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Machine Learning & Knowledge Extraction
for Health Informatics
University of Verona
Module 2 - Day 2 – April 2017

Health Data Jungle: From the underlying physics of data to the Kullback-Leibler Divergence

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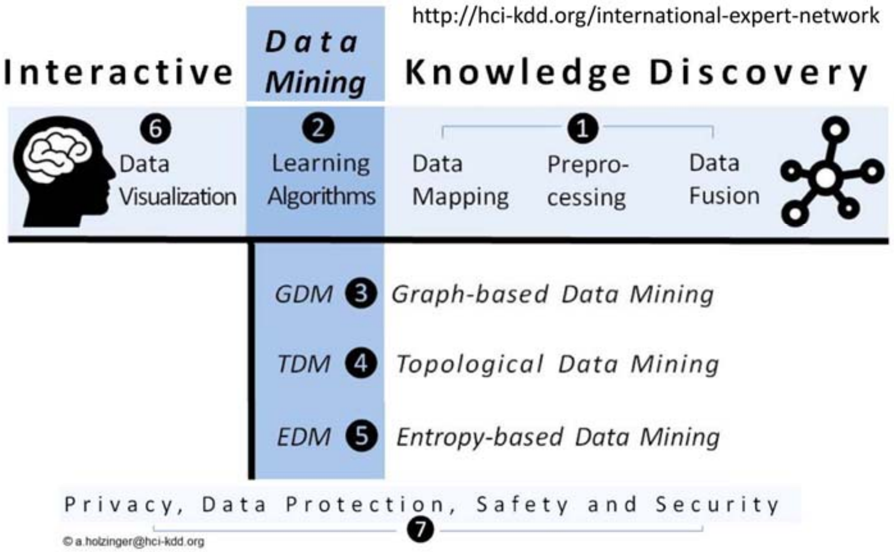
http://hci-kdd.org/mini-make-machine-learning-knowledge-extraction-health

Red thread through the lecture today

- 01 Data – the underlying physics of data
- 02 Biomedical data sources – taxonomy of data
- 03 Data integration, mapping, fusion
- 04 Probabilistic Information
- 05 Information Theory – Information Entropy
- 06 Cross- Entropy - Kullback-Leibler Divergence

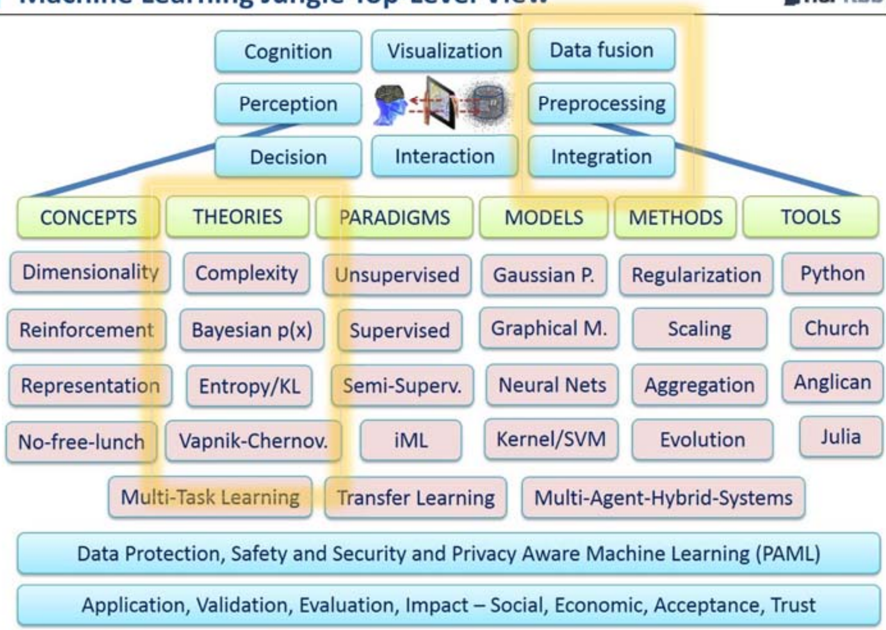
ML needs a concerted effort fostering integrated research

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



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

Machine Learning Jungle Top-Level View



Holzinger, A. 2016. Machine Learning for Health Informatics. In: LNCS 9605, pp. 1-24, doi:10.1007/978-3-319-50478-0_1.

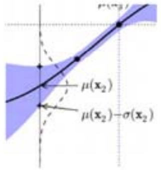
Image source: http://www.hutui6.com/reflection-wallpapers.html

Warm-up Quiz


1

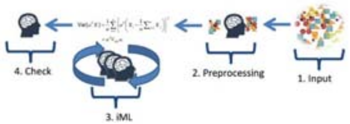
2

$$p(\theta|\mathcal{D}) = \frac{p(\mathcal{D}|\theta) * p(\theta)}{p(\mathcal{D})}$$
3


4


5

6



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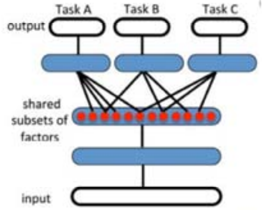
8



9

Question: Where is the Biologist in this image?

Image source: http://www.efmc.info/medchemwatch-2014-1/lab.php

Domingos, P. 2015. The Master Algorithm: How the Quest for the Ultimate Learning Machine Will Remake Our World, Penguin UK.

Repetition of Bayes - on the work of Laplace

What is the simplest mathematical operation for us?

$$p(x) = \sum_x (p(x,y)) \quad (1)$$

How do we call repeated adding?

$$p(x,y) = p(y|x) * p(y) \quad (2)$$

Laplace (1773) showed that we can write:

$$p(x,y) * p(y) = p(y|x) * p(x) \quad (3)$$

Now we introduce a third, more complicated operation:

$$\frac{p(x,y) * p(y)}{p(y)} = \frac{p(y|x) * p(x)}{p(y)} \quad (4)$$

We can reduce this fraction by $p(y)$ and we receive what is called Bayes rule:

$$p(x,y) = \frac{p(y|x) * p(x)}{p(y)} \qquad p(h|d) = \frac{p(d|h)p(h)}{p(d)} \quad (5)$$

Practical Example: Diagnoses

- Your MD has bad news and good news for you.
- Bad news first: You are tested positive for a serious disease, and the test is 99% accurate (T)
- Good news: It is a rare disease, striking 1 in 10,000 (D)
- **How worried would you now be?**

$$posterior\ p(x) = \frac{likelyhood * prior\ p(x)}{evidence} \qquad p(h|d) = \frac{p(d|h)p(h)}{p(d)}$$

$$p(T=1|D=1) = p(d|h) = \ 0{,}99\ \ and$$
$$p(D=1) = p(h) = 0{,}0001$$

$$p(D=1 \,|\, T=1) = \frac{(0{,}99)*(0{,}0001)}{(1-0{,}99)*(1-0{,}0001)+0{,}99*0{,}0001} =$$

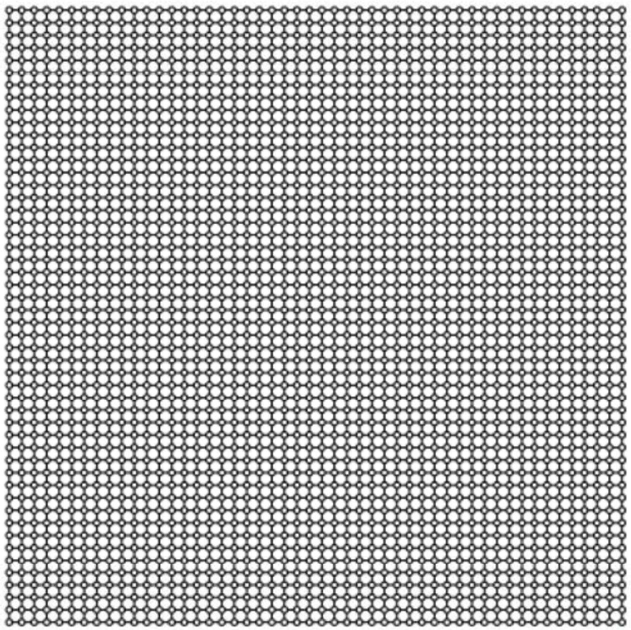
= 0,0098

Key Problems

- 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 in high-dimensions (manual handling of the data is 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.

What is this?



Goal of Machine Learning in Health Informatics

Statistical inference & Decision support:

Better a good solution in time, than a perfect solution never …

01 The underlying physics of data

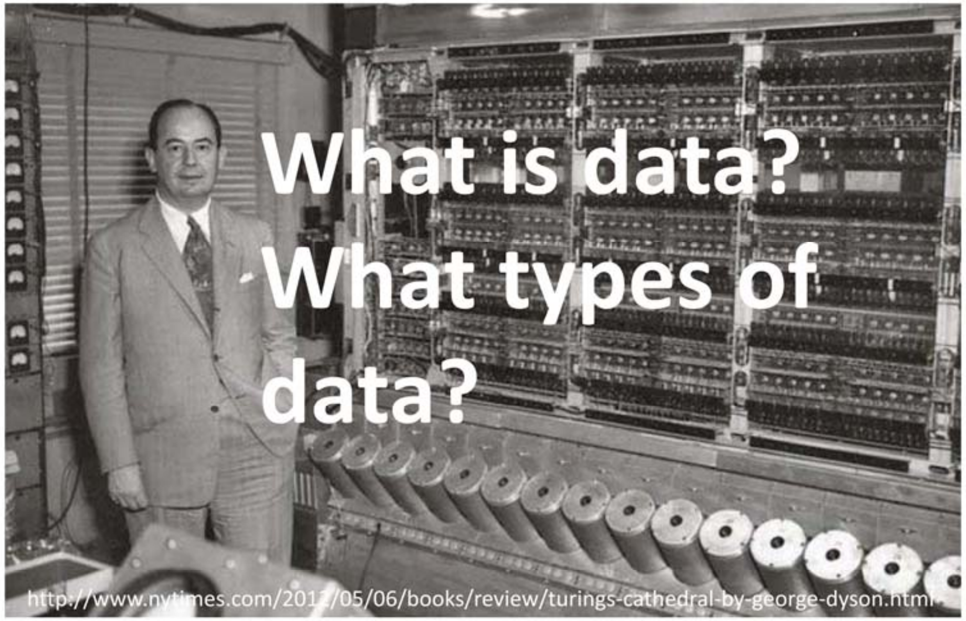
Traditional Statistics versus Machine Learning

- 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

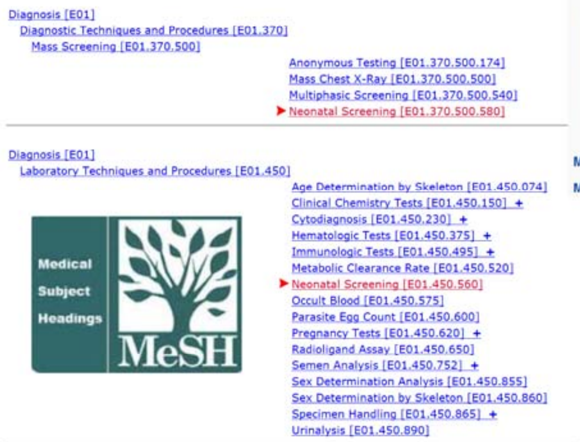
- Data in Machine Learning
- High-dimensional data ($\gg \mathbb{R}^{100}$)
- Problem: not noise , but complexity
- Much structure, but the structure can **not** be represented by a simple model

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

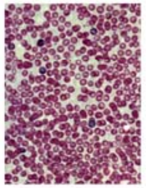
Institute for Advanced Study, Princeton University



Example: Neonatal Screening (1/3)

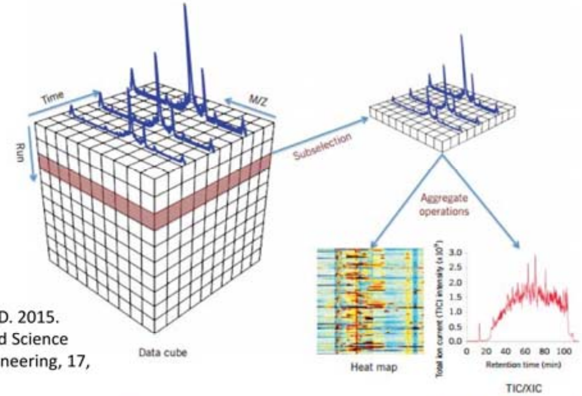


http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&index=15177&view=expanded#TreeE01.370.500.580



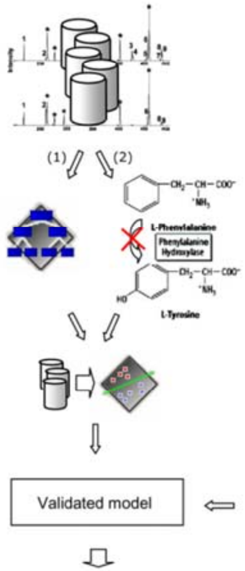
Amino acids (symbols)	Fatty acids (symbols)	Fatty acids (symbols)
Alanine (Ala)	Free carnitine (C0)	Hexadecenoyl-carnitine (C16:1)
Arginine (Arg)	Acetyl-carnitine (C2)	Octadecenoyl-carnitine (C18:1)
Argininosuccinate (Argsuc)	Propionyl-carnitine (C3)	Decenoyl-carnitine (C10:2)
Citrulline (Cit)	Butyryl-carnitine (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.



