


UniversityHospital Heidelberg

1st European Workshop on Tissue Imaging and Analysis

From Virtual Microscopy to Medical Systems Biology

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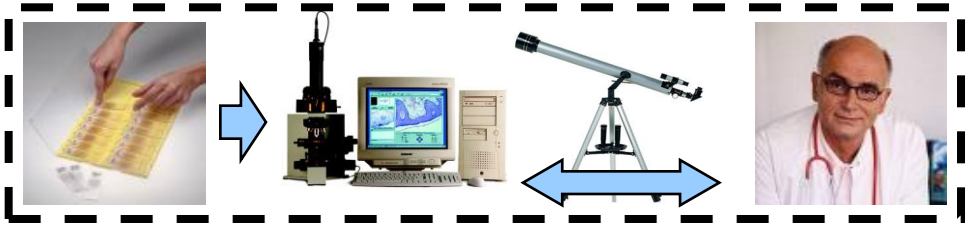
What is Virtual Microscopy?

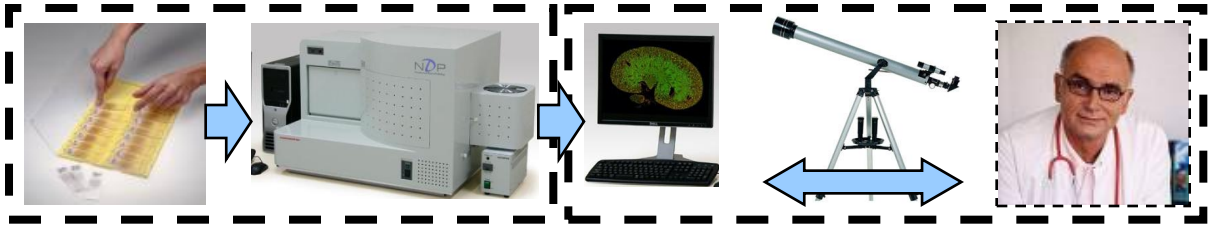
Virtual Microscopy refers to the automatic microscopic imaging of specimen mounted on glass slides and to making the digital slides available for further processing.

What is it good for?

Virtual Microscopy – the Telescope

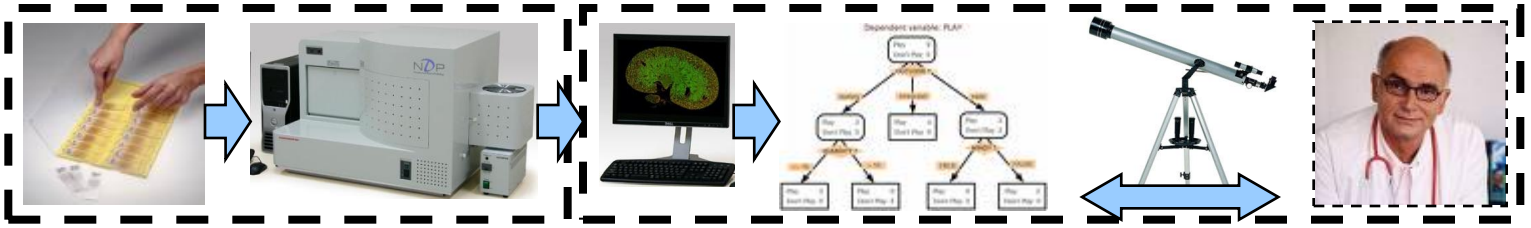
- VM historically emerged from the idea of remotely controlling a microscope
- Key achievement of VM:
  full digitalisation of the slide
- *Impressive examples: Session „e-Learning“*





Virtual Microscopy – the Jet Engine

- Computational image processing: the jet engine for the pathologist
- High-throughput: fast evaluation of many slides
- Quantitative measurements
  - From sampling to measurement
  - Measuring gene / protein abundance
  - Measuring morphology
- *Sessions Research-, Industrial- and Clinical Applications*



