185.A83 Machine Learning for Health Informatics
2016S, VU, 2.0 h, 3.0 ECTS
Di, 12.04.2016 17:00-20:00
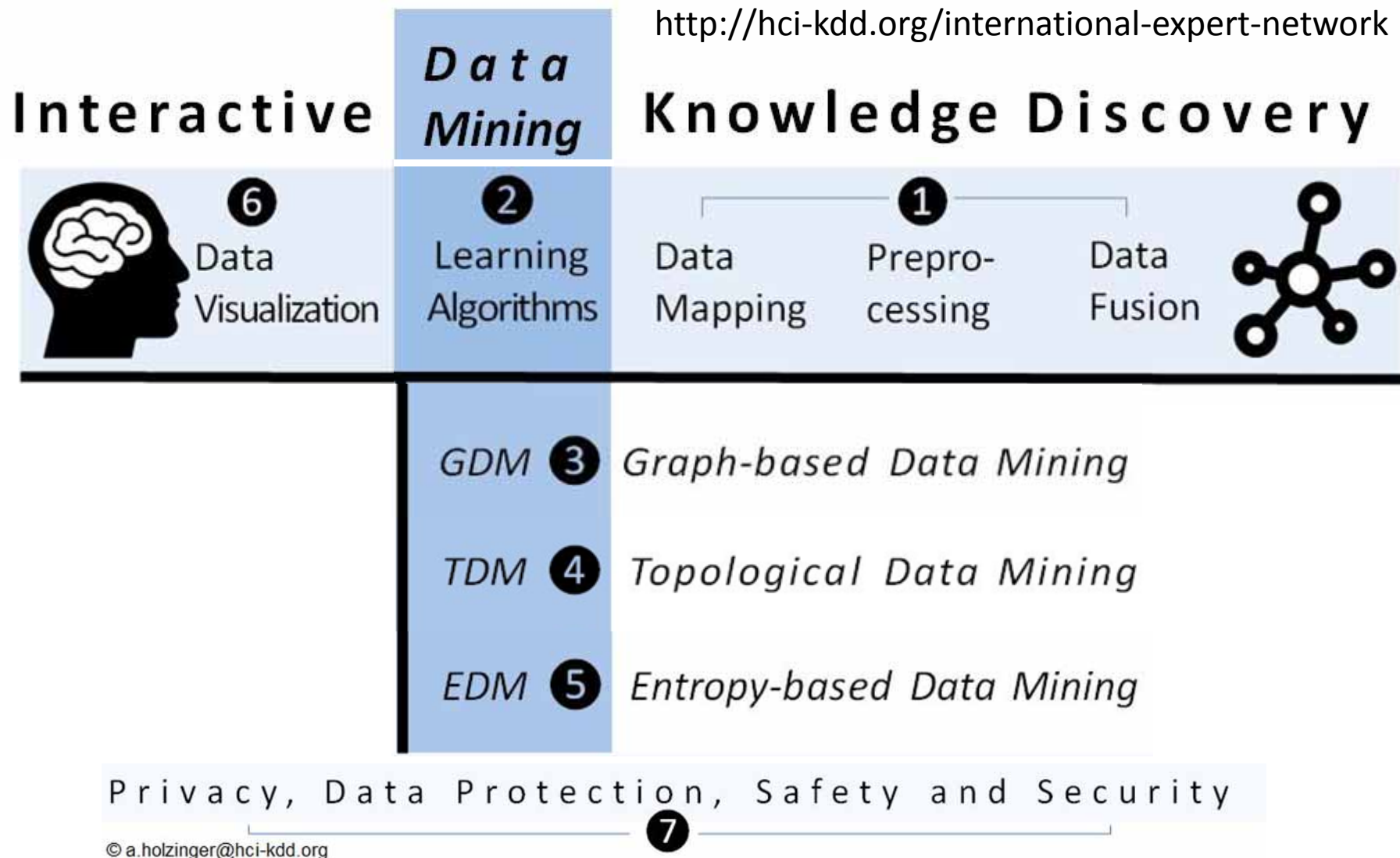
Health Data Jungle:
Selected Topics on Fundamentals of Data
and Information Entropy

a.holzinger@hci-kdd.org
http://hci-kdd.org/machine-learning-for-health-informatics-course

http://hci-kdd.org/international-expert-network

Interactive **Data Mining** **Knowledge Discovery**

- ⑥ Data Visualization
- ② Learning Algorithms
- Data Mapping
- ① Prepro-cessing
- Data Fusion

GDM ❸ Graph-based Data Mining

TDM ❹ Topological Data Mining

EDM ❺ Entropy-based Data Mining

Privacy, Data Protection, Safety and Security ❼
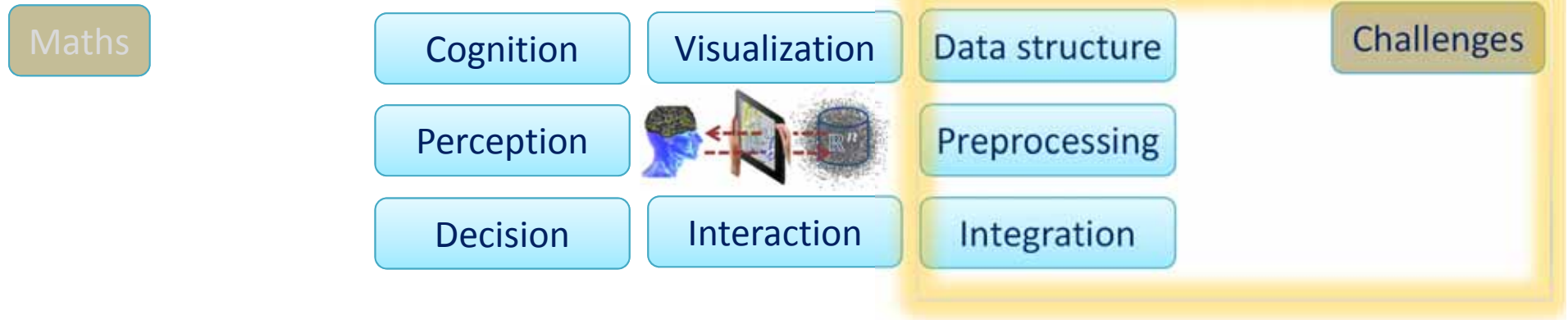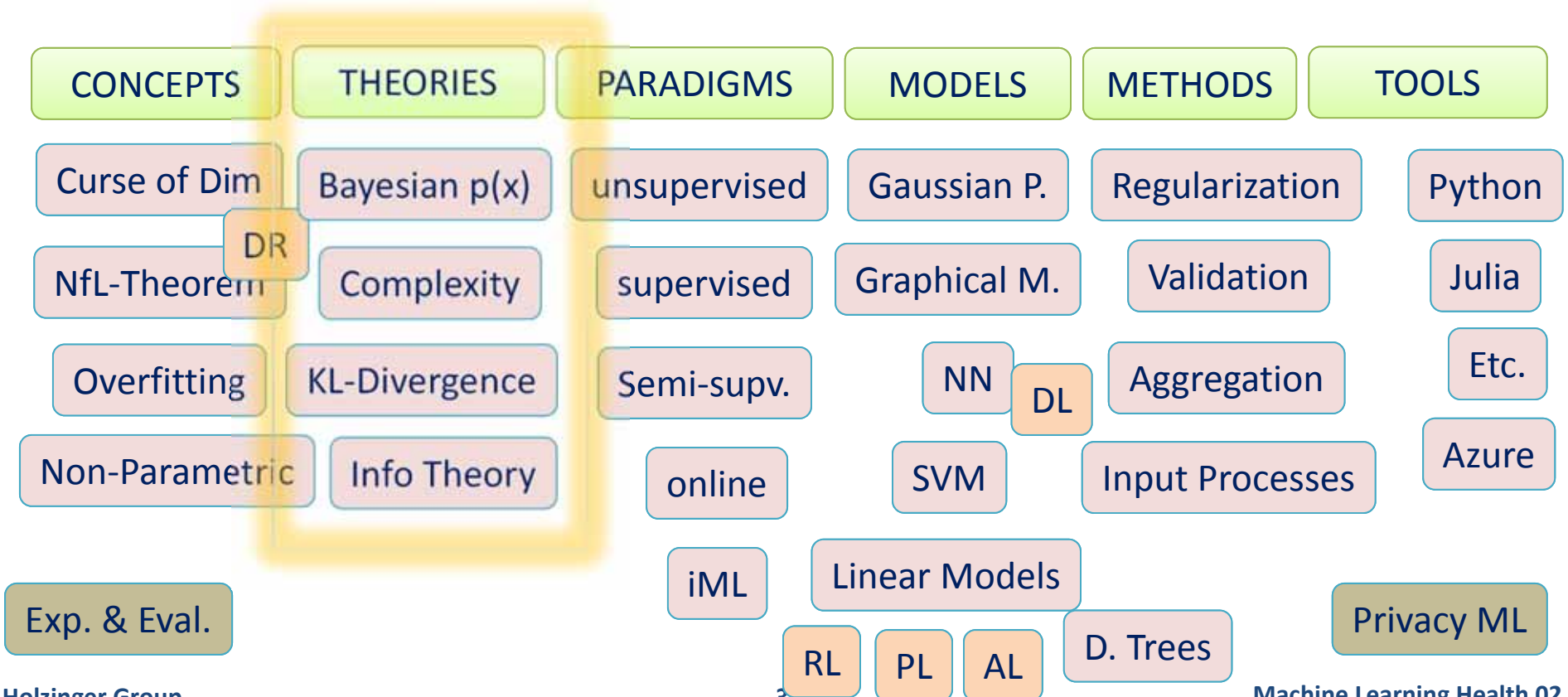
© a.holzinger@hci-kdd.org

Holzinger, A. 2014. Trends in Interactive Knowledge Discovery for Personalized Medicine: **Cognitive Science meets Machine Learning.** IEEE Intelligent Informatics Bulletin, 15, (1), 6-14.

Maths

Cognition	Visualization	Data structure	Challenges
Perception		Preprocessing	
Decision	Interaction	Integration	

Always with a focus/application in health informatics

CONCEPTS	THEORIES	PARADIGMS	MODELS	METHODS	TOOLS
Curse of Dim	Bayesian p(x)	unsupervised	Gaussian P.	Regularization	Python
NfL-Theorem DR	Complexity	supervised	Graphical M.	Validation	Julia
Overfitting	KL-Divergence	Semi-supv.	NN DL	Aggregation	Etc.
Non-Parametric	Info Theory	online	SVM	Input Processes	Azure
		iML	Linear Models		
Exp. & Eval.		RL PL AL	D. Trees		Privacy ML

- 1) Data – underlying physics of data
- 2) Biomedical data sources – taxonomy of data
- 3) Data structures – data integration, data fusion
- 4) Clinical data view – information - knowledge
- 5) Probabilistic Information
- 6) Information Theory – Information Entropy
- 7) Cross- Entropy - Kullback-Leibler Divergence
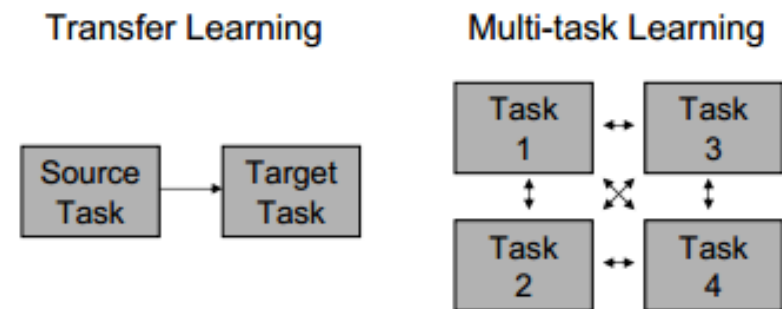- 8) Mutual Information – PMI (pointwise MI)

- Heterogeneous, distributed, inconsistent data sources (need for **data integration** & fusion) [1]

- **Complex data** (high-dimensionality – challenge of dimensionality reduction and visualization) [2]

- Noisy, uncertain, missing, dirty, and imprecise, imbalanced data (challenge of **pre-processing**)

- The discrepancy between data-information-knowledge (**various definitions**)

- **Big data** sets (manual handling of the data is awkward, and often impossible) [3]

1. Holzinger A, Dehmer M, & Jurisica I (2014) Knowledge Discovery and interactive Data Mining in Bioinformatics - State-of-the-Art, future challenges and research directions. BMC Bioinformatics 15(S6):I1.
2. Hund, M., Sturm, W., Schreck, T., Ullrich, T., Keim, D., Majnaric, L. & Holzinger, A. 2015. Analysis of Patient Groups and Immunization Results Based on Subspace Clustering. In: LNAI 9250, 358-368.
3. Holzinger, A., Stocker, C. & Dehmer, M. 2014. Big Complex Biomedical Data: Towards a Taxonomy of Data. in CCIS 455. Springer 3-18.

- Big data with many training sets (this is good for ML!)

- # Small number of data sets, rare events

- # Very-high-dimensional problems

- # Complex data – NP-hard problems

- # Missing, dirty, wrong, noisy, …, data

- # GENERALISATION

- # TRANSFER

Transfer Learning

Source Task → Target Task

Multi-task Learning

Task 1 ↔ Task 3
Task 2 ↔ Task 4

Torrey, L. & Shavlik, J. 2009. Transfer learning. Handbook of Research on Machine Learning Applications and Trends: Algorithms, Methods, and Techniques, 242-264, doi:10.4018/978-1-60566-766-9.ch011.
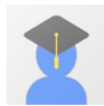
Natasha Noy
Google Inc.
Verified email at acm.org
Cited by 21492
Semantic Web   ontologies   data integration

Erhard Rahm
Professor of Computer Science, University of Leipzig
Verified email at informatik.uni-leipzig.de
Cited by 18199
Data integration   Databases   large_scale_data_management   Big_Data   Web Data Management

Christian Bizer
Professor of Information Systems, University of Mannheim
Verified email at informatik.uni-mannheim.de
Cited by 17496
Linked Data   Web Science   Data integration   Web Data Management

Karl Aberer
Professor of Computer and Communication Sciences, EPFL
Verified email at epfl.ch
Cited by 13199
information management   data management   data integration   trust management   semantic web

Kevin Chen-Chuan Chang
University of Illinois at Urbana-Champaign
Verified email at illinois.edu
Cited by 12119
Data Management   Data Integration   Databases   Data Mining

Benno Schwikowski
Head, Systems Biology Lab, Pasteur Institute, Paris
Verified email at pasteur.fr
Cited by 11925
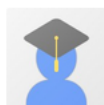Systems Biology   Data Integration   Network biology   Computational Modelling   Algorithms

Wensheng Wu
Assistant Professor of Computer Science, UNC Charlotte
Verified email at uncc.edu
Cited by 10769
Database systems   data integration   information retrieval   Web technology

AnHai Doan
Professor of Computer Science, University of Wisconsin-Madison
Verified email at cs.wisc.edu
Cited by 10477
data integration   data/schema/ontology matching   information extraction   knowledge bases   crowdsourcing

Helen Parkinson
Team Leader, Samples, Phenotypes and Ontologies
Verified email at ebi.ac.uk
Cited by 10353
Bioinformatics   Computational Biology   Ontologies   Semantic Web technologies   Data Integration

Anil Wipat
Professor of Bioinformatics Newcastle University
Verified email at ncl.ac.uk
Cited by 9963
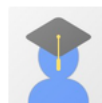bioinformatics   data integration   synthetic biology   systems biology

Hadi Quesneville
INRA, UR1164, Recharch Unit in Genomics info, Versailles, France
Verified email at versailles.inra.fr
Cited by 8579
Genomics   Bioinformatics   Repeat annotation   Data integration   Genome analysis
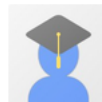
Tom Heath
Open Data Institute
Verified email at theodi.org
Cited by 8107
Semantic Web   Linked Data   Data integration   Data Science   Open Data

Zachary G. Ives
Professor of Computer and Information Science, University of Pennsylvania
Verified email at cis.upenn.edu
Cited by 7798
Databases   data integration   distributed systems   web data management

Richard Cyganiak
DERI, NUI Galway
Verified email at cyganiak.de
Cited by 7057
Semantic Web   Linked Data   Data integration   Web Technology

Jessica C Kissinger
Director, Institute of Bioinformatics, Professor of Genetics, University of Georgia
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Genetics   Genomics   Bioinformatics   Data Integration   Protist Parasites

Silvana Castano
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Verified email at unimi.it
Cited by 5813
Data Integration   Knowledge discovery   Database   Semantic Web

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Bioinformatics   Evolution   Phylogenetics   Databases   Data integration

John M. Hancock
Computational Biologist
Verified email at tgac.ac.uk
Cited by 5599
ontologies   data integration   phenotype   gene evolution   repetitive sequences

Lucian Popa
IBM Almaden Research Center
Verified email at us.ibm.com
Cited by 5212
Data Management   Databases   Data Integration
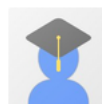
Peter Li
Data Organisation Manager, GigaScience, BGI Hong Kong
Verified email at gigasciencejournal.com
Cited by 5100
Bioinformatics   systems biology   data integration

Felix Naumann
Professor of Computer Science, Hasso Plattner Institute
Verified email at hpi.de
Cited by 4962
Databases   Data Profiling   Data Integration   Data Cleansing   Data Quality
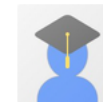
Werner Nutt
Professor of Computer Science, Free University of Bozen-Bolzano
Verified email at inf.unibz.it
Cited by 4829
Data Management   Data Quality   Data Integration   Ontologies   Data on the Web

Peter AC 't Hoen
Associate Professor Bioinformatics, Leiden University Medical Center
Verified email at lumc.nl
Cited by 4792
bioinformatics   data integration   genomics

Xin Luna Dong
Google Inc.
Verified email at google.com
Cited by 4638
Data integration   data quality
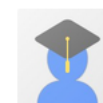
Akhil Datta-Gupta
Texas A&M University, College Station, TX USA
Verified email at tamu.edu
Cited by 4440
Reservoir Characterization   Data integration   Streamline Simulation   Unconventional Reservoir Modeling

Ulf Leser
Knowledge Management in Bioinformatics, Humboldt-Universität zu Berlin
Verified email at informatik.hu-berlin.de
Cited by 4217
Bioinformatics   Text Mining   Graph Databases   Scientific Workflow   Data Integration

Mark D Wilkinson
BBVA-UPM Industry Chair on Biotechnology and Isaac Peral Distinguished Researcher, ...
Verified email at illuminae.com
Cited by 3844
semantic web   interoperability   web services   data integration   workflows

Uwe Scholz
Bioinformatician, IPK Gatersleben, Stadt Seeland, Germany
Verified email at ipk-gatersleben.de
Cited by 3534
Bioinformatics   Databases   Data Integration   Sequence Analysis   Next Generation Sequencing
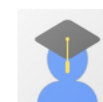
Anish Das Sarma
Senior Research Scientist, Google Research
Verified email at google.com
Cited by 3224
Information Management   Data Integration   Web

Alkis Simitsis
Hewlett Packard Labs, Palo Alto
Verified email at hpe.com
Cited by 3211
Databases   Data Management   Business Intelligence   Big Data   Data Integration

Status as of 04.04.2016

1) Data – underlying physics of data

- Data in traditional Statistics

- Low-dimensional data ($< \mathbb{R}^{100}$)

- Problem: Much noise in the data

- Not much structure in the data but it can be represented by a simple model

- Data in Machine Learning

- High-dimensional data ($\gg \mathbb{R}^{100}$)

- Problem: not noise , but complexity

- Much structure, but the structure can **not** be represented by a simple model

Lecun, Y., Bengio, Y. & Hinton, G. 2015. Deep learning. Nature, 521, (7553), 436-444.

What is data?
What types of
data?

http://www.nytimes.com/2012/05/06/books/review/turings-cathedral-by-george-dyson.html

Example: Neonatal Screening (1/3)

Diagnosis [E01]
 Diagnostic Techniques and Procedures [E01.370]
  Mass Screening [E01.370.500]
      Anonymous Testing [E01.370.500.174]
      Mass Chest X-Ray [E01.370.500.500]
      Multiphasic Screening [E01.370.500.540]
      ► Neonatal Screening [E01.370.500.580]

Newborn screening

Intervention

MeSH	D015997
MedlinePlus	007257

Diagnosis [E01]
 Laboratory Techniques and Procedures [E01.450]
      Age Determination by Skeleton [E01.450.074]
      Clinical Chemistry Tests [E01.450.150] +
      Cytodiagnosis [E01.450.230] +
      Hematologic Tests [E01.450.375] +
      Immunologic Tests [E01.450.495] +
      Metabolic Clearance Rate [E01.450.520]
      ► Neonatal Screening [E01.450.560]
      Occult Blood [E01.450.575]
      Parasite Egg Count [E01.450.600]
      Pregnancy Tests [E01.450.620] +
      Radioligand Assay [E01.450.650]
      Semen Analysis [E01.450.752] +
      Sex Determination Analysis [E01.450.855]
      Sex Determination by Skeleton [E01.450.860]
      Specimen Handling [E01.450.865] +
      Urinalysis [E01.450.890]

Medical Subject Headings MeSH

http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&index=15177&view=expanded#TreeE01.370.500.580
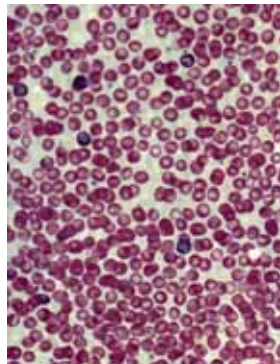
Amino acids (symbols)	Fatty acids (symbols)	Fatty acids (symbols)
Alanine (Ala)	Free carnitine (C0)	Hexadecenoyl-carnitine (C16:1)
Arginine (Arg)	Acetyl-carnitine (C2)	Octadecenoyl-carnitine (C18:1)
Argininosuccinate (Argsuc)	Propionyl-carnitine (C3)	Decenoyl-carnitine (C10:2)
Citrulline (Cit)	Butyryl-carnitine (C4)	Tetradecadienoyl-carnitine (C14:2)
Glutamate (Glu)	Isovaleryl-carnitine (C5)	Octadecadienoyl-carnitine (C18:2)
Glycine (Gly)	Hexanoyl-carnitine (C6)	Hydroxy-isovaleryl-carnitine (C5-OH)
Methionine (Met)	Octanyl-carnitine (C8)	Hydroxytetradecadienoyl-carnitine (C14-OH)
Ornitine (Orn)	Decanoyl-carnitine (C10)	Hydroxypalmitoyl-carnitine (C16-OH)
Phenylalanine (Phe)	Dodecanoyl-carnitine (C12)	Hydroxypalmitoleyl-carnitine (C16:1-OH)
Pyroglutamate (Pyrglt)	Myristoyl-carnitine (C14)	Hydroxyoleyl-carnitine (C18:1-OH)
Serine (Ser)	Hexadecanoyl-carnitine (C16)	Dicarboxyl-butyryl-carnitine (C4-DC)
Tyrosine (Tyr)	Octadecanoyl-carnitine (C18)	Glutaryl-carnitine (C5-DC)
Valine (Val)	Tiglyl-carnitine (C5:1)	Methylglutaryl-carnitine (C6-DC)
Leucine + Isoleucine (Xle)	Decenoyl-carnitine (C10:1)	Methylmalonyl-carnitine (C12-DC)
	Myristoleyl-carnitine (C14:1)	

Fourteen amino acids and 29 fatty acids are analyzed from a single blood spot using MS/MS. The concentrations are given in μmol/L.

Data cube

Heat map

TIC/XIC
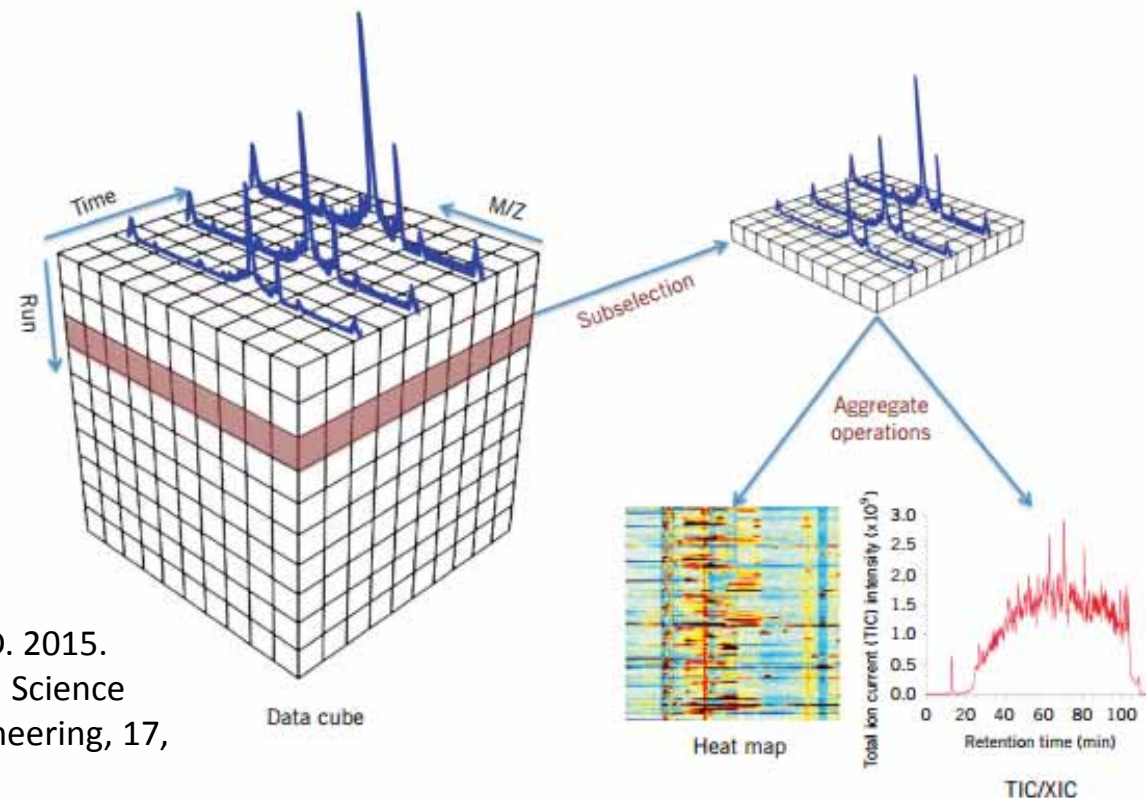
Yao, Y., Bowen, B. P., Baron, D. & Poznanski, D. 2015. SciDB for High-Performance Array-Structured Science Data at NERSC. Computing in Science & Engineering, 17, (3), 44-52, doi:10.1109/MCSE.2015.43.

