Developing Risk Reduction Strategies through Metabolic Profiling

W-N Paul Lee, MD

Harbor-UCLA

1) **Risk reduction strategies: prevention, intervention and treatment.**

2) **Strategies are designed based on information: knowledge of genome and its expression, knowledge of proteins and their structural and spatial relationships, and knowledge of metabolic functions.**

Biochemical Reaction

$$\vec{v}_0 = \frac{\vec{V} s_0}{s_0 + K_m}$$

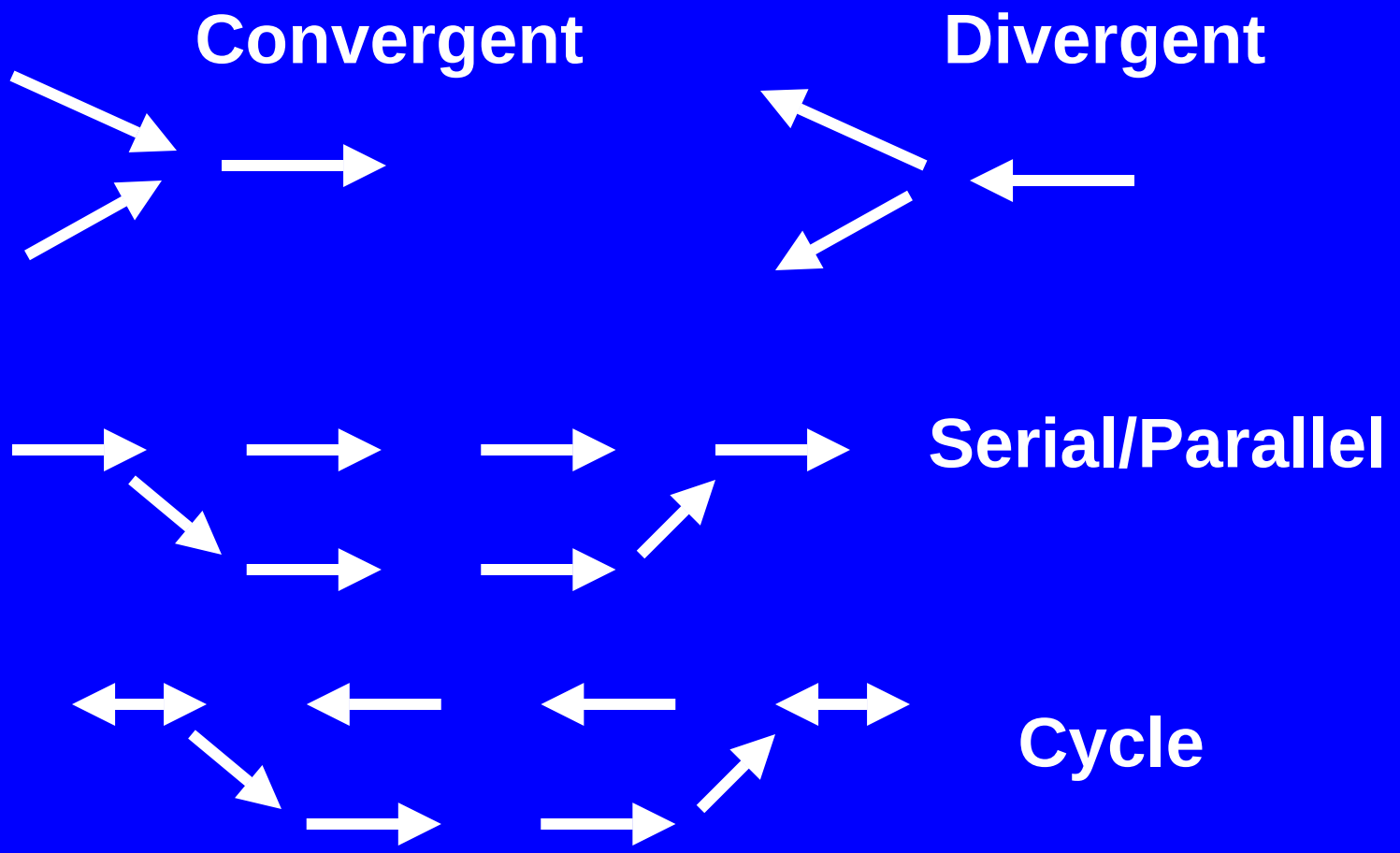
Dependence on substrate and genomic/proteomic variables

