**Introduction**

- **Boolean Network**
  - Discovering Boolean Relationships
  - Analyze pairs of genes. Analyze the four different quadrants. Identify same quadrant. Record the Boolean relationships. ACPB high \( \rightarrow \) GABRB1 low GABRB1 high \( \rightarrow \) ACPB low

- **GBM**
  - Glioblastoma multiforme (GBM) is a cancer that grows in the supporting tissue of the brain and spinal cord. Its tumors are usually made up of many different kinds of cells, making the disease very difficult to treat. For most adults with GBM, the median survival rate is 2-3 years.

- **TCGA**
  - The Cancer Genome Atlas is a joint project between the National Human Genome Research Institute and the National Cancer Institute to make cancer data from major labs readily available with the goal of furthering cancer research and treatment. GBM is just one of 20 cancers represented.

**Objectives**

We used Boolean Networks to investigate TCGA GBM data on a large scale with integrative analysis of gene expression, mutation, methylation, copy number alteration.

**Methods**

- We mainly used Boolean relations to perform integrative analysis of cancer.
- We built the Boolean network using different types of data for the same samples such as expression, copy number, mutation and methylation.
- We systematically analyzed the Boolean network using the following methods:
  - Look for relations between expression, methylation and copy number/mutation.
  - Look for relations between copy number and mutation.
  - Look for relations between known categories of TCGA GBM and mutation, expression and copy number.
  - Look for chains of Boolean implications.

**Results**

- **Boolean Relations between genomic alterations**
  - Boolean relations between mutations and/or chromosomal alterations are interesting and could represent various events important to cancer:
    - Mutually Exclusive Hits on the Same Pathway
    - Group-Specific Events
    - Loss of Heterozygosity
    - Temporal Ordering of genomic events
  - Since chromosomal segments tend to be deleted or copied in chunks, the copy number data is organized according to cytobands.
  - A virtual gene was added to the Boolean network for each cytoband by merging CNA information of genes in the same cytoband.

- **HILO Relations - Mutual Exclusion**
  - A high \( \rightarrow \) B low represents a mutual exclusion between A and B
  - Could represent group-specific events or hits that are alternative ways of achieving the same effect, thus suggesting that they are on the same pathway

**HIHI relations on the same gene - Loss of Heterozygosity (LOH)**

- A_mut high \( \rightarrow \) A_del_high implies all samples where the A is mutated also have A deleted
  - Represents double hits to gene A, which means LOH, ie loss of normal function of one allele of a gene in which the other allele was already inactivated

**HIHI relations between different genes/ chromosomal regions**

- Cancer progresses in a sequence of mutations that cause increased proliferation, defective checkpoints in the cell cycle, turn off programmed cell death (apoptosis), and cause cells to migrate (metastasis).
- A high \( \rightarrow \) B high where A and B are genomic alterations could represent a temporal ordering where B occurs first followed by A

**Discussion**

- This work validated the ability of Boolean Network in finding various relation between genes and chromosomes in genomics in the development of cancer.
- This work confirmed many findings from previous work, including:
  - Genes associated with the four subtypes of GBM
  - Important genes in GBM, including RBB1, CDKN2A and PTEN
  - The role of IDH1 in hyper-methylation
  - Significant deletion in chromosome 7 and amplification in chromosome 10 and their close relationship.
- This work also found new strong relations that haven’t been found before:
  - New Mutational Exclusion Relations
  - HIHI relations which may suggest temporal sequence of process in the development of GBM
  - HIHI relations between expression and mutation of the same gene, which suggest the loss of heterozygosity in GBM patient.
  - Many other inter-chromosomal relations that are very interesting and require further investigation.

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**References**

[1] Roel G.W. Verhaak, etc. “An integrated genomic analysis identifies clinically relevant subtypes of glioblastomas characterized by abnormalities in PDGFRα, IDH1, EGFR and NF1.” Cancer Cell 2010, Jan 19, 17(1): 98