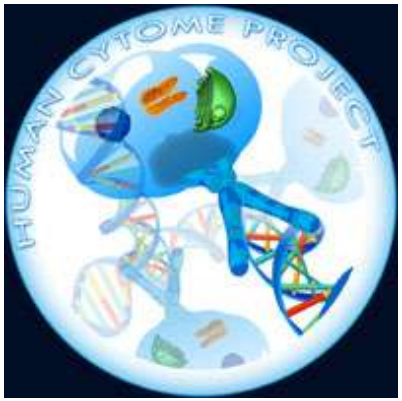
A Human Cytome Project



Peter Van Osta

MAIA SCIENTIFIC

European Microscopy Congress
Antwerp, Belgium
Friday 27August 2004

A Human Cytome Project

- Definitions
- Introduction and rationale
- Research concepts
- Proposal of a strategy

- Round table discussion

- Conclusion

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Cytome - Cytomics

- **Cytomes** can be defined as cellular systems and subsystems and functional components of the body.

- **Cytomics** is the study of the heterogeneity of *cytomes* or more precisely the study of molecular single cell phenotypes resulting from genotype and exposure in combination with exhaustive bioinformatics knowledge extraction.

- The word Cytomics was first used in 2001 by:
  Davies E, Stankovic B, Azama K, Shibata K, Abe S.
  "Novel components of the plant cytoskeleton: A beginning to plant "**cytomics**"
  Plant Science, Invited Review, Plant Science (160)2 (2001) pp. 185-196.

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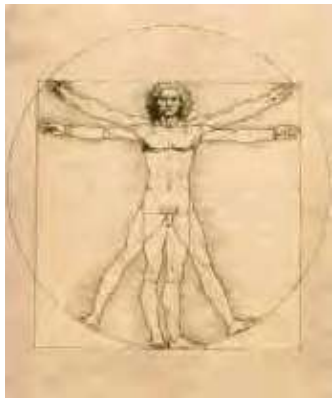
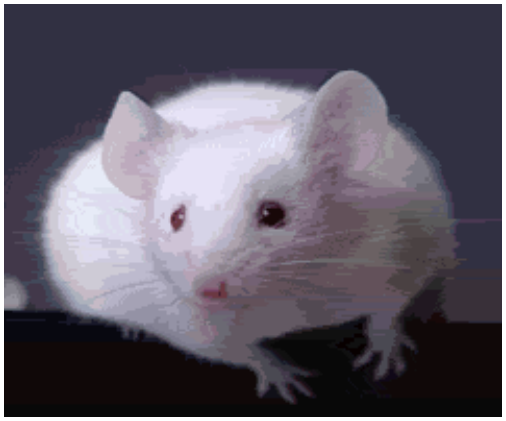
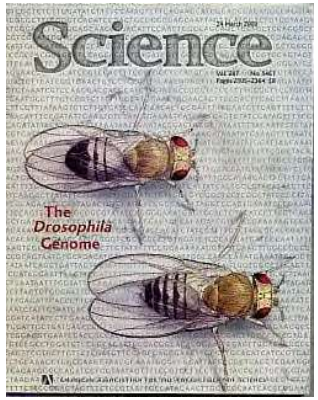
Why do we need a Human Cytome Project ?



