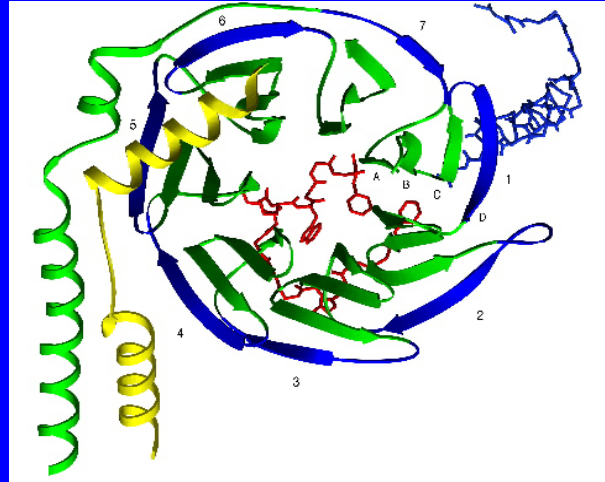


**Fatty Acids Homeostasis;  
the search for  
the key regulatory factors.**

- Andrew Knyazev, Math CU Denver**
- Min Han, MCDB CU Boulder**

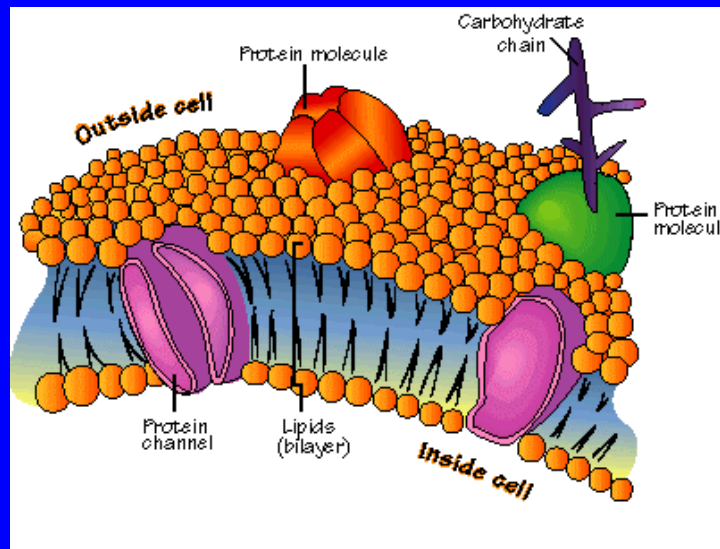
# Biological roles for Fatty Acids

**Molecules**



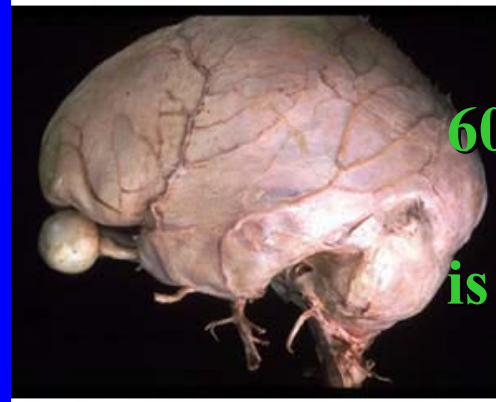
**Protein  
modifications**

**Cells**

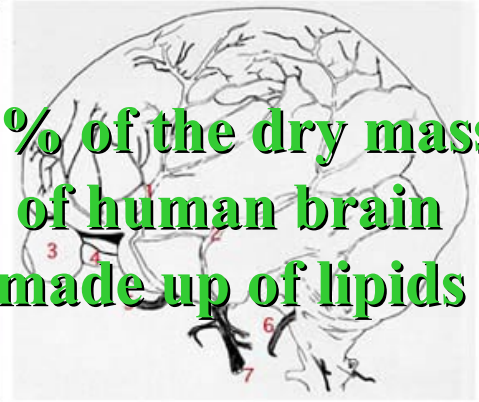


**Membrane Structure  
and Energy Storage**

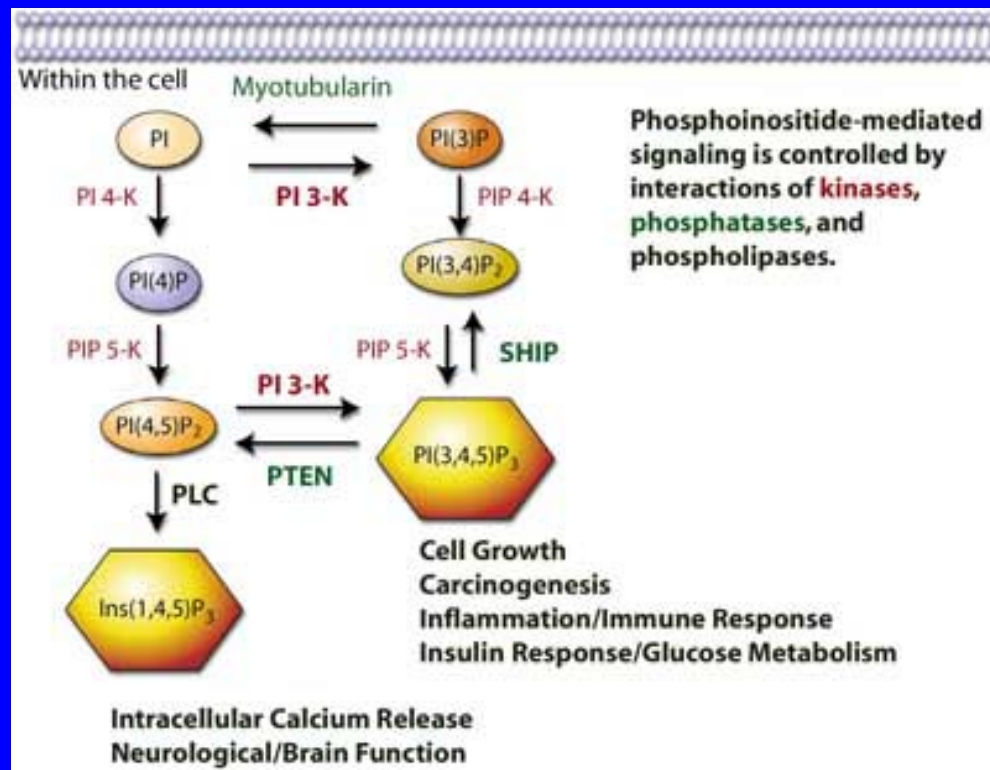
# Organs



60% of the dry mass of human brain is made up of lipids



# Systems Lipid Signaling



# Fatty Acids Composition in Diseases

**Diabetes**

**Hypertension**

**Heart failure and Diabetic cardiomyopathy**

**Refsum Syndrome**

**Atopic disease**

**Cancer**

**Schizophrenia**

**Bipolar and attention deficit hyperactivity**

**Depression**

**Mood disorders**

# FA metabolic proteins in diseases



## **Activation of Fatty Acid Synthetase (FAS)**

Tumor cells from a variety of human cancers.