Linear Pathways

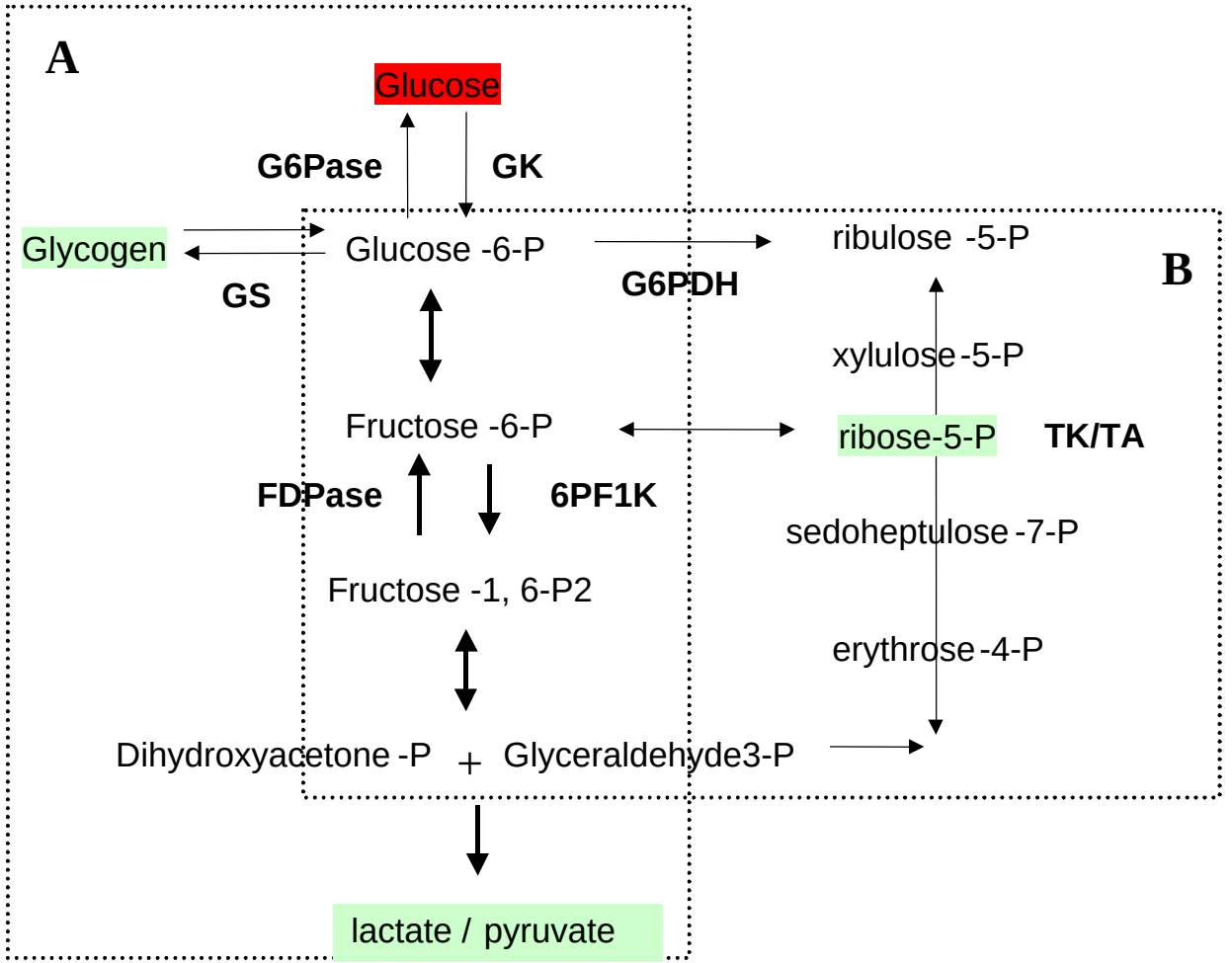
Linear unidirectional pathway

Genomics, proteomics and metabolomics give equivalent information.