Human ≅ 30,000 genes
3,2000 Mb or 3.2 billion base pairs



Mouse ≅ 30,000 genes
2,500 Mb

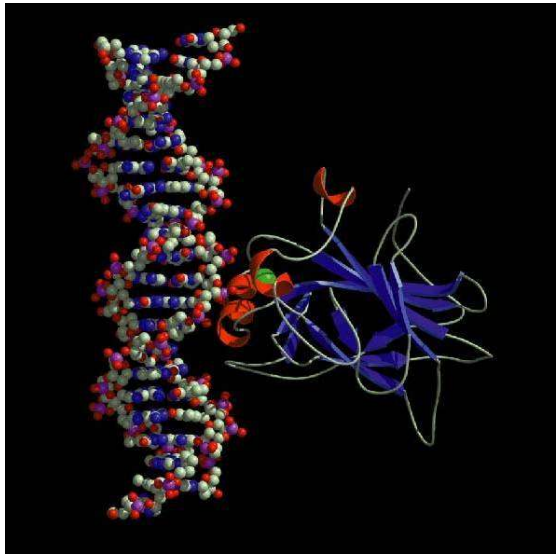


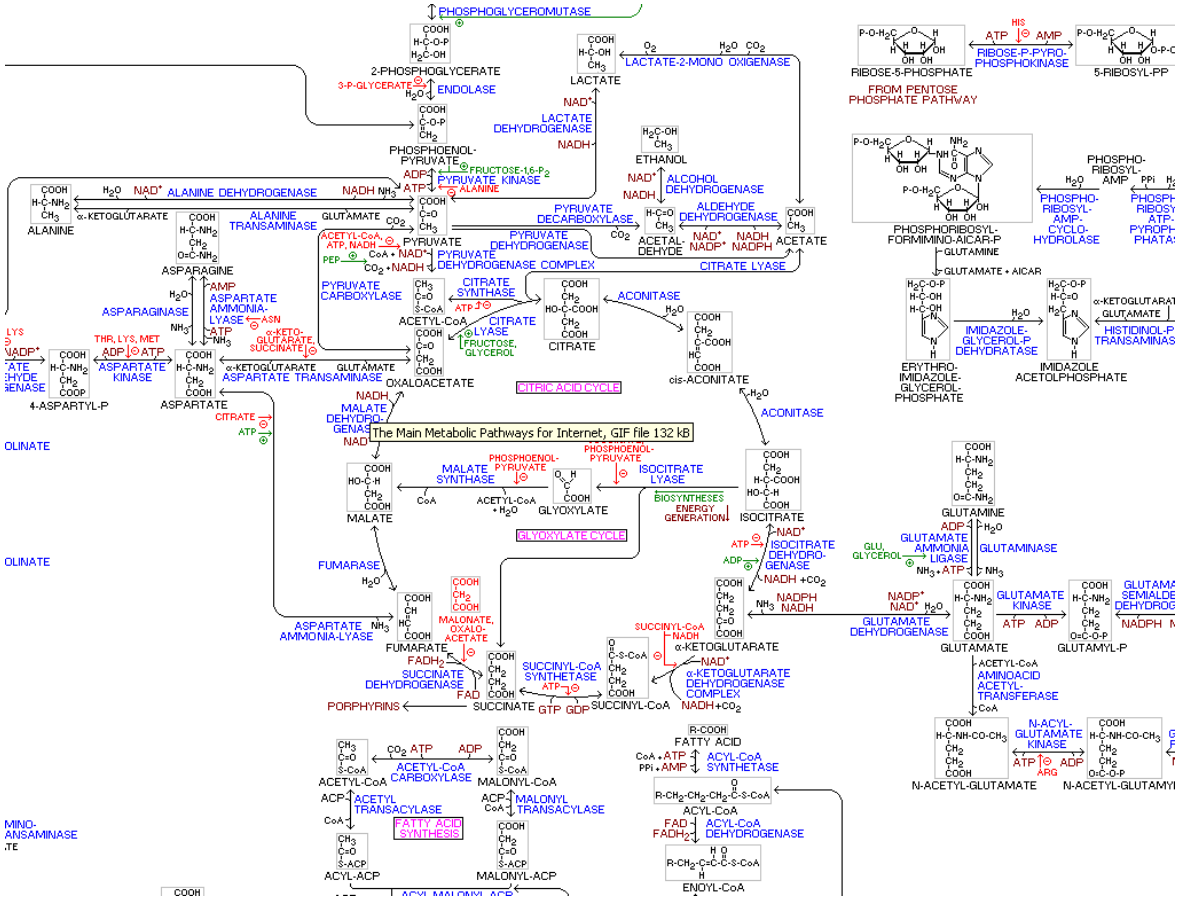
Drosophila ≅ 13,601 genes
165 Mb

C. elegans ≅19,000 genes
97 Mb

Complexity and differentiation of organisms is not only explained from the relative complexity of their genomes

