Data Integration in Early Drug Development Phase

The QSTAR Modeling Framework

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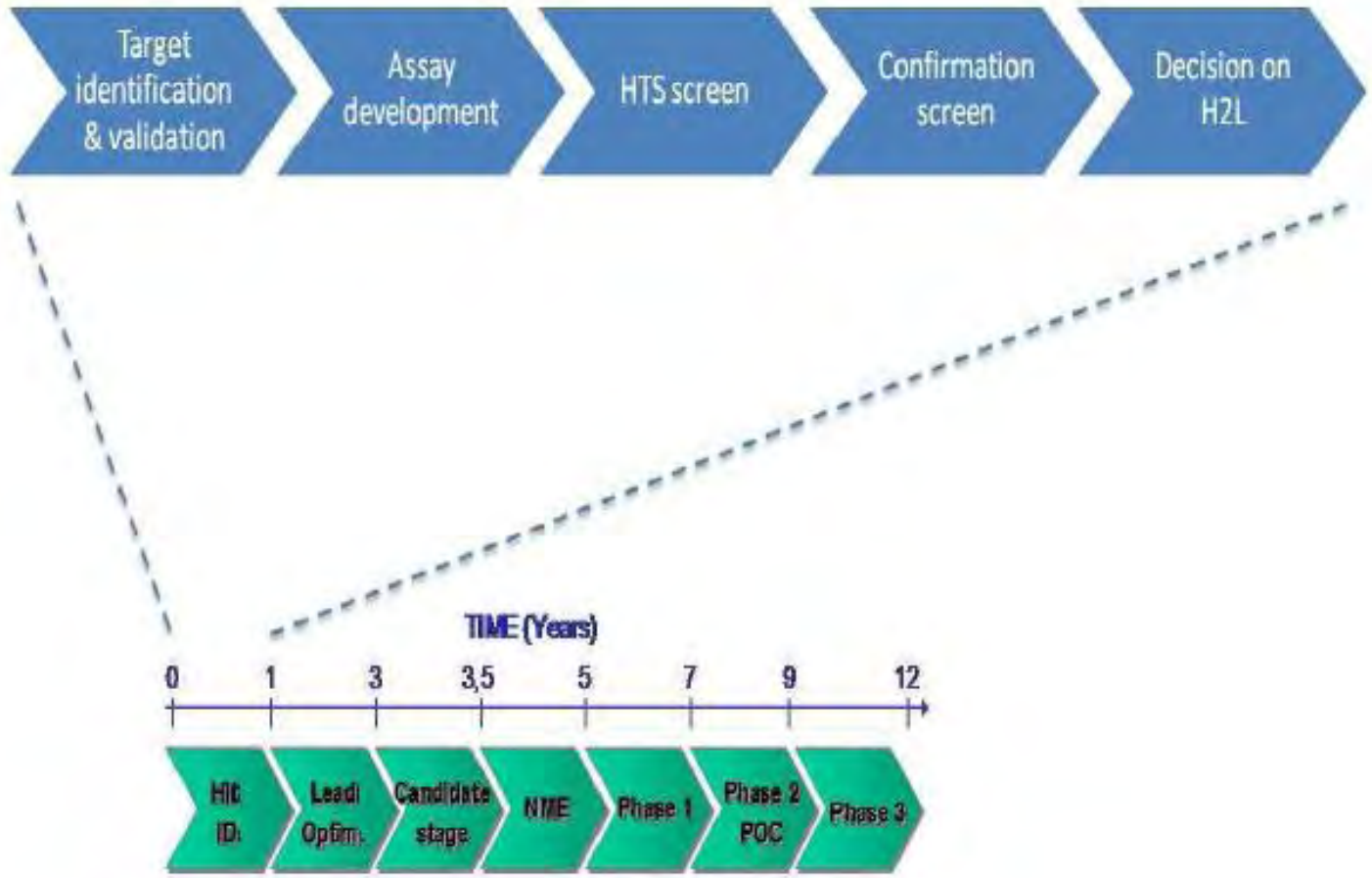
Outline

- Background and Data Structure
- **Gene X Bioassay X Fingerprint Analysis**
- Co-clustering framework
- Biclustering Framework
- QSTAR Consortium

