

About mechanistic underpinnings of genetic interactions

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About the presentation

- Basic concepts
- Genetic interactions
- Metabolic maps
- Flux Balance Analysis (FBA)
- Mechanistic underpinnings through examples
- Improving FBA

Basic concepts

- Unmutated wild type population, W
- Usually effects of genes are examined thru gene deletions
- Mutant population for gene A , W_A

Fitness of a population

- Rate of population growth compared to wild type growth
- Marked here with f
- For wild type W , $f(W) = 1$
- For lethal mutation W_{Dead} , $f(W_{\text{Dead}}) = 0$
- Essential and nonessential genes

Genetic interactions

- Relation of genes, proteins and fitness
- Overlapping and redundancy cause genetic interactions
- We limit to the case of pairwise interactions

Interactions mathematically

- In a simplified case for noninteracting genes A and B, it holds that $f(W_{AB}) \approx f(W_A) * f(W_B)$

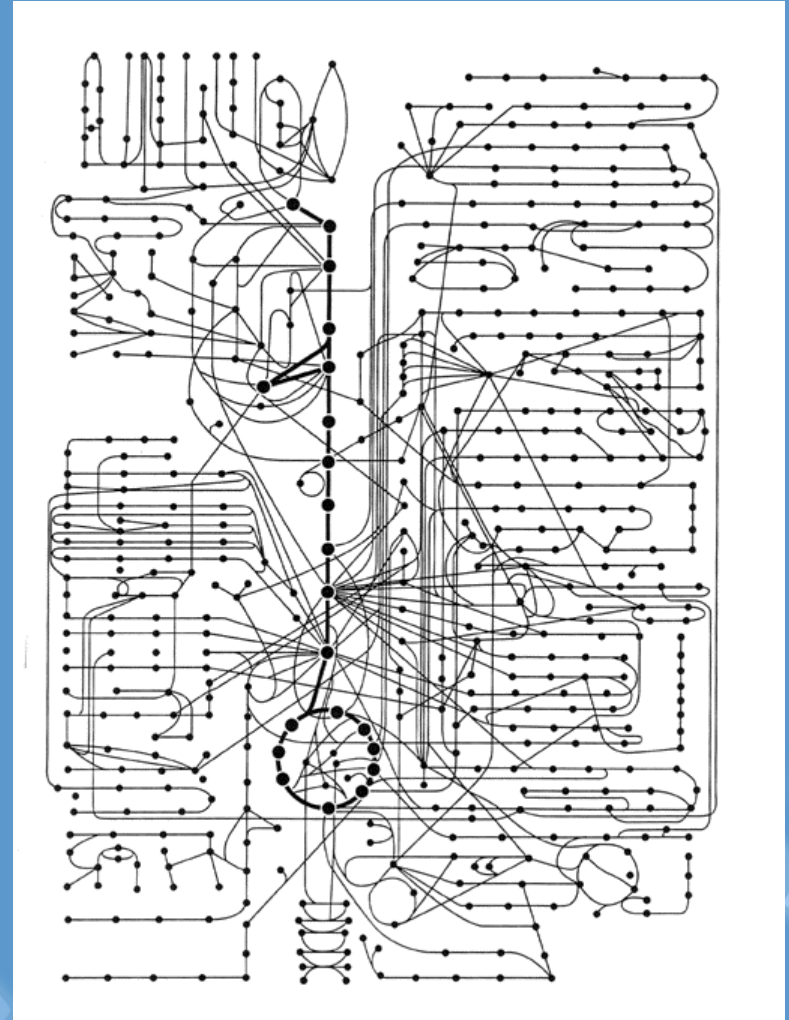
- Therefore the interaction effect ε is

$$\varepsilon(AB) = f(W_{AB}) - f(W_A) * f(W_B)$$

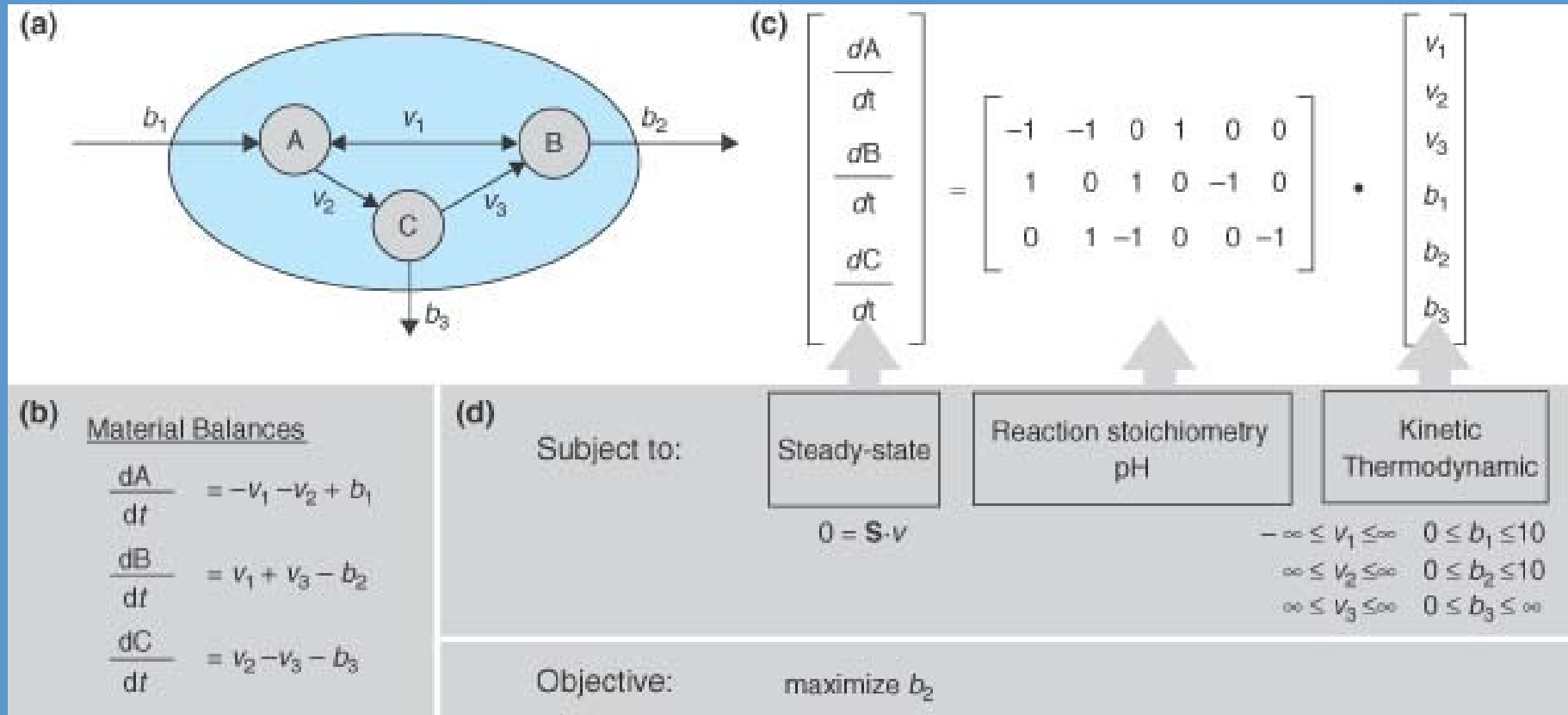
- Interaction is called negative, neutral or positive according to the sign of $\varepsilon(AB)$

Metabolic map

- Model of an organism
- Edges = reactions, nodes = metabolites
- Directed reaction diagram with weights



Principle of FBA



Terzer et al: Genome-scale metabolic networks (WIREs Sys Biol and Med, 2009)

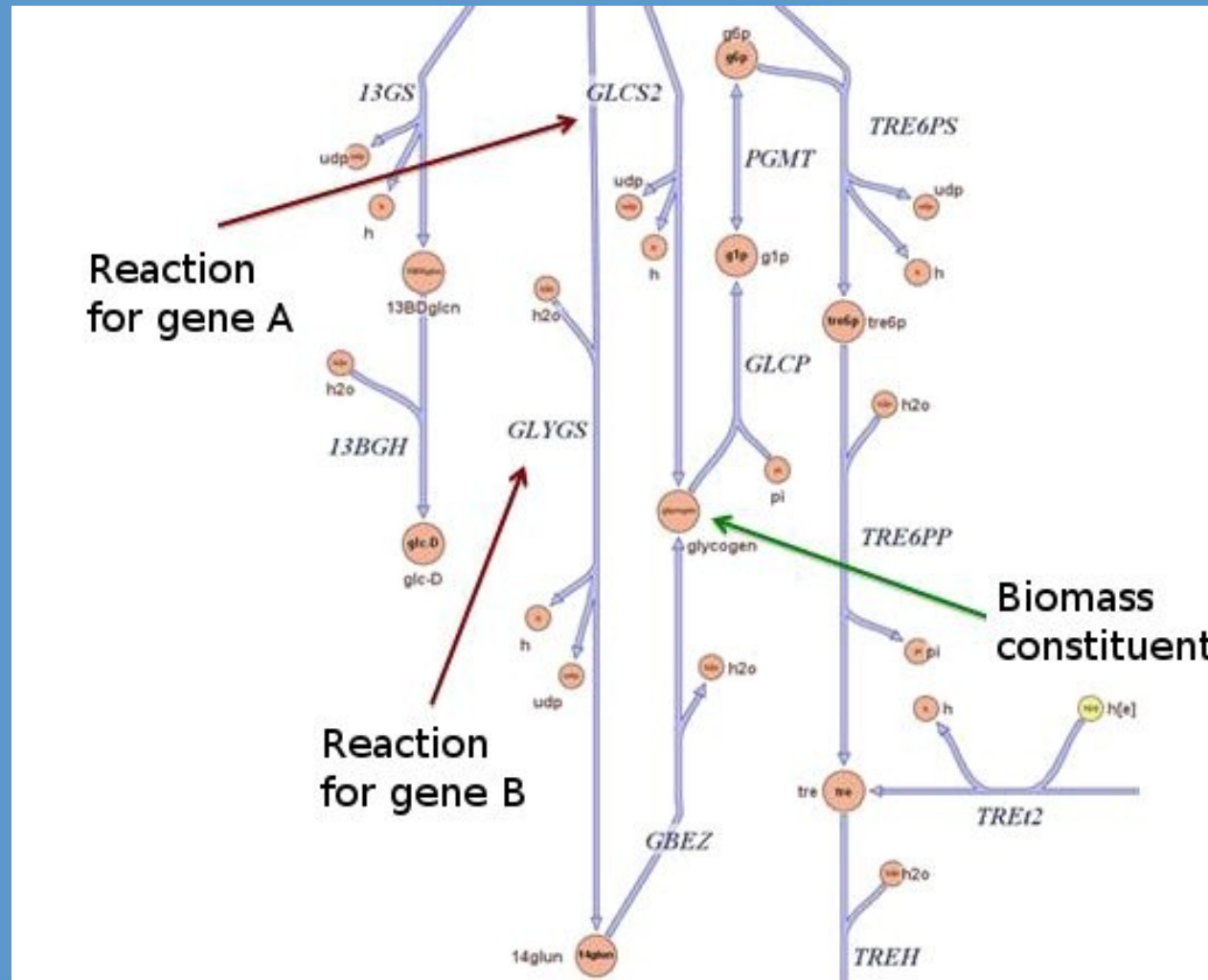
Flux Balance Analysis (FBA)

