## Workshop Machine Learning for Biomedicine at TU Graz

# Machine Learning (aML – iML) for Biomedical Informatics


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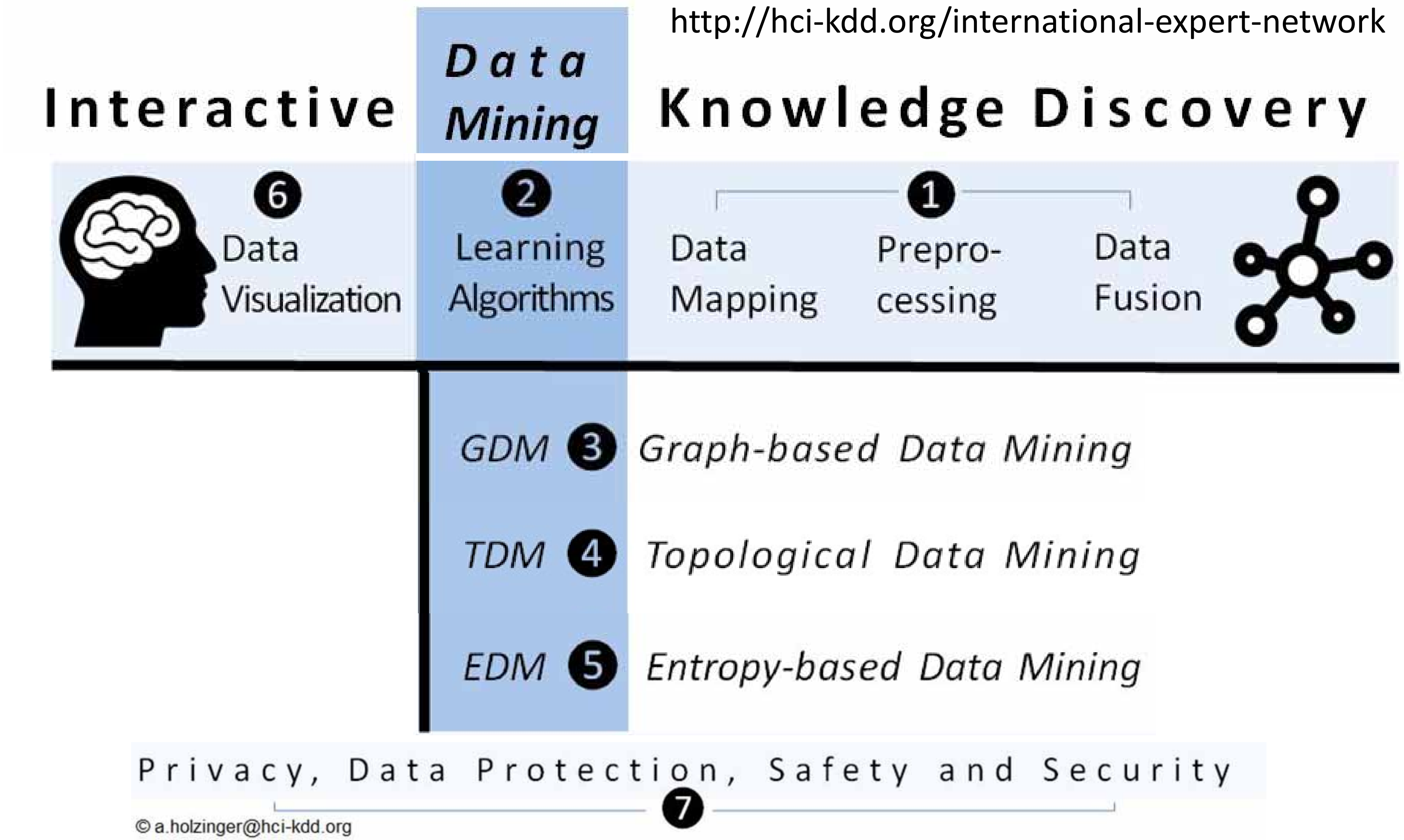
**&**