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.



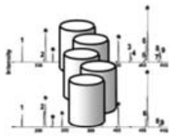
Real predictive power of the screening model

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

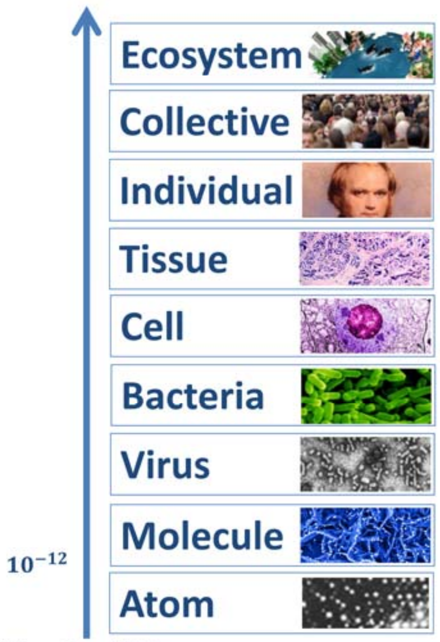
(2) Logistic regression analysis with expert knowledge (diagnostic flags) as model input variables

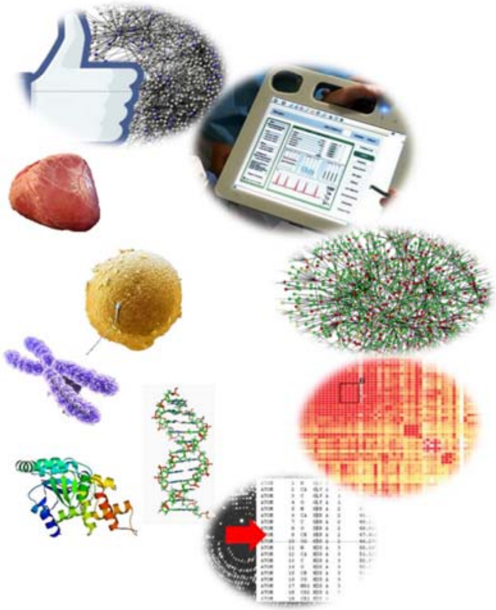
Training and 10-fold-cross validation



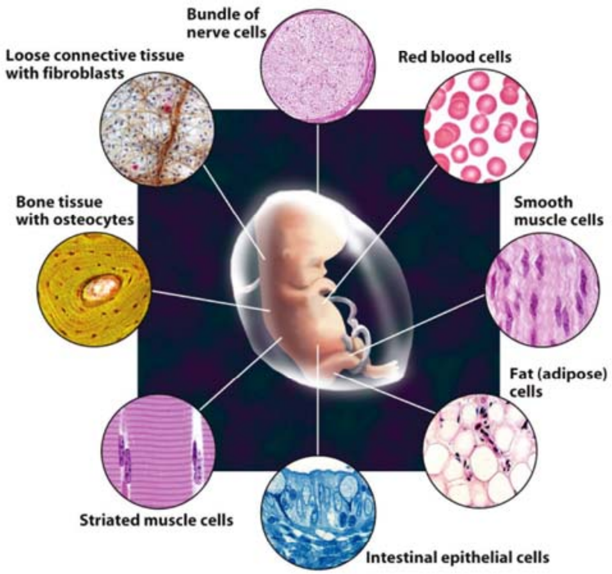
Larger database of control individuals (n=98,411) in order to estimate the specificity of a representative screening population

02 Biomedical data sources: Taxonomy of data



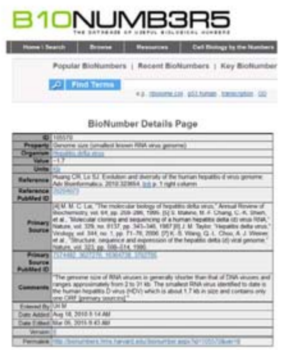


Example: Type of Cells



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

To get a feeling of biological data sources (bionumbers)

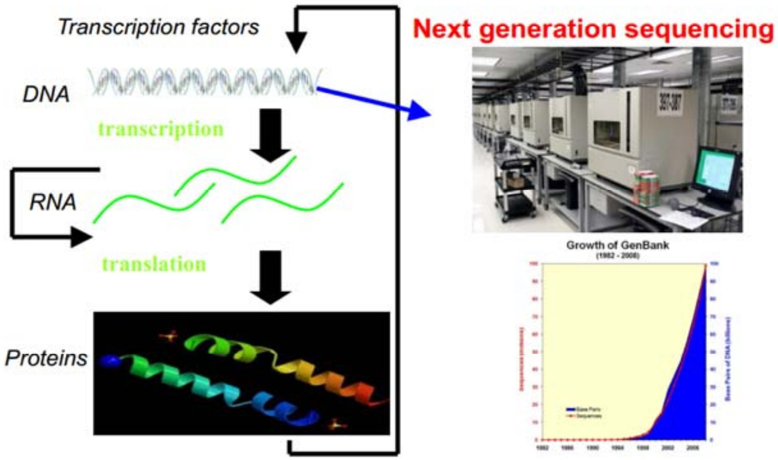


bionumbers.hms.harvard.edu/

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

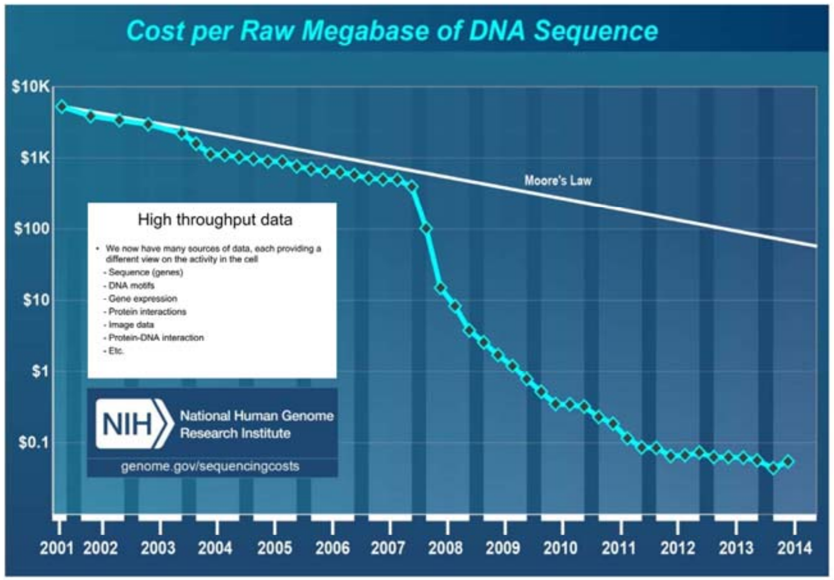
	Organism	# of protein-coding genes	# of genes naïve estimate: (genome size /1000)	BNID
viruses	HIV 1	9	10	105769
	Influenza A virus	10-11	14	105767
	Bacteriophage λ	66	49	105770
	Epstein Barr virus	80	170	103246
prokaryotes	*Buchnera sp.*	610	640	105757
	T. maritima	1,900	1,900	105766
	S. aureus	2,700	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

Biological data is getting more complex (big sowieso ;)

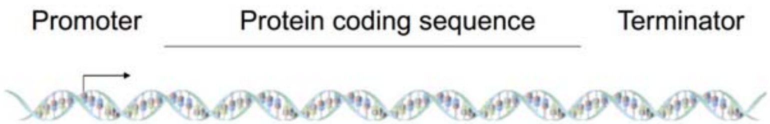


Navlakha, S. & Bar-Joseph, Z. 2011. Algorithms in nature: the convergence of systems biology and computational thinking. *Molecular Systems Biology*, 7.

Costs more decreasing than in Moor's law (also cost!)



Example: Genetic Data

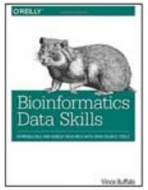


ATGAAGCTACTGTCTTCTATCGAACAAGCATGCGATATTTGCCGACTTAAAAAGCTCAAG
TGCTCCAAAGAAAAACCGAAGTGCGCCAAGTGTCTGAAGAACAACTGGGAGTGTCGCTAC
TCTCCCAAAACCAAAAGGTCTCCGCTGACTAGGGCACATCTGACAGAAGTGGAATCAAGG
CTAGAAAGACTGGAACAGCTATTTCTACTGATTTTTCCTCGAGAAGACCTTGACATGATT
TTGAAAATGGATTCTTTACAGGATATAAAAGCATTGTTAACAGGATTATTTGTACAAGAT
AATGTGAATAAAGATGCCGTCACAGATAGATTGGCTTCAGTGGAGACTGATATGCCTCTA
ACATTGAGACAGCATAGAATAAGTGCGACATCATCATCGGAAGAGAGTAGTAACAAAGGT
CAAAGACAGTTGACTGTATCGATTGACTCGGCAGCTCATCATGATAACTCCACAATTCCG
TTGGATTTTATGCCCAGGGATGCTCTTCATGGATTTGATTGGTCTGAAGAGGATGACATG
TCGGATGGCTTGCCCTTCCTGAAAACGGACCCCAACAATAATGGGTTCTTTGGCGACGGT
TCTCTCTTATGTATTCTTCGATCTATTGGCTTTAAACCGGAAAATTACACGAACTCTAAC
GTTAACAGGCTCCCGACCATGATTACGGATAGATACACGTTGGCTTCTAGATCCACAACA
TCCCGTTTACTTCAAAGTTATCTCAATAATTTTCACCCCTACTGCCCTATCGTGCACTCA
CCGACGCTAATGATGTTGTATAATAACCAGATTGAAATCGCGTCGAAGGATCAATGGCAA
ATCCTTTTTAACTGCATATTAGCCATTGGAGCCTGGTGTATAGAGGGGGAATCTACTGAT
ATAGATGTTTTTTACTATCAAAATGCTAAATCTCATTTGACGAGCAAGGTCTTCGAGTCA

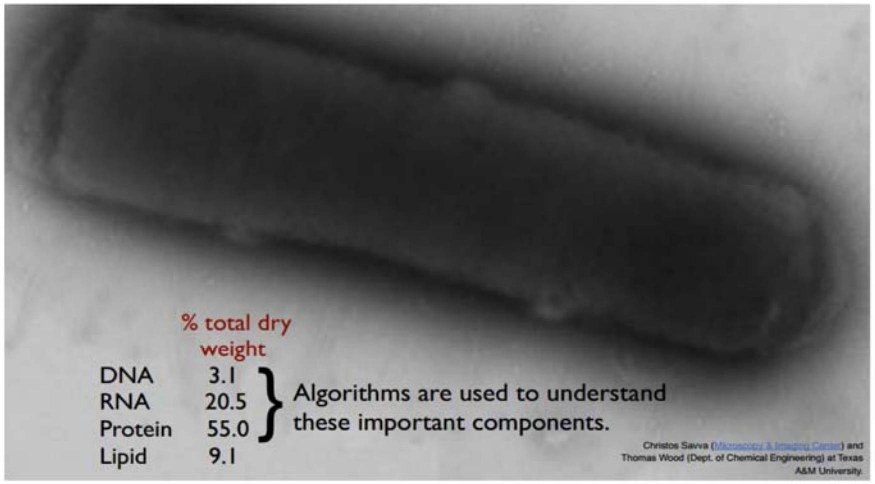
Second Letter

1st letter	U	C	A	G	3rd letter
U	UUU, UUC: Phe UUA, UUG: Leu	UCU, UCC, UCA, UCG: Ser	UAU, UAC: Tyr UAA: Stop UAG: Stop	UGU, UGC: Cys UGA: Stop UGG: Trp	U C A G
C	CUU, CUC, CUA, CUG: Leu	CCU, CCC, CCA, CCG: Pro	CAU, CAC: His CAA, CAG: Gln	CGU, CGC, CGA, CGG: Arg	U C A G
A	AUU, AUC, AUA: Ile AUG: Met	ACU, ACC, ACA, ACG: Thr	AAU, AAC: Asn AAA, AAG: Lys	AGU, AGC: Ser AGA, AGG: Arg	U C A G
G	GUU, GUC, GUA, GUG: Val	GCU, GCC, GCA, GCG: Ala	GAU, GAC: Asp GAA, GAG: Glu	GGU, GGC, GGA, GGG: Gly	U C A G

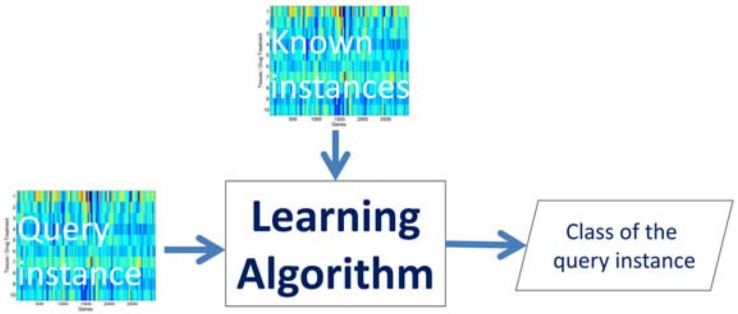
For further reading this is recommended: Buffalo, V. 2015. Bioinformatics Data Skills: Reproducible and Robust Research with Open Source Tools, Sebastopol (CA), O'Reilly.