DRUG DISCOVERY STAGES

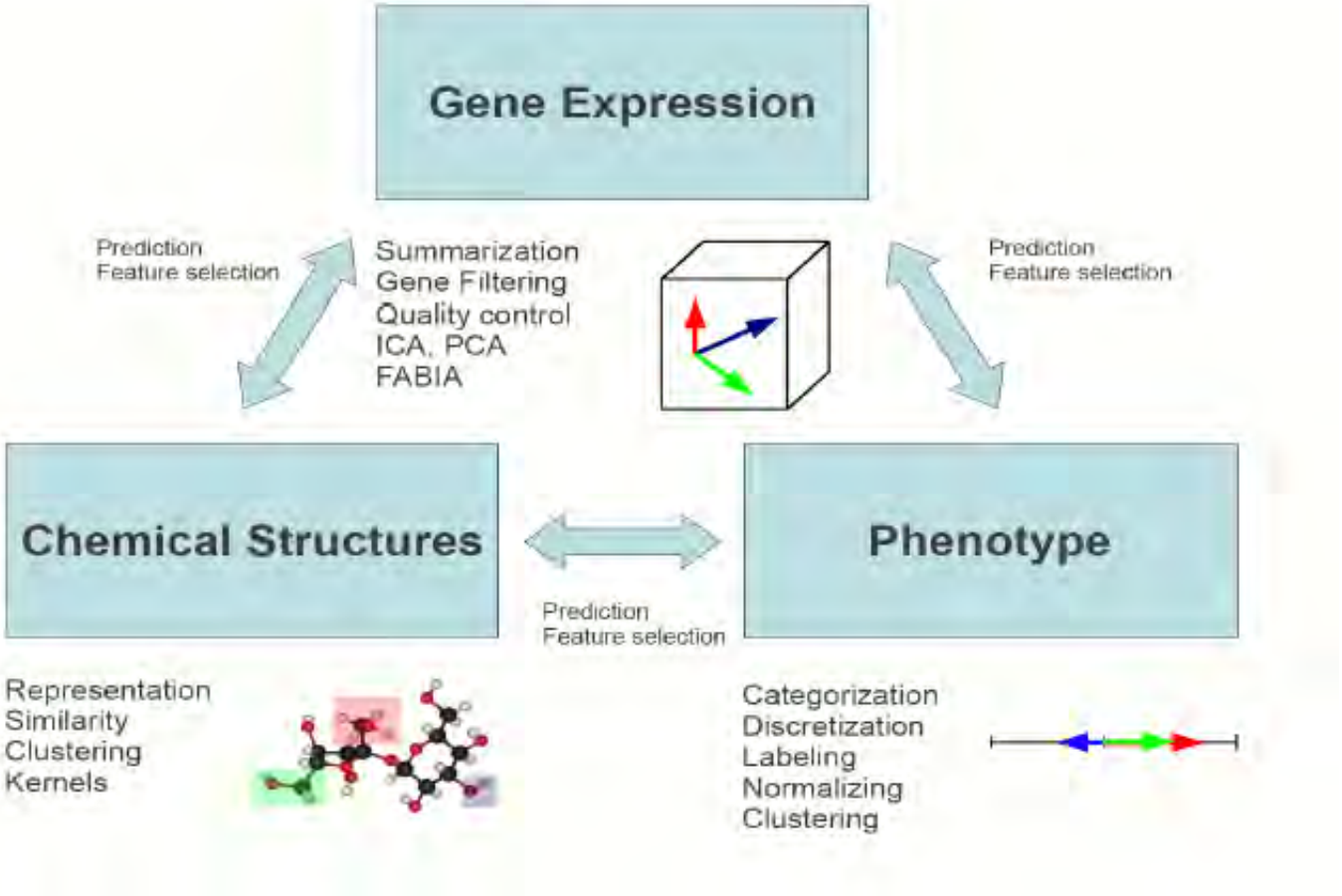


Drug Discovery Phases

DRUG DISCOVERY STAGES

- The tradition drug discovery approach relies mostly on chemical properties at early stage
- Potential side effects are often identified in later toxicity studies
- Less than 25% of success rate in Phase III trials
- Early identification of potential sides effects may prevent expensive Phase II & Phase III trials.
- Early toxicity detection can be facilitated by incorporating relevant biological data in the early stages of drug developments, particularly in lead optimisation.

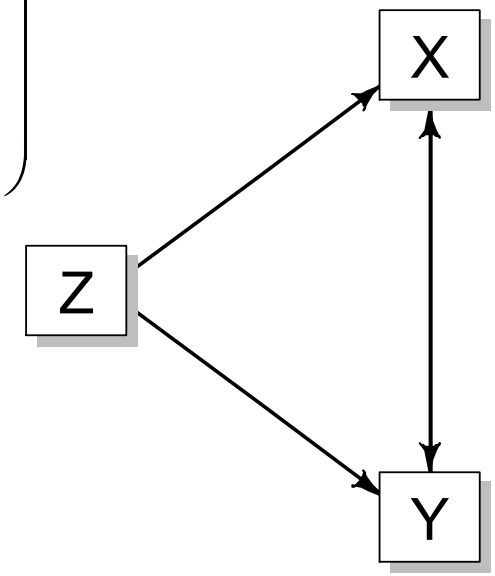
QSTAR: FRAMEWORK



QSTAR: Data Structures

$$Z_{M\times C} = \begin{pmatrix} z_{11} & z_{12} & \cdots & z_{1C} \\ z_{21} & z_{22} & \cdots & z_{2C} \\ \vdots & \vdots & \ddots & \vdots \\ z_{M1} & z_{M2} & \cdots & z_{MC} \end{pmatrix}$$

Chemical Structure



$$X_{G\times C} = \begin{pmatrix} x_{11} & x_{12} & \cdots & x_{1C} \\ x_{21} & x_{22} & \cdots & x_{2C} \\ \vdots & \vdots & \ddots & \vdots \\ x_{g1} & x_{g2} & \cdots & x_{gC} \end{pmatrix}$$

Gene Expression

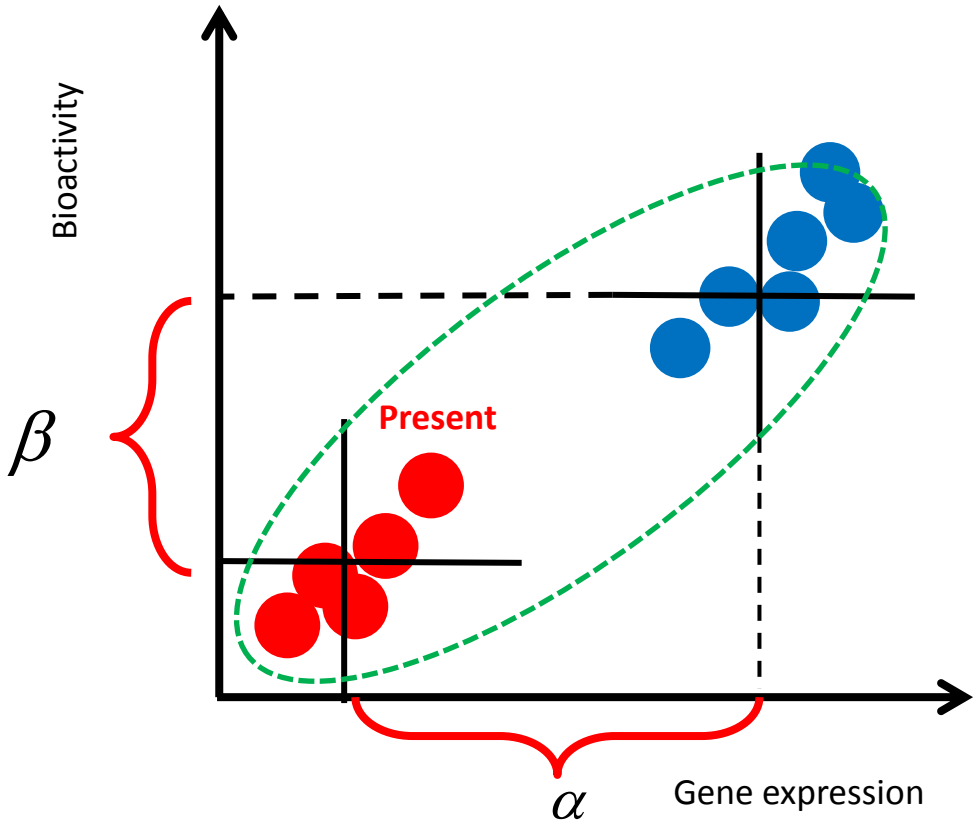
Bioactivity

$$Y_{N\times C} = \begin{pmatrix} y_{11} & y_{12} & \cdots & y_{1C} \\ y_{21} & y_{22} & \cdots & y_{2C} \\ \vdots & \vdots & \ddots & \vdots \\ y_{N1} & y_{N2} & \cdots & y_{NC} \end{pmatrix}$$

