + \gamma_2 e_{k \times k} H_2 + \Phi_2 \]

Based on the KKT conditions \( \psi_{ij} W_{ij} = 0 \) and \( \phi_{ij} (H_1)_{ij} = 0 \), we get the following equations for \( W_{ij}, (H_1)_{ij} \) and \( (H_2)_{ij} \):

\[ -2 \sum_{I=1}^{2} (X_i H_I^T)_{ij} W_{ij} + [2 \sum_{I=1}^{2} (W H_I H_I^T) + 2\gamma_1 W]_{ij} W_{ij} = 0, \]

\[ (-W^T X_1 - \frac{\lambda_2}{2} H_2 B^T)_{ij} W_{ij} + (W^T W H_1 + \gamma_2 e_{k \times k} H_1)_{ij} W_{ij} = 0, \]

\[ (-W^T X_2 - \lambda_1 H_2 A - \frac{\lambda_2}{2} H_1 B)_{ij} W_{ij} + (W^T W H_2 + \gamma_2 e_{k \times k} H_2)_{ij} W_{ij} = 0. \]

Then we can get the following updating rules:

\[ h_{ij}^{1} = h_{ij}^{1} \frac{(W^T X_1 + \frac{\lambda_2}{2} H_2 B^T)_{ij}}{\left| \frac{W^T W + \gamma_2 e_{k \times k} H_1} \right|_{ij}}, \]

\[ h_{ij}^{2} = h_{ij}^{2} \frac{(W^T X_2 + \lambda_1 H_2 A + \frac{\lambda_2}{2} H_1 B)_{ij}}{\left| \frac{W^T W + \gamma_2 e_{k \times k} H_2} \right|_{ij}}. \]

We have the following theorem to guarantee the convergence of the above updating rules to a local optimum.

**Theorem 1** The objective function \( F \) of the SNMNMF problem is nonincreasing under the above updating rules. The objective function is finite and invariant under these updates if and only if \( W, H_1, H_2 \) are at a stationary point.

The principle of convergence proof of NMF can be easily expanded to prove this theorem. A difference to NMF is that the objective function \( F \) here can be unbounded below. Only the objective is finite, the SNMNMF can get a stable local solution. Here, we show that \( F \) is nonincreasing under the updating rules. In particular, here we prove that the \( F \) is nonincreasing under the updating rule for \( H_1 \), and same feature under the updating rule for \( W \) can be similarly proved. We will adopt the same strategy used in (Lee and Seung, 2001) that introduced an auxiliary function in the Expectation-Maximization algorithm. The following is the definition of the auxiliary function.

**Definition** \( G(h, h') \) is an auxiliary function for \( F(h) \) if the conditions \( G(h, h') \geq F(h), G(h, h) = F(h) \) are satisfied.

Due to the following property, the auxiliary function is very useful for the proof.

**Lemma 1** If \( G \) is an auxiliary function of \( F \), then \( F \) is nonincreasing under the update \( h_{(t+1)} = \arg\min G(h, h^{(t)}) \).

With a proper auxiliary function, the updating rule for \( H_1 \) is exactly the update in this Lemma. Taking into account any element \( (H_1)_{ab} \) in \( H_1 \), we use the \( F_{ab} \) to denote the part of \( F \) that is only relevant to \( (H_1)_{ab} \). It is easy to see that

\[ F_{ab}' = \left( \frac{\partial F}{\partial H_1} \right)_{ab} = (2W^T X_1 + 2W^T W H_1 - \lambda_2 H_2 B^T + \gamma_2 e_{k \times k} H_1)_{ab} \]

\[ F_{ab}'' = 2(W^T W + \gamma_2 e_{k \times k})_{ab} \]

Because the update is essentially element-wise, it is sufficient to show that each \( F_{ab} \) is nonincreasing under the updating rule for \( H_1 \),
Lemma 2 Function

\[ G(h, (H_1)_{ab}^{(t)}) = F_{ab}((H_1)_{ab}^{(t)}) + F'_{ab}((H_1)_{ab}^{(t)}) (h - (H_1)_{ab}^{(t)}) + \left(\frac{W^T W + \gamma_2 e_{k \times k}}{1 - \lambda} \right)_{ab} (h - (H_1)_{ab}^{(t)})^2 \]  

is an auxiliary function for \( F_{ab} \).