Getting to fly: the Value Chain

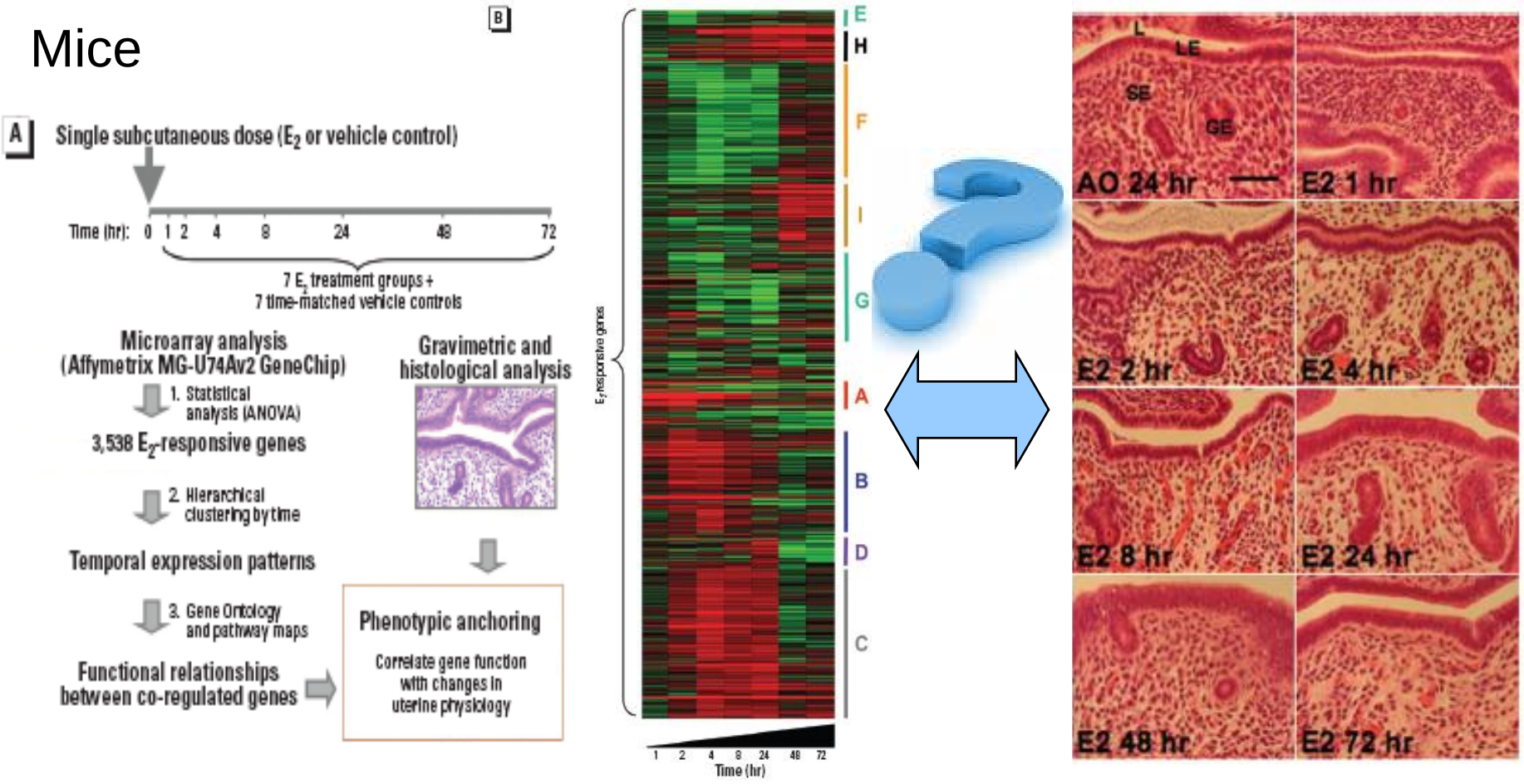
- Image processing: the jet engine for the pathologist
- **But it takes more to build a flying jet plane**
- Pathology will face total integration towards a pathology value chain
  - Integration of image analysis and protocols
  - Towards faster and better diagnoses

Histology | Staining | Virtual Microscopy | Image processing

Industrial Exhibition + Talks in Session Industrial Applications

Morphological or Phenotypic „Anchoring“ as a first step towards Systems Pathology

Mice



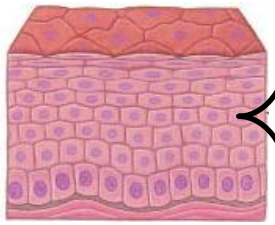
Moggs et al., „Phenotypic Anchoring of Gene Expression Changes during Estrogen-Induced Uterine Growth“, Env. Health Persp. 2004, [Syngenta]

What is Systems Biology?