## **Mutant forms of phytanoyl-CoA 2-hydroxylase, PAHX**

Refsum's syndrome



## **Defects of carnitine-palmitoyl transferase, CPT-II**

Variable myopathy



## **Upregulation of alpha-methylacyl-CoA racemase**

Prostate cancer



## **Transcriptional repression of stearoyl-CoA desaturase-1**

Leptin-mediated weight loss



## **Increase in cytosolic phospholipase A**

Dyslexia



## **Deletion in the long chain FA elongase, ELOVL4**

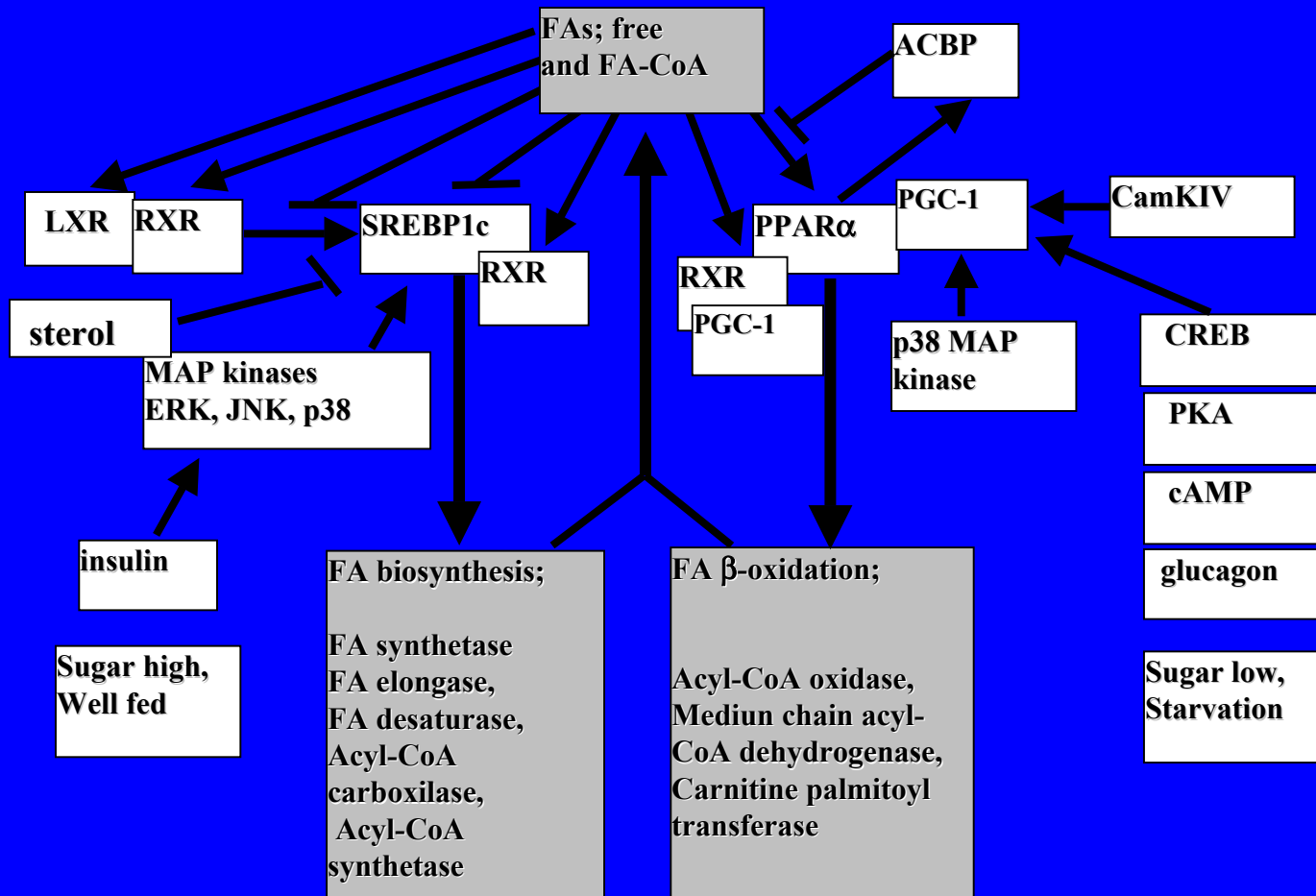
Stargardt's-like macular degeneration

# FA Homeostasis

- **Is a critical warrant of the proper functioning of the Fatty Acids molecules**
- **The mechanism of Fatty Acid homeostasis is not understood**
- **FA metabolism is regulated on the transcriptional level**
- **Nuclear receptors affect FA metabolic gene expression**
- **Fatty Acids affect NR transcriptional activity**