Baumgartner, C., Bohm, C. & Baumgartner, D. 2005. Modelling of classification rules on metabolic patterns including machine learning and expert knowledge. Journal of Biomedical Informatics, 38, (2), 89-98, doi:10.1016/j.jbi.2004.08.009.
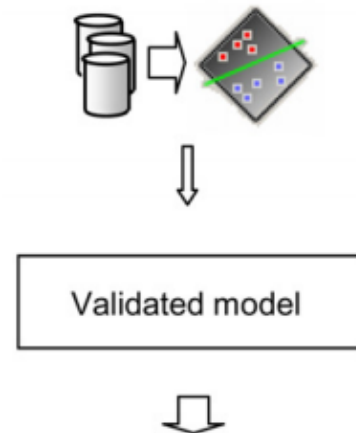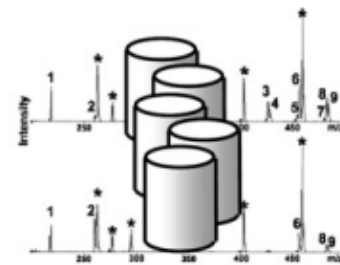

DB of high-dimensional metabolic data including cases designated as PAHD (n=94), MCADD (n=63) and 3-MCCD (n=22), and a randomly sampled number of controls (n=1241)
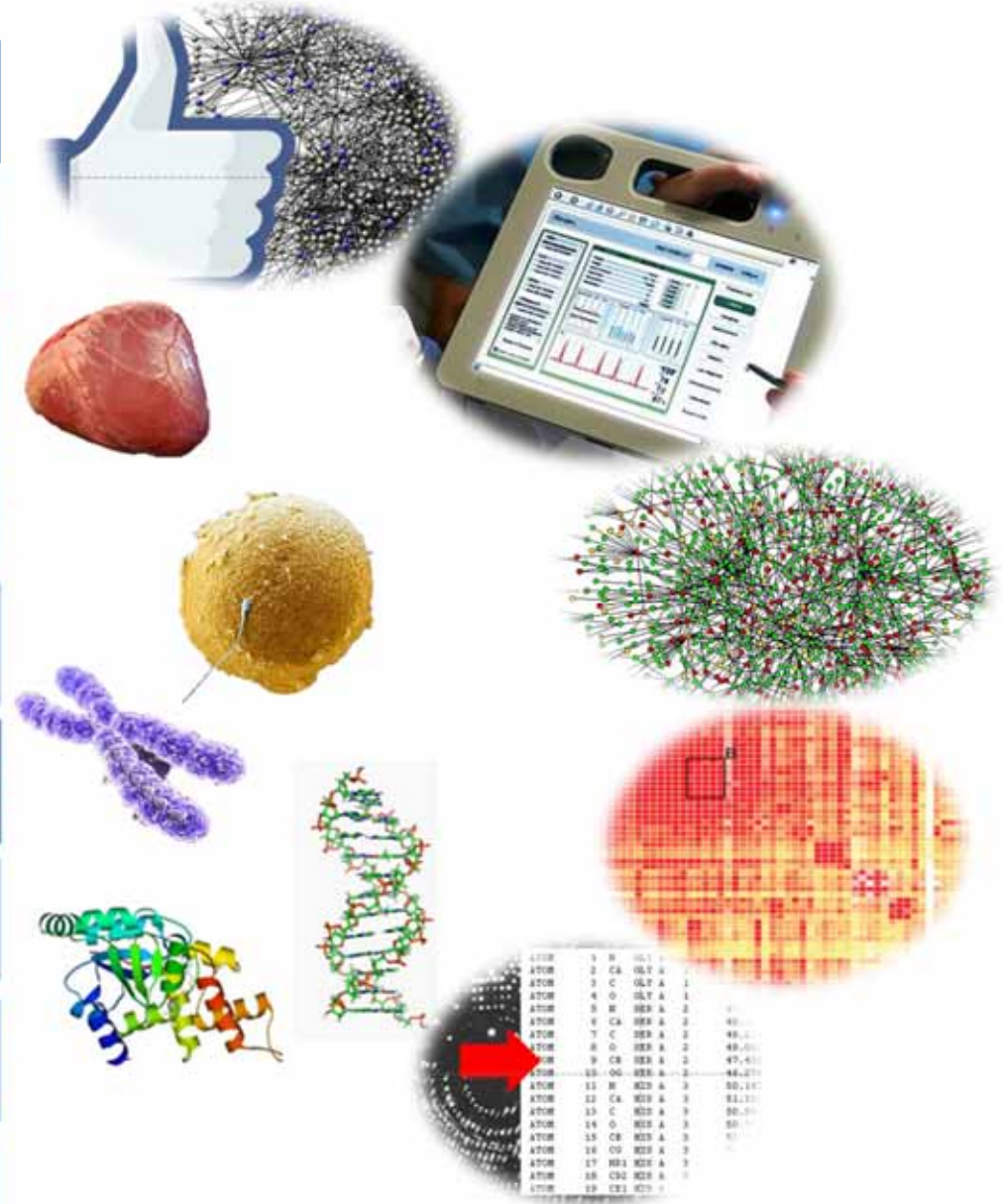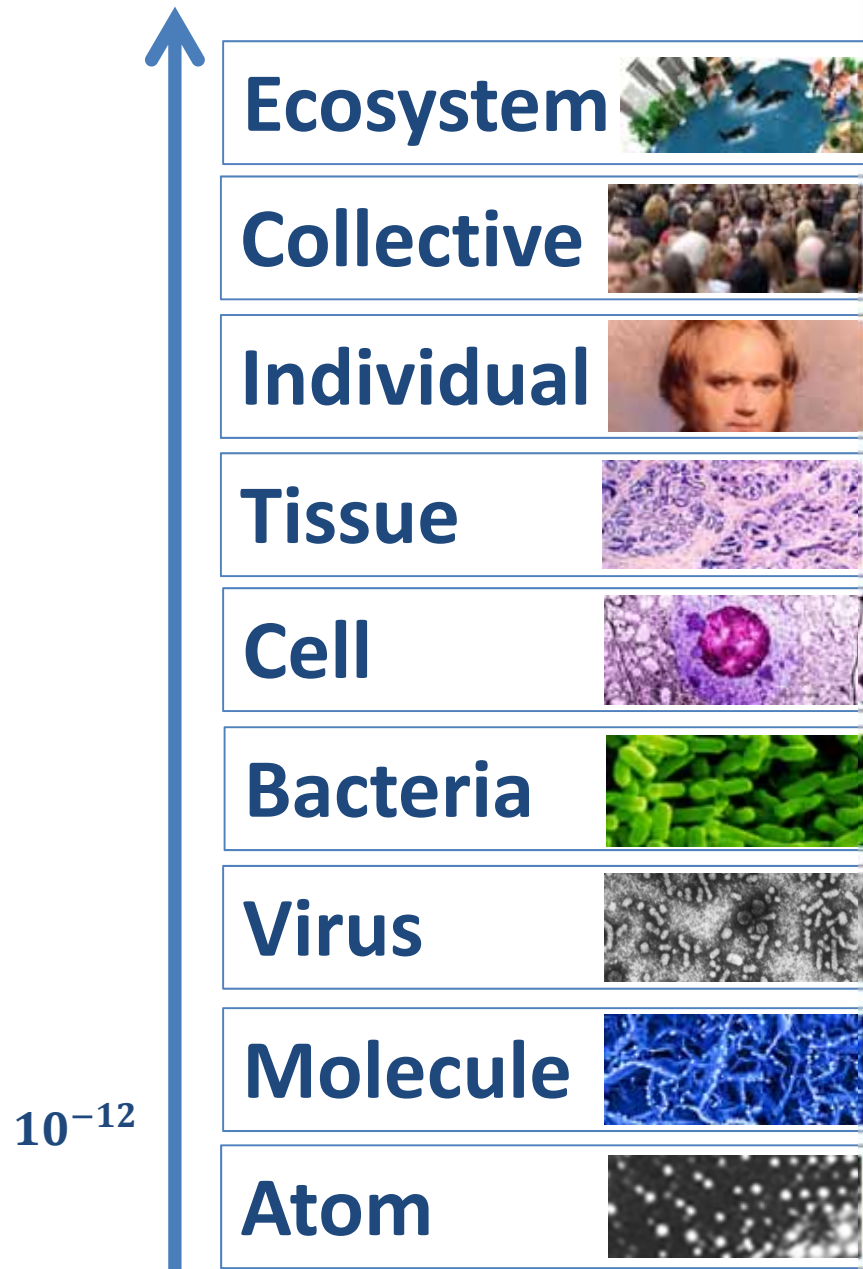
Construction of classification models
(1) decision tree paradigm with internal feature selection strategy

(2) Logistic regression analysis with expert knowledge (diagnostic flags) as model input variables

Training and 10-fold-cross validation
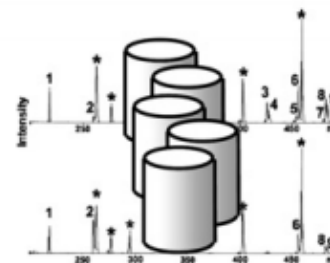
Larger database of control individuals (n=98,411) in order to estimate the specificity of a representative screening population

Validated model

Real predictive power of the screening model

2) Biomedical data sources – Taxonomy of data

Ecosystem

Collective

Individual

Tissue

Cell

Bacteria

Virus

10^{-12}

Molecule

Atom
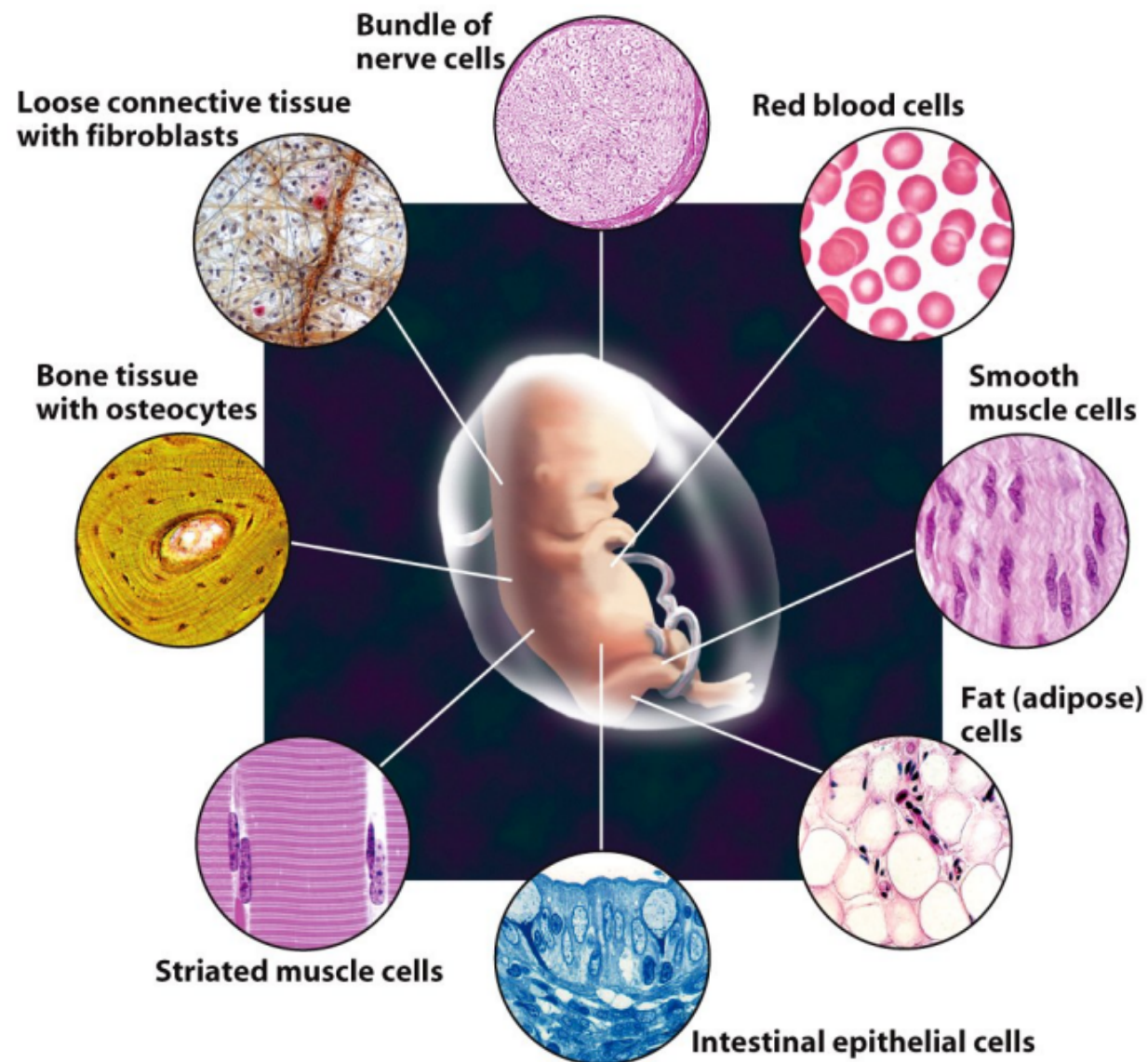
Karp, G. 2010. Cell and Molecular Biology: Concepts and Experiments, Gainesville, John Wiley.

B10NUMB3R5

THE DATABASE OF USEFUL BIOLOGICAL NUMBERS

Home | Search   Browse   Resources   Cell Biology by the Numbers

Popular BioNumbers | Recent BioNumbers | Key BioNumbers

🔍 Find Terms

e.g. ribosome coli, p53 human, transcription, OD

BioNumber Details Page

|	
ID	105570
Property	Genome size (smallest known RNA virus genome)
Organism	Hepatitis delta virus
Value	~1.7
Units	kb
Reference	Huang CR, Lo SJ. Evolution and diversity of the human hepatitis d virus genome. Adv Bioinformatics. 2010:323654. link p. 1 right column
Reference PubMed ID	20204073
Primary Source	[4] M. M. C. Lai, "The molecular biology of hepatitis delta virus," Annual Review of Biochemistry, vol. 64, pp. 259-286, 1995. [5] S. Makino, M.-F. Chang, C.-K. Shieh, et al., "Molecular cloning and sequencing of a human hepatitis delta (d) virus RNA," Nature, vol. 329, no. 6137, pp. 343-348, 1987 [6] J. M. Taylor, "Hepatitis delta virus," Virology, vol. 344, no. 1, pp. 71-76, 2006. [7] K.-S. Wang, Q.-L. Choo, A. J. Weiner, et al., "Structure, sequence and expression of the hepatitis delta (d) viral genome," Nature, vol. 323, pp. 508-514, 1986.
Primary Source PubMed ID	7574482, 3027276, 16364738, 3762705
Comments	"The genome size of RNA viruses is generally shorter than that of DNA viruses and ranges approximately from 2 to 31 kb. The smallest RNA virus identified to date is the human hepatitis D virus (HDV) which is about 1.7 kb in size and contains only one ORF [primary sources]."
Entered By	Uri M
Date Added	Aug 18, 2010 6:14 AM
Date Edited	Mar 05, 2015 9:43 AM
Version	8
Permalink	http://bionumbers.hms.harvard.edu/bionumber.aspx?id=105570&ver=8

bionumbers.hms.harvard.edu/

http://book.bionumbers.
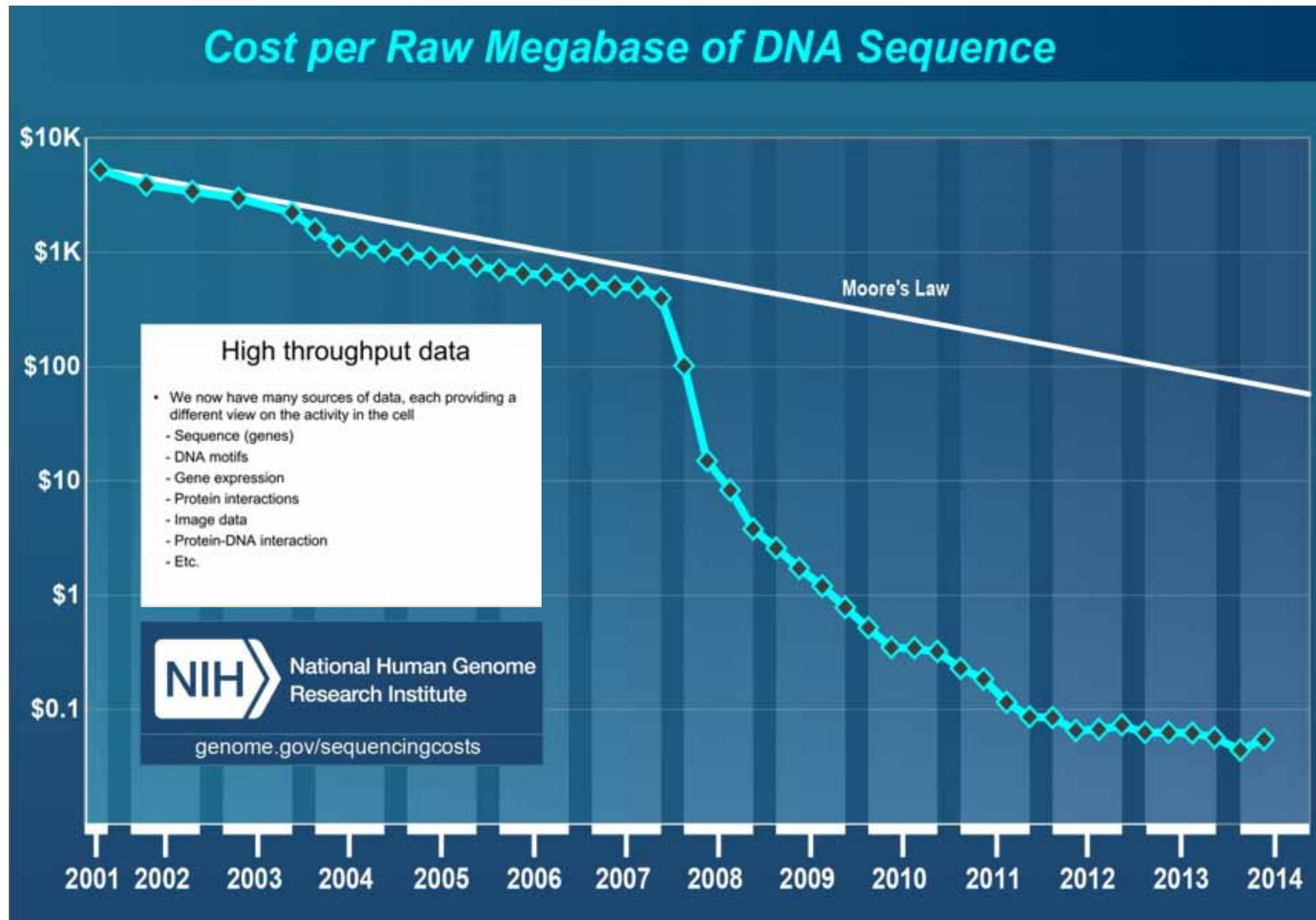org/how-many-genes-
are-in-a-genome/

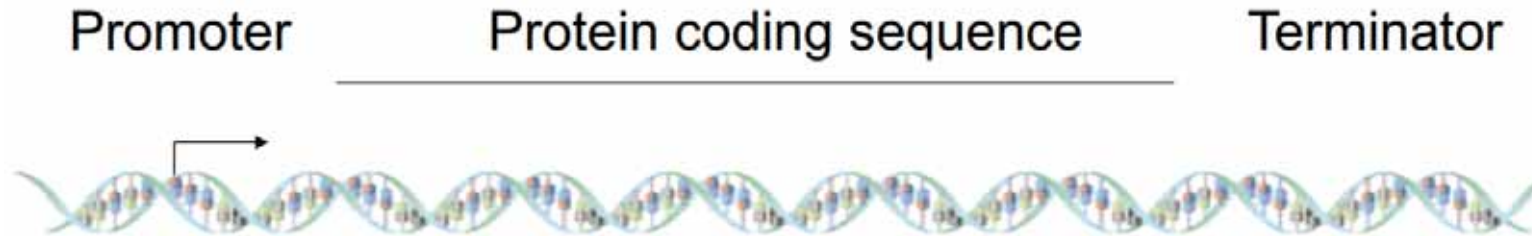|	Organism	# of protein-coding genes	# of genes naïve estimate: (genome size /1000)	BNID
viruses	HIV 1	9	10	105769
	Influenza A virus	10-11	14	105767
	Bacteriophage λ	66	49	105770
	Epstein Barr virus	80	170	103246
prokaryotes	Buchnera sp.	610	640	105757
	T. maritima	1,900	1,900	105766
	S. aureus	2,700	2,900	105500
	V. cholerae	3,900	4,000	105760
	B. subtilis	4,400	4,200	111448
	E. coli	4,300	4,600	105443
eukaryotes	S. cerevisiae	6,600	12,000	105444
	C. elegans	20,000	100,000	101364
	A. thaliana	27,000	140,000	111380
	D. melanogaster	14,000	140,000	111379
	F. rubripes	19,000	400,000	111375
	Z. mays	33,000	2,300,000	110565
	M. musculus	20,000	2,800,000	100308
	H. sapiens	21,000	3,200,000	100399, 111378
	T. aestivum (hexaploid)	95,000	16,800,000	105448, 102713
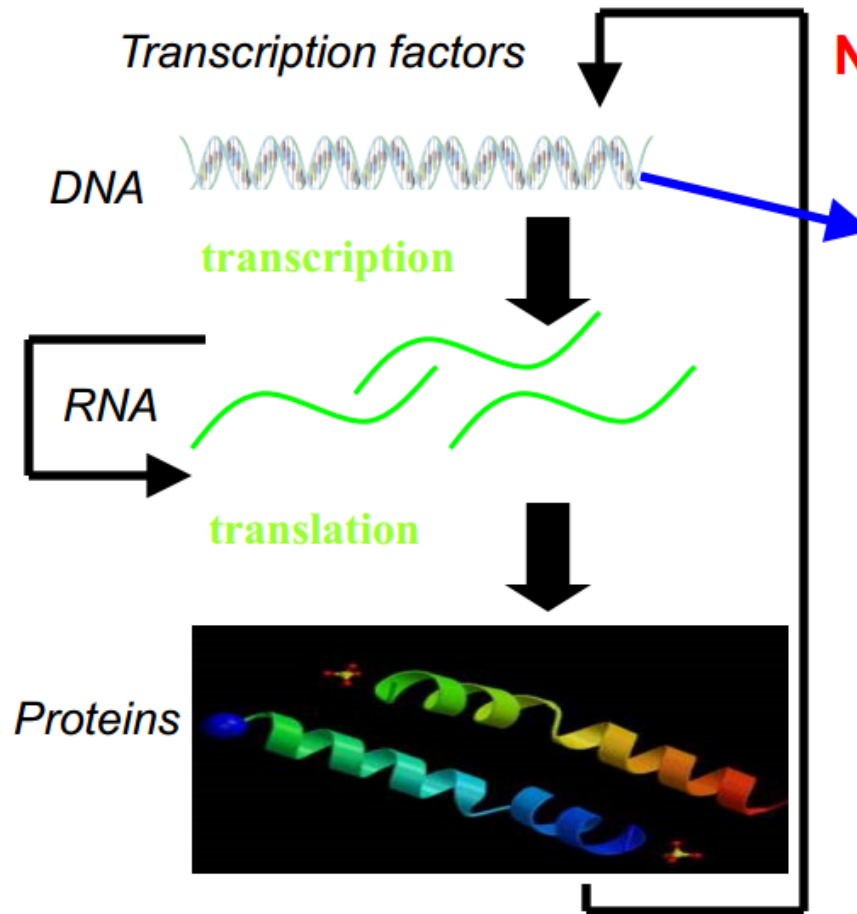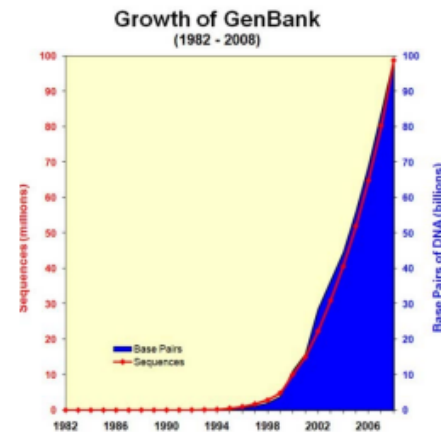
Navlakha, S. & Bar-Joseph, Z. 2011. Algorithms in nature: the convergence of systems biology and computational thinking. *Molecular Systems Biology,* 7.
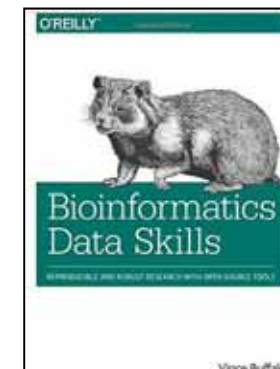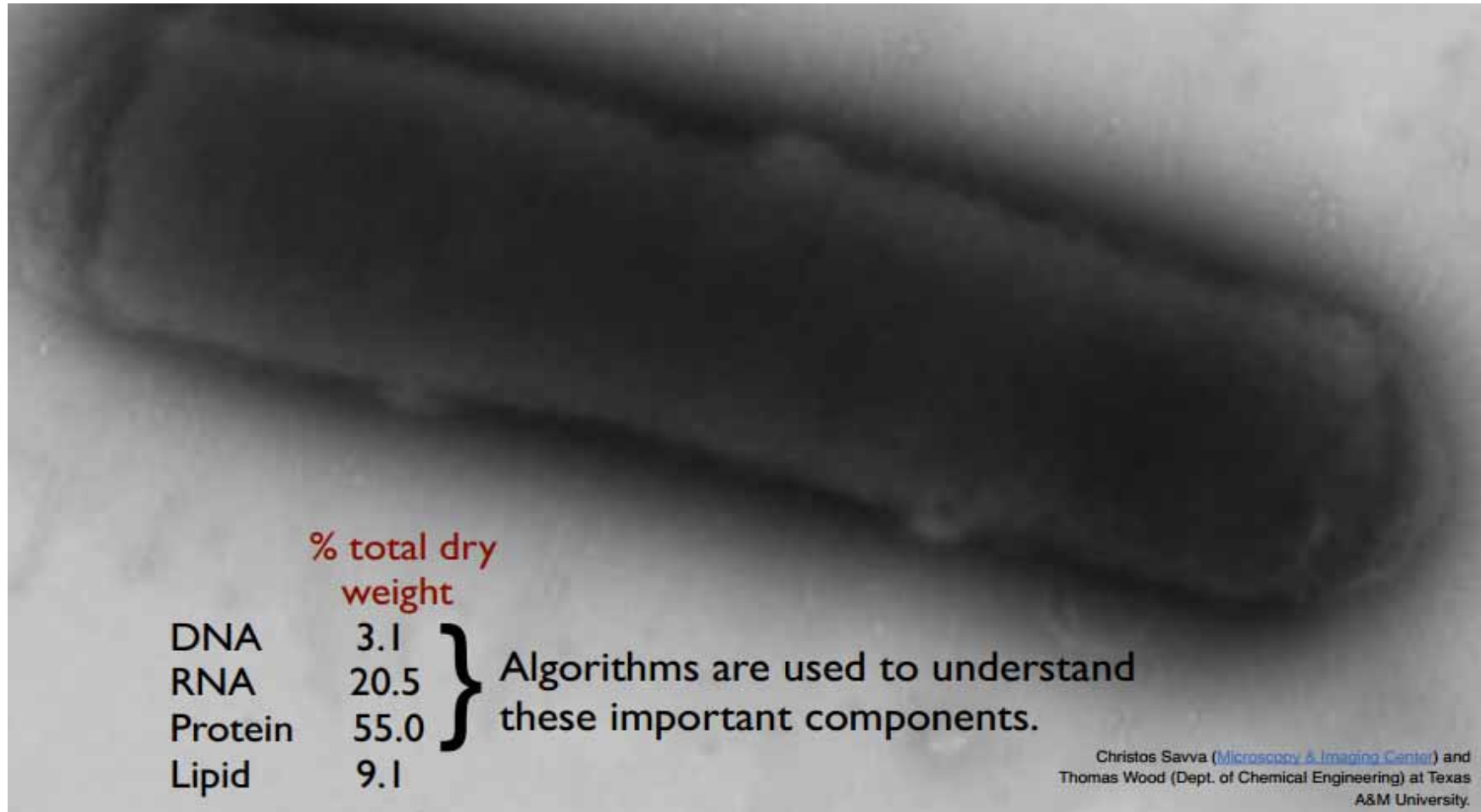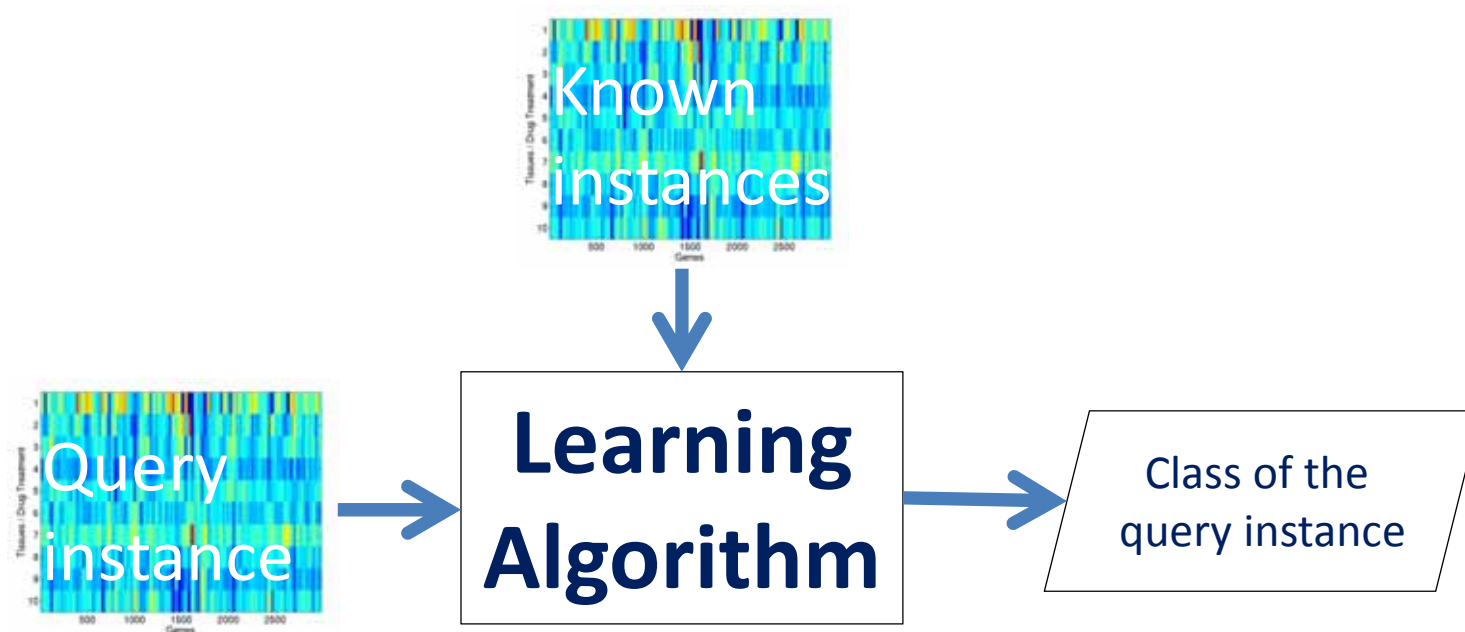
Cost per Raw Megabase of DNA Sequence

High throughput data

- We now have many sources of data, each providing a different view on the activity in the cell
  - Sequence (genes)
  - DNA motifs
  - Gene expression
  - Protein interactions
  - Image data
  - Protein-DNA interaction
  - Etc.

NIH National Human Genome Research Institute

genome.gov/sequencingcosts

For further reading this is recommended: Buffalo, V. 2015. Bioinformatics Data Skills: Reproducible and Robust Research with Open Source Tools, Sebastopol (CA), O'Reilly.

	% total dry weight	
DNA	3.1	
RNA	20.5	Algorithms are used to understand these important components.
Protein	55.0	
Lipid	9.1	

Christos Savva (Microscopy & Imaging Center) and Thomas Wood (Dept. of Chemical Engineering) at Texas A&M University.

Known instances

Query instance

Learning Algorithm
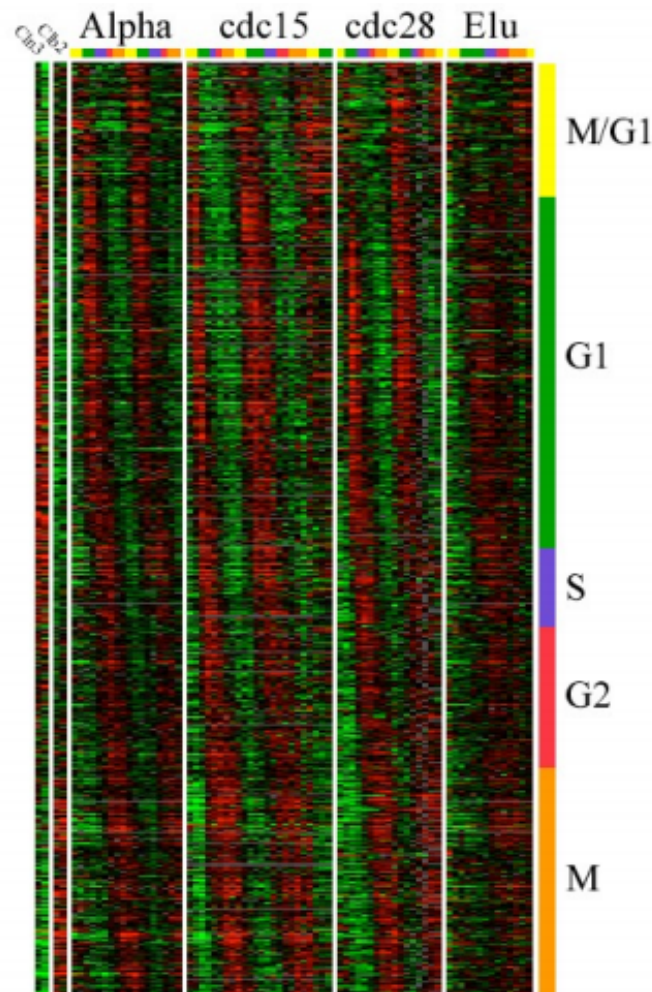
Class of the query instance

Features are key to learning and understanding!