**Institute of Information Systems and Computer Media, Graz University of Technology**


# ML needs a concerted effort fostering integrated research




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



# Our central hypothesis: Information bridges 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.*

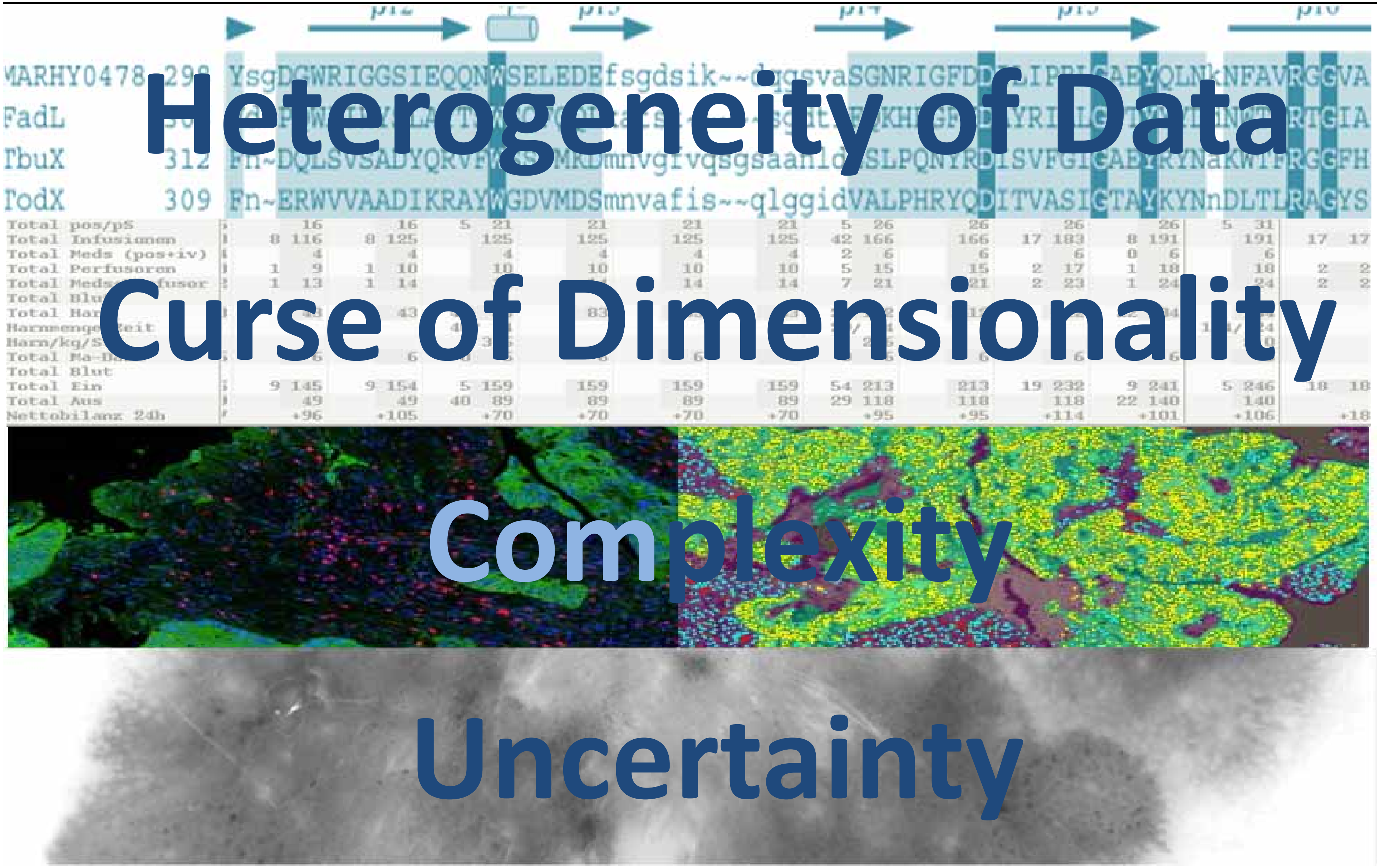

Where is the problem in building this bridge?

Hans Holbein d.J., 1533,
The Ambassadors,
London: National Gallery

Lopez-Paz, D., Muandet, K., Schölkopf, B. & Tolstikhin, I. 2015. Towards a learning theory of cause-effect inference. Proceedings of the 32nd International Conference on Machine Learning, JMLR, Lille, France.

https://www.youtube.com/watch?v=9KiVNIUMmCc

# What are the problems?




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.