**What are genetic responses to the altered Fatty Acid composition?**

# Fatty Acid Metabolism is Transcriptionally Regulated



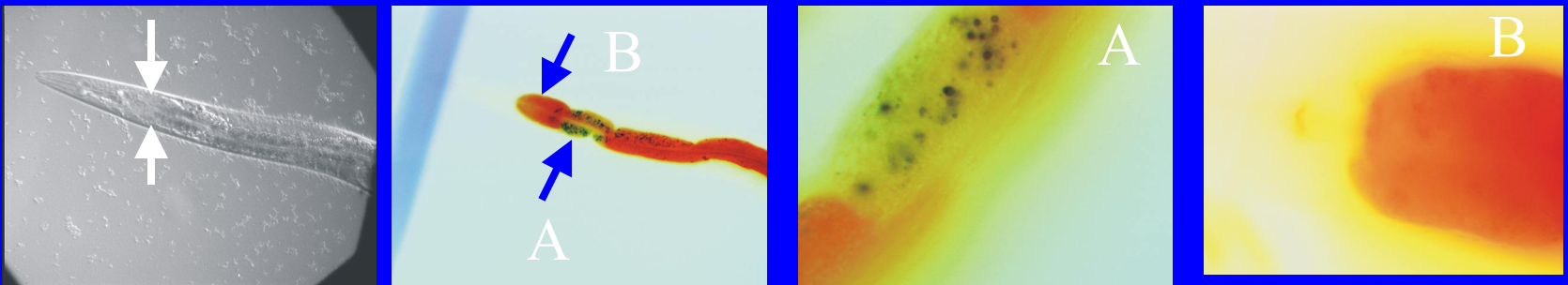
**How FA biosynthesis and degradation**  
**are coordinated to maintain**  
**biologically important FA balance?**

**Novel Model and Methodology to study  
Fatty Acid Metabolism and Homeostasis**

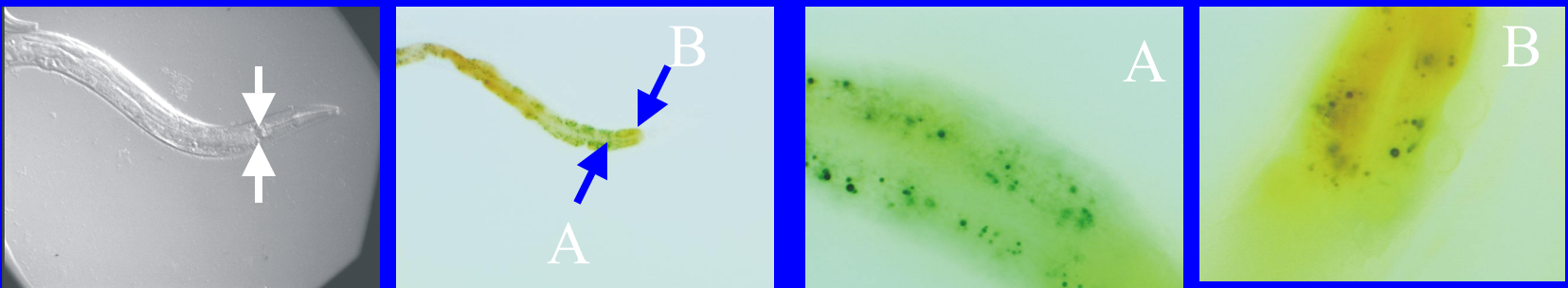
## *C. elegans* model

*C. elegans* synthesize various FAs.