Organization of Pathways



Example of Metabolic Network



1) Perturbation the glucose metabolic network affects both the forward and reverse reactions of these substrate cycles.

2) The response to precursor is specific resulting in a change of direction and magnitude of redistribution of metabolic intermediates.

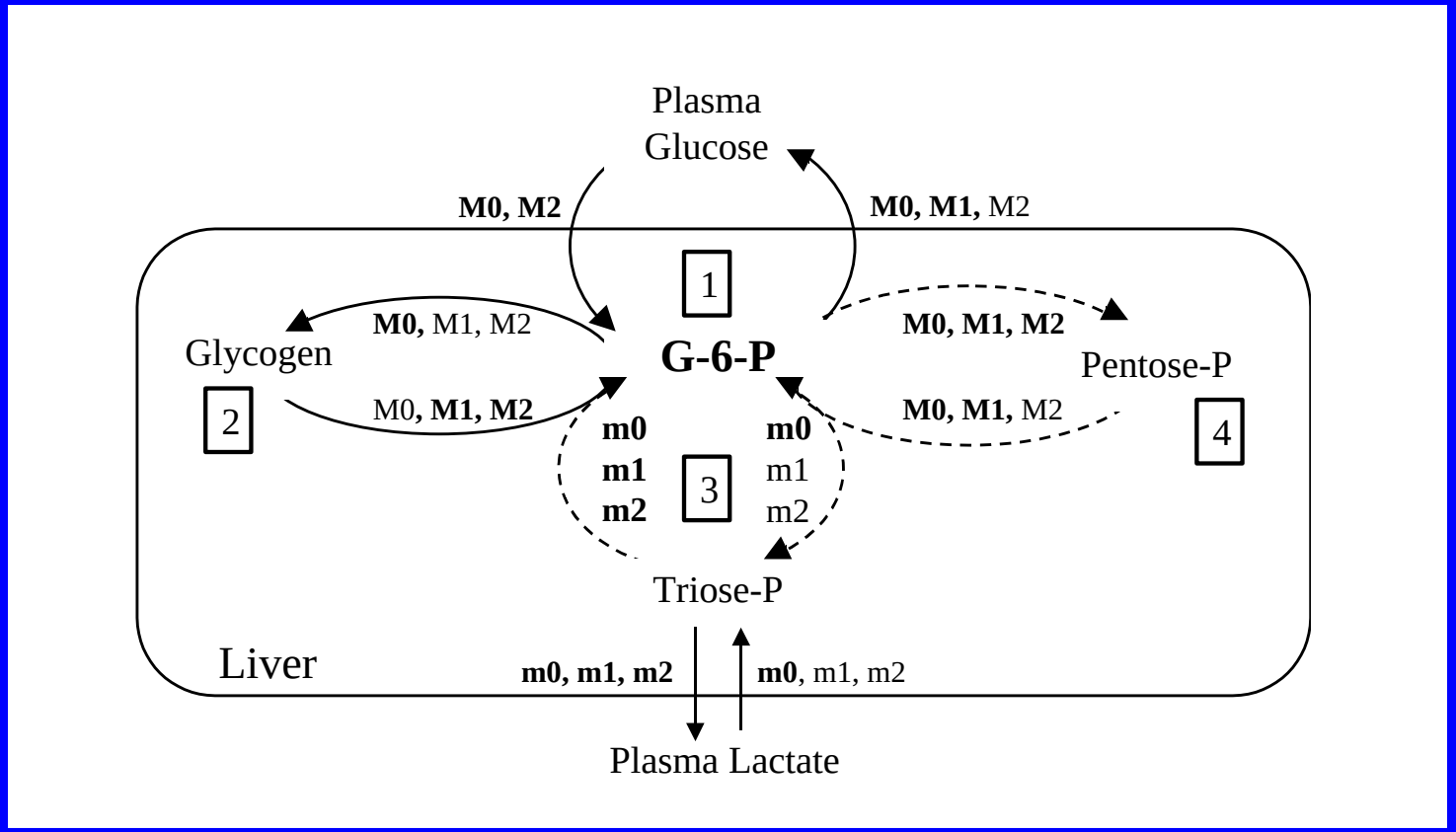
3) The interconnection of these cycles allows optimal distribution of substrate throughout the network.