Example Species: Bacterium E. coli



What can ML do with such data?



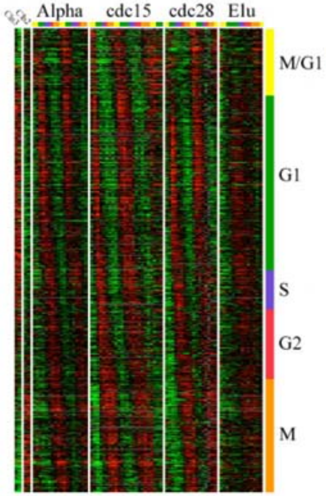
Features are key to learning and understanding!

Where do we get the data sets from?

BMJ OPEN DATA CAMPAIGN

- 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

Example Data Set from an High-Throughput Experiment



- 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

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

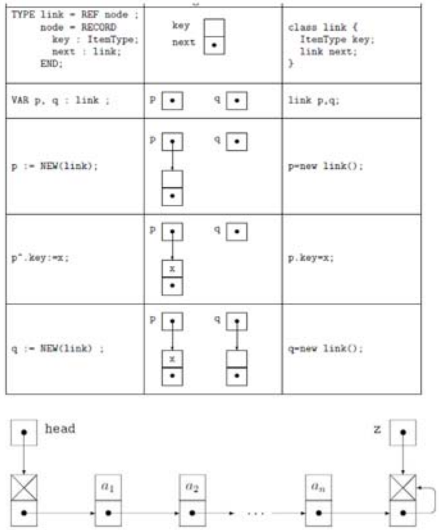
Taxonomy of data

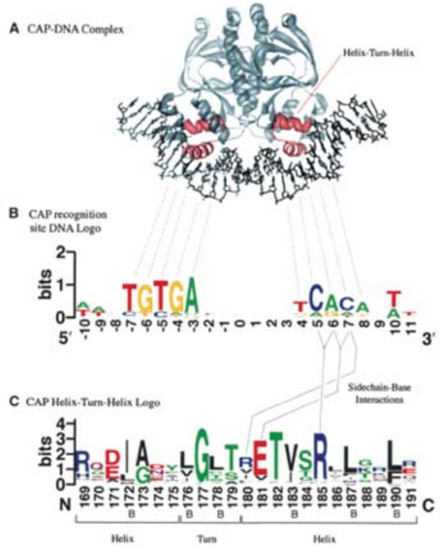
- **Physical level** -> bit = binary digit = **b**asic **i**ndissoluble uni**t** (= Shannon, Sh), ≠ Bit (!) in Quantum Systems -> qubit
- **Logical Level** -> integers, booleans, characters, floating-point numbers, alphanumeric strings, …
- **Conceptual (Abstract) Level** -> data-structures, e.g. lists, 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

Taxonomy of data at Hospital Level

- **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, …

Example Data Structures (1/3): List

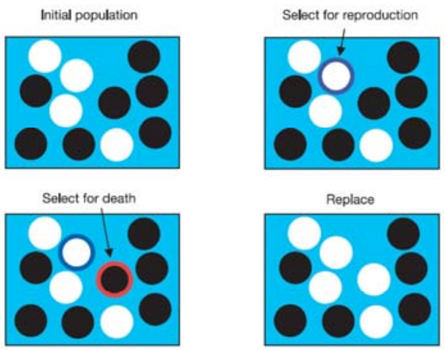


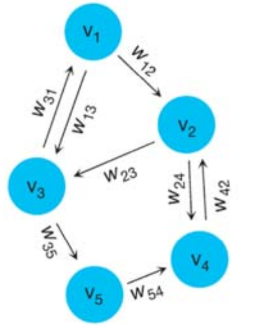


Crooks, G. E., Hon, G., Chandonia, J. M. & Brenner, S. E. (2004) WebLogo: A sequence logo generator. Genome Research, 14, 6, 1188-1190.

Example Data Structures (2/3): Graph

Evolutionary dynamics act on populations. Neither genes, nor cells, nor individuals evolve; only populations evolve.



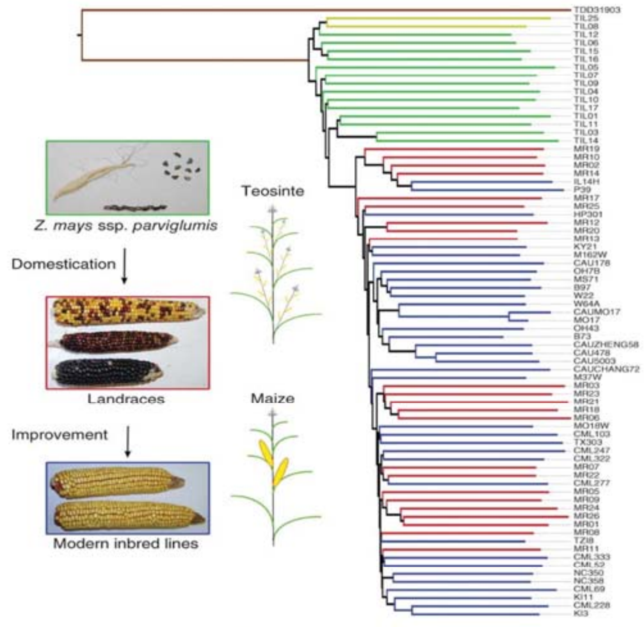


$$W=\begin{bmatrix} 0 & w_{12} & w_{13} & 0 & 0 \\ 0 & 0 & w_{23} & w_{24} & 0 \\ w_{31} & 0 & 0 & 0 & w_{35} \\ 0 & w_{42} & 0 & 0 & 0 \\ 0 & 0 & 0 & w_{54} & 0 \end{bmatrix}$$

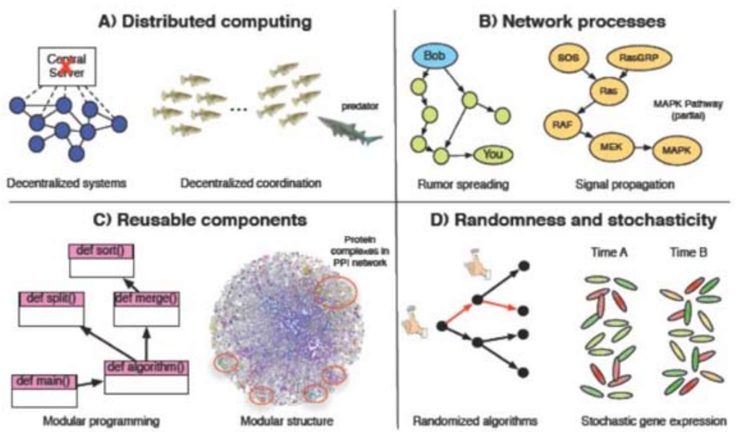
Lieberman, E., Hauert, C. & Nowak, M. A. (2005) Evolutionary dynamics on graphs. *Nature, 433, 7023, 312-316.*

Example Data Structures (3/3) Tree

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



Algorithms in nature: Shared principles

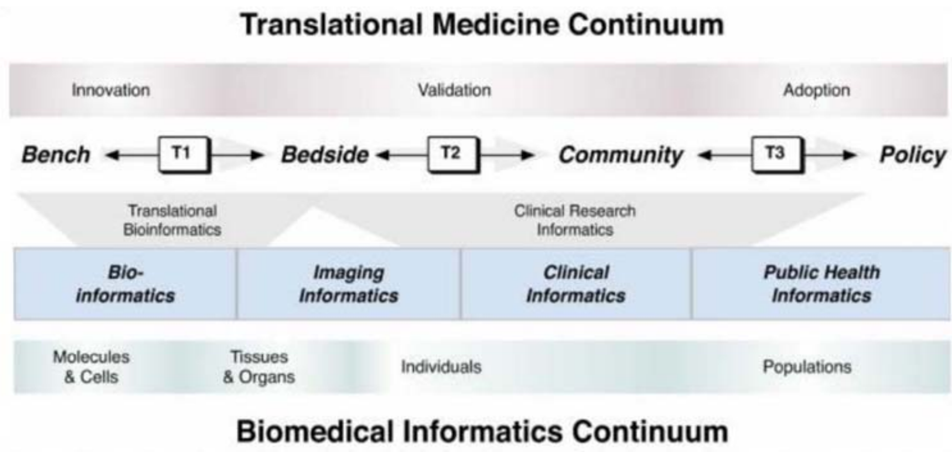


http://cacm.acm.org/magazines/2015/1/181614-distributed-information-processing-in-biological-and-computational-systems/abstract

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

Translational Health Informatics Continuum



Sarkar, I. 2010. Biomedical informatics and translational medicine. Journal of Translational Medicine, 8, (1), 2-12.

Biomedical Research needs Open Data Access

- 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/

03 Data Integration, mapping, fusion

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

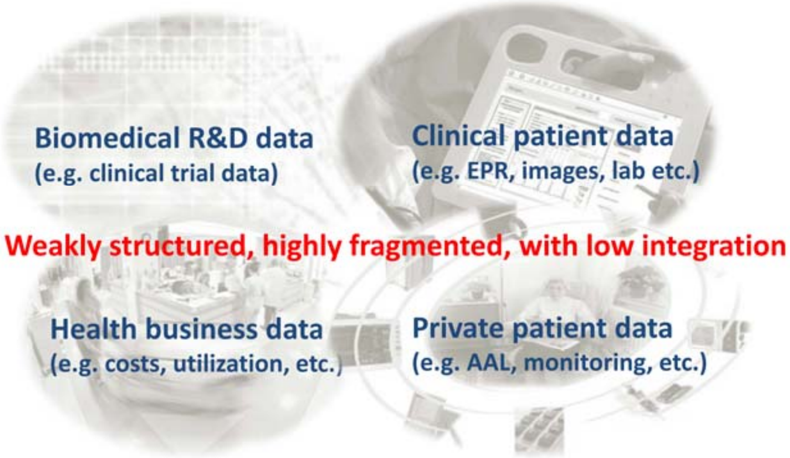
Navlakha, S. & Bar-Joseph, Z. 2014. Distributed information processing in biological and computational systems. *Commun. ACM,* 58, (1), 94-102, doi:10.1145/2678280.

In medicine we have two different worlds …

Our central hypothesis: Information may bridge this gap

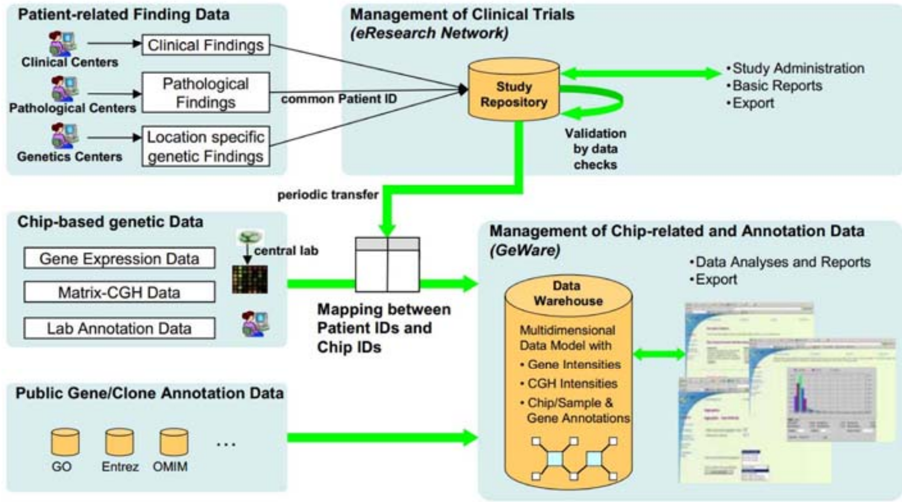
Holzinger, A. & Simonic, K.-M. (eds.) 2011. *Information Quality in e-Health. Lecture Notes in Computer Science LNCS 7058, Heidelberg, Berlin, New York: Springer.*

Not only a problem at cell level …



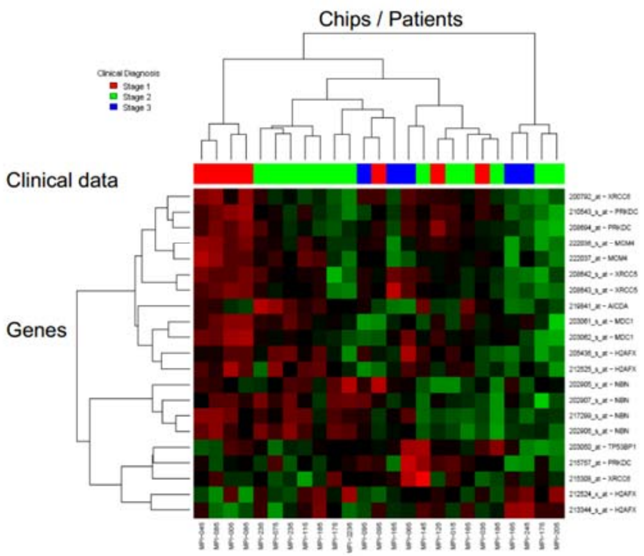
Manyika, J., Chui, M., Brown, B., Bughin, J., Dobbs, R., Roxburgh, C. & Byers, A. H. (2011) *Big data: The next frontier for innovation, competition, and productivity. Washington (DC), McKinsey Global Institute.*

Example Data Integration Architecture



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.