Mutants have abnormal FA composition

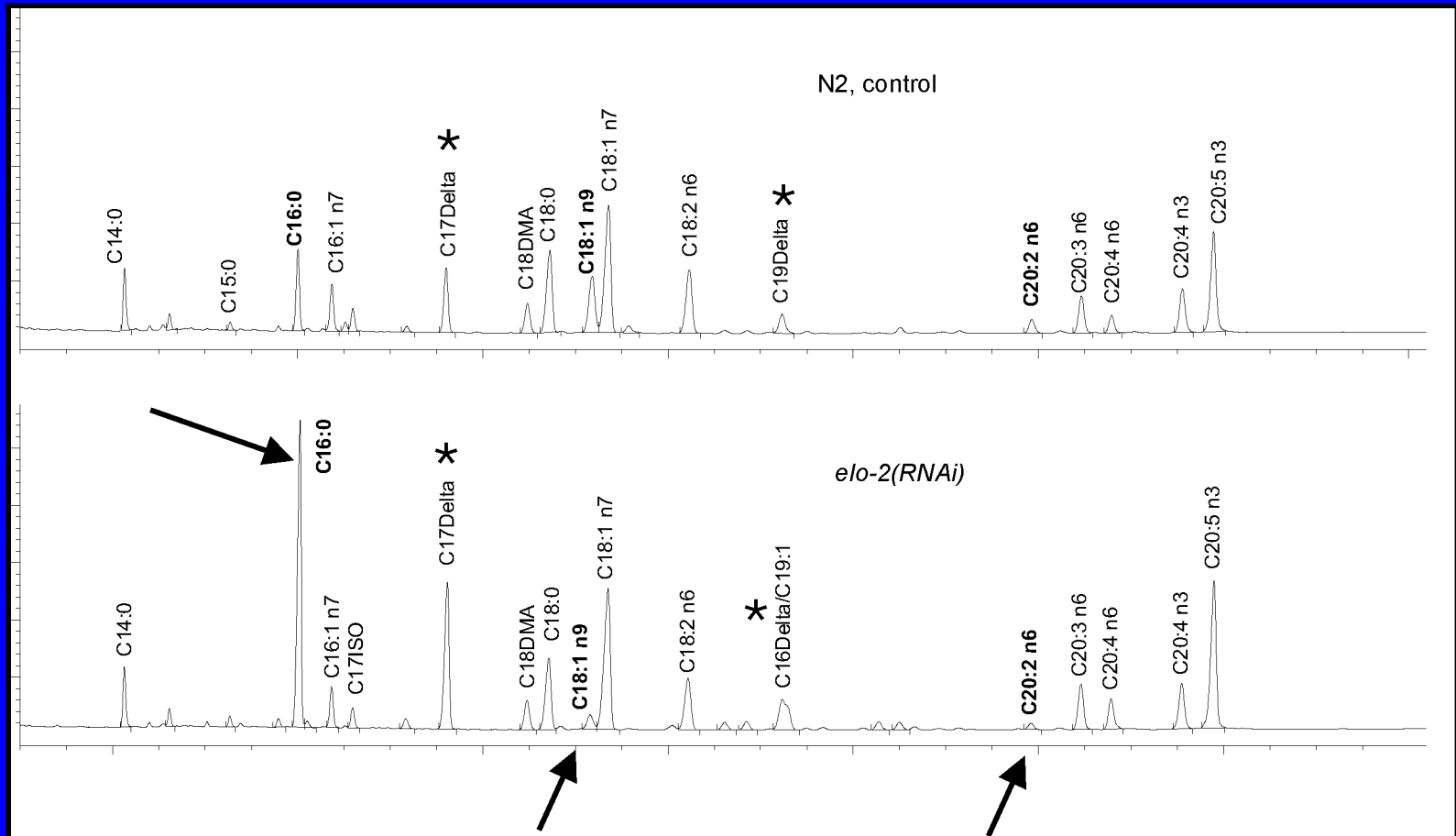


N2, wild type *C. elegans*