- Antithesis to reductionist paradigm who has successfully identified most of the components and interactions of biological systems: Is about putting together rather than taking apart (Denis Noble).
- How do interactions between components of biological systems give rise to the function and behavior of that system?
- Emergence: the arising of novel and coherent structures, patterns during the process of self-organization in complex systems (the whole is greater than the sum of its parts).
- Observation: diseases are a kind of tissue reorganization.

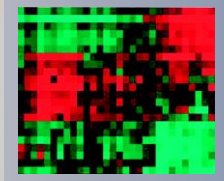
→ **Medical Systems Biology / Systems Pathology must include tissue self organization as a key aspect.**

Towards Systems Pathology



Sample

Cell lysate



Genomics Value Chain

→Many genes parallel, novel genes, find genetic signatures

Morphology Value Chain

→Few genes, large sample numbers, find biomarker reliability

Novel Therapeutics

Systems Pathology / Medical Systems Biology

Novel Diagnostics

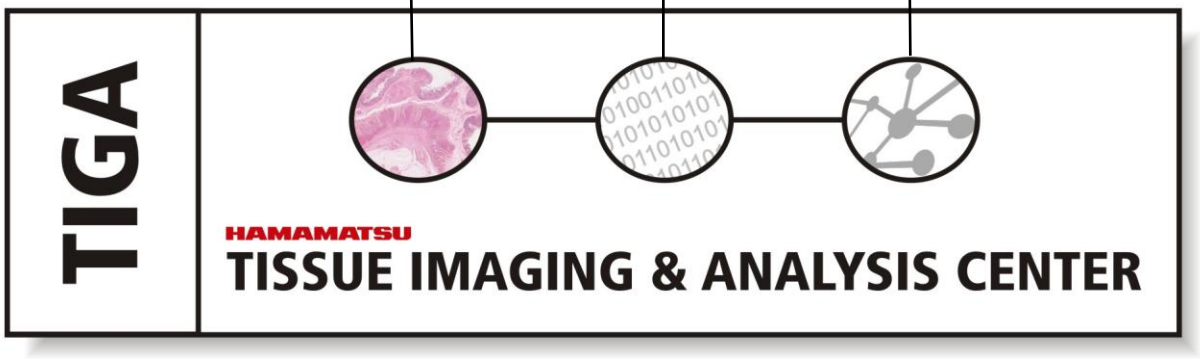
Research + Clinical Session (e.g. Tomakidi, Halama, Wentzensen)

Tissue Imaging and Analysis Center

Quantitative
Tissue Measurements
(Microscopy, Image analysis)

Simulation and
Classification of Tissues
(Modelling, Diagnostics)

Tissue Wet-Lab
(Genomics, Tissue Cell Culture)



Institute of Medical Biometry & Informatics Heidelberg

Institute of Pathology Heidelberg

BioQuant
MODEL base of LIFE

HAMAMATSU
PHOTON IS OUR BUSINESS

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

TIGA Partner Program

- New Partner in February 09
  - Sponsoring company
  - Extension of our „Pathology Value Chain“
  - State-of-the art histological processing equipment

ThermoFisher
SCIENTIFIC

Summary: From Virtual Microscopy to Medical Systems Biology

- Virtual Microscopy is essential:
  - „Telescope“ for morphological information
  - „Jet-engine“ for pathology by image processing
  - „Jet plane“ needs integration of „morphology value chain“ and „genomics value chain“
  - Key component of Medical Systems Biology and Systems Pathology.

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Institutional members:

Institute of Medical Biometry & Informatics Heidelberg
IPH Institute of Pathology Heidelberg
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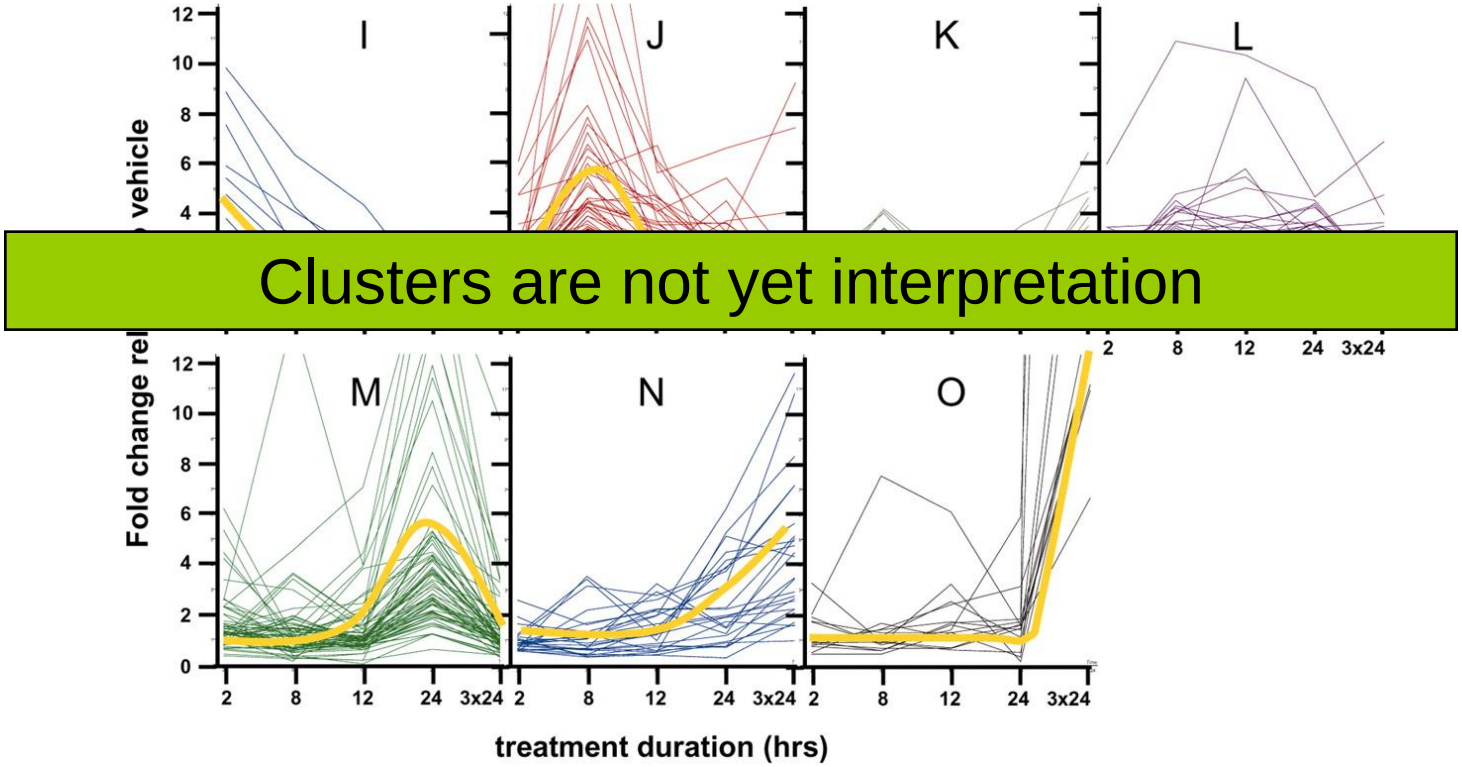
NCT Nationales Centrum für Tumorerkrankungen Heidelberg
dkfz. German Cancer Research Center in the Helmholtz Association

Unsupervised Clustering



Clusters are not yet interpretation

Fig. 2. K-means clusters of responses passing the empirical Bayes and ANOVA screening steps (labeled *I–O*, as in Table 4). A pseudogene line is drawn in bold yellow to illustrate a representative response that defines the response pattern in each cluster.

Fertuck et al. „Identification of temporal patterns ..“, (Estrogen on mice uteri), Physiol. Genomics 2003 [US-Food-Safety]

