NIH/NCI R21-CA209848

ALGORITHMS FOR LITERATURE-GUIDED MULTI-PLATFORM IDENTIFICATION OF CANCER SUBTYPES

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ITCR 2017 Annual Meeting, Santa Cruz, CA

BACKGROUND

- Cancer subtype identification:
  - Can offer opportunities for more personalized & targeted cancer treatment.

- Great achievements have been made:
  - The Cancer Genome Atlas (TCGA):
    - Integrative approach using multiple genomic data types.
    - e.g., mRNA expression, somatic mutation, copy number alteration, DNA methylation, …
  - iCluster+ (Mo et al., 2013, *PNAS*).
    - A statistical framework for integrative analysis of multiple data types to identify cancer subtypes.

BACKGROUND

- Cancer subtype identification is often implemented at the gene level:
  - Gene-level findings are sometimes not reproducible between different studies (Glaab, 2015, *Brief Bioinform*).
  - Genes with weak effects might be missed in gene-level analyses (Tyekucheva et al., 2011, *Genome Biol*).

- Pathway-level analysis:
  - Pathway-level findings have been reported to be more robust & reproducible (Glaab, 2015, *Brief Bioinform*).
  - Aggregation of signals within a pathway can potentially improve statistical power to identify key pathways.

BACKGROUND

- Challenges in pathway-level analyses:
  - Incompleteness of pathway knowledge.
  - Heterogeneity in completeness & quality among existing pathway databases.
  - Optimal strategies to combine pathway knowledge from multiple databases remain to be explored, especially when we combine databases for different aspects of biology.

- Biomedical literature:
  - Can potentially supplement incompleteness of pathway annotations because it provides comprehensive information about the relationship among genes.
  - Can potentially serve as a common knowledgebase to integrate multiple existing pathway databases.

BACKGROUND

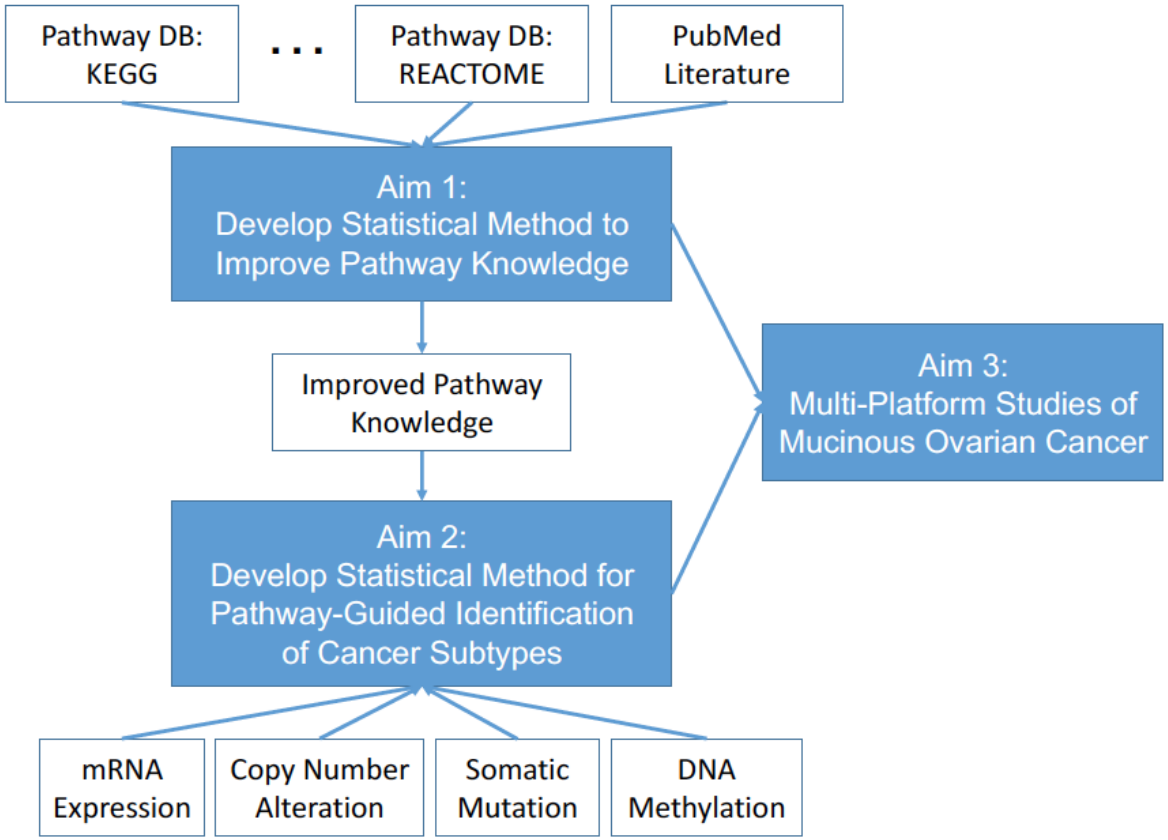
- Current challenges:
  - Pathway knowledge in existing databases & biomedical literature are not fully utilized and investigated for the cancer subtype identification.
  - There is a need for an effective statistical approach to improve pathway knowledge by integrating multiple existing pathway databases, also along with biomedical literature.