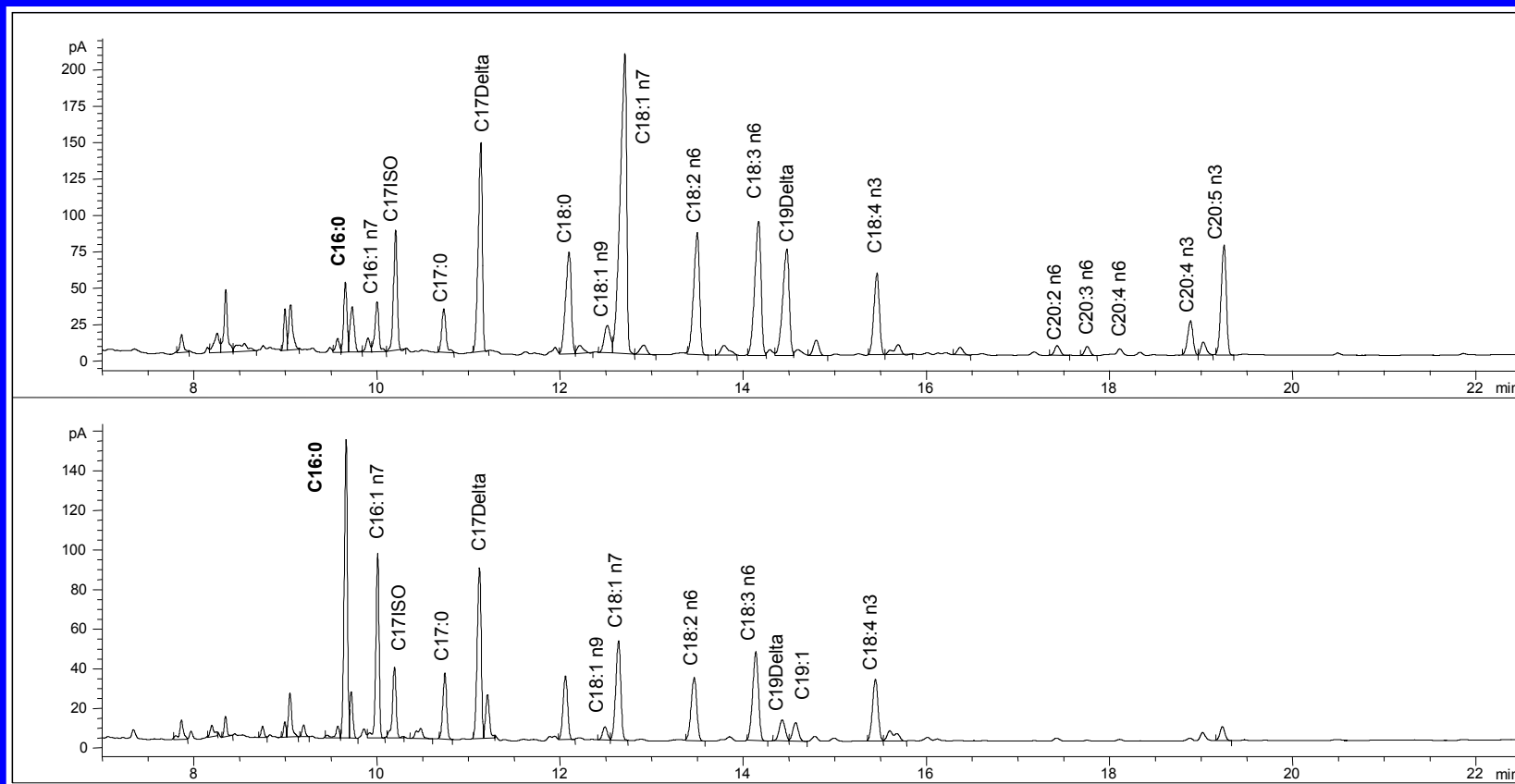
*elo-2(RNAi)*, genetically engineered worms accumulating palmitate.