- Billions of biological data sets are openly available, here only some examples:

- General Repositories:
  - GenBank, EMBL, HMCA, …

- Specialized by data types:
  - UniProt/SwissProt, MMMP, KEGG, PDB, …

- Specialized by organism:
  - WormBase, FlyBase, NeuroMorpho, …

- Details: http://hci-kdd.org/open-data-sets

Figure from Spellman et al., Molecular Biology of the Cell, 9:3273-3297, 1998

- this figure depicts one yeast gene-expression data set

  - each row represents a gene

  - each column represents a measurement of gene expression (mRNA abundance) at some time point

  – red indicates that a gene is being expressed more than some baseline; green means less

- **Physical level** -> bit = binary digit = **b**asic **i**ndissoluble uni**t** (= Shannon, Sh), ≠ Bit (!) in Quantum Systems -> qubit

- **Logical Level** -> integers, booleans, characters, floating-point numbers, alphanumeric strings, …

- **Conceptual (Abstract) Level** -> data-structures, e.g. lists, arrays, trees, graphs, …

- **Technical Level** -> Application data, e.g. text, graphics, images, audio, video, multimedia, …

- **"Hospital Level"** -> Narrative (textual) data, numerical measurements (physiological data, lab results, vital signs, …), recorded signals (ECG, EEG, …), Images (x-ray, MR, CT, PET, …) ; -omics

- **Clinical workplace data sources**
  - Med.docs: text (non-standardized (free-text), semi-structured, standard terminologies (ICD, SNOMED-CT)
  - Measurements: lab results, ECG, EEG, EOG, …
 - Surveys, Clinical studies, trials
- **Image data sources**
  - Radiology: MRI (256x256, 200 slices, 16 bit per pixel, uncompressed, ~26 MB); CT (512x512, 60 slices, 16 bit per pixel, uncompressed ~32MB; MR, US;
  - Digital Microscopy : WSI (15mm slide, 20x magn., 24 bits per pixel, uncompressed, 2,5 GB, WSI 10 GB; confocal laser scanning, etc.
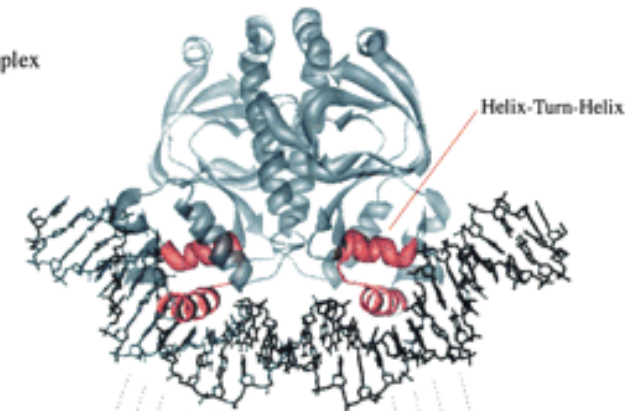- **-omics data sources**
  - Sanger sequencing, NGS whole genome sequencing (3 billion reads, read length of 36) ~ 200 GB; NGS exome sequencing ("only" 110,000,000 reads, read length of 75) ~7GB; Microarray, mass-spectrometry, gas chromatography, …

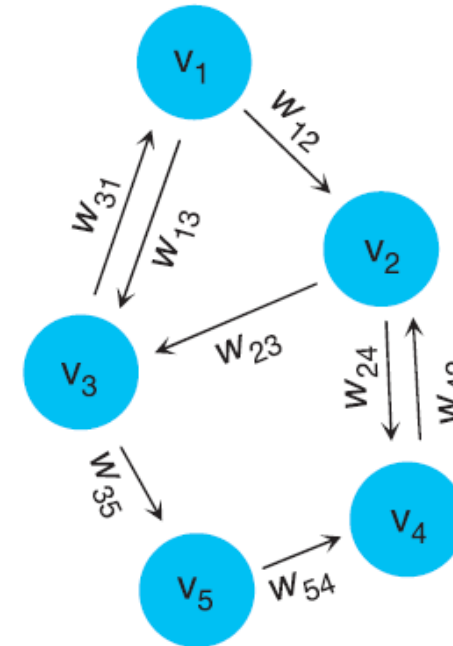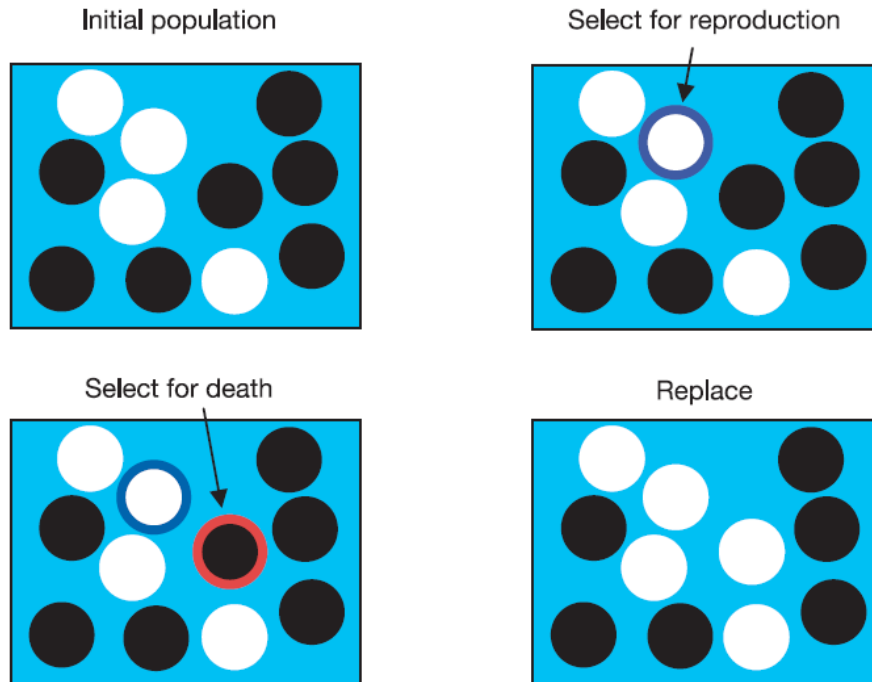| TYPE link = REF node ;
    node = RECORD
        key : ItemType;
        next : link;
    END;
	key
	next
		class link {
		    ItemType key;
		    link next;
		}

VAR p, q : link ;	p q	link p,q;
p := NEW(link);	p q	p=new link();
p^.key:=x;	p q x	p.key=x;
q := NEW(link) ;	p q x	q=new link();
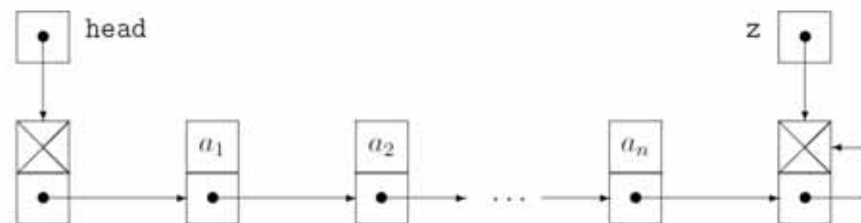
Crooks, G. E., Hon, G., Chandonia, J. M. & Brenner, S. E. (2004) WebLogo: A sequence logo generator. Genome Research, 14, 6, 1188-1190.
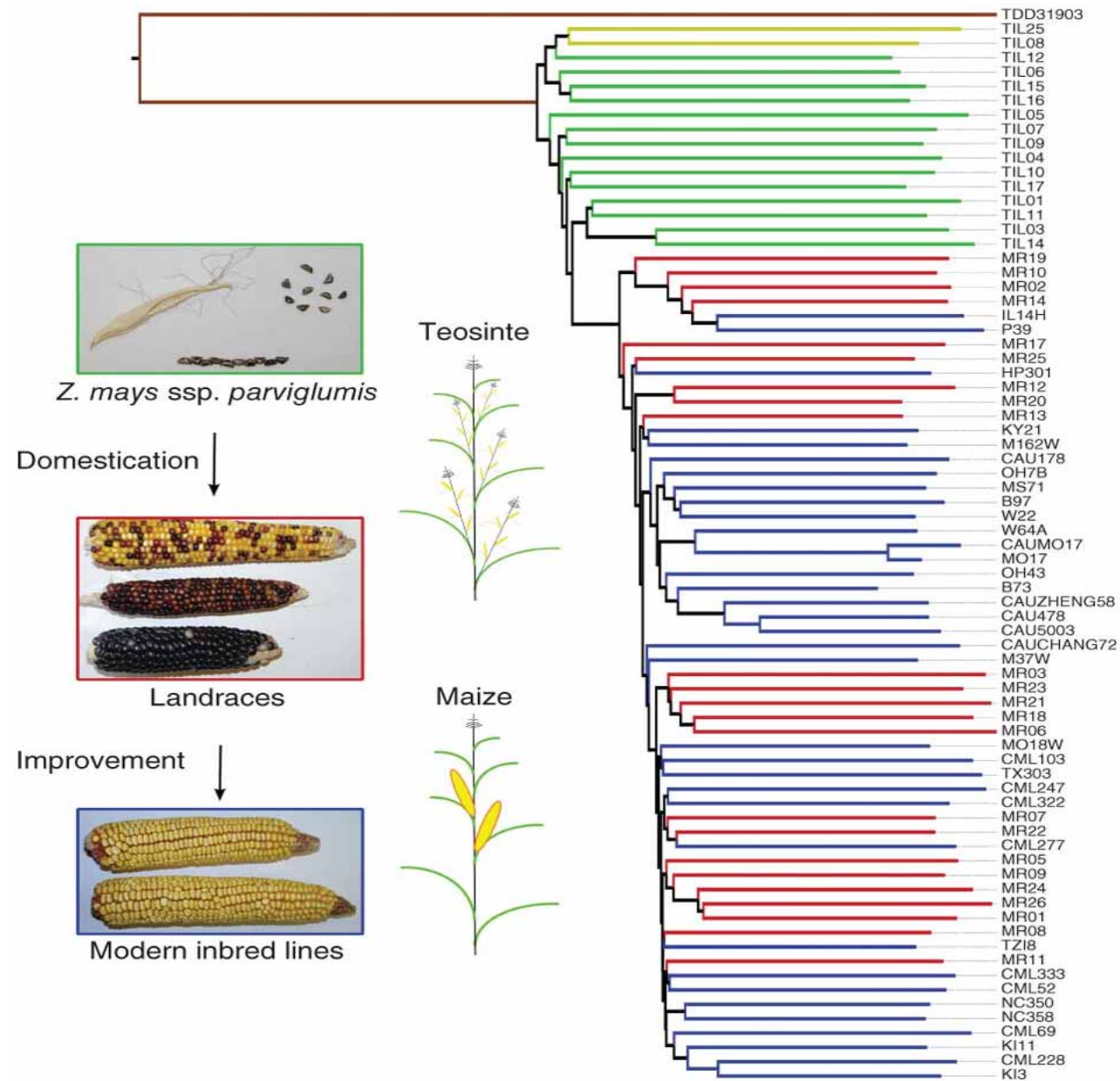
Evolutionary dynamics act on populations.
Neither genes, nor cells, nor individuals evolve;
only populations evolve.

Initial population

Select for reproduction

Select for death

Replace

Lieberman, E., Hauert, C. & Nowak, M. A.
(2005) Evolutionary dynamics on graphs.
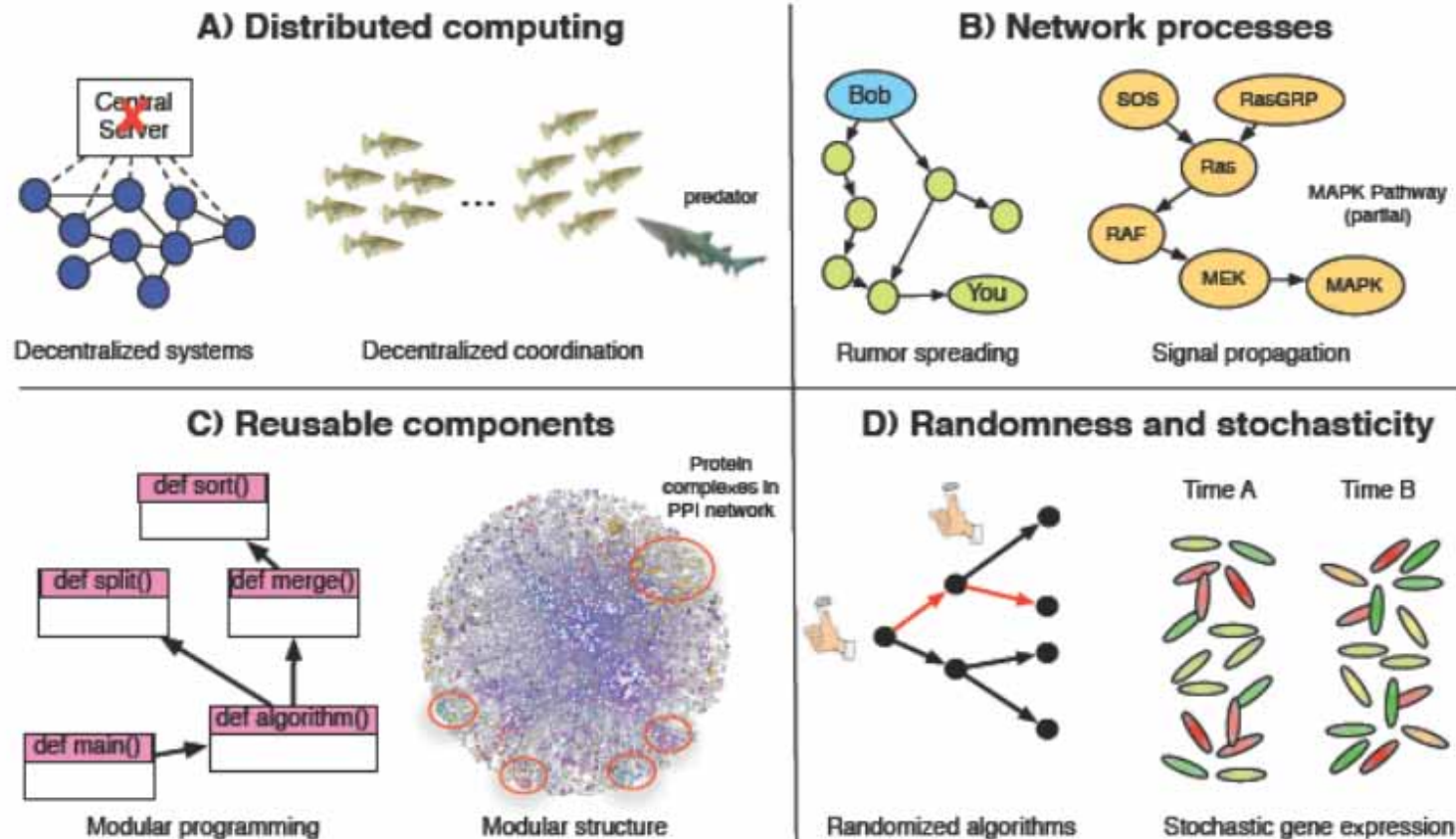*Nature, 433, 7023, 312-316.*

$$W = \begin{bmatrix} 0 & w_{12} & w_{13} & 0 & 0 \\ 0 & 0 & w_{23} & w_{24} & 0 \\ w_{31} & 0 & 0 & 0 & w_{35} \\ 0 & w_{42} & 0 & 0 & 0 \\ 0 & 0 & 0 & w_{54} & 0 \end{bmatrix}$$

Hufford et. al. 2012. Comparative population genomics of maize domestication and improvement. *Nature Genetics, 44, (7), 808-811.*

A) Distributed computing
Decentralized systems — Decentralized coordination — predator

B) Network processes
Rumor spreading — Signal propagation — MAPK Pathway (partial)

C) Reusable components
Modular programming — Modular structure — Protein complexes in PPI network

D) Randomness and stochasticity
Randomized algorithms — Stochastic gene expression — Time A — Time B

http://cacm.acm.org/magazines/2015/1/181614-distributed-information-processing-in-biological-and-computational-systems/abstract

Navlakha, S. & Bar-Joseph, Z. 2014. Distributed information processing in biological and computational systems. Commun. ACM, 58, (1), 94-102.

https://www.youtube.com/watch?v=4u47nwHzqI4&feature=youtu.be
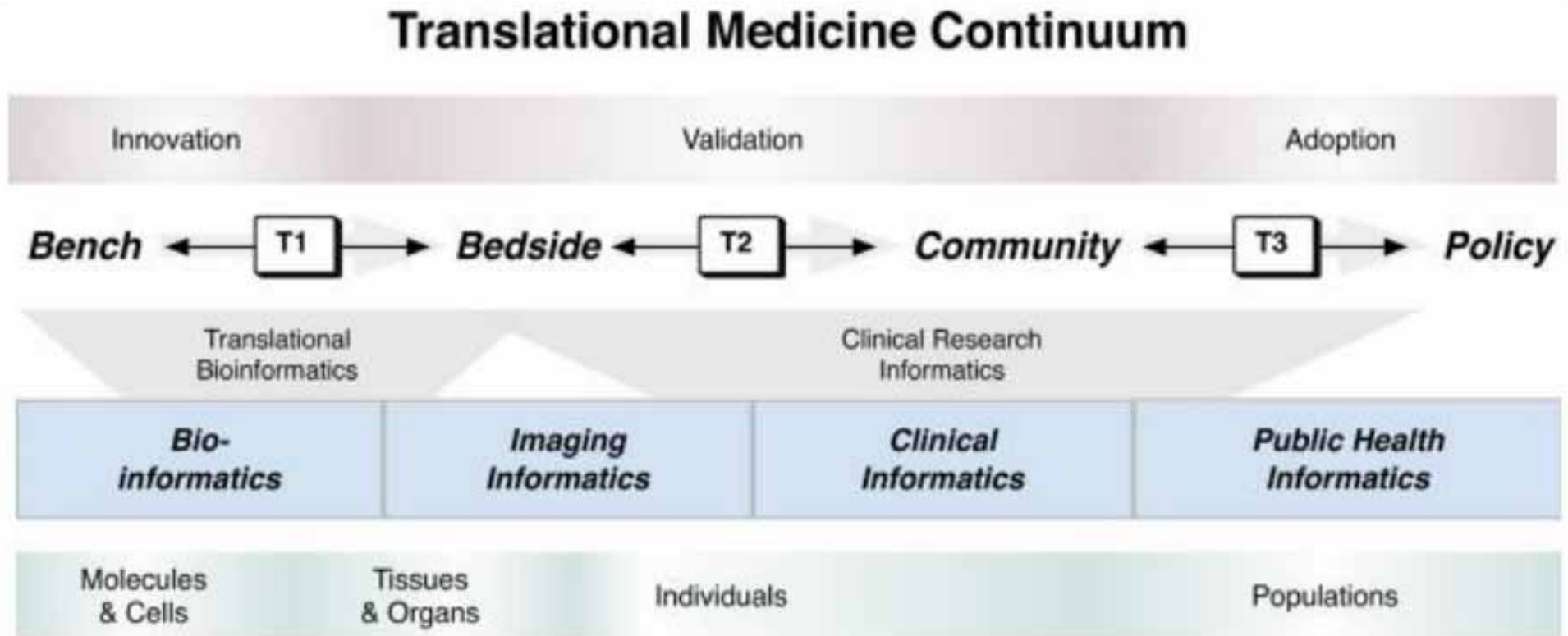
Sarkar, I. 2010. Biomedical informatics and translational medicine. Journal of Translational Medicine, 8, (1), 2-12.

- Grand Challenges in this area:
- – Production of Open Data Sets
- – Synthetic data sets for learning algorithm testing
- – Privacy preserving machine learning
- – Data leak detection
- – Data citation
- – Differential privacy
- – Anonymization and pseudonymization
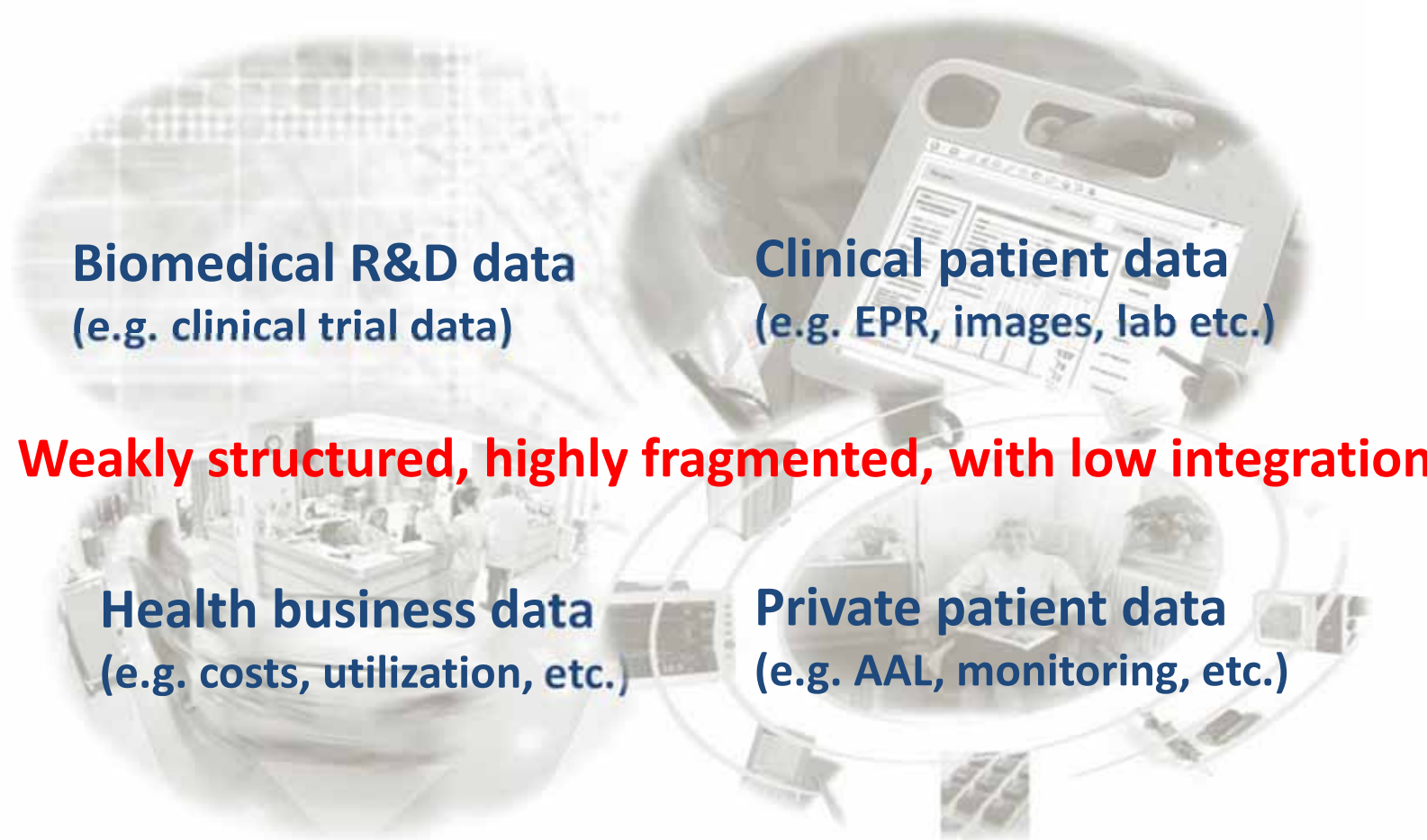- – Evaluation and benchmarking

Please visit:
http://hci-kdd.org/privacy-aware-machine-learning-for-data-science/

Unsolved Problem:
Data Integration and
Data Fusion in the
Life Sciences

How to combine these different data types together to obtain a unified view of the activity in the cell is one of the major challenges of systems biology

Navlakha, S. & Bar-Joseph, Z. 2014. Distributed information processing in biological and computational systems. *Commun. ACM,* 58, (1), 94-102, doi:10.1145/2678280.

Biomedical R&D data
(e.g. clinical trial data)

Clinical patient data
(e.g. EPR, images, lab etc.)

Weakly structured, highly fragmented, with low integration

Health business data
(e.g. costs, utilization, etc.)

Private patient data
(e.g. AAL, monitoring, etc.)

Manyika, J., Chui, M., Brown, B., Bughin, J., Dobbs, R., Roxburgh, C. & Byers, A. H. (2011) *Big data: The next frontier for innovation, competition, and productivity. Washington (DC), McKinsey Global Institute.*
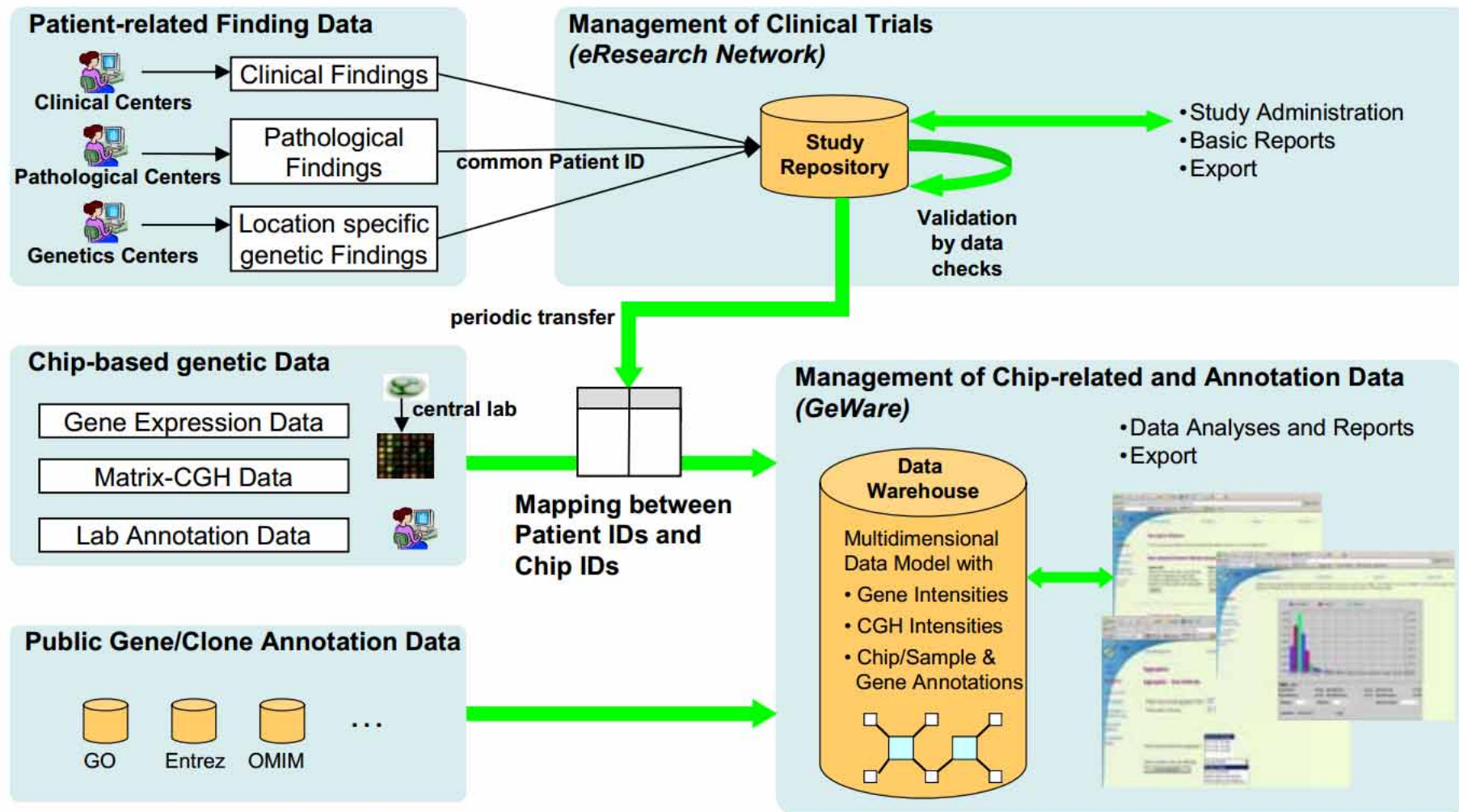
Kirsten, T., Lange, J. & Rahm, E. 2006. An integrated platform for analyzing molecular-biological data within clinical studies. Current Trends in Database Technology–EDBT 2006. Heidelberg: Springer, pp. 399-410, doi:10.1007/11896548_31.
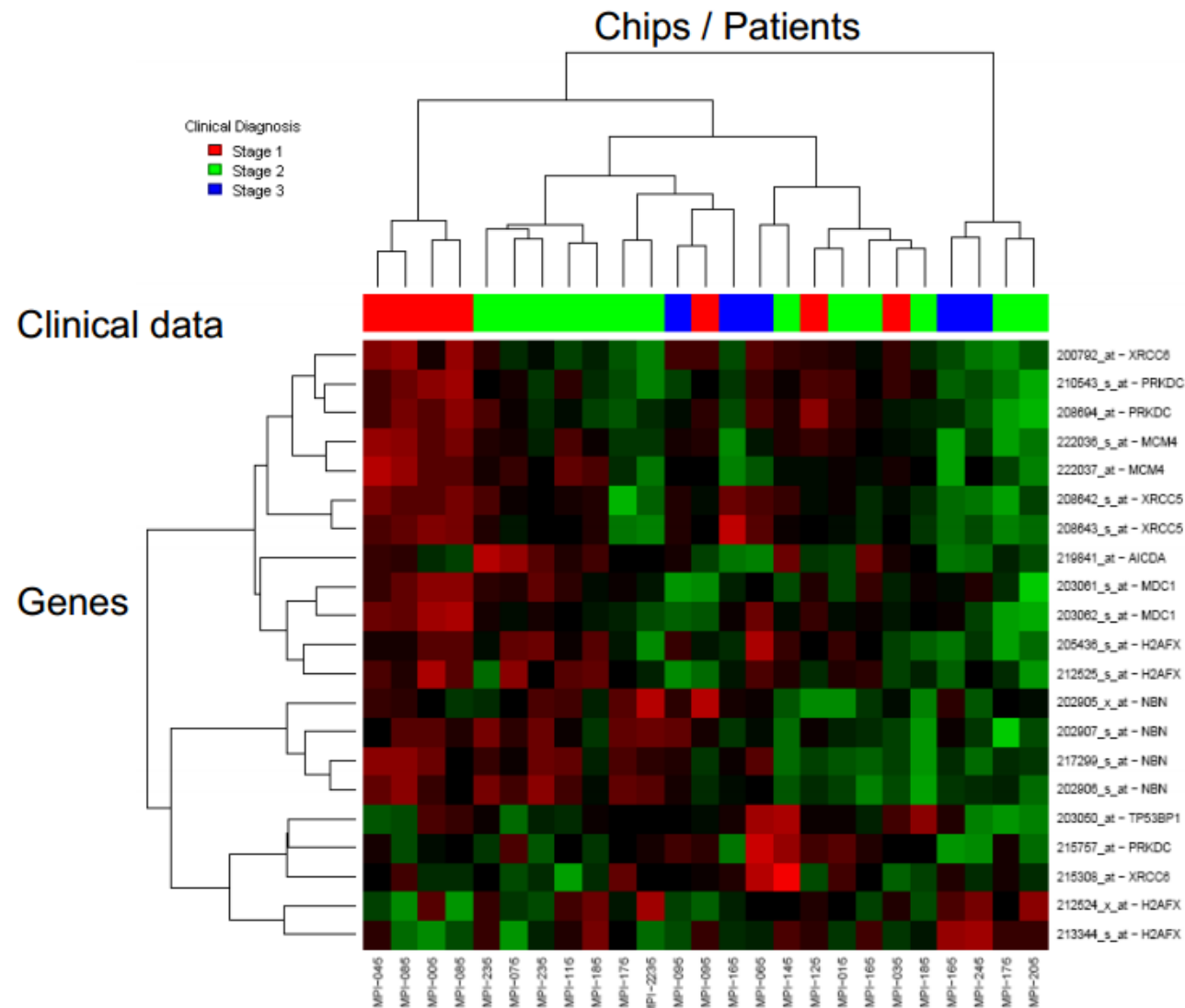
Kirsten, T., Lange, J. & Rahm, E. 2006. An integrated platform for analyzing molecular-biological data within clinical studies. Current Trends in Database Technology–EDBT 2006. Heidelberg: Springer, pp. 399-410, doi:10.1007/11896548_31.