Proof Obviously, \( G(h, h) = F_{ab}(h) \). We here only show that \( G(h, (H_1)_{ab}^{(t)}) \geq F_{ab}(h) \). To achieve this, we compare the Taylor series expansion of \( F_{ab}(h) \)

\[ F_{ab}(h) = F_{ab}((H_1)_{ab}^{(t)}) + F'_{ab}((H_1)_{ab}^{(t)}) (h - (H_1)_{ab}^{(t)}) + \left(\frac{W^T W + \gamma_2 e_{k \times k}}{1 - \lambda} \right)_{ab} (h - (H_1)_{ab}^{(t)})^2 \]  

with the auxiliary function \( G(h, (H_1)_{ab}^{(t)}) \) to find that \( G(h, (H_1)_{ab}^{(t)}) \geq F_{ab}(h) \) is equivalent to

\[ \left(\frac{W^T W + \gamma_2 e_{k \times k}}{1 - \lambda} \right)_{ab} \geq \left(\frac{W^T W + \gamma_2 e_{k \times k}}{1 - \lambda} \right)_{aa}. \]

Obviously, we have

\[ \left(\frac{W^T W + \gamma_2 e_{k \times k}}{1 - \lambda} \right)_{ab} \geq \lambda \left(\frac{W^T W + \gamma_2 e_{k \times k}}{1 - \lambda} \right)_{aa}. \]  

Thus \( G(h, (H_1)_{ab}^{(t)}) \geq F_{ab}(h) \) holds.

Proof of Theorem 1 We can get the the following updating rule based on the auxiliary function \( G(h, (H_1)_{ab}^{(t)}) \):

\[ (H_1)_{ab}^{(t+1)} = (H_1)_{ab}^{(t)} - \frac{F'_{ab}((H_1)_{ab}^{(t)})}{2W^T W + \lambda_2 H_2 B^T}_{ab} \]

\[ = (H_1)_{ab}^{(t)} \left(\frac{W^T X_1 + \lambda_2 H_2 B^T}{W^T W + \gamma_2 e_{k \times k}} \right)_{ab}. \]  

Due to the property of the auxiliary function \( G(h, (H_1)_{ab}^{(t)}) \) for \( F_{ab}, F_{ab} \) is nonincreasing under this updating rule.

0.3 Initialization of the algorithm

We initialize the \( W, H_1 \) and \( H_2 \) matrices by assigning the uniformly distributed values ranging from 0 to 1 to their entries. We note that, under different runs of the algorithm, the objective function only have minor changes.

0.4 Parameter selection

The method proposed here requires setting of several parameters. Given that 41 miRNAs in the data sets have been previously reported to be related with ovarian cancer (Koturbash et al., 2010), and which can have multiple regulatory combination with other miRNAs and the 57 miRNA clusters contained in the data sets (miRNA cluster data from the miRBase website [http://www.mirbase.org/]) with a genomic cutoff distance of 50kb, see Materials and Methods), we set the number of co-module to 50. As to the parameters \( \lambda_1, \lambda_2, \gamma_1, \gamma_2 \), they were empirically determined by relative size of each corresponding term of the objective function (Figure S1A). To test the robustness of our result with respect to the initial parameters, we ran our method using several different combinations. We found that more than 60% of the genes were consistently grouped together and most of the enriched terms are the same for these different settings (Figure S1B). Here the consistency measure is defined as the ratio of gene pairs present in the same modules across different results under different settings.

0.5 Permutation test for between correlations

We show the sum of Pearson’s correlation coefficients (PPCs) for the miRNA-gene modules 32 and 40 and their distributions of 1000 random chosen miRNA-gene modules respectively (Figure S3).

0.6 Module size distribution

We run the proposed method on the ovarian cancer dataset and obtained 50 ‘co-modules’ which are composed by a set of miRNAs and a set of genes which are denoted as miRNAs modules and gene modules respectively. We show the module size distribution in Figure S4 and each co-module contains 3.8 miRNAs and 78 genes.
0.7 The literature review support for the overlapping miRNAs

We search any two miRNAs of the overlapping miRNAs for each co-module and see if they are related with the same biological processes uncovered by other studies. The ones supported by literature review were listed in Table S1.

0.8 The co-modules are highly enriched with cancer genes

We listed the modules that are enriched with ovarian cancer genes based on the IPA system in Table S2.

0.9 Illustration of the signals of $W$ basis vectors

Based on the basis matrix $W$, we can divide the samples into three groups. We show the signals of co-module 39 and 40 with corresponding dividing lines (Figure S5).

0.10 The EBC method

The EBC method integrated two types of information to identify miRNA-gene regulatory module. The method has the following major steps (Figure S6): (1) Calculate miRNA-gene correlation matrix based on the (inverse) correlations in the expressions across samples, and convert the correlation matrix into a miRNA-gene correlation network. (2) Construct a miRNA-gene regulatory network by combining the constructed miRNA-gene correlation network and the corresponding predicted miRNA-gene regulatory network. (3) Enumerate all maximal bicliques as candidate regulatory modules, remove the ones with genes less than ten, and postprocess candidate modules.

The maximal bicliques in a bipartite network can have quite big overlap. For example, the maximal biclique 1 and 2 have a large number of overlapping genes, and their combinations and maximal biclique 3 only have two genes difference (Figure S7).