QSTAR: Gene X Bioassay X Fingerprint Analysis

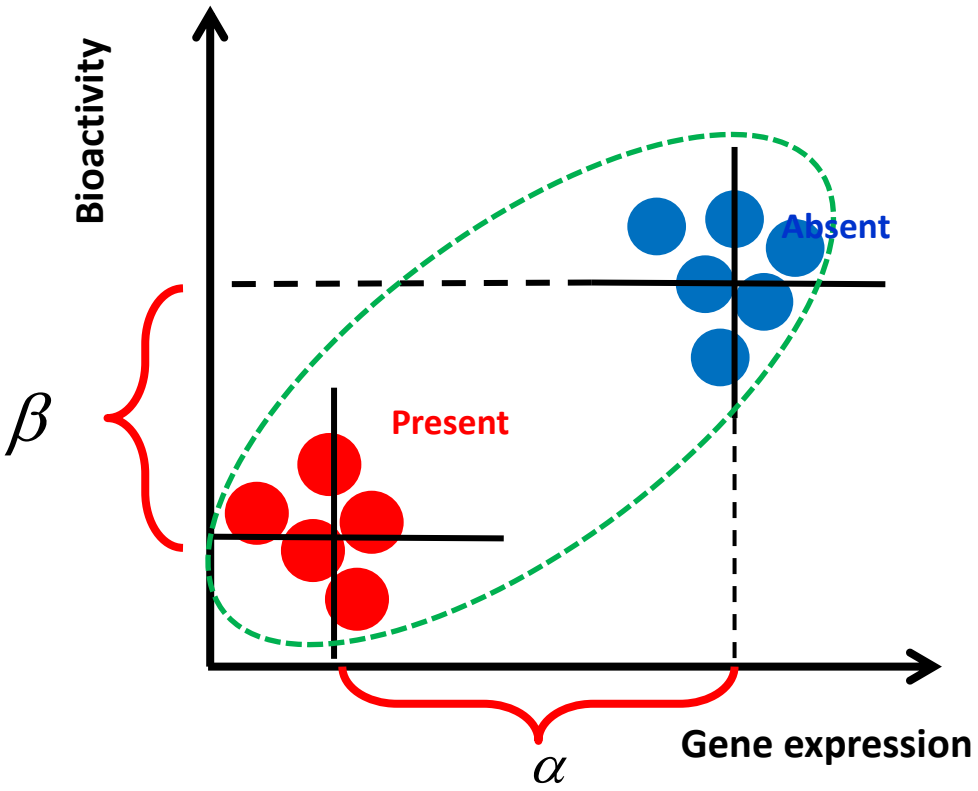
- To find a group of genes that are jointly associated with chemical structure and bioactivity data.
- To find a group of genes that are associated with a chemical structure, but that are conditionally independent of bioactivity data.

QSTAR: Joint Modelling



- Significant association between gene expression and fingerprint
- Significant association between bioactivity and fingerprint
- Significant association between gene expression and bioactivity data

QSTAR: Joint Modelling



- Significant association between gene expression and fingerprint
- Significant association between bioactivity and fingerprint
- **NO** association between gene expression and bioactivity data

QSTAR: Joint Modelling

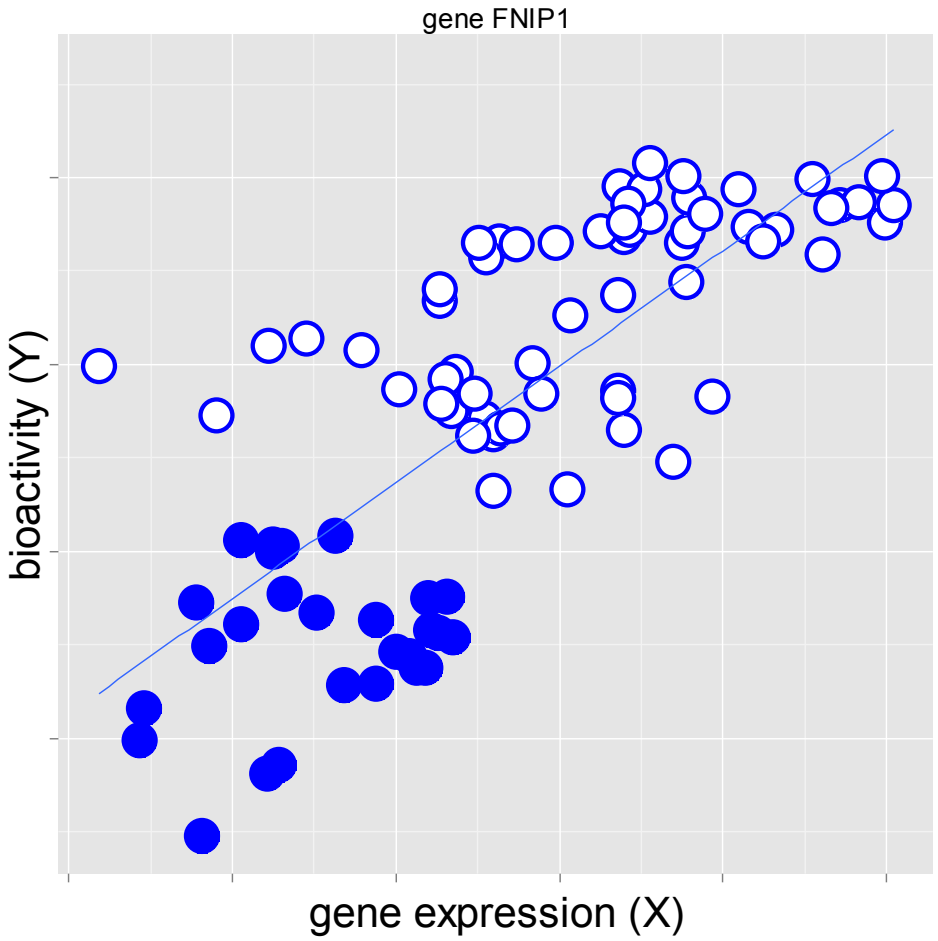
$$\begin{pmatrix} X_j \\ Y_i \end{pmatrix} \sim N\begin{pmatrix} \mu_{jk} + \alpha_{jk} \times Z_{jk} & \Sigma_{ij} \\ \mu_{ik} + \beta_{ik} \times Z_{ik}, & \end{pmatrix}$$

Where,

$$\Sigma_{ij} = \begin{pmatrix} \sigma^2_{X_j} & \sigma_{X_j Yi} \\ \sigma_{X_j Y_i} & \sigma^2_{Y_i} \end{pmatrix}$$