- NIH/NCI R21-CA209848 (MPI: D Chung & L Kelemen):
  - Aims to develop novel algorithms to improve robustness & interpretability in identification of cancer subtypes & key molecular features.
  - Integration of multiple genomic data types, biomedical literature, & existing pathway databases.

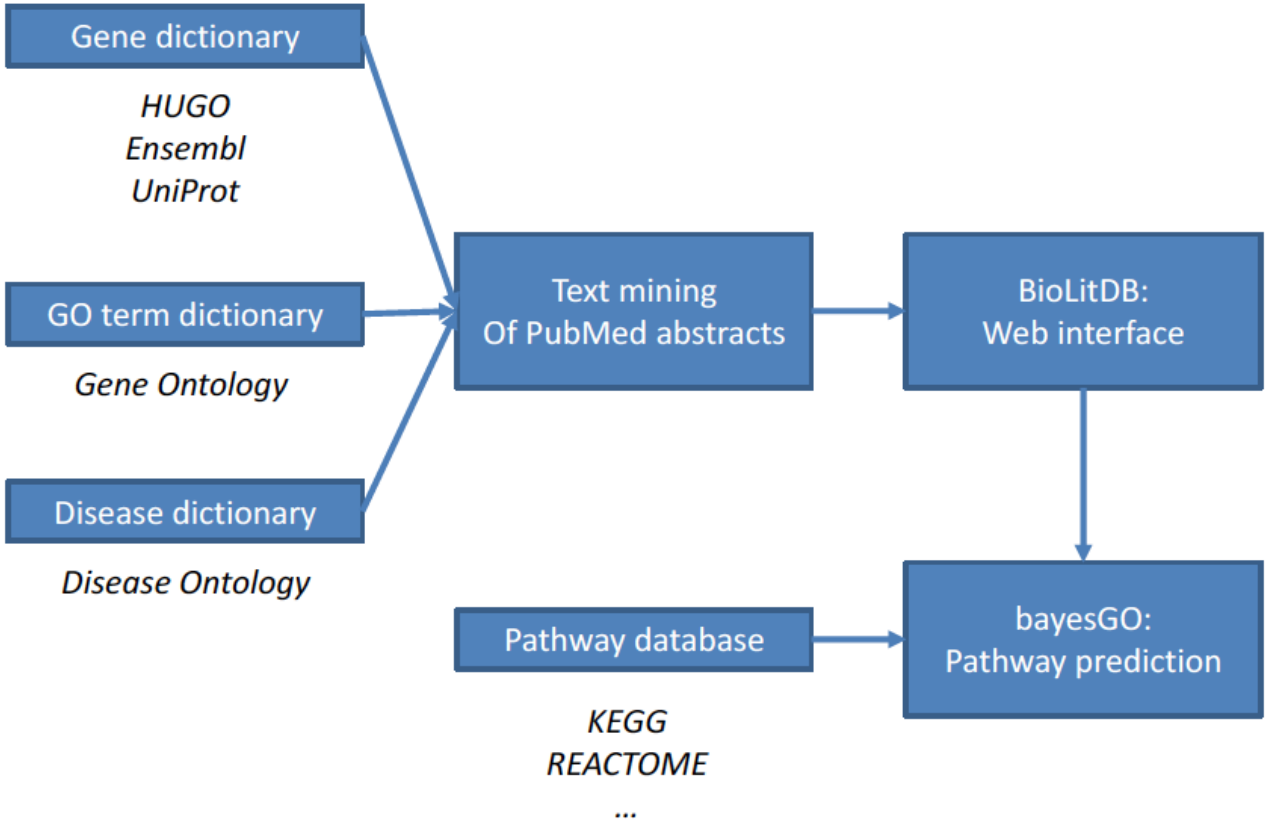
SPECIFIC AIMS

Improve pathway knowledge by integrating biomedical literature with multiple existing pathway databases.