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Table S1. Summary of collected function roles of the enriched overlapping miRNAs based on literature search.

| No. | Function description according to literature abstract | Reference |
|-----|------------------------------------------------------|-----------|
| 10  | Tumor suppressor function through regulating Rb/E2F1 activity (miR-449a/449b) | Yang et al. (2009) |
|     | Targets of p53 and control of cell proliferation and adhesion-independent growth (mir-34b/34c) | Corney et al. (2007) |
| 14  | Repression of the (miR-143/145 cluster) by oncogenic Ras initiates a tumor-promoting feed-forward pathway | Kent et al. (2010) |
|     | Smooth muscle cell (SMC) differentiation and vascular pathogenesis (miR-143/145 cluster) | Elia et al. (2009) |
|     | (miR-143/145) modulate cytoskeletal dynamics and responsiveness of smooth muscle cells to injury. | Xin et al. (2009) |
| 16  | Might be important biomarkers for the early detection and prognostic assessment of prostate cancer | Yin et al. (2010) |
|     | Repress FOXO1 expression, affect cell cycle control and apoptotic responses in endometrial cancer | Myatt et al. (2010) |
|     | Expression depending on mismatch repair status and characteristic of undifferentiated proliferative states | Sarver et al. (2009) |
|     | Upregulated in prostate cancer and useful diagnostic and prognostic indicators | Schaefer et al. (2010) |
|     | Differential expressed, related with peculiar tumourigenetic pathways and be potential biomarkers | Cho et al. (2009) |
|     | The development of the cochlea (from the patterning to the differentiation of the cochlear structures) | Sacheli et al. (2009) |
| 17  | Both partners of the (miR-144/451 cluster) confer protection against simulated I/R-induced cardiomyocyte death via targeting CUGBP2-COX-2 pathway | Rasmussen et al. (2010) |
|     | (miR-144/451 cluster) tunes gene expression to impart a robustness to erythropoiesis | Rasmussen et al. (2010) |
| 19  | Amplification and overexpression of (miR-30b, miR-30d and KHDRBS3) at 8q24.22-q24.23 in medulloblastoma | Lu et al. (2009) |
| 20  | See 16 | See 16 |
| 42  | Deficient expressed signature associated with Renal ischemia reperfusion injury (IRI) | Godwin et al. (2010) |
|     | miR-199a/miR-214 cluster is down-regulated in both murine and human cytomegalovirus infection and manifests similar antiviral properties in mouse and human cells | Santhakumar et al. (2010) |
|     | Through mir-199a/214, TWISTing stemness, inflammation and proliferation of epithelial ovarian cancer cells | Magrelli et al. (2009) |
|     | Deregulation of miRNAs is a recurrent event in human ovarian cancer and that miR-214 induces cell survival and cisplatin resistance primarily through targeting the PTEN/Akt pathway | Yang et al. (2008) |

Table S2. Summary of gene modules that are enriched with ovarian cancer genes based on the IPA system. q-value, the B-H multiple test corrected p-value.

| No. | Ovarian cancer genes | genes | q-value |
|-----|----------------------|-------|---------|
| 2   | FN1, INHBA, MMP3, MMP1, POSTN, PTGS2, SERPINE1, VCAN | 8     | 2.87e-02 |
| 4   | C11orf9, EFNB2, FGF18, KLK6, KLK8, KLK10, KLK11, SCGB2A1 | 8     | 6.06e-02 |
| 6   | DACH1, EEFA12, MMP3, S100P, SLIT2, WT1 | 6     | 5.73e-02 |
| 14  | ABCA8, DIRAS3, GSTM5, HSD11B1, ITLN1, MUM1L1 | 6     | 4.89E-03 |
| 22  | DACH1, FAM54A, KPNA2, RRM2, S100P, TOP2A, TMY5 | 7     | 5.75e-03 |
| 23  | CALB2, CFH, CXCL14, FABP4, FGF1, INHBA, PDGFRB, PEG3, POSTN, SLIT2, TIMP3, VCAN1, VCAN | 13    | 1.62E-03 |
| 28  | DUSP4, EYA2, IFT27, IGFBP1, KLK5, KLK7, KLK8, MMP3, MMP7, PRKCB, S100P, SCGB2A1, VTN1, WFDC2, WT1 | 15    | 4.49E-07 |
| 34  | CCL4, CSF1R, GPR65, IGFBP1, KLK7, LCN2, MMP7, SCGB2A1 | 8     | 2.29E-02 |
| 39  | FOLR1, HMGA2, HOXB6, KLK11, PROM1, S100A2, TACSTD2, VAV3 | 8     | 5.66E-02 |
| 40  | FAM54A, HIST2H2A3, KRT23, PAEP, SLPI, TIMP1, TOP2A, VTN1 | 8     | 4.88E-02 |
| 42  | FLRT2, HOXA4, IGFBP4, KIT, PDGFR, PEG3, SEMA3C, SERPINA5, TUBB2A | 9     | 3.32E-02 |
| 48  | CXCL14, FLT1, IL6, INHBA, PLA1, POSTN, TIMP3, VCAN | 8     | 2.20E-03 |
| 49  | CEACAM6, GPX3, LCN2, PEG3, S100A2, VAV3 | 6     | 4.34E-02 |