

Investigations of Aerospace Medical Factors using a Systems Biology Approach



Federal Aviation
Administration



Our Mission:

- **Discover sets of molecular markers that are diagnostic for factors that affect aviation/transportation safety.**
- **Markers will have dual-functionality for regulatory and forensic applications.**
 - Potentially different markers for pre and post-mortem samples
- **Targeted therapeutics**
 - Minimize side effects by specifically targeting affected pathways
- **Human study design**
 - Lack of good animal models for the factors we study



Human Genome Project Video



3d.wmv



The Central Dogma

- **DNA is a storage molecule**
 - but is not informative for the current state of the cell
- **messenger RNA (mRNA) is the active nucleic acid molecule**
 - Transcribed from the gene (DNA) as a primary transcript
- **exons are the units spliced into mRNA from the primary transcript**
- **Proteins are translated from mRNA on ribosomes and made of amino acids**
 - Proteins are what gets things done; enzymes, structure, regulation



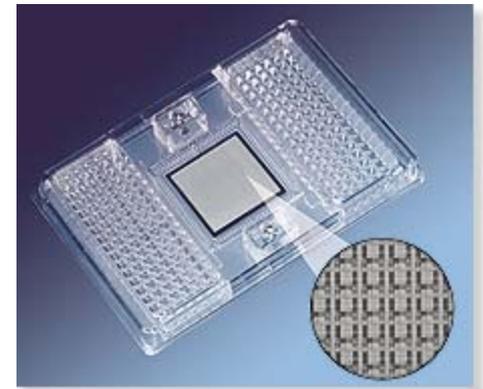
Considerations and Goals

- **We investigate aerospace medical factors from a gene/protein expression viewpoint**
 - What markers change expression level in response to a change in the environment?
 - How is human performance affected by the environment?
 - The big questions...
- **What is the correlation between marker expression level and human performance?**
- **What combination of markers best measures human performance decrements?**



Factors of Interest: No objective test

- **Fatigue is a detrimental human factor of interest across all modes of transportation**
 - Prevent accidents/incidents due to fatigue using “Lab-on-a-Chip” technologies (real-time biological assays in extremely small volumes)
- **Hypoxia is aviation specific**



Factors of Interest, cont.

- **Alcohol use**
 - ~40% of alcohol positives can not be differentiated between ingested and post-mortem sources
- **Radiation implicated in increased breast and skin cancer rates in flight crew**



Molecular Stability Project

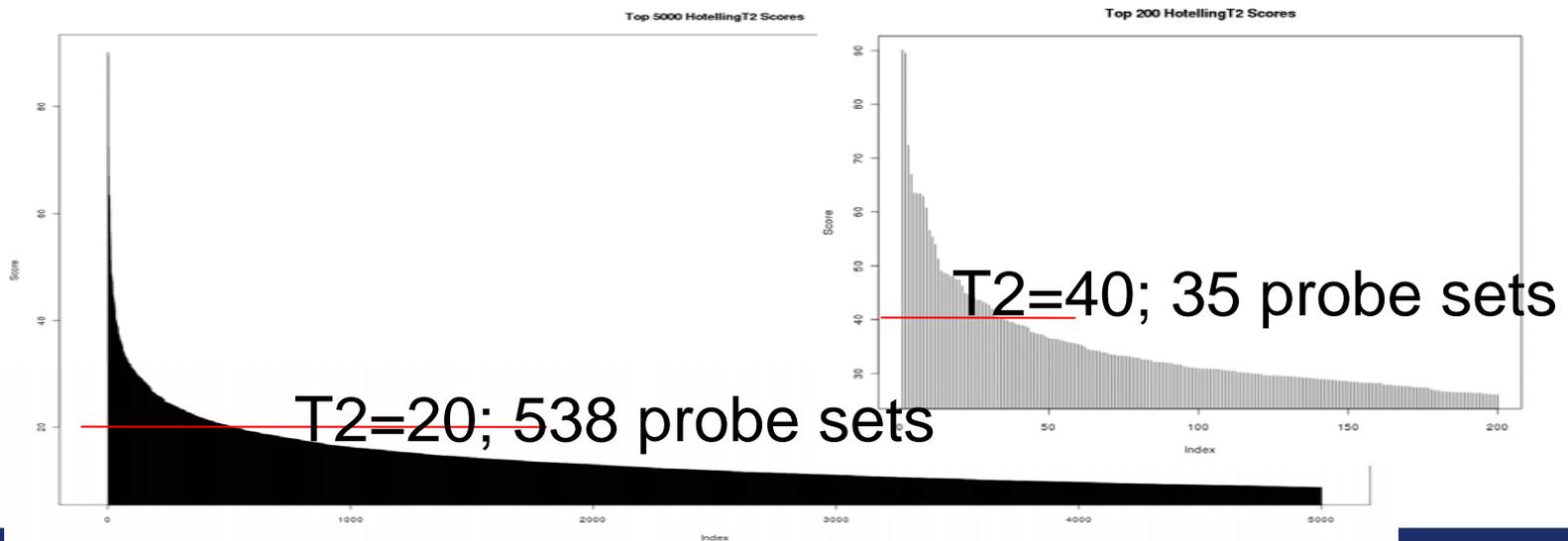
- **Currently involves collecting an additional tube of blood from accident victims during autopsy**
 - Expanding to other tissues from the same victims
- **Purify and assay for RNA degradation**
 - BioAnalyzer 2100
 - qPCR
- **Important for us to understand the degree of degradation**