# Fatty Acid Composition in *elo-2(RNAi)* mutants



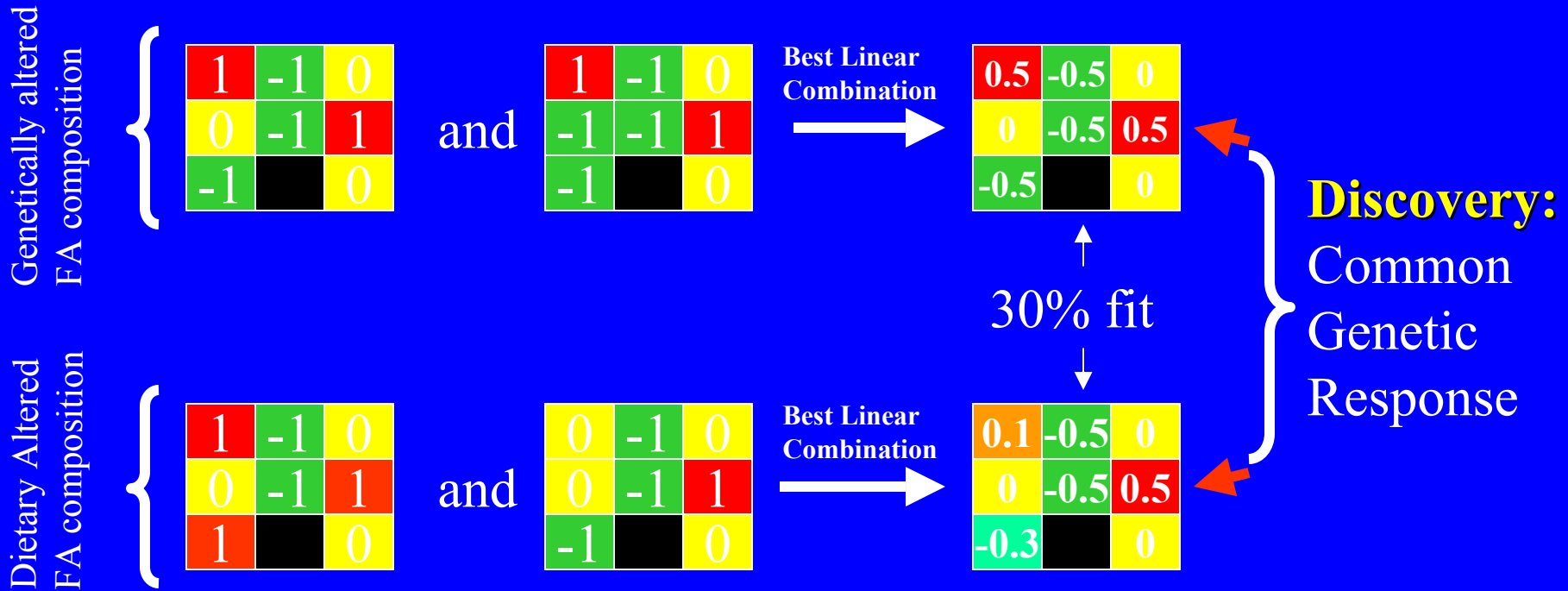
# Fatty Acid Composition

in *elo-1(gk48);elo-2(RNAi)* mutants





# SVD-based all-against-all Analysis.



*SVD- singular value decomposition*

*Control is target RNA from N2 wild type in all experiments*

# Advantages of the novel SVD all-against-all approach

- **qualitatively new knowledge discovery compared to the standard pair-wise analysis**
- **processing of 100s vs. 100s microarrays simultaneously**
- **independent of DNA chip's slots order**
- **fully automatic**

The ultimate goal is to contribute to the understanding of the FA homeostasis by discovering and characterization of its key regulatory mechanisms

- **This is the first introduction of the *C. elegans* model organism using a high throughput screen for transcription factors involved in the FA homeostasis.**
- **Developing the *C. elegans* model will allow further screen for drugs targeting specific metabolic enzymes and proteins in live animal.**