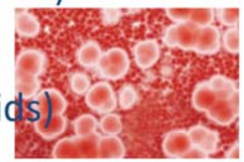
Example: Integrated Data Set



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.

-Omics-data jungle

- **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)



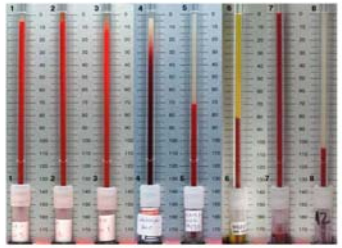
Omics-data integration

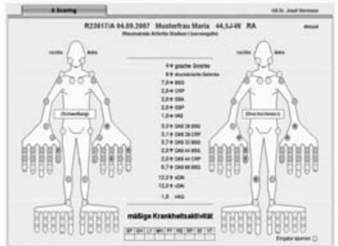
Genomics	Transcriptomics	Proteomics	Metabolomics	Protein–DNA interactions	Protein–protein interactions	Fluxomics	Phenomics
Genomics (sequence annotation)	• ORF validation • Regulatory element identification[74]	• SNP effect on protein activity or abundance	• Enzyme annotation	• Binding-site identification[75]	• Functional annotation[79]	• Functional annotation	• Functional annotation[71,103] • Biomarkers[125]
	Transcriptomics (microarray, SAGE)	• Protein: transcript correlation[20]	• Enzyme annotation[109]	• Gene-regulatory networks[76]	• Functional annotation[80] • 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[80,102]		• 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.***

Example of typical clinical data sets

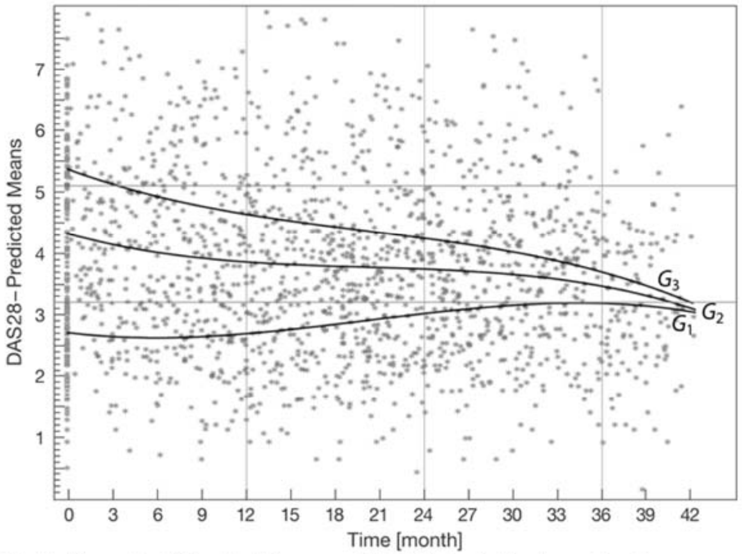
- 50+ Patients per day ~ 5000 data points per day …
- Aggregated with specific scores (Disease Activity Score, DAS)
- Current patient status is related to previous data
- = convolution over time
- ⇒ **time-series data**





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.*

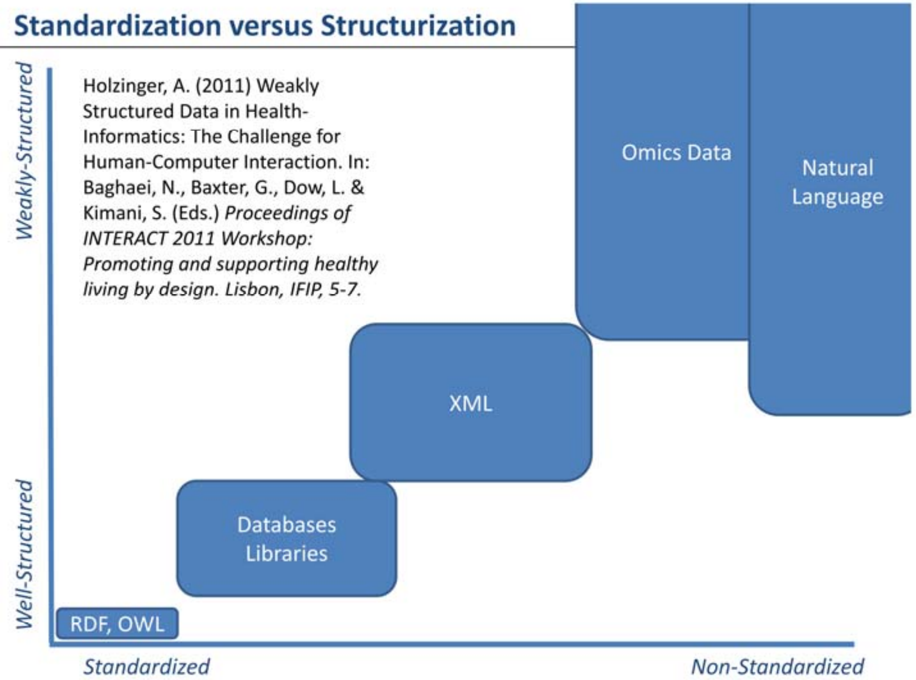
DAS28 Predicted Mean Responses



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.*



Data Dimensionality examples

- 0-D data = a data point existing isolated from other data, e.g. integers, letters, Booleans, etc.
- 1-D data = consist of a string of 0-D data, e.g. Sequences representing nucleotide bases and amino acids, SMILES etc.
- 2-D data = having spatial component, 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. PDB records
- 3-D data = having 3-D spatial component, e.g. image voxels, e-density maps, etc.
- H-D Data = data having arbitrarily high dimensions

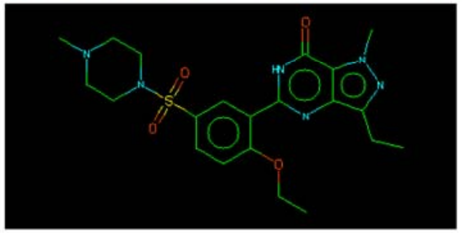
Example: 1-D data (univariate sequential data objects)

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



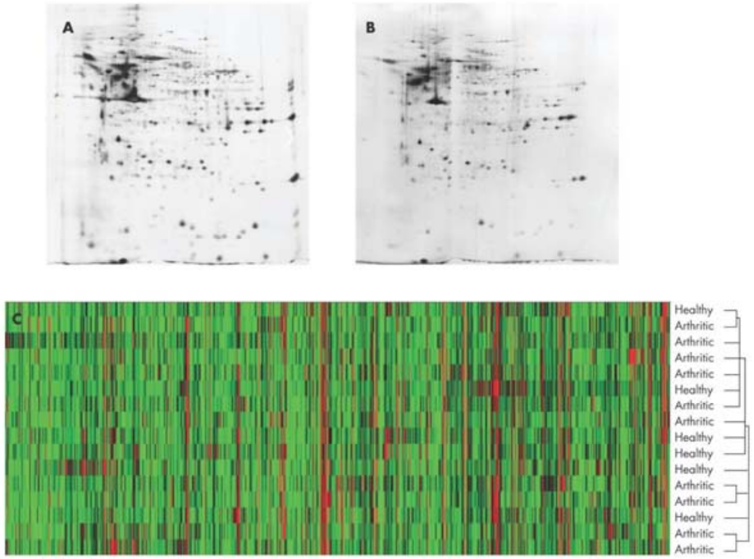
...is Canonicalizable

...is Comprehensive

...is Well Documented

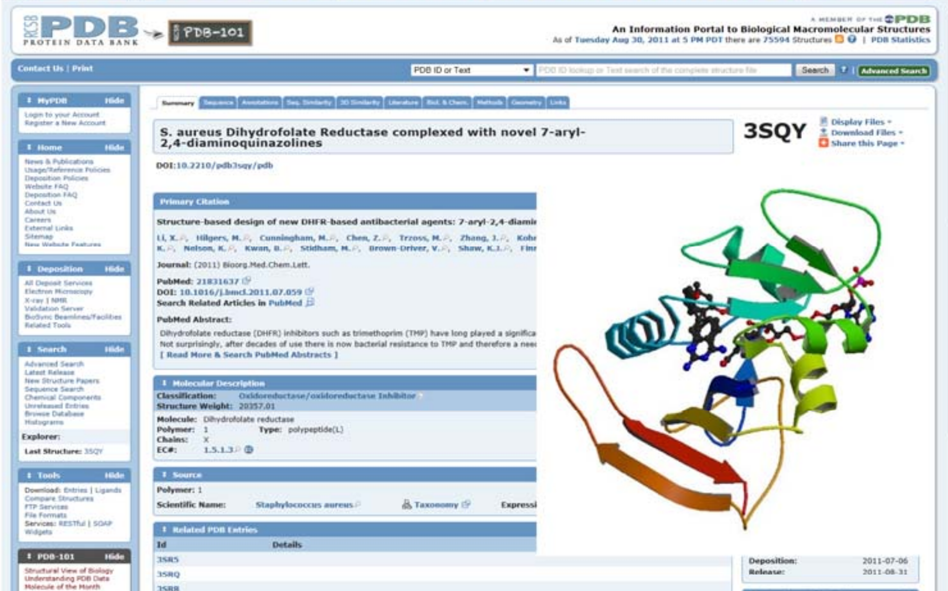
http://www.daylight.com/dayhtml_tutorials/languages/smiles/index.html

Example: 2-D data (bivariate data)



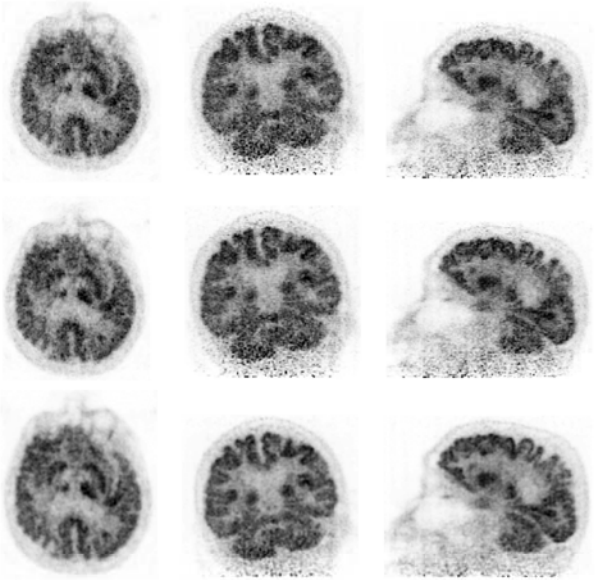
Kastrinaki et al. (2008) Functional, molecular & proteomic characterisation of bone marrow mesenchymal stem cells in rheumatoid arthritis. *Annals of Rheumatic Diseases, 67, 6, 741-749.*

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



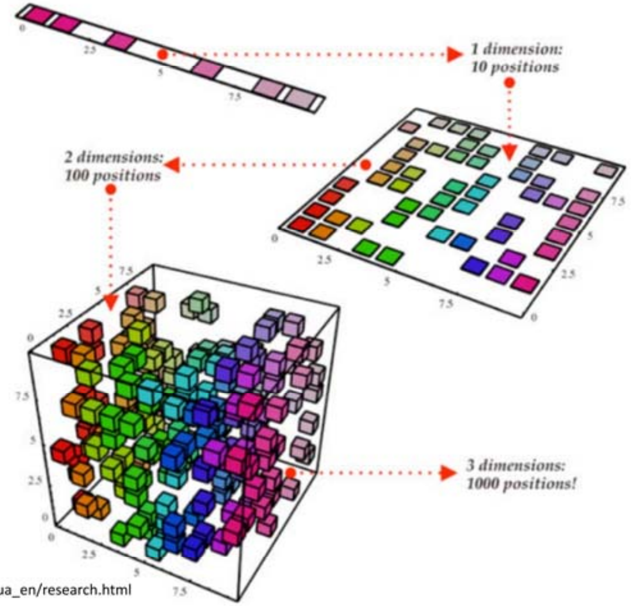
http://www.pdb.org

Example: 3-D Voxel data (volumetric picture elements)