From Genes to Proteins to Pathways



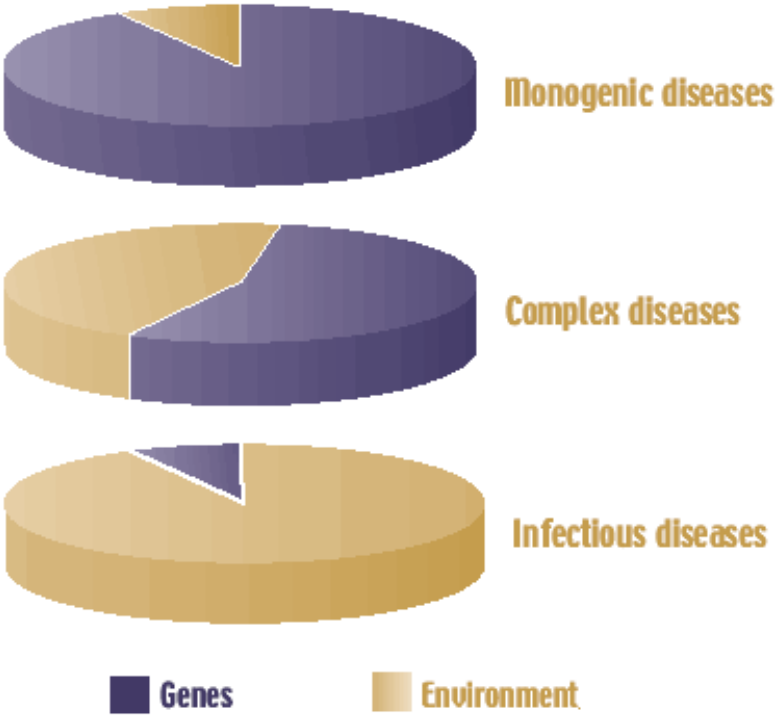


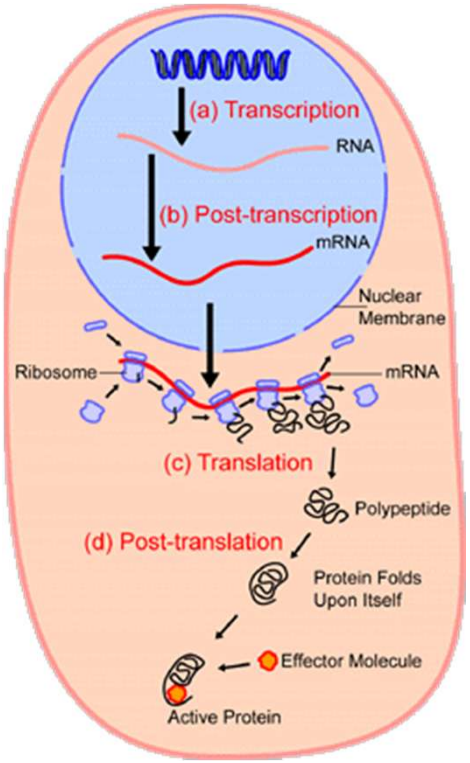
From gene to 3D protein structure

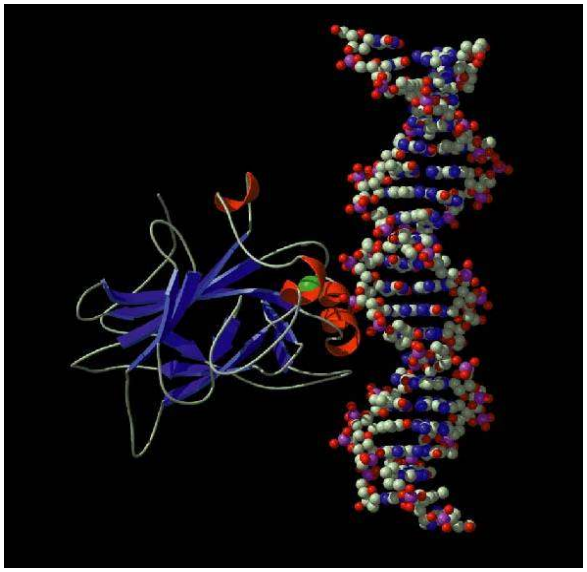
Metabolic pathways

The complexity of interacting metabolic pathways is not only predicted from the gene or protein structure

Environment - Cell – Genome
A web of interactions







Environment

Cell
Cytome

From Gene to Protein
Genome - Proteome

Instead of concentrating on molecular targets within the relatively infinite network of highly redundant molecular pathways of cells, one can primarily focus on the end result, represented by molecular phenotypes of cells as a consequence of both genotype and environment.