Improve identification of cancer subtypes & key molecular features, by integrating pathway annotation with multiple genomic data types.

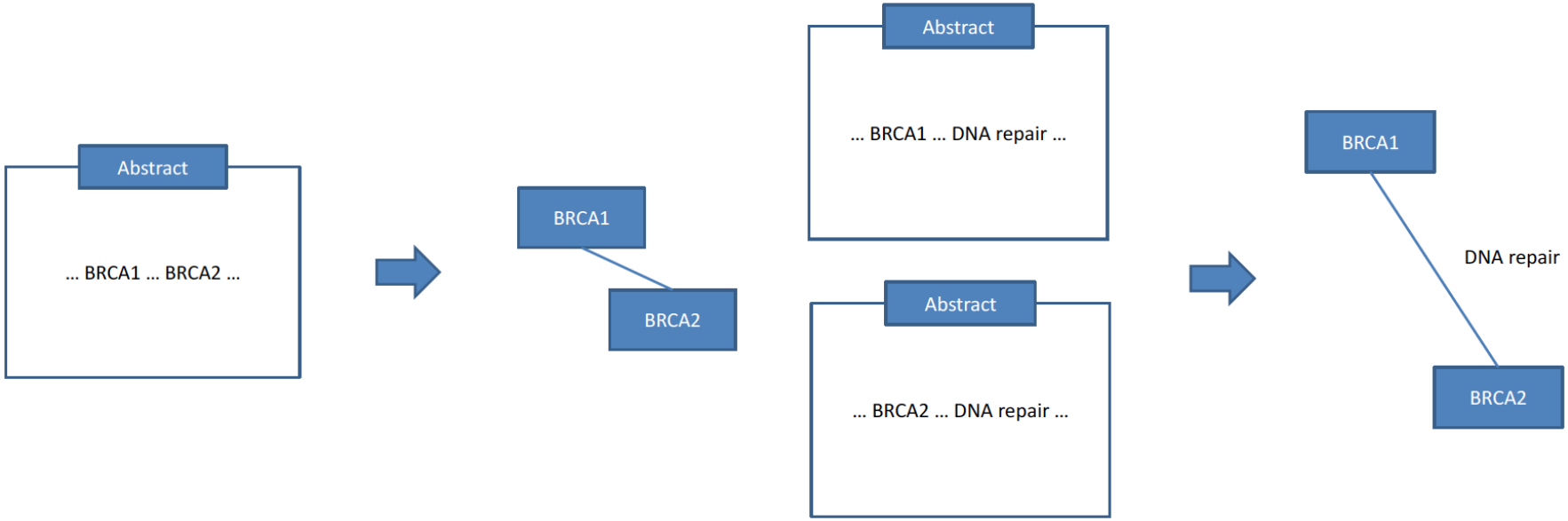


AIM 1. BIOMEDICAL LITERATURE + EXISTING PATHWAY DATABASES



AIM 1. BIOMEDICAL LITERATURE + EXISTING PATHWAY DATABASES

- **Ontology fingerprint**:
  - Collaboration with W. Jim Zheng, UT Health at Houston.
  - Qin et al. (2014), *NAR*.



AIM 1. BIOMEDICAL LITERATURE + EXISTING PATHWAY DATABASES

- **Ontology fingerprint**:
  - Association measures between genes and GO terms using hypergeometric tests.
  - *p*-values become smaller as more abstracts are shared.
  - Take into account how much each gene & GO term have been studied in biomedical literature.