- **Gen**omics (sequence annotation)
- **Transcript**omics (microarray)
- **Prote**omics (Proteome Databases)
- **Metabol**omics (enzyme annotation)
- **Flux**omics (isotopic tracing, metabolic pathways)
- **Phen**omics (biomarkers)
- **Epigen**omics (epigenetic modifications)
- **Microbi**omics (microorganisms)
- **Lipid**omics (pathways of cellular lipids)
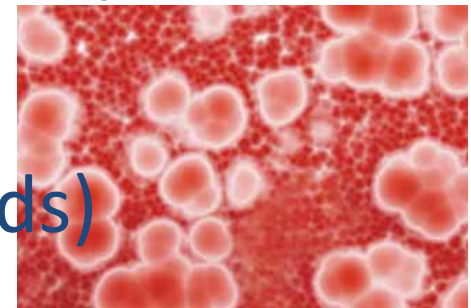
Genomics	Transcriptomics	Proteomics	Metabolomics	Protein–DNA interactions	Protein–protein interactions	Fluxomics	Phenomics
Genomics (sequence annotation)	• ORF validation • Regulatory element identification[74]	• SNP effect on protein activity or abundance	• Enzyme annotation	• Binding-site identification[75]	• Functional annotation[79]	• Functional annotation	• Functional annotation[71,101] • Biomarkers[125]
	Transcriptomics (microarray, SAGE)	• Protein: transcript correlation[20]	• Enzyme annotation[109]	• Gene-regulatory networks[76]	• Functional annotation[89] • Protein complex identification[82]		• Functional annotation[102]
		Proteomics (abundance, post-translational modification)	• Enzyme annotation[99]	• Regulatory complex identification	• Differential complex formation	• Enzyme capacity	• Functional annotation
			Metabolomics (metabolite abundance)	• Metabolic-transcriptional response		• Metabolic pathway bottlenecks	• Metabolic flexibility • Metabolic engineering[109]
				Protein–DNA interactions (ChIP–chip)	• Signalling cascades[89,102]		• Dynamic network responses[84]
					Protein–protein interactions (yeast 2H, coAP–MS)		• Pathway identification activity[89]
						Fluxomics (isotopic tracing)	• Metabolic engineering
							Phenomics (phenotype arrays, RNAi screens, synthetic lethals)

Joyce, A. R. & Palsson, B. Ø. 2006. The model organism as a system: integrating'omics' data sets. *Nature Reviews Molecular Cell Biology, 7*, *198-210.*

- 50+ Patients per day ~ 5000 data points per day ...

- Aggregated with specific scores (Disease Activity Score, DAS)

- Current patient status is related to previous data

- = convolution over time

- ⇒ **time-series data**
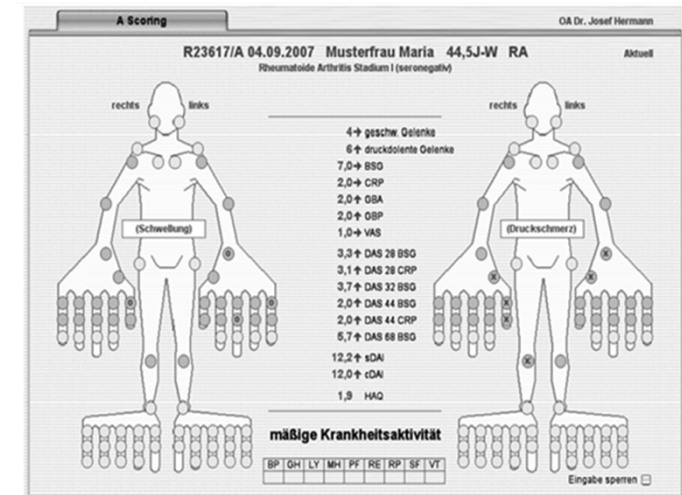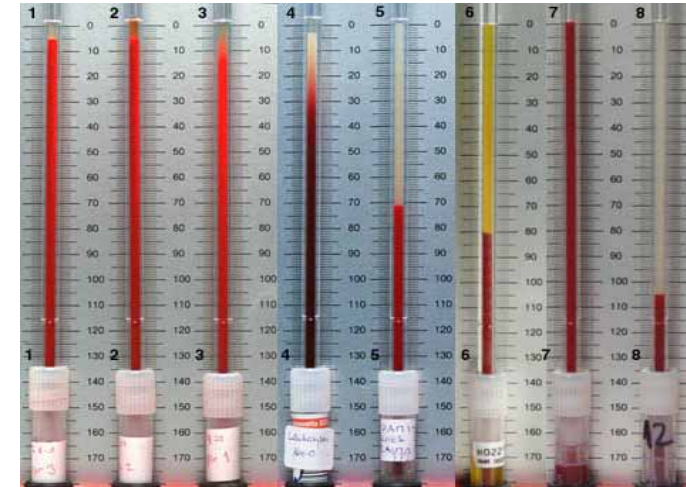
Simonic, K. M., Holzinger, A., Bloice, M. & Hermann, J. (2011). *Optimizing Long-Term Treatment of Rheumatoid Arthritis with Systematic Documentation. Pervasive Health - 5th International Conference on Pervasive Computing Technologies for Healthcare, Dublin, IEEE, 550-554.*

Simonic, K. M., Holzinger, A., Bloice, M. & Hermann, J. (2011). *Optimizing Long-Term Treatment of Rheumatoid Arthritis with Systematic Documentation. Pervasive Health - 5th International Conference on Pervasive Computing Technologies for Healthcare, Dublin, IEEE, 550-554.*

Standardization versus Structurization

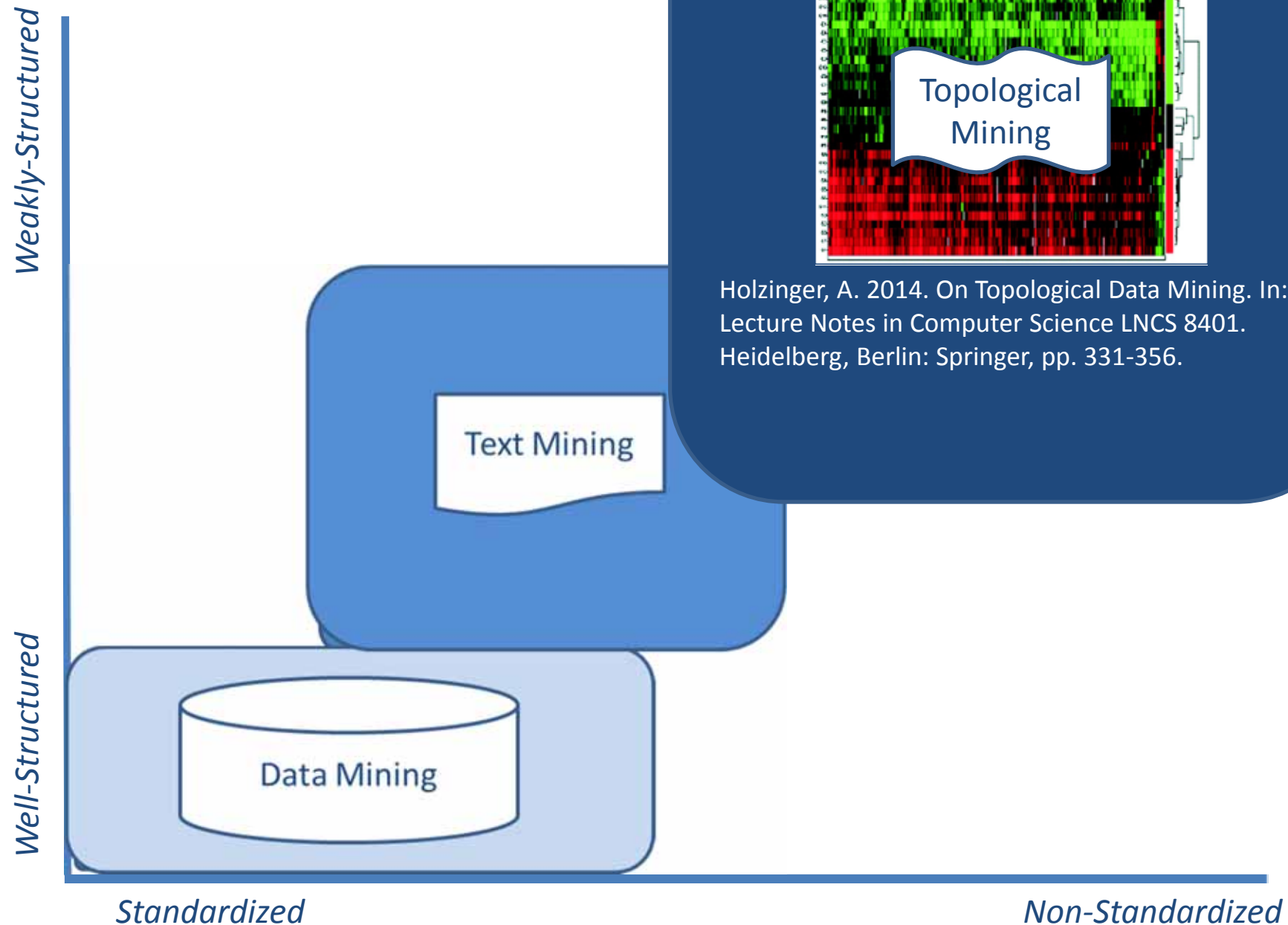Holzinger, A. (2011) Weakly Structured Data in Health-Informatics: The Challenge for Human-Computer Interaction. In: Baghaei, N., Baxter, G., Dow, L. & Kimani, S. (Eds.) *Proceedings of INTERACT 2011 Workshop: Promoting and supporting healthy living by design. Lisbon, IFIP, 5-7.*

Weakly-Structured

Well-Structured

Omics Data

Natural Language Text

XML

Databases Libraries

RDF, OWL

Standardized   *Non-Standardized*

Methods for Mining …

Weakly-Structured ↑

Well-Structured

Topological Mining

Holzinger, A. 2014. On Topological Data Mining. In: Lecture Notes in Computer Science LNCS 8401. Heidelberg, Berlin: Springer, pp. 331-356.

Text Mining

Data Mining

Standardized → *Non-Standardized*
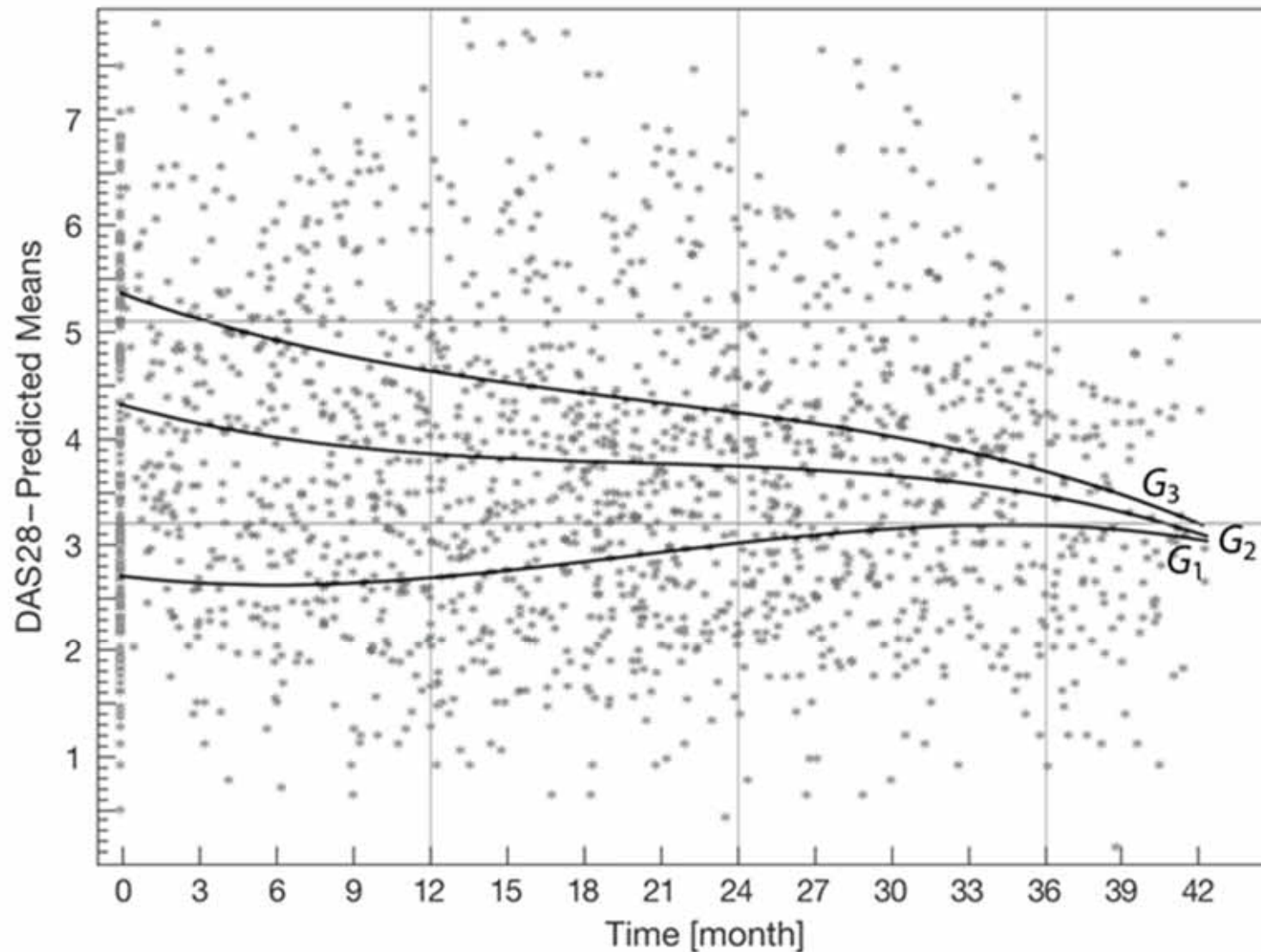
- 0-D data = a <u>data point</u> existing isolated from other data, e.g. integers, letters, Booleans, etc.

- 1-D data = consist of a <u>string</u> of 0-D data, e.g. Sequences representing nucleotide bases and amino acids, SMILES etc.

- 2-D data = having <u>spatial component</u>, such as images, NMR-spectra etc.

- 2.5-D data = can be stored as a 2-D matrix, but can represent biological entities in three or more dimensions, e.g. <u>PDB records</u>

- 3-D data = having <u>3-D spatial component</u>, e.g. image voxels, e-density maps, etc.

- H-D Data = data having arbitrarily <u>high dimensions</u>

SMILES (Simplified Molecular Input Line Entry Specification)

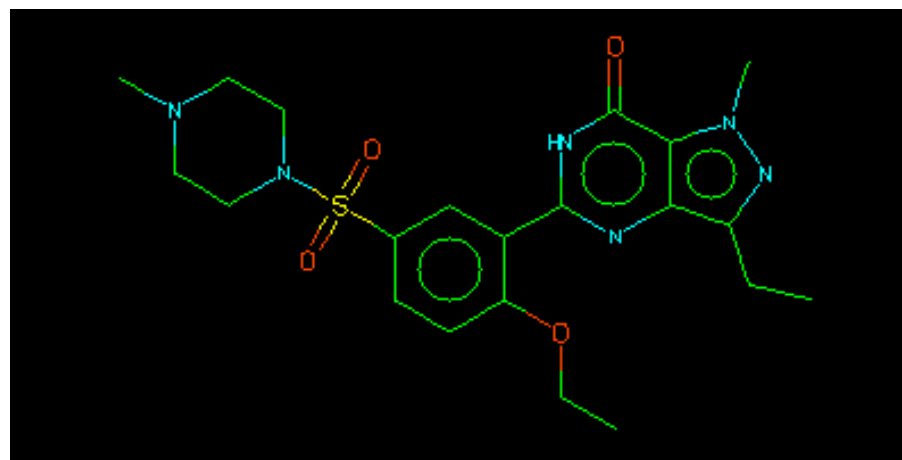… is a compact machine and human-readable chemical nomenclature:

e.g. Viagra:

CCc1nn(C)c2c(=O)[nH]c(nc12)c3cc(ccc3OCC)S(=O)(=O)N4CCN(C)CC4

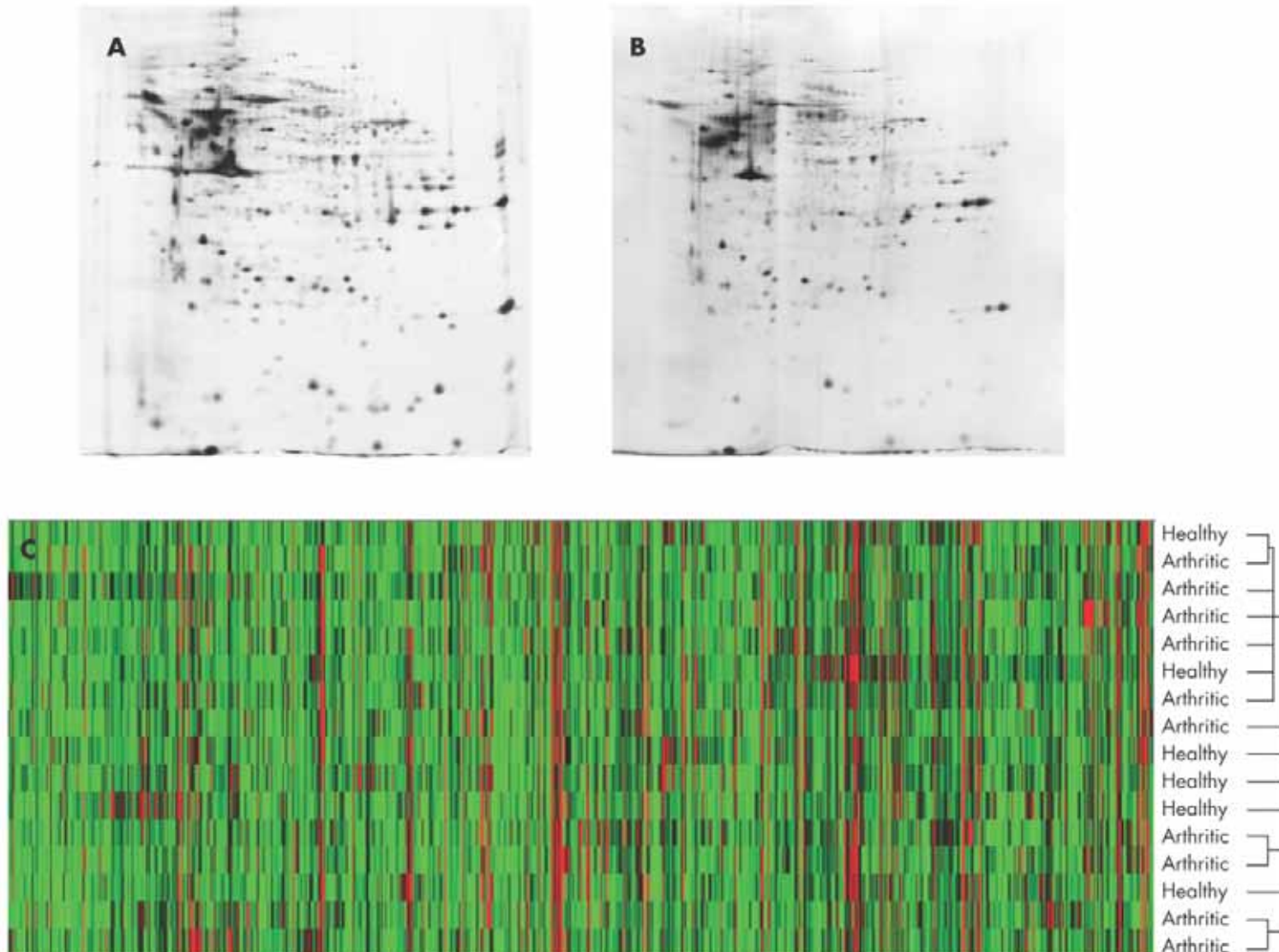…is Canonicalizable

…is Comprehensive

…is Well Documented

http://www.daylight.com/dayhtml_tutorials/languages/smiles/index.html

Kastrinaki et al. (2008) Functional, molecular & proteomic characterisation of bone marrow mesenchymal stem cells in rheumatoid arthritis. *Annals of Rheumatic Diseases, 67, 6, 741-749.*

Example: 2.5-D data (structural information & metadata)

http://www.pdb.org

Scheins, J. J., Herzog, H. & Shah, N. J. (2011) Fully-3D PET Image Reconstruction Using Scanner-Independent, Adaptive Projection Data and Highly Rotation-Symmetric Voxel Assemblies. *Medical Imaging, IEEE Transactions on*, 30, 3, 879-892.

1 dimension:
10 positions

2 dimensions:
100 positions

3 dimensions:
1000 positions!
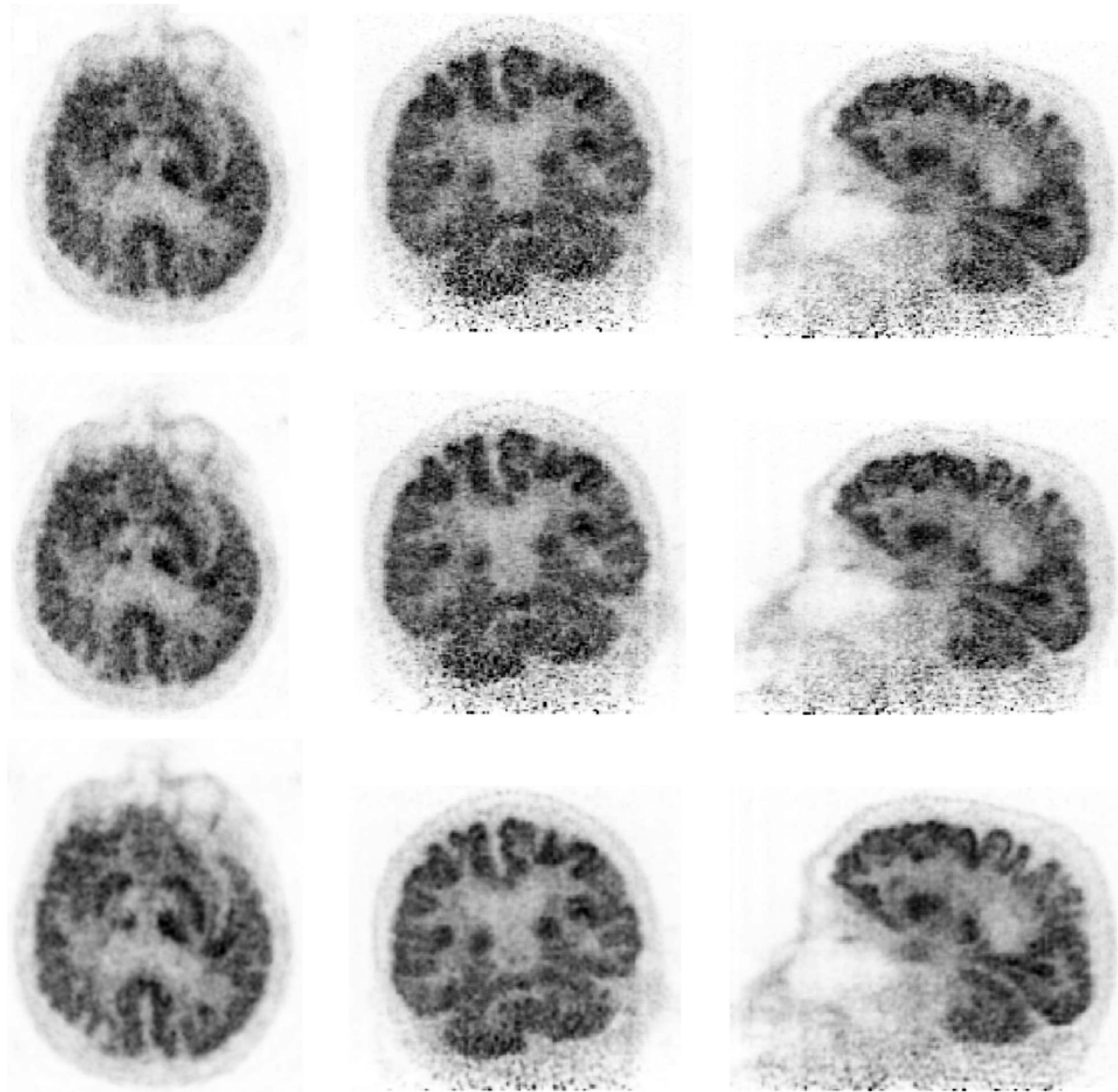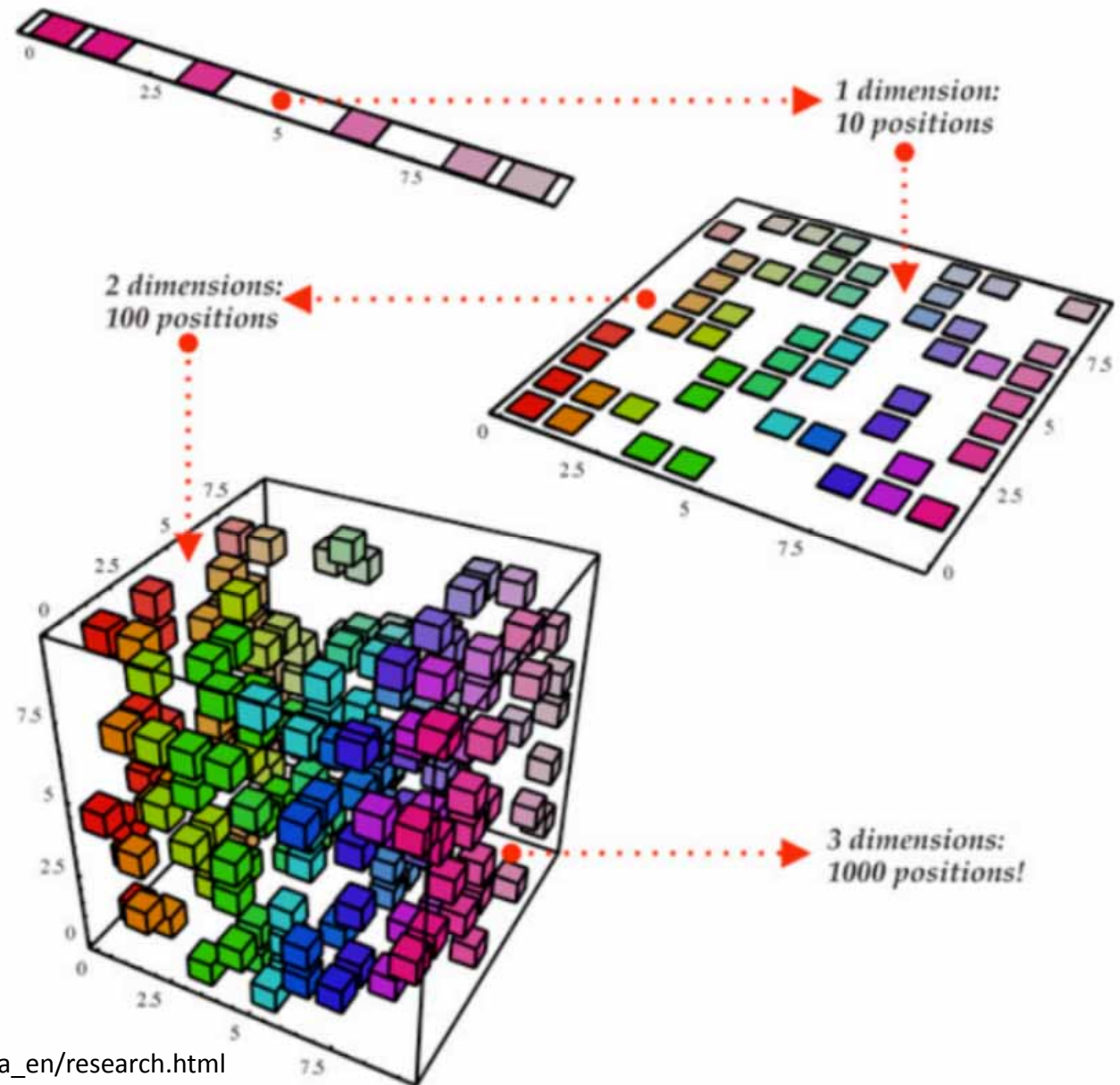
Bengio, S. & Bengio, Y. 2000. Taking on the curse of dimensionality in joint distributions using neural networks. IEEE Transactions on Neural Networks, 11, (3), 550-557.