Metabolic function of a living system can be characterized by the distribution of substrates, the direction of net fluxes and changes in substrate cycles.

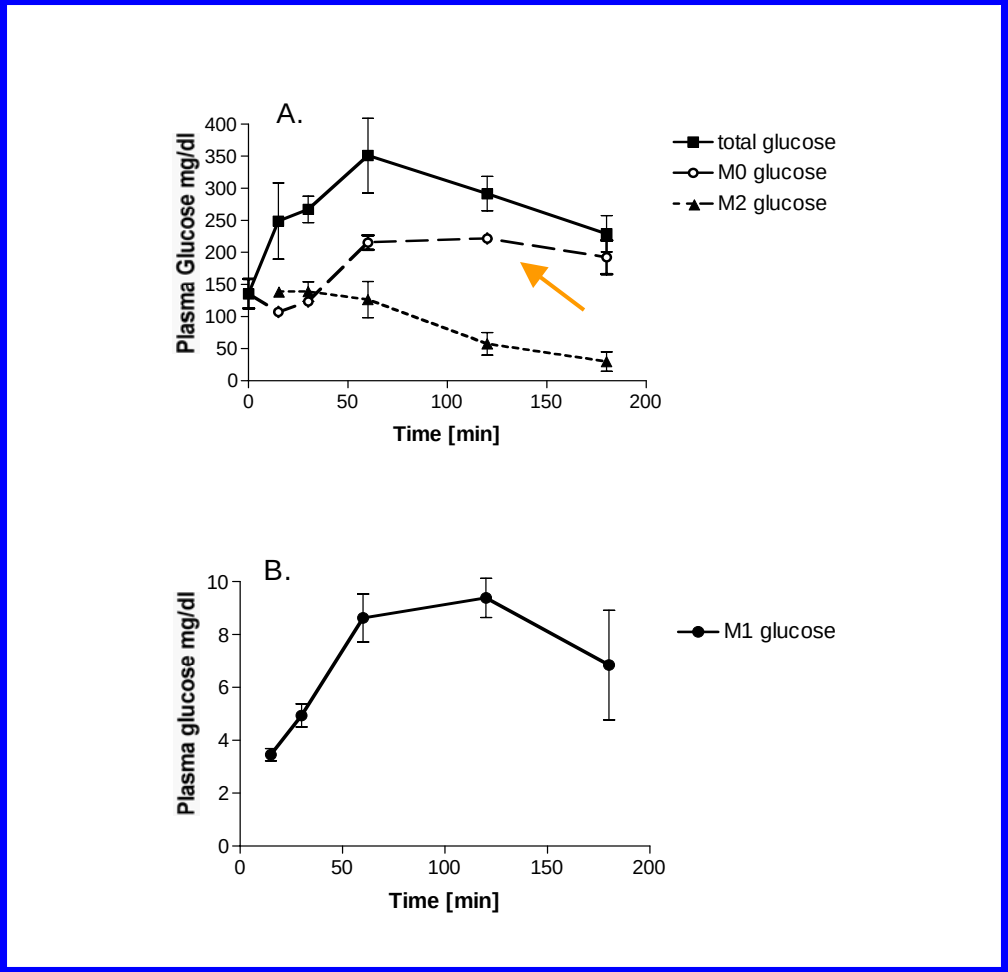
Metabolic Profiling can be achieved with the use of appropriate stable isotope tracers and mass spectrometry (GC/MS or LC/MS).

The study of substrate cycles in hepatocytes is a powerful tool for the screening of drugs which may affect hormone signaling pathways as related to hepatic glucose metabolism in diabetes.