Ontology fingerprint of BRCA1

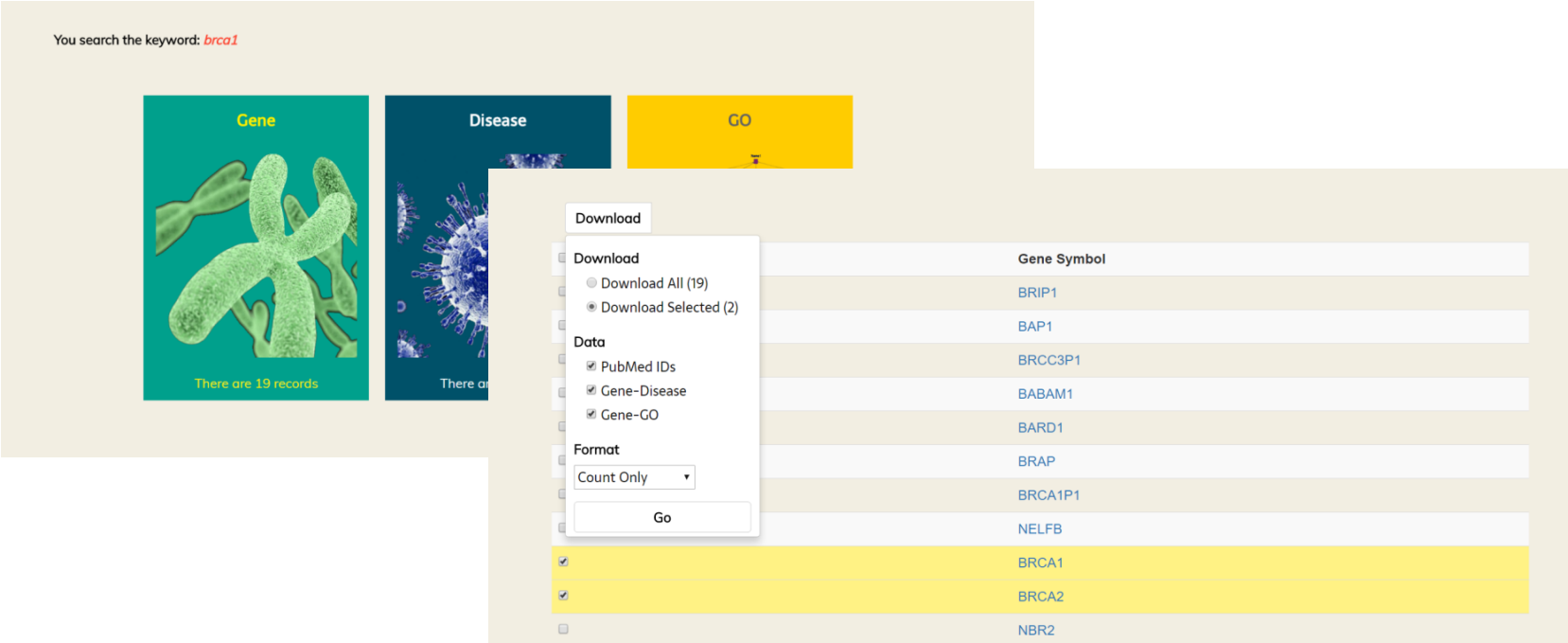
DNA repair	3.48e-158
Double-strand break repair	1.20e-25
Methylation	1.21e-18
Cell cycle checkpoint	3.64e-18
Mismatch repair	8.95e-13

Ontology fingerprint of BRCA2

DNA repair	1.95e-36
Strand invasion	8.32e-13
DNA recombination	5.86e-12
Double-strand break repair	1.61e-08
Recombination repair	2.37e-07