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Functional Genomics: Research Concepts

- current vision:
  - elucidation of the organisation of genetic networks and protein pathways and of their contribution to cellular and organismal phenotype (Collins FS et al. Nature (2003) 422: 835-847)
- problem: high complexity, long time frame with 30-40.000 genes
- examples:
  - 3D protein structure
    30 years of research do no permit to exactly predict 3D protein structures from amino acid sequences (20 amino acids)
  - pharmaceutical industry
    investment doubling during last 10 years provided only half as many new candidate substances than during preceeding 10 years

HCP-V

Courtesy of Gunter Valet

Functional Genomics: Research Concepts

- human cytome project as shortcut:
  - differential screening of molecular single cell phenotypes e.g. diseased versus healthy, differentiated versus undifferentiated
  - molecular hotspot identification by standardized relational classification
- advantage: immediate application potential
  - predictive medicine by cytomics for personalized medicine
  - identification of new drug targets using retrograde pathway modelling of molecular hotspots by systems biology
  - relevant information is collected at reduced complexity

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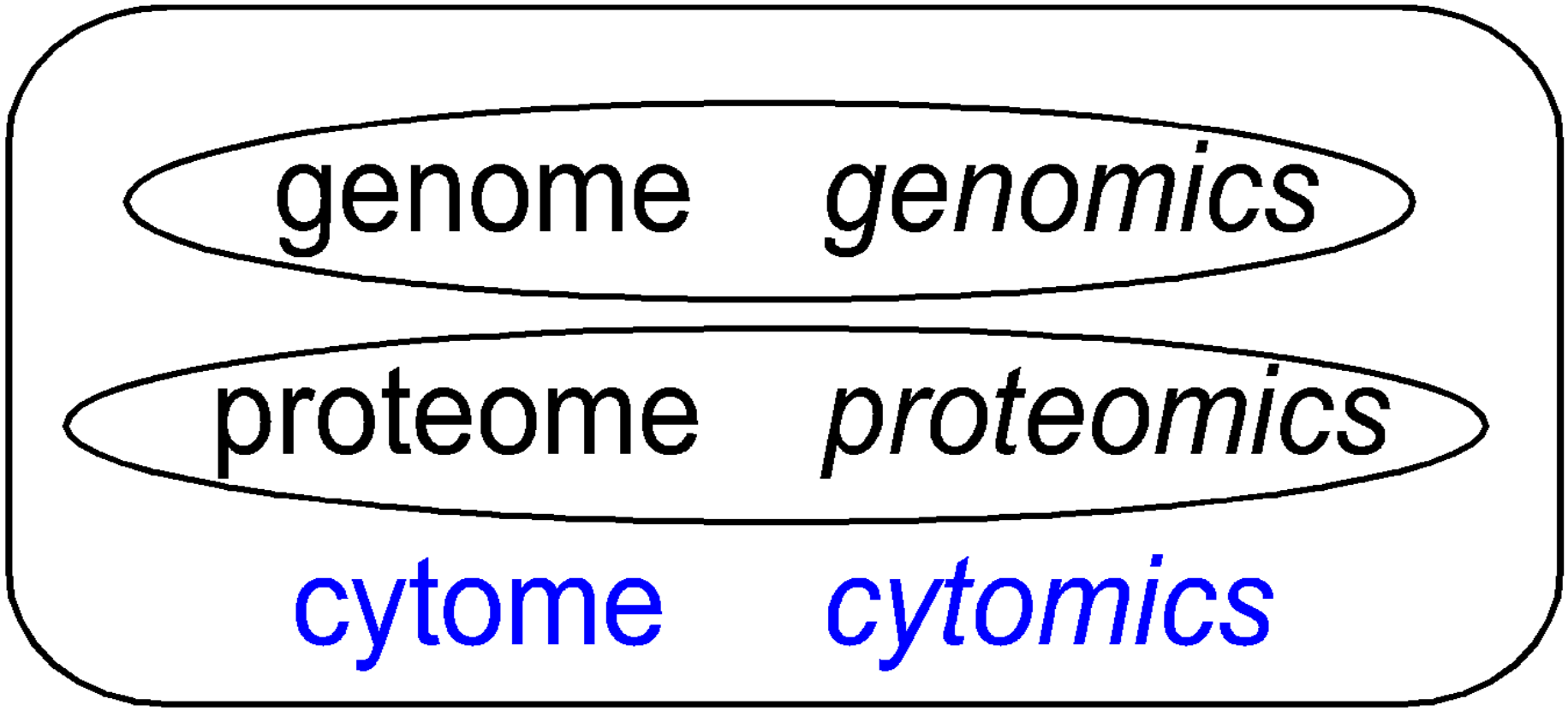
Categories