Outputs and Analyses

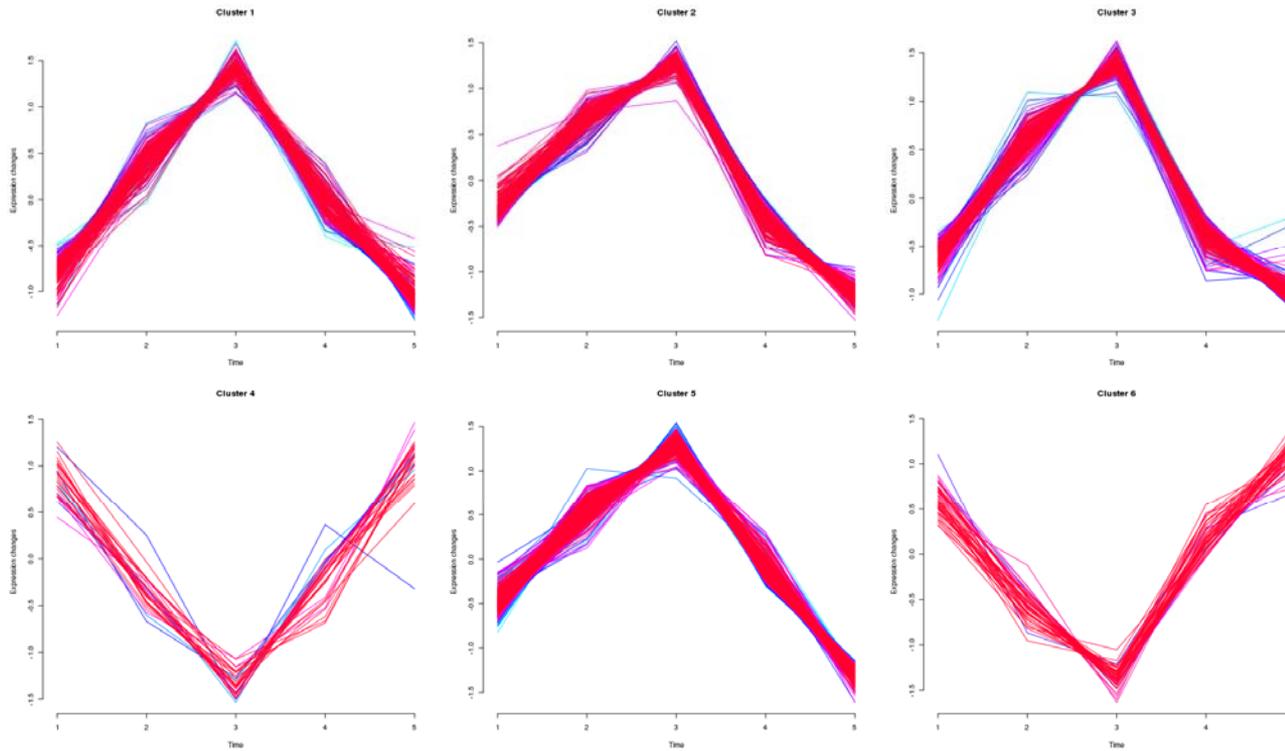
- **Differential expression testing**

- timecourse[#] package in Bioconductor applied to microarray data
- Generate at least two lists from ranked likelihoods of differential expression for:
 - Markers (highest likelihood probe sets)
 - Biology of FOI from a less stringent list