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.*

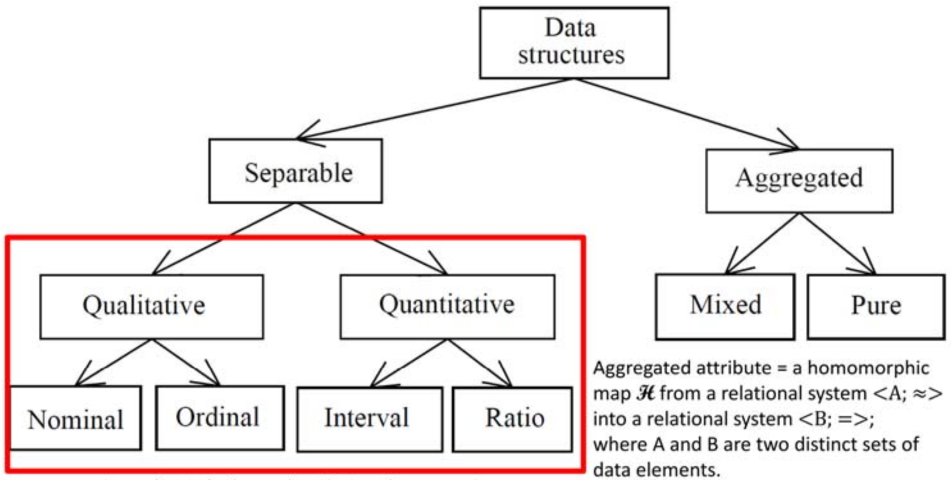
Note: The curse of dimensionality



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

Example: Data structures - Classification



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 $\mathcal{H}$ 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	=, ≠
ORDINAL	Determination of more/less	Isotonic $x' = f(x)$ x … mono-tonic incr.	$x \mapsto f(x)$	Median, Percentiles	=, ≠, >, <
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.	=, ≠, >, <, -, +
RATIO	Determination of equality or ratios	Similarity $x' = ax$	$x \mapsto rx$	Coefficient of variation	=, ≠, >, <, -, +, *, ÷

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

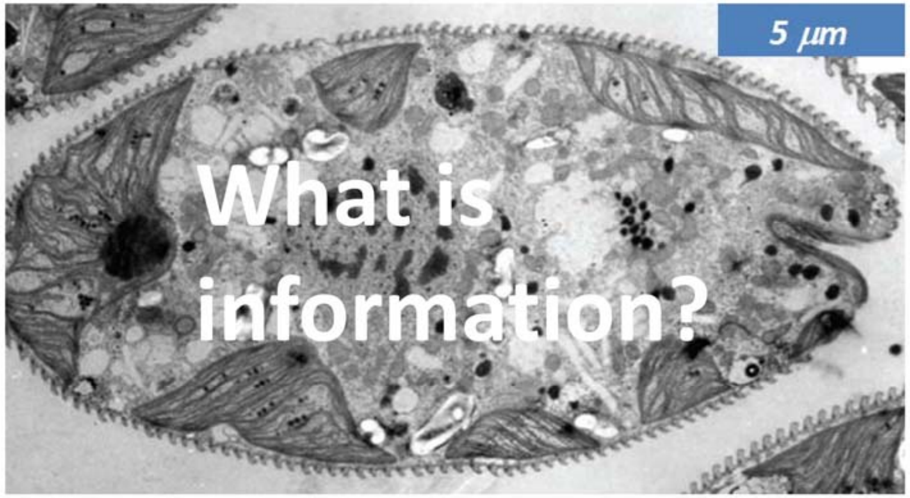
- Bridging the gap between natural sciences and clinical medicine (who has seen genomics and patient data integrated in routine?)
- Organizational barriers, data provenance, data ownership, privacy, accessibility, usability, fair use of data, security, safety, data protection
- Combine Ontologies with Machine Learning
- Stochastic Ontologies, Ontology learning
- Integration of data from wet-labs with in-silico experimental data (e.g. tumor growth simulation)

04 Probabilistic Information p(x)

- **Boolean models**
- **Algebraic models**
- **Probabilistic models *)**

*) Our probabilistic models 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 predictions – 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.



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

Information is everywhere …

- 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.

For ML and Health always remember

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

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

$$p(x_i, y_j) = p(y_j|x_i)P(x_i)$$

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 Law of Total Probability = data modelling

Bayes' Rule in words
d **… data;** ***h*** **… hypothesis**
H ={H_1, H_2, … , H_n} … Hypothesis space

$$\forall h, d \ \ldots$$

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

Posterior Probability

Likelihood

Prior Probability

Sum over space of alternative hypotheses

Evidence = marginal likelihood

Always remember:

The inverse probability allows to infer unknowns, learn from data 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 (e.g. for MCMC)

   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 $P(\theta\,|\mathcal{D})$

Parameter Estimation

- General setting:
  - Given a (hypothesized & probabilistic) model that governs the random experiment
  - The model gives a probability of any data $p(D|\ )$ that depends on the parameter θ
  - Now, given actual sample data $X = \{x_1, \dots, x_n\}$, 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 optimization problem

Maximum Likelihood vs. Bayesian

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

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

  - **Problem: massive amount of data necessary**
- 2) Bayesian estimation (use posterior)

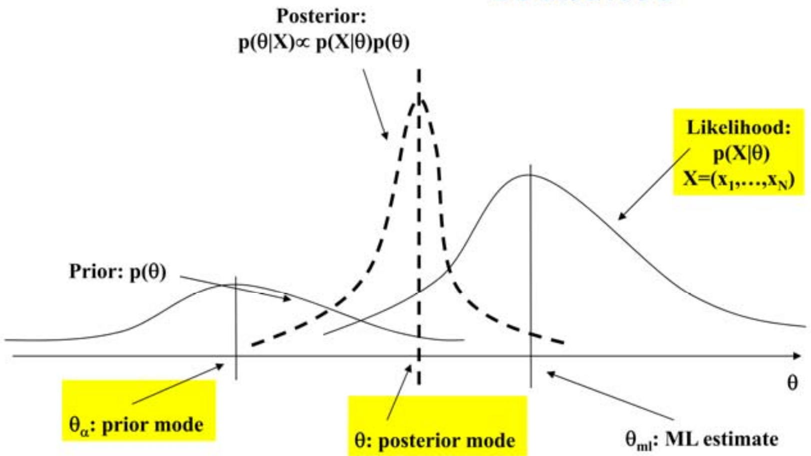
$$\hat{\theta} = \arg\max_{\theta} P(X|\theta) = \arg\max_{\theta} P(X|\theta)\, P(\theta)$$

  - "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

Illustration of Bayesian Estimation

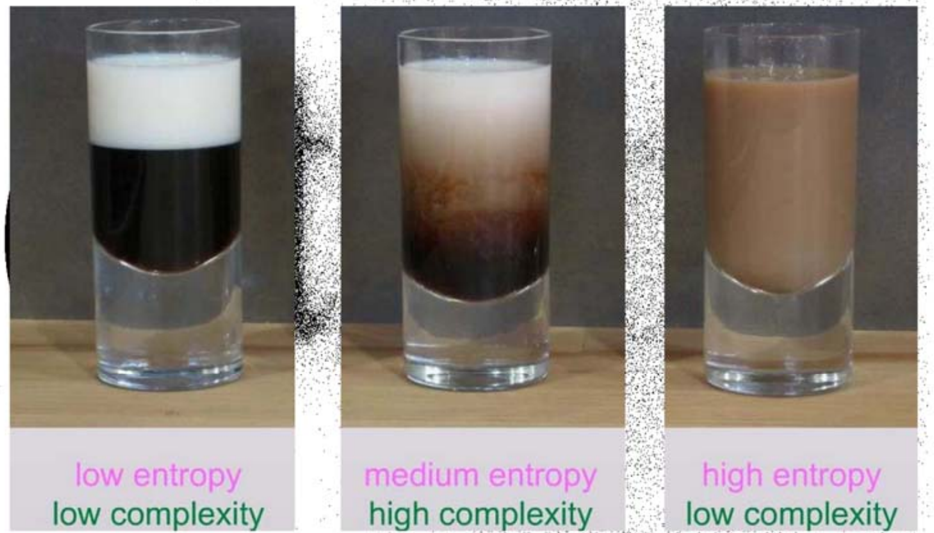
$$posterior\ p(x) = \frac{likelyhood * prior\ p(x)}{evidence}$$



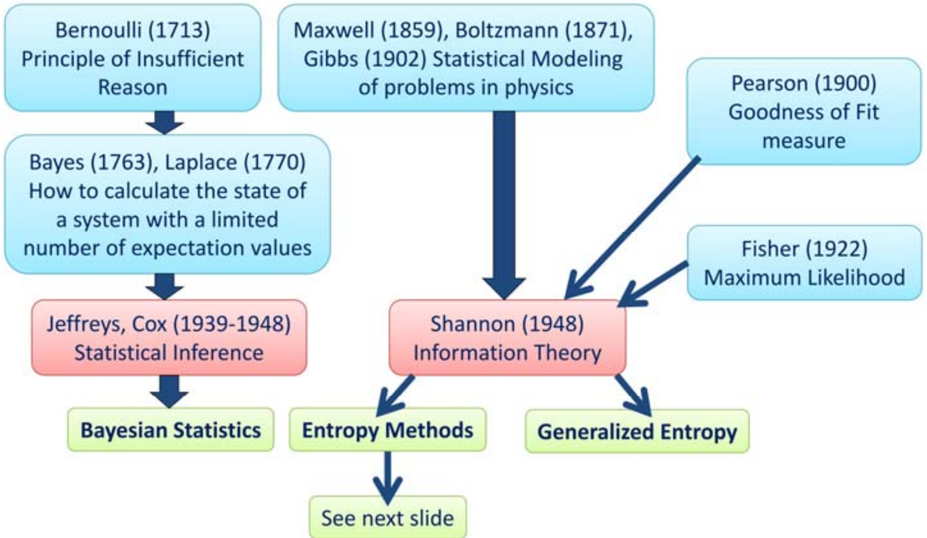
For more basic information: Bishop, C. M. 2007. *Pattern Recognition and Machine Learning,* Springer. For application examples in Text processing refer to: Jiang, J. & Zhai, C. X. 2007. An empirical study of tokenization strategies for biomedical information retrieval. *Information Retrieval,* 10, (4-5),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

05 Information Theory & Entropy

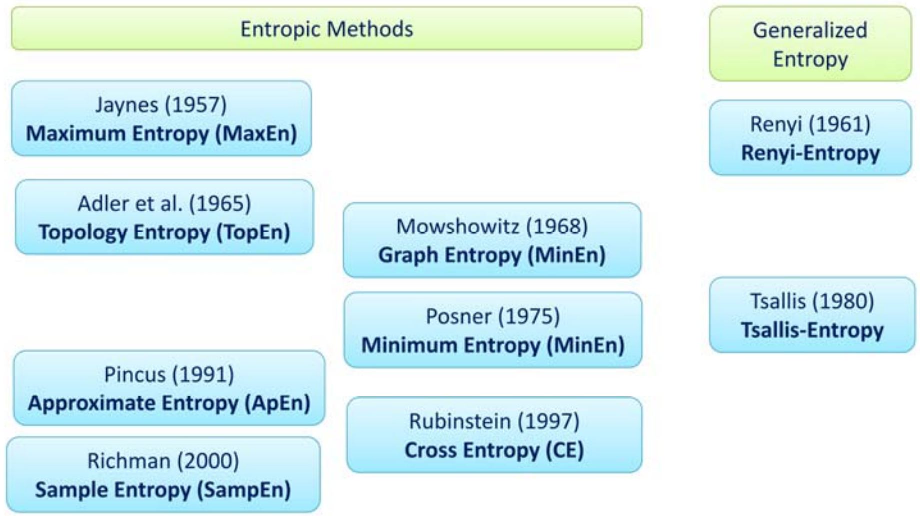
- Information is the reduction of uncertainty
- If something is 100 % certain its uncertainty = 0
- Uncertainty is a max. if all choices are equally probable
- Uncertainty (as information) sums up for independent sources



http://www.scottaaronson.com

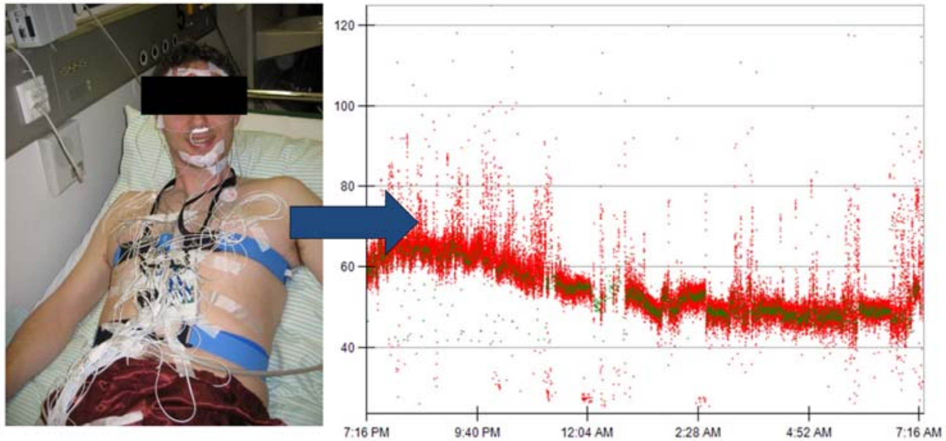


confer also with: Golan, A. (2008) Information and Entropy Econometric: A Review and Synthesis. *Foundations and Trends in Econometrics, 2, 1-2, 1-145.*



Holzinger, A., Hörtenhuber, M., Mayer, C., Bachler, M., Wassertheuer, 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.