- cytome: cellular network (cell system, organ, organism)
- *cytomics:* study of molecular single cell phenotypes resulting from genotype and exposure in combination with exhaustive bioinformatic knowledge extraction

Courtesy of Gunter Valet

A Human Cytome Project

- Definitions
- Introduction and rationale
- Research concepts
- Proposal of a strategy
  - Milestones and targets
  - Data evaluation strategies
  - Technology
- Round table discussion
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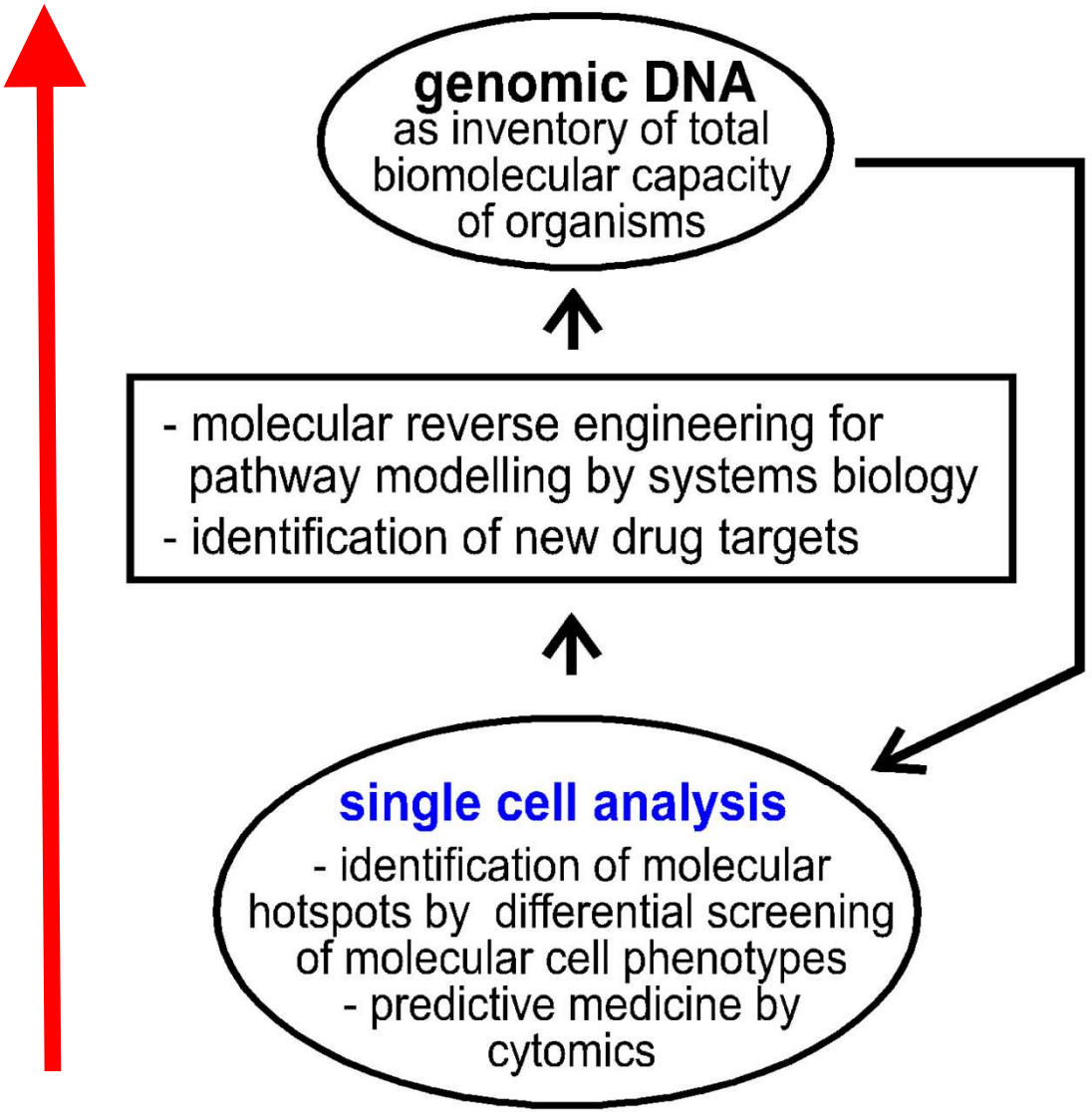
Human Cytome Project



cells as elementary units

Courtesy of Gunter Valet

Human Cytome Project
proposed milestones: medicine

- leukemia/lymphomas: stem cell transplantation versus chemo-therapy
- rheumatoid diseases: early identification of high and low therapy requiring patients
- allergies: detection of predisease sensitization for asthma, neurodermitis, ekzema a.o. in risk families for early preventive therapy
- infections: prediction of infection and disease course in newborn, intensive care and elderly patients to apply early preventive therapies