Compound Signatures

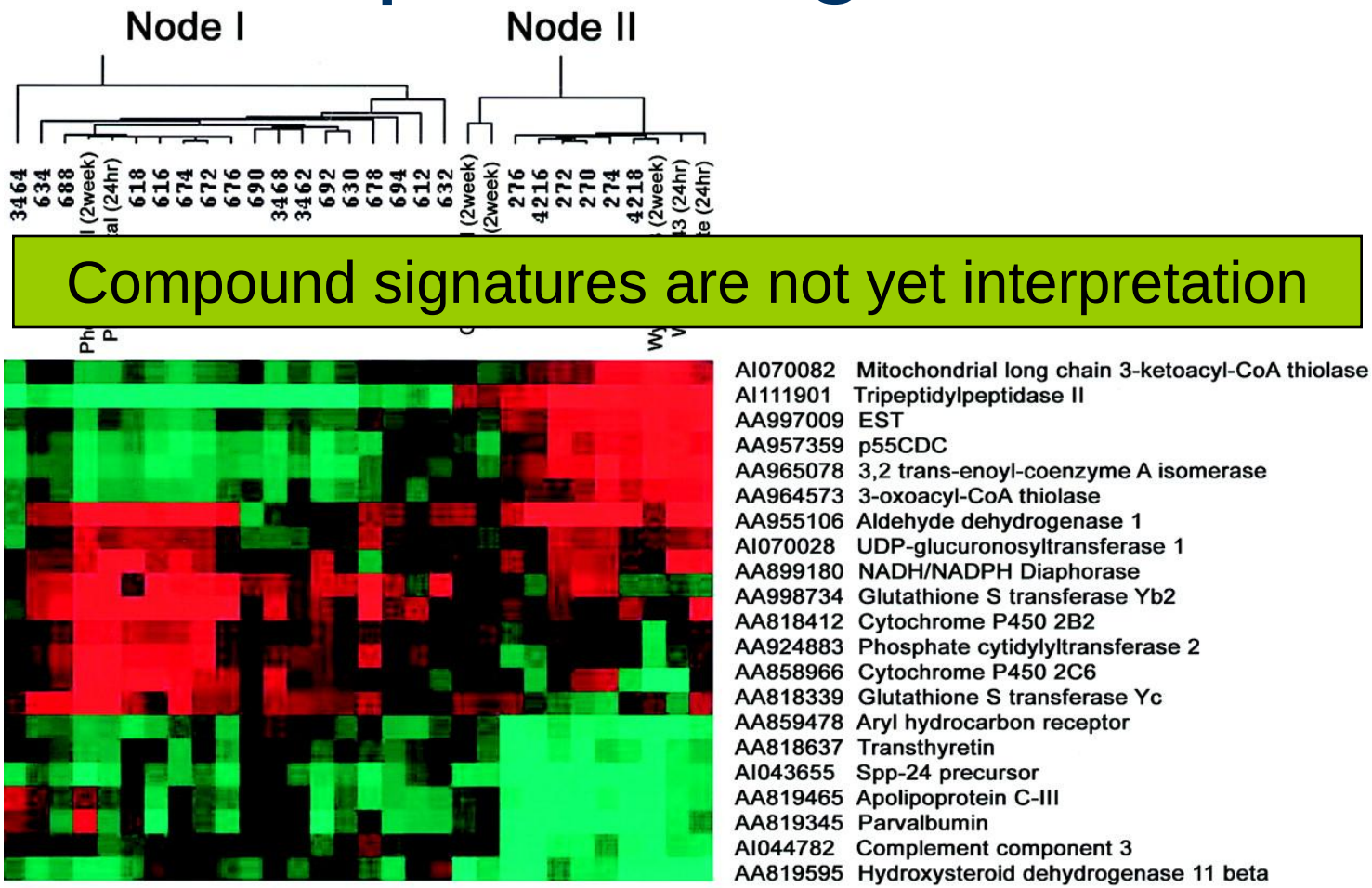


FIG. 2. Clustering diagram of samples in the study. The algorithm (Eisen *et al*., 1998) was used to cluster the gene expression profiles for known and coded compounds for the set of derived discriminatory genes used in this study. The diagram illustrates that all of the compounds separate into 2 distinct nodes. Node I represents samples that are related to phenobarbital and Node II represents samples classified as peroxisome proliferators. Red indicates genes that are induced by treatment and green indicates repression of expression by treatment.

Hamadeh et al. „Prediction of Compound Signature …“, Tox. Sc. 2002 [Boehringer-Ingelheim]

Systems Toxicology by Waters & Fostel 2004

Histopathology & Arrays separated !