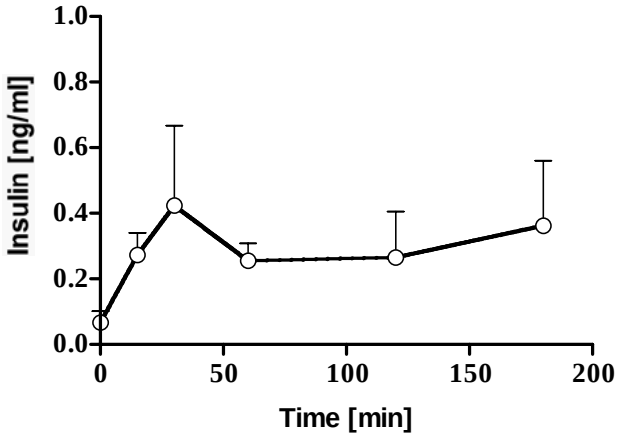
Substrate Cycles during IPGTT

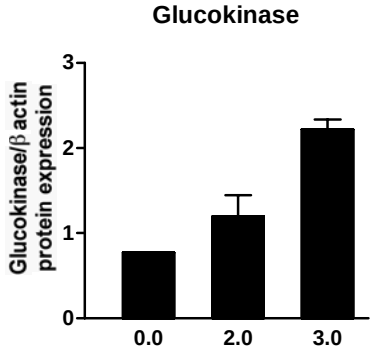


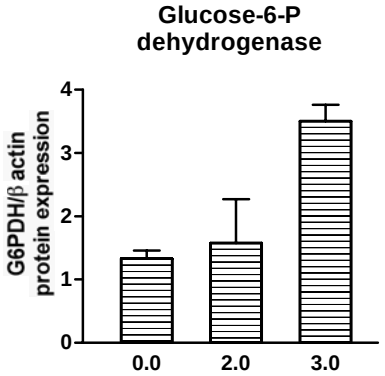
Glucose Isotopomers during IPGTT

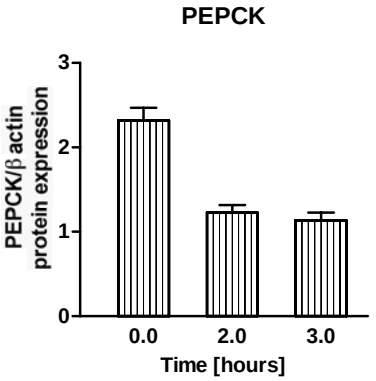


Time Course of Plasma Insulin and Molecular events



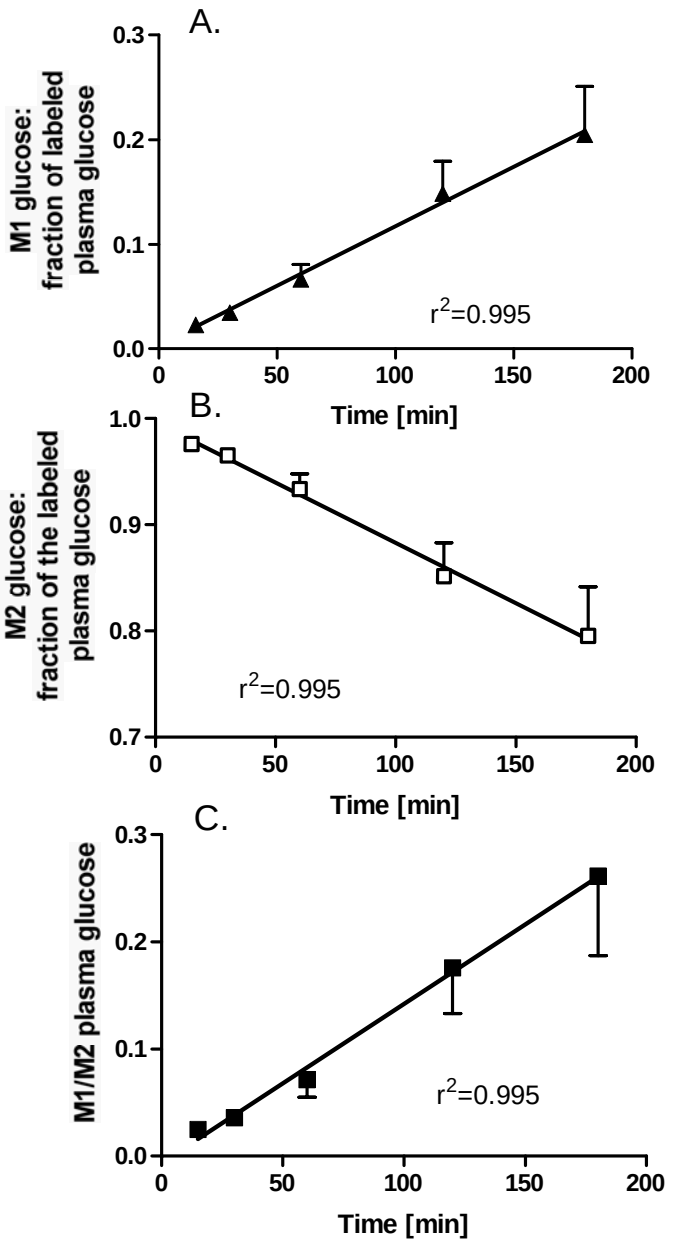






Recycling is glucose dependent.

$$\frac{d(M1/M2)}{dt} = \frac{dM1}{(M2)dt} - \frac{M1}{M2(M2)}\frac{dM2}{dt}$$



Concentration dependent nature of glucose recycling cannot be derived from genomic or proteomic information alone. Therefore, metabolic information is absolutely necessary in order to have a better understanding of biological behavior.

The induction of expressions and subsequent modification of enzymes by hormones are modulated by substrate cycles of the glucose metabolic network.

Futile cycling minimizes the impact of acute changes in substrate concentration during IPGTT.

G6Pase/GK futile cycle is associated with insulin resistance in diseases like Cushing's syndrome and diabetes.