Outputs and Analyses

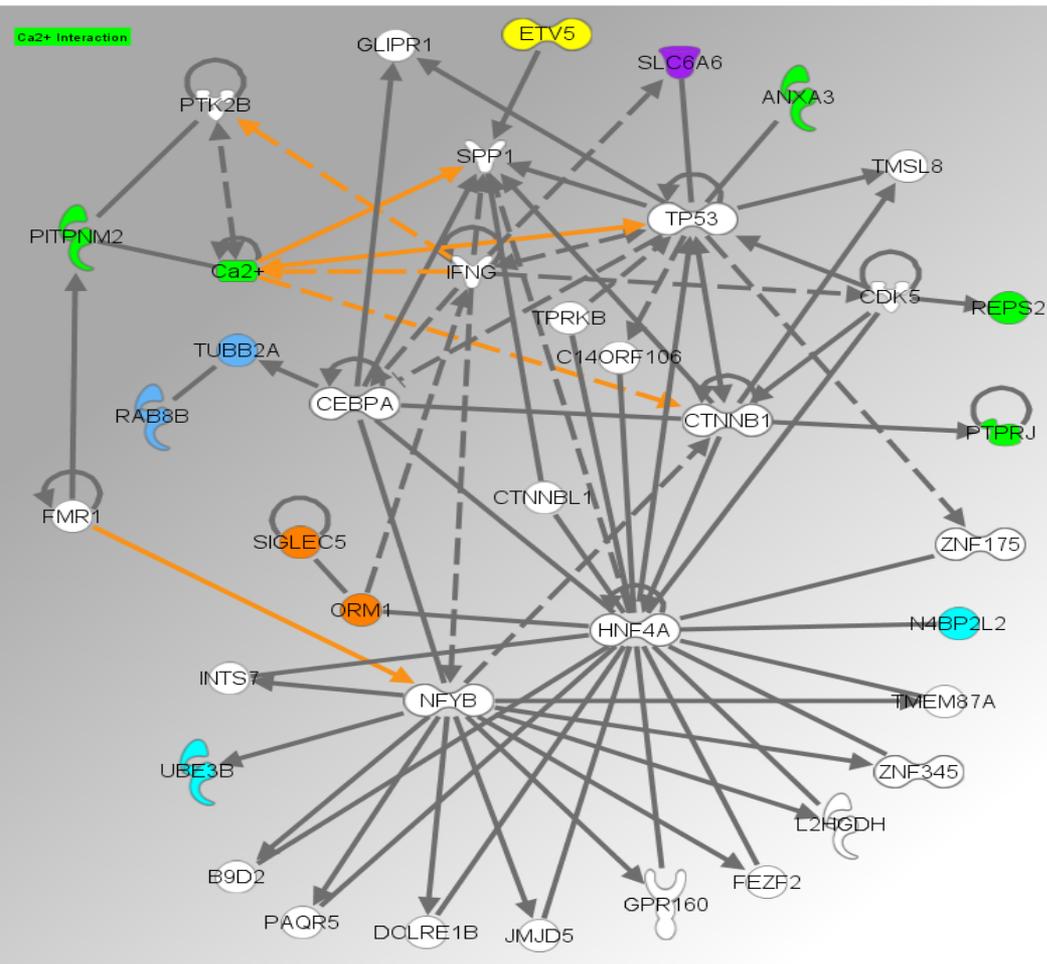
- **Cluster for time-dependent expression patterns**



Outputs and Analyses

- **Pathway analysis in Ingenuity***

Path Designer Networks 1,4 Merged 1



*<http://ingenuity.com>



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Outputs and Analyses II

- **Ontology analysis of entire dataset by GSR**
 - Molecular function
 - Biological process
 - Cellular compartment
- **Promoter analysis for TFBS**
 - Co-regulatory factors
- **qPCR validation of candidate markers**
- **Correlation to cognitive data**



Investigatory Work Flow of the Future

Mechanical Black Box

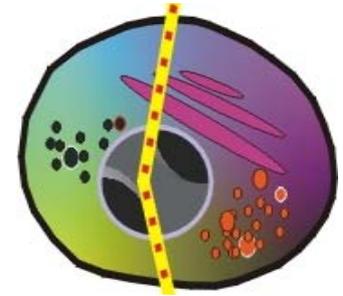


Mechanical
Factors



Human
Factors

Cellular Black Box



Monitors 48 parameters of flight data, and the CVR recorded a little more than 30 minutes of conversation and other audible cockpit noises.

Monitors 40,000 genes associated with stimuli experienced by the human body.

Interpretation

Accident Cause



Summary

- **For a host of aeromedically important factors, a range of molecular signatures will be developed that strongly correlate to degrees of lessened human performance**
- **These molecular signatures will enable regulatory agencies to write fact-based regulations that will increase aviation safety, save lives, and decrease accident and incursion rates**
- **This research will keep the FAA at the forefront of aerospace medicine research and maintain our reputation as a world-class research organization**



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