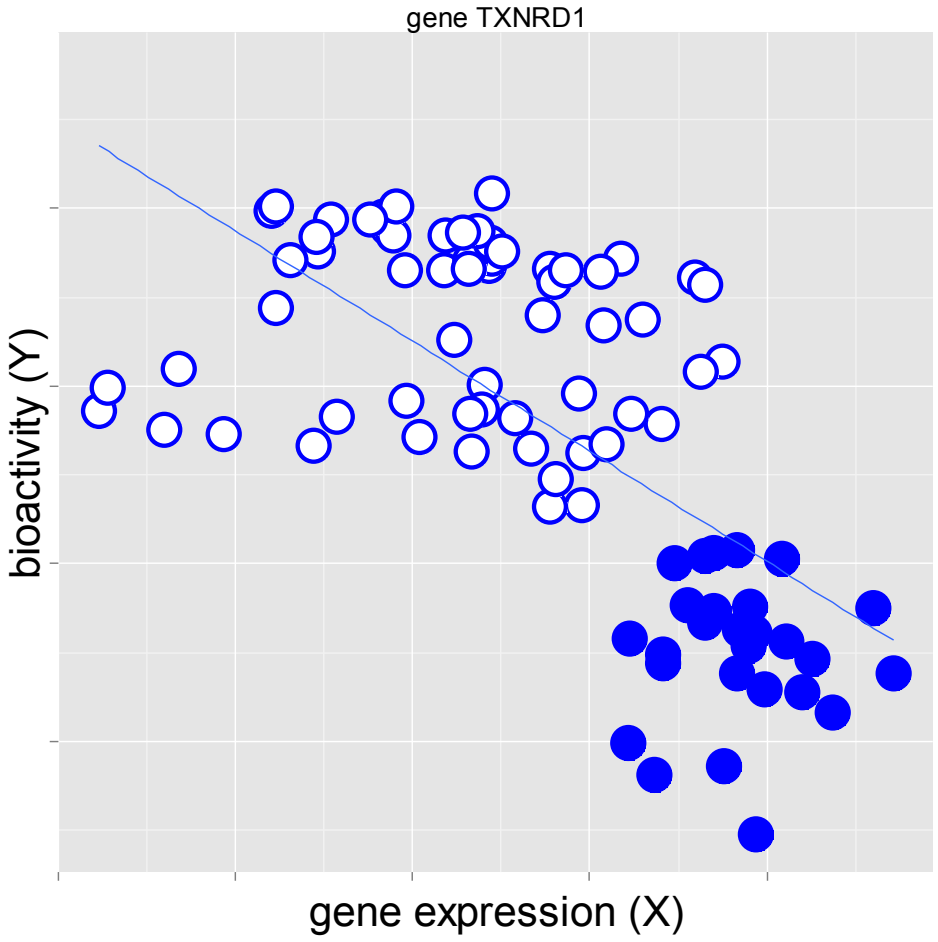
- β_{ik} denotes the effect of the kth fingerprint on the ith bioassay
- α_{jk} denotes the effect of the kth fingerprint on the j^{th} gene.

QSTAR: Joint Modelling



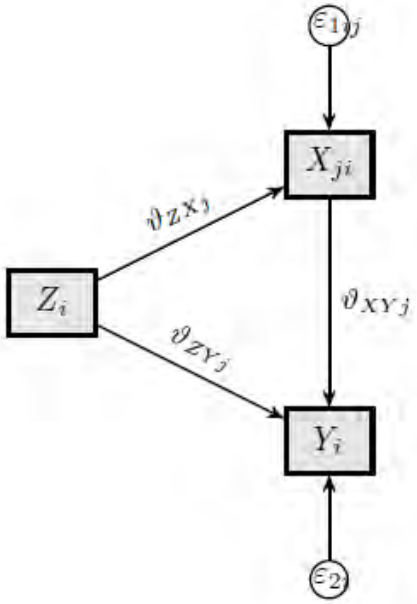
- Examples of genes with significant association with fingerprint and bioactivity data

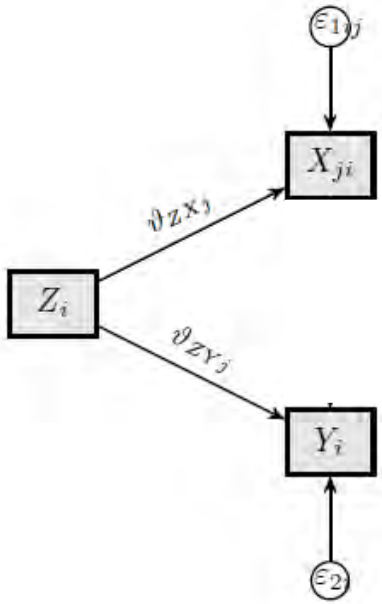
QSTAR: Joint Modelling



- Examples of genes with significant association with fingerprint, but conditionally independent of bioactivity

QSTAR: Path Analysis





- To find genes with direct and indirect effect of chemical structures on bioactivity data
- To find genes with only direct effect of chemical structure

QSTAR: Path Analysis

$$Y_i = \vartheta_{zyj} Z_k + \varepsilon_{2j}$$

$$X_j = \vartheta_{xyj} Y_i + \vartheta_{zxj} Z_k + \varepsilon_{1j}$$

- ϑ_{zyj} is the total effect of the kth fingerprint on the ith bioassay
- ϑ_{zxj} is the Direct effect the fingerprint on the jth gene
- $\omega_{zxj} = \vartheta_{xyj} * \vartheta_{zyj}$ is the indirect effect of the fingerprint on gene expression given the bioactivity data

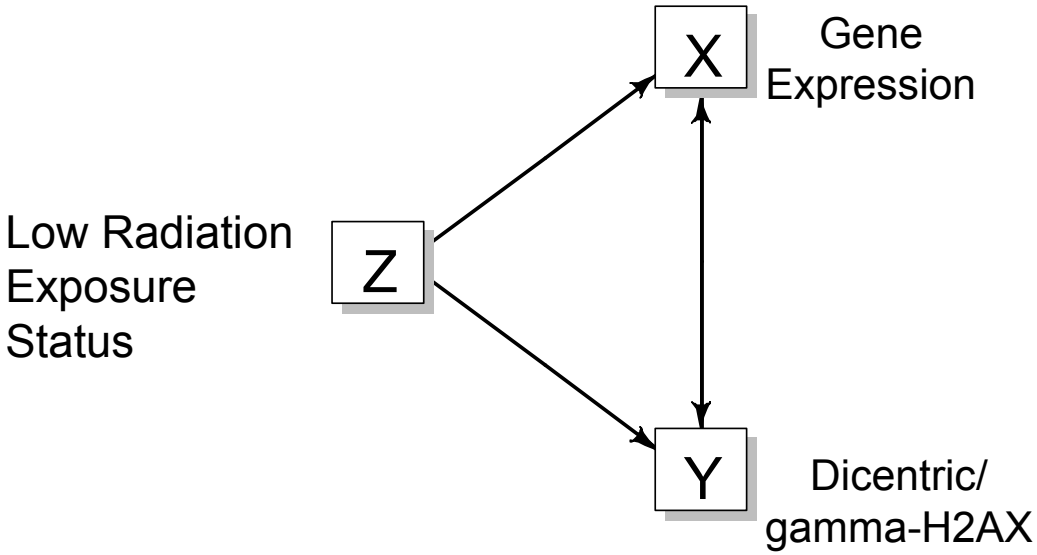
QSTAR: Conditional Model

$$g\{E(X_j \mid Z_k)\} = \theta_{1i} + \theta_{2i} Z_k$$

$$g\{E(X_j \mid Z_k, Y_i)\} = \varphi_0 + \varphi_{1i} Y_i + \varphi_{2i} Z_k$$

- θ_{2i} is the unadjusted effect of fingerprint on gene expression data.
- φ_{2i} is the adjusted effect of fingerprint on gene expression data
- This conditional modelling framework fits within the principle of generalised linear model

Relevance to Radiation Study



- These modelling framework can potentially be used as a surrogate marker identification/validation in low radiation studies.

