

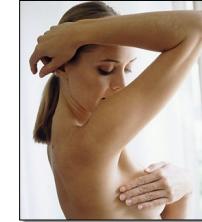
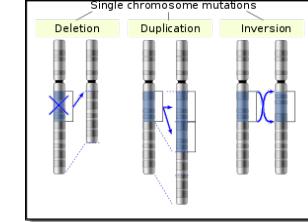
BIOINFORMATICS

A Computer Science approach to understanding LIFE from the DNA point of view

Programming Life 2014
Marcel Reinders
May 9, 2014

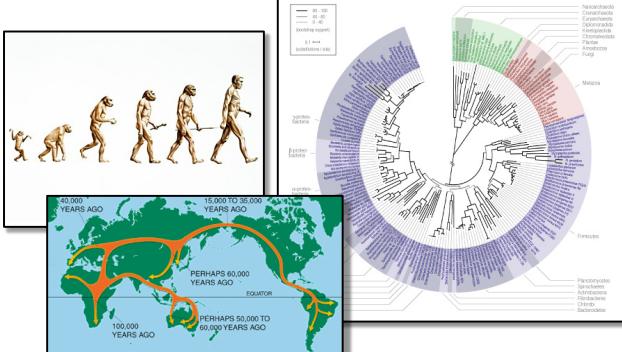
 1

Understanding diseases

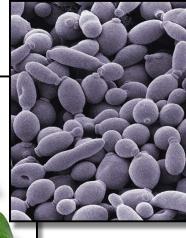
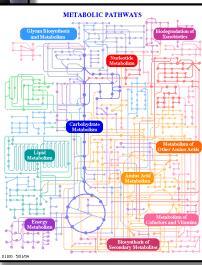
 2

Understanding Evolution



 3

Improving the environment by understanding cells

 4

Measuring molecules in the cell

Microarray mRNA

Immunoprecipitation interactions

cristallography protein structure

Massa-spectrometry proteins & metabolites

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Bioinformatics: Organize and interpret the data

MEDICINE

FOOD

INSIGHT

INDUSTRIAL FERMENTATION

THERAPY

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Bioinformatics: Marriage of disciplines

BIOLOGY

CHEMISTRY

MATHEMATICS

COMPUTER SCIENCE

ENGINEERING

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Bioinformatics – Oxford English Dictionary

(Molecular) bio – *informatics*: bioinformatics is conceptualising biology in terms of molecules (in the sense of physical chemistry) and applying "*informatics techniques*" (derived from disciplines such as applied maths, computer science and statistics) to understand and organise the *information* associated with these molecules, on a large scale. In short, bioinformatics is a management information system for molecular biology and has many practical applications.

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Bioinformatics - Wikipedia

Bioinformatics is the application of computer science and information technology to the field of biology and medicine. Bioinformatics deals with **algorithms, databases and information systems, web technologies, artificial intelligence and soft computing, information and computation theory, software engineering, data mining, image processing, modeling and simulation, signal processing, discrete mathematics, control and system theory, circuit theory, and statistics**, for generating new knowledge of biology and medicine, and improving & discovering new models of computation (e.g. DNA computing, neural computing, evolutionary computing, immuno-computing, swarm-computing, cellular-computing).



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Delft Bioinformatics Lab

The Delft Bioinformatics Lab

Welcome

In the Delft Bioinformatics Lab (part of the Delft BioScience & Bioinformatics Cluster), we develop novel computer models and algorithms to further fundamental biological knowledge, apply these models and algorithms to advance the state-of-the-art in health care and industry, and teach students in these areas. To this end, we closely collaborate with researchers and educators in molecular and cell biology, medicine and biochemistry.

Research

- People
- Publications
- Highlights
- Software
- Events
- Calendar
- Contact

Education

- Courses
- BSc projects
- MSc projects
- Student meetings

User login

Username: Password:

Upcoming events

- Biobike: Erik vd Akker Bas vd Berg (1 hour) (Event)
- DBL colloquium: Kees Abrahams (5 hours) (Event)
- Biolet: Dick de Ridder (7 days) (Event)
- Biolet: Erdzhan Taskesen (21 days) (Event)

New publications

- Laboratory evolution of new lactate transporter genes in the yeast mutant of Saccharomyces cerevisiae and their application to the PDK2 alleles by whole-genome resequencing and transcriptome analysis

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Example projects

- Molecular classification
- Predicting protein complexes
- Metabolomics
- Protein engineering
- Expression atlases
- Gene network inference
- Next generation sequencing
- Clinical genetics
- Insertional mutagenesis
- Gene therapy



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Molecular classification

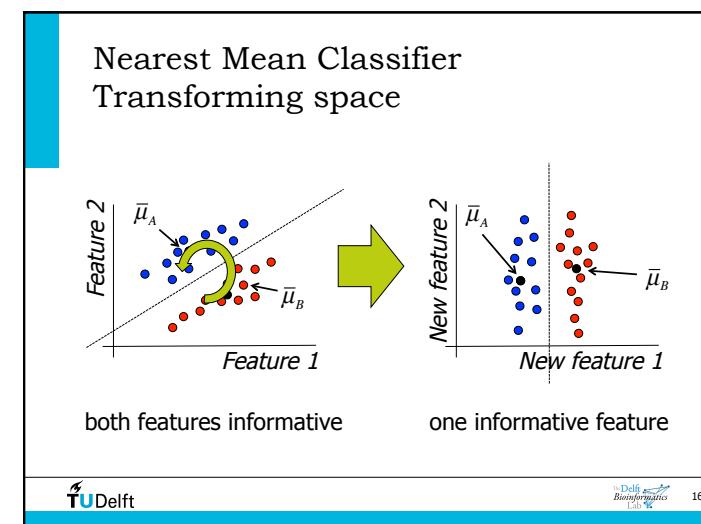
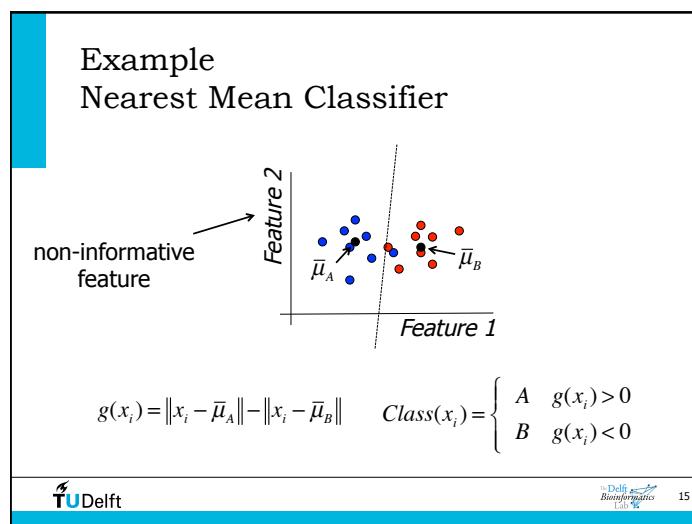
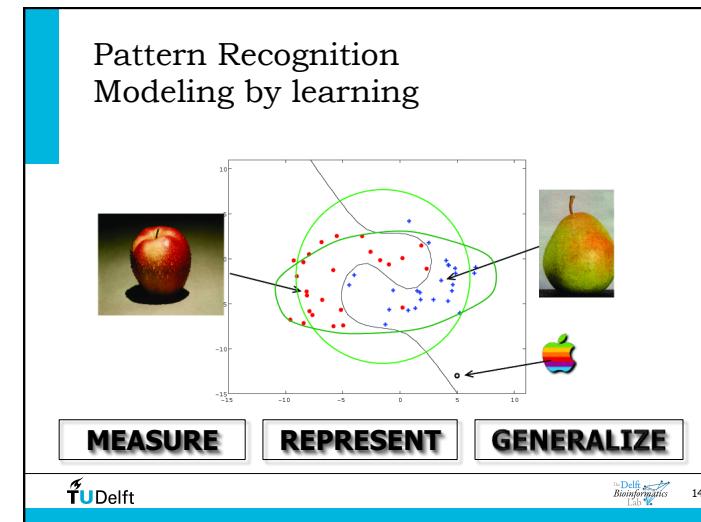
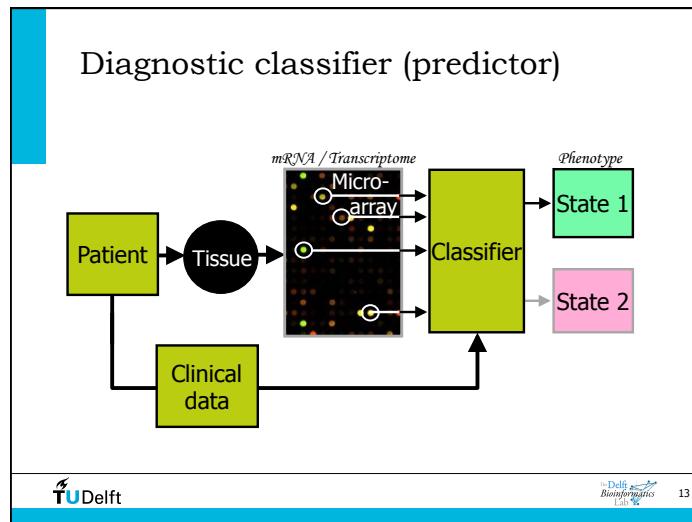
Predicting disease states using gene expressions

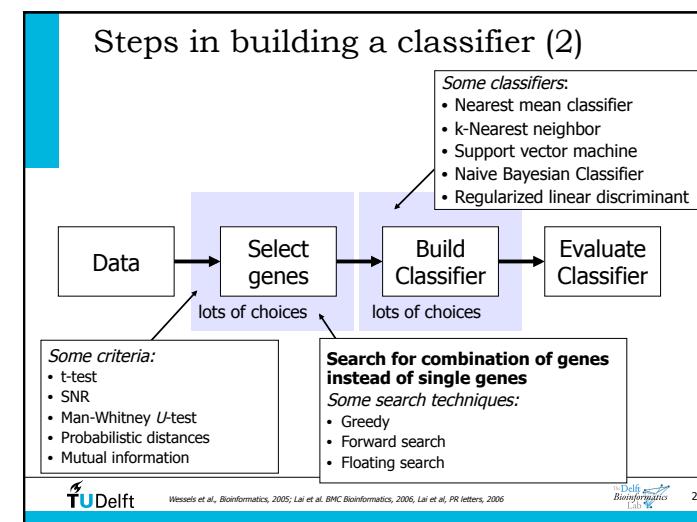
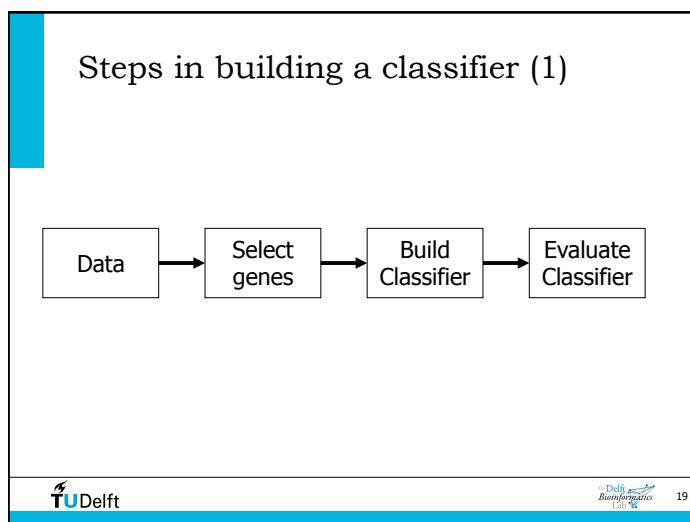
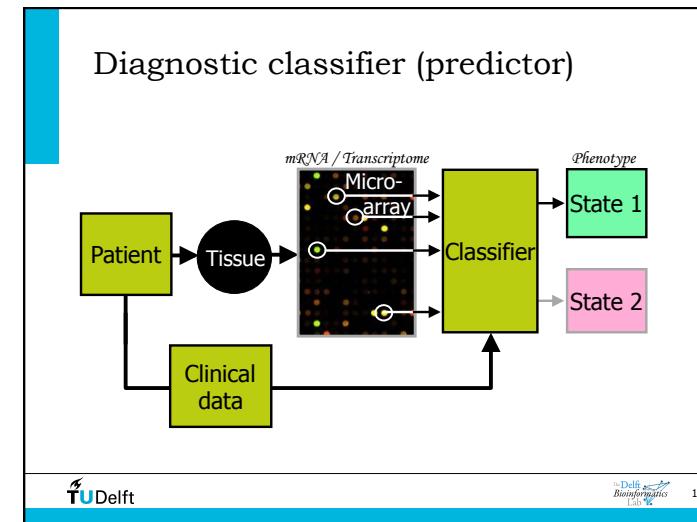
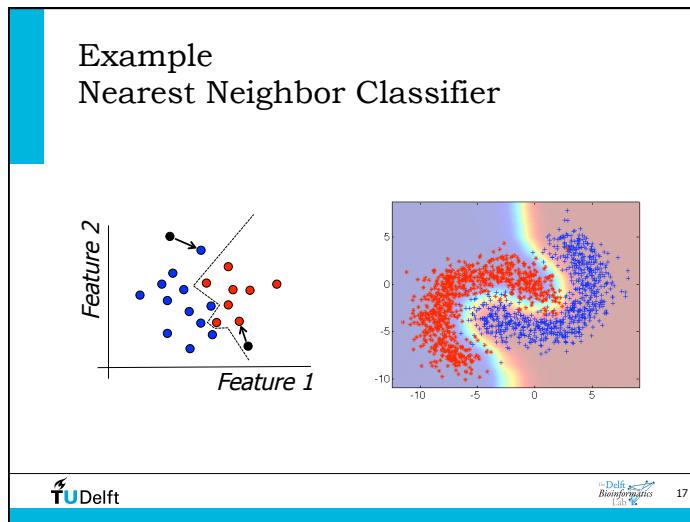
Carmen Lai, Martin van Vliet, Herman van Haagen, van den Akker, Lodewyk Wessels