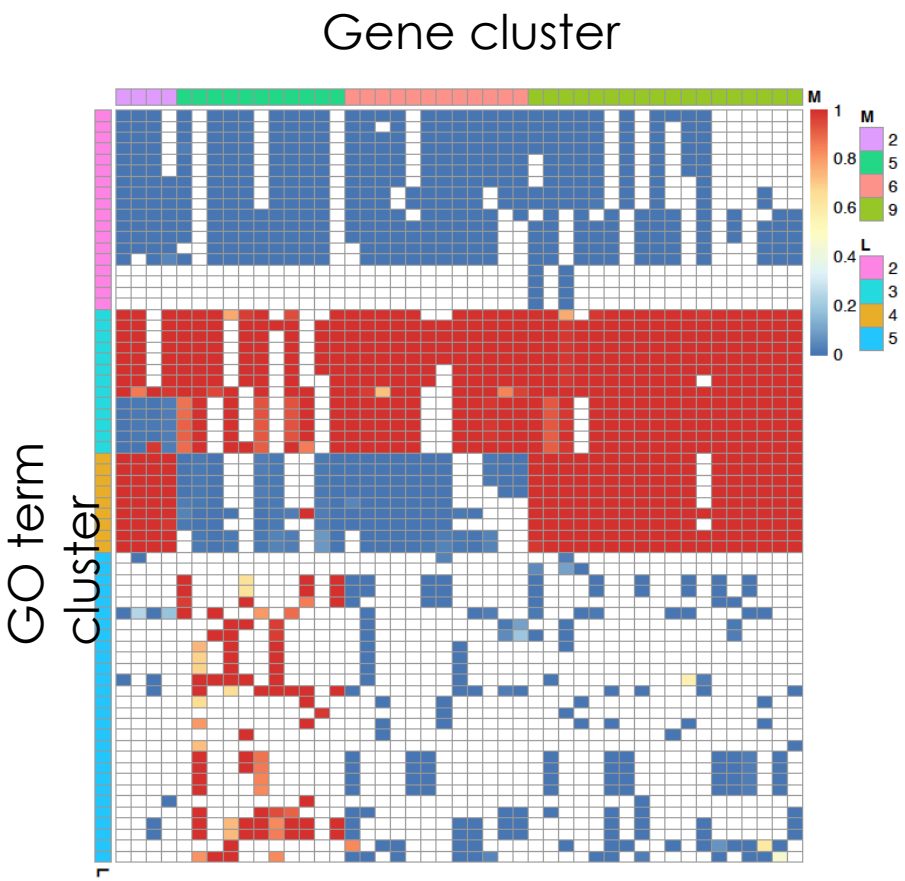
AIM 1. LITERATURE + EXISTING PATHWAY DATABASE

- **BioLitDB**: Web interface for literature mining.
  - Gene names, disease names, & gene ontology terms.
  - Currently internally developed & tested.
  - Plan public dissemination by end of this year.



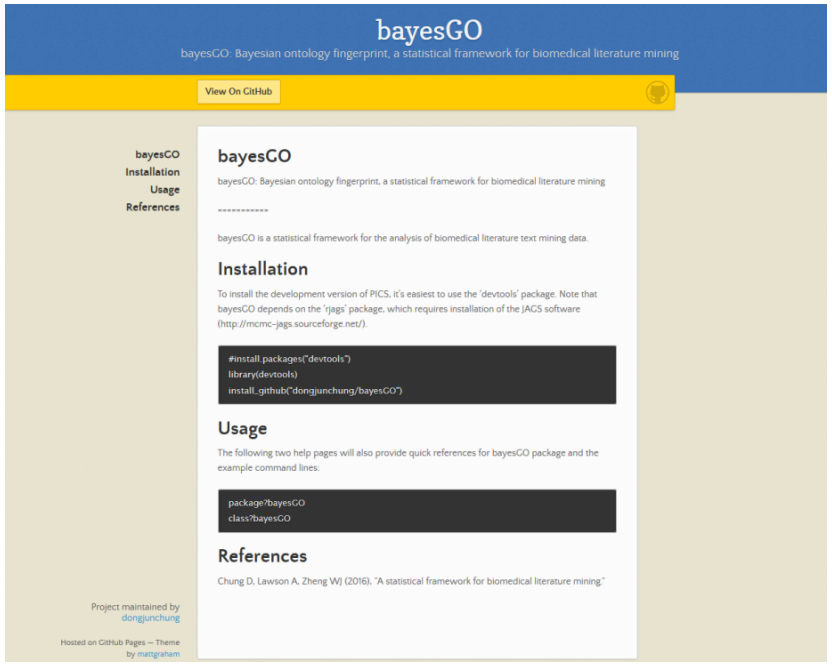
AIM 1. BIOMEDICAL LITERATURE + EXISTING PATHWAY DATABASES

- **bayesGO**:
  - Bayesian bi-clustering approach to identify novel pathways using the ontology fingerprint data.
  - Take care of redundancy & inter-correlation among GO terms.
  - Facilitate interpretation of novel pathways by automatically assigning groups of GO terms to each novel pathway.



AIM 1. BIOMEDICAL LITERATURE + EXISTING PATHWAY DATABASES

- **bayesGO**:
  - Chung et al. (2017), To appear in *Statistics in Medicine*.
  - **R package 'bayesGO'.**
    - bayesGO(): Fit model.
    - predict(): Gene and GO term clustering.
    - plot(): Plot the association heatmap.



https://dongjunchung.github.io/bayesGO/

AIM 1. BIOMEDICAL LITERATURE + EXISTING PATHWAY DATABASES

- Work in Progress:
- **BioLitDB**:
  - Improve user interface & public dissemination.
  - Incorporate pathway identification & visualization tools.
- **bayesGO**:
  - Integrate biomedical literature with multiple existing pathway databases.
    - A semi-supervised clustering approach that utilizes multiple existing pathway databases as prior knowledge for the pathway prediction based on biomedical literature data.
  - Utilize the GO tree structure information.