QSTAR: Co-clustering Framework

- To find a group of compounds with a similar chemical structures and bioactivity data and their corresponding discriminating gene signatures

QSTAR: Weighted Clustering

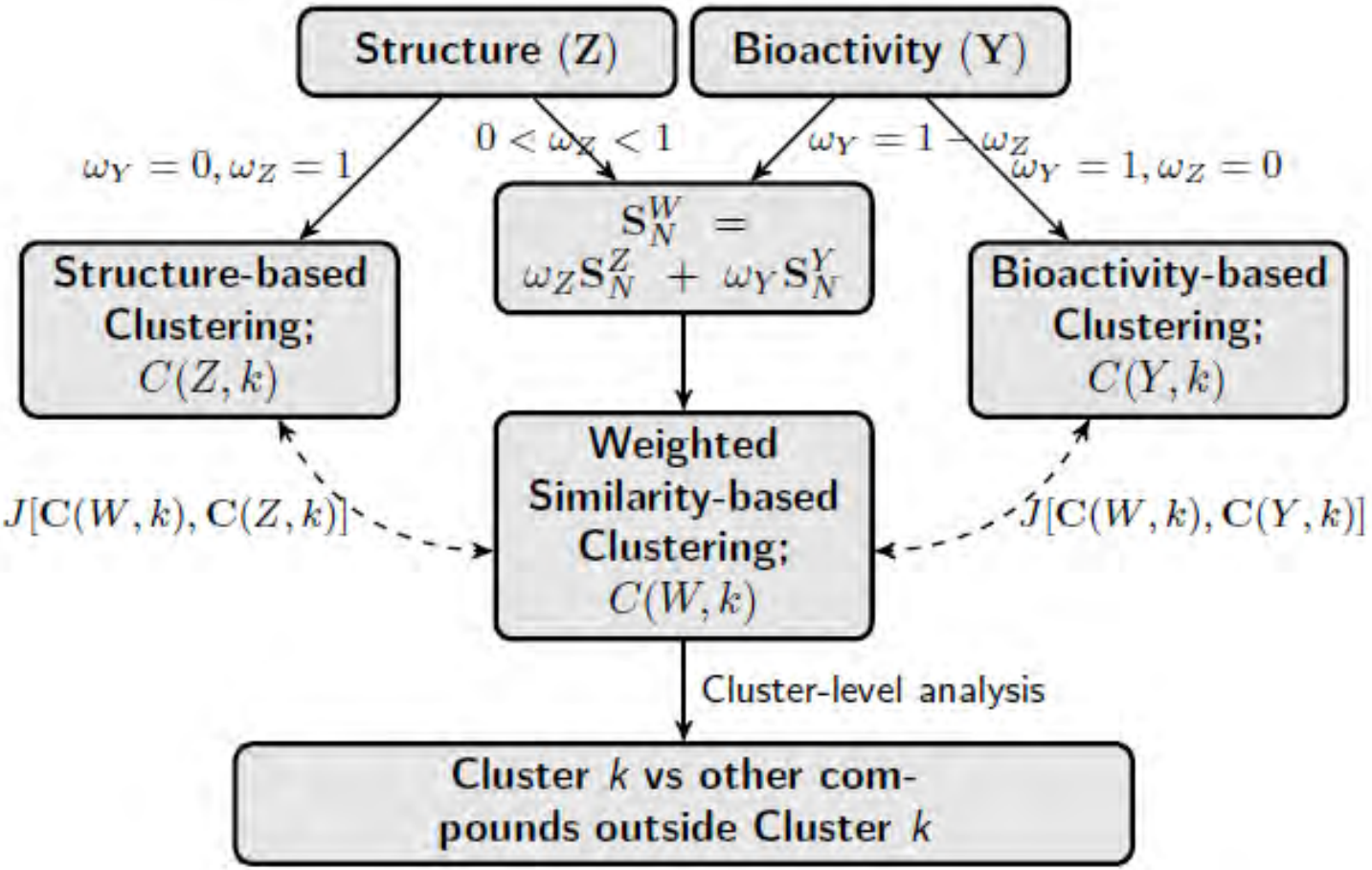
- There are several methods for simultaneous analysis of gene expression data to overcome the limitation of gene-by-gene analysis.

- Some of the methods are variation of penalised-likelihood approach
  - Elastic net
  - LASSO

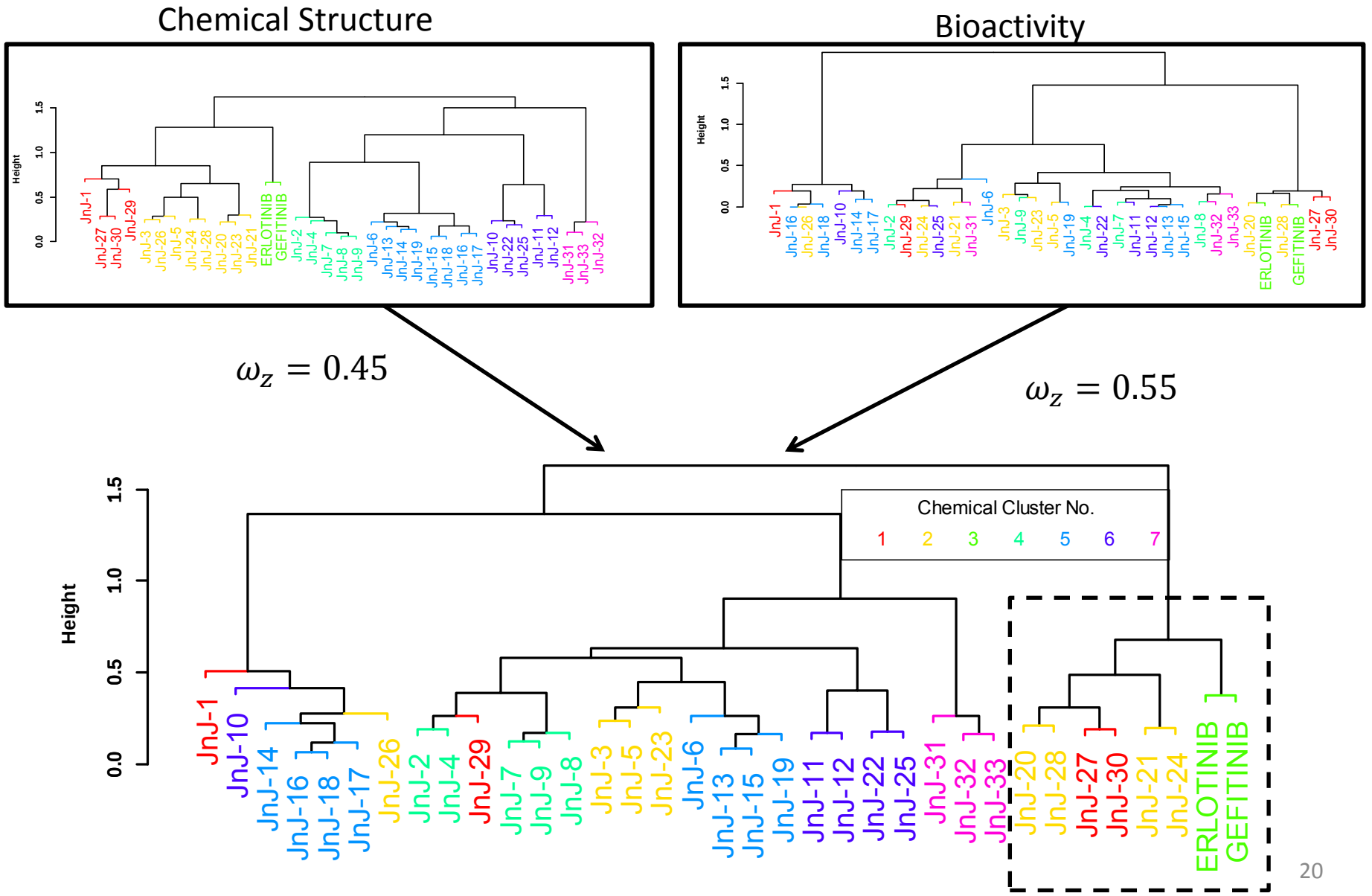
- Clustering methods have also been considered for this purpose
  - Hierarchical clustering method
  - K-means