Example of the usefulness of ApEn (1/3)



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)

Example of the usefulness of ApEn (2/3)

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

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

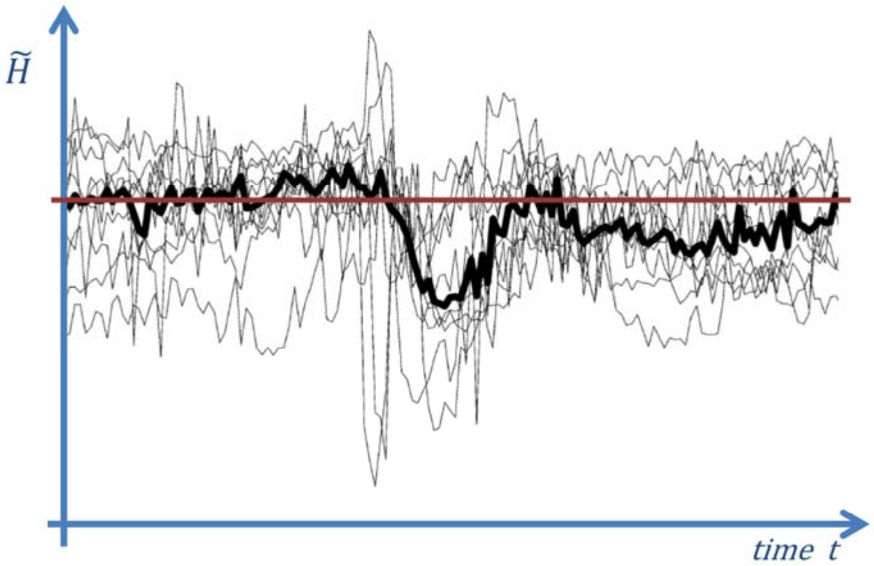
$$\|\vec{X}_i, \vec{X}_j\| = \max_{k=1,2,\dots,m} \left(|x_{(i+k-1)} - x_{(j+k-1)}|\right)$$

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

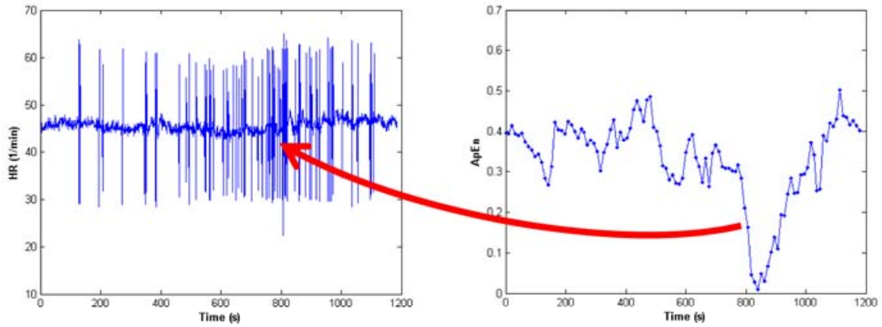
$$C_r^m(i) = \frac{N^m(i)}{N-m+1} \qquad \phi^m(r) = \frac{1}{N-m+1} \sum_{t=1}^{N-m+1} \ln C_r^m(i)$$

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.*

Example: ApEn (2)

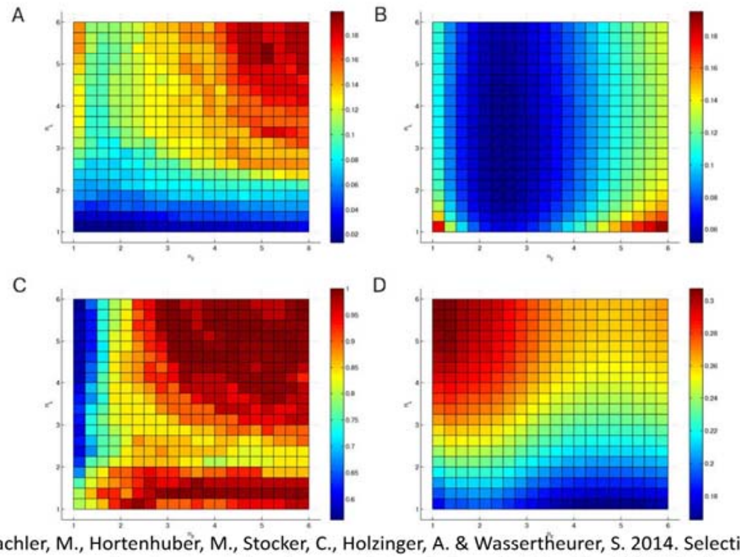


ApEn



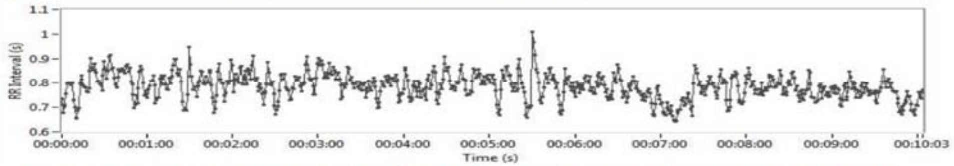
Holzinger, A., Hörtenhuber, M., Mayer, C., Bachler, M., Wassertheurer, S., Pinho, A. & Koslicki, D. 2014. On Entropy-Based Data Mining. In: Holzinger, A. & Jurisica, I. (eds.) Interactive Knowledge Discovery and Data Mining in Biomedical Informatics, Lecture Notes in Computer Science, LNCS 8401. Berlin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

Significance of FuzzyMEn for different nL and nF, N=1000



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.

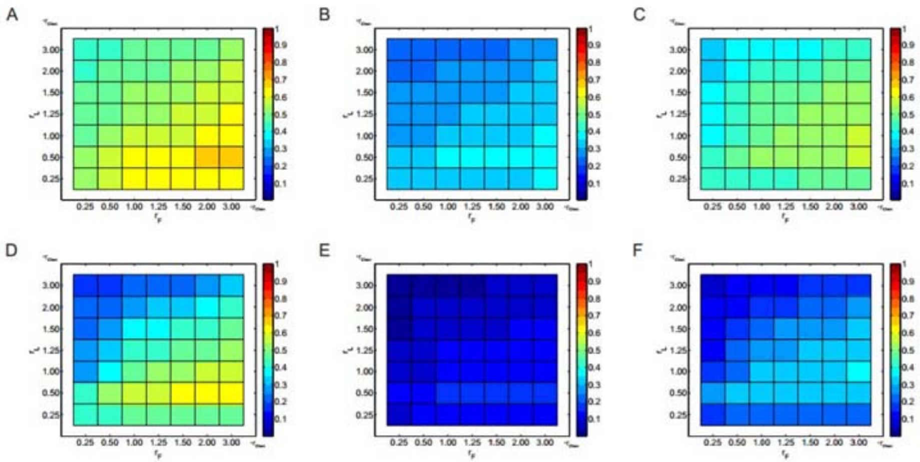
Summary: Example Heart Rate Variability



- 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.

Baseline: A,B,C – After treatment: D,E,F N=1200



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.

06 Cross-Entropy Kullback-Leibler Divergence

Entropy – KL-Div. – Mutual Information

- Entropy:
  - Measure for the **uncertainty** of random variables
- Kullback-Leibler divergence:
  - **comparing two distributions**
- Mutual Information:
  - measuring the **correlation** of two random variables

Solomon Kullback & Richard Leibler (1951)

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.

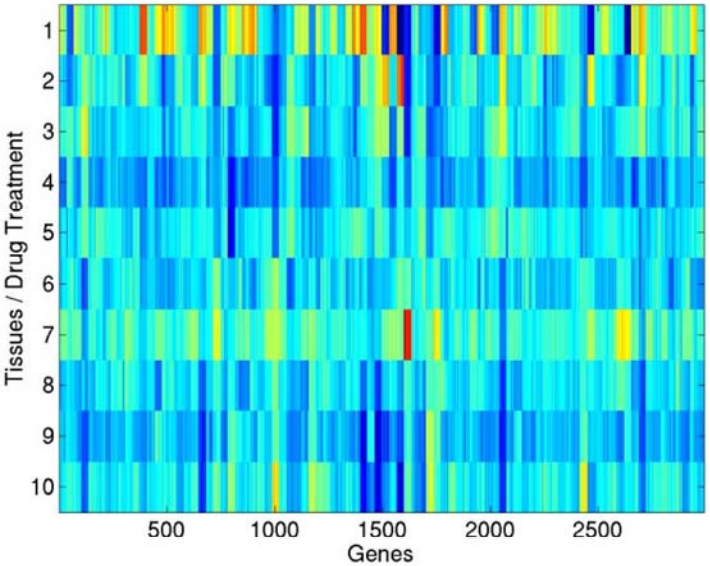
R. A. Fisher, in his original introduction of the *criterion of sufficiency*, required "that the statistic chosen should summarize the whole of the relevant information supplied by the sample," (p. 316 of [5]). Halmos and Savage in a recent paper, one of the main results of which is a generalization 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 1907-1994

Richard Leibler 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



Remember Shannon Entropy

$$\mathrm{H}[x] = -\sum_{x} p(x) \log_2 p(x)$$

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

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

Conditional Entropy

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

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

The Kullback-Leibler Divergence

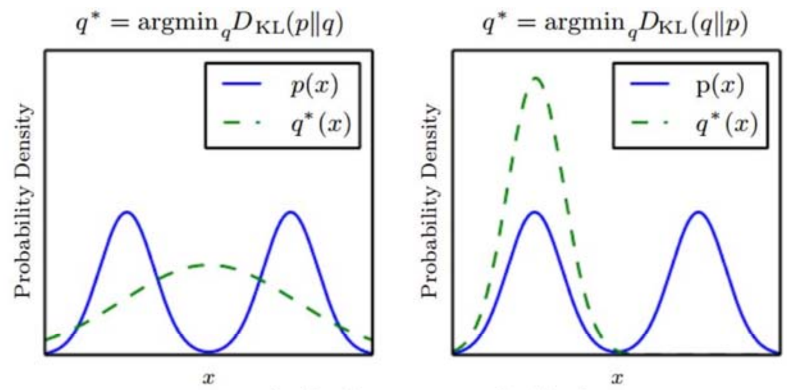
$$\begin{aligned}\mathrm{KL}(p\|q) &= -\int p(\mathbf{x}) \ln q(\mathbf{x})\, \mathrm{d}\mathbf{x} - \left(-\int p(\mathbf{x}) \ln p(\mathbf{x})\, \mathrm{d}\mathbf{x}\right) \\ &= -\int p(\mathbf{x}) \ln \left\{\frac{q(\mathbf{x})}{p(\mathbf{x})}\right\} \mathrm{d}\mathbf{x}\end{aligned}$$

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

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

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

Note: KL is not symmetric!



$$\mathrm{KL}(p\|q) \not\equiv \mathrm{KL}(q\|p)$$

Goodfellow, I., Bengio, Y. & Courville, A. 2016. Deep Learning, Cambridge (MA), MIT Press.

Entropy measures generally …

- … 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**

Mutual Information
and Point Wise MI

Mutual Information I(X;Y): Comparing two distributions

$$\mathrm{I}[\mathbf{x},\mathbf{y}] \equiv \mathrm{KL}(p(\mathbf{x},\mathbf{y})\|p(\mathbf{x})p(\mathbf{y})) = -\iint p(\mathbf{x},\mathbf{y}) \ln\left(\frac{p(\mathbf{x})p(\mathbf{y})}{p(\mathbf{x},\mathbf{y})}\right) \mathrm{d}\mathbf{x}\,\mathrm{d}\mathbf{y}$$

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

- 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.