# 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.

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

**Thomas Bayes**
**1701 - 1761**

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

## 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**

$$p(h|d) = \frac{p(d|h)p(h)}{p(d)}$$

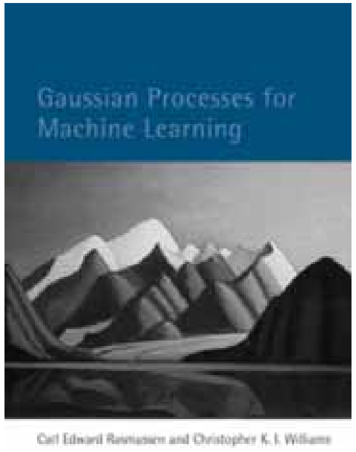
$$posterior\ p(x) = \frac{likelyhood * prior\ p(x)}{evidence}$$

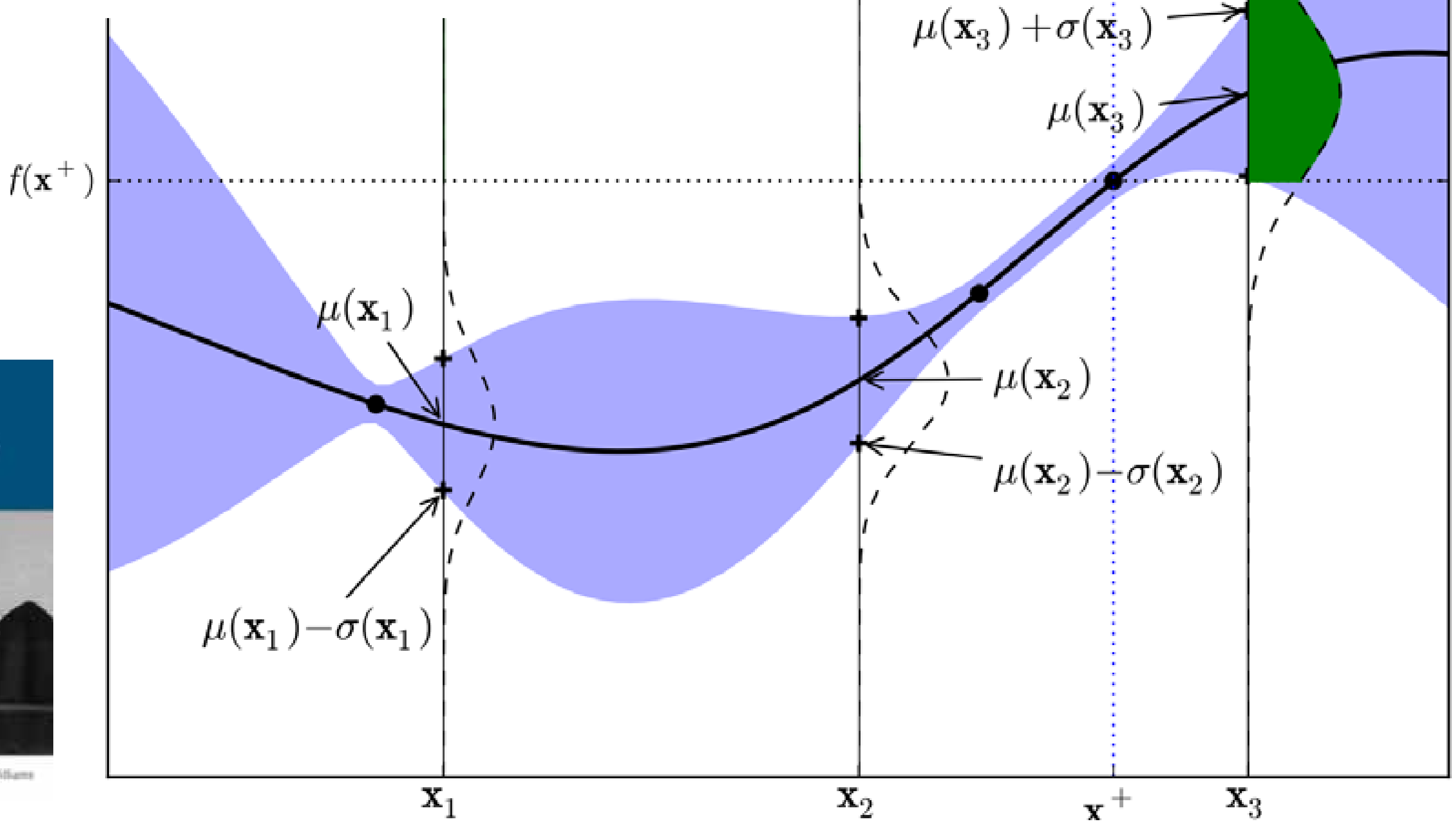
**The inverse probability allows to infer unknowns, <u>learn from data</u> and make predictions …**