- **In co-clustering approach, we are interested in multi-view clustering of two data matrices.**

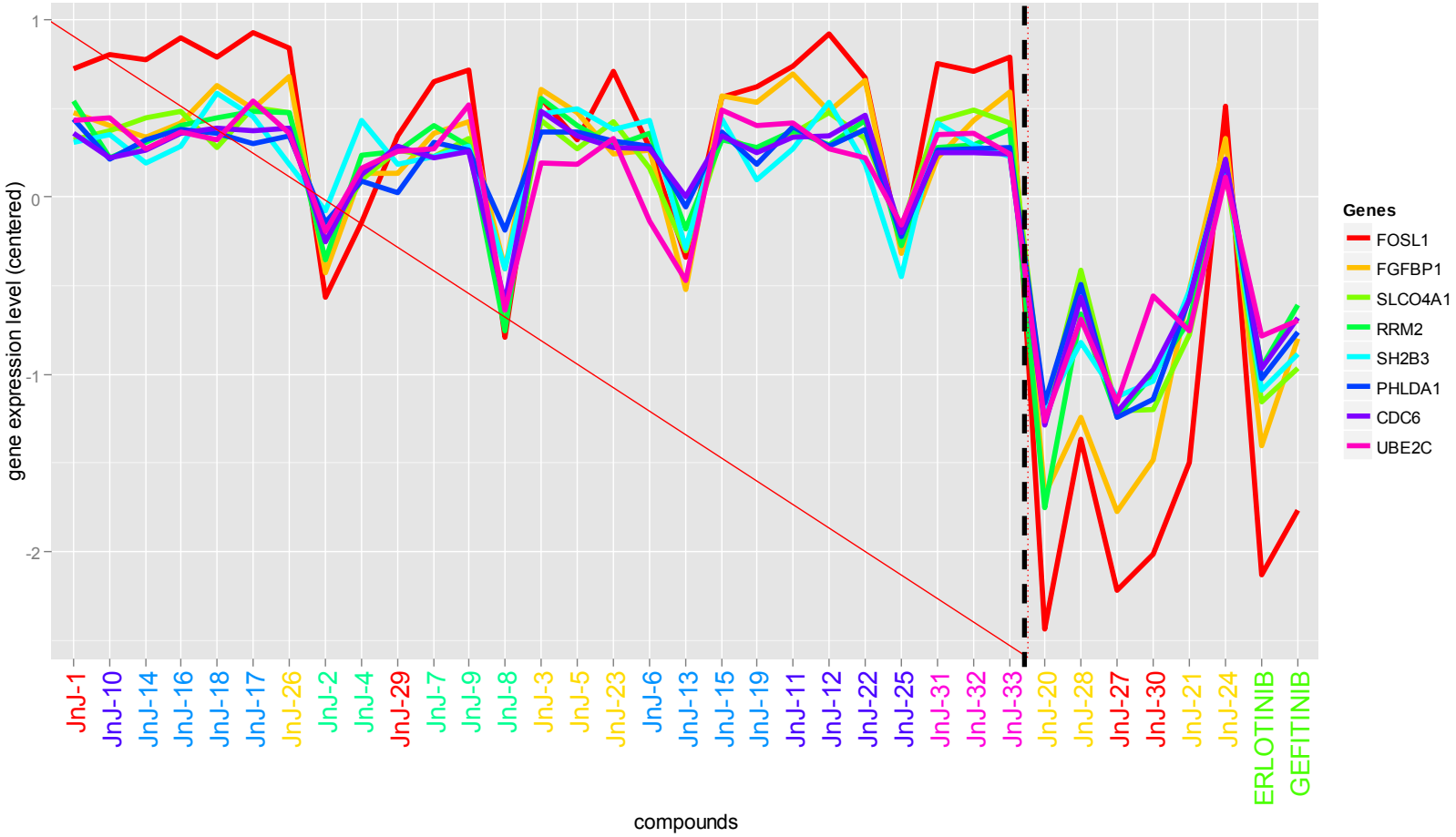
QSTAR: Weighted Clustering



QSTAR: Weighted Clustering



QSTAR: Weighted Clustering

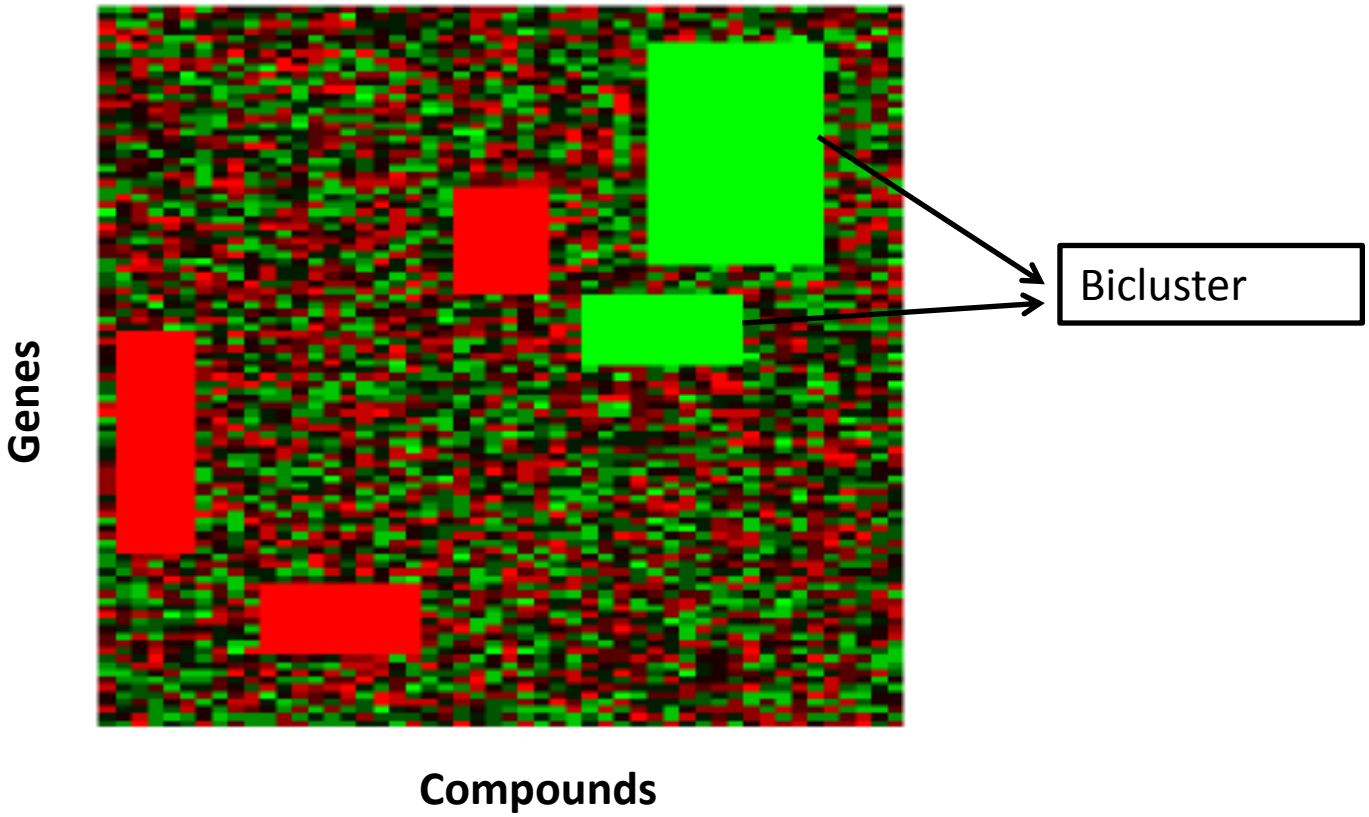