AIM 2. CANCER SUBTYPE IDENTIFICATION

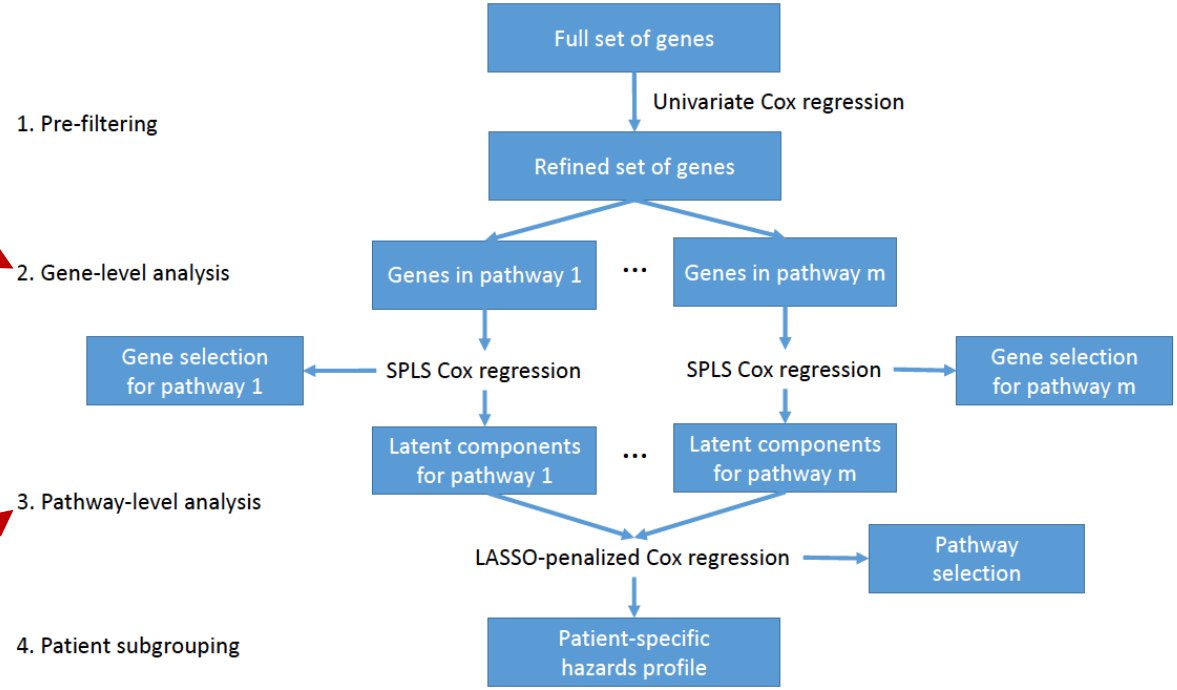
- **pathclust**:
  - Simultaneous identification of patient subgroups & key molecular features.
    - Identify key pathways, along with key genes in each pathway, associated with patient subgrouping.
  - Utilization of pathway information.
    - Improve robustness & stability in patient subgrouping.
  - Utilization of survival outcomes, if available.
    - Guide identification of patient subgroups and key molecular features using their association with survival.

AIM 2. CANCER SUBTYPE IDENTIFICATION

- **pathclust**:
  - Multi-step approach integrating sparse partial least squares (SPLS) and LASSO Cox regression approaches.