- Steady state, flux constraints, unlimited resources
- Optimize biomass production
- Many applications: Study of growth media, interactions, etc.

Mechanistic underpinnings

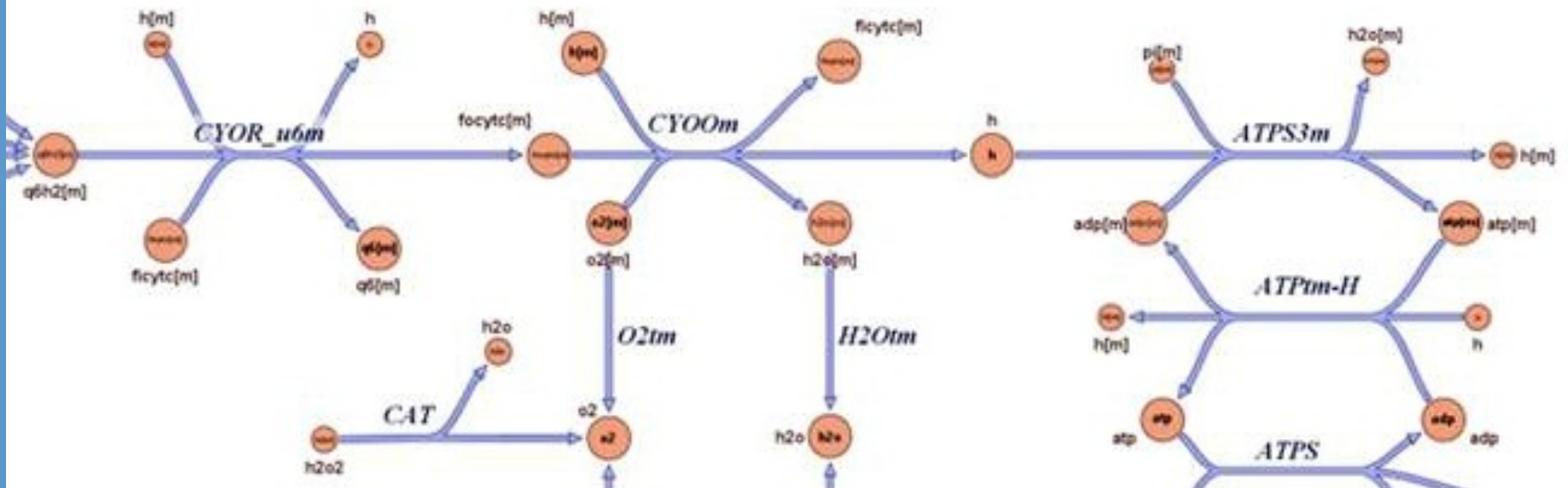
- Study of metabolic network connecting the interacting genes
- Next few examples found using yeast metabolic network
- Synthetic lethal
- Co-equality

Example of synthetic lethal



Example of co-equality

Oxidative Phosphorylation



- In same pathway close to each other

Improving FBA

- All optimal solutions instead of one (flux variability analysis)
- Time-dependent modelling
- Transcriptional regulation