- Group of genes linked to the selected cluster

QSTAR: Biclustering Framework

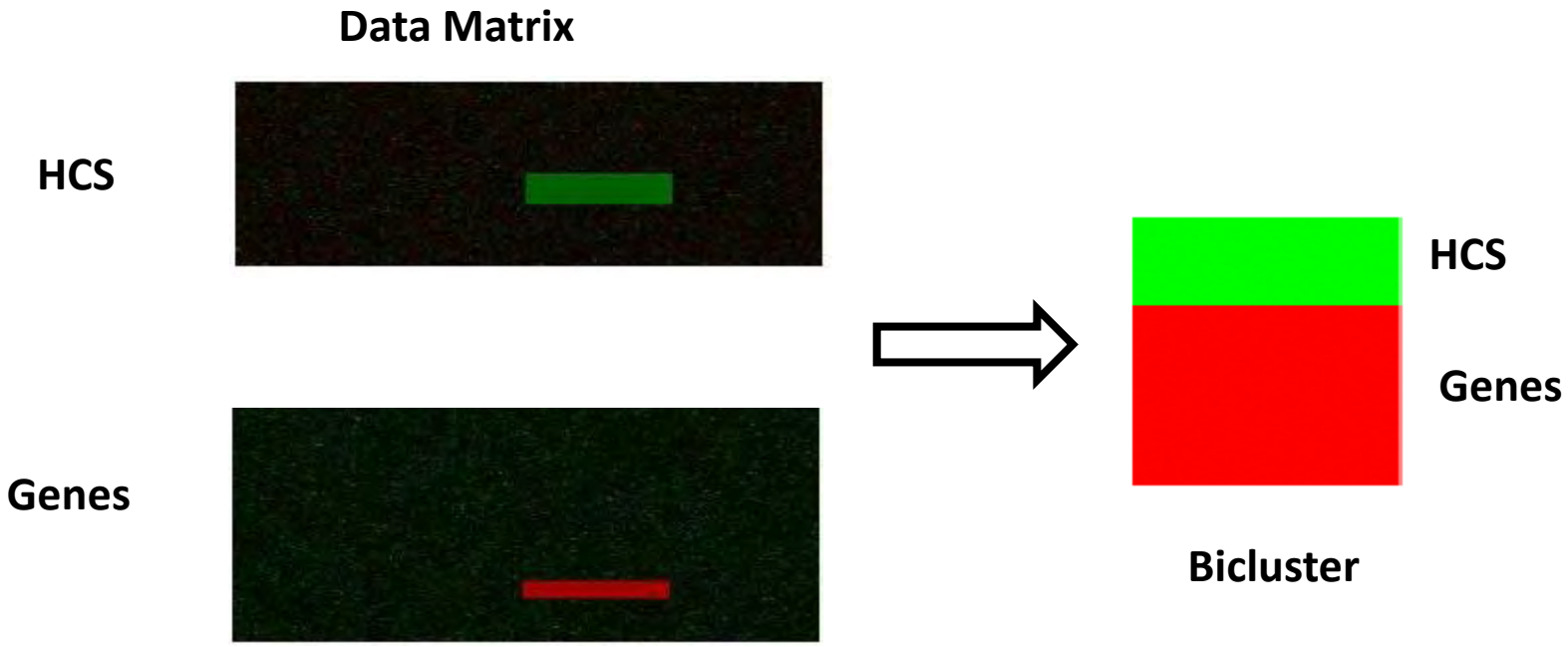
- To find similar local patterns two matrices. Illustration with gene expression matrix and high content screening matrix

