environmental bioinformatics
Computational Toxicology Center

Introduction and Overview

William Welsh, Center Director
Panos G. Georgopoulos, Center Associate Director

Consortium Members

Computational Chemodynamics Laboratory,
Environmental & Occupational Health Sciences Institute

Department of Environmental & Occupational Medicine

Department of Pharmacology

Informatics Institute

Department of Biomedical Engineering

Department of Chemical & Biochemical Engineering

Department of Environmental Sciences

Department of Statistics

Computer Aided Systems Laboratory,
Department of Chemical Engineering

Department of Chemistry

Program in Applied and Computational Mathematics

Center for Toxicoinformatics,
National Center for Toxicological Research

Objectives and General Approach

Objectives

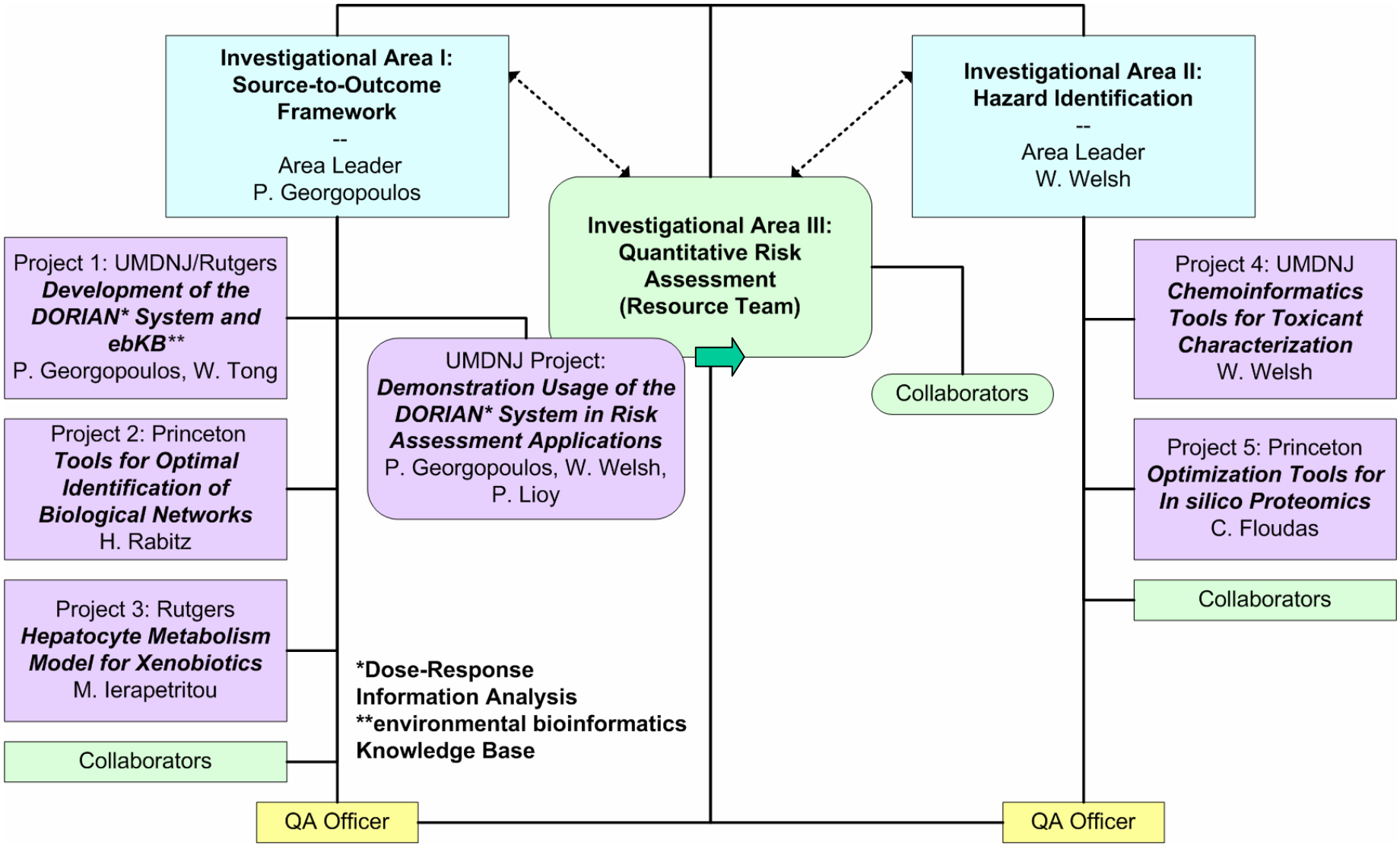
- To address, in a systematic and integrative manner, multiple elements of the toxicant *Source-to-Outcome sequence (Investigational Area I)* through the development of an integrated, modular, computational framework
- To develop predictive cheminformatics tools for toxicant characterization and *Hazard Identification (Investigational Area II)*
- To demonstrate the above tools through applications in *Quantitative Risk Assessment (Investigational Area III)*
  - *particular emphasis will be on methods that quantify and reduce uncertainties*

General Approach

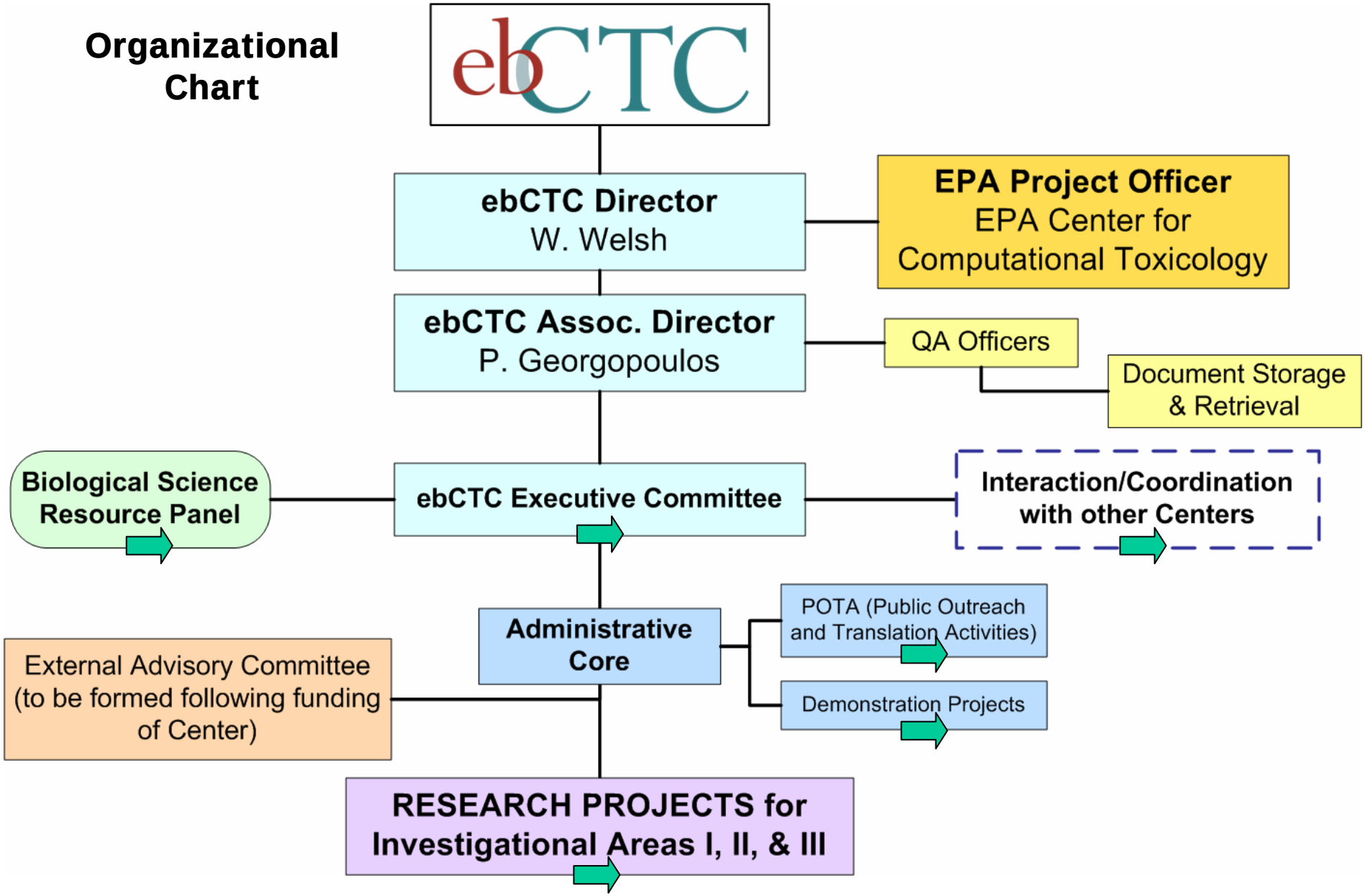
- A computational/engineering/systems perspective
  - *team of computational scientists and engineers, with diverse backgrounds in bioinformatic, cheminformatic and enviroinformatic applications*
- The new framework and tools will build upon an extensive base of past developments
- The research effort will emphasize interaction and collaboration
  - *with existing centers and laboratories at the ebCTC investigators institutions*
  - *with USEPA centers and laboratories (internal and external)*

Research activities of proposed effort will be organized in 5 projects

- **Each project will develop a set of "stand-alone" components addressing specific CT problems**
- **Research Project 1 will provide an integrative framework for Investigational Area 1**
- **Project 4 will address the core issues of Area 2**