=> Integration of Morphology and Genomics necessary

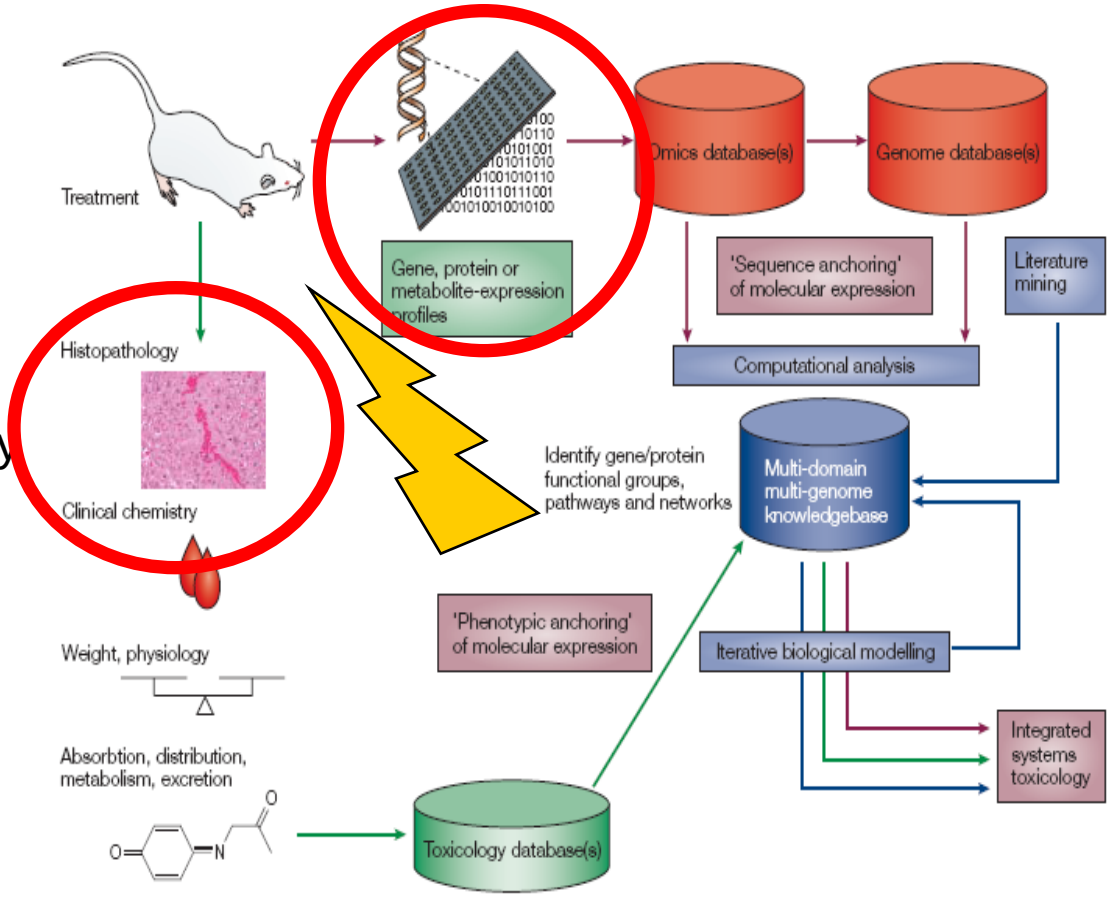


Figure 2 | **A framework for systems toxicology.** This figure indicates the paths from the initial observation (rat in upper left) to an integrated toxicogenomics knowledgebase (blue cylinder), and so to systems toxicology (bottom right). The '-omics' data stream is shown by the clockwise path from rat to knowledgebase; and the 'traditional' toxicology approach is shown in the anti-clockwise path. The knowledgebase will integrate both data streams, along with literature-based knowledge; and by virtue of iterative modelling, will lead to a systems toxicology understanding. The framework involves 'phenotypic anchoring' (to toxicological endpoints and study design information) and 'sequence anchoring' (to genomes) of multi-domain molecular-expression datasets in the context of conventional indices of toxicology, and the iterative biological modelling of the resulting data.

Waters, Fostel, „Toxicogenomics“, Nature Review Genetics 2004

Virtual Microscopy

Virtual microscopy provides

- Automatic microscopy of full tissue slides
- Batch scanning of large section sets
- Fluorescence scanning with color separation of three channels of e.g. stroma / nuclei / biomarker
- In connection with automated image processing: high-throughput spatial analysis of tissues
- Quantitative morphological tissue data provides framework for microarray-data