# … machine learning!

# GP = distribution, observations occur in a cont. domain, e.g. t or space

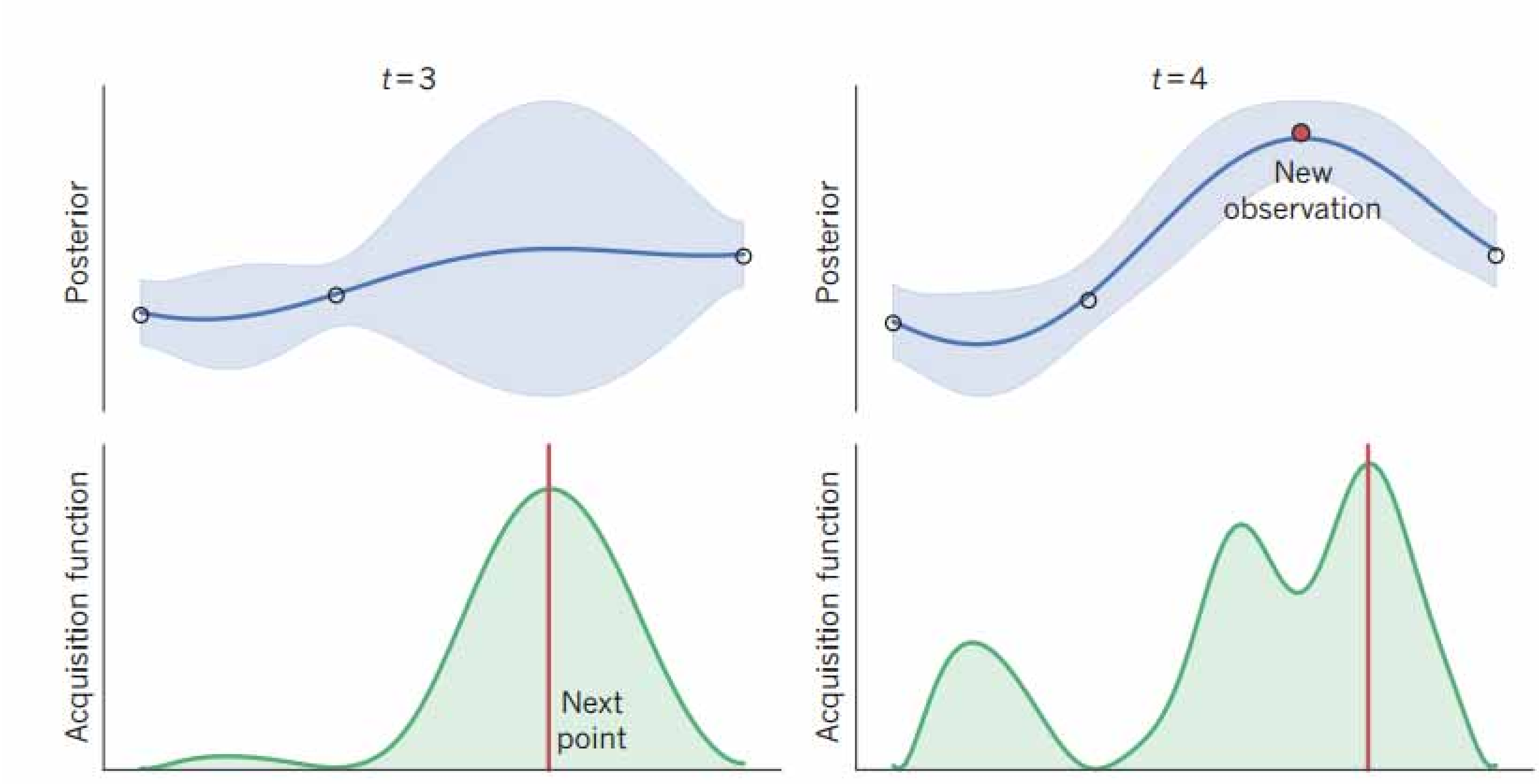
$$\overbrace{p(f(x)|\mathcal{D})}^{\text{GP posterior}} \propto \overbrace{p(\mathcal{D}|f(x))}^{\text{Likelihood}}\,\overbrace{p(f(x))}^{\text{GP prior}}$$