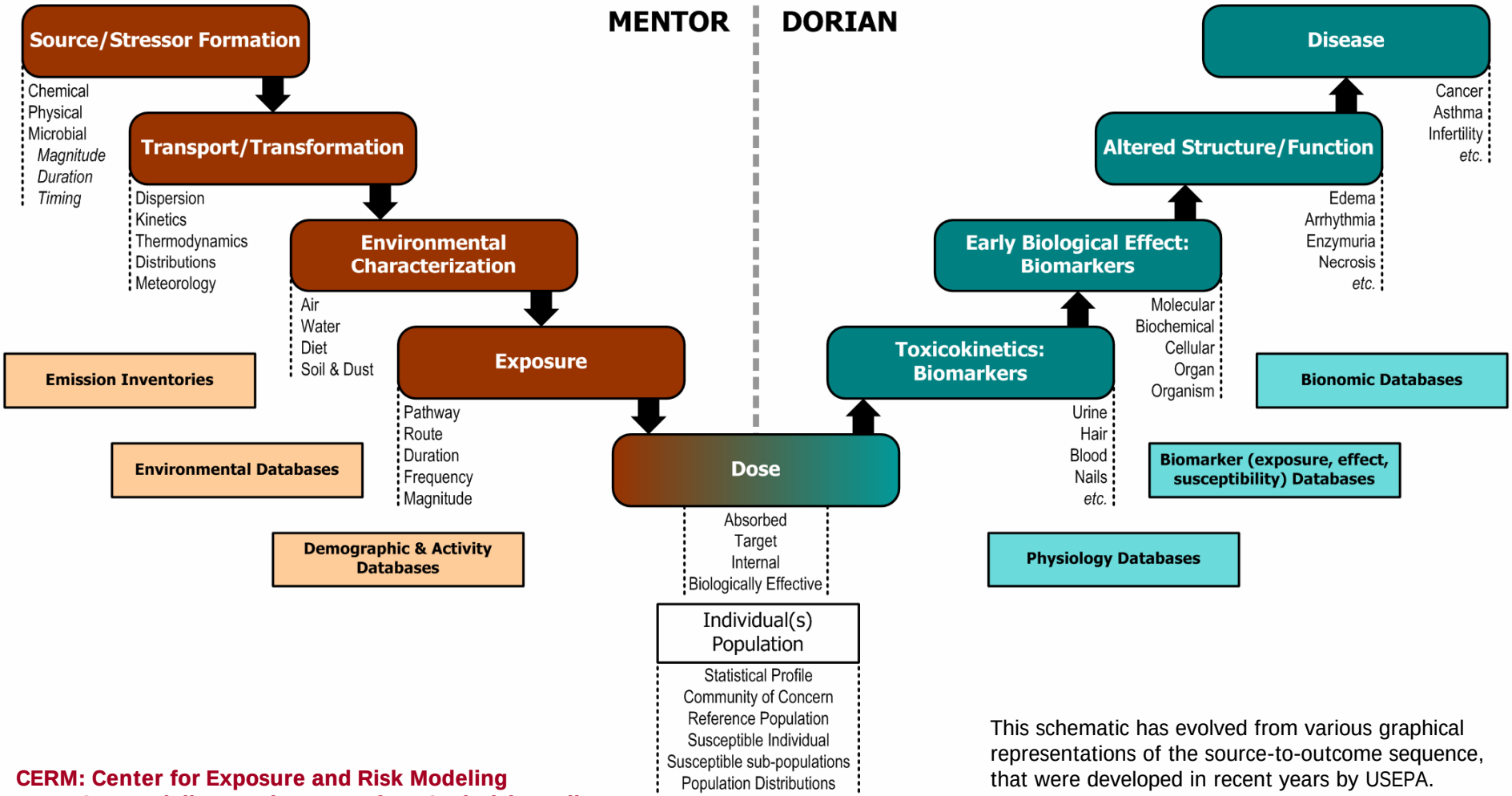


Organizational Chart



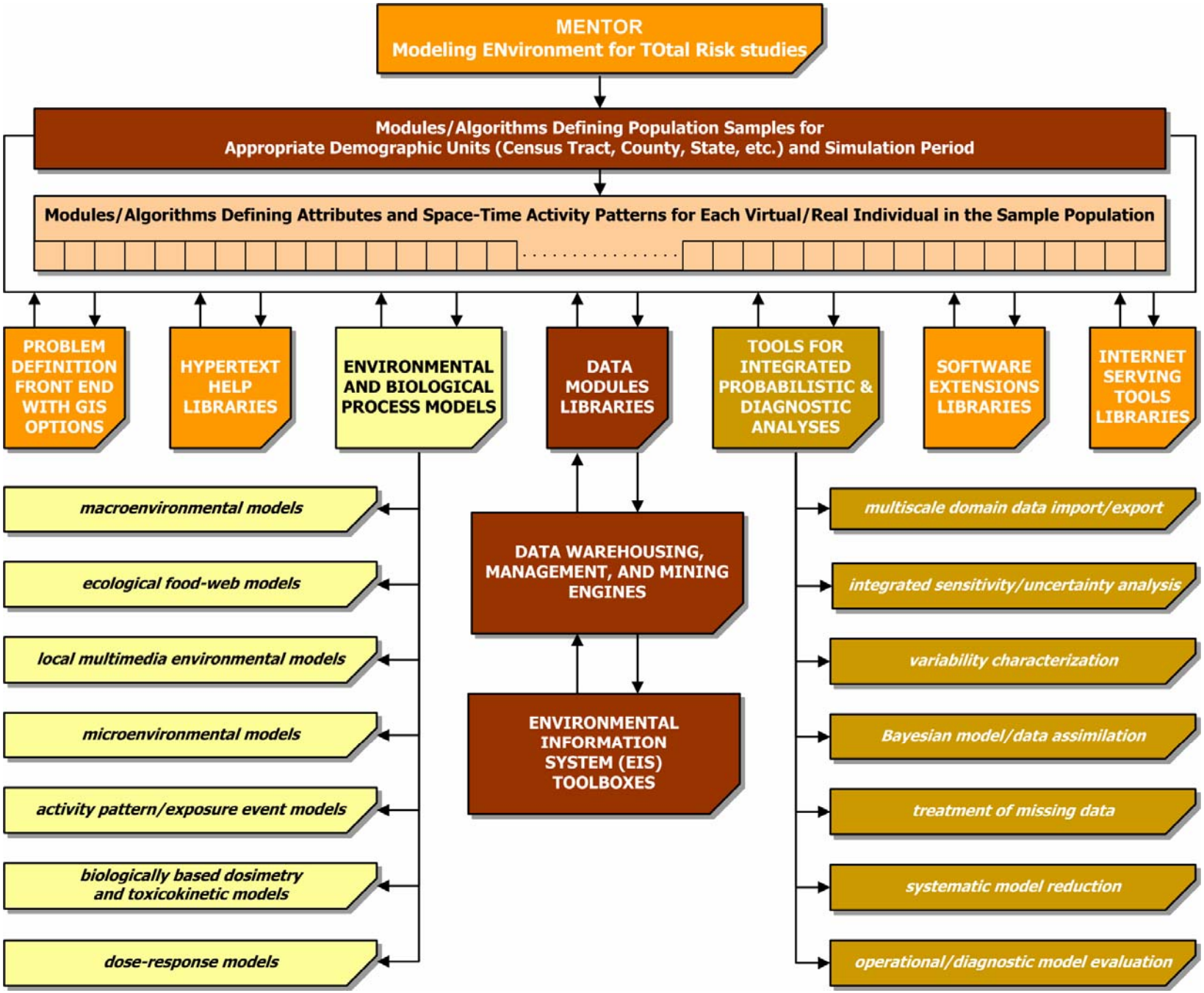
Some Background Information

MENTOR & DORIAN Address the Source-to-Outcome Continuum



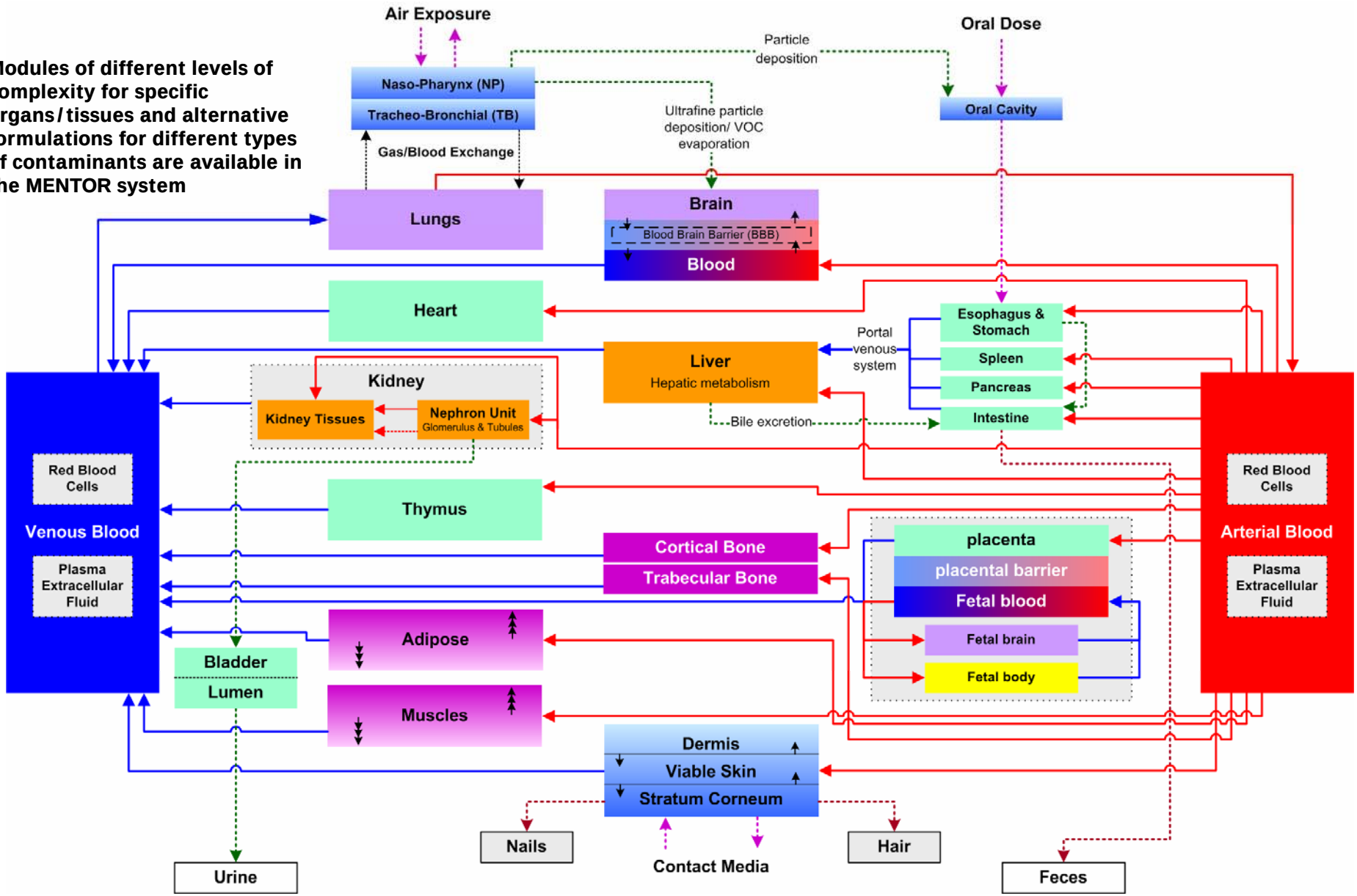
This schematic has evolved from various graphical representations of the source-to-outcome sequence, that were developed in recent years by USEPA.

CERM: Center for Exposure and Risk Modeling
MENTOR: Modeling ENvironment for TOtal Risk studies
ebCTC: environmental bioinformatics and Computational Toxicology Center
DORIAN: DOse-Response Information Analysis system

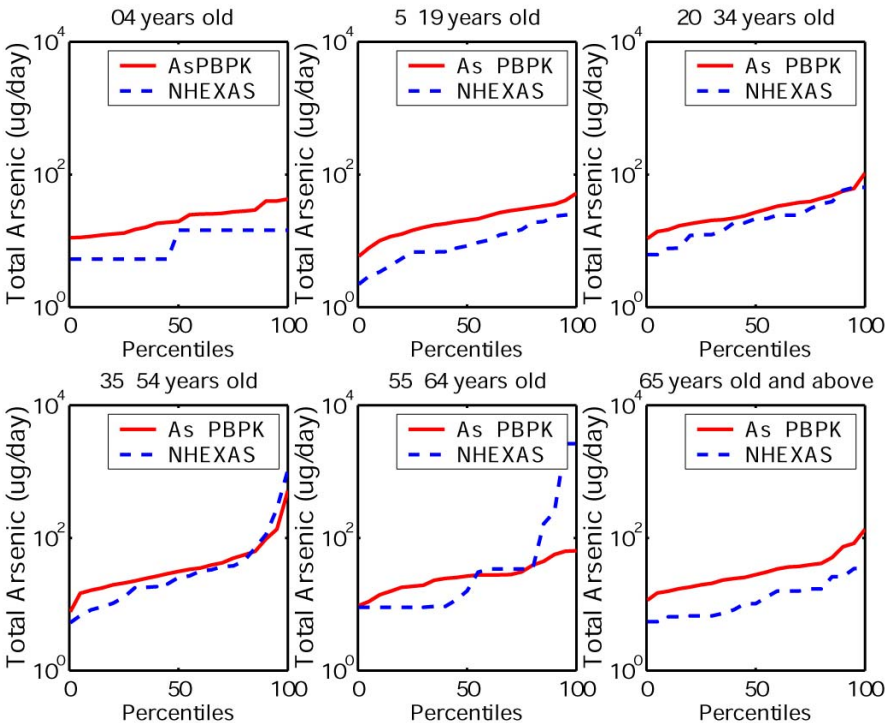

MENTOR
Modeling ENvironment for TOtal Risk studies
Modules/Algorithms Defining Population Samples for
Appropriate Demographic Units (Census Tract, County, State, etc.) and Simulation Period
Modules/Algorithms Defining Attributes and Space-Time Activity Patterns for Each Virtual/Real Individual in the Sample Population
PROBLEM DEFINITION FRONT END WITH GIS OPTIONS
HYPERTEXT HELP LIBRARIES
ENVIRONMENTAL AND BIOLOGICAL PROCESS MODELS
DATA MODULES LIBRARIES
TOOLS FOR INTEGRATED PROBABILISTIC & DIAGNOSTIC ANALYSES
SOFTWARE EXTENSIONS LIBRARIES
INTERNET SERVING TOOLS LIBRARIES
macroenvironmental models
ecological food-web models
local multimedia environmental models
microenvironmental models
activity pattern/exposure event models
biologically based dosimetry and toxicokinetic models
dose-response models
DATA WAREHOUSING, MANAGEMENT, AND MINING ENGINES
ENVIRONMENTAL INFORMATION SYSTEM (EIS) TOOLBOXES
multiscale domain data import/export
integrated sensitivity/uncertainty analysis
variability characterization
Bayesian model/data assimilation
treatment of missing data
systematic model reduction
operational/diagnostic model evaluation

The physiologically based toxicokinetic modules in MENTOR aim to characterize cumulative and aggregate exposure, uptake and target tissue dose

Modules of different levels of complexity for specific organs / tissues and alternative formulations for different types of contaminants are available in the MENTOR system

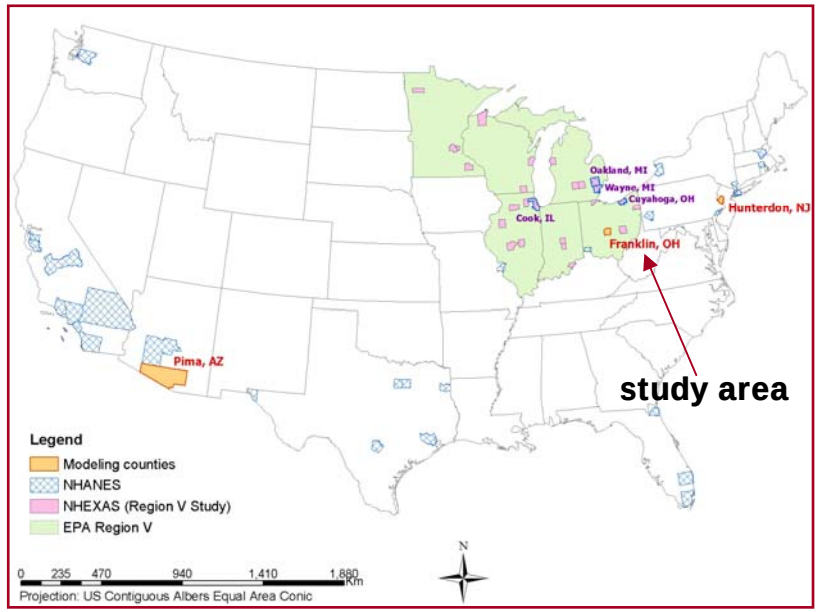


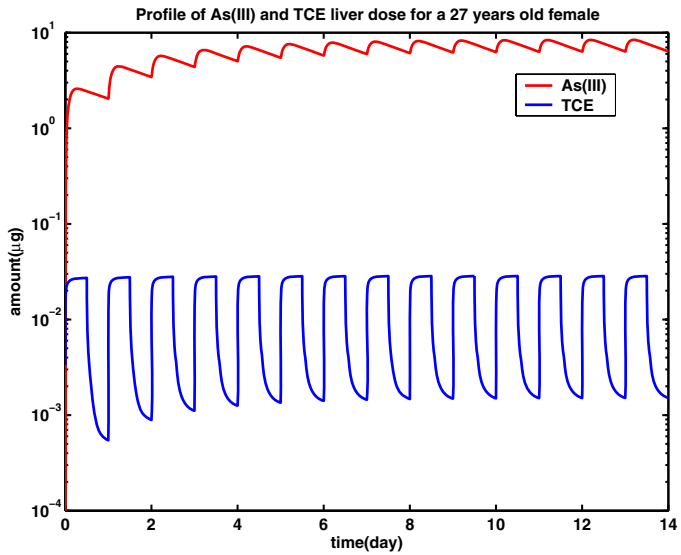
Application of MENTOR/SHEDS-4M for combined Arsenic (III) and Trichloroethylene (TCE) population exposure and dose calculation: NHEXAS-V Case Study



Comparison of cumulative distributions of total arsenic amount in urine from MENTOR/SHEDS-4M calculations and measurements from the NHEXAS study for 6 age groups in Franklin County, OH

SHEDS: Stochastic Human Exposure and Dose Simulation

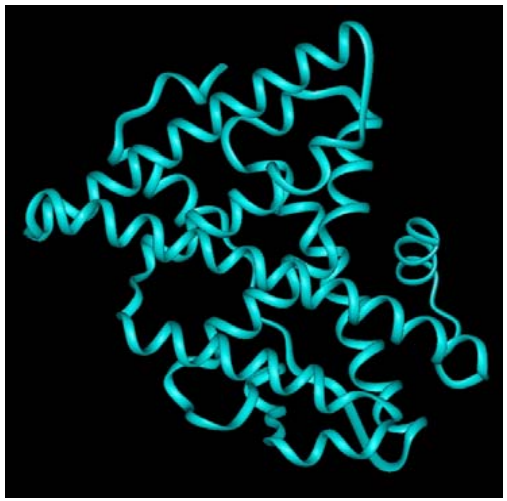




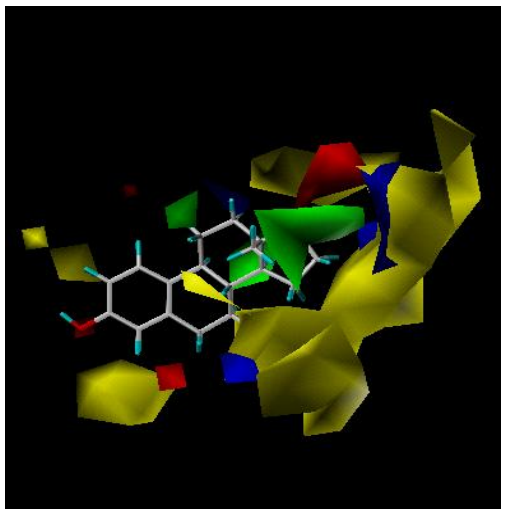
Calculated profiles of liver doses of Arsenic and TCE from a 14 day hypothetical repeated exposure for a 27 year old female

Integrated Approach

Structure-based Design

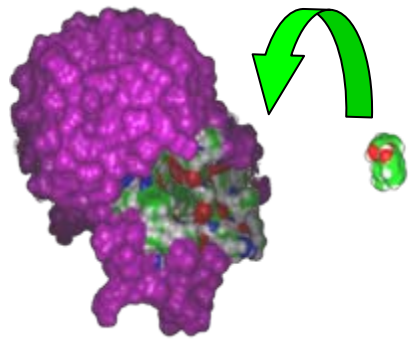


Ligand-based Design



Predictive Molecular Toxicology

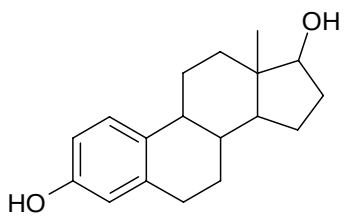
	1: CLOGP	3: MOL_WEIGHT	4: ACTIVITY	5: COMFA	6
18	4.27	323.4140	TRIAL-PREP.	69.00	
19	3.59	291.3110	ANTIINFLAMMATORIE	61.00	
20	3.25	285.2740	ANTIINFLAMMATORIE	56.00	
21	3.57	301.7290	ANTIINFLAMMATORIE	57.00	
22	-	350.4540	FUNGICIDES	62.00	