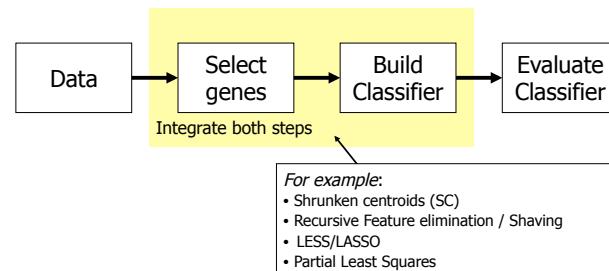
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Steps in building a classifier (3)

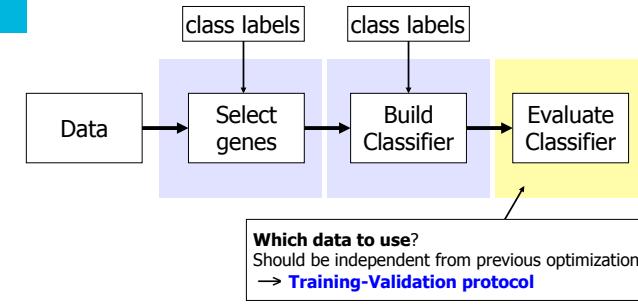


Wessels et al., Bioinformatics, 2005; Lai et al. BMC Bioinformatics, 2006; Lai et al. PR letters, 2006



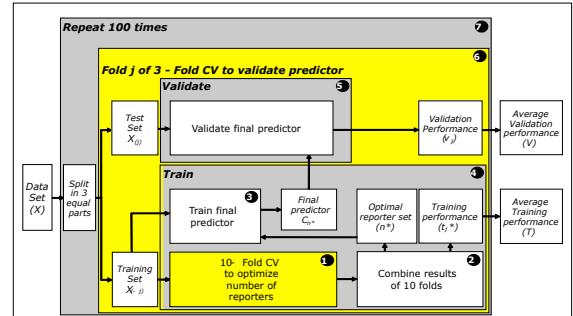
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Steps in building a classifier (4)

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Training-validation protocol “Double-loop cross-validation”



Wessels et al., Bioinformatics, 2005



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Comparing classifier strategies

Reporter Selection	Classifier	Breast cancer					Lung					Prostate					OVS				
		SC	PLS	INN	RFLD(0)	RFLD(1)	RFLD(10)	lnSVC	SC	PLS	INN	RFLD(0)	RFLD(1)	RFLD(10)	lnSVC	SC	PLS	INN	RFLD(0)	RFLD(1)	RFLD(10)
SC	0.0	0.0	1.9	0.7	4.6	0	0.05	4.6	0.0	0.0	0.0	3.5	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DLLC	2.3	0.8	1.6	0.8	1.6	1.1	3.35	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
SRGC	3.2	0.6	5.8	1	2.4	5	2.8	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
INN	2.6	8	2.8	0.8	5.8	4.6	3.7	8	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
RFLD(0)	3.0	2.6	1.2	1.2	2.6	2.6	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
RFLD(1)	3.1	0.6	3	0.5	2.4	2.4	3.05	4.1	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05
RFLD(10)	2.2	0.7	1.6	1.3	2.8	5	1.9	5	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
lnSVC	2.2	0.9	1.6	0	2.5	4.7	1.5	4.7	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
SC	2.3	6.8	3.2	1.5	3	3.7	3.1	6.8	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
DLLC	1.2	0.2	0.2	0.2	2.9	1.7	0.2	2.55	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
SRGC	2.9	5.3	1.1	3	2.02	3	4	3.2	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9
INN	2.6	8	1	1	13.1	13.9	7.1	11.25	13.9	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25
INN	11	12	1	13.1	13.9	7.1	11.25	13.9	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25
RFLD(0)	10.2	10	0.2	7.8	13.8	6.4	9	13.8	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2
RFLD(1)	10.4	12	0.3	8.3	12.1	6.6	9.35	12.1	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4
RFLD(10)	7.2	2.8	0.7	36.8	0	14.2	5	36.8	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
RFLD(0)	7.2	2.5	0.5	30.8	0	14.2	5	30.8	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
RFLD(1)	7.2	2.5	0.5	30.8	0	14.2	5	30.8	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
RFLD(10)	6.5	3.2	0.6	6.1	0.2	7.4	4.65	7.4	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
SC	1	1.7	0.7	1	4.3	0.3	0.05	4.3	1	1	1	1	1	1	1	1	1	1	1	1	1
lnSVC	3.1	6.2	1	5.3	1.2	1.2	2.15	6.2	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.1

Simple classifier + filtering strategy performs best

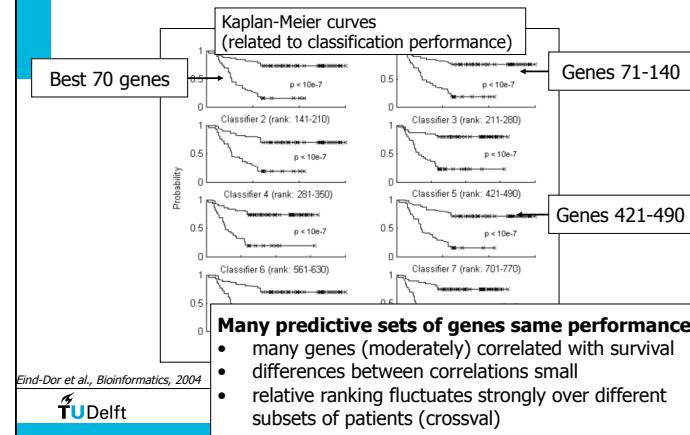


Wessels et al., Bioinformatics, 2005



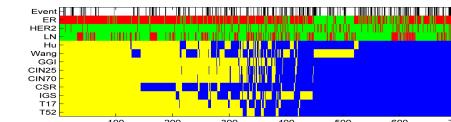
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But, we don't understand everything

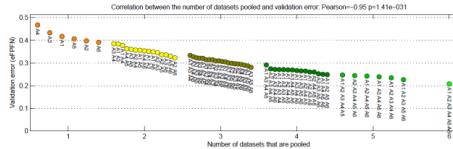


Cross platforms

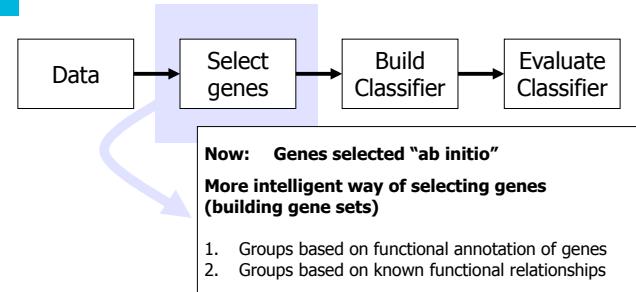
- Signature concordance is limited



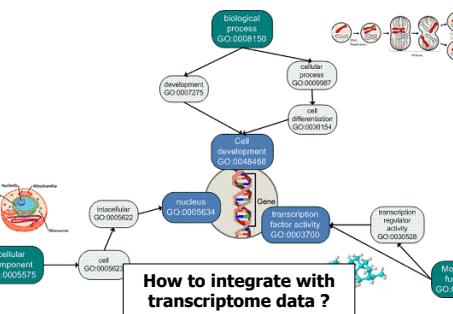
- Pooling datasets leads to better performance

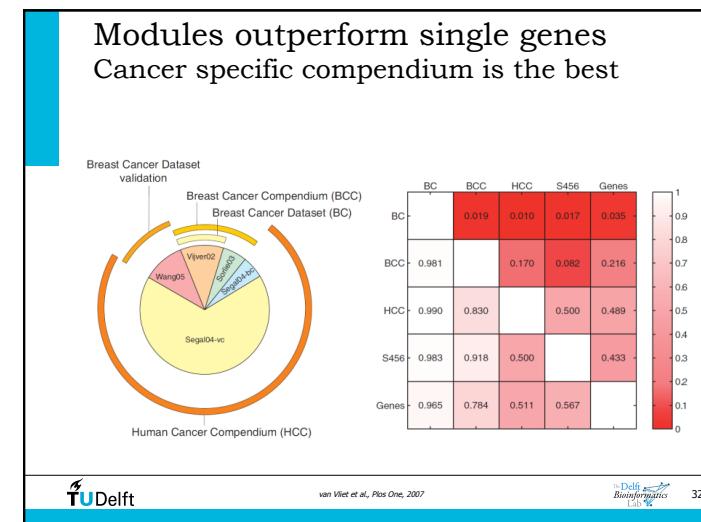
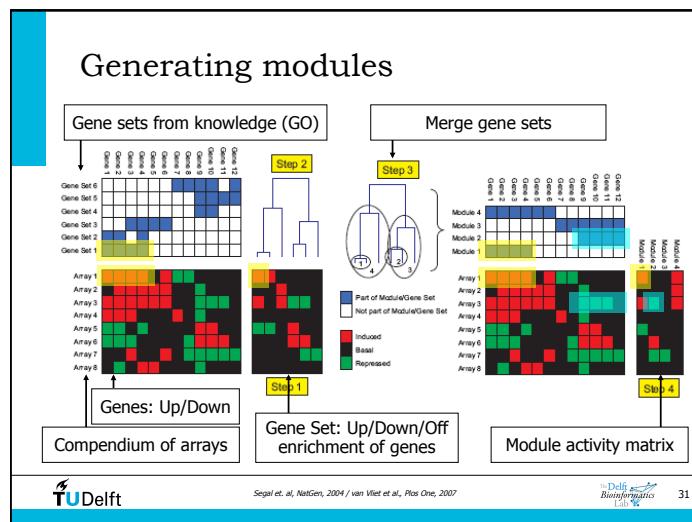
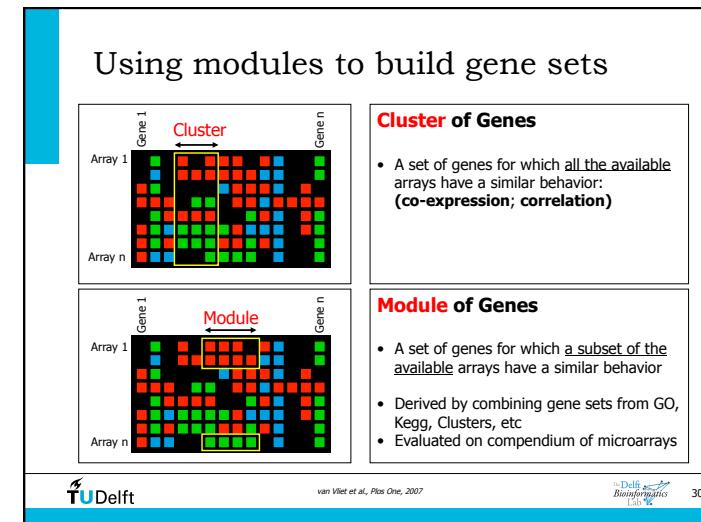
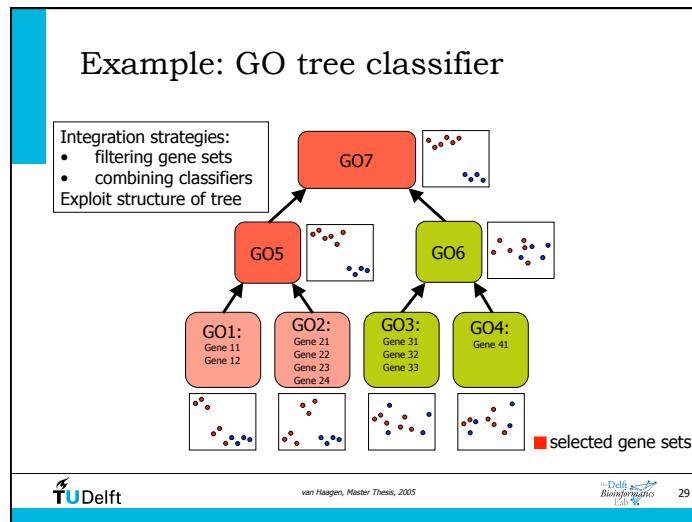


Steps in building a classifier (5)

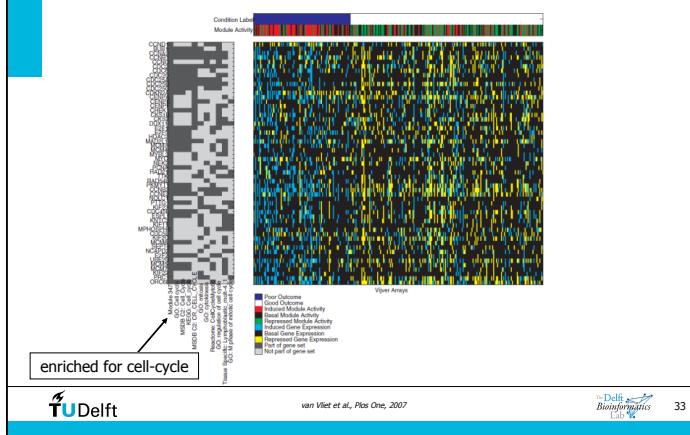


Gene Ontology Database (GO): Gene Annotations

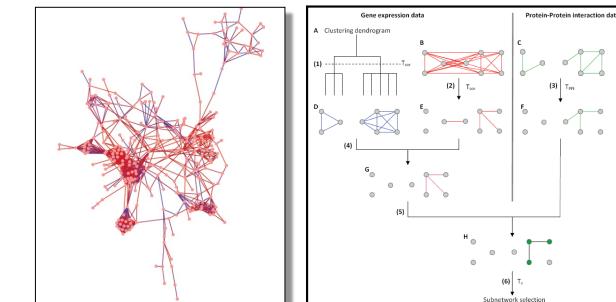




Modules improve interpretability

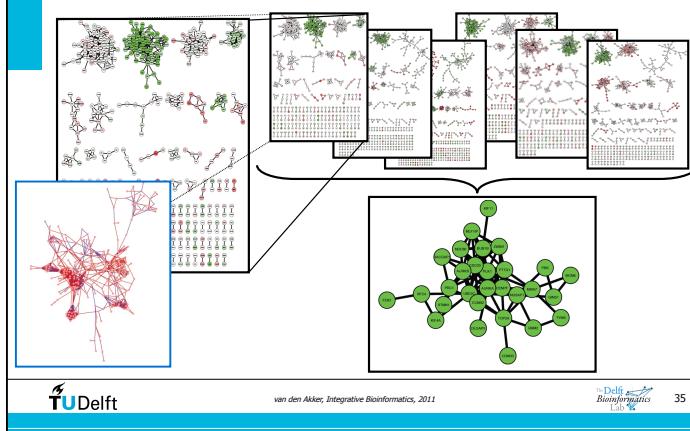


Protein interaction networks & expression correlation



 van den Akker, Integrative Bioinformatics, 2011  34

PPI & correlation modules give robust networks



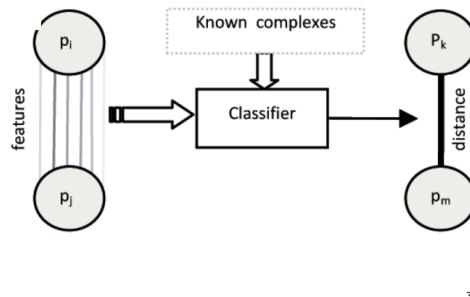
Predicting protein complexes

Integrating information

Van Berlo, Hulsman, de Ridder

The Delft Bioinformatics Lab

Predicting “interacting” proteins



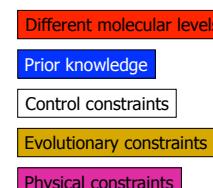
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Protein interaction

- Make use of large number of features (48 features):

- Gene expression correlation
- Experimental data (DIP)
- Reports of interaction in literature
- Shared annotation
- Gene co-regulation
- Gene co-evolution
- Interologs (interacting homologs)
- Gene co-location on genome



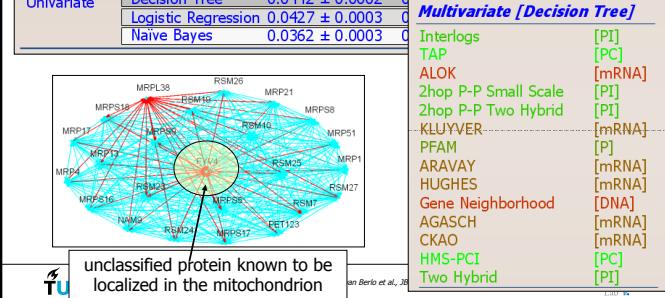
How to integrate the data?

- Common language needed:
 - p -values, integrated by (e.g.) Fisher's method
(Hwang et al., PNAS, 2005)
 - features, integrated by classifiers
(Qi et al., PROTEINS, 2006)
 - classifiers, integrated by ensemble methods
(Shen et al., Bioinformatics, 2006)
 - kernels, integrated by kernel combination
(Ben-Hur et al., Bioinformatics, 2005)



Feature-based integration

Rank Method	Classifier	Mean T (AUC_{FPP})	Mean V (AUC_{FSP})	k^*
Multivariate	Decision Tree	0.0445 ± 0.0012	0.0449 ± 0.0003	14
	Logistic Regression	0.0424 ± 0.0009	0.0424 ± 0.0004	19
	Naive Bayes	0.0400 ± 0.0007	0.0402 ± 0.0005	10
Univariate	Decision Tree	0.0442 ± 0.0002	0.0449 ± 0.0003	14
	Logistic Regression	0.0427 ± 0.0003	0.0427 ± 0.0004	19
	Naive Bayes	0.0362 ± 0.0003	0.0402 ± 0.0005	10



Kernel-based integration

- Kernels seem attractive to integrate the different data, as they allow us to use prior knowledge on **relations** in our data:

• Vector data	polynomial, RBF kernels
• Sequences	BLAST, spectrum, motif, alignment kernels
• Structured data	diffusion kernel
• Graphs	label sequence kernel, tree kernel
• Kernels	convolution, RBF kernels



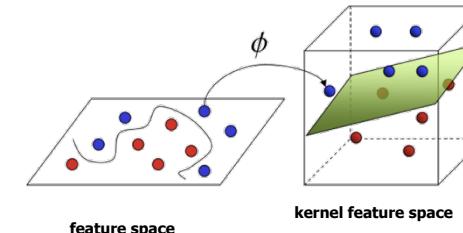
Hulsmans et al., TCBB, 2009



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Kernel-based classification

- Transform data points x_i to another space $\phi(x_i)$ in which data is linearly separable

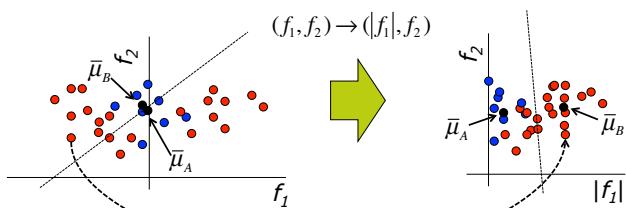


Sidestep: non-linear classification using kernels



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Example



Sidestep: non-linear classification using kernels



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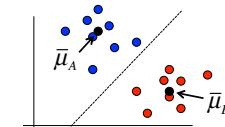
Nearest mean classifier

- Nearest mean classifier

$$g(x_i) = \|x_i - \bar{\mu}_A\| - \|x_i - \bar{\mu}_B\|$$

- Rewritten in inner products

$$\begin{aligned} g(x_i) &= (\langle \bar{\mu}_A, \bar{\mu}_A \rangle - 2\langle x_i, \bar{\mu}_A \rangle) - (\langle \bar{\mu}_B, \bar{\mu}_B \rangle - 2\langle x_i, \bar{\mu}_B \rangle) \\ g(x_i) &= \langle x_i, \bar{\mu}_B \rangle - \langle x_i, \bar{\mu}_A \rangle + b \end{aligned}$$



Changing b allows to create ROC curve ("prior" on classes)



Sidestep: non-linear classification using kernels



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Kernel-based Nearest mean classifier

- Transform x_i to another space $\phi(x_i)$

$$g(x_i) = \|\phi(x_i) - \phi(\bar{u}_A)\| - \|\phi(x_i) - \phi(\bar{u}_B)\|$$

- Rewritten in inner products

$$g(x_i) = \langle \phi(x_i), \phi(\bar{u}_B) \rangle - \langle \phi(x_i), \phi(\bar{u}_A) \rangle + b$$

- Kernel: Denotes inner product of transformed vectors

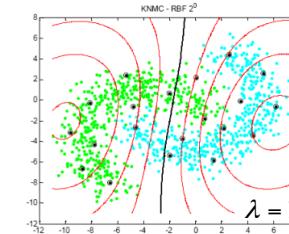
$$g(x_i) = K(x_i, \bar{u}_B) - K(x_i, \bar{u}_A) + b$$

- Don't need to specify $\phi(x_i)$, only $K(x_i, x_j)$



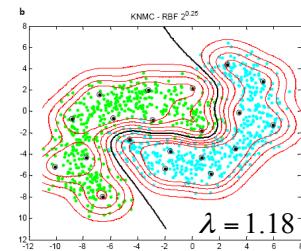
Kernel-based Nearest mean classifier

- Use a nonlinear kernel function $K(x_i, x_j) = e^{-\lambda d(x_i, x_j)}$
- Parameter λ regulates 'amount' of nonlinearity



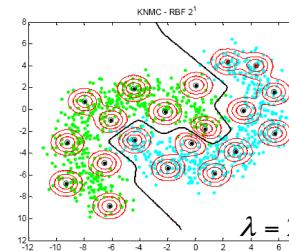
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Kernel-based Nearest mean classifier

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Kernel-based integration

- Kernels seem attractive to integrate the different data, as they allow us to use prior knowledge on **relations** in our data:

• Vector data	polynomial, RBF kernels
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• Structured data	diffusion kernel
• Graphs	label sequence kernel, tree kernel
• Kernels	convolution, RBF kernels



Hulsmann et al., TCBB, 2009



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Kernel combination

- Weighted combination [**LKC**]: $K_C = \sum_i w_i K_i$
- Gaussian RBF kernel applied on this combined kernel using distance in kernel space [**NKC**]:

$$K_G(x, y) = e^{-\frac{d(x, y)^2}{2\sigma^2}} = e^{-\sum_i \frac{w_i}{2\sigma^2} (K_i(x, x) + K_i(y, y) - 2K_i(x, y))}$$

- Weight optimization:
 - Equal weighting (reference) [EW]
 - Kernel Alignment [KA]: $\max \text{corr}(K_C, y y^\top)$ ($y \in \{-1, +1\}^m$)
 - Maximize SVM margin
 - Score optimality (classification performance: AUC) [PAUC]

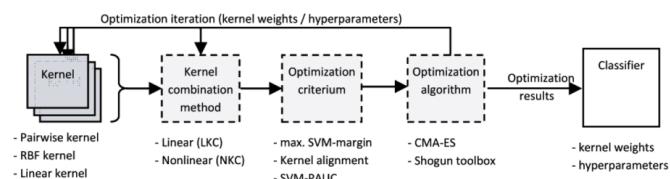


Hulsmann et al., TCBB, 2009



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Optimization scheme

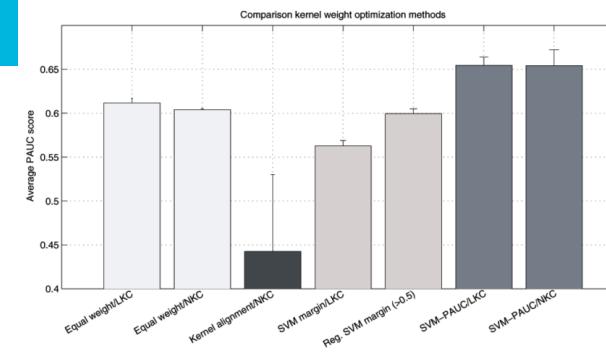


Hulsmann et al., TCBB, 2009



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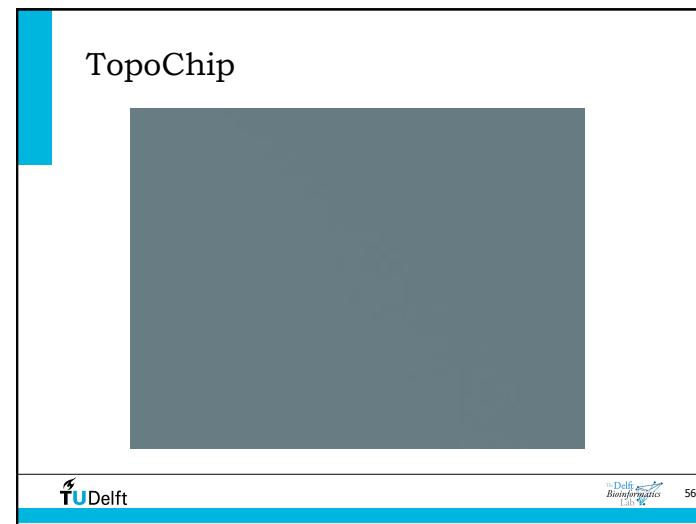
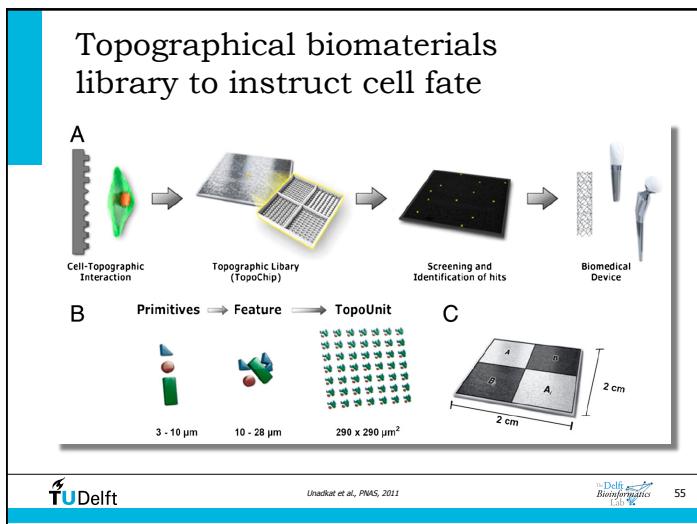
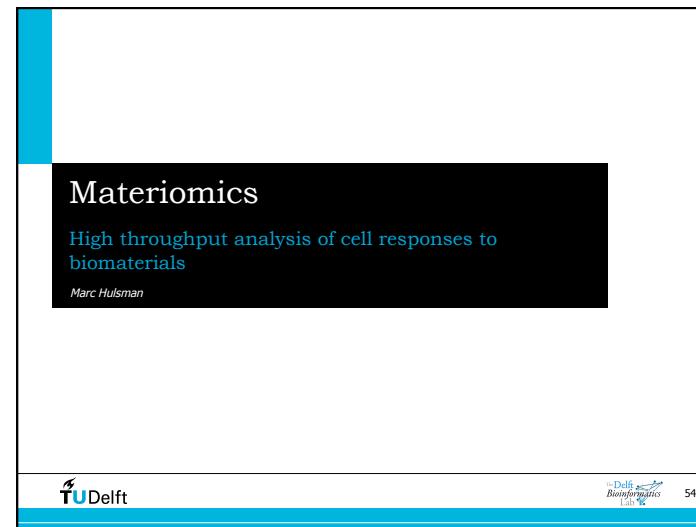
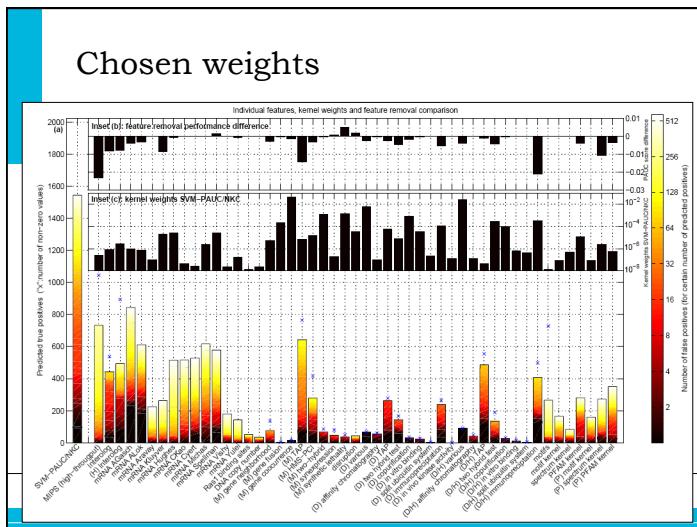
Test performance results

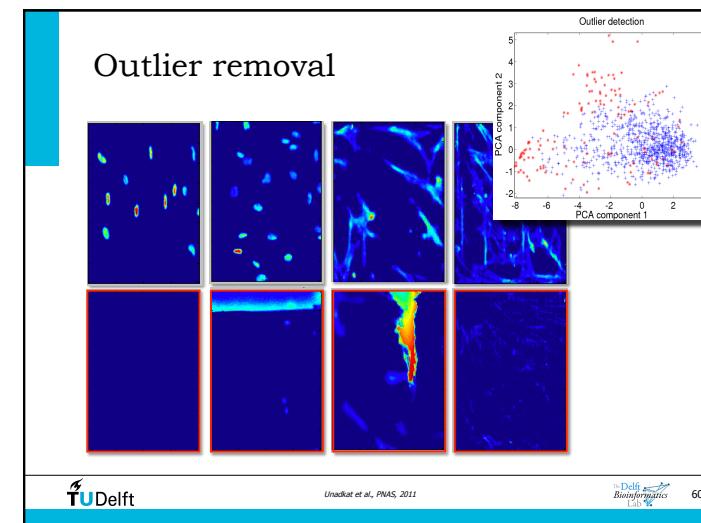
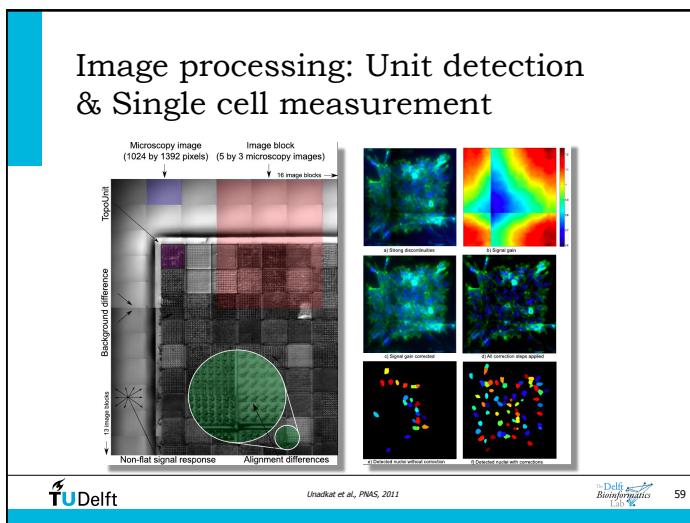
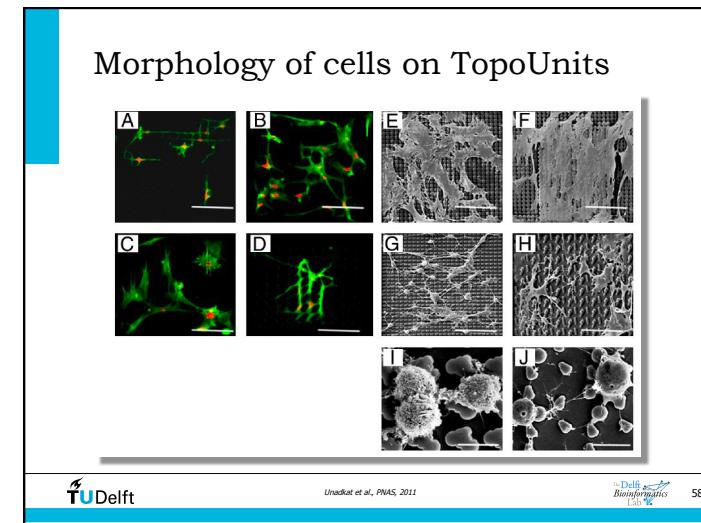
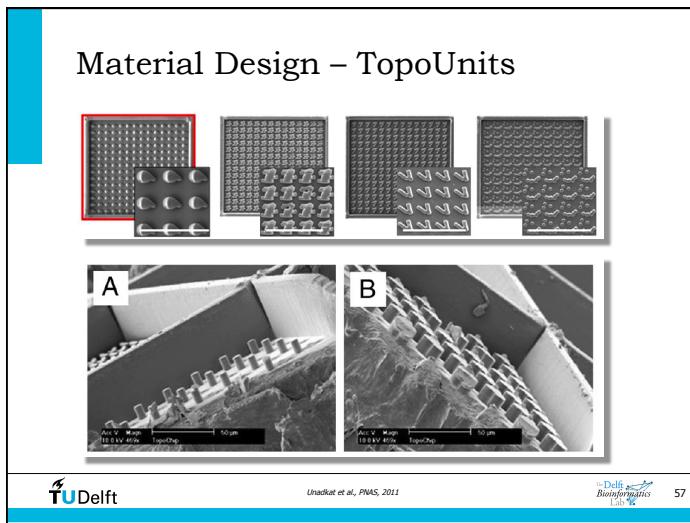


Hulsmann et al., TCBB, 2009

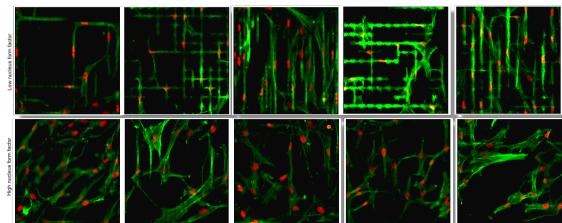


52





Optimize for nucleus form factor



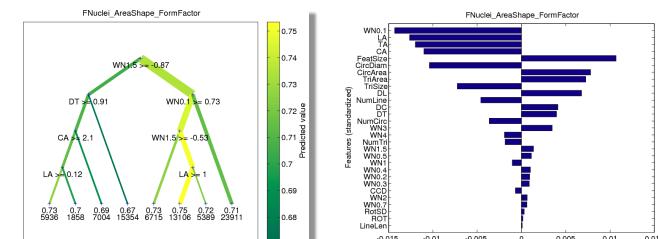
Top: 5 best ones
Bottom: 5 worst ones

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Unadkat et al. PNAS 201

The Delft
Rising Stars

Régress nucleus form factor by material properties

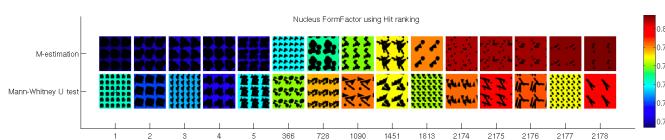


Gackat et al. RNA5S 3

The Delft
Piping Foundation

6

Rankings of TopoUnits



TU Delft

Unadkat et al. PNAS 201

The Delft
Bioinformatics

Protein engineering

Protein (re)design to improve protein secretion rate

Bastiaan van den Berg, Dick de Ridde

The Delft
Bioinformatics
Lab

6

Why optimize production/secretion?

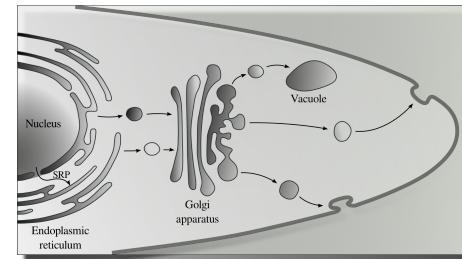
Aspergillus niger widely used for industrial enzyme production

enzymes →

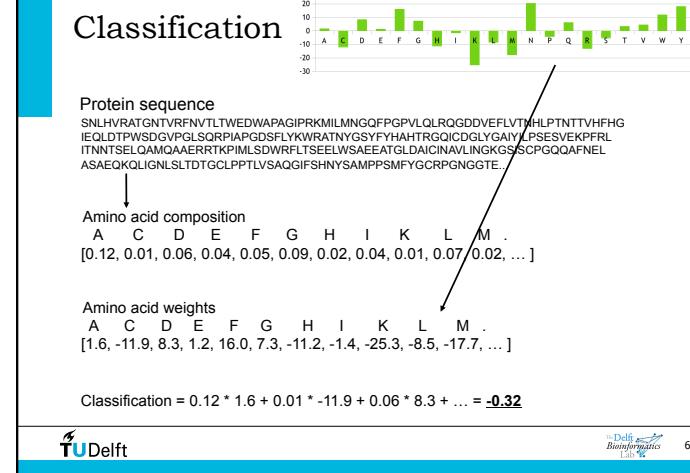
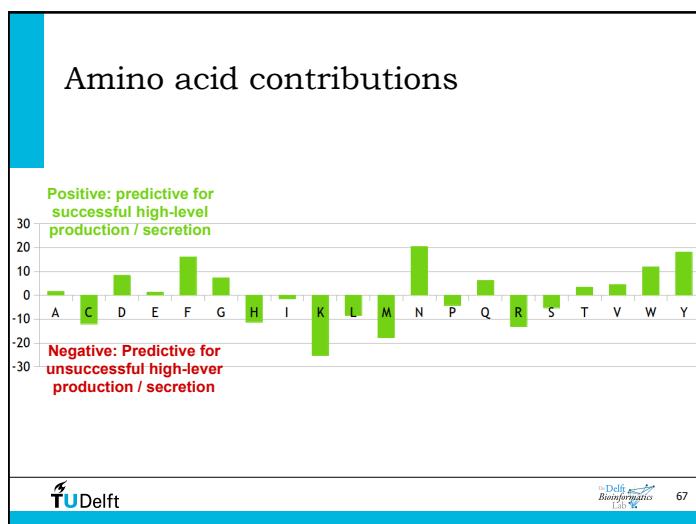
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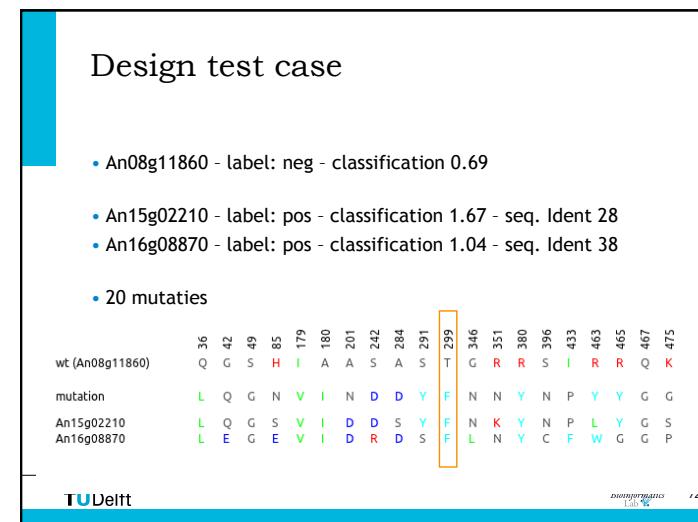
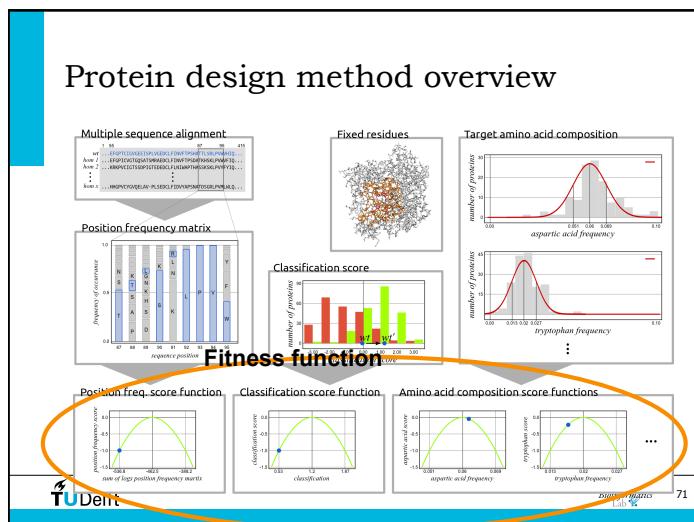
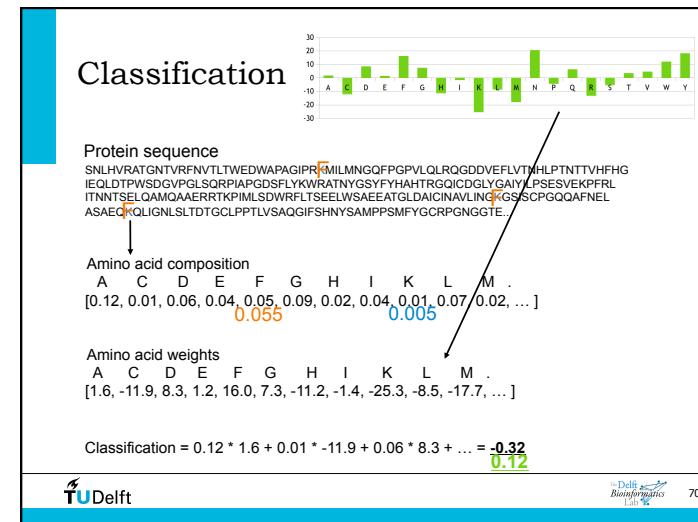
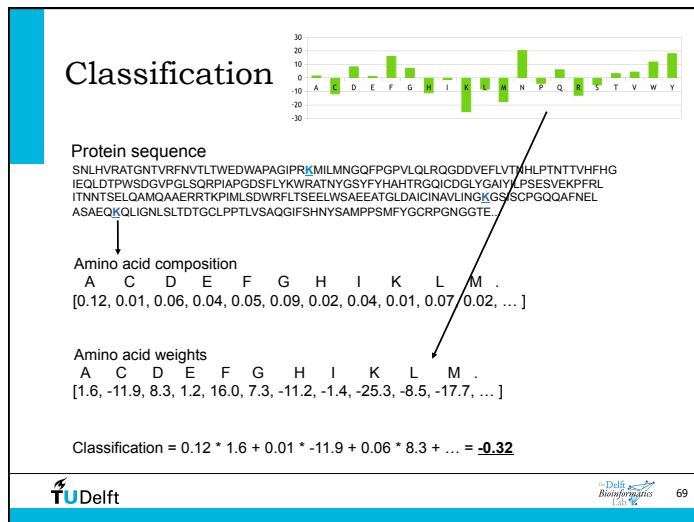
Protein secretion

N-terminal signal peptide targets protein to secretion pathway



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Design test case

Sequence logo showing positions 36 to 463. A box highlights position 299. Below the logo are two protein structure visualizations. The top one shows a red stick at position 299. The bottom one shows a green stick at position 299. A legend indicates: Red – wild-type position 299 T; Green – positive position 299 F; Blue – redesign position 299 F.

Red – wild-type position 299 T
Green – positive position 299 F
Blue – redesign position 299 F

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Expression atlases

Linking Gene Expressions to Imaging Data in the Mammalian Brain

Ahmed Mahfouz, Sjoerd Huisman, Boudewijn Lelieveldt

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Measuring gene activity in brain
Allen Brain Atlas

The diagram shows a 3D brain model with a blue sphere indicating a specific region. Below it, a stack of grayscale images shows a brain section being analyzed. An inset shows a 50x magnification view of a brain slice with a small white square indicating a region of interest. This region is then shown at 400x magnification with red '+' symbols indicating active genes. The TU Delft Bioinformatics Lab logo is at the bottom right.

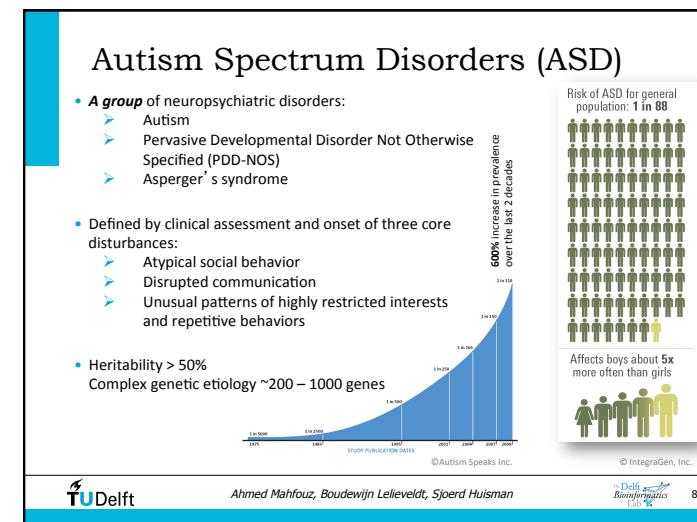
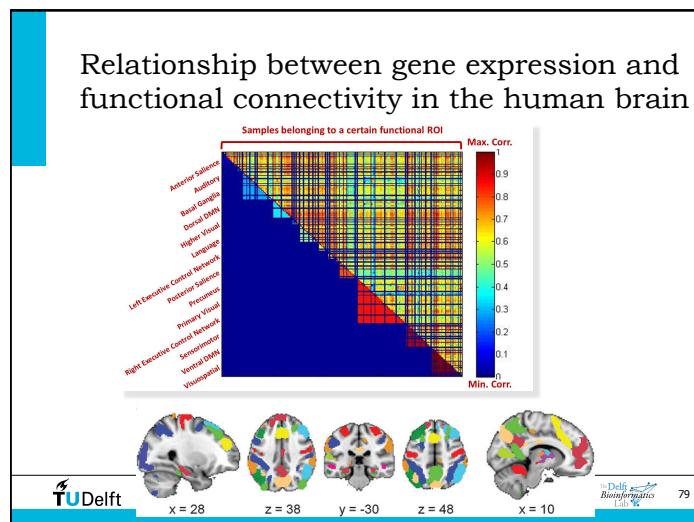
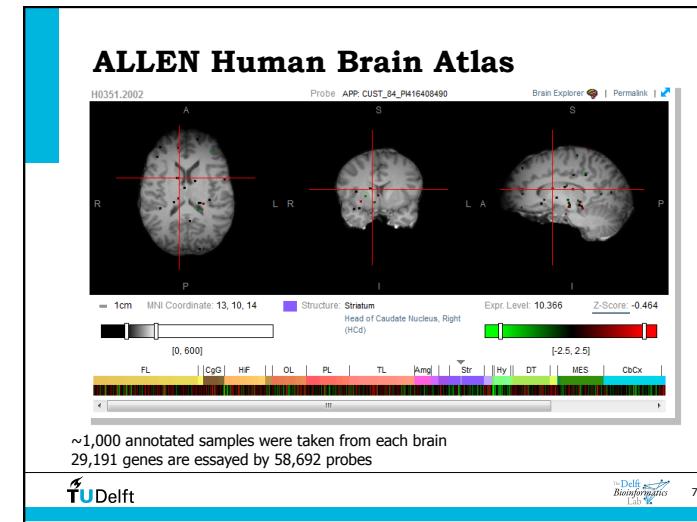
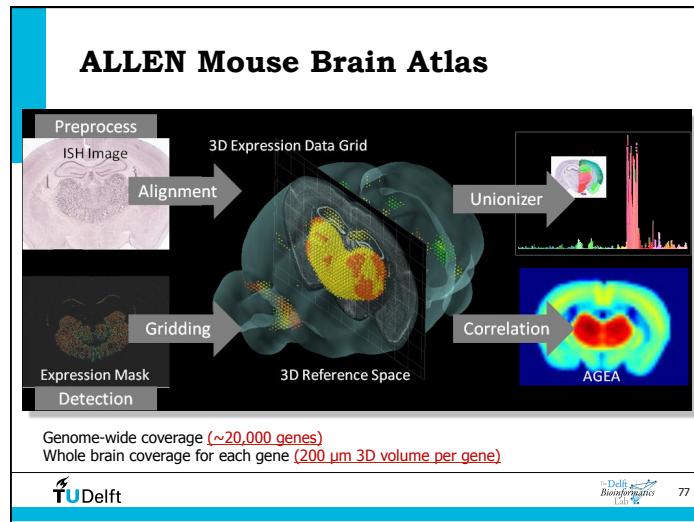
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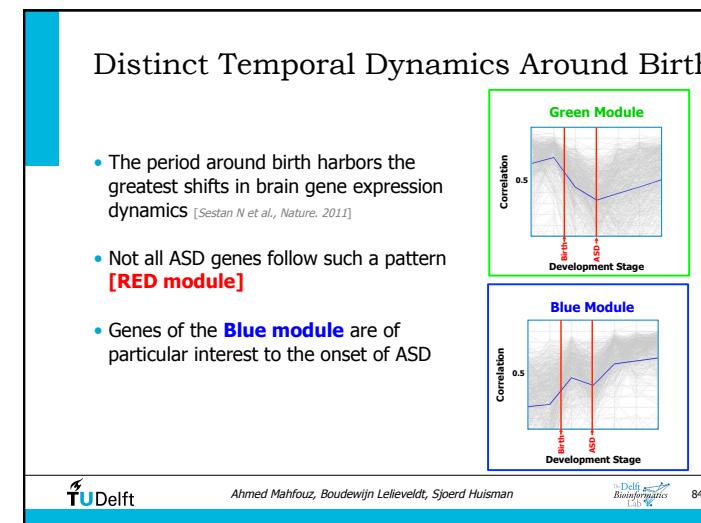
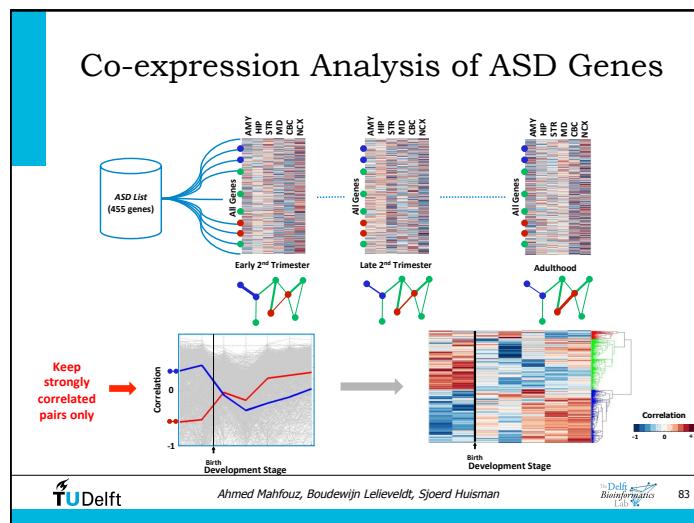
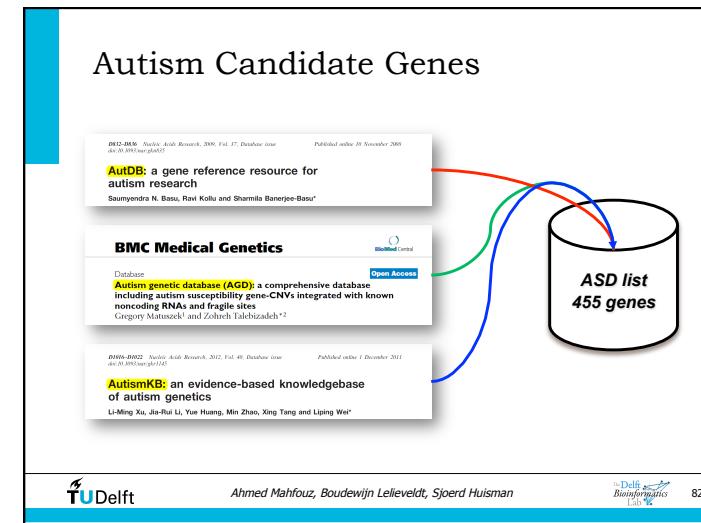
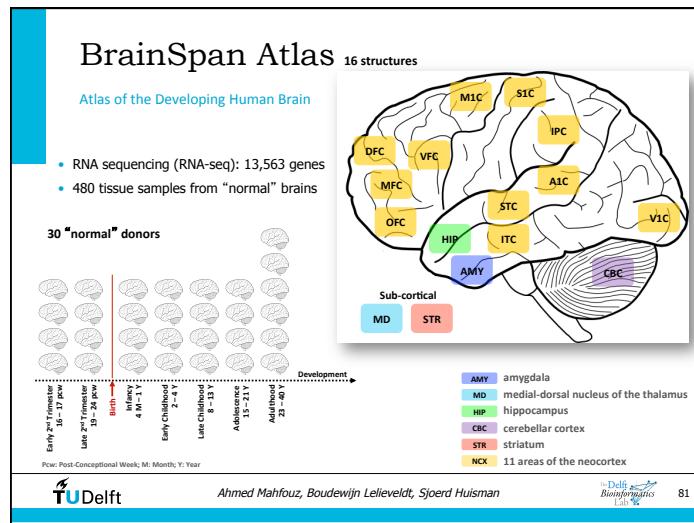
Ahmed Mahfouz, Boudewijn Lelieveldt, Sjoerd Huisman

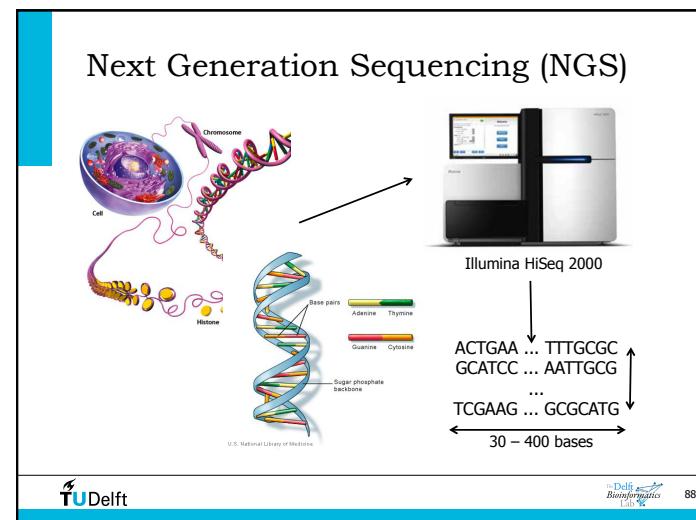
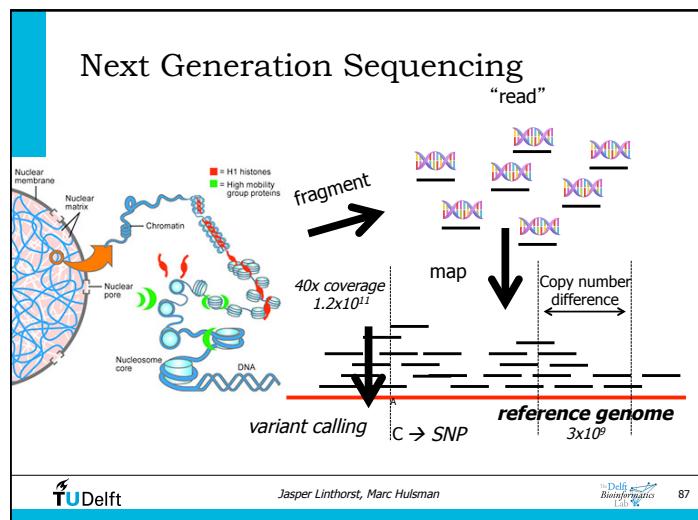
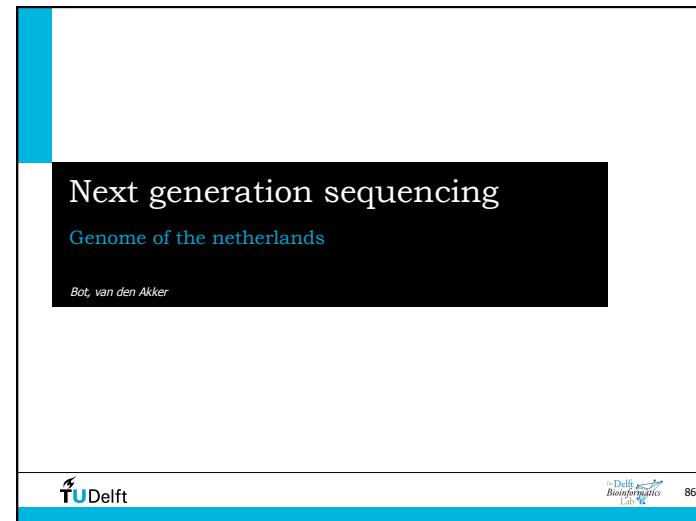
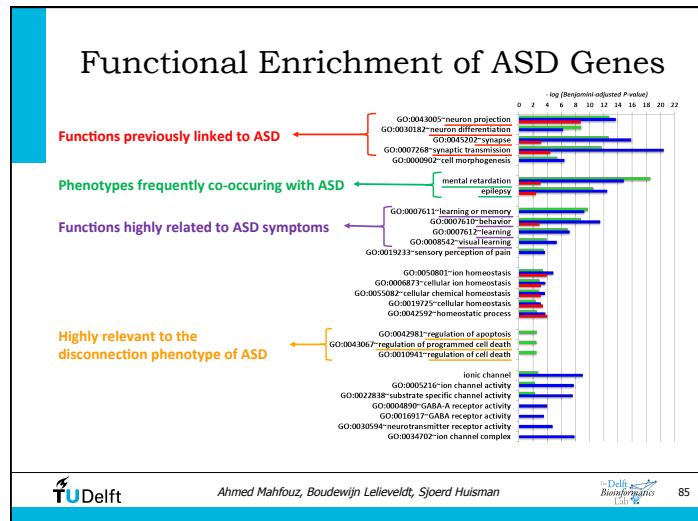
Gene expression atlases

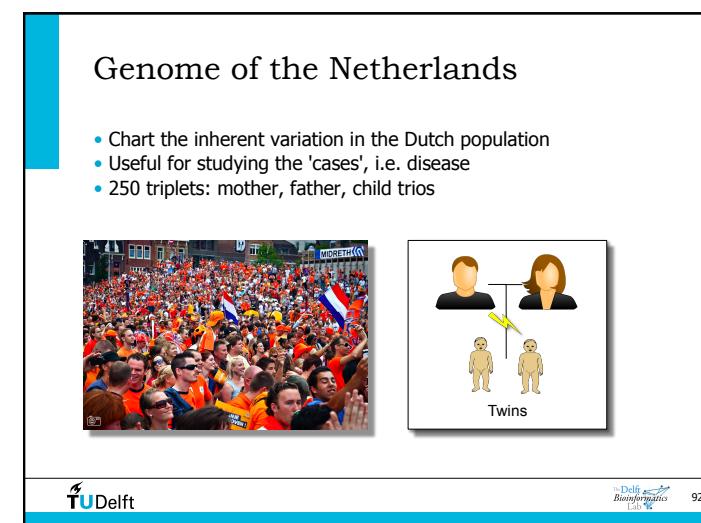
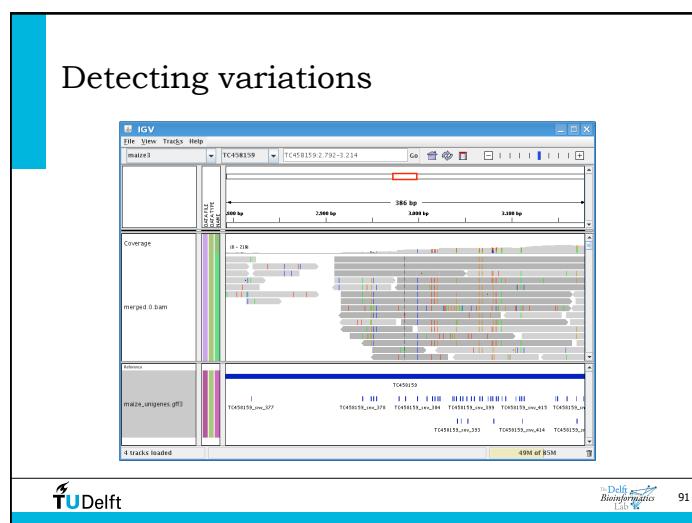
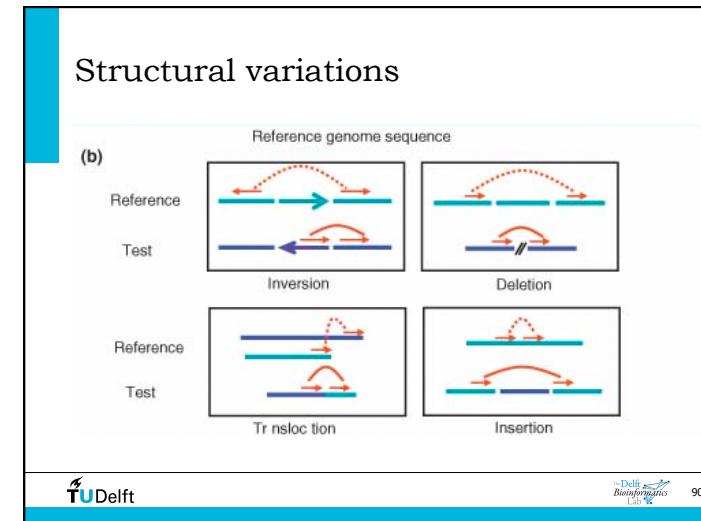
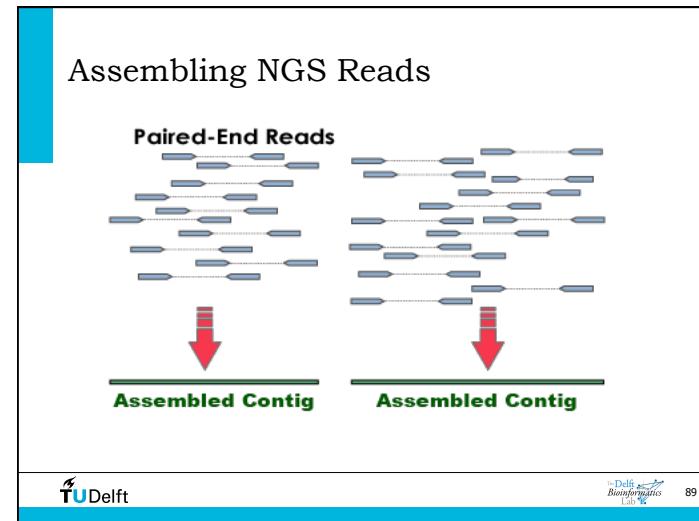
A grayscale brain section with colored dots representing gene expression levels. Red dots are concentrated in the central region, while green and blue dots are more widespread. The TU Delft Bioinformatics Lab logo is at the bottom right.

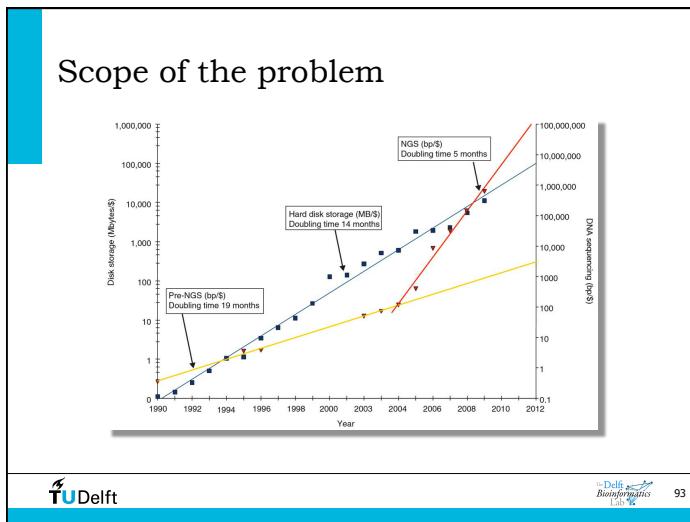
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The New York Times

Business Day

DNA Sequencing Caught in Deluge of Data

Published: November 30, 2011 (Page 2 of 2)

Randy Knorr for The New York Times
R. Richard McComie and Michael Schatz at Cold Spring data center.

Enlarge This Image

Straining under the load and facing budget constraints, federal officials talked earlier this year about shutting the archive, to the dismay of researchers. It will remain open, but certain big sequencing projects will now have to pay to store their data there.

If the problem is tough for human genomes, it is far worse for the field

MOST 1

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What's Popular

Drug Laws More Than Room for D

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BGI – Beijing Genomics Institute

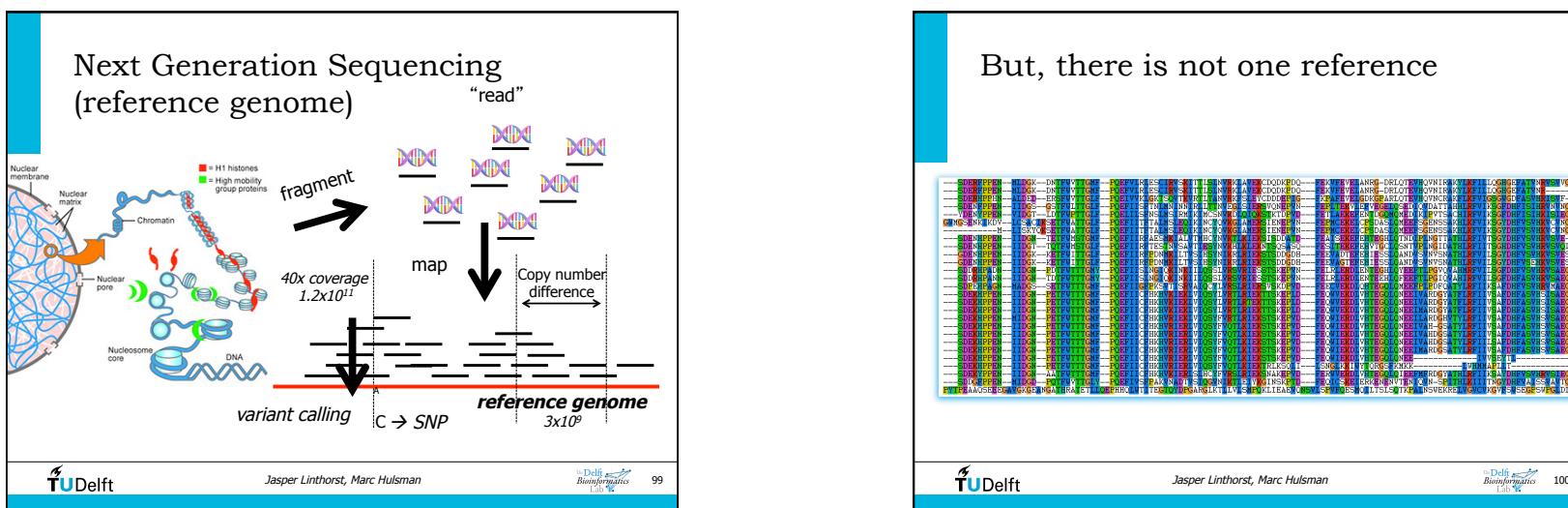
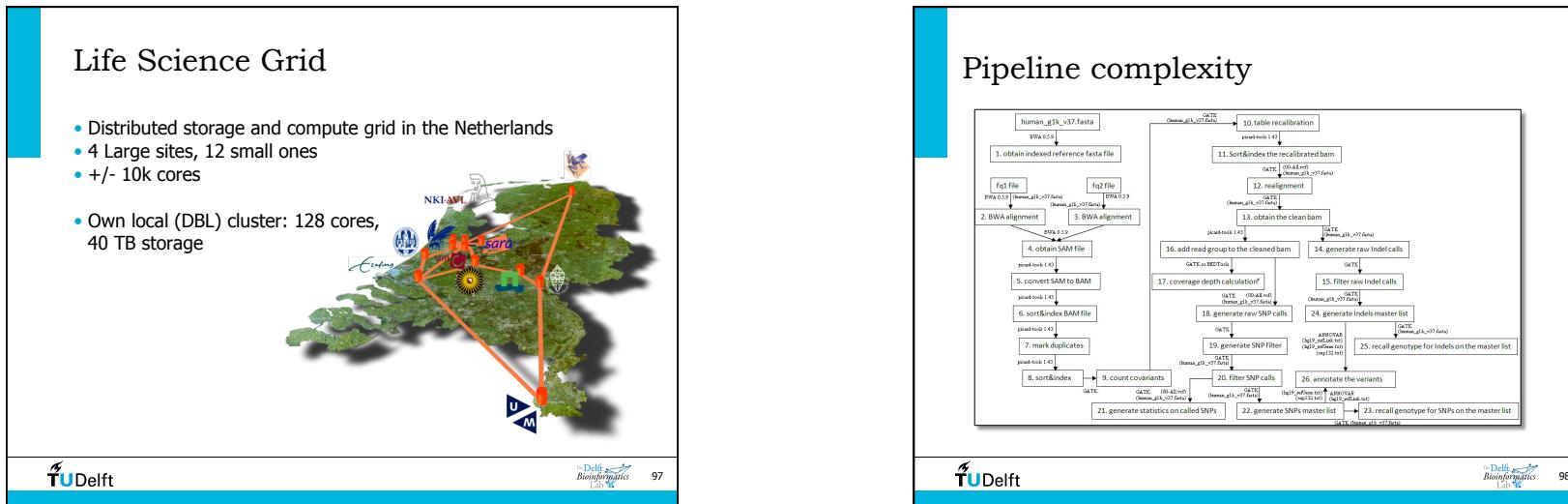
- Sequenced: Panda genome, rice genome, and many more
- 3M project: 1M people, 1M plants, 1M microorganisms

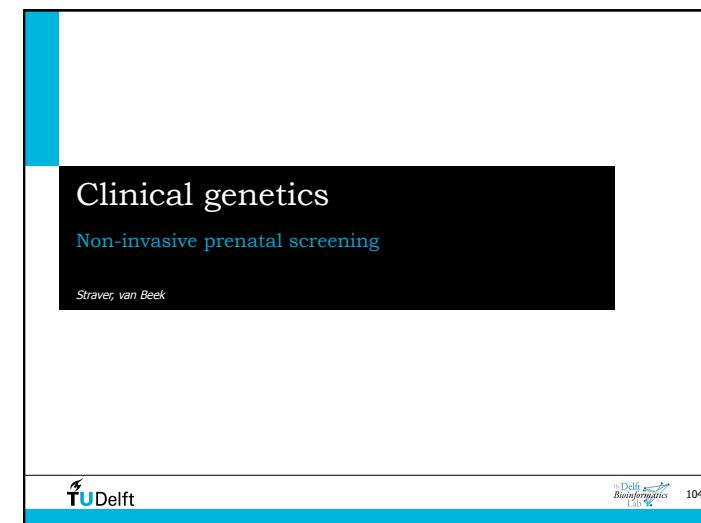
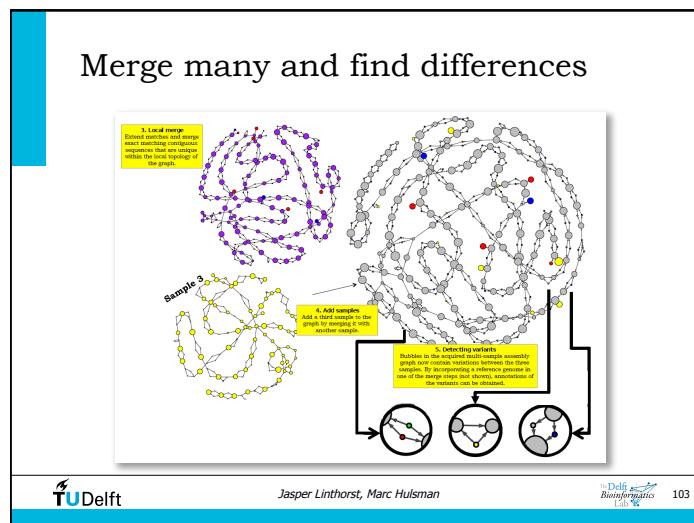
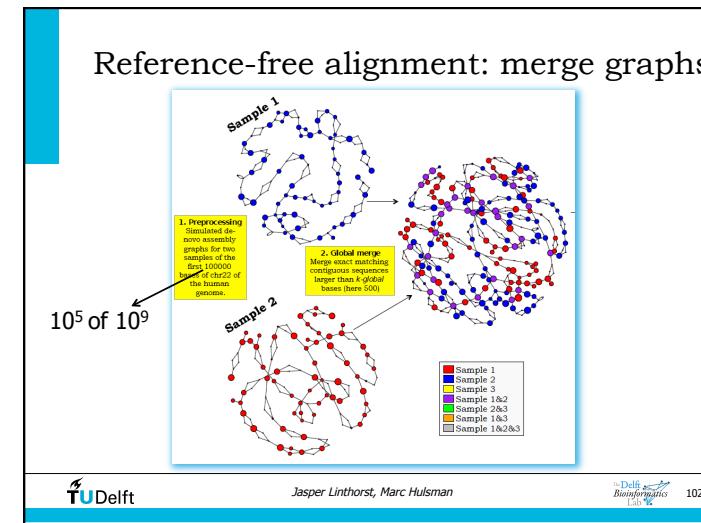
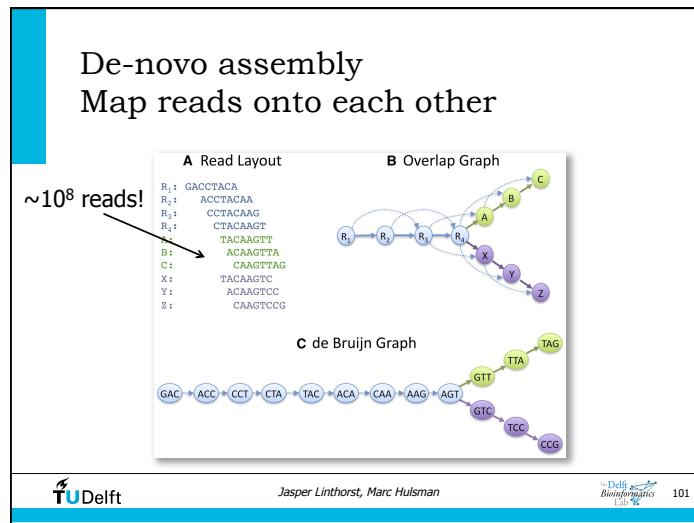
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Moving data

- Data now transported using hard disks
- Building a fiber-optic network between life science clusters
- <http://www.surfnet.nl/nl/thema/eyr/Pages/Default.aspx>

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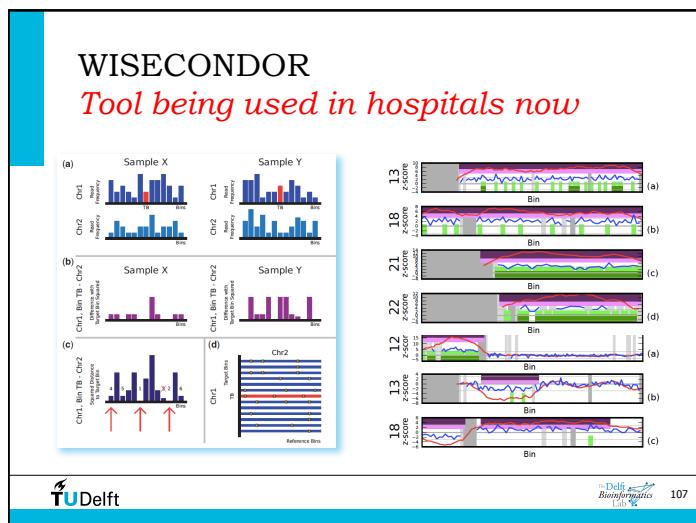
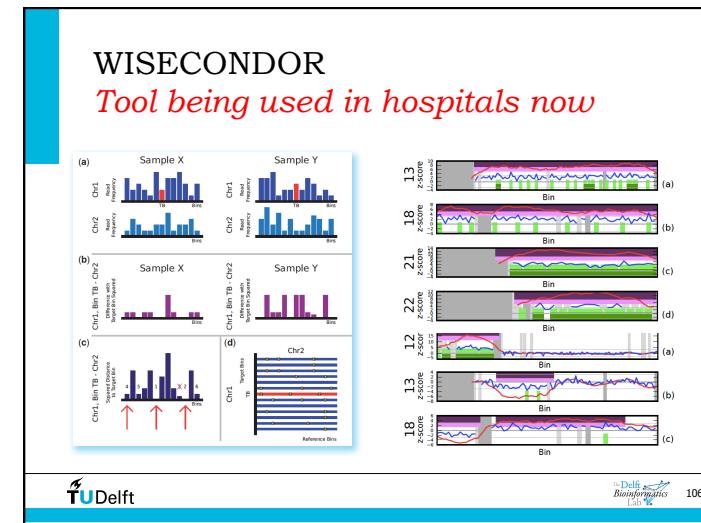


Non-Invasive Prenatal Diagnosis (NIPD)

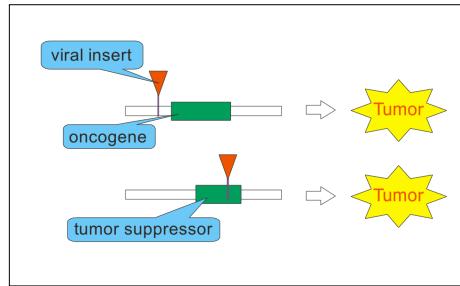
Cell Free DNA from the mother and fetus flow together in the maternal bloodstream.

Harmony PRENATAL TEST™

TU Delft Bioinformatics Lab 105



Discovering genes involved in tumour development (1)

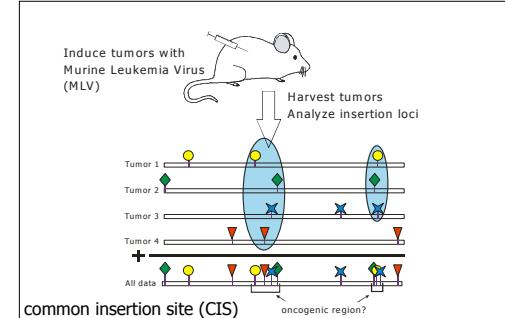


Uren et al., Cell, 2008 ; de Ridder et al., Plos Comp. Bio. 2006; de Ridder et al., Bioinformatics 2007



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Discovering genes involved in tumour development (2)

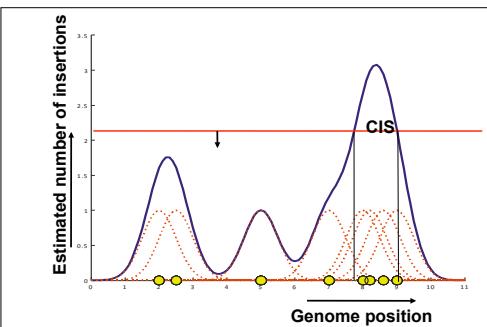


Uren et al., Cell, 2008 ; de Ridder et al., Plos Comp. Bio. 2006; de Ridder et al., Bioinformatics 2007



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Find CIS's by Gaussian Kernel Convolution

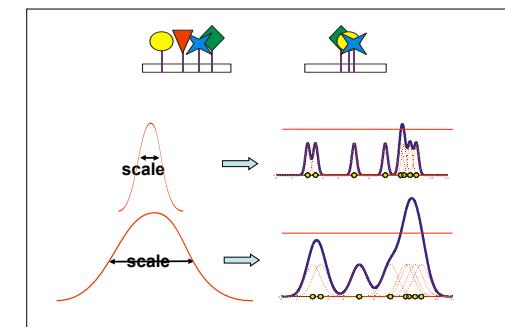


Uren et al., Cell, 2008 ; de Ridder et al., Plos Comp. Bio. 2006; de Ridder et al., Bioinformatics 2007



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Different kernels different scales

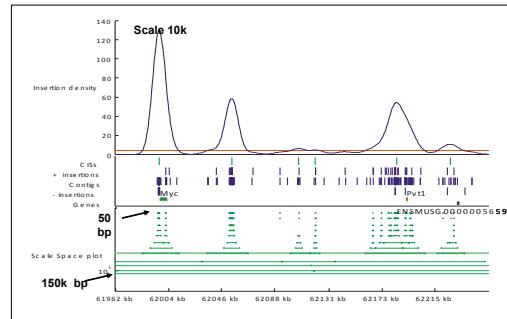


Uren et al., Cell, 2008 ; de Ridder et al., Plos Comp. Bio. 2006; de Ridder et al., Bioinformatics 2007



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Scale-space representation of insertion data

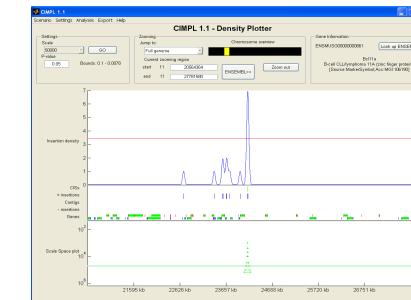


Uren et al., Cell, 2008 ; de Ridder et al., Plos Comp. Bio. 2006; de Ridder et al., Bioinformatics 2007



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CIMPL tool for biologist to inspect insertion data



Uren et al., Cell, 2008 ; de Ridder et al., Plos Comp. Bio. 2006; de Ridder et al., Bioinformatics 2007



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Gene therapy

Secondary leukemia in children treated by gene therapy for severe combined immunodeficiency

De Ridder



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X-SCID

- X-linked severe combined immunodeficiency:
 - mutation in interleukin-2 receptor β (IL-2R β)
 - patients develop no immune system: “bubble boy disease”
 - traditional therapy: bone marrow transplant



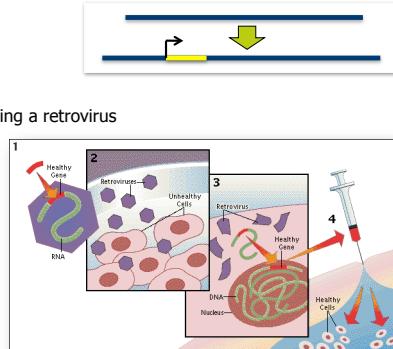
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116

Gene therapy

- Gene therapy:
 - extract bone marrow
 - insert IL-2R β gene using a retrovirus
 - radiate bone to remove original marrow
 - re-insert bone marrow, populate immune system

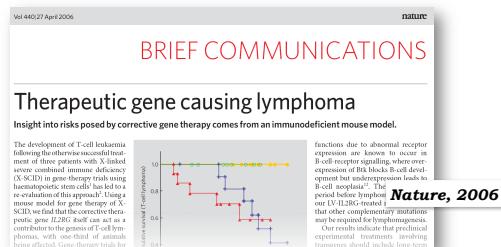


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Leukemia

- Mouse tests: the IL-2R β gene itself is an *oncogene*
 - Message: gene therapy is OK, just not for X-SCID



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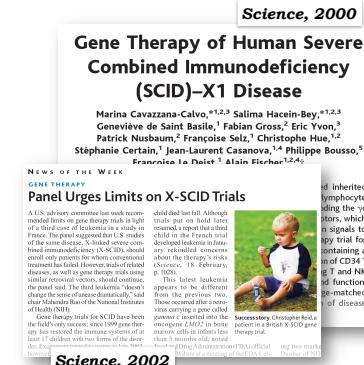
11

X-SCID gene therapy

- French & UK trials:
17 patients successfully treated (2000-2002)

- 3/10 French patients developed leukemia within few years (now 4)

- US trials halted

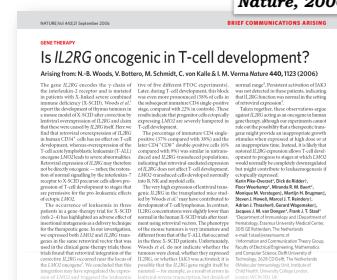


det. Exo
however

11

Leukemia (2)

- Doubts after tests in human T-cells:
IL-2R β itself may not be the problem
 - Also: why 3/10 cases in France, but 0/10 in UK?
 - Perhaps it's an overdose
of viral integration in
development genes,
which are often
oncogenes (e.g. LMO2)



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Leukemia (3)

Assessed viral integration sites in mice, interpreted in terms of genes involved in T-cell development: Cochran-Armitage test for trend

Leukemia (4)

Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients

J. Clinical Investigation, Blood, Leukemia, 2007-2008

Impact

- Conclusion: gene therapy methods themselves are problematic
- Result: adapted protocols, mainly much lower virus dose

Springer Protocols, 2009

Methods in Molecular Biology 506

Genetic Modification of Hematopoietic Stem Cells

Methods and Protocols

Edited by Christopher Baum

Human Press

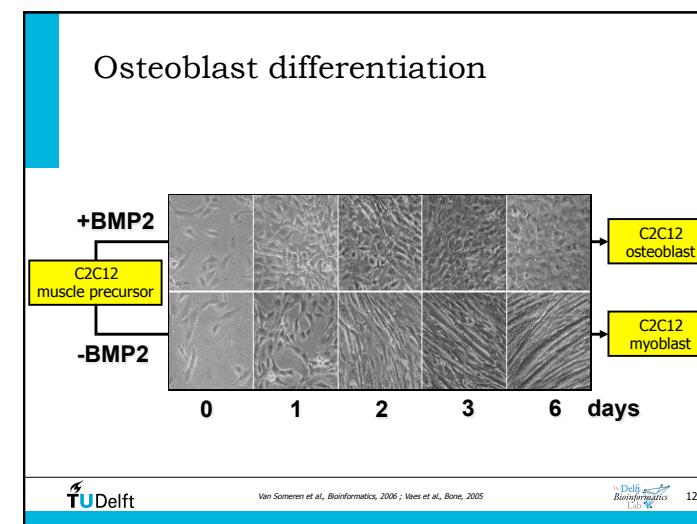
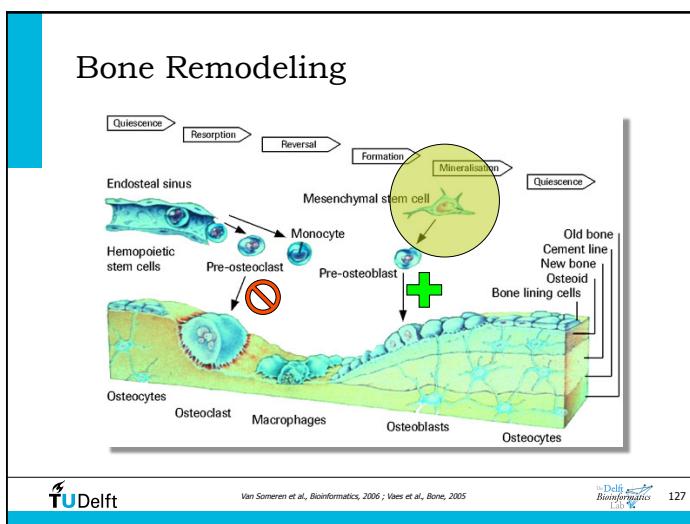
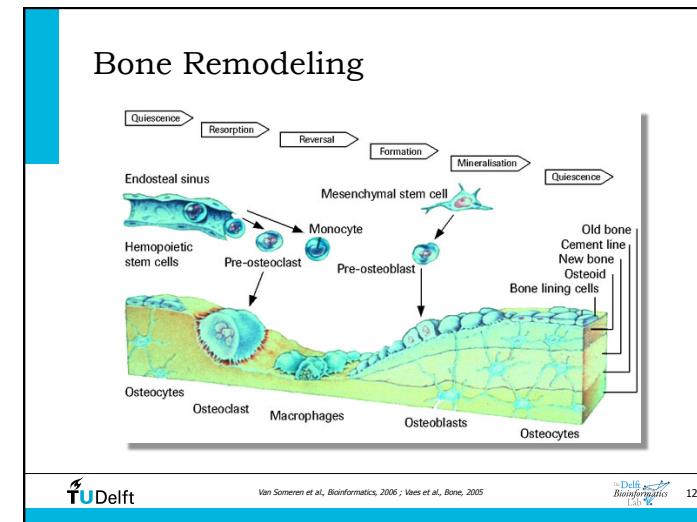
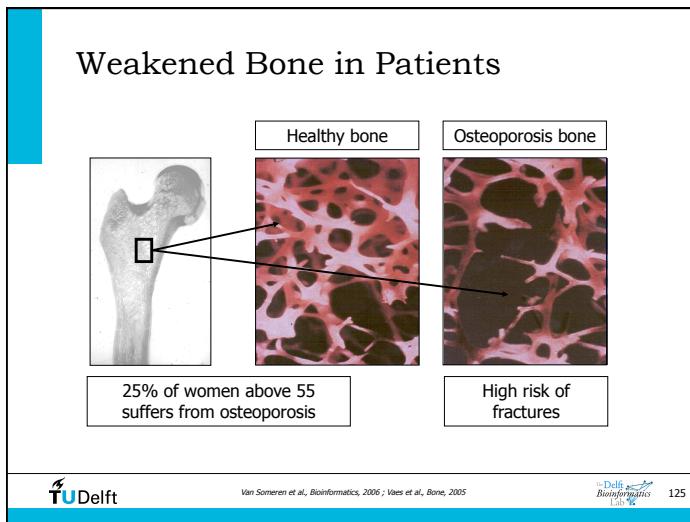
The bottom right corner features the TU Delft logo and the text 'Bioinformatics Lab'.

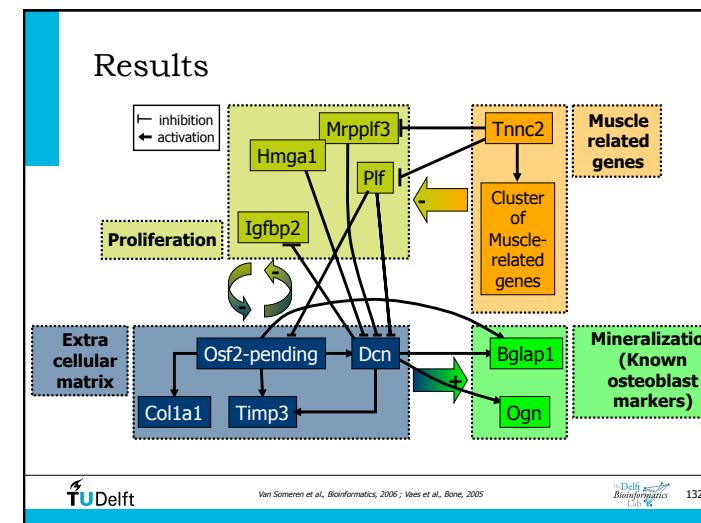
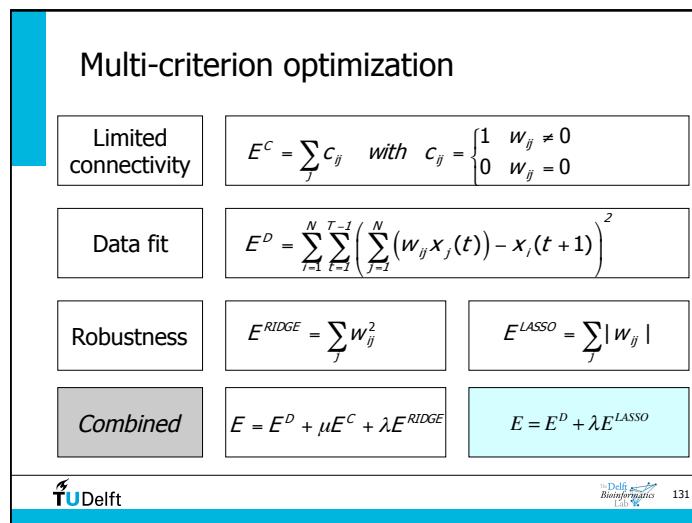
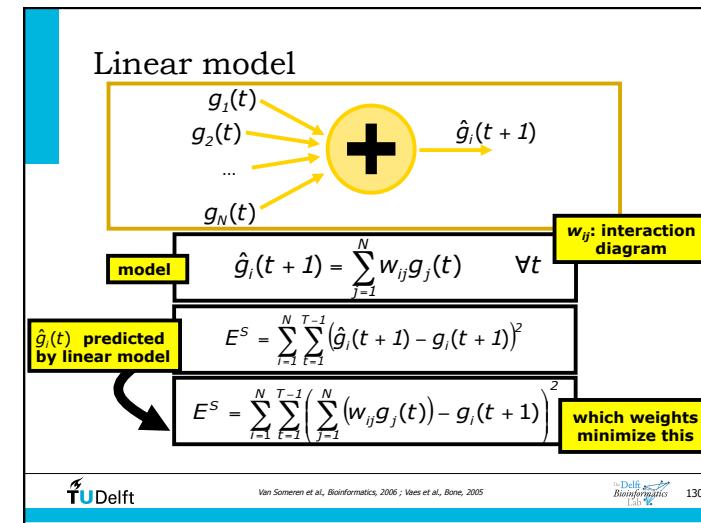
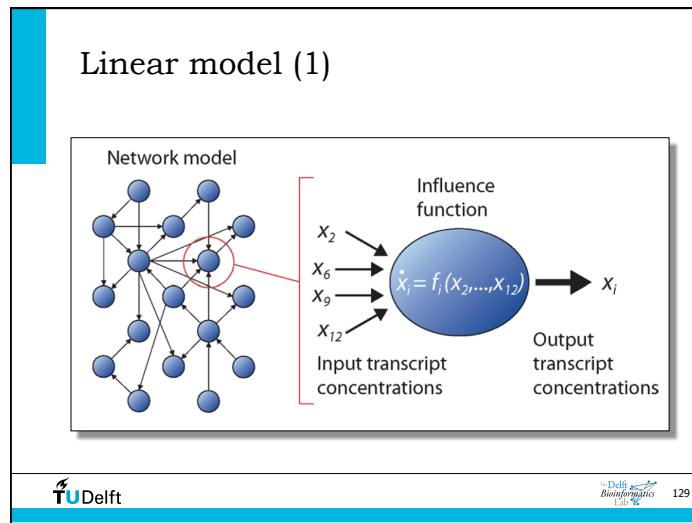
Gene network inference

Network Analysis of the Murine Osteoblast Differentiation Network

Van Someren

The bottom right corner features the TU Delft logo and the text 'Bioinformatics Lab'.

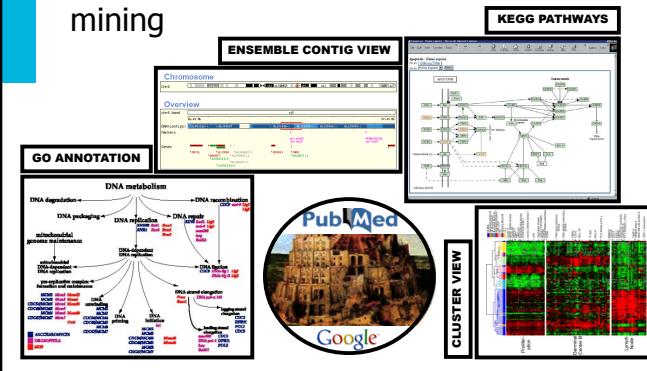




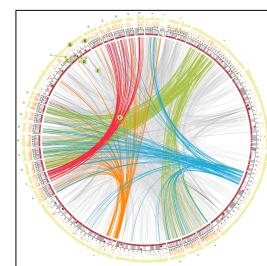
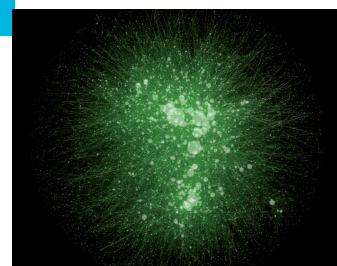
And other topics



Data management, organization and mining



Visualizations - The Interactome



Simulations - Virtual Cell