Brochu, E., Cora, V. M. & De Freitas, N. 2010. A tutorial on Bayesian optimization of expensive cost functions, with application to active user modeling and hierarchical reinforcement learning. arXiv:1012.2599.

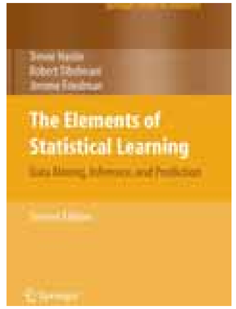
# Example: Bayesian Optimization (Toy example only 1-D)




Goal: maximize some true unknown function $f$ (not shown). Information about this function is gained by making observations (circles, top), which are evaluations of the function at specific $x$ values.

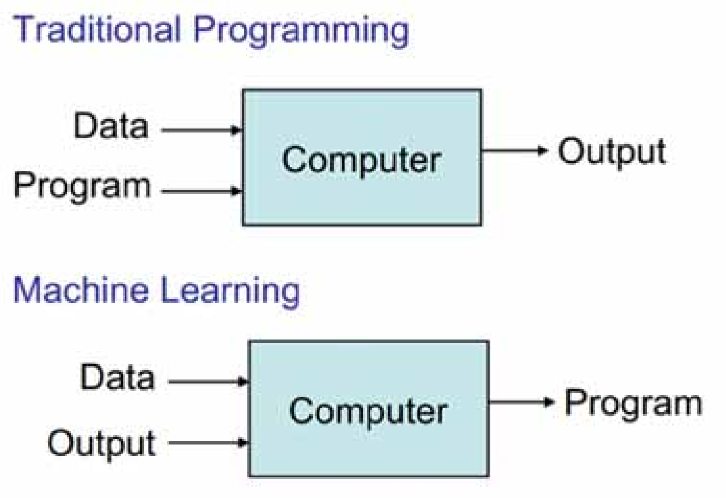
Ghahramani, Z. 2015. Probabilistic machine learning and artificial intelligence. Nature, 521, (7553), 452-459.

# Machine Learning and Statistics are closely related




- Machine Learning is the development of algorithms which can **learn from data**
- and the assessment of **uncertainty,**
- Pre-history in **statistical learning.**
- **Automating automation - getting computers to program themselves – let the data do the work!**

Hastie, T., Tibshirani, R. & Friedman, J. 2009. The Elements of Statistical Learning: Data Mining, Inference, and Prediction. Second Edition, New York, Springer.



- … to understand the underlying principles of learning from data,
- … finding unknown unknowns –
- … finding the unusual and dealing with uncertainties.

- Many aspects of intelligence and learning depend on **probabilistic representation of uncertainty:**
- Forecasting
- Knowledge discovery
- Probabilistic programming
  e.g. Stochastic Python, Julia
- Universal inference algorithms
- Global optimization
- Etc.

- Progress in ML is driven by the explosion in the availability of “**big” data** and **low-cost computation.**
- **Health is amongst the biggest challenges**

Jordan, M. I. & Mitchell, T. M. 2015. Machine learning: Trends, perspectives, and prospects. Science, 349, (6245), 255-260.

- Tom Mitchell: A scientific field is best defined by the **central question it studies.**
- ML seeks to answer the question
- *“How can we build computer systems that* ***automatically*** *improve with experience, and what are the fundamental laws that govern all learning processes?”*

# Origin of ML: first def. by Arthur Samuel (1959)

SOME STUDIES IN
MACHINE LEARNING USING
THE GAME OF CHECKERS

*by A. L. Samuel*

Samuel, A. L. 1959. Some studies in machine learning using the game of checkers. IBM Journal of research and development, 3, (3), 210-229.

Field of Study that gives computers the ability to **learn** [from Data] **without explicitly being programmed …**