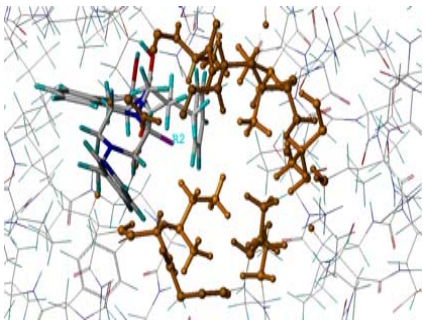


Virtual Screening of Databases

Shape Signatures Tool

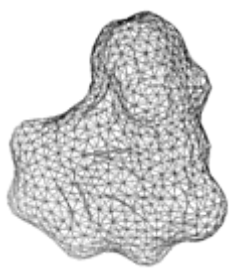
START

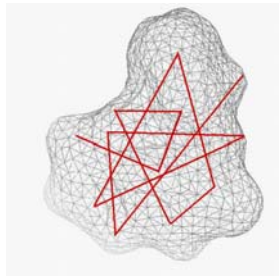


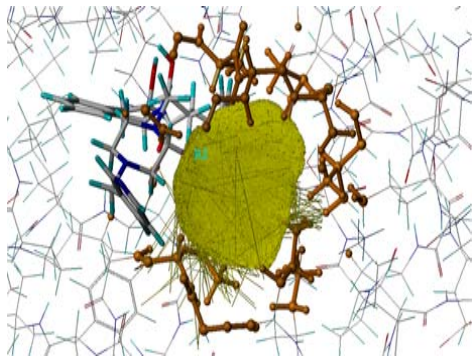


Small molecule or
Protein binding pocket

PROCESSING



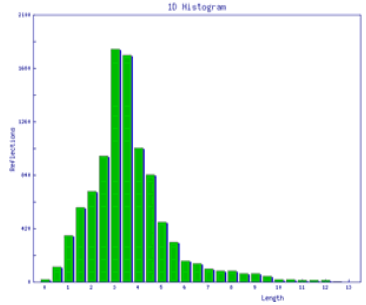




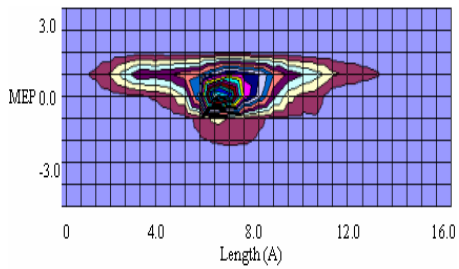
Ray tracing to
generate the raw data

OUTPUT

Shape (1D)



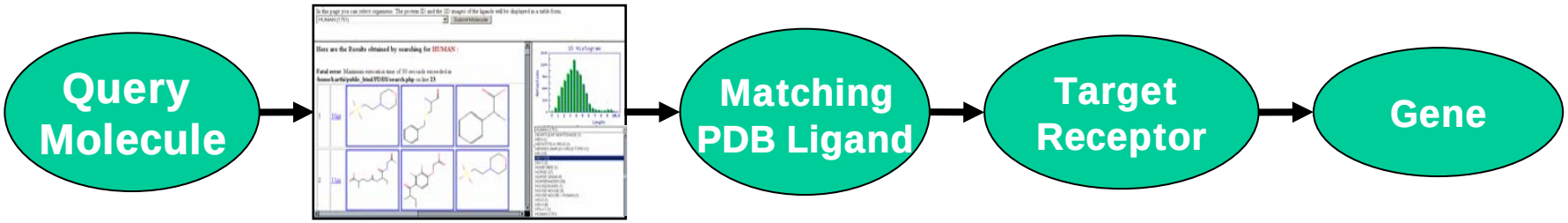
Shape + Charge (2D)



1D and 2D
Shape Signatures

From Molecules to Mechanism

Shape Sigs PDB Ligands



KEGG Metabolic Pathways:
- http://www.genome.ad.jp/kegg/metabolism.html

EMP - Enzymes and Metabolic Pathways:
- http://emp.mcs.anl.gov/

WIT - Metabolic Reconstruction:
- http://wit.mcs.anl.gov/WIT2/

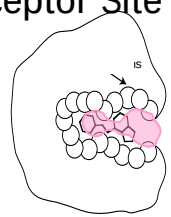
UM-BBD - Microbial Biocatalysis/Biodegradatation:
- http://umbbd.ahc.umn.edu/

EcoCyc - E. coli Genes and Metabolism:
- http://www.ecocyc.org/

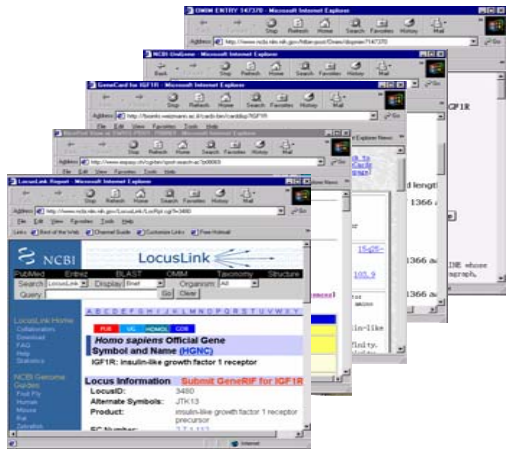
Metalgen - Genes and Metabolism:
- http://indigo.genetique.uvsq.fr/

Boehringer Mannheim - Biochemical Pathways:
- http://www.expasy.org/cgi-bin/search-biochem-index

Receptor Site Pocket



Public Databases



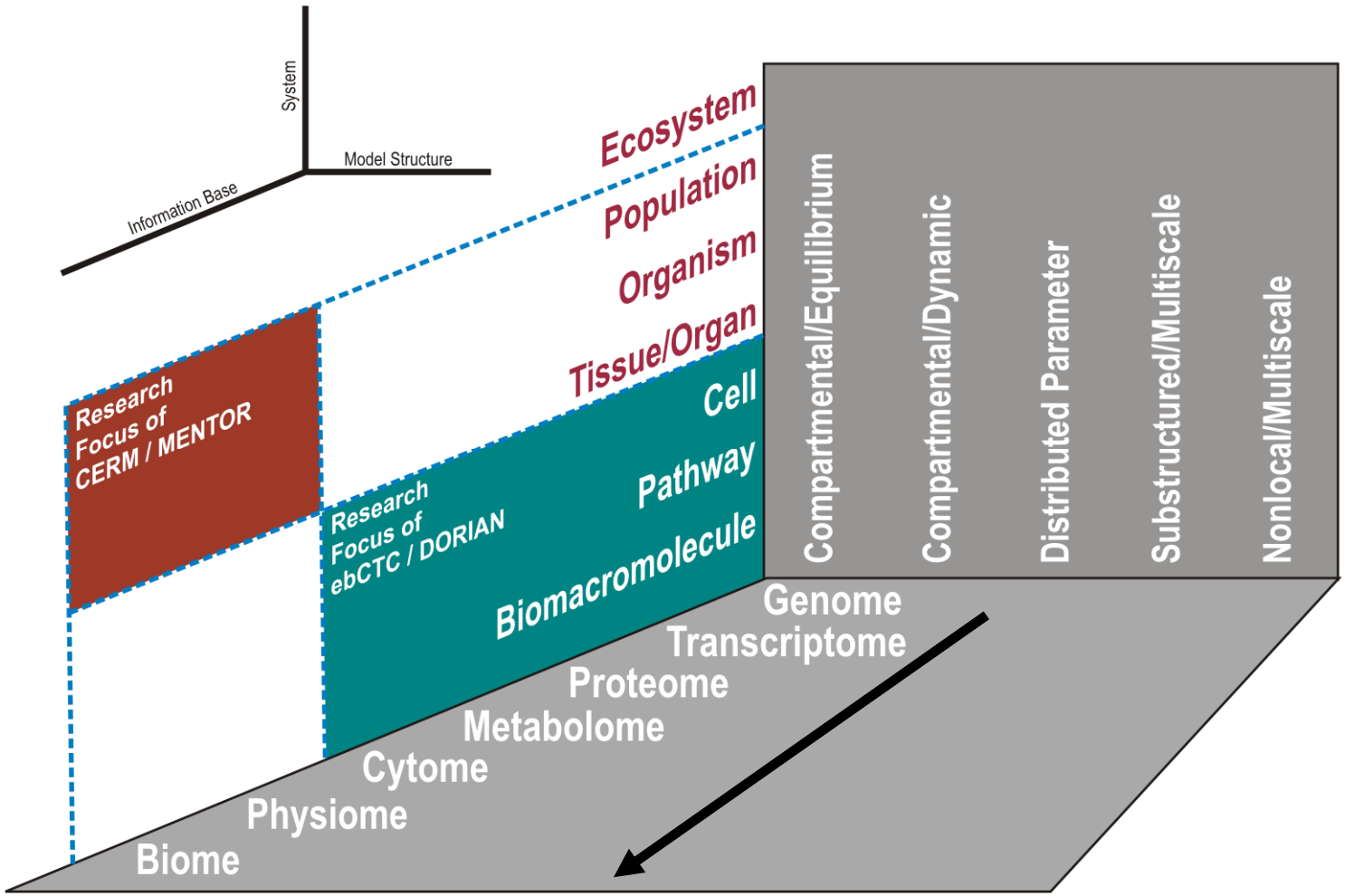
Investigational Area 1 – Research Project 1: Development and Application of the DORIAN System

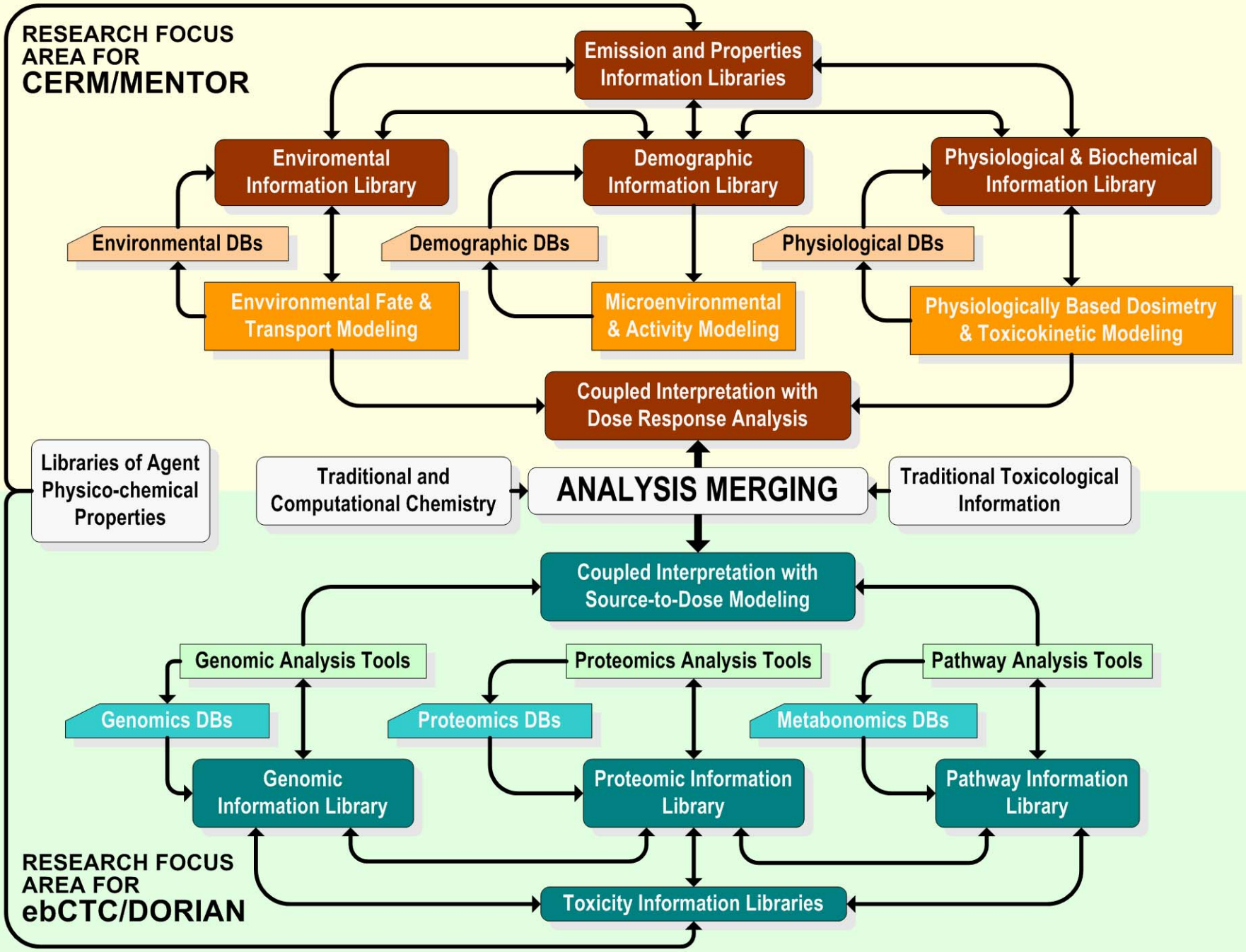
Dr. Panos Georgopoulos, P.I.,
Director, Computational Chemodynamics Laboratory
Co-Director, Center for Exposure and Risk Modeling
Environmental and Occupational Health Sciences Institute (EOHSI),
a joint institute of UMDNJ-RWJ Medical School and Rutgers University
Department of Environmental and Occupational Medicine,
UMDNJ-RWJ Medical School
Dr. Weida Tong, Co-P.I.
Director, Center for Toxicoinformatics,
National Center for Toxicological Research (NCTR)
US Food and Drug Administration (FDA)
Department of Pharmacology, UMDNJ-RWJ Medical School

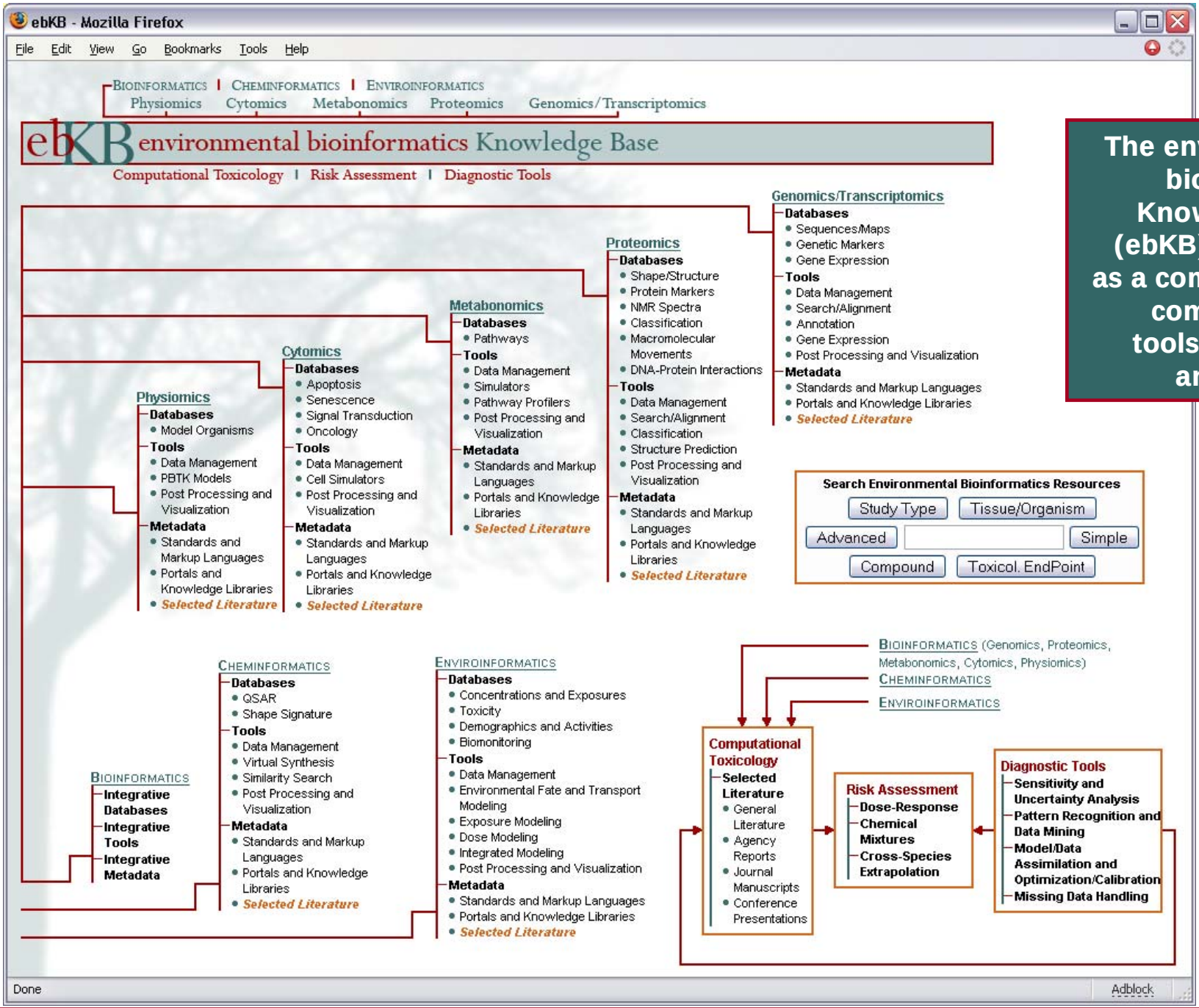
Area 1 - Project 1:
Development and Application of a
Dose-Response Information Analysis (DORIAN) System