http://www.iro.umontreal.ca/~bengioy/yoshua_en/research.html

$$f : X \rightarrow \mathbb{R}$$
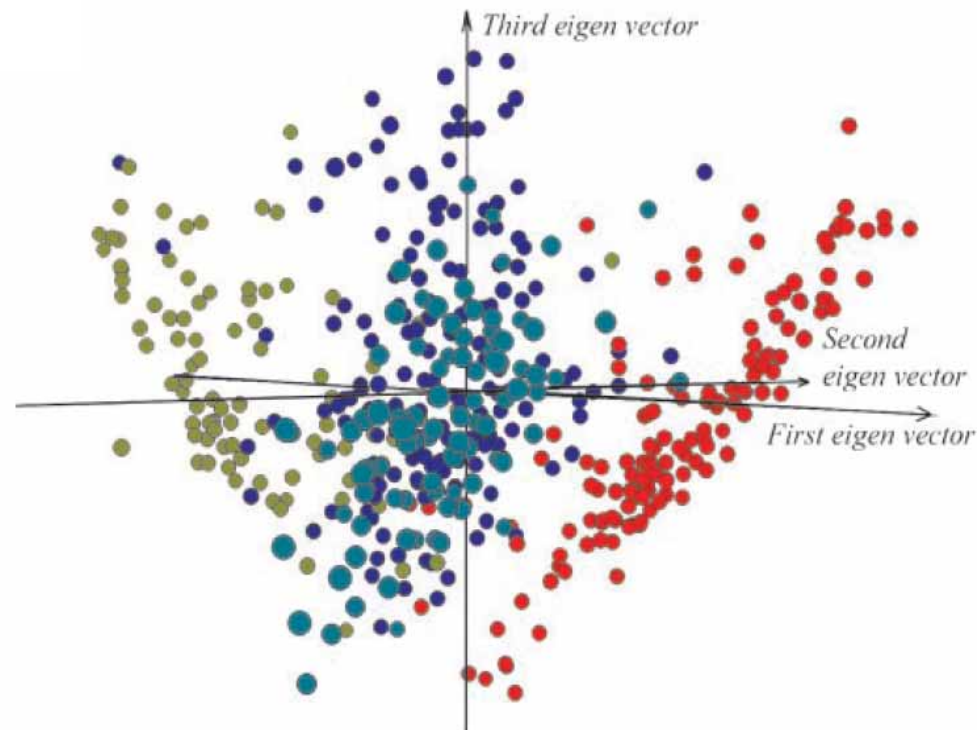
Hou, J., Sims, G. E., Zhang, C. & Kim, S.-H. 2003. A global representation of the protein fold space. *Proceedings of the National Academy of Sciences, 100, (5), 2386-2390.*

Let us collect n-dimensional i observations: $\boldsymbol{x}_i = [x_{i1}, \ldots, x_{in}]$
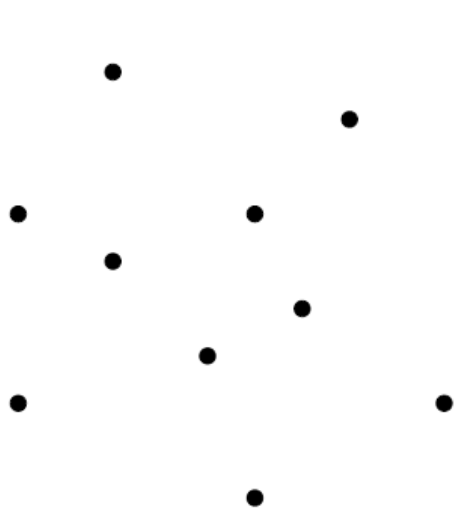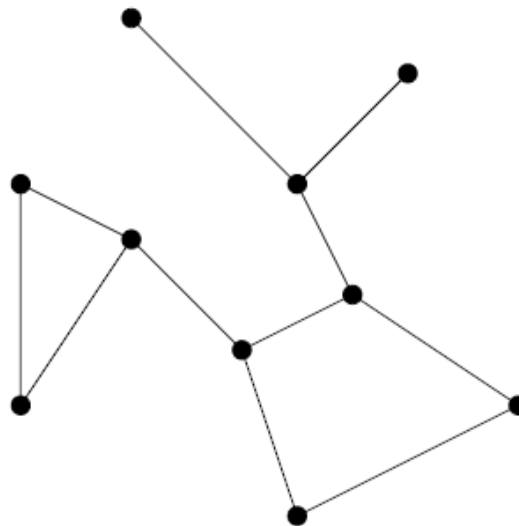
Point cloud in $\mathbb{R}^2$ **topological space**   **metric space**
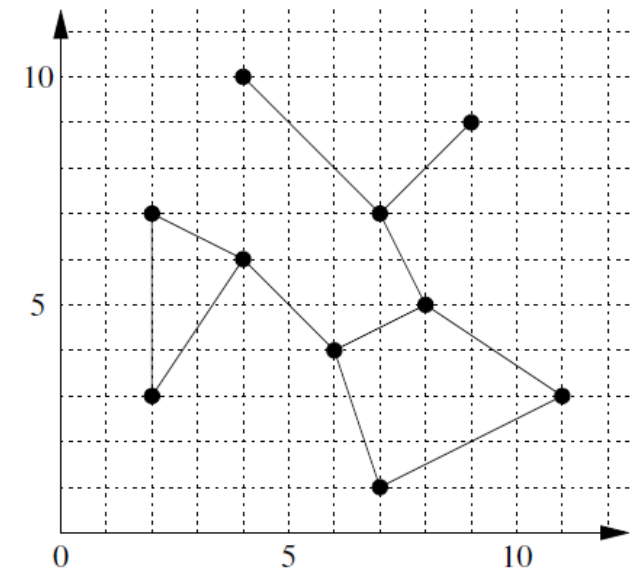
Zomorodian, A. J. 2005. *Topology for computing, Cambridge (MA), Cambridge University Press.*

A set S with a metric function d is a metric space
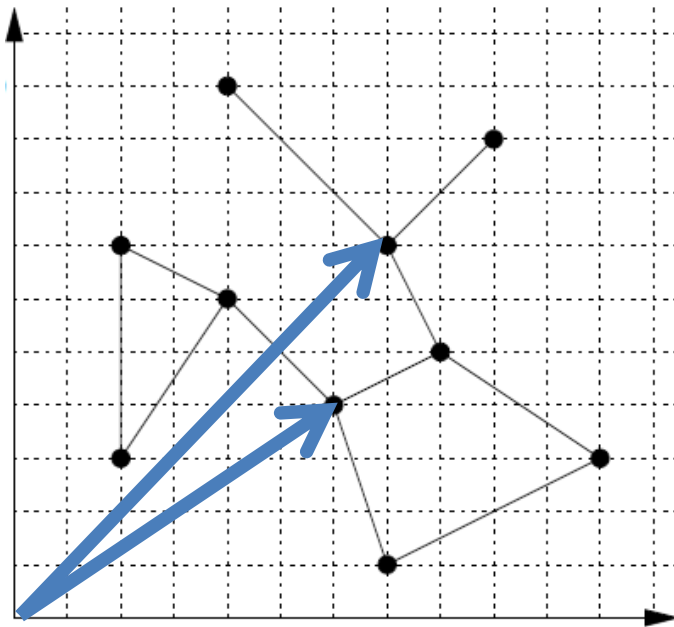
$$d_{ij} = \sqrt{\sum_{k=1}^{p} (x_{ik} - x_{jk})^2}$$

Doob, J. L. 1994. *Measure theory, Springer New York.*
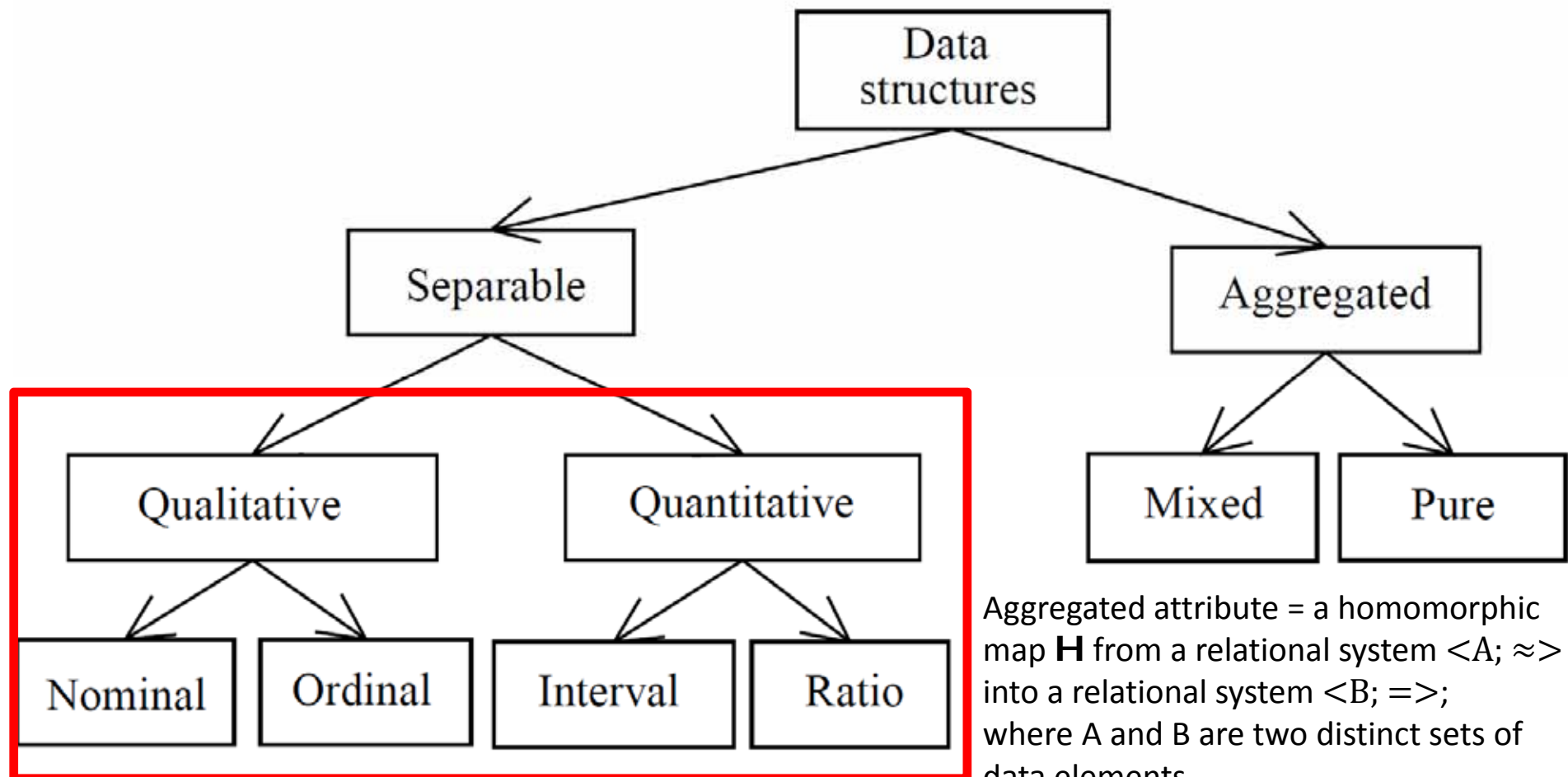
Dastani, M. (2002) The Role of Visual Perception in Data Visualization. *Journal of Visual Languages and Computing, 13, 601-622.*

Aggregated attribute = a homomorphic map **H** from a relational system $<A; \approx>$ into a relational system $<B; =>$; where A and B are two distinct sets of data elements.

This is in contrast with other attributes since the set B is the set of data elements instead of atomic values.

Categorization of Data (Classic "scales")

Scale	Empirical Operation	Mathem. Group Structure	Transf. in $\mathbb{R}$	Basic Statistics	Mathematical Operations
NOMINAL	Determination of equality	Permutation $x' = f(x)$ x … 1-to-1	$x \mapsto f(x)$	Mode, contingency correlation	$=, \neq$
ORDINAL	Determination of more/less	Isotonic $x' = f(x)$ x … mono-tonic incr.	$x \mapsto f(x)$	Median, Percentiles	$=, \neq, >, <$
INTERVAL	Determination of equality of intervals or differences	General linear $x' = ax + b$	$x \mapsto rx+s$	Mean, Std.Dev. Rank-Order Corr., Prod.-Moment Corr.	$=, \neq, >, <, -, +$
RATIO	Determination of equality or ratios	Similarity $x' = ax$	$x \mapsto rx$	Coefficient of variation	$=, \neq, >, <, -, +, *, \div$

Stevens, S. S. (1946) On the theory of scales of measurement. *Science, 103, 677-680.*

- Bridging the gap between natural sciences and clinical medicine

- Organizational barriers, data provenance, data ownership, privacy, accessibility, usability, fair use of data, security, safety

- Combine Ontologies with Machine Learning

- Stochastic Ontologies, Ontology learning

- Integration of data from wet-labs with in-silico experimental data (e.g. tumor growth simulation)

4) Clinical view on data – information, and knowledge

Implicit Knowledge

Explicit Knowledge

Medical Professional

Information

Inter-action

Patient or Bioprocess

Data → Inter-pretation

Data → Inter-pretation

Data → Inter-pretation

Interpreted Data

Induction → Body of Knowledge
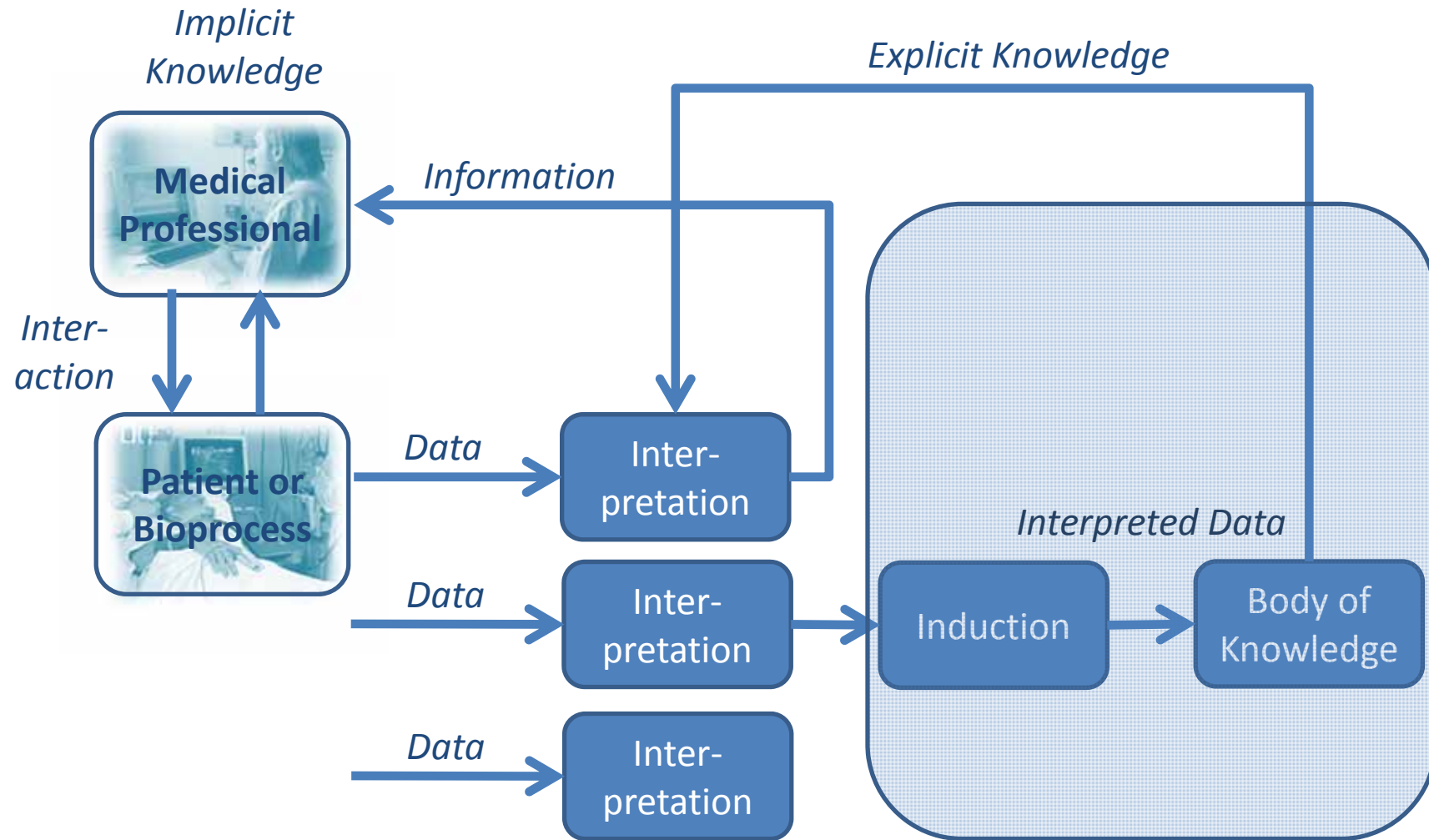
Bemmel, J. H. v. & Musen, M. A. (1997) *Handbook of Medical Informatics. Heidelberg, Springer.*

Induction

Symptoms
Diagnoses
…
Images
Visualizations
Biosignals
…
HIS
MIS
RIS
PACS

…

Nosology
Pathology
Physiology
Anatomy
…
Therapeutic
Knowledge

Experience
Pre-Knowledge
Intuition

many
patients

general
knowledge

Deduction

single
patient

general
knowledge
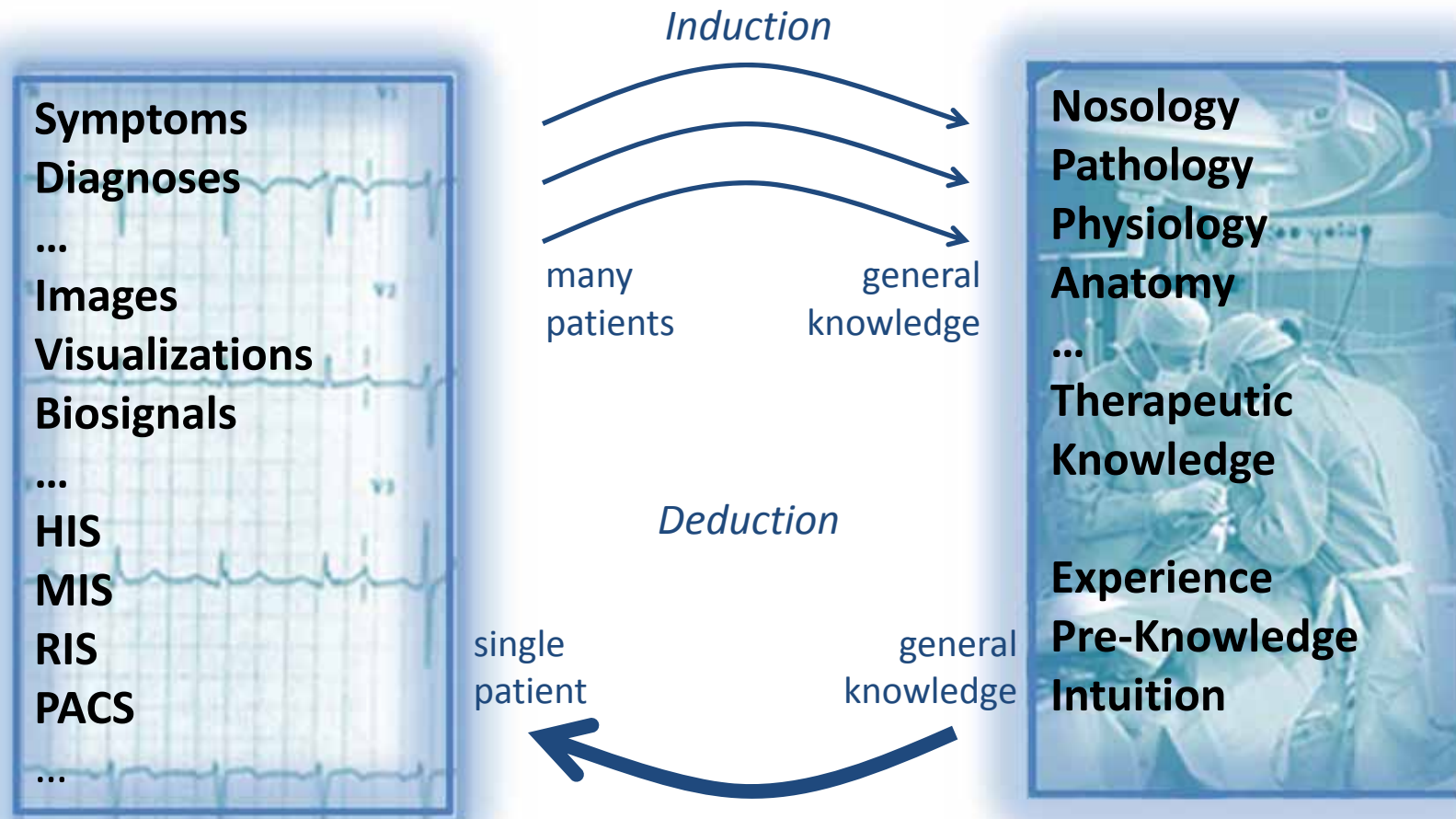
Holzinger (2007)
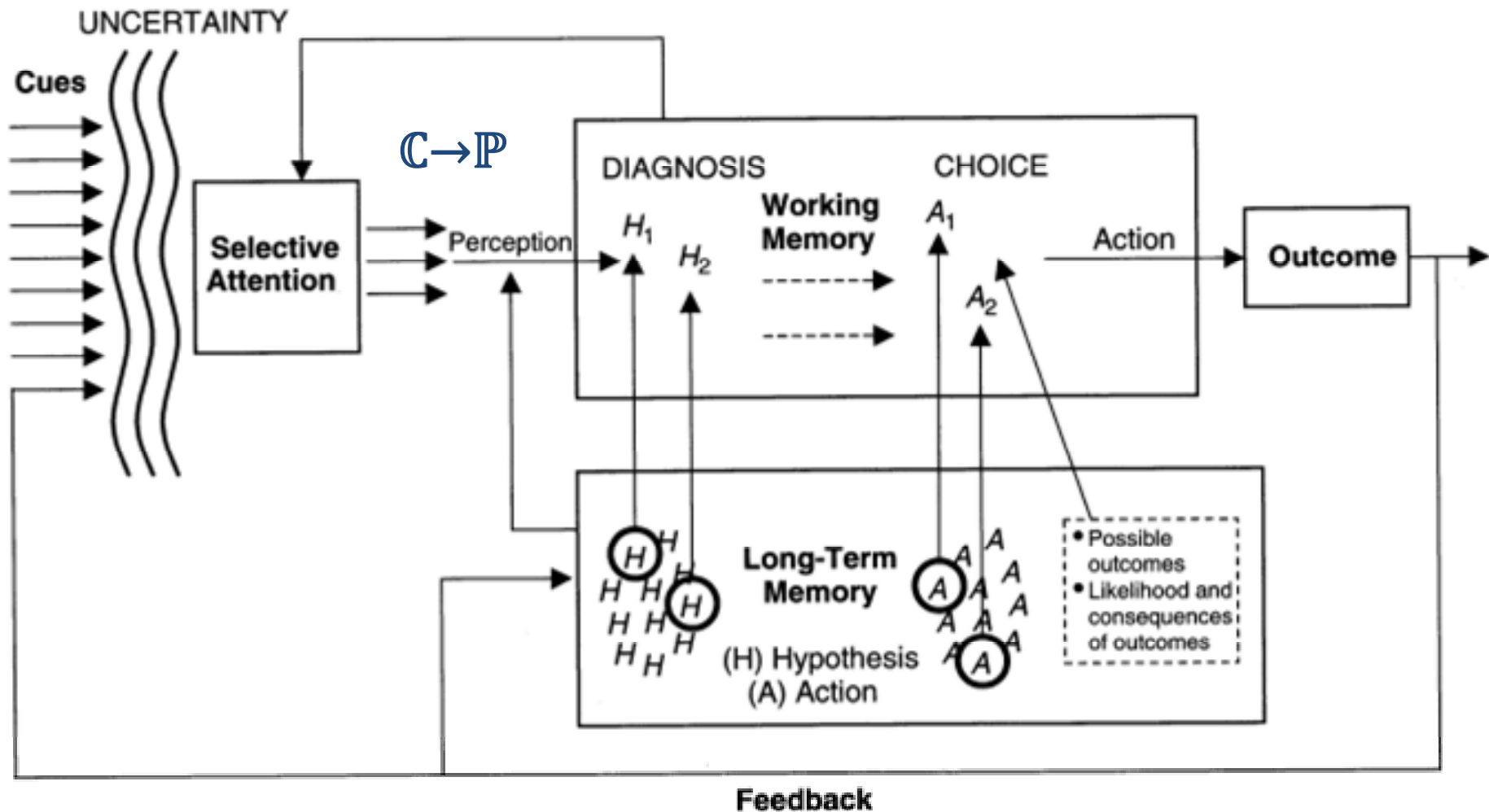
Wickens, C. D. (1984) *Engineering psychology and human performance. Columbus: Merrill.*

Data   **Information**   **Knowledge**

World

Mental Models
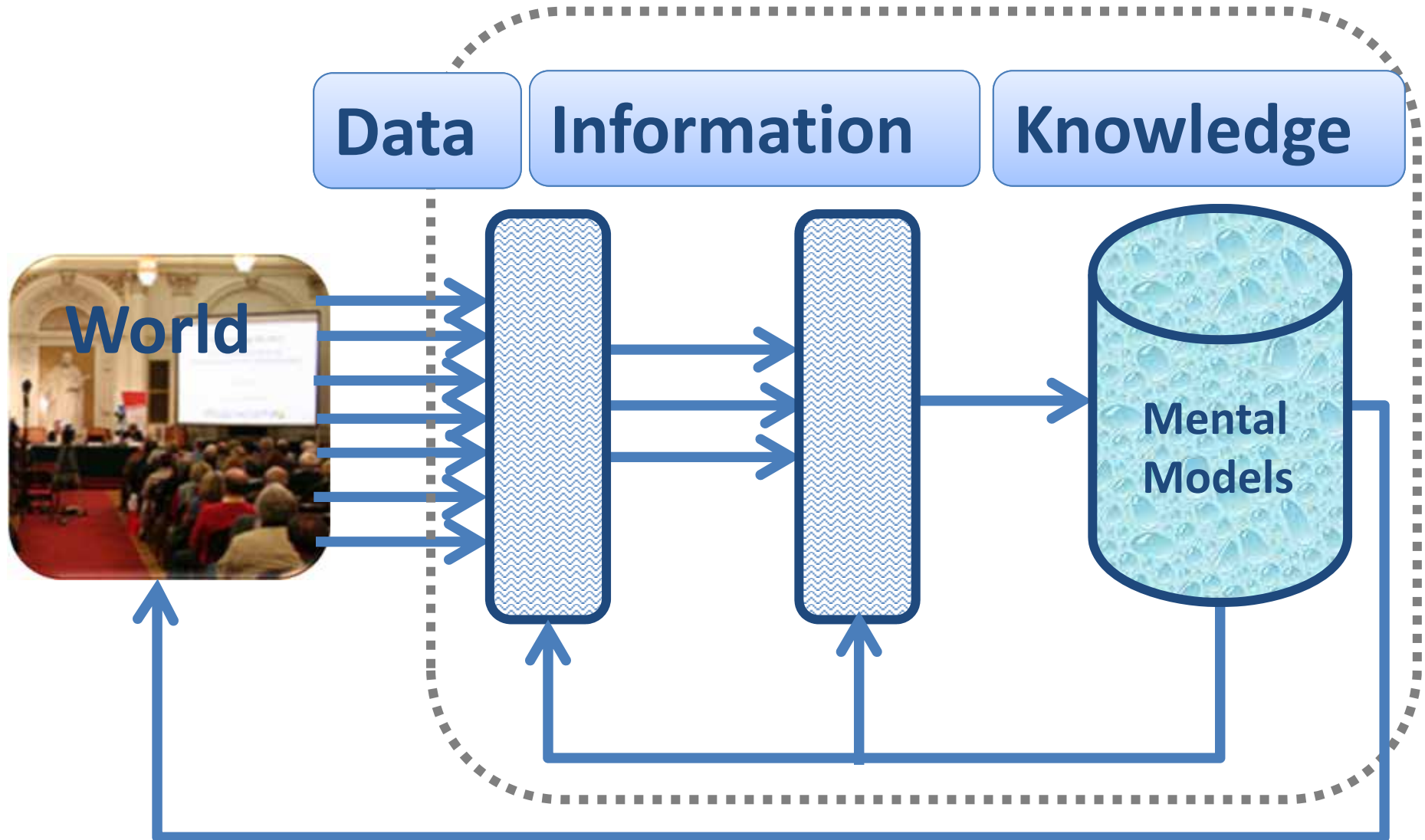
Knowledge := a set of expectations

5 μm

What is information?
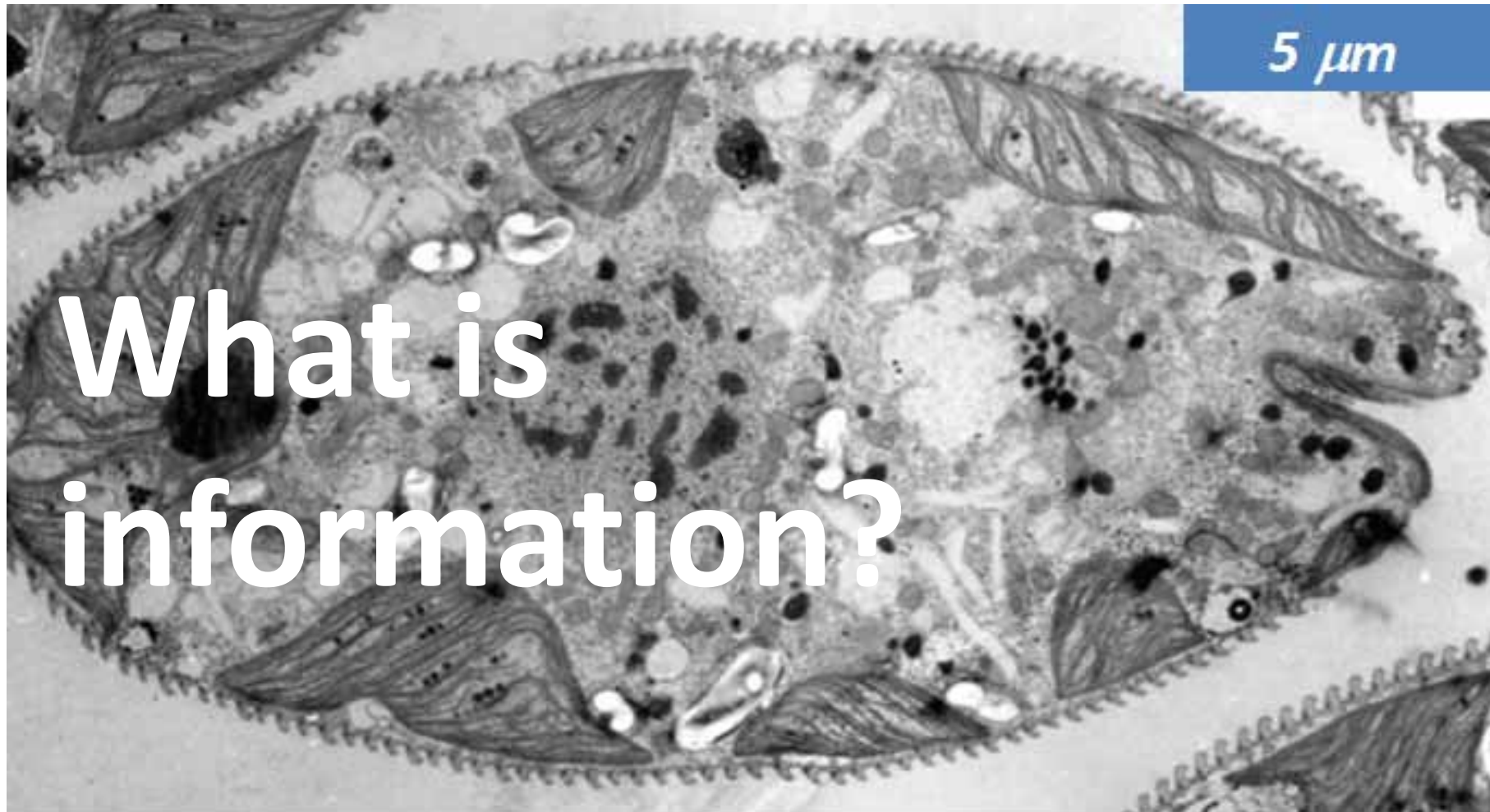
Lane, N. & Martin, W. (2010) The energetics of genome complexity.
Nature, 467, 7318, 929-934.