Example: Disease-Disease Relationship

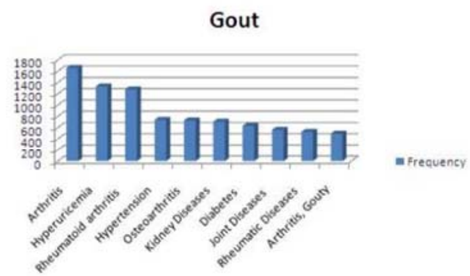
Let two words, w_i and w_j, have probabilities $P(w_i)$ and $P(w_j)$. Then their mutual information *PMI* (w_i, w_j) is defined as:

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

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

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

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



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.

Open Questions, future outlook, hot topics, challenges

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

Limitations and Open Problems

- The case of higher order statistical structure in the data – nonlinear and hierarchical ?
- Outliers in the data – noise models?
- There are $\frac{D(D+1)}{2}$ parameters in a multi-variate Gaussian model – what happens if $D \gg$? dimensionality reduction

Thank you!

Questions

Sample Questions (1)

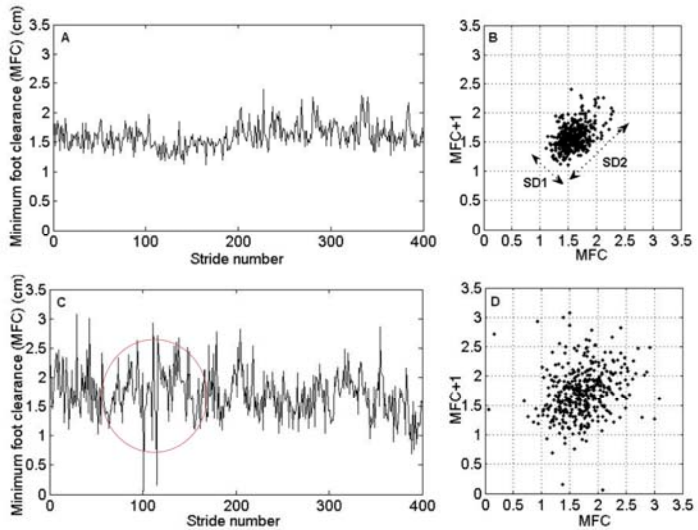
- What are the grand challenges in ML for health?
- What is the key problem before you can apply ML?
- Describe the taxonomy of data at Hospital level!
- What does translational medicine mean?
- Give an example for a 2.5D-data set!
- Why would be the combination of ontologies with machine learning provide 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?

Sample Questions (2)

- 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?

Appendix

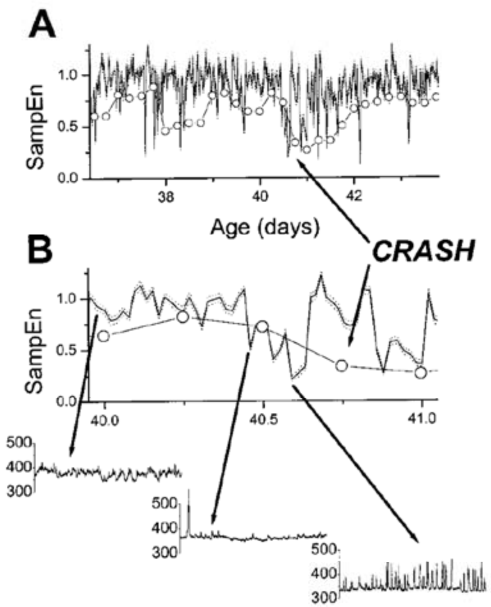
Back-up Slide: Poincare Plot for gait analysis



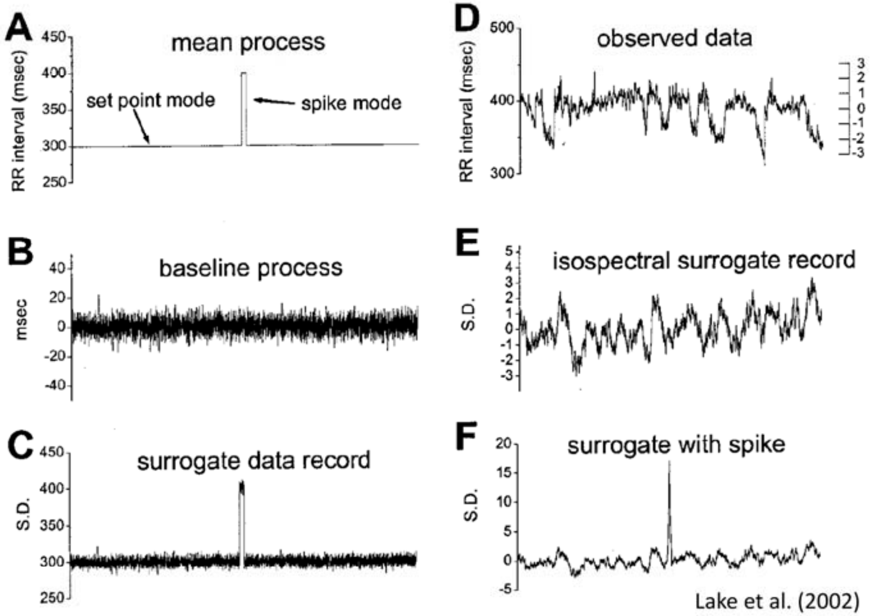
Khandoker, A., Palaniswami, M. & Begg, R. (2008) A comparative study on approximate entropy measure and poincare plot indexes of minimum foot clearance variability in the elderly during walking. *Journal of NeuroEngineering and Rehabilitation, 5, 1, 4.*

Back-up Slide: SampEn (1/2)

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.***



Backup: SampEn (2/2) Surrogate data heart rate variability



Lake et al. (2002)

Backup Slide: Comparison ApEn - SampEn

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:

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

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

$$C_r^m(i)=V^m(i)/(N-m+1) \quad \text{where} \quad V^m(i)=no.\ of\ d[X(i),X(j)]\le r \quad (3)$$

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:

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

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)

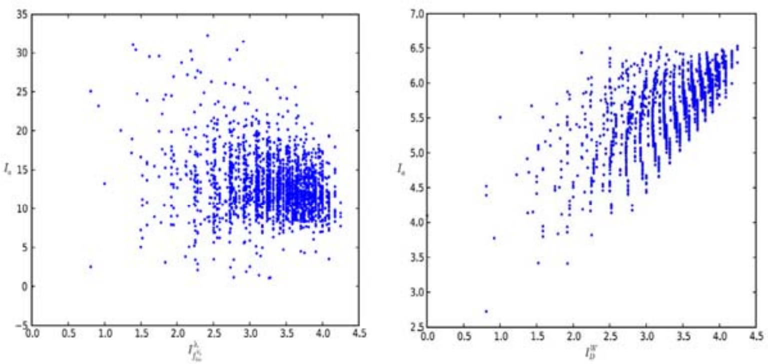
$$A^m(r)=\frac{1}{N-m}\sum_{i=1}^{N-m}A_i^m(r) \quad (11)$$

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

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

Backup Slide: Graph Entropy Measures

- 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.*

Backup: English/German Subject Codes OEFOS 2012

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

http://www.statistik.at

Backup: English/German Subject Codes OEFOS 2012

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

http://www.statistik.at

Advance Organizer (1/2)

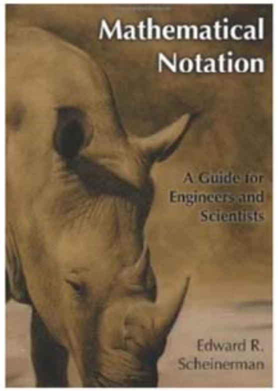
- **Abduction** = cyclical process of generating possible explanations (i.e., identification of a set of hypotheses that are able to account for the clinical case on the basis of the available data) and testing those (i.e., evaluation of each generated hypothesis on the basis of its expected consequences)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

Advance Organizer (2/2)

- **Induction** = deriving a likely general conclusion from a set of particular statements;
- **Information** = derived from the data by interpretation (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" (explicit knowledge). This knowledge is used for the interpretation of other data and to gain implicit knowledge 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 reach a conclusion 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

Mathematical Notation

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



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
$p(y \mid \mathbf{x})$	Conditional density
$t(\mathbf{x})$	Target function

Glossary

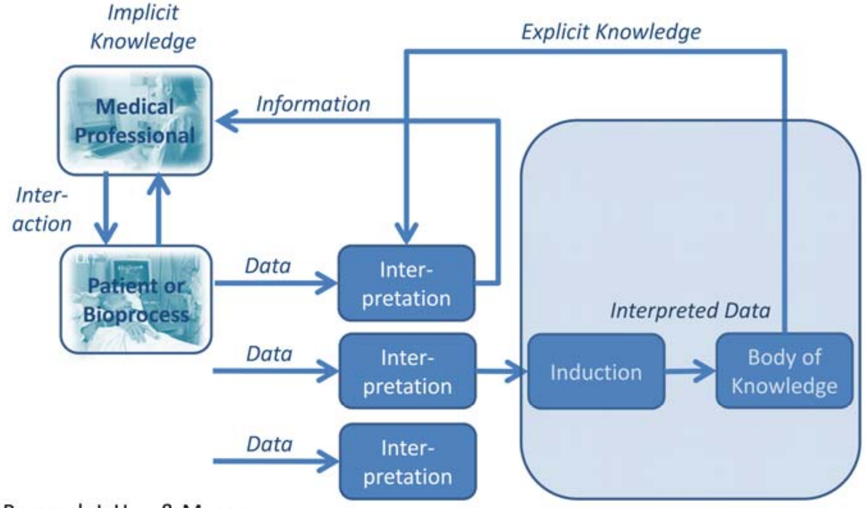
- ApEn = Approximate Entropy;
- $\mathbb{C}_{data}$ = Data in computational space;
- DIK = Data-Information-Knowledge-3-Level Model;
- DIKW = Data-Information-Knowledge-Wisdom-4-Level Model;
- GraphEn = Graph Entropy;
- H = Entropy (General);
- HRV = Heart Rate Variability;
- MaxEn = Maximum Entropy;
- 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;

Scientists in data integration - selection - incomplete!

Status as of 04.04.2016

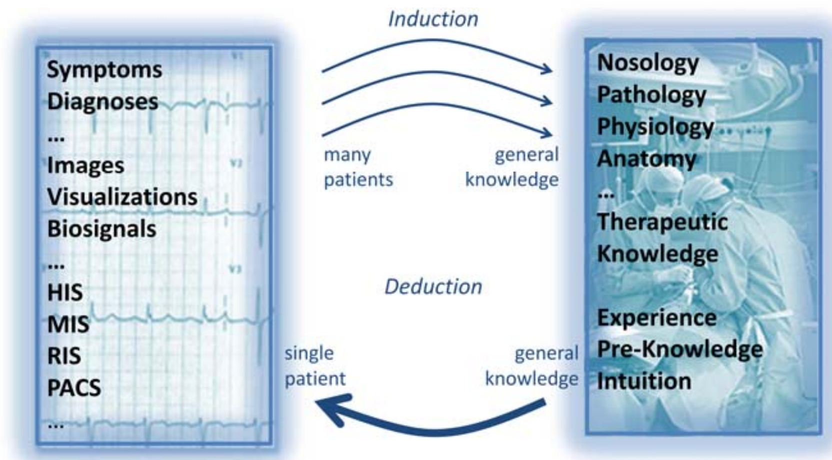
Clinical view on data – information, and knowledge

Clinical View of Data, Information, Knowledge



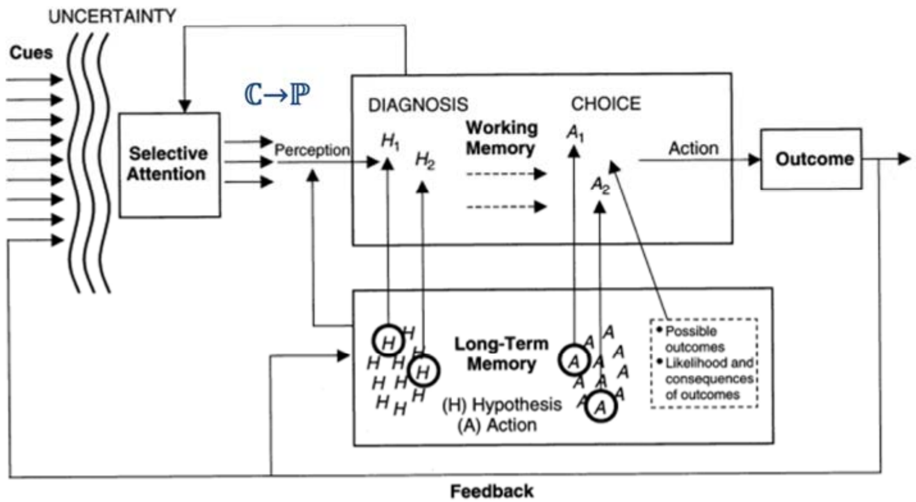
Bemmel, J. H. v. & Musen, M. A. (1997) *Handbook of Medical Informatics.* *Heidelberg, Springer.*