- **Component 1:** Development and deployment of an environmental bioinformatics Knowledge Base (ebKB)
- **Component 2:** Development of ebTrack system for integrated management of eb (genomic, transcriptomic, proteomic, metabonomic) data
  - *it will build upon (and ensure interoperability with) FDA's ArrayTrack*
  - *it will provide an interface to modules of DORIAN and linkages to components of MENTOR and other external (public and commercial) software systems*
- **Development of DORIAN:**
  - ***Component 3:*** *Implementation of Bayesian tools for characterizing and reducing uncertainties in mechanistic modeling of toxicity pathways*
  - ***Component 4:*** *Development of diagnostic tools for sensitivity and stability analysis of mechanistic models and of statistical methods for data analysis*
  - ***Component 5:*** *Enhancement of tools for Quantitative Risk Assessment*
    - cross-species extrapolation, chemical mixtures, and dose-response models
- **Component 6:** Support of applications (case studies) demonstrating enhanced Quantitative Risk Assessments

Research Focus Areas CERM / MENTOR and ebCTC / DORIAN

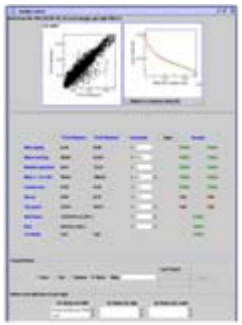



RESEARCH FOCUS AREA FOR CERM/MENTOR
Emission and Properties Information Libraries
Enviromental Information Library
Demographic Information Library
Physiological & Biochemical Information Library
Environmental DBs
Demographic DBs
Physiological DBs
Envvironmental Fate & Transport Modeling
Microenvironmental & Activity Modeling
Physiologically Based Dosimetry & Toxicokinetic Modeling
Coupled Interpretation with Dose Response Analysis
Libraries of Agent Physico-chemical Properties
Traditional and Computational Chemistry
ANALYSIS MERGING
Traditional Toxicological Information
Coupled Interpretation with Source-to-Dose Modeling
Genomic Analysis Tools
Proteomics Analysis Tools
Pathway Analysis Tools
Genomics DBs
Proteomics DBs
Metabonomics DBs
Genomic Information Library
Proteomic Information Library
Pathway Information Library
RESEARCH FOCUS AREA FOR ebCTC/DORIAN
Toxicity Information Libraries

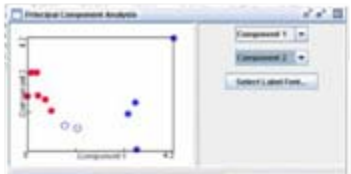


The environmental bioinformatics Knowledge Base (ebKB) will evolve as a comprehensive compendium of tools, databases, and literature

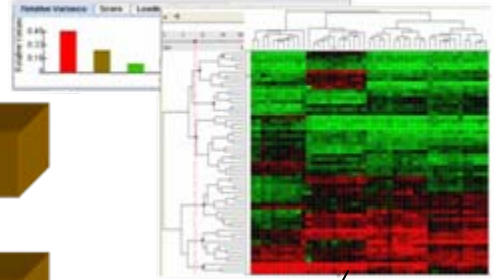
An example application of using ArrayTrack / ebTrack for microarray data analysis, presenting all the important steps involved



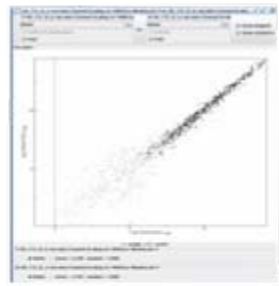
Data uploading and QC



PCA



2-way HCA



Scatter Plot

Data Import

Normalization

Four normalization methods, including LOWESS

Apply to

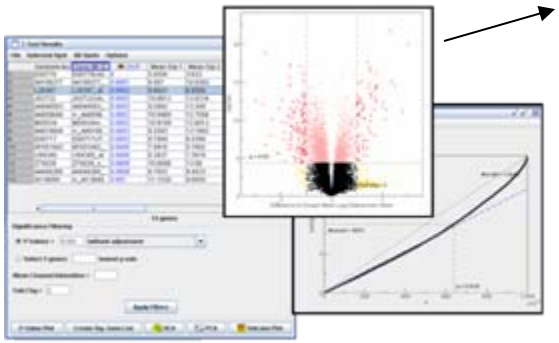
Gene Selection

Data Exploration

Expression pattern using the bar chart plot

Apply to

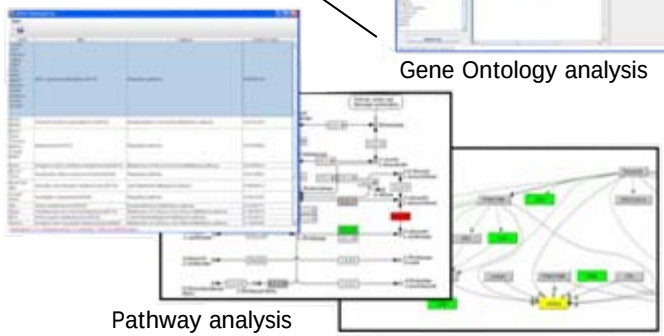
Interpretation



Significant genes can be identified based on:

- Cut-off of p-value (with or without Banferroni correction), fold-change, intensity or combinations thereof
- **Volcano Plot** (considering both *p* and fold-change
- **P-value Plot** (considering false positives/negatives)

Gene Ontology analysis



Pathway analysis

Individual gene analysis

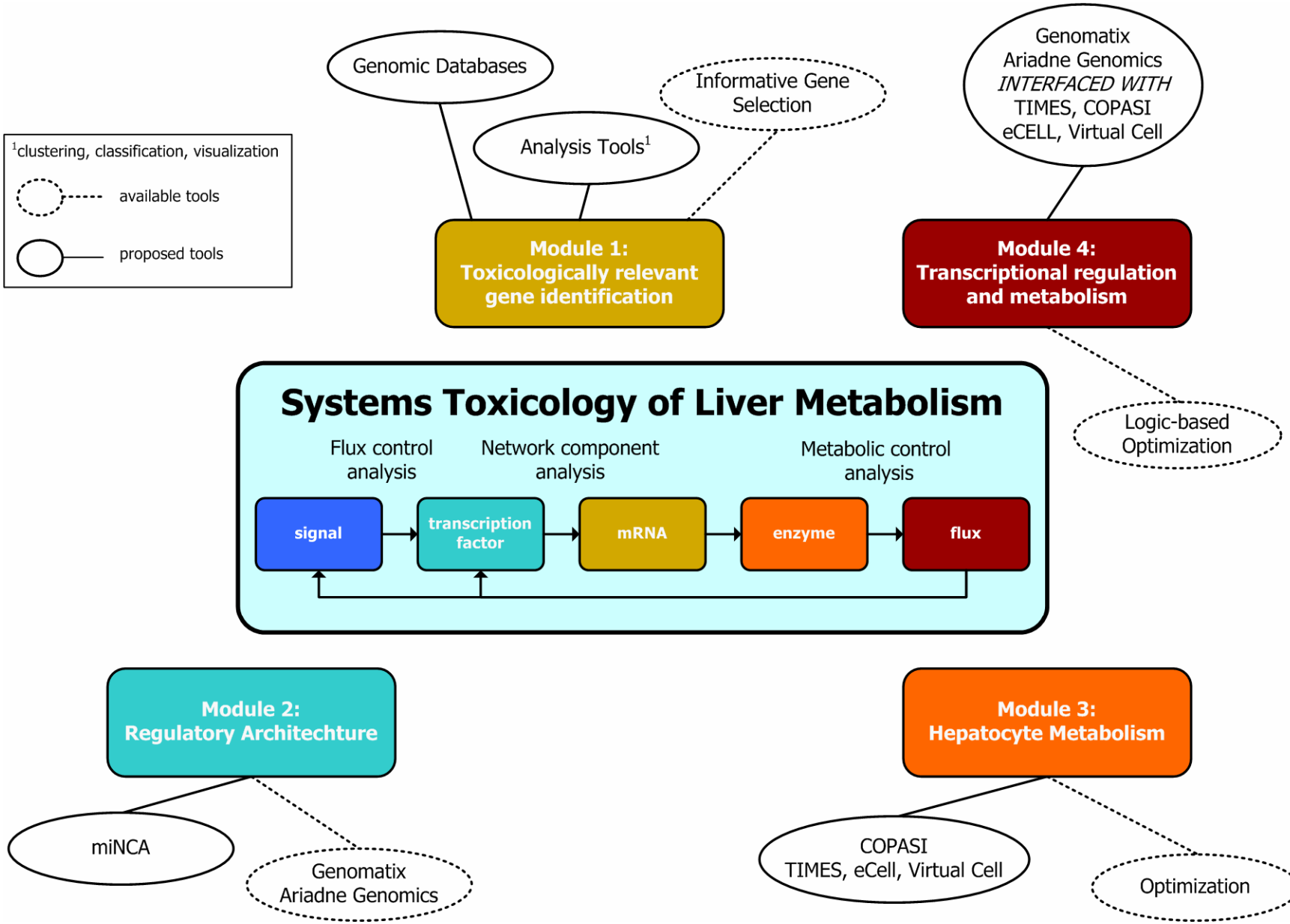
Investigational Area 1 – Research Project 2: Hepatocyte Metabolism Model for Xenobiotics

Dr. Marianthi Ierapetritou, P.I.
Department of Chemical & Biochemical Engineering, Rutgers University
Dr. Ioannis Androulakis, Co-P.I.
Department of Chemical & Biochemical Engineering
and Department of Biomedical Engineering, Rutgers University

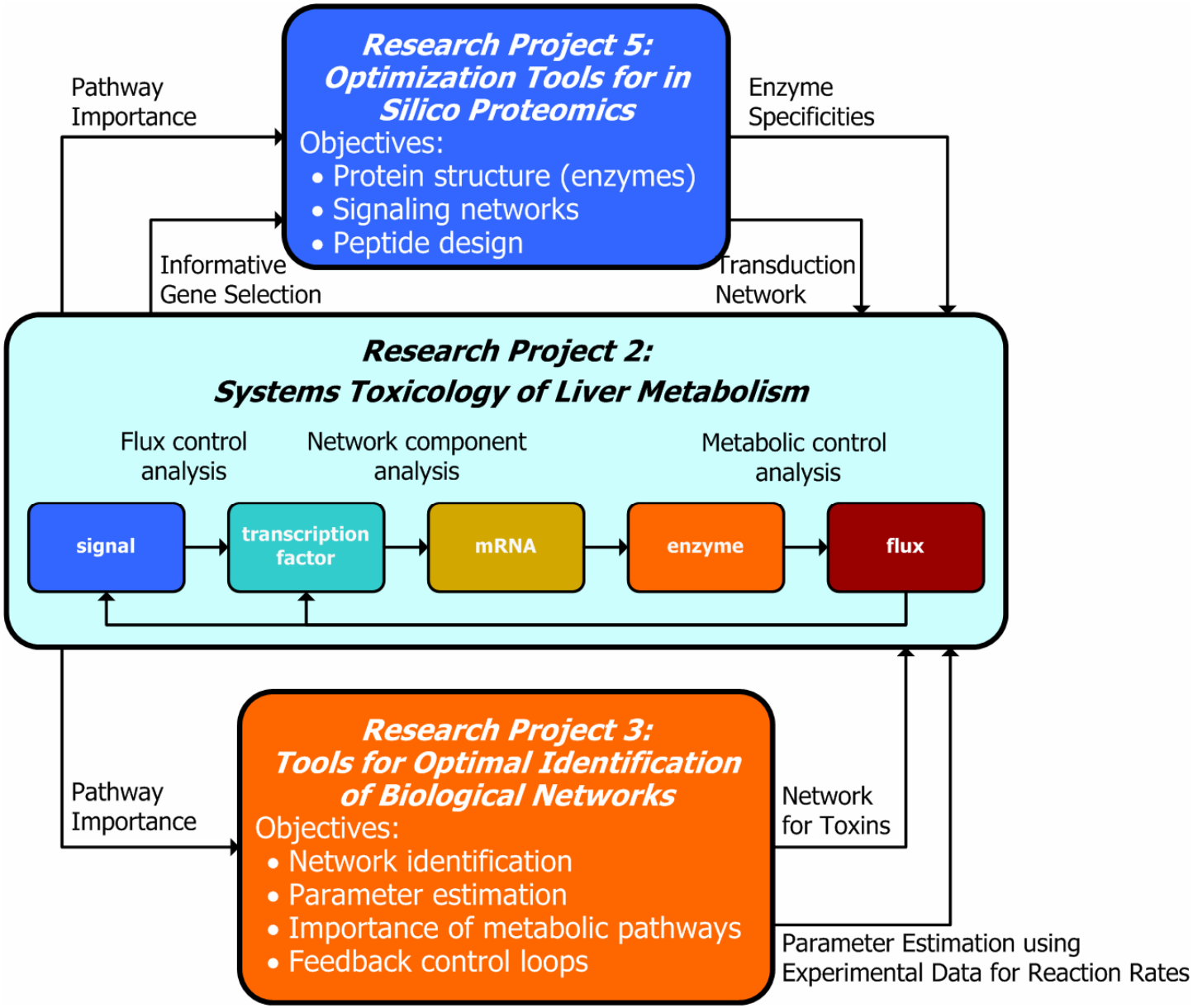
Area 1 – Project 2:
Hepatocyte Metabolism Modeling for Xenobiotics

- **Component 1:** Identification of maximally informative, minimal sets of toxicologically relevant genes
- **Component 2:** Development of toxicologically relevant regulatory networks
- **Component 3:** Expansion of the Rutgers hepatocyte model to incorporate xenobiotic metabolism
    - *based on available experimental data (genomic and metabonomic) and developed mathematical tools*
- **Component 4:** Incorporation of transcriptional regulation in order to assess the changes in hepatocyte phenotypic phase space

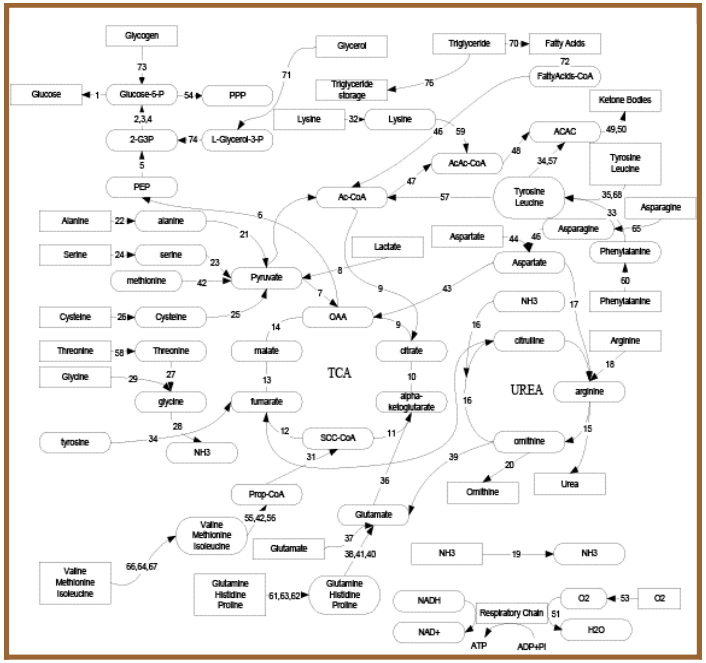
Framework for Systems Toxicology of Liver