Implications of Metabolic Network on Risk Reduction Strategies

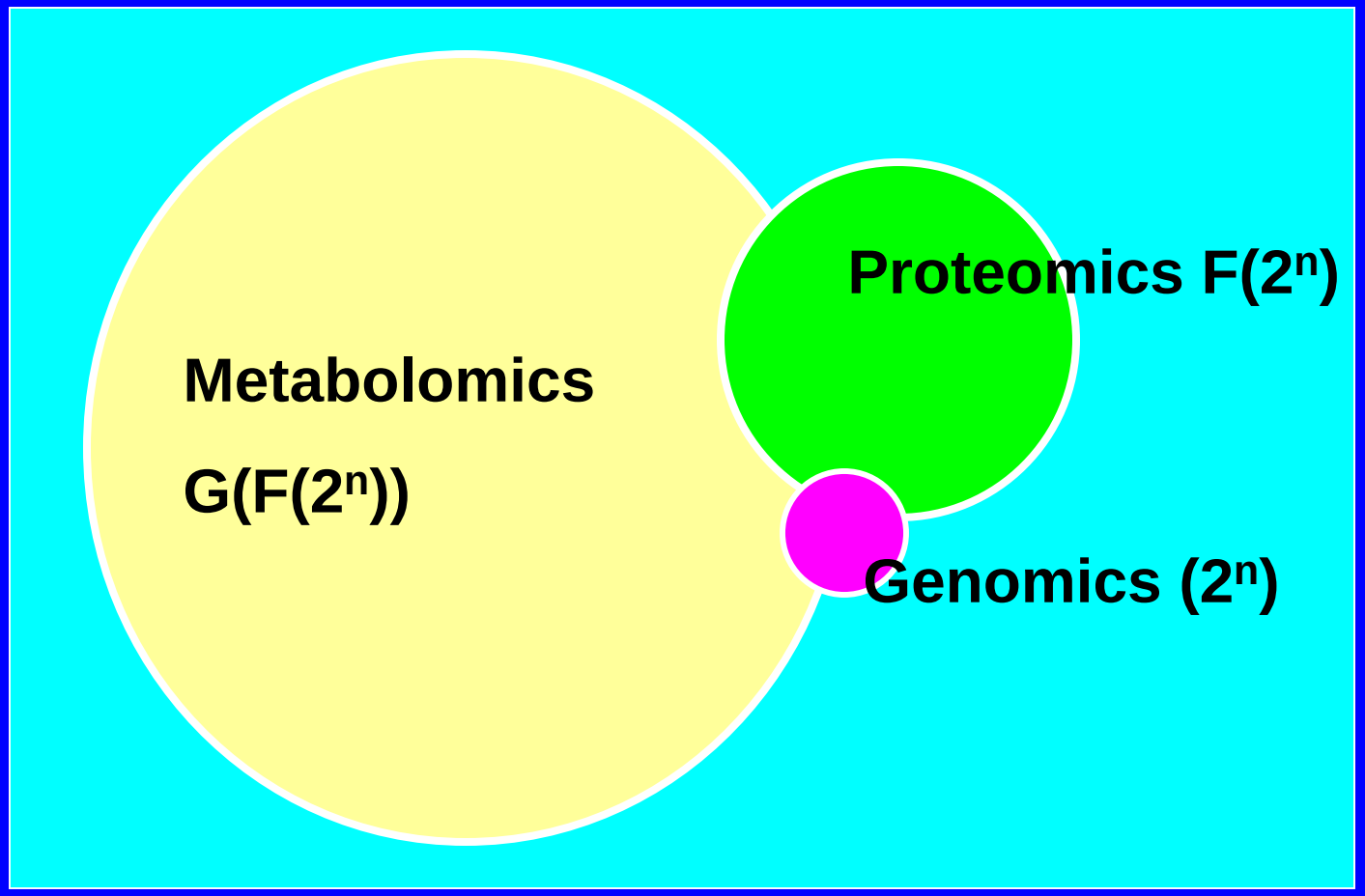
1) Each intervention or treatment will have multiple endpoints.
2) Conventional dose-response curves are usually not applicable.
3) Dynamic assessment is required.
4) Environmental context (substrate environment) is important.

Metabolic Profiling is the dynamic assessment of redistribution of substrates for a particular state of genetic expressions and substrate environment.

Metabolic Profiling allows the determination of various metabolic end-points of the metabolic network. Dose-response curve for each metabolic end-point can be constructed.

Risk Reduction Strategies can be developed to optimize between the attainment of desirable end-points and the avoidance of undesirable end-points.

Relative Bio-Informatic Units



Universe of Bio-Informatics

Conceptual Considerations of Bio-Informatics Disciplines

	Genomics	Proteomics	Metabolic Profiling
Mechanism	Genetic / Environment		
Genotype / phenotype	Genotype / Phenotype		
Dynamic vs Static	Static (scalar)	Static (scalar)	Dynamic (vector)
Comparison with language	Words (dictionary)	Grammar (rules)	Story

Practical Considerations of Bio-Informatics Disciplines

	Genomics	Proteomics	Metabolic Profiling
Data acquisition	Multiplexing and parallel processes	Multiplexing and parallel processes	Multiplexing and parallel processes
Data Analysis	Pattern recognition	Structural models	Metabolic models
Data Storage and retrieval	Search by genes	Search by proteins	Search by metabolic function

Conclusion

Metabolic Profiling is essential to the development of risk reduction strategies. Metabolic Profiling provides a metabolic mechanism for drug action or toxicity, and an understanding of dose response relationship for potential therapeutic benefits and untoward reactions.

Acknowledgement

Grant Acknowledgements:

This work is supported in part by Grant PHS M01-RR0045 of the General Clinical Research Unit, Grant P01-CA42710 of the UCLA Clinical Nutrition Research Unit Stable Isotope Core, and a grant from NIDDK (R01 DK56090) to WP Lee.

Collaborators:

Irwin Kurland
Marta Cascante
Jun Xu
Silvia Marin Martinez
Laszlo G. Boros
Sara Bassilian
Shu Lim