QSTAR: Biclustering



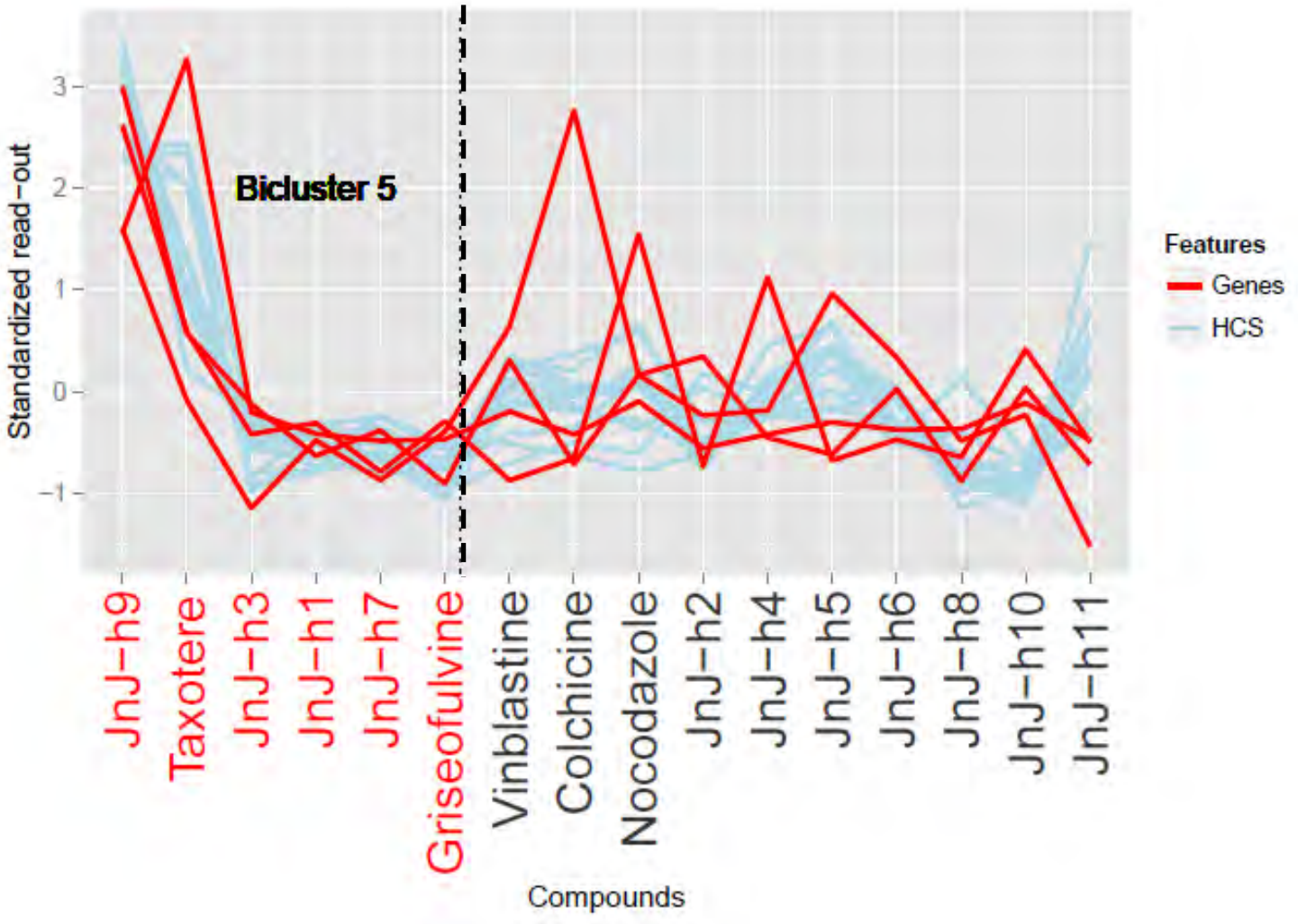
- Finding local patterns in gene expression data based on simultaneous clustering of genes and compounds

QSTAR: Multiview Biclustering



- Methods:
  - FABIA
  - Multiple Factor Analysis /Sparse Multiple Factor Analysis

QSTAR: Gene expression and High Content screening



QSTAR: Pathway Analysis

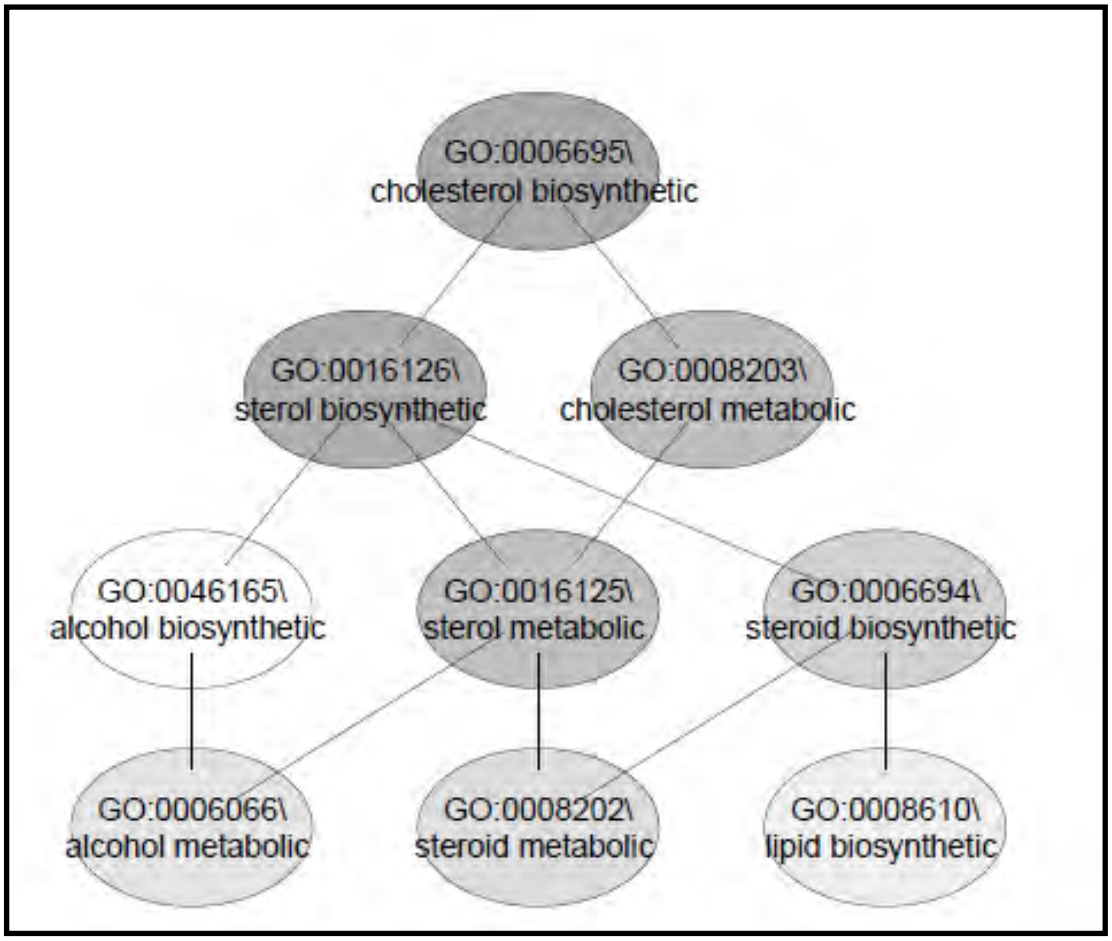
- Exploring potential biological pathways based on existing literatures and database
- Exploring target predictions based on existing literature and database

QSTAR: Pathway Analysis

- The are publicly available databases for gene annotations and functions
  - KEEG (http://www.genome.jp/kegg/)
  - GO (http://geneontology.org/page/go-database)

- The identified bioassay and chemical structures can also be explored further using:
  - chEMBL (https://www.ebi.ac.uk/chembl/)
  - drugBank (http://www.drugbank.ca/)

QSTAR: Pathway Analysis



- Example of MPL pathway analysis

QSTAR CONSORTIUM (http://www.qstar-consortium.org/)

- Janssen Pharmaceuticals scientists from various therapeutic areas such as Oncology, Neurology, Infectious Diseases
- Academic collaborations: chemoinformatics, statistics, machine learning, platform-specific data preprocessing
- Further Janssen Pharmaceuticals team members from: Medicinal chemistry, chemoinformactics, systems biology, molecular profiling, statistics, IT, HTS, exploratory toxicology

Thank you