Interactions / Integration of Project 2 with Projects 3 and 5



Metabolic Analysis of Hepatocyte Metabolism



1. Metabolic Flux Analysis to determine internal flux distribution

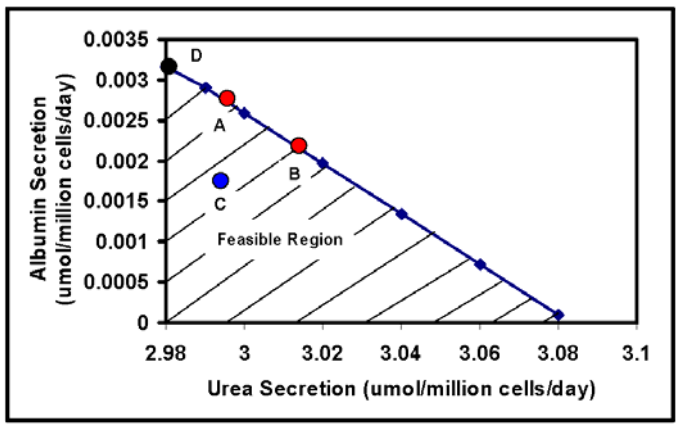
Metabolites	HI	LI+AA	Optimal values
Urea synthesis	2.7 ± 0.48	1.8 ± 0.99	**2.76**
Arginine uptake	0.29 ± 0.008	0.16 ± 0.092	**0.303**

$$\max v_{urea}$$

$$\text{subject to: } \sum_{j=1}^{N} S_{ij} v_j = 0, \quad i = 1,....,M$$

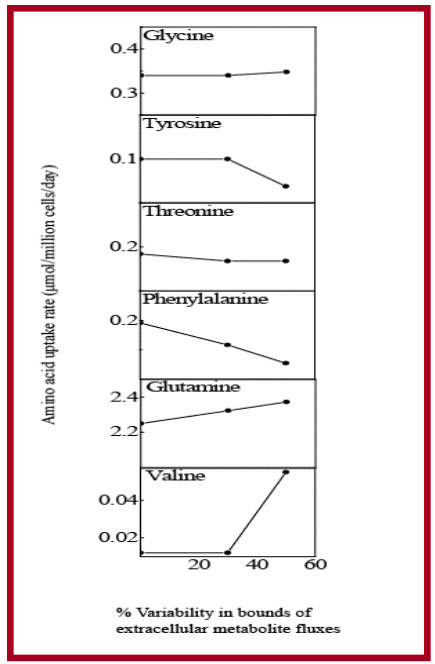
$$v_j^{min} \le v_j \le v_j^{max}$$

2. Optimize cell response to specific perturbation

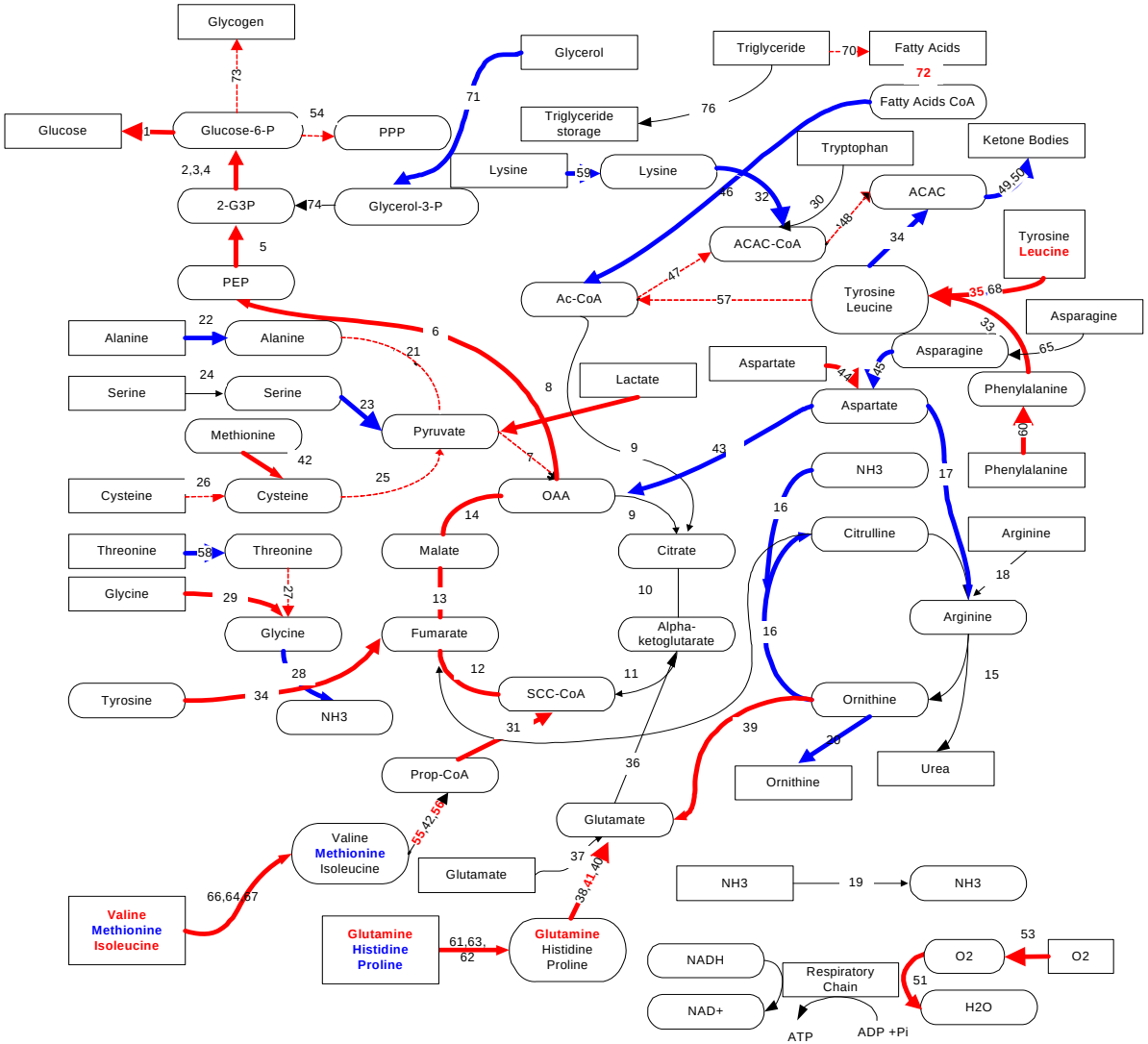


3. Systematically consider the different cell function such as albumin and urea shown here

4. Account for uncertainty and the effects in system response



Important Pathways for Urea and Albumin Production



$$\min_{\lambda_j} \Phi = \sum_{j=1}^{N} \lambda_j$$

$$\text{subject to: } \sum_{j=1}^{N} S_{ij} v_j = b_i, \quad i = 1,\ldots,M$$

$$v_j^{min} \lambda_j \le v_j \le v_j^{max} \lambda_j, \quad j = 1,\ldots,N$$

5. Identify the important pathways

Thick red lines correspond to higher fluxes for Optimal Condition w Knockouts vs. w/o Knockouts.

Thick blue lines correspond to lower fluxes. Dotted red lines correspond to reactions not important in Optimal Condition.

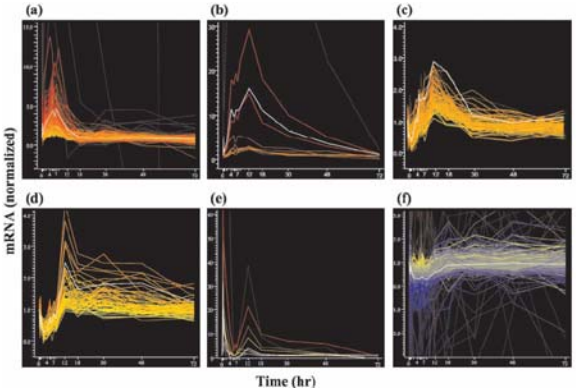
Bold red amino acids in albumin synthesis reaction correspond to amino acids participating at a higher rate into albumin synthesis.

24 ARG + 32 ASP + 61 ALA + 24 SER + 35 CYS + 57 GLU + 17 **GLY** + 21 TYR + 33 THR + 53 LYS + 26 **PHE** + 25 GLN + 30 PRO + 15 HIS + 6 MET + 20 **ASN** + TRP + 35 **VAL** + 13 **ISO** + 56 **LEU** + 2332 ATP → albumin + 2332 ADP + 2332

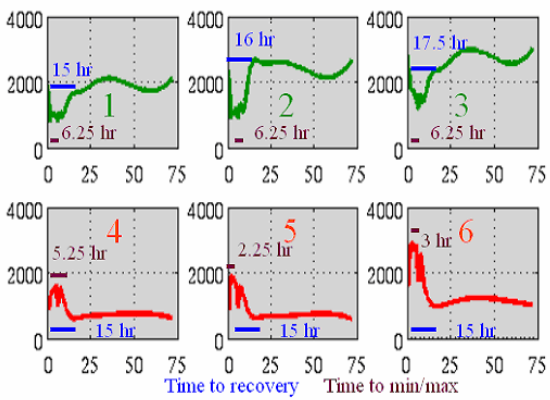
References:

- Sharma, Ierapetritou, Yarmush, Biotechnology and Bioengineering 92(3), 321, 2005
- Ierapetritou et al. AIChE Annual Meeting, 2005.

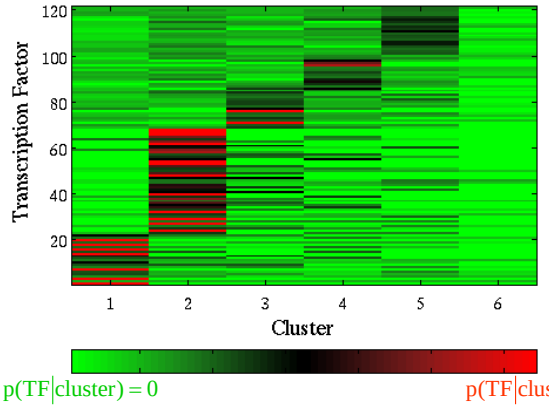
Liver-specific Toxicologically Relevant Regulatory Networks



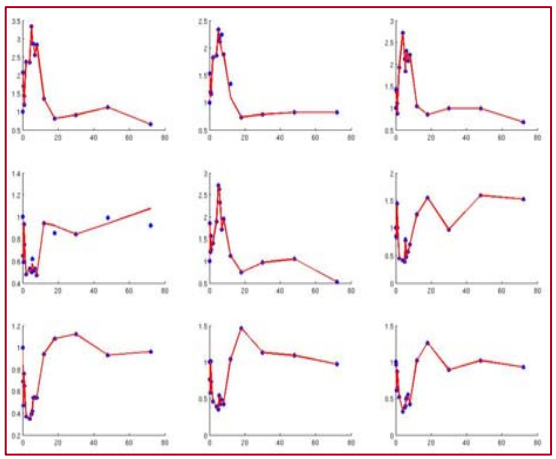
1. Temporal expression profiling of rat liver specific genes



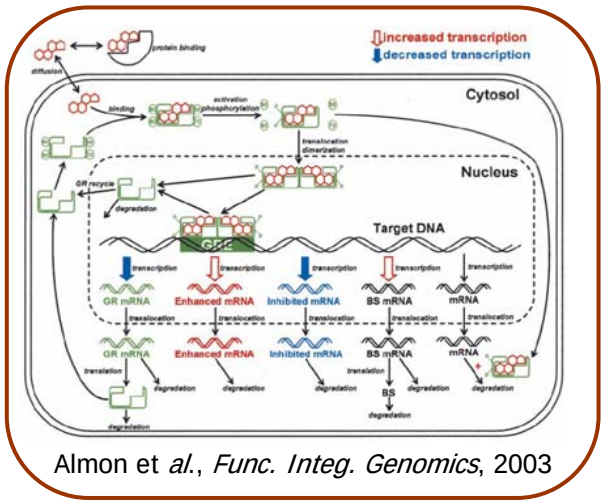
2. Identification of maximally informative expression motifs[a]



3. Regulatory network identification using TRAFAC and Genomatix and quantification using miNCA[b]



4. Identification of regulatory mechanisms responsible for observed transcriptional dynamic responses



Almon et *al.*, *Func. Integ. Genomics*, 2003

$$\min : \sum_i \sum_t eP(i,t) + eN(i,t)$$

$$s.t.$$

$$eP(i,t) \geq 0 \quad \forall i,t$$

$$eN(i,t) \geq 0 \quad \forall i,t$$

Objective definition through the use of positive slack variables

$$E(i,t) - \sum_j A(i,j)P(j,t) = eP(i,t) - eN(i,t) \quad \forall i,t$$

$$A_{\min} y(i,j) \leq A(i,j) \leq A_{\max} y(i,j) \quad \forall i,j$$

$$A(i,j)^2 - y(i,j)\varepsilon \geq 0 \quad \forall i,j$$

$$\sum_i \sum_j y(i,j) = N$$

Connections and Complexity Definition

$$\sum_j 1 - y(i,j) \geq L - 1 \quad \forall i$$

$$\sum_i y(i,j) \geq 1 \quad \forall j$$

$$M = Y^T Y$$

$$M = C^T C$$

$$C(i,i) \geq 0 \quad \forall i$$

Linear Independence Criteria Cholesky Decomposition

$$(i,j) \notin Y^{Super\ Set} \Rightarrow y(i,j) = 0 \quad \forall i,j$$

A in A_0

$$|P(j,t) - P^{exp}(j,t)| < \varepsilon$$

Constraints on regulatory strength

References:
- (a) Vitolo, Roth and Androulakis, FOSBE Conference, 2005
- (b) Yang, Roth and Androulakis, AIChE Meeting, 2005

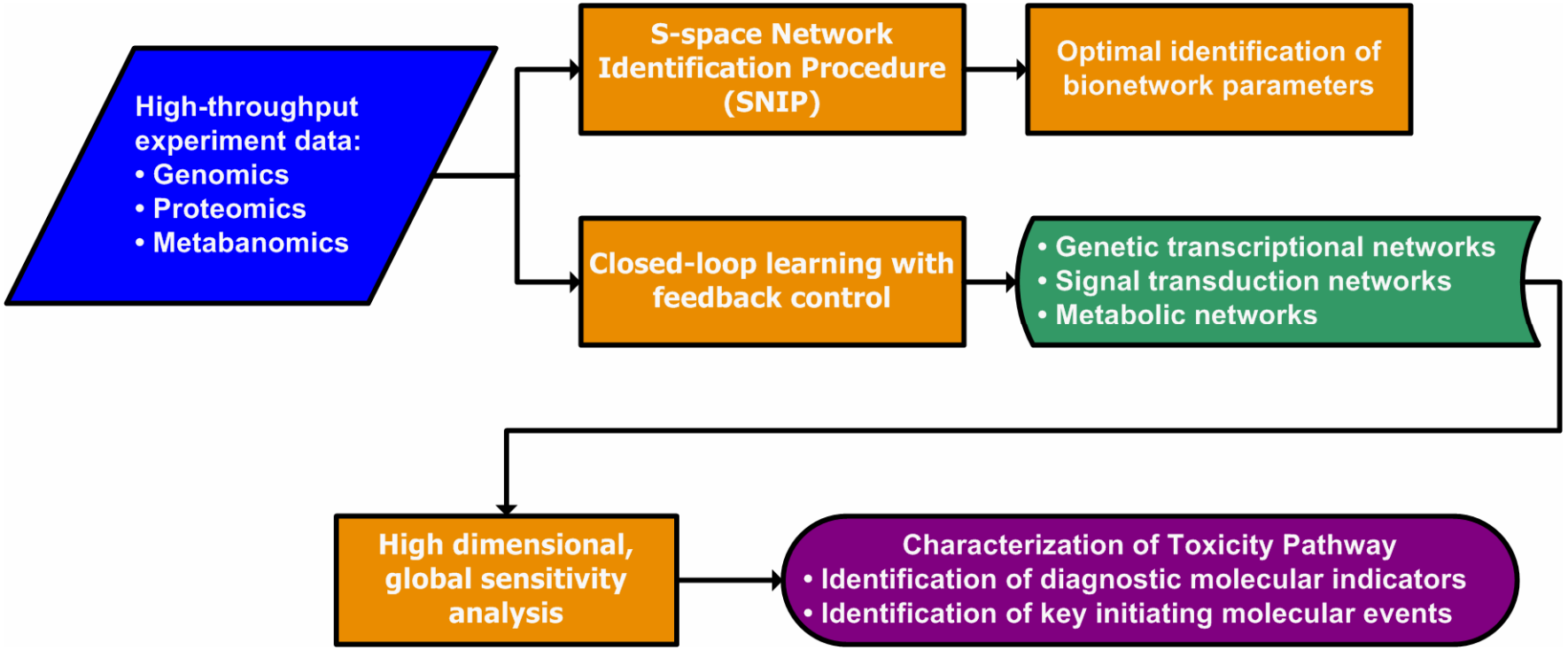
Investigational Area 1 – Research Project 3: Development of Computational Tools for Optimal Identification of Biological Networks