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Human Cytome Project
proposed milestones: cytome characterization

- stem cell differentiation & cell cycle:	relationally standarized description of differentiation and cell cylce phases
- cell proteomics:	molecular topology of intracellular proteins
- cell organelles:	systematics of molecular organelle function
- drug target identification:	retrograde pathway modelling of molecular hotspots

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Predictive Medicine by Cytomics

= therapy dependent individualized
disease course prediction

1. diseases represent molecular changes in cellular systems or organisms (cytomes)
2. cytomics: study of molecular cell phenotypes in combination with exhaustive bioinformatic know-ledge extraction
3. cell phenotypes result from genotype and exposure
4. goal: individualized predictions >95% correct

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Data Evaluation Strategies

wanted: individualized predictions

typical: group oriented predictions like:

- smoking increases risk for lung cancer
- food quality and lifestyle increase average weight
- *problem:* no individualized predictions for lung cancer or overweight emerge from group oriented data evaluation

VAL

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Data Evaluation Strategies

individualized predictions (non parametric)

- exhaustive information collection and knowledge extraction by data pattern classification (data sieving)

group oriented predictions (parametric)

- statistical
- cluster
- multivariate
- principal component
- fuzzy logic
- neural network

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Data Pattern Classification

features:

- accuracy for correct predictions and diagnosis
- multiplicity to account for the many combinatorial possibilities of genotype and exposure influences on cellular phenotypes

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Principle of Data Pattern Classification

a.) disease classification masks
(schematic 10 param.)

	disease course prediction
0 0 0 0 0 0 0 0 0 0	stationary
+ + + + + + + + + +	improvement
− − − − − − − − − −	deterioration

b.) ***high accuracy*** at low risk of random coincidence between patient and disease classification masks:

0.0017% $(1/3^{10})$ probability for random coincidence with 10 parameter masks and

0.046% $(1/3^{7})$ for random coincidence with parameter masks

c.) patient classification masks
(some examples)

	disease course prediction
0 − 0 0 0 + 0 0 − 0	stationary
0 0 + 0 0 + 0 − 0 0	stationary
− 0 0 0 + 0 − 0 0 0	stationary
+ + + 0 0 0 0 0 0 0	stationary
− 0 − 0 0 0 0 0 − 0	stationary
• • •	...

d.) ***high multiplicity*** of patient classification at correct prediction in case partial coincidence like 7 out of 10 parameters:

$$\frac{10! * 2^3}{7! * 3!}$$ = 960 possible patient classification masks as potential result of genotype and exposure influences

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Exploring the Human Cytome Technology

- Advanced microscopy techniques:
  - Confocal and laser scanning microscopy,, spectral imaging, fluorescence resonance energy transfer (FRET), digital microscopy, …
- High Content Screening:
  - High speed and large volume screening, …
- Flow Cytometry
  - Fast imaging in flow, …
- Biomolecular analysis techniques:
  - Single-cell polymerase chain reaction (PCR), labelling of biomolecules by quantum dots, …
- Bioinformatics:
  - Data exploration, statistics and data management, …

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Round table Discussion

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Conclusion

A Human Cytome Project ?

Monday 01 December 2003 at 10:57:46
bionet.cellbiol newsgroup

Hi,

I was wondering if there is already something going on to set up a sort of "Human Cytome Project" ?
In my opinion the hardware and most of the software seems to be available to set up such a project ?
For the cellular level, light-microscopy based reader technology would be very interesting to use ?

Studying and mapping the genome, transcriptome and proteome at the organizational level of the cell for various cell types and organ models could provide us with a lot of information of what actually goes on in organisms in the spatio-spectro-temporal space ?

I have been thinking (working) about a concept which could provide the basic framework for exploring and managing this cellular level of biological organization research on a large scale, but I would like to know if there is already some thought/work going on in the direction of setting up an initiative such as a "Human Cytome Project" ?

This is just an idea, so I am really interested to hear if there is something in it, or even if it is not worth while what I just wrote.

Best regards,

Peter Van Osta.

References

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  P. Van Osta

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