From Patient Data to Medical Knowledge



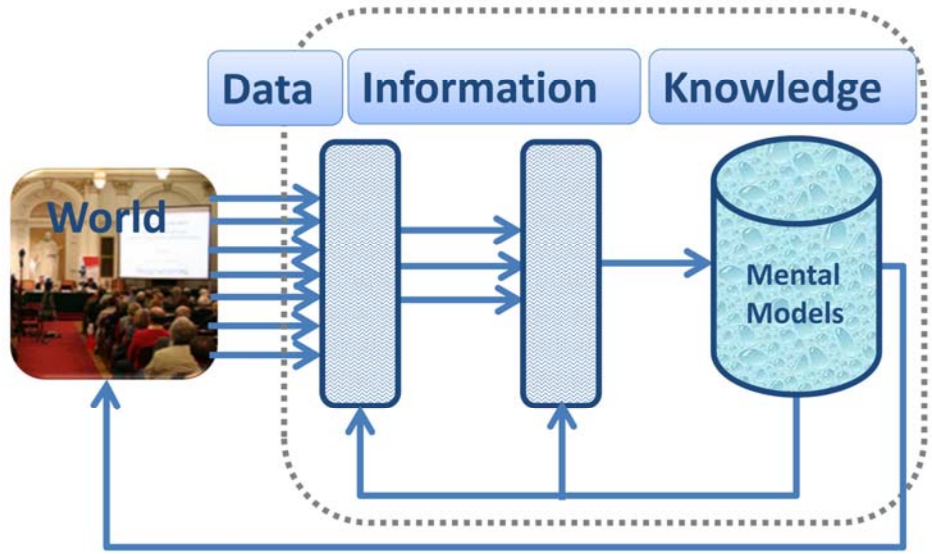
Holzinger (2007)

Human Information Processing Model



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

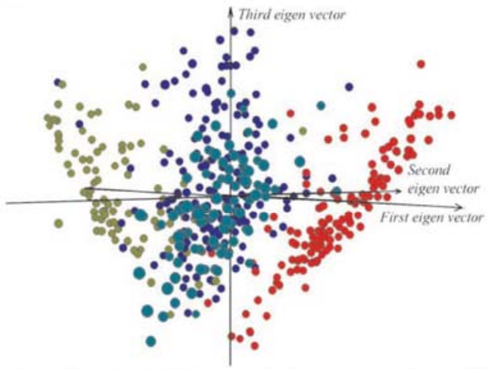
Our definition of Knowledge – adaptive agent



Knowledge := a set of expectations

A space as a set of points

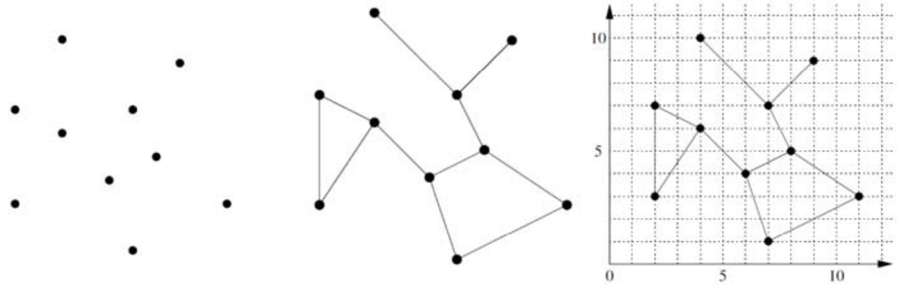
$$f : X \to \mathbb{R}$$



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.*

Point Cloud Data Sets

Let us collect n-dimensional i observations: $\boldsymbol{x}_i = [x_{i1}, \dots, x_{in}]$

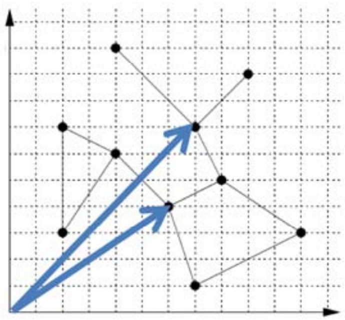


Point cloud in $\mathbb{R}^2$ **topological space** **metric space**

Zomorodian, A. J. 2005. *Topology for computing, Cambridge (MA), Cambridge University Press.*

Example Metric Space

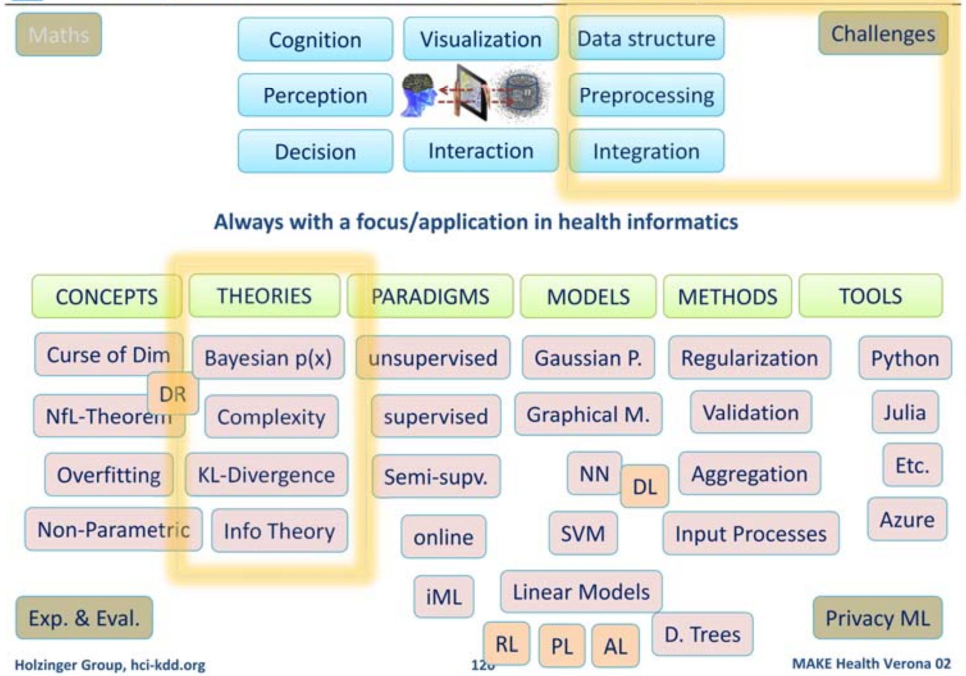
A set S with a metric function d is a metric space



$$d_{ij} = \sqrt{\sum_{k=1}^{p} (x_{ik} - x_{jk})^2}$$

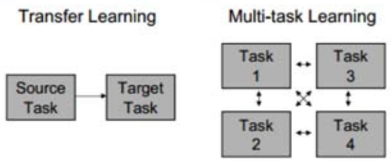
Doob, J. L. 1994. *Measure theory, Springer New York.*

ML-Jungle Top Level View and the focus of today …



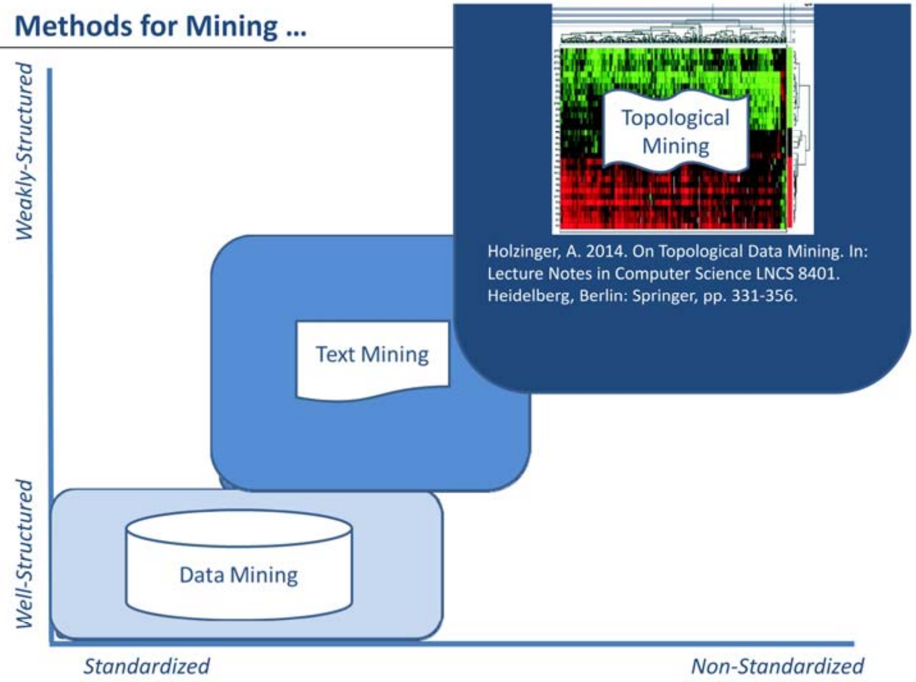
Grand challenges in Machine Learning for Health

- 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**



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.

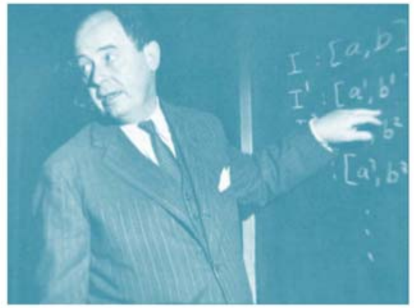
Methods for Mining …



Discrete versus continuous random variable

- $X: S \rightarrow \mathbb{R}$ ("measure" of outcome)
- Events can be defined according to X
  - $E(X=a) = \{s_i | X(s_i)=a\}$
  - $E(X \geq a) = \{s_i | X(s_i) \geq a\}$
- 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**

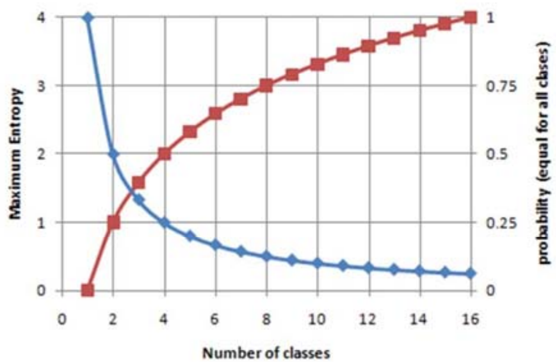
εντροπια



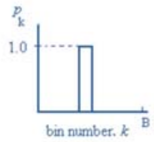
My greatest concern was what to call it. I thought of calling it "information", but the word was overly used, so I decided to call it "uncertainty". When I discussed it with John von Neumann, he had a better idea. Von Neumann told me, "You should call it entropy, for two reasons. In the first place your 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.*

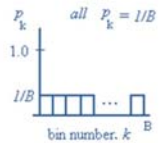
$$\log_2 \frac{1}{p} = -\log_2 p \qquad H = -\sum_{i=1}^{N} p_i log_2(p_i)$$



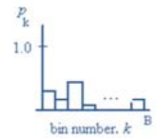
Shannon, C. E. (1948) A Mathematical Theory of Communication. *Bell System Technical Journal, 27, 379-423.*



$$H_B = -\sum_{k=1} p_k \log_2 p_k = -1 * \log_2(1) = 0$$



$$H_B = -\sum_{k=1}^{B} \frac{1}{B} \log_2 \frac{1}{B} = \log_2(B)$$



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

Background on Information Theory

- 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

Vapnik – Chervonenkis

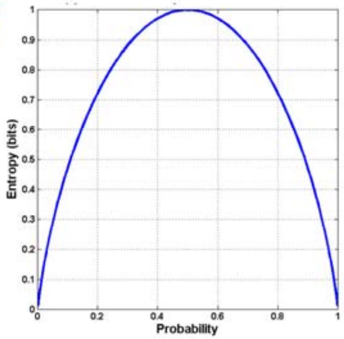
- The VC dimension is a measure of the capacity of a space of functions that can be learned by a statistical classification algorithm. It is defined as the cardinality of the largest set of points that the algorithm can shatter. It is a core concept in Vapnik–Chervonenkis theory

Vapnik, V. N. & Chervonenkis, A. Y. 1971. On the Uniform Convergence of Relative Frequencies of Events to Their Probabilities. Theory of Probability & Its Applications, 16, (2), 264-280, doi:10.1137/1116025.

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

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

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



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.*

- 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.