Dr. Herschel Rabitz, P.I.
Department of Chemistry and
Program in Applied and Computational Mathematics,
Princeton University

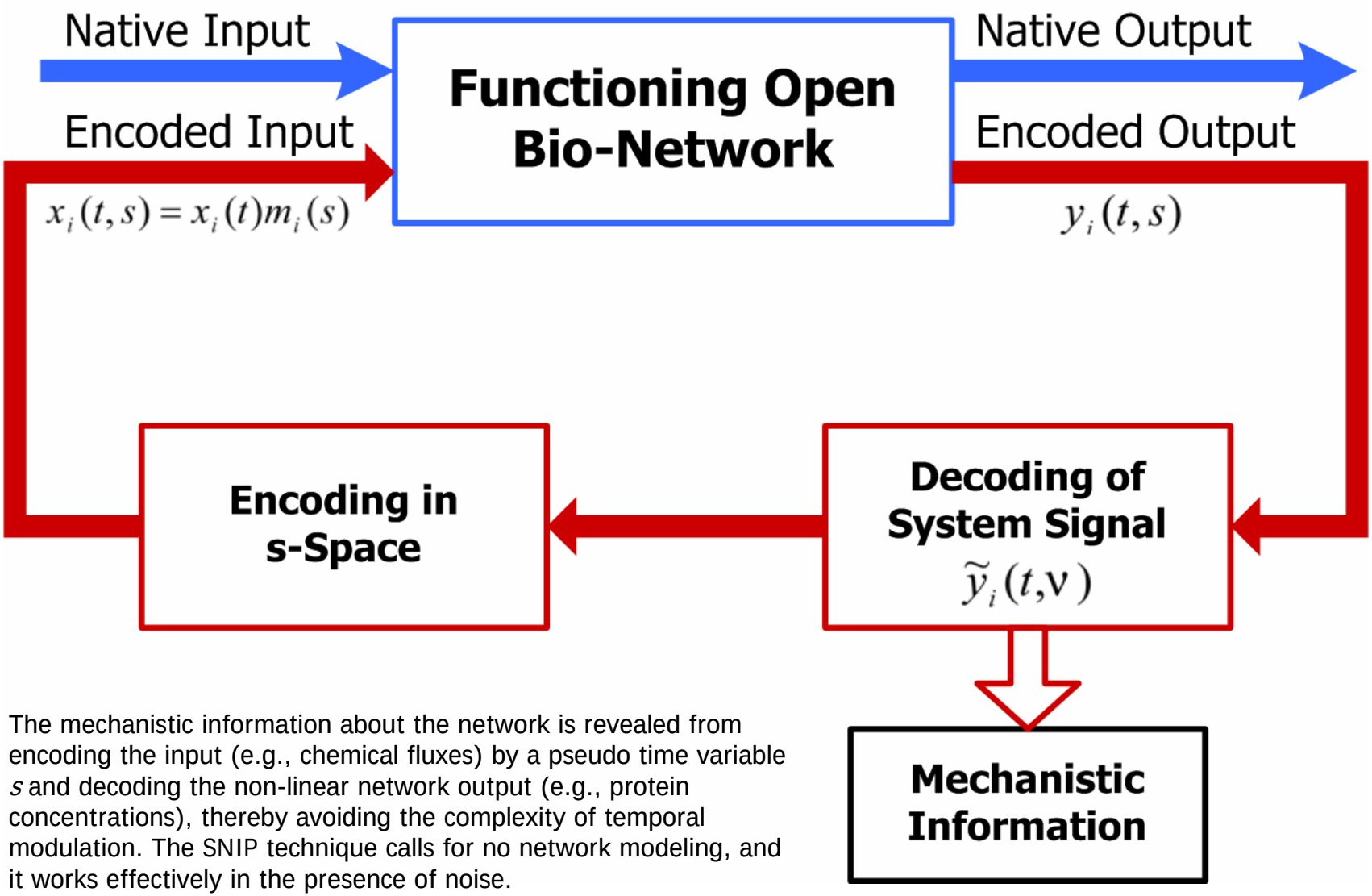
Area 1 - Project 3:
Tools for Optimal Identification of Biological Networks

- **Component 1**: Efficient biological network identification tools to infer network structure from available laboratory data
- **Component 2**: Robust optimization tools to extract quantitative information of system parameters (e.g., rate constants, diffusion coefficients, binding affinities, etc.)
- **Component 3**: Global sensitivity tools to identify the most effective molecular target or pathways of biological networks
    - *for guiding the subsequent laboratory experiment in a reliable and cost-effective fashion*
- **Component 4**: Optimal feedback control tools to infer networks with feedback loops

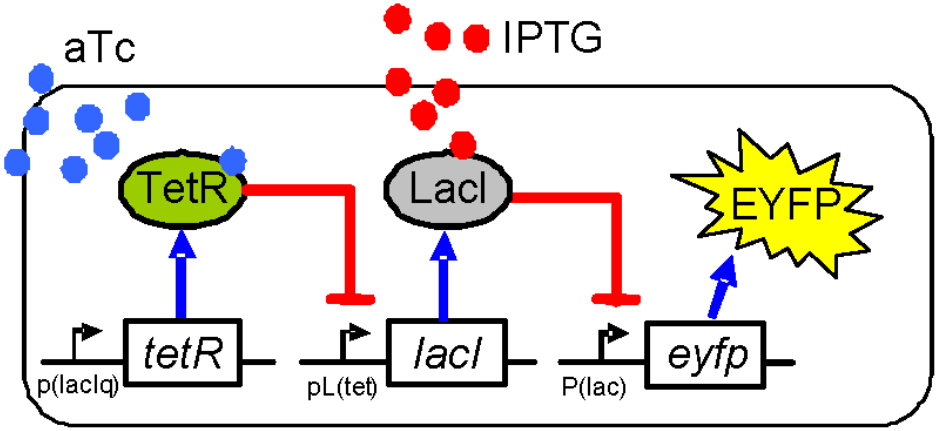
Structure of the biological network analysis for characterizing toxicity pathway by analyzing the high-throughput genomics, proteomics, and metabonomics data through the computational framework



General operation of the S-space Network Identification Procedure (SNIP) technique in identifying non-linear network connectivities

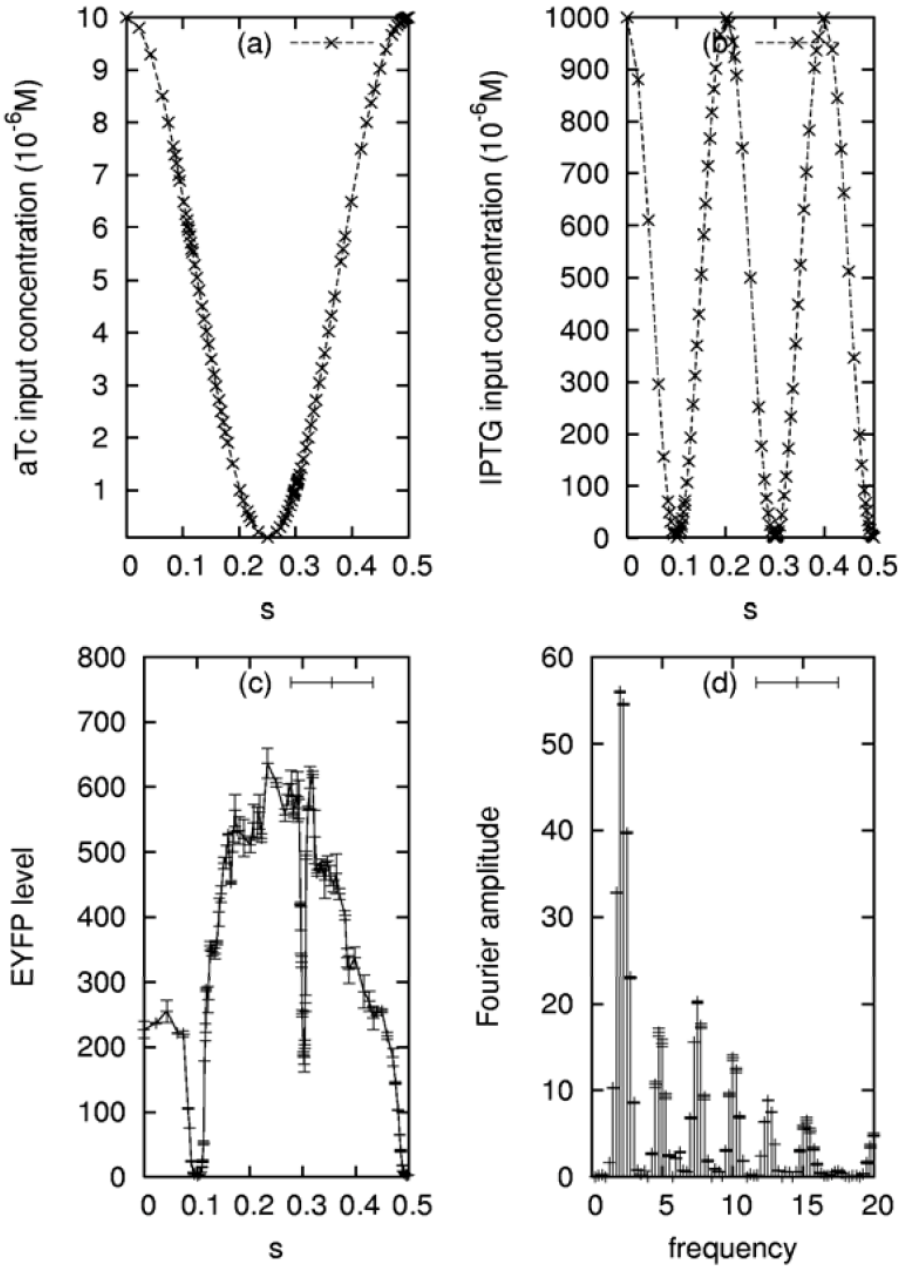


The mechanistic information about the network is revealed from encoding the input (e.g., chemical fluxes) by a pseudo time variable *s* and decoding the non-linear network output (e.g., protein concentrations), thereby avoiding the complexity of temporal modulation. The SNIP technique calls for no network modeling, and it works effectively in the presence of noise.



Circuit diagram of a synthetic transcriptional cascade. The SNIP technique was used to identify the functional connectivities between the two circuit inputs aTc, IPTG, and the output EYFP.

Different amounts of aTc and IPTG inputs are being applied in a series of encoding experiments (a and b) into the E. coli cells containing the circuit. EYFP fluorescence levels (c) following the encoding were measured as the output and Fourier decoded (d) to reveal the regulatory input-output relationships.



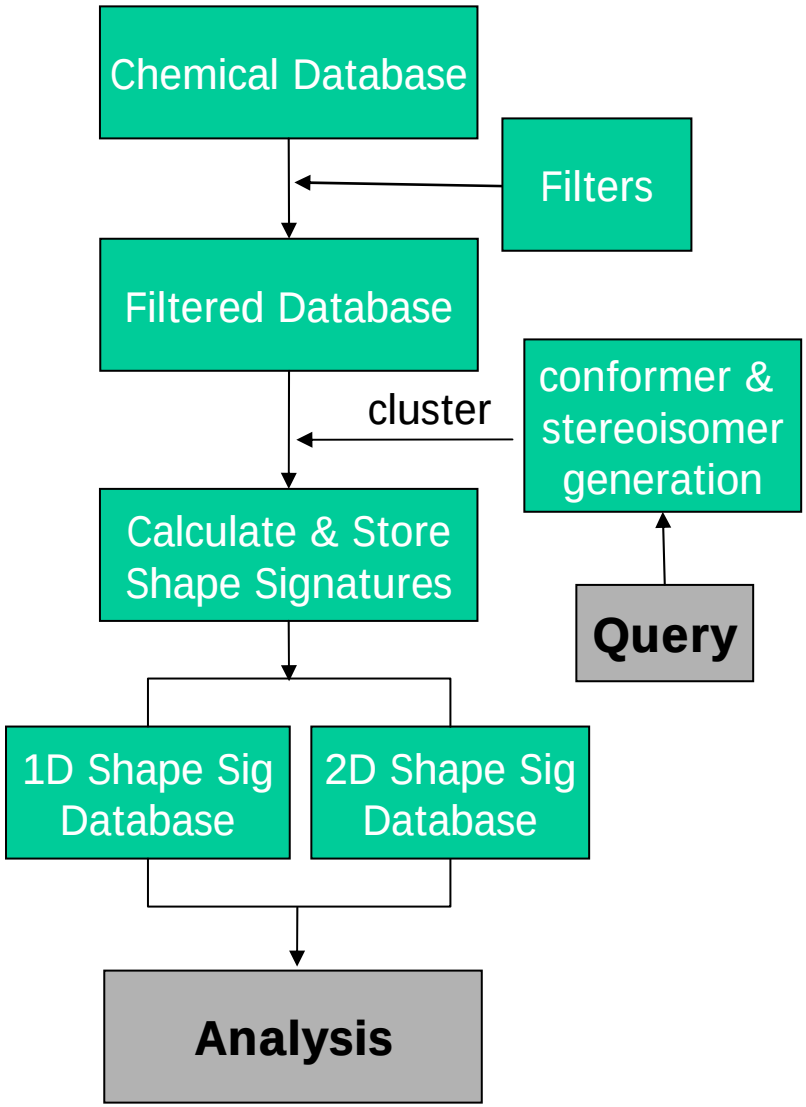
Investigational Area 2 – Research Project 4: Cheminformatics Tools for Toxicant Characterization

Dr. William Welsh, P.I.
Director, UMDNJ Informatics Institute
Department of Pharmacology, UMDNJ-RWJ Medical School

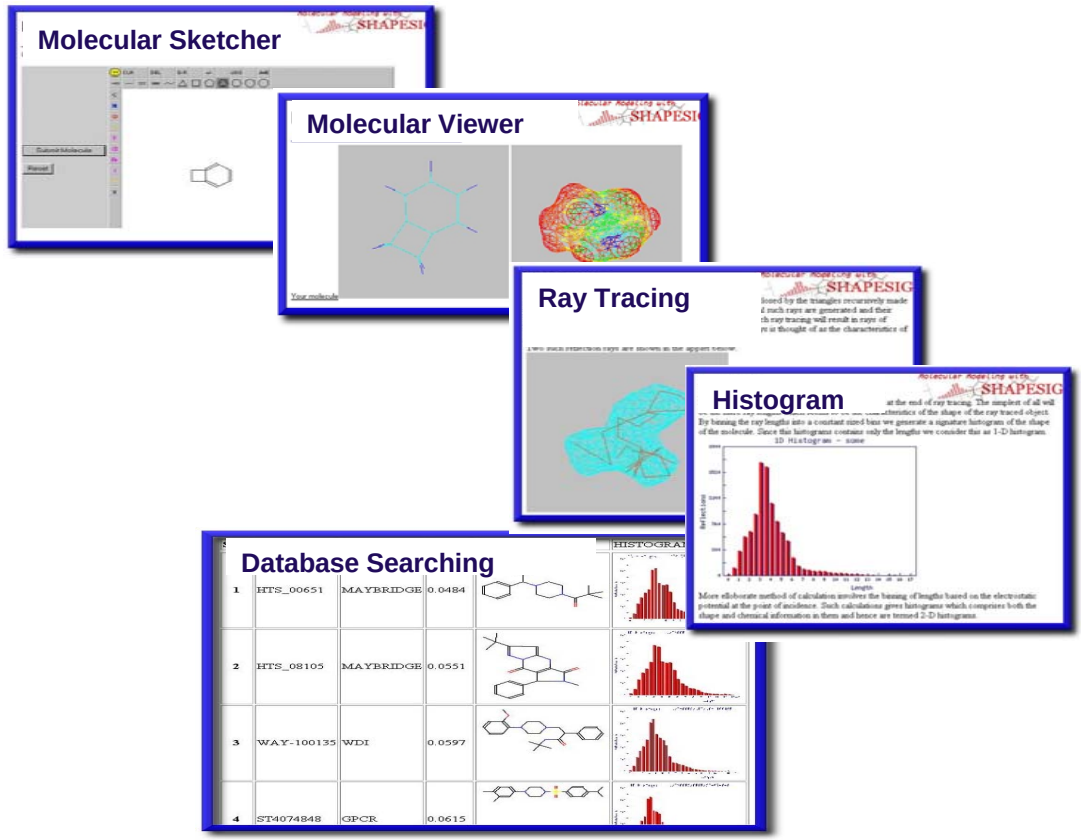
Area 2 – Project 4:
Chemoinformatics Tools for Toxicant Characterization