Simultaneous gene selection & dimension reduction for each pathway, using SPLS

Identification of parsimonious set of key pathways, using LASSO



AIM 2. CANCER SUBTYPE IDENTIFICATION

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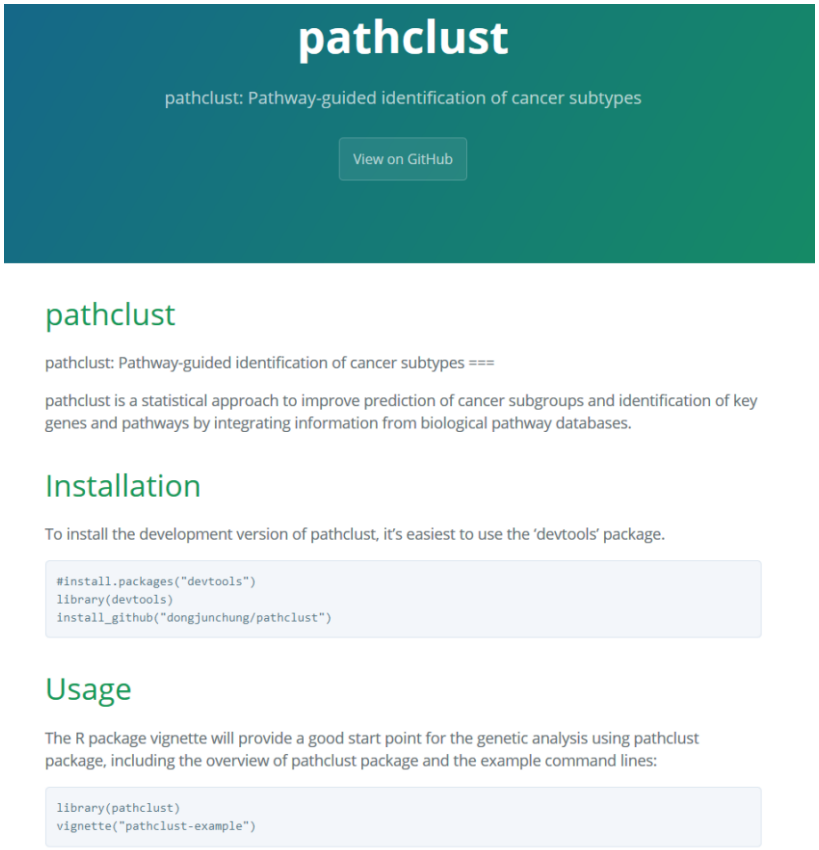


- **R package 'pathclust'**
  - prefilter(): Prefiltering.
  - selectGene(): Gene selction. -> coef()
  - selectPath(): Pathway selection. -> coef()
  - predict(): Patient subgroup prediction.
  - plot(): Plot Kaplan-Meier, Hazard ratio, and ROC curves for predicted subgroups.

- YouTube tutorial video:
  - https://youtu.be/0qaovmMJPpY

AIM 2. CANCER SUBTYPE IDENTIFICATION

- Work in progress:
- **pathclust**:
  - Joint analysis of multiple genomic data types.
  - Simultaneous utilization of multiple pathway databases.
  - Incorporate various approaches to handle the issue of gene overlap between pathways.
  - Implement a Bayesian approach to unify the framework & to incorporate various prior knowledge.
- Application:
  - Utilize novel pathway knowledge generated from Aim 1, which integrates biomedical literature with multiple existing pathway databases.

AIM 3. MUCINOUS OVARIAN CANCER SUBTYPE IDENTIFICATION

- Mucinous ovarian cancer (MOC):
  - Still relatively less studied; its subtypes remain poorly characterized in spite of its severity.
  - In need of improved treatments targeted to MOC.

- Planned work:
  - The statistical methods developed in Aims 1 & 2 will be applied to our cancer genomic data for MOC patients.
    - BioLitDB, bayesGO, & pathclust.
  - Will also be integrated with corresponding TCGA data for colorectal cancer, endometrial cancer, & gastro-esophageal adenocarcinoma.

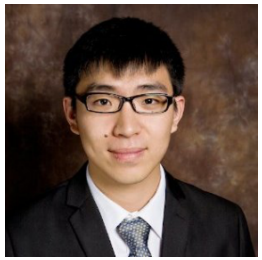
NATIONAL CANCER INSTITUTE
Informatics Technology for Cancer Research

ACKNOWDGEMENT

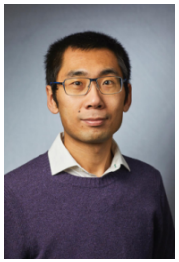
Chung lab, MUSC

Dongjun Chung (Biostatistics)

Zhenning Yu



Zequn Sun



Wei Wei (Yale Cancer Center)

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Collaborators

Andrew Lawson (Biostatistics)

Gary Hardiman (Bioinformatics, Center for Genomic Medicine)

- **Questions?**
  - Lab website: https://sites.google.com/site/statdchung/
  - GitHub: https://github.com/dongjunchung/
  - e-mail: chungd@musc.edu.