▪Boolean

▪Algebraic

▪Probabilistic *)

*) Our probabilistic model describes data which we can observe from our environment – and if we use the mathematics of probability theory , in order to express the uncertainties around our model then the inverse probability allows us to infer unknown unknowns … learning from data and making predcitons – the core essence of machine learning and of vital importance for health informatics

Ghahramani, Z. 2015. Probabilistic machine learning and artificial intelligence. Nature, 521, (7553), 452-459, doi:10.1038/nature14541.

61

5) Probabilistic Information p(x)

Probabilistic Information p(x)

Bayes, T. (1763). An Essay towards solving a Problem in the Doctrine of Chances (Postum communicated by Richard Price). Philosophical Transactions, 53, 370-418.

Thomas Bayes
1701 - 1761

$$p(x_i) = \sum P(x_i, y_j) \qquad p(x_i, y_j) = p(y_j|x_i)P(x_i)$$

Bayes' Rule is a corollary of the Sum Rule and Product Rule:

$$p(x_i|y_j) = \frac{p(y_j|x_i)p(x_i)}{\sum p(x_i, y_j)p(x_i)}$$

Barnard, G. A., & Bayes, T. (1958). Studies in the history of probability and statistics: IX. Thomas Bayes's essay towards solving a problem in the doctrine of chances. Biometrika, 45(3/4), 293-315.

Bayes' Rule in words
d ... data; *h* ... hypothesis
H ={H$_1$, H$_2$, ... , H$_n$} ... Hypothesis space

$$\forall h, d \ \ ...$$

Likelihood

Prior Probability

Posterior Probability

$$p(h|d) = \frac{p(d|h)p(h)}{\sum_{h \in H} p(d|h')\, p(h')}$$

Evidence

Sum over space of alternative hypotheses

The inverse probability allows to infer unknowns, <u>learn from data</u> and make **predictions:**

1) Maximum-Likelihood Learning

finds a parameter setting, that maximizes the p(x) of the data: $P(\mathcal{D}|\theta)$

2) Maximum a Posteriori Learning

assumes a prior over the model parameters $P(\theta)$ and finds a parameter setting that maximizes the posterior: $P(\theta|\mathcal{D}) \propto P(\theta)P(\mathcal{D}|\theta)$.

3) Bayesian Learning

assumes a prior over the model parameters and computes the posterior distribution $P(\theta|\mathcal{D})$.

- $X: S \rightarrow \mathbb{R}$ ("measure" of outcome)
- Events can be defined according to X
  - $E(X=a) = \{s_i \mid X(s_i)=a\}$
  - $E(X \geq a) = \{s_i \mid X(s_i) \geq a\}$
- Consequently, probabilities can be defined on X
  - $P(X=a) = P(E(X=a))$
  - $P(a \geq X) = P(E(a \geq X))$
- **partitioning the sample space**

- ## General setting:

  - ### Given a (hypothesized & probabilistic) model that governs the random experiment

  - ### The model gives a probability of any data $p(D|\theta)$ that depends on the parameter θ

  - ### Now, given actual sample data $X=\{x_1,...,x_n\}$, what can we say about the value of θ?

- ## Intuitively, take your best guess of θ -- "best" means "best explaining/fitting the data"

- ## Generally an <u>optimization problem</u>

- 1) Maximum likelihood estimation (given X)
  - "Best" means "data likelihood reaches maximum"

$$\hat{\theta} = \arg\max_{\theta} P(X|\theta)$$

  - **Problem: small sample**

- 2) Bayesian estimation (use posterior)

$$\hat{\theta} = \arg\max_{\theta} P(X|\theta) = \arg\max_{\theta} P(X|\theta)\, P(\theta)$$

  - "Best" means being consistent with our "prior" knowledge and explaining data well
  - **Problem: how to define prior?**

An example can be found in: Banerjee, O., El Ghaoui, L. & D'aspremont, A. 2008. Model selection through sparse maximum likelihood estimation for multivariate gaussian or binary data. *The Journal of Machine Learning Research,* 9, 485-516. Available via: http://arxiv.org/pdf/0707.0704

$$posterior\ p(x) = \frac{likelyhood * prior\ p(x)}{evidence}$$

Posterior:
$$p(\theta|X) \propto p(X|\theta)p(\theta)$$

Likelihood:
$$p(X|\theta)$$
$$X=(x_1,...,x_N)$$

Prior: $p(\theta)$

θ_α: prior mode

θ: posterior mode

θ_{ml}: ML estimate

θ
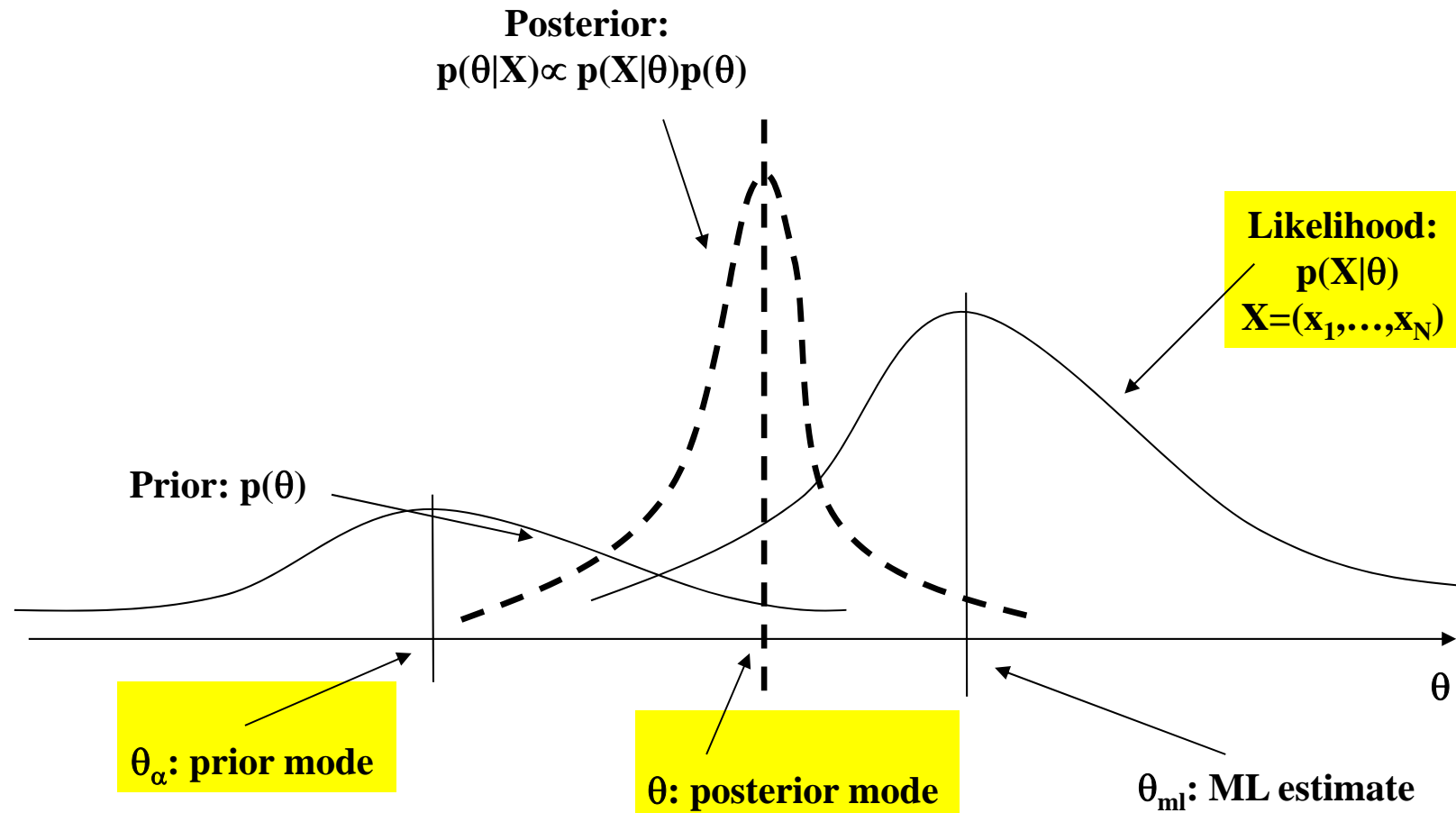
For more basic information: Bishop, C. M. 2007. *Pattern Recognition and Machine Learning,* Springer.
For application examples in Text processing refer to: Jiang, J. & Zhai, C. X. 2007. An empirical study of tokenization strategies for biomedical information retrieval. *Information Retrieval,* 10, (4-5), 341-363.

6) Information Theory – Information Entropy

- Communication (Hartley, Nyquist, Shannon)
- Coding Theory (Fano, Hamming, Reed, Solomon)
- Cryptography (Hellman, Rivest, Shamir, Adleman)
- Complexity (Kolmogovov, Chaitin) Computation, Chaos
- Cybernetics (Wiener, von Neumann, Langton)
- Foundations (Brillouin, Bennet, Landauer)
- Canonical Quantum Gravity (Wheeler, De-Witt)
- Metabiology (Conrad, Chaitin)

Unification via Information (Carlo Rovelli's books)

Universe's ultimate mechanism for existence might be
Information: "it from bit" (Wheeler's last speculation)

Manca, V. 2013. Infobiotics: Information in Biotic Systems, Heidelberg, Springer, doi:10.1007/978-3-642-36223-1.

- Information is the reduction of uncertainty

- If something is 100 % certain its uncertainty = 0

- Uncertainty is a max. if all choices are equally probable

- Uncertainty (as information) sums up for independent sources

low entropy
low complexity

medium entropy
high complexity

high entropy
low complexity

http://www.scottaaronson.com

My greatest concern was what to call it. I thought of calling it "information", but the word was overly used, so I decided to call it "uncertainty". When I discussed it with John von Neumann, he had a better idea. Von Neumann told me, "You should call it entropy, for two reasons. In the first place your uncertainty function has been used in statistical mechanics under that name, so it already has a name. In the second place, and more important, nobody knows what entropy really is, so in a debate you will always have the advantage."

Tribus, M. & McIrvine, E. C. (1971) Energy and Information. *Scientific American, 225, 3, 179-184.*

$$Q \ldots P = \{p_1, \ldots, p_n\} \qquad H(Q) = -\sum_{i=1}^{n}(p_i * \log p_i)$$

$$Qb = \{a_1, a_2\} \text{ with } P = \{p, 1-p\}$$

$$H(Qb) = p * \log\frac{1}{p} + p * \log\frac{1}{1-p}$$

Shannon, C. E. (1948) A Mathematical
Theory of Communication. *Bell System
Technical Journal, 27, 379-423.*

Shannon, C. E. & Weaver, W. (1949) *The
Mathematical Theory of Communication.
Urbana (IL), University of Illinois Press.*
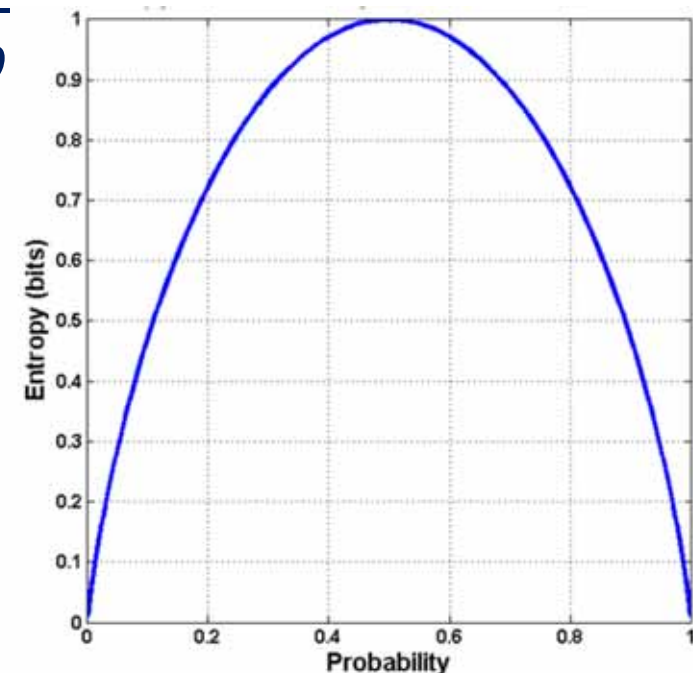
$$\log_2 \frac{1}{p} = -\log_2 p \qquad\qquad H = -\sum_{i=1}^{N} p_i \log_2(p_i)$$
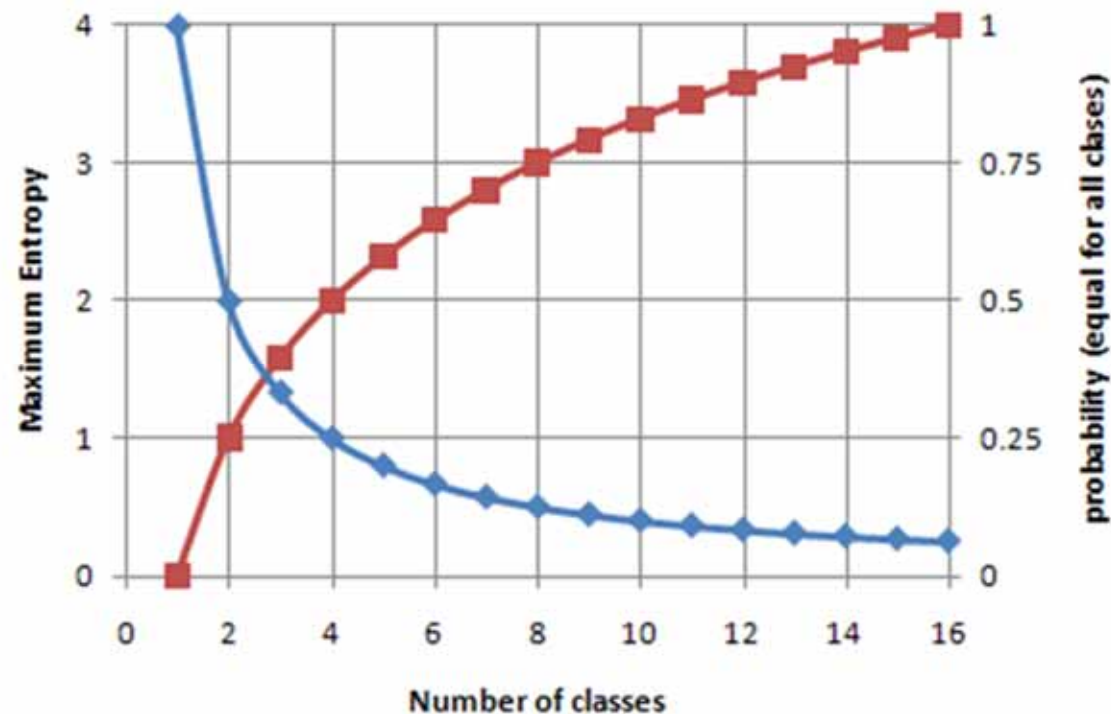
Shannon, C. E. (1948) A Mathematical Theory of Communication. *Bell System Technical Journal, 27, 379-423.*
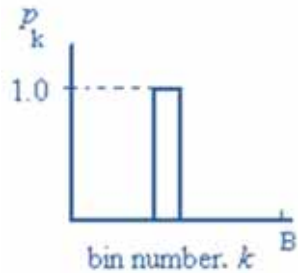
$$H_B = -\sum_{k=1}^{} p_k \, \log_2 p_k = -1 * \log_2(1) = 0$$
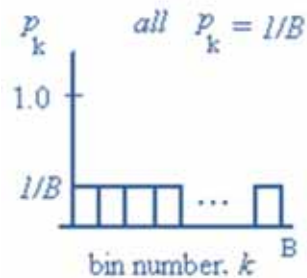
$$H_B = -\sum_{k=1}^{B} \frac{1}{B} \log_2 \frac{1}{B} = \log_2(B)$$

$$H = H_{max} = \log_2 N$$

- 1) Set of noisy, complex data

- 2) Extract information out of the data

- 3) to support a previous set hypothesis

- Information + Statistics + Inference

- = powerful methods for many sciences

- Application e.g. in biomedical informatics for analysis of ECG, MRI, CT, PET, sequences and proteins, DNA, topography, for modeling etc. etc.

Mayer, C., Bachler, M., Hortenhuber, M., Stocker, C., Holzinger, A. & Wassertheurer, S. 2014. Selection of entropy-measure parameters for knowledge discovery in heart rate variability data. BMC Bioinformatics, 15, (Suppl 6), S2.

An overview on the History of Entropy

Bernoulli (1713)
Principle of Insufficient
Reason

Maxwell (1859), Boltzmann (1871),
Gibbs (1902) Statistical Modeling
of problems in physics

Pearson (1900)
Goodness of Fit
measure

Bayes (1763), Laplace (1770)
How to calculate the state of
a system with a limited
number of expectation values

Fisher (1922)
Maximum Likelihood

Jeffreys, Cox (1939-1948)
Statistical Inference

Shannon (1948)
Information Theory

Bayesian Statistics

Entropy Methods

Generalized Entropy

See next slide
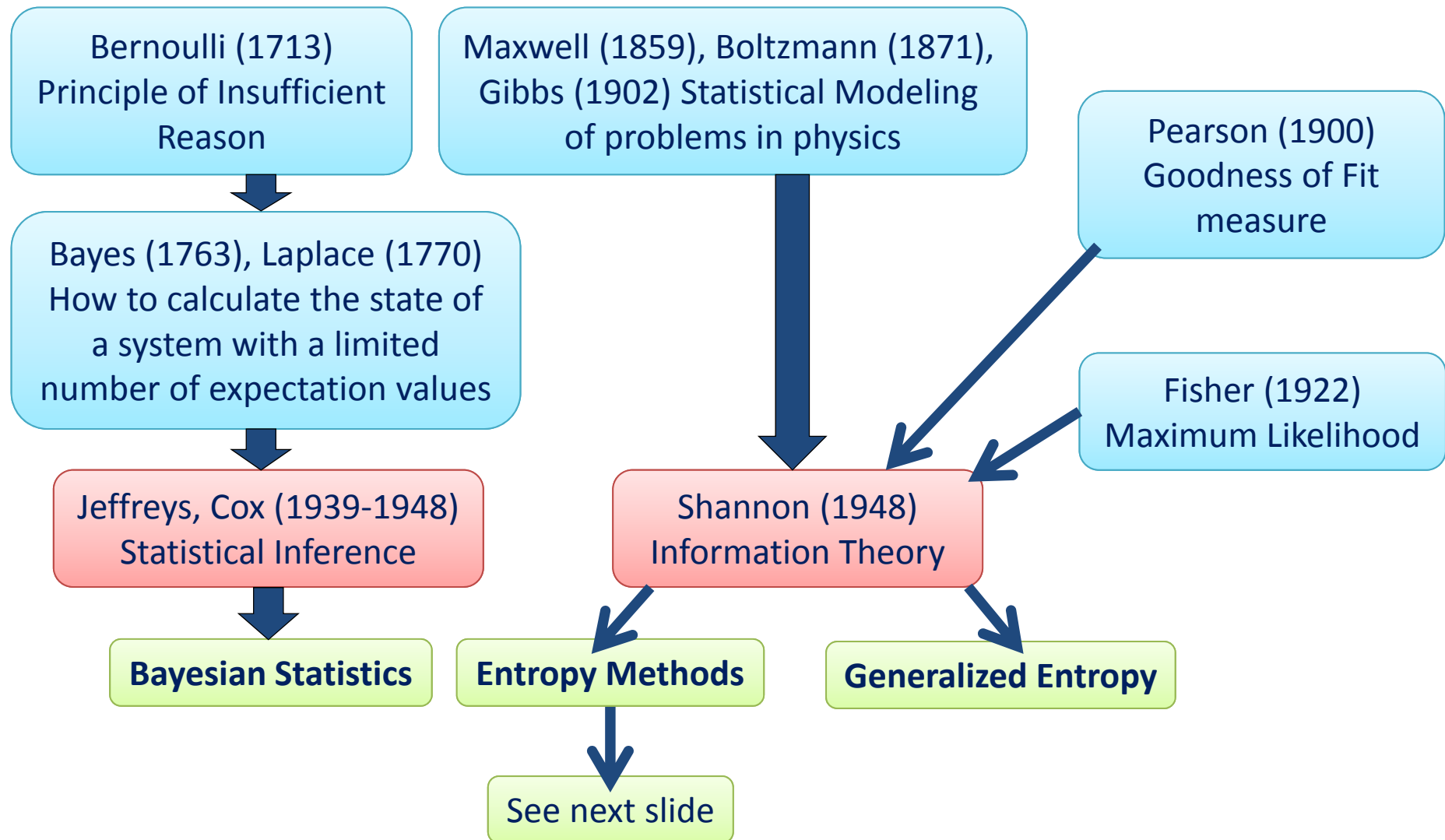
confer also with: Golan, A. (2008) Information and Entropy Econometric: A Review and Synthesis. *Foundations and Trends in Econometrics, 2, 1-2, 1-145.*
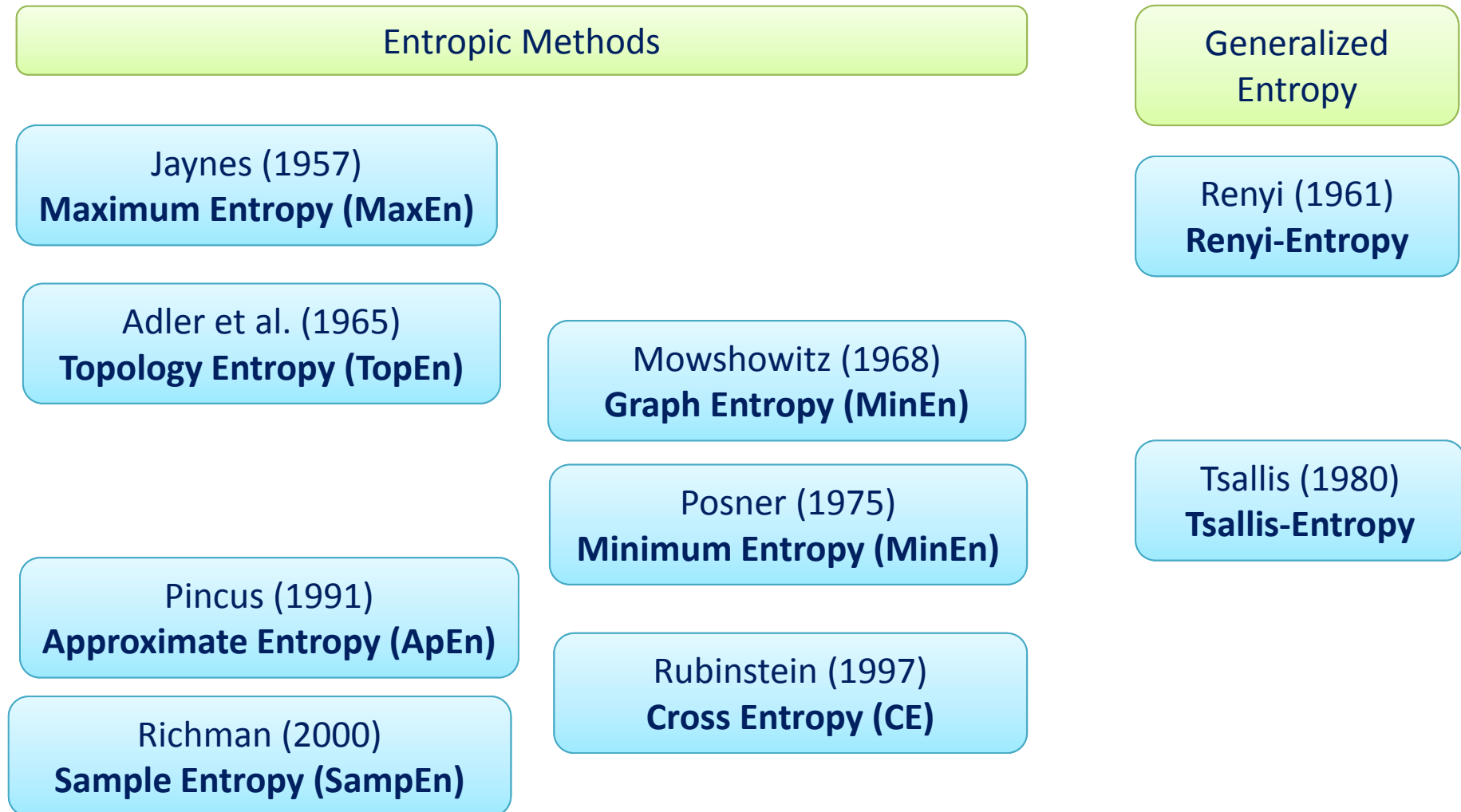
Entropic Methods

Generalized Entropy

Jaynes (1957)
Maximum Entropy (MaxEn)

Renyi (1961)
Renyi-Entropy

Adler et al. (1965)
Topology Entropy (TopEn)

Mowshowitz (1968)
Graph Entropy (MinEn)

Posner (1975)
Minimum Entropy (MinEn)

Tsallis (1980)
Tsallis-Entropy

Pincus (1991)
Approximate Entropy (ApEn)

Rubinstein (1997)
Cross Entropy (CE)

Richman (2000)
Sample Entropy (SampEn)

Holzinger, A., Hörtenhuber, M., Mayer, C., Bachler, M., Wassertheurer, S., Pinho, A. & Koslicki, D. 2014. On Entropy-Based Data Mining. In: Holzinger, A. & Jurisica, I. (eds.) Lecture Notes in Computer Science, LNCS 8401. Berlin Heidelberg: Springer, pp. 209-226.

- Developed by Claude Shannon in the 1940s

- Maximizing the amount of information that can be transmitted over an imperfect communication channel

- Data compression (entropy)

- Transmission rate (channel capacity)

Claude E. Shannon: A Mathematical Theory of Communication, Bell System Technical Journal, Vol. 27, pp. 379–423, 623–656, 1948

- Feature selection:
- If we use only a few words to classify docs, what kind of words should we use?
- P(Topic| "computer"=1) vs p(Topic | "the"=1): which is more random?
- Text compression:
- Some documents (less random) can be compressed more than others (more random)
- Can we quantify the "compressibility"?
- In general, given a random variable X following distribution p(X),
- How do we measure the "randomness" of X?
- How do we design optimal coding for X?
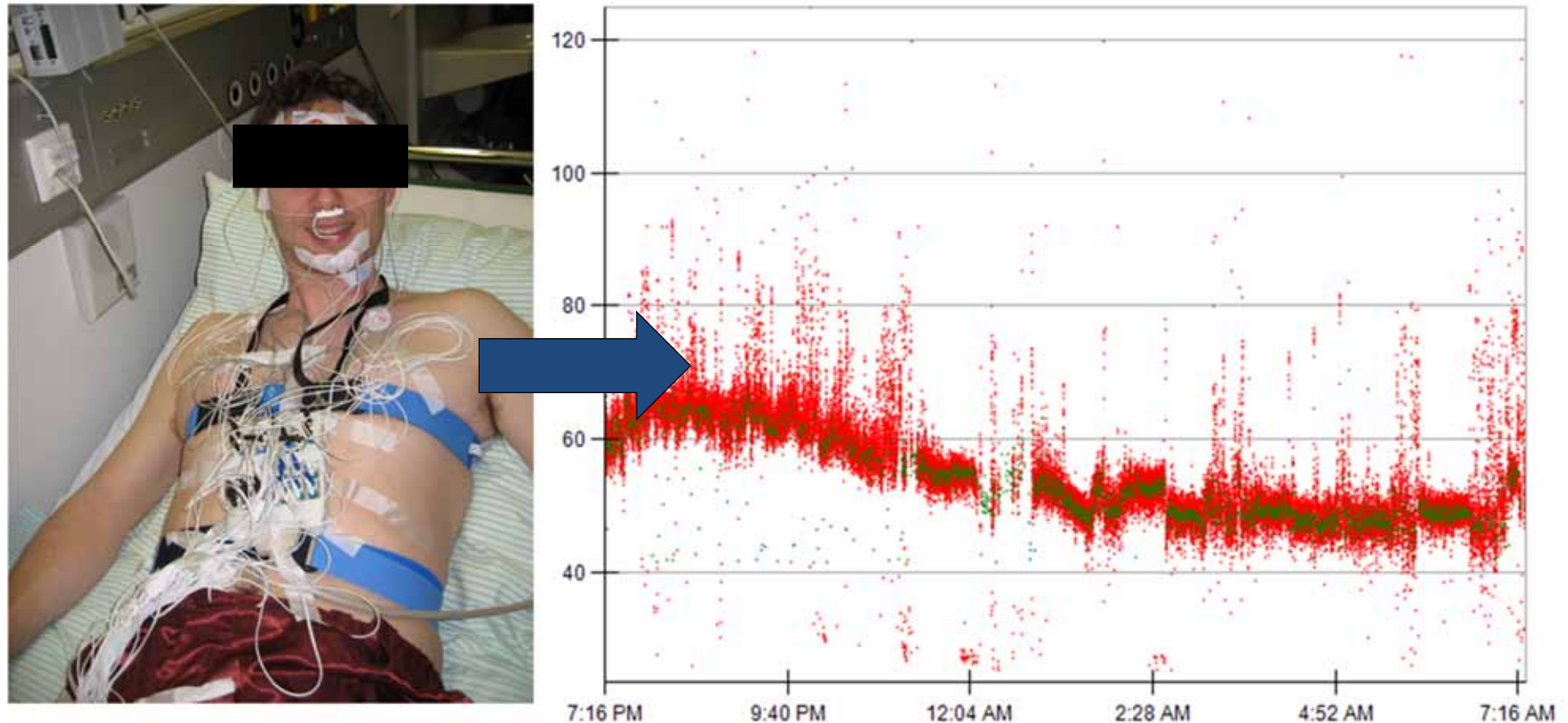
Holzinger, A., Stocker, C., Bruschi, M., Auinger, A., Silva, H., Gamboa, H. & Fred, A. 2012. On Applying Approximate Entropy to ECG Signals for Knowledge Discovery on the Example of Big Sensor Data. *In: Huang, R., Ghorbani, A., Pasi, G., Yamaguchi, T., Yen, N. & Jin, B. (eds.) Active Media Technology, Lecture Notes in Computer Science, LNCS 7669. Berlin Heidelberg: Springer, pp. 646-657.*

EU Project EMERGE (2007-2010)

$$Let: \langle x_n \rangle = \{x_1, x_2, \dots, x_N\}$$

$$\vec{X}_i = (x_i, x_{(i+1)}, \dots, x_{(i+m-1)})$$

$$\|\vec{X}_i, \vec{X}_j\| = \max_{k=1,2,\dots,m} \left(\left| x_{(i+k-1)} - x_{(j+k-1)} \right| \right)$$

$$\widetilde{H}(m,r) = \lim_{N \to \infty} [\phi^m(r) - \phi^{m+1}(r)]$$

$$C_r^m(i) = \frac{N^m(i)}{N-m+1} \qquad \phi^m(r) = \frac{1}{N-m+1} \sum_{t=1}^{N-m+1} \ln C_r^m(i)$$

Pincus, S. M. (1991) Approximate Entropy as a measure of system complexity. *Proceedings of the National Academy of Sciences of the United States of America, 88, 6, 2297-2301.*
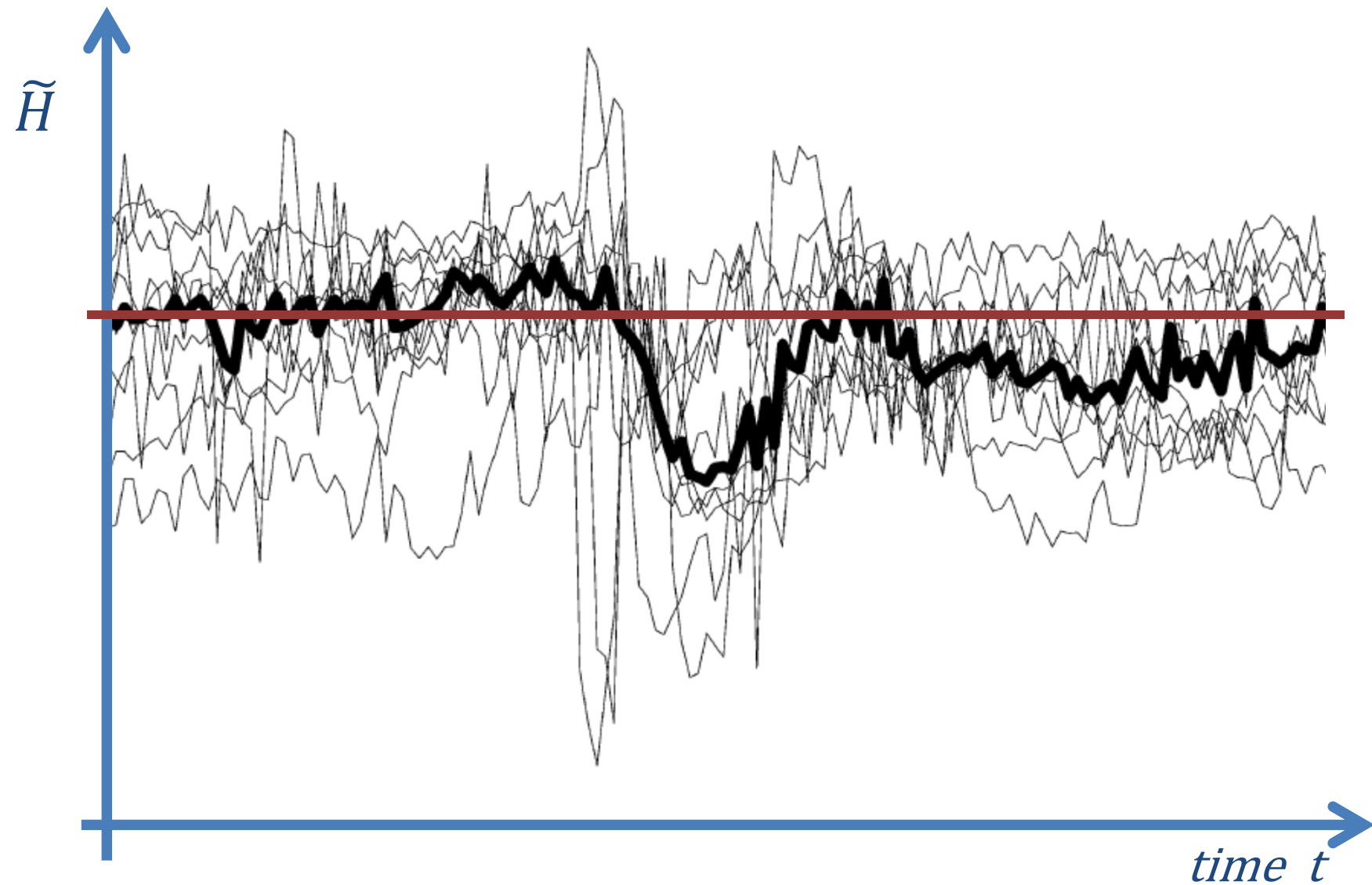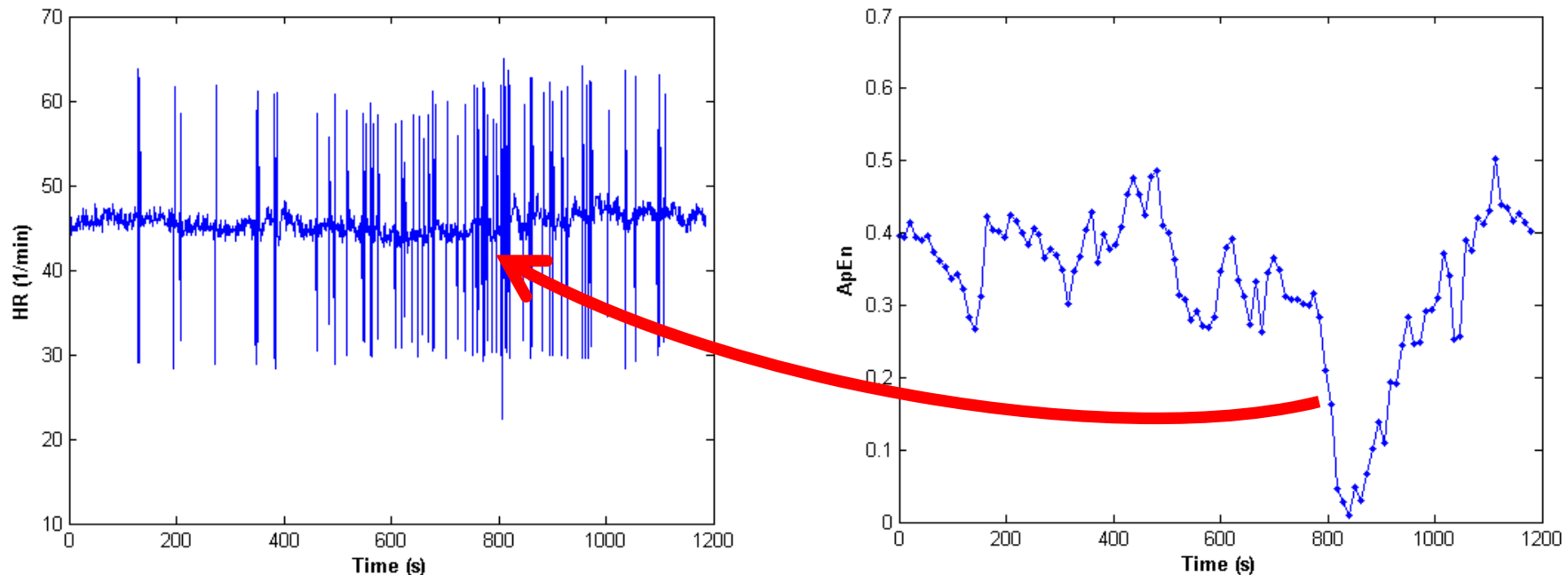
Holzinger, A., Hörtenhuber, M., Mayer, C., Bachler, M., Wassertheurer, S., Pinho, A. & Koslicki, D. 2014. On Entropy-Based Data Mining. In: Holzinger, A. & Jurisica, I. (eds.) Interactive Knowledge Discovery and Data Mining in Biomedical Informatics, Lecture Notes in Computer Science, LNCS 8401. Berlin Heidelberg: Springer, pp. 209-226.
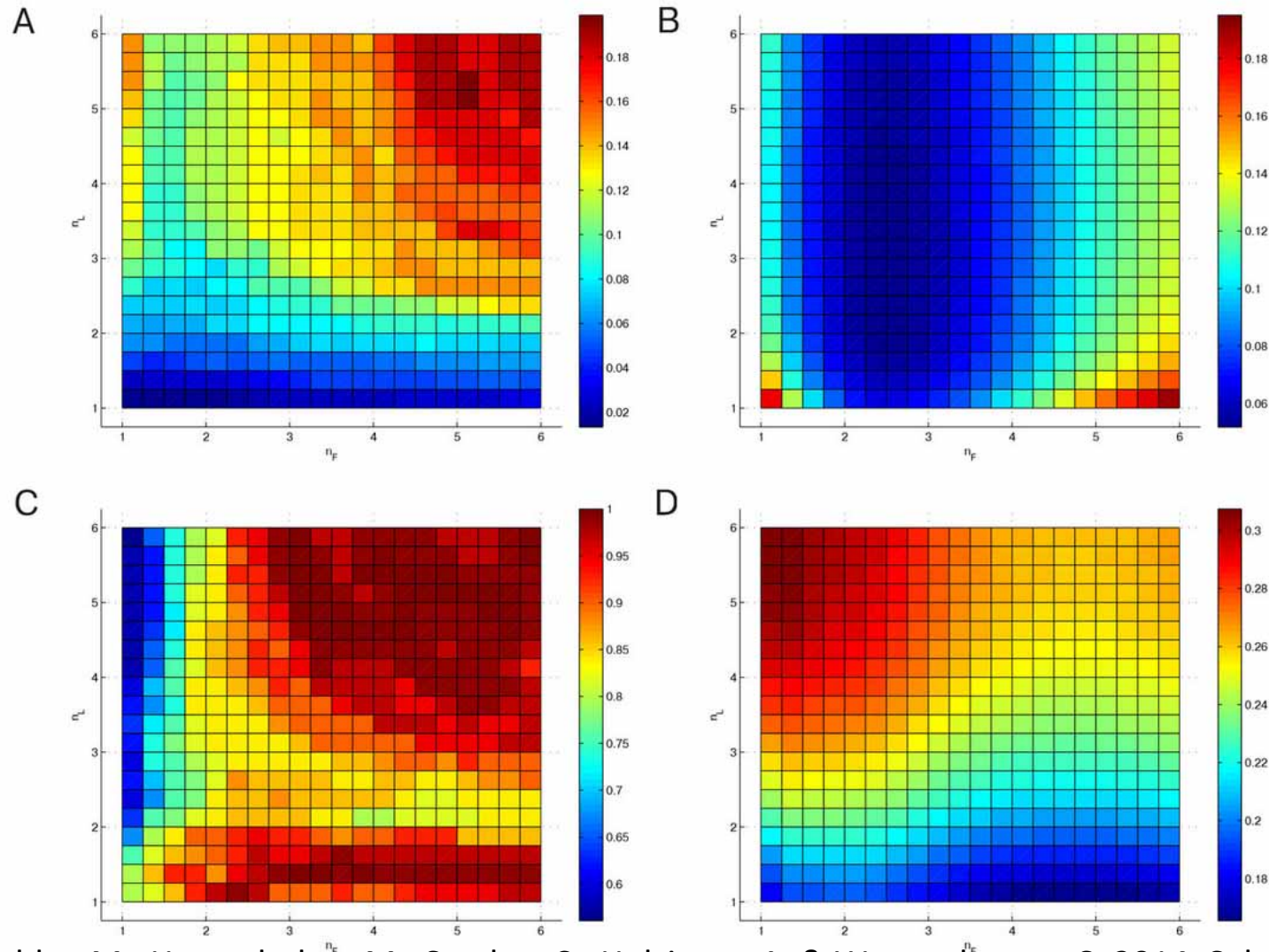
Mayer, C., Bachler, M., Hortenhuber, M., Stocker, C., Holzinger, A. & Wassertheurer, S. 2014. Selection of entropy-measure parameters for knowledge discovery in heart rate variability data. *BMC Bioinformatics,* 15, (Suppl 6), S2, doi:doi:10.1186/1471-2105-15-S6-S2.
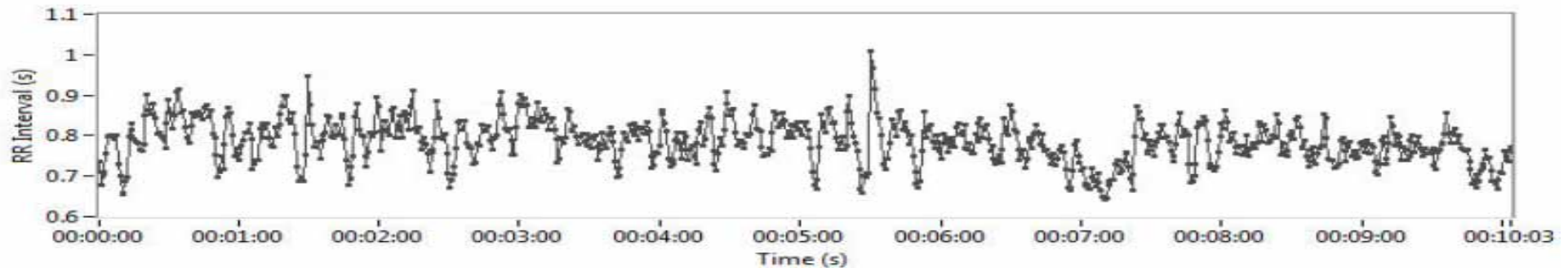
- Heart Rate Variability (HRV) can be used as a marker of cardiovascular health status.

- Entropy measures represent a family of new methods to quantify the variability of the heart rate.

- Promising approach, due to ability to discover certain patterns and shifts in the "apparent ensemble amount of randomness" of stochastic processes,

- measure randomness and **predictability of processes.**

Mayer, C., Bachler, M., Holzinger, A., Stein, P. K. & Wassertheurer, S. 2016. The Effect of Threshold Values and Weighting Factors on the Association between Entropy Measures and Mortality after Myocardial Infarction in the Cardiac Arrhythmia Suppression Trial (CAST). Entropy, 18, (4), 129, doi::10.3390/e18040129.
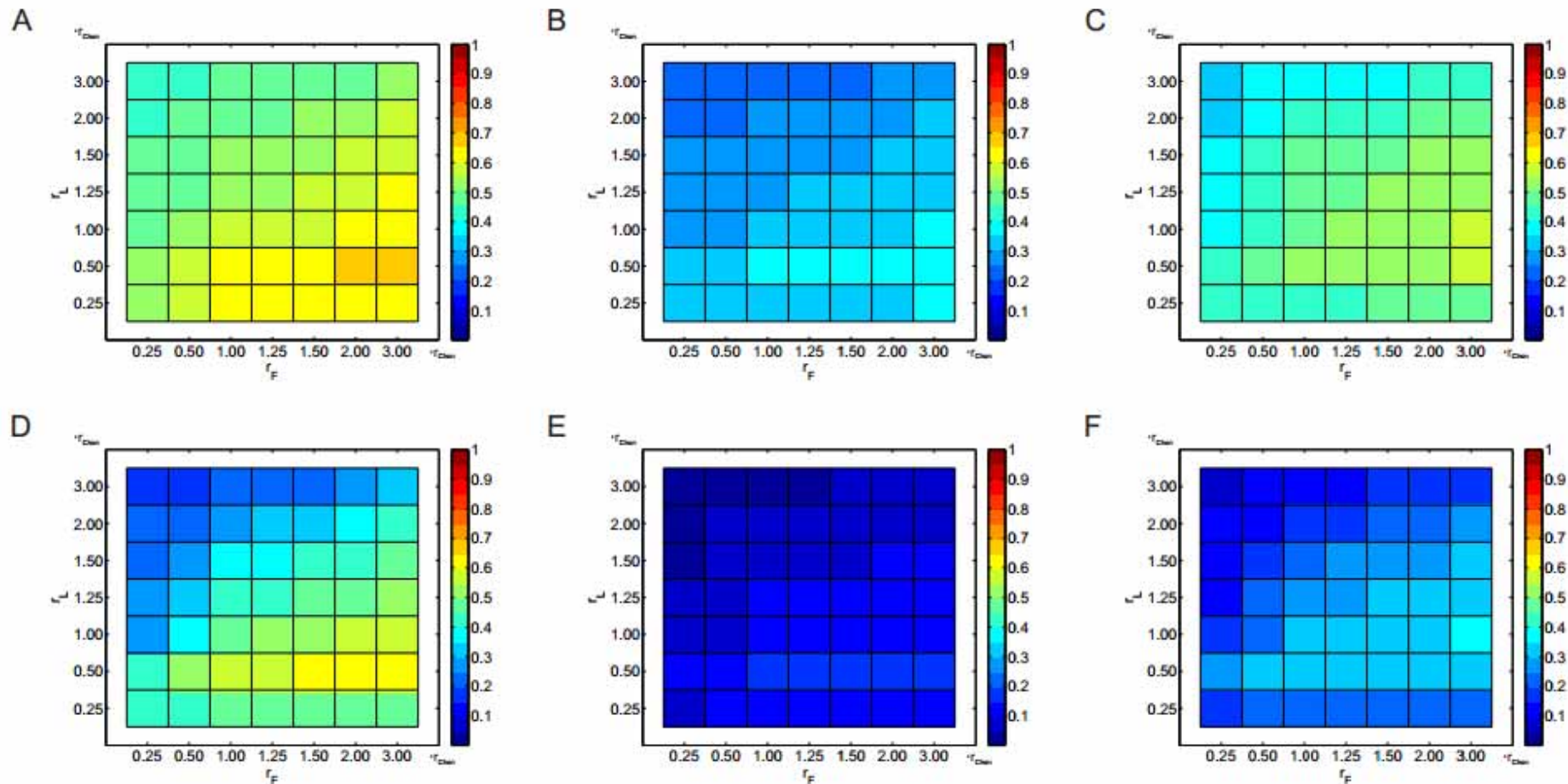
Mayer, C., Bachler, M., Holzinger, A., Stein, P. K. & Wassertheurer, S. 2016. The Effect of Threshold Values and Weighting Factors on the Association between Entropy Measures and Mortality after Myocardial Infarction in the Cardiac Arrhythmia Suppression Trial (CAST). Entropy, 18, (4), 129, doi::10.3390/e18040129.

7) Cross-Entropy Kullback-Leibler Divergence

- Entropy:
  - Measure for the **uncertainty** of random variables

- Kullback-Leibler divergence:
  - **comparing two distributions**

- Mutual Information:
  - measuring the **correlation** of two random variables

ON INFORMATION AND SUFFICIENCY

By S. Kullback and R. A. Leibler

The George Washington University and Washington, D. C.

1. Introduction. This note generalizes to the abstract case Shannon's definition of information [15], [16]. Wiener's information (p. 75 of [18]) is essentially the same as Shannon's although their motivation was different (cf. footnote 1, p. 95 of [16]) and Shannon apparently has investigated the concept more completely. R. A. Fisher's definition of information (intrinsic accuracy) is well known (p. 709 of [6]). However, his concept is quite different from that of Shannon and Wiener, and hence ours, although the two are not unrelated as is shown in paragraph 2.

R. A. Fisher, in his original introduction of the *criterion of sufficiency*, required "that the statistic chosen should summarize the whole of the relevant information supplied by the sample," (p. 316 of [5]). Halmos and Savage in a recent paper, one of the main results of which is a generalization of the well known Fisher-Neyman theorem on sufficient statistics to the abstract case, conclude, "We think that confusion has from time to time been thrown on the subject by ... , and (c) the assumption that a sufficient statistic contains all the information in only the technical sense of 'information' as measured by variance," (p. 241 of [8]). It is shown in this note that the information in a sample as defined herein, that is, in the Shannon-Wiener sense cannot be increased· by any statistical operations and is invariant (not decreased) if and only if sufficient statistics are employed. For a similar property of Fisher's information see p. 717 of [6], Doob [19].

We are also concerned with the statistical problem of discrimination ([3], [17]), by considering a measure of the "distance" or "divergence" between statistical populations ([1], [2], [13]) in terms of our measure of information. For the statistician two populations differ more or less according as to how difficult it is to discriminate between them with the best test [14]. The particular measure of divergence we use has been considered by Jeffreys ([10], [11]) in another connection. He is primarily concerned with its use in providing an invariant density of *a priori* probability. A special case of this divergence is Mahalanobis' generalized distance [13].

Solomon Kullback Richard Leibler
1907-1994   1914-2003

Kullback, S. & Leibler, R. A. 1951. On information and sufficiency. The annals of mathematical statistics, 22, (1), 79-86, www.jstor.org/stable/2236703
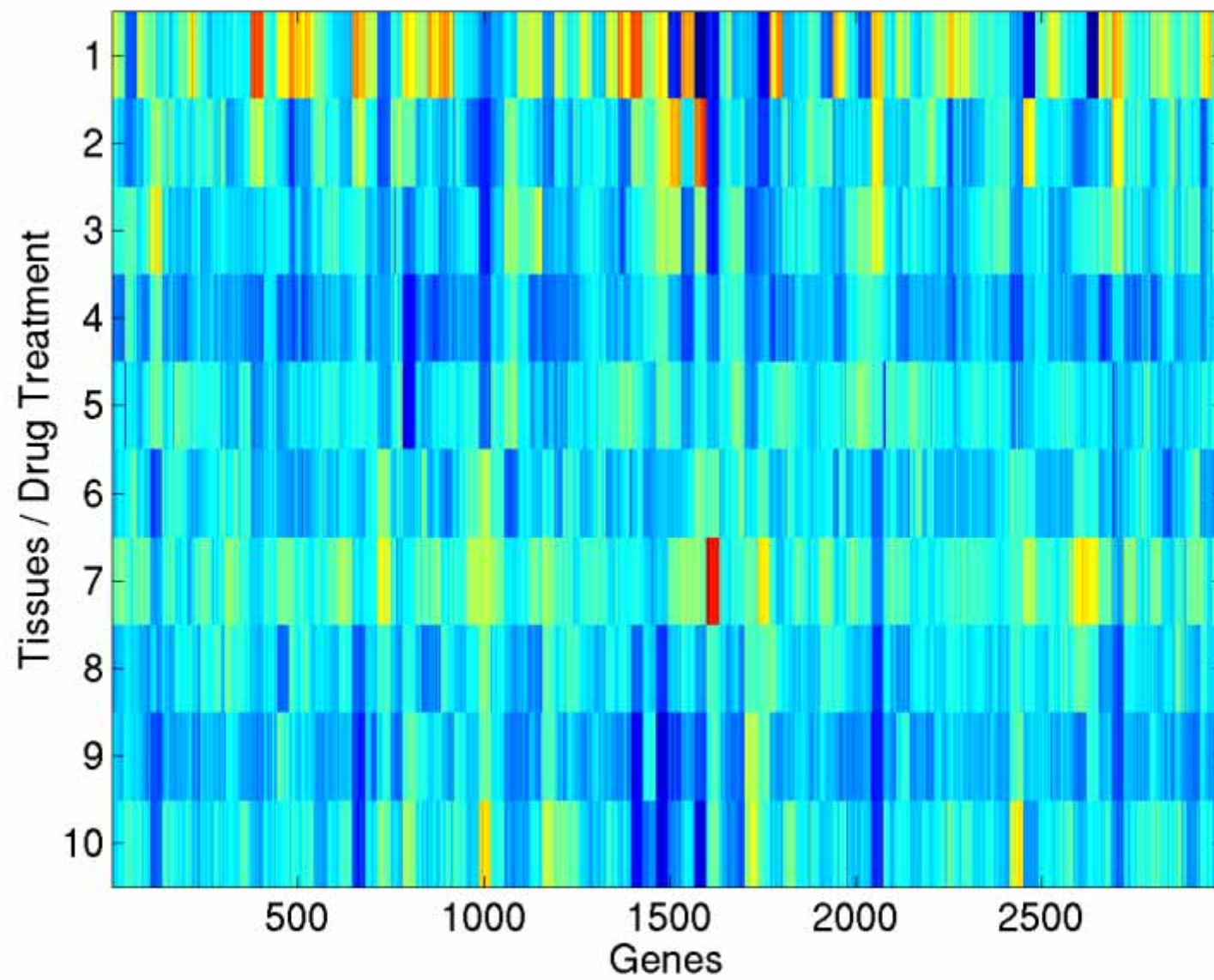
$$H[x] = -\sum_x p(x) \log_2 p(x)$$

Important quantity in
- coding theory
- statistical physics
- machine learning

$$H[\mathbf{y}|\mathbf{x}] = -\iint p(\mathbf{y}, \mathbf{x}) \ln p(\mathbf{y}|\mathbf{x}) \, d\mathbf{y} \, d\mathbf{x}$$

$$H[\mathbf{x}, \mathbf{y}] = H[\mathbf{y}|\mathbf{x}] + H[\mathbf{x}]$$

$$\mathrm{KL}(p\|q) = -\int p(\mathbf{x}) \ln q(\mathbf{x})\, \mathrm{d}\mathbf{x} - \left(-\int p(\mathbf{x}) \ln p(\mathbf{x})\, \mathrm{d}\mathbf{x}\right)$$

$$= -\int p(\mathbf{x}) \ln \left\{\frac{q(\mathbf{x})}{p(\mathbf{x})}\right\} \mathrm{d}\mathbf{x}$$

$$\mathrm{KL}(p\|q) \simeq \frac{1}{N} \sum_{n=1}^{N} \{-\ln q(\mathbf{x}_n|\boldsymbol{\theta}) + \ln p(\mathbf{x}_n)\}$$

$$\mathrm{KL}(p\|q) \geqslant 0 \qquad \mathrm{KL}(p\|q) \neq \mathrm{KL}(q\|p)$$

KL-divergence is often used to measure the distance between two distributions

- … are **robust** against noise;

- … can be applied to **complex time series** with good replication;

- … is **finite** for stochastic, noisy, composite processes;

- … the values correspond directly to irregularities – good for detecting **anomalies**

8) Mutual Information
and
Point Wise MI
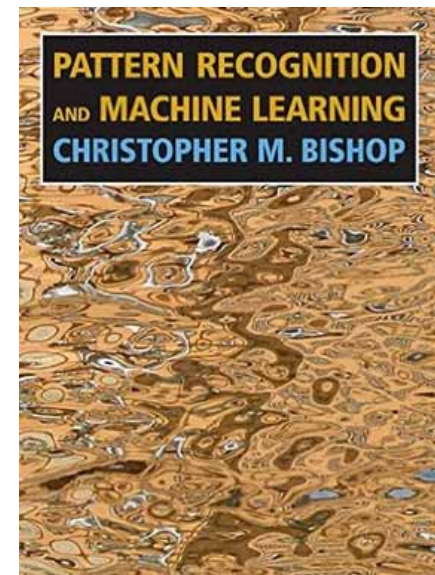
$$I[\mathbf{x}, \mathbf{y}] \equiv KL(p(\mathbf{x}, \mathbf{y})\|p(\mathbf{x})p(\mathbf{y}))$$

$$= -\iint p(\mathbf{x}, \mathbf{y}) \ln\left(\frac{p(\mathbf{x})p(\mathbf{y})}{p(\mathbf{x}, \mathbf{y})}\right) d\mathbf{x}\, d\mathbf{y}$$

$$I[\mathbf{x}, \mathbf{y}] = H[\mathbf{x}] - H[\mathbf{x}|\mathbf{y}] = H[\mathbf{y}] - H[\mathbf{y}|\mathbf{x}]$$

- Measures how much reduction in uncertainty of X given the information about Y

- Measures correlation between X and Y

- Related to the "channel capacity" in the original Shannon information theory

Bishop, C. M. 2007. *Pattern Recognition and Machine Learning,* Heidelberg, Springer.

Let two words, w_i and w_j, have probabilities $P(w_i)$ and $P(w_j)$.
Then their mutual information $PMI(w_i, w_j)$ is defined as:

$$PMI(w_i, w_j) = \log\left(\frac{P(w_i, w_j)}{P(w_i)\,P(w_j)}\right)$$

For w_i denoting *rheumatoid arthritis* and w_j representing *diffuse scleritis* the following simple calculation yields:

$$P(w_i) = \frac{94,834}{20,033,079}, \quad P(w_j) = \frac{74}{20,033,079}$$

$$P(w_i, w_j) = \frac{13}{94,834}, \quad PMI(w_i, w_j) = 7,7.$$

Gout
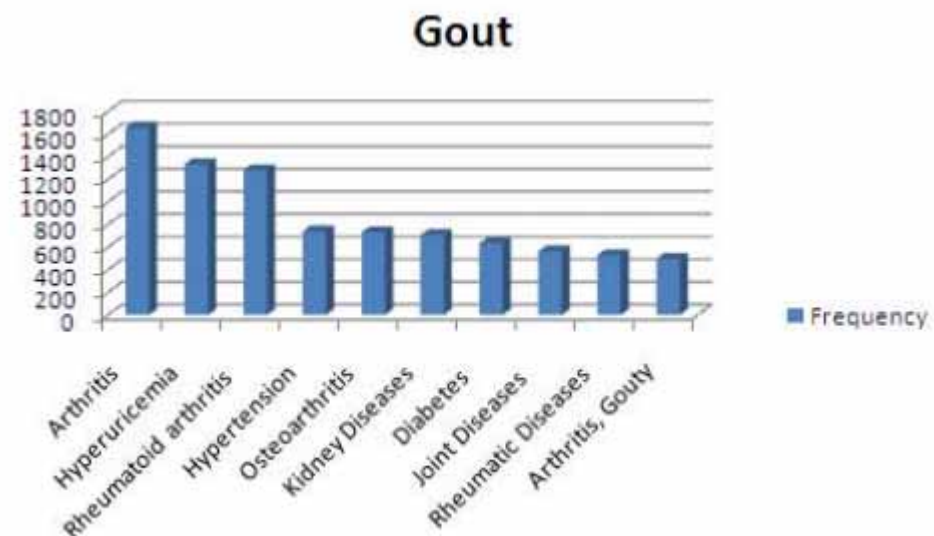
Holzinger, A., Simonic, K. M. & Yildirim, P. Disease-Disease Relationships for Rheumatic Diseases: Web-Based Biomedical Textmining an Knowledge Discovery to Assist Medical Decision Making. 36th Annual IEEE Computer Software and Applications Conference (COMPSAC), 16-20 July 2012 2012 Izmir. IEEE, 573-580, doi:10.1109/COMPSAC.2012.77.

$$SCP(x,y) = p(x|y) \cdot p(y|x) =$$

$$\frac{p(x,y)}{p(y)} \cdot \frac{p(x,y)}{p(x)} = \frac{p(x,y)^2}{p(x) \cdot p(y)}$$

Table 4 Comparison of FACTAs ranking of related concepts from the category Symptom for the query "rheumatoid arthritis" created by the methods co-occurrence frequency, PMI, and SCP

Frequency		PMI		SCP	
pain	5667	impaired body balance	7,8	swollen joints	0.002
Arthralgia	661	ASPIRIN INTOLERANCE	7,8	pain	0.001
fatigue	429	Epitrochlear lymphadenopathy	7,8	Arthralgia	0.001
diarrhea	301	swollen joints	7,4	fatigue	0.000
swollen joints	299	Joint tenderness	7	erythema	0.000
erythema	255	Occipital headache	6,2	splenomegaly	0.000
Back Pain	254	Neuromuscular excitation	6,2	Back Pain	0.000
headache	239	Restless sleep	5,8	polymyalgia	0.000
splenomegaly	228	joint crepitus	5,7	joint stiffness	0.000
Anesthesia	221	joint symptom	5,5	Joint tenderness	0.000
dyspnea	218	Painful feet	5,5	hip pain	0.000
weakness	210	feeling of malaise	5,5	metatarsalgia	0.000
nausea	199	Homan's sign	5,4	Skin Manifestations	0.000
Recovery of Function	193	Diffuse pain	5,2	neck pain	0.000
low back pain	167	Palmar erythema	5,2	Eye Manifestations	0.000
abdominal pain	141	Abnormal sensation	5,2	low back pain	0.000

Holzinger, A., Yildirim, P., Geier, M. & Simonic, K.-M. 2013. Quality-Based Knowledge Discovery from Medical Text on the Web. In: Pasi, G., Bordogna, G. & Jain, L. C. (eds.) Quality Issues in the Management of Web Information, Intelligent Systems Reference Library, ISRL 50. Berlin Heidelberg: Springer, pp. 145-158, doi:10.1007/978-3-642-37688-7_7.

- 1) Challenges include –omics data analysis, where KL divergence and related concepts could provide important measures for discovering biomarker.

- 2) Hot topics are new entropy measures suitable for computations in the context of complex/uncertain data for ML algorithms.

- Inspiring is the abstract geometrical setting underlying ML main problems, e.g. Kernel functions can be completely understood in this perspective. Future work may include entropic concepts and geometrical settings (see lecture 5).

- The case of higher order statistical structure in the data – nonlinear and hierarchical ?

- Outliers in the data – noise models?

- There are $\dfrac{D(D+1)}{2}$ parameters in a multi-variate Gaussian model – what happens if $D \gg$?
  dimensionality reduction
  (see next lecture :-)

Thank you!

- What are the grand challenges in ML for health?
- What is the key problem before you can apply ML?
- Describe the taxonomy of data at Hospital level!
- What does translational medicine mean?
- Give an example for a 2.5D-data set!
- Why would be the combination of ontologies with machine learning provide a benefit?
- How did Van Bemmel and Musen describe the interplay between data-information-knowledge?
- What is the "body-of-knowledge" in medical jargon?
- How do human process information?

- What was our definition of "knowledge"?

- What is the huge benefit of a probabilistic model?

- Please explain Bayes law with view on ML!

- What is information in the sense of Shannon?

- Why is information theory for us important?

- Which benefits provide entropic methods for us?

- Why is feature selection so important?

- What can you do with the Kullback-Leibler Divergence?
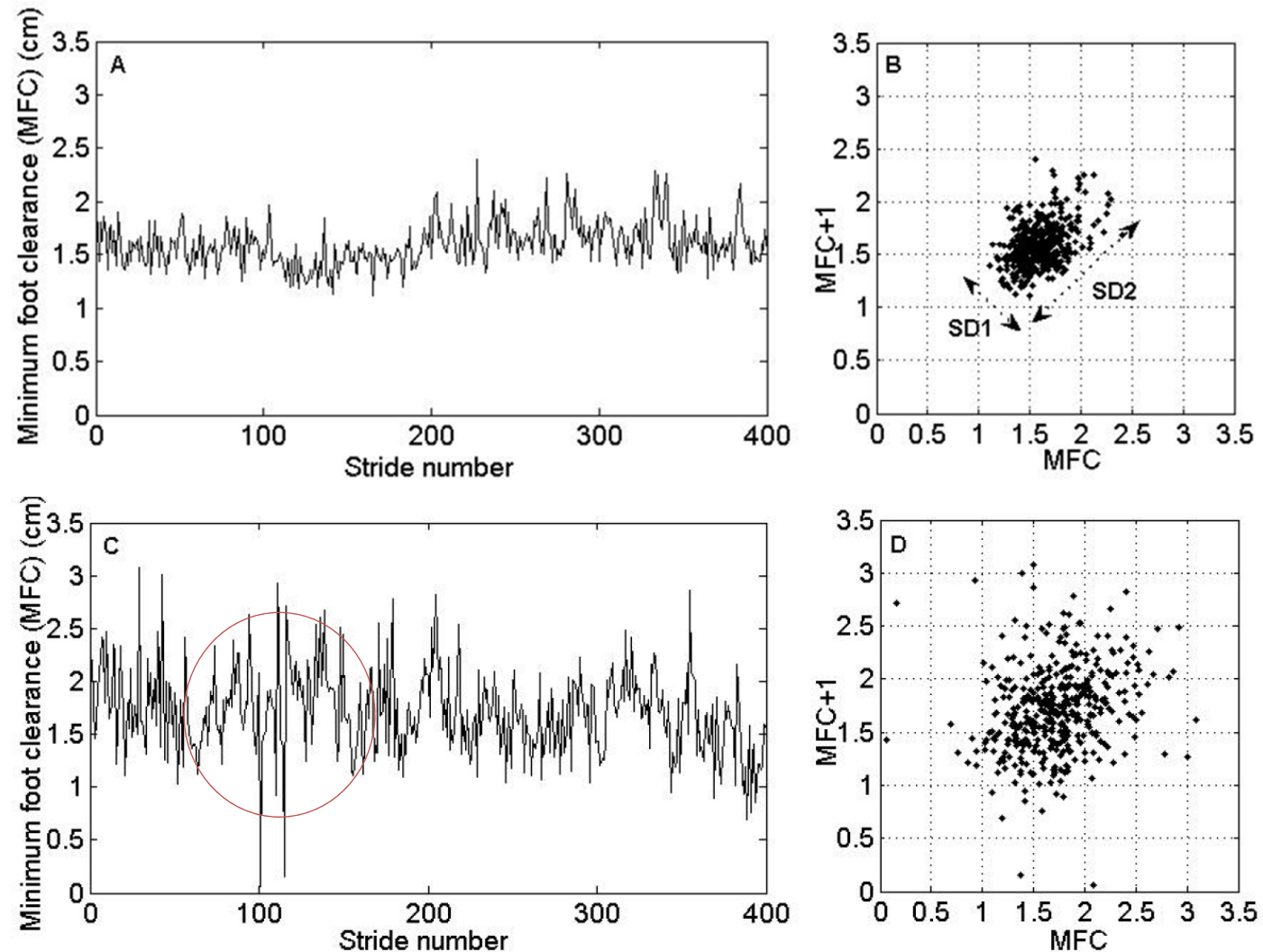
Khandoker, A., Palaniswami, M. & Begg, R. (2008) A comparative study on approximate entropy measure and poincare plot indexes of minimum foot clearance variability in the elderly during walking. *Journal of NeuroEngineering and Rehabilitation, 5, 1, 4.*

Lake, D. E., Richman, J. S., Griffin, M. P. & Moorman, J. R. (2002) Sample entropy analysis of neonatal heart rate variability. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology, 283, **3, R789-R797.***
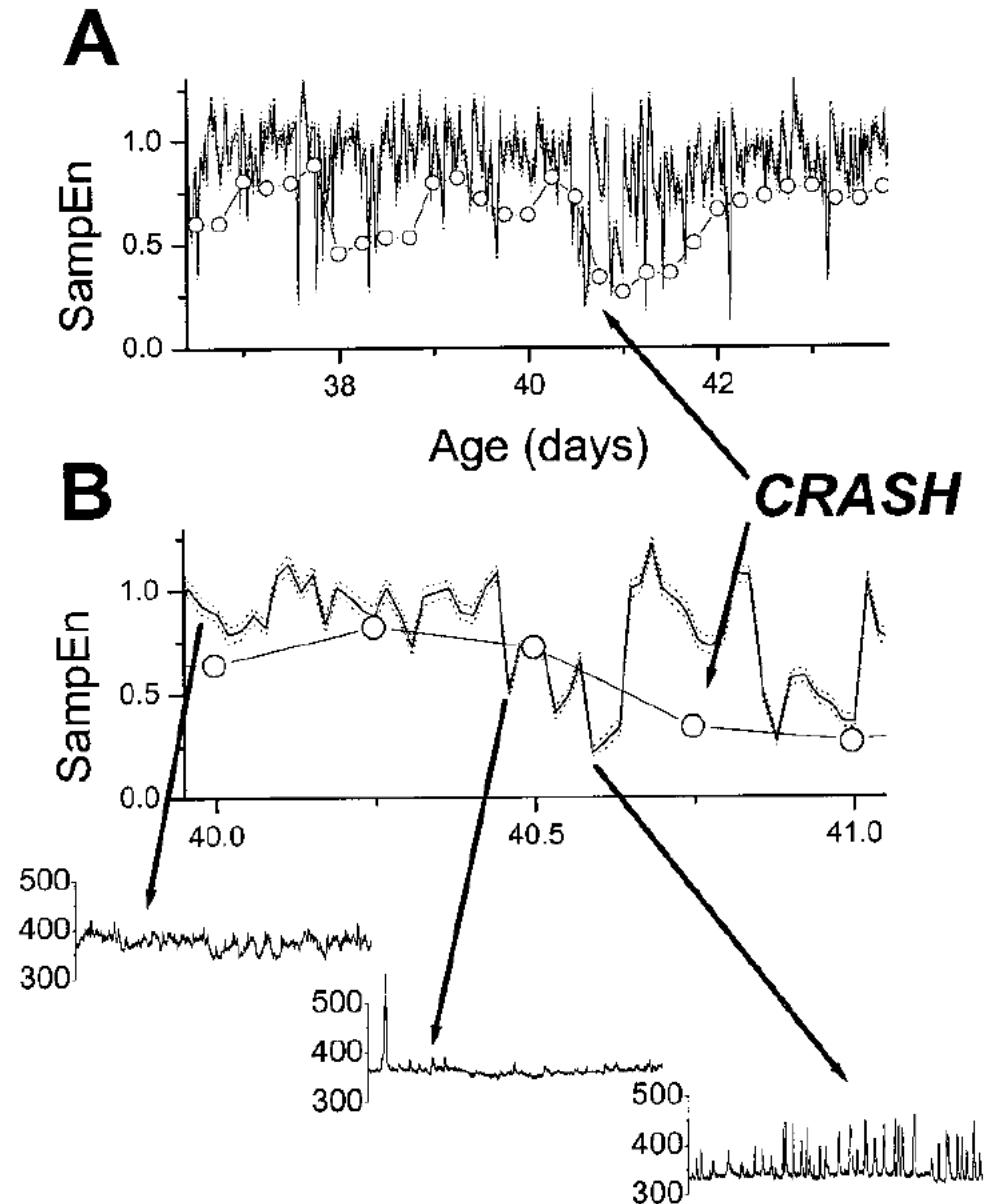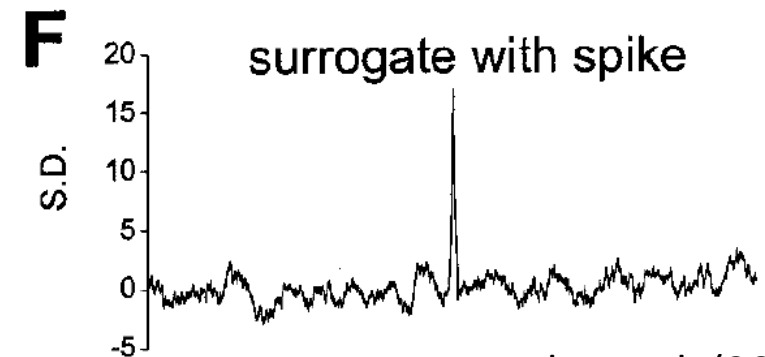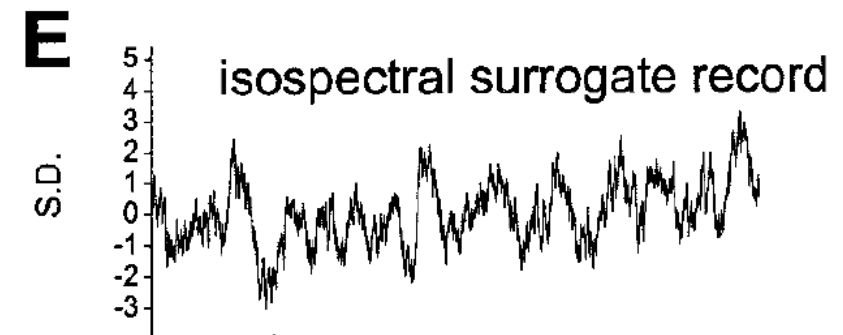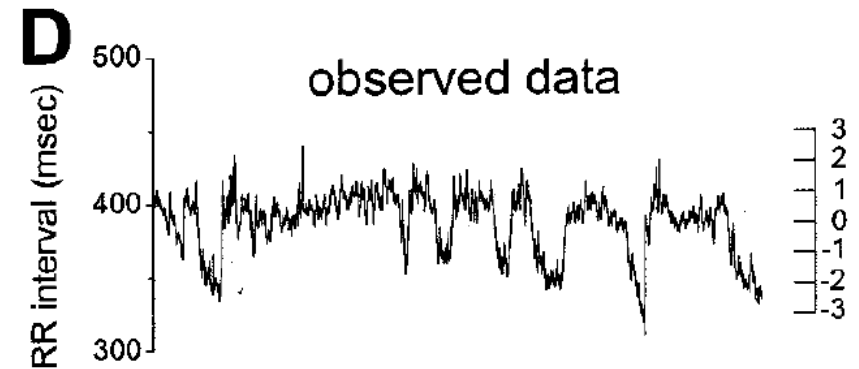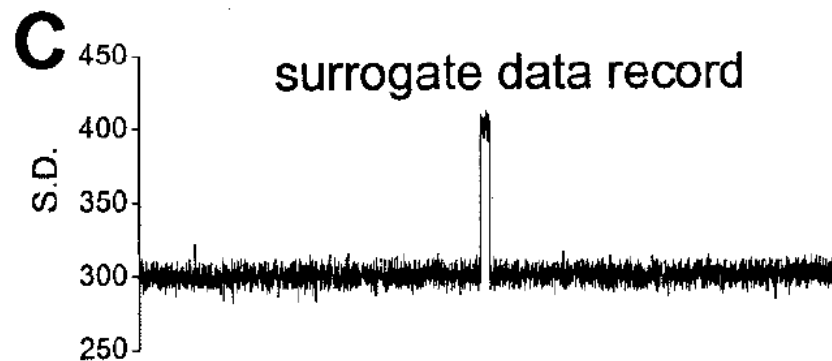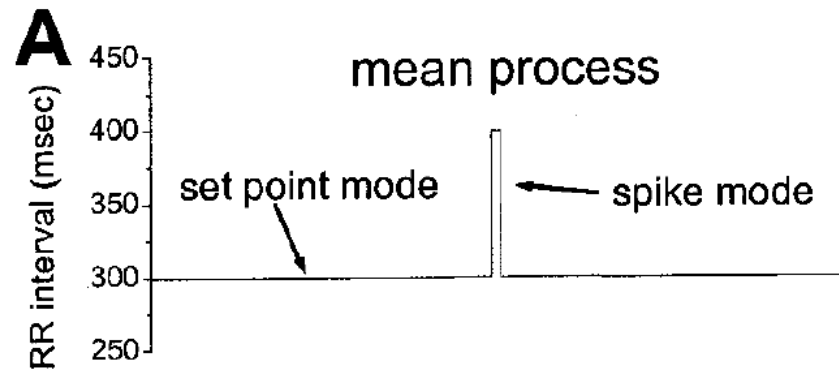
Lake et al. (2002)

ApEn

Given a signal x(n)=x(1), x(2),…, x(N), where N is the total number of data points, ApEn algorithm can be summarized as follows [1]:

1) Form *m*-vectors, *X(1)* to *X(N-m+1)* defined by:

$$X(i) = [x(i), x(i+1), ..., X(i+m-1)] \quad i = 1, N-m+1 \quad (1)$$

2) Define the distance *d[X(i),X(j)]* between vectors *X(i)* and *X(j)* as the maximum absolute difference between their respective scalar components:

$$d[X(i), X(j)] = \max_{k=0, m-1} [|x(i+k) - x(j+k)|] \quad (2)$$

3) Define for each i, for i=1, N-m+1, let

$$C_r^m(i) = V^m(i)/(N-m+1) \quad (3)$$

where $V^m(i) = no. of\ d[X(i), X(j)] \le r$

4) Take the natural logarithm of each $C_r^m(i)$, and average it over *i* as defined in step 3):

$$\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln(C_r^m(i)) \quad (4)$$

5) Increase the dimension to m+1 and repeat steps 1) to 4).
6) Calculate ApEn value for a finite data length of *N*:

$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \quad (5)$$

Xinnian, C. et al. (2005). *Comparison of the Use of Approximate Entropy and Sample Entropy: Applications to Neural Respiratory Signal. Engineering in Medicine and Biology IEEE-EMBS 2005, 4212-4215.*

SampEn

Given a signal x(n)=x(1), x(2),…, x(N), where N is the total number of data points, SampEn algorithm can be summarized as follows [5]:

1) Form *m*-vectors, *X(1)* to *X(N-m+1)* defined by:

$$X(i) = [x(i), x(i+1), ..., X(i+m-1)] \quad i = 1, N-m+1 \quad (6)$$

2) Define the distance $d_m[X(i), X(j)]$ between vectors *X(i)* and *X(j)* as the maximum absolute difference between their respective scalar components:

$$d_m[X(i), X(j)] = \max_{k=0, m-1} [|x(i+k) - x(j+k)|] \quad (7)$$

3) Define for each i, for i=1, N-m, let

$$B_i^m(r) = \frac{1}{N-m-1} \times no.\ of\ d_m[X(i), X(j)] \le r,\ i \ne j \quad (8)$$

4) Similarly, define for each i, for i=1, N-m, let

$$A_i^m(r) = \frac{1}{N-m-1} \times no.\ of\ d_{m+1}[X(i), X(j)] \le r, i \ne j \quad (9)$$

5) Define $B^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r)$ (10)

$$A^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r) \quad (11)$$

6) SampEn value for a finite data length of *N* can be estimated:

$$SampEn(m, r, N) = -\ln\left(A^m(r)/B^m(r)\right) \quad (12)$$

- The most important question: Which kind of structural information does the entropy measure detect?
- the topological complexity of a molecular graph is characterized by its number of vertices and edges, branching, cyclicity etc.
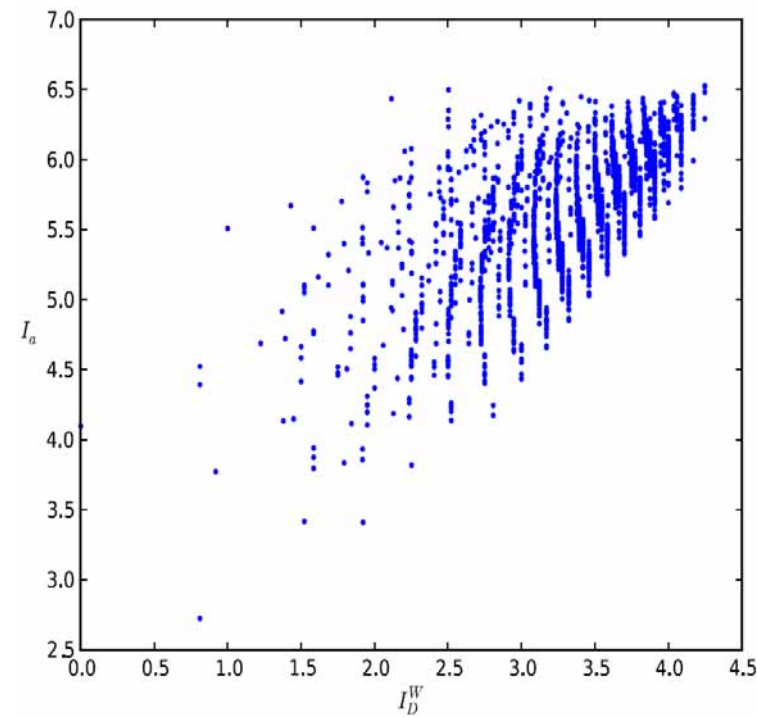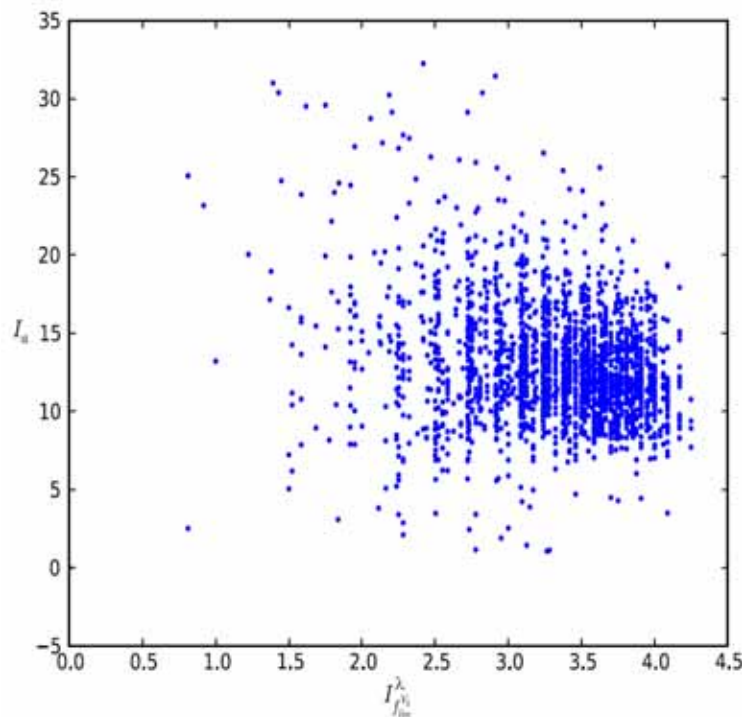
Dehmer, M. & Mowshowitz, A. (2011) A history of graph entropy measures. *Information Sciences, 181, 1, 57-78.*

106005	Bioinformatics	Bioinformatik
106007	Biostatistics	Biostatistik
304005	Medical Biotechnology	Medizinische Biotechnologie
305901	Computer-aided diagnosis and therapy	Computerunterstützte Diagnose und Therapie
304003	Genetic engineering, -technology	Gentechnik, -technologie
3906 (old)	Medical computer sciences	Medizinische Computerwissenschaften
305906	Medical cybernetics	Medizinische Kybernetik
305904	Medical documentation	Medizinische Dokumentation
305905	Medical informatics	Medizinische Informatik
305907	Medical statistics	Medizinische Statistik

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Code	English	German
102001	Artificial Intelligence	Künstliche Intelligenz
102032	Computational Intelligence	Computational Intelligence
102033	Data Mining	Data Mining
102013	Human-Computer Interaction	Human-Computer Interaction
102014	Information design	Informationsdesign
102015	Information systems	Informationssysteme
102028	Knowledge engineering	Knowledge Engineering
102019	Machine Learning	Maschinelles Lernen
102020	Medical Informatics	Medizinische Informatik
102021	Pervasive Computing	Pervasive Computing
102022	Software development	Softwarenetwicklung
102027	Web engineering	Web Engineering

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- … be aware of the types and categories of different data sets in biomedical informatics;

- … know some differences between data, information, knowledge and wisdom;

- … be aware of standardized/non-standardized and well-structured/un-structured data;

- … have a basic overview on information theory and the concept of information entropy;

- … a basic understanding of the Kullback-Leibler Divergence;

- **Abduction** = cyclical process of generating possible explanations (i.e., identification of a set of hypotheses that are able to account for the clinical case on the basis of the available data) and testing those (i.e., evaluation of each generated hypothesis on the basis of its expected consequences) for the abnormal state of the patient at hand;

- **Abstraction** = data are filtered according to their relevance for the problem solution and chunked in schemas representing an abstract description of the problem (e.g., abstracting that an adult male with haemoglobin concentration less than 14g/dL is an anaemic patient);

- **Artefact/surrogate** = error or anomaly in the perception or representation of information trough the involved method, equipment or process;

- **Data** = physical entities at the lowest abstraction level which are, e.g. generated by a patient (patient data) or a (biological) process; data contain no meaning;

- **Data quality** = Includes quality parameter such as : Accuracy, Completeness, Update status, Relevance, Consistency, Reliability, Accessibility;

- **Data structure** = way of storing and organizing data to use it efficiently;

- **Deduction** = deriving a particular valid conclusion from a set of general premises;

- **DIK-Model** = Data-Information-Knowledge three level model

- **DIKW-Model** = Data-Information-Knowledge-Wisdom four level model

- **Disparity** = containing different types of information in different dimensions

- **Heart rate variability (HRV) =** measured by the variation in the beat-to-beat interval;

- **HRV artifact** = noise through errors in the location of the instantaneous heart beat, resulting in errors in the calculation of the HRV, which is highly sensitive to artifact and errors in as low as 2% of the data will result in unwanted biases in HRV calculations;

- **Induction** = deriving a <u>likely general conclusion</u> from a set of particular statements;
- **Information** = derived from the data by <u>interpretation</u> (with feedback to the clinician);
- **Information Entropy =** a measure for uncertainty: highly structured data contain low entropy, if everything is in order there is no uncertainty, no surprise, ideally H = 0
- **Knowledge** = obtained by inductive reasoning with previously interpreted data, collected from many similar patients or processes, which is added to the "body of knowledge" (<u>explicit knowledge</u>). This knowledge is used for the interpretation of other data and to gain <u>implicit knowledge</u> which guides the clinician in taking further action;
- **Large Data** = consist of at least hundreds of thousands of data points
- **Multi-Dimensionality** = containing more than three dimensions and data are multi-variate
- **Multi-Modality** = a combination of data from different sources
- **Multivariate** = encompassing the simultaneous observation and analysis of more than one statistical variable;
- **Reasoning** = process by which clinicians <u>reach a conclusion</u> after thinking on all facts;
- **Spatiality** = contains at least one (non-scalar) spatial component and non-spatial data
- **Structural Complexity** = ranging from low-structured (simple data structure, but many instances, e.g., flow data, volume data) to high-structured data (complex data structure, but only a few instances, e.g., business data)
- **Time-Dependency** = data is given at several points in time (time series data)
- **Voxel** = volumetric pixel = volumetric picture element

"In mathematics you don't understand things. You just get used to them" –
John von Neumann

Mathematical Notation
A Guide for Engineers and Scientists
Edward R. Scheinerman

Data

n	Number of samples
d	Number of input variables
$\mathbf{X} = [\mathbf{x}_1, \ldots, \mathbf{x}_n]$	Matrix of input samples
$\mathbf{y} = [y_1, \ldots, y_n]$	Vector of output samples
$\mathbf{Z} = [\mathbf{X}, \mathbf{y}]$	Combined input–output training data or
$\mathbf{Z} = [\mathbf{z}_1, \ldots, \mathbf{z}_n]$	Representation of data points in a feature space

Distribution

P	Probability
$F(\mathbf{x})$	Cumulative probability distribution function (cdf)
$p(\mathbf{x})$	Probability density function (pdf)
$p(\mathbf{x}, y)$	Joint probability density function
$p(\mathbf{x}; \omega)$	Probability density function, which is parameterized
$p(y|\mathbf{x})$	Conditional density
$t(\mathbf{x})$	Target function
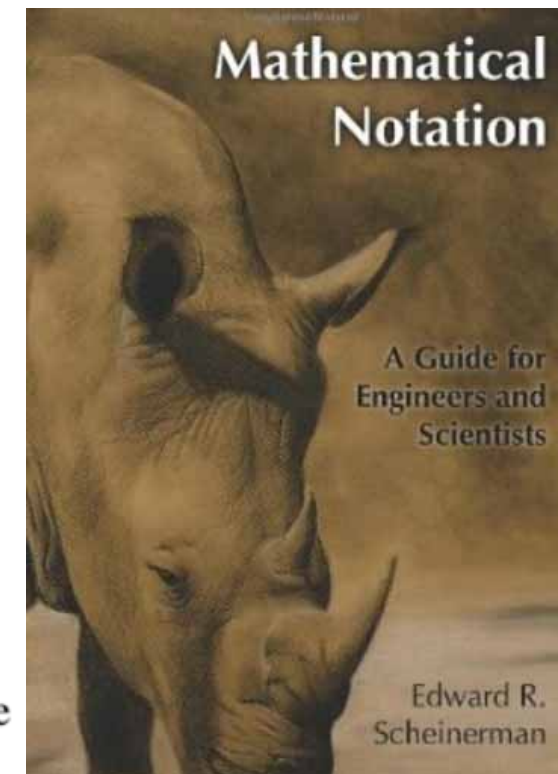
- ApEn = Approximate Entropy;
- $\mathbb{C}_{data}$ = Data in computational space;
- DIK = Data-Information-Knowledge-3-Level Model;
- DIKW = Data-Information-Knowledge-Wisdom-4-Level Model;
- GraphEn = Graph Entropy;
- H = Entropy (General);
- HRV = Heart Rate Variability;
- MaxEn = Maximum Entropy;
- MinEn = Minimum Entropy;
- NE = Normalized entropy (measures the relative informational content of both the signal and noise);
- $\mathbb{P}_{data}$ = Data in perceptual space;
- PDB = Protein Data Base;
- SampEn = Sample Entropy;