- **Component 1**: Shape Signatures tool that rapidly matches organic and organometallic chemicals with each other or, alternatively, against target receptor sites/subsites
- **Component 2**: Polynomial Neural Network (PNN) that automatically generates physically-intuitive linear or non-linear QSAR models
- **Component 3**: Virtual high-throughput screening (vHTS) that predicts ligand binding affinity and provides mechanistic information (toxicity pathways)

Flowchart



Shape Signatures User Interface

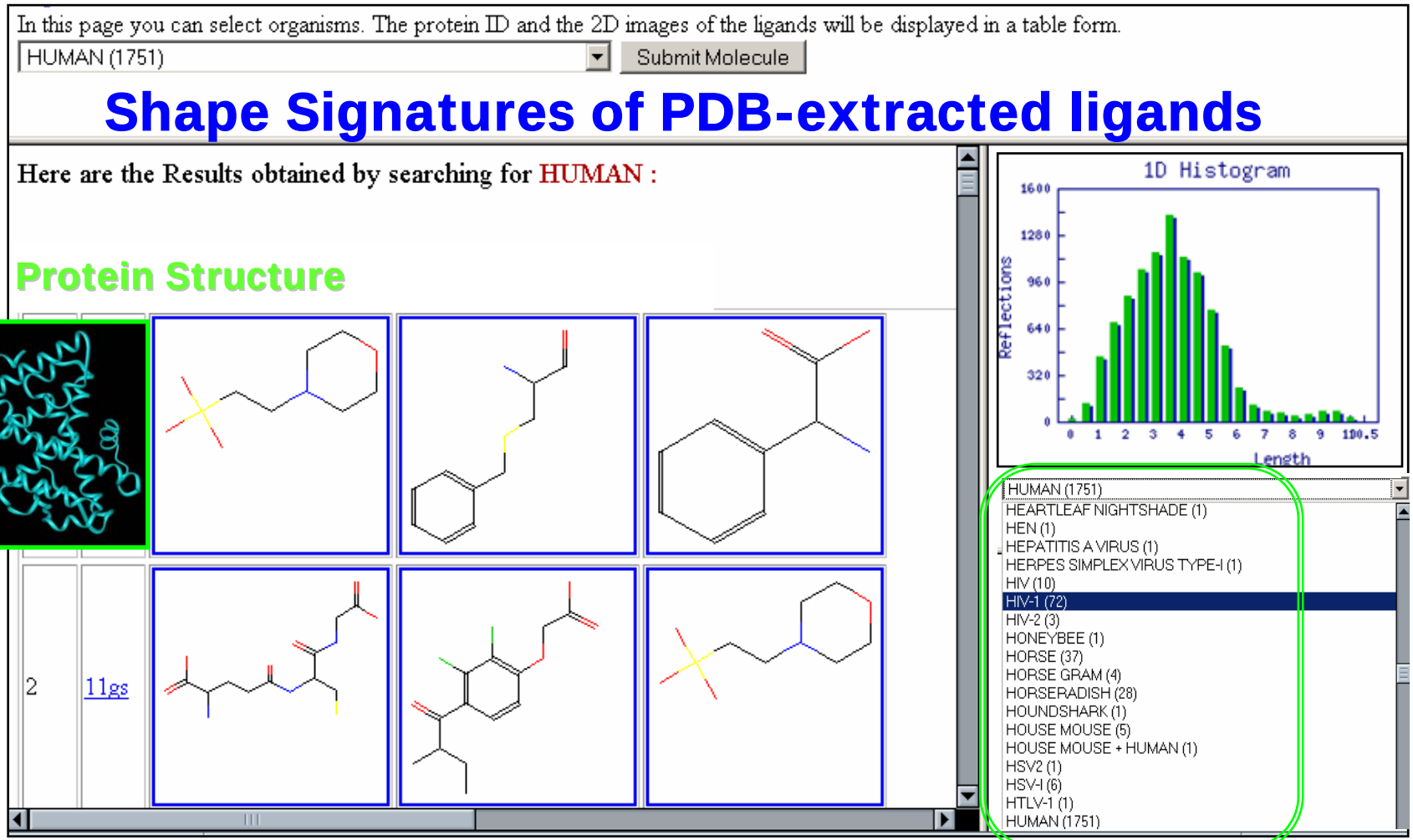


Shape Signature Databases

- Current Database >2 million cmpds
- Directed kinase and GPCR databases
- PDB-extracted ligand database

Novel Discovery Platform

Protein Data Bank (PDB): World Repository of 30K
Protein-Ligand Crystal Structures (http://www.rcsb.org/pdb/)



Species / Protein Family

Schematic of the hierarchical framework, using the EDKB as an example

Modules shaded blue will be implemented and integrated during the Project.

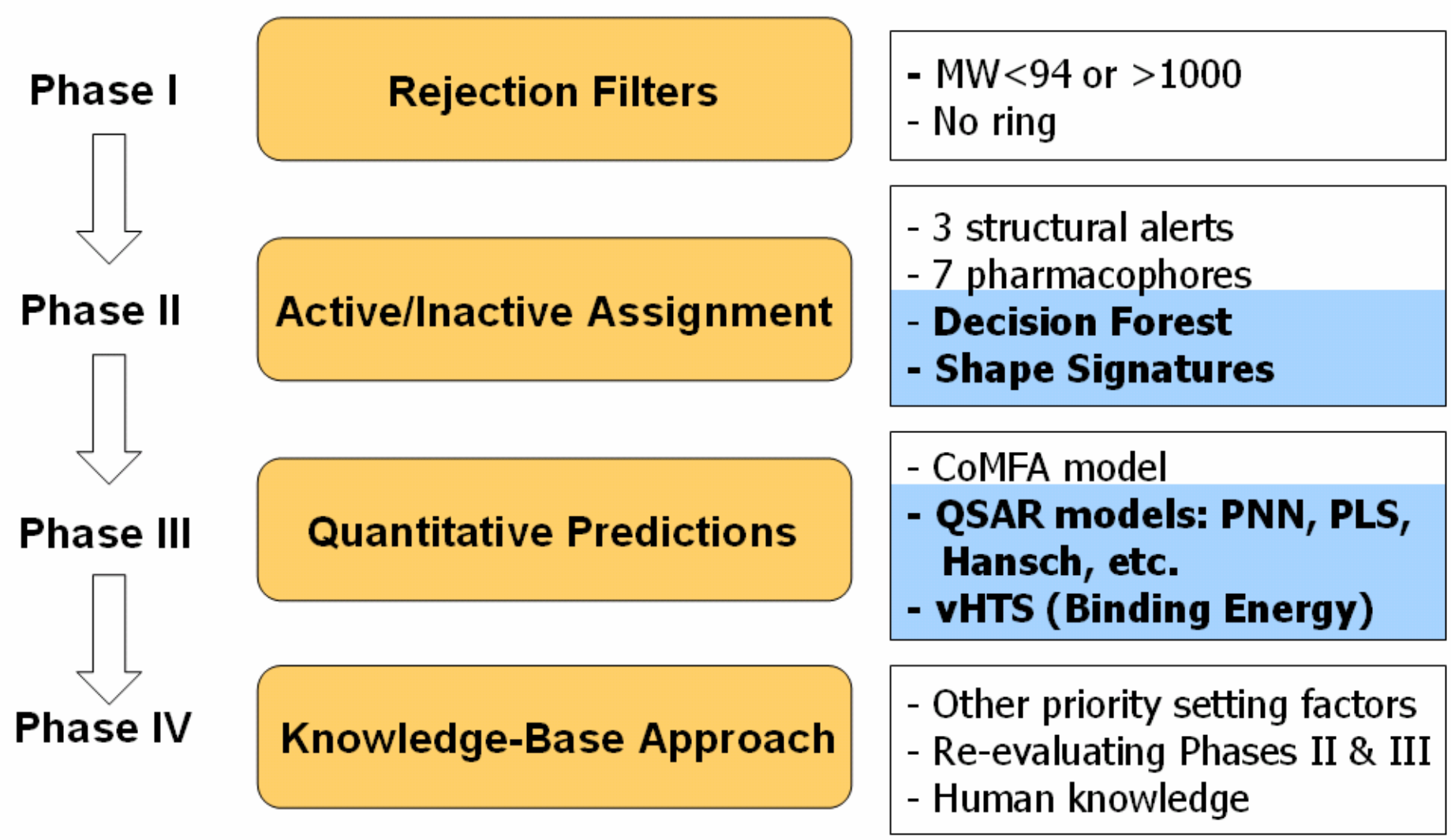
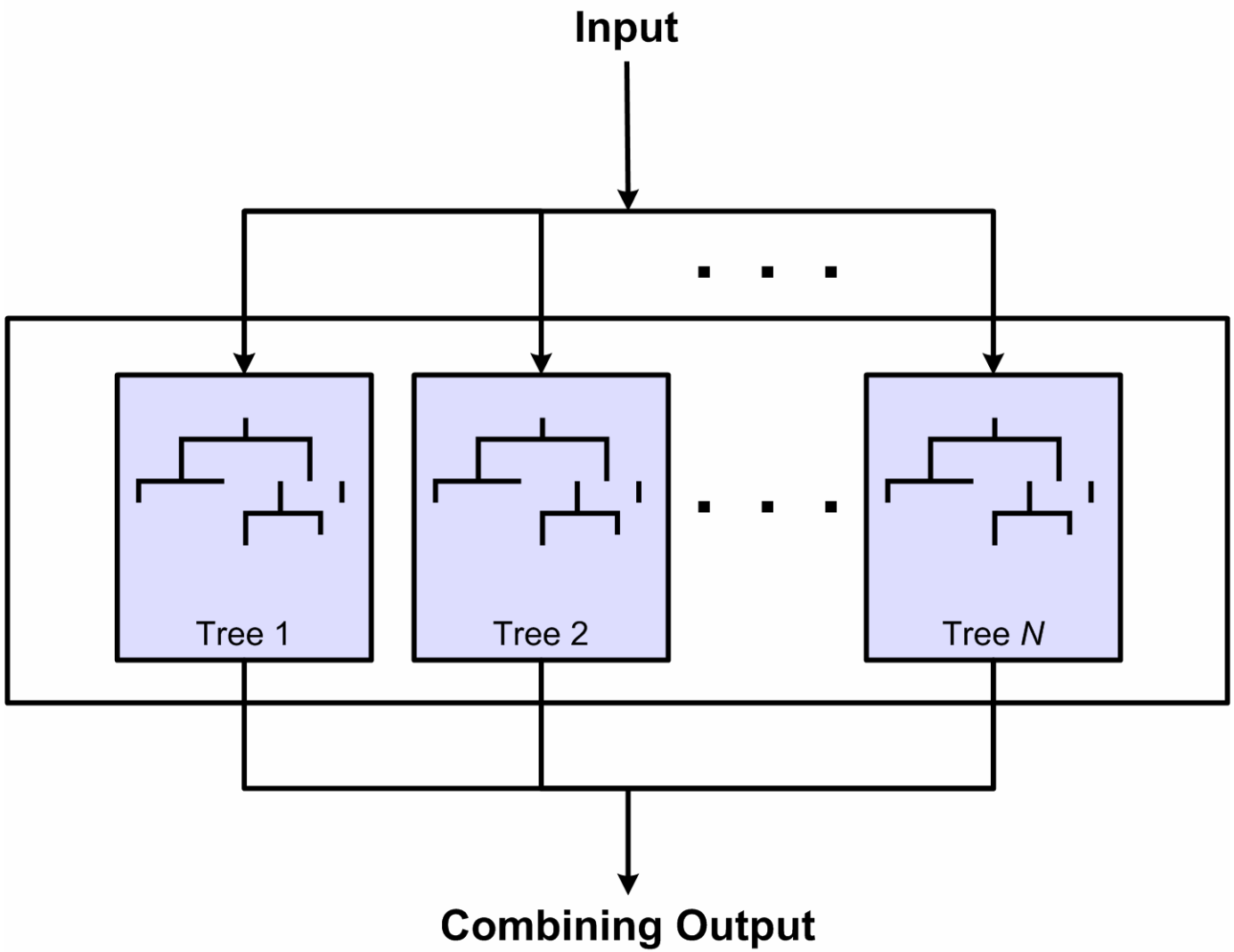
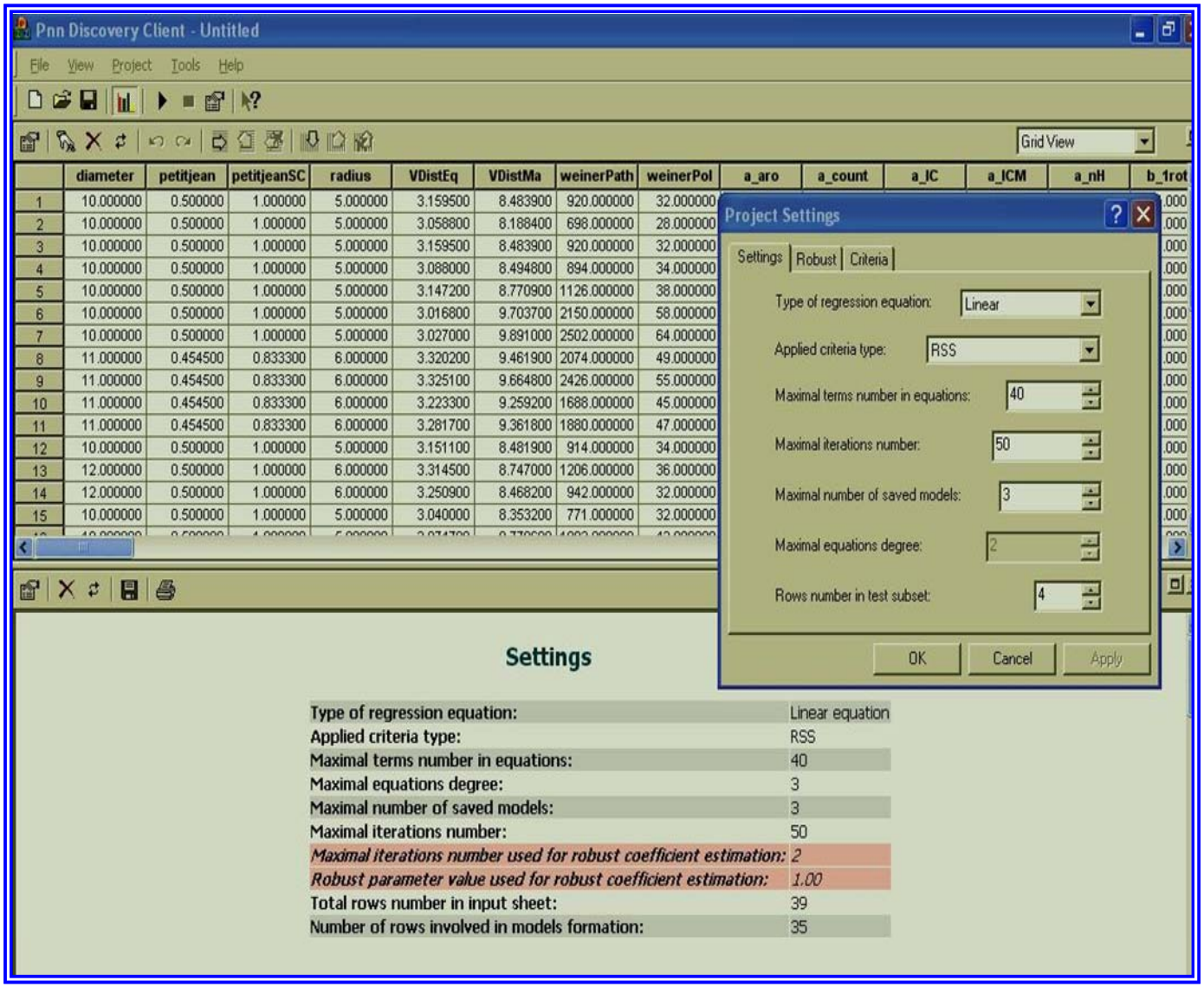


Illustration of a Decision Forest



User interface for the Polynomial Neural Network (PNN)



- Produces linear or non-linear QSAR models in parametric form
- User control of model complexity
- Insensitive to irrelevant variables and outliers
- Yields predictive models, even for sparse or noisy data sets
- Trains rapidly, thus amenable to large data sets
- Promising new tool for applications in computational toxicology

Investigational Area 2 – Research Project 5: Optimization Tools for In Silico Structural Proteomics

Dr. Christodoulos Floudas, P.I.
Director, Computer-Aided Systems Laboratory
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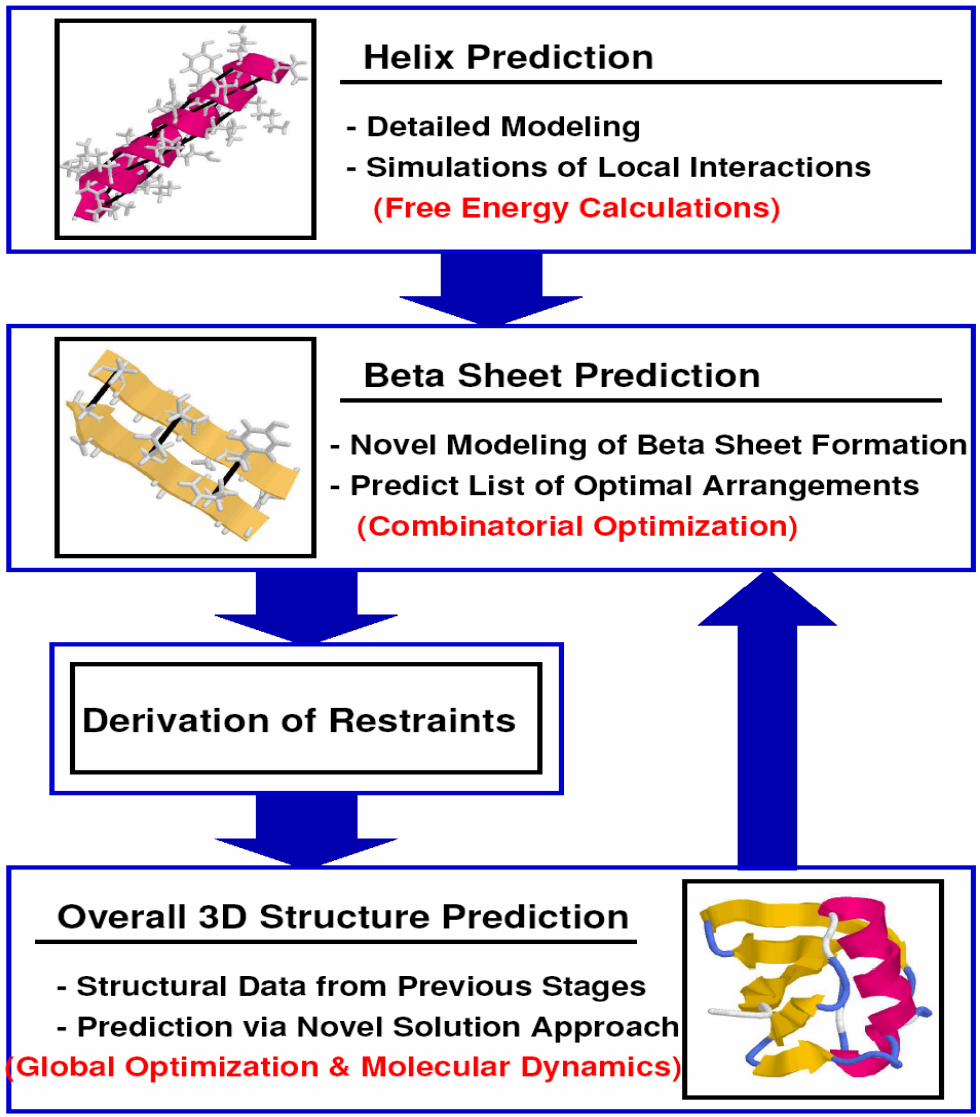
Program in Applied and Computational Mathematics,
Princeton University

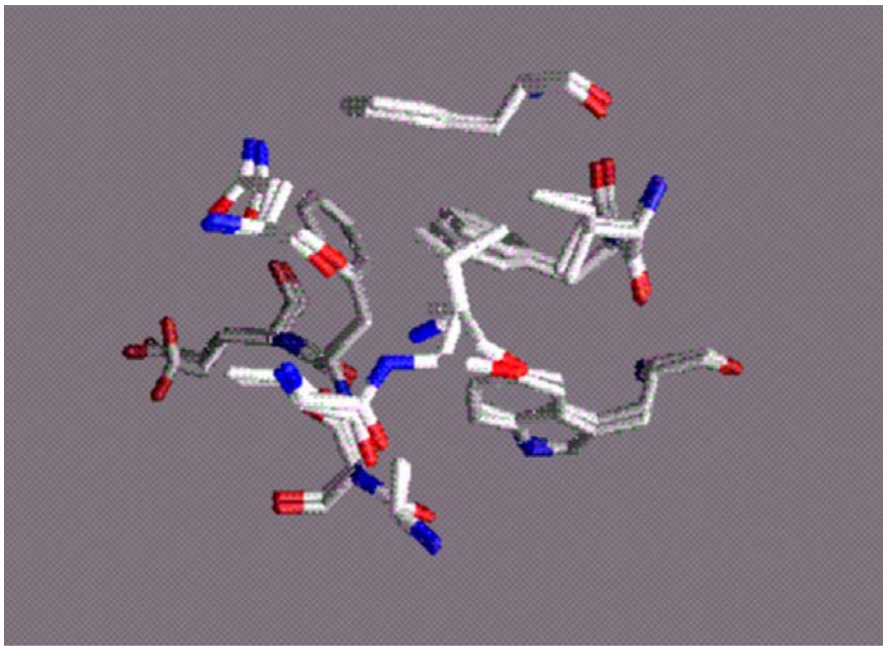
Area 2 – Project 5:
Optimization Tools for *in Silico* Proteomics

- **Component 1:** Customized computational methods for protein structure prediction and *de novo* protein design
  - *specific focus on the important families of Glutathione Transferases (GST) (cytosolic, mitochondrial and microsomal GST)*
- **Component 2:** Computational methods for elucidating the topology of signal transduction networks
  - *Emphasis on addressing uncertainties in experimental data and models*
- **Component 3:** *De novo* computational proteomics methods for peptide and protein identification via tandem mass spectroscopy

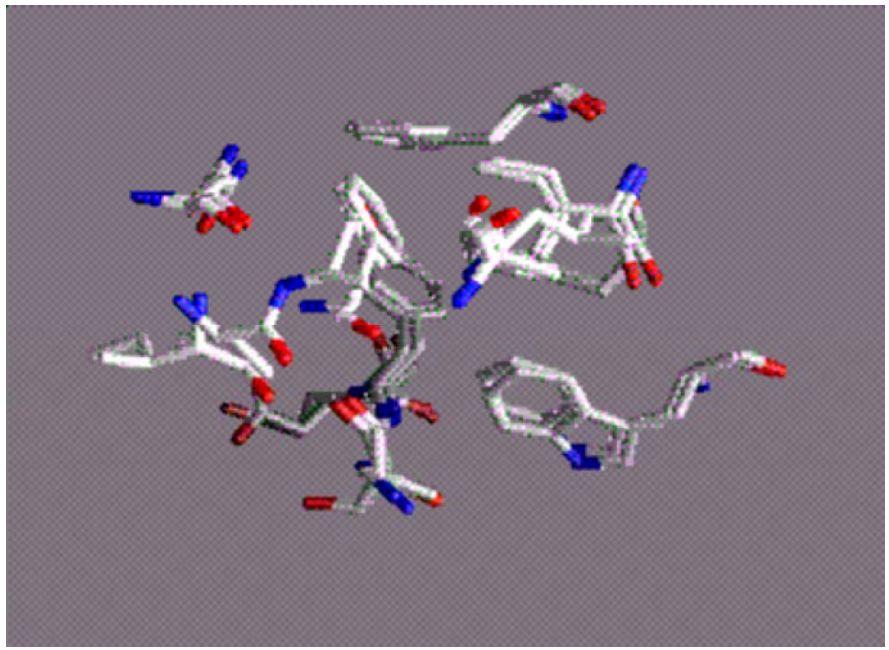
Overall flowchart for first principles structure prediction using ASTRO-FOLD



Prediction of HLA class II molecules through deterministic global optimization: Comparison with crystallographic data



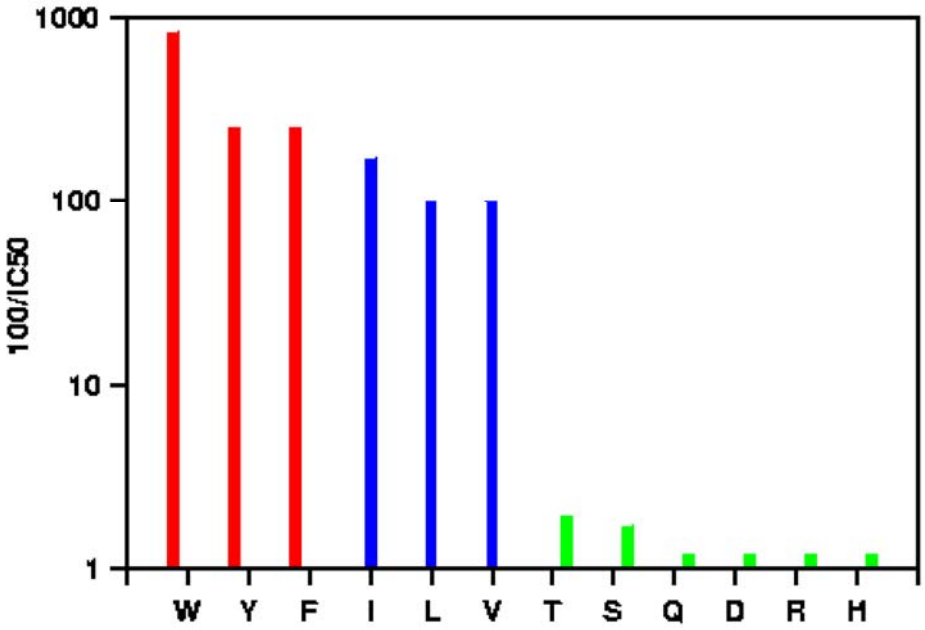
Superposition of the Predicted Pocket 1 of HLA-DR3 antigen vs Crystallographic Data



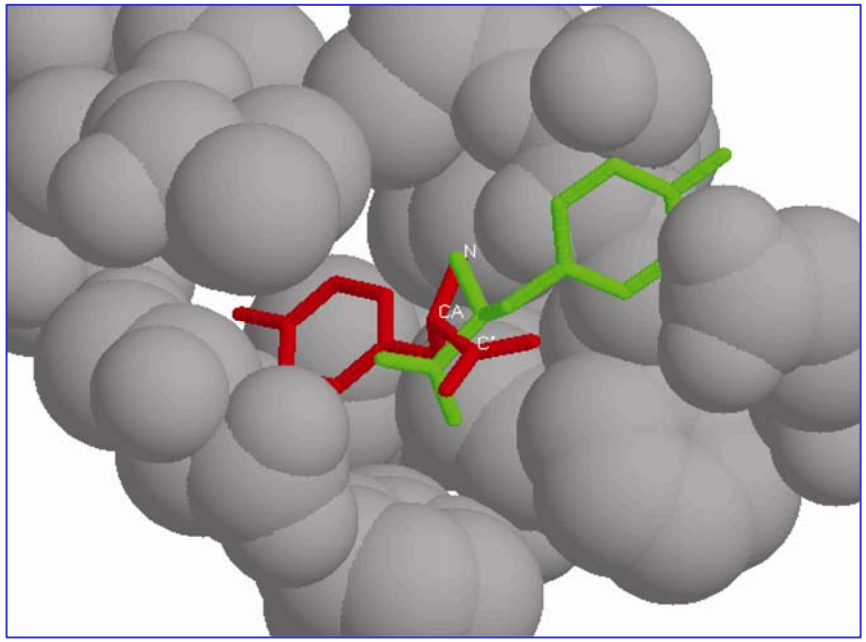
Superposition of the Predicted Pocket 1 of I-E^k antigen vs Crystallographic Data

The structures shown were predicted from the crystallographic structural data of HLA-DR1 and deterministic global optimization. A selection of five "pockets" was identified at the binding site of HLA-DR1. Each of these pockets of HLA-DR1 differs from HLA-DR3 and I-E^k by one, two, three or four amino acids.

Binding affinity evaluation in HLA-DR1 pockets via the volume solvation method



Literature data on pocket 1 competitive binding assays. Global optimization data agree with these data.



Global (red) vs local (green) conformations of tyrosine in pocket 1, as estimated through the volume solvation method.

The global minimum conformation of tyrosine (as shown to the right) corresponds more closely to the crystallographically determined conformation than the corresponding local minimum conformation.

A schematic of major interactions among:
(a) Research Projects,
(b) Projects and Public Outreach and Translation Activities (POTA) and
(c) Quantitative Risk Assessment (QRA) demonstration case studies

Concluding / Commencing Comments

- Projects are “open”
  - *Emphasis is on the development of computational tools*
  - *Case studies will allow testing and refinement for real-world biological application*
- Interactions/collaborations are invited
  - *An iterative process is expected for refining the definition of needs and solutions for specific toxicological problems*
  - *Demonstration/evaluation studies should be defined in a collaborative setting*

We look forward to pursuing opportunities
for productive and mutually beneficial collaborations

Quantitative Risk Assessment Resource Team

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- Scientific Director, Rutgers University Cell and DNA Reporting

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- Professor, School of Natural Sciences, Institute for Advanced Study

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- Associate Dean, Oncology Program, UMDNJ-RWJMS

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- Director, Protein Data Bank, Rutgers University

Patrick Sinko
- Professor and Chair, Department of Pharmaceutics, School of Pharmacy, Rutgers University

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Interaction/Coordination with:

- BIOMAPS Institute for Quantitative Biology, Rutgers
- Bionomics Center, EOHSI (UMDNJ/Rutgers)
- Cancer Institute, UMDNJ
- Cell and DNA Repository, Rutgers
- Center for Discrete Mathematics and Theoretical Computer Science (DIMACS), Rutgers
- Center for Exposure and Risk Modeling (CERM), EOHSI (UMDNJ/Rutgers)
- Informatics Institute, UMDNJ
- Institute of Integrative Genomics, Princeton
- Molecular Bioinorganic Institute, Princeton
- National Institute for Environmental Health Sciences (NIEHS) Center, EOHSI (UMDNJ/Rutgers)
- Pharmacogenomics Center, UMDNJ
- Protein Data Bank, Rutgers
- Toxicoinformatics Center, FDA
- W.M. Keck Center for Collaborative Neuroscience, Rutgers

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Administrative Core

Administrative Support

Outreach & Training

- Fred Roberts, Center for Discrete Mathematics and Theoretical Computer Science, Rutgers University

Demonstration of Research Projects

BACK

Public Outreach and Training Activities (POTA)

will be handled by the Center for Discrete Mathematics and Theoretical Computer Science (DIMACS) at Rutgers University

- DIMACS is directed by Fred Roberts
  - *Professor II of Mathematics, Rutgers*
  - *Biological Mathematical and Physical Sciences (BIOMAPS), Institute for Quantitative Biology*

BACK

Research activities of proposed effort will be organized in 5 projects

- **Each project will develop a set of "stand-alone" components addressing specific CT problems**
- **Research Project 1 will provide an integrative framework for Investigational Area 1**
- **Project 4 will address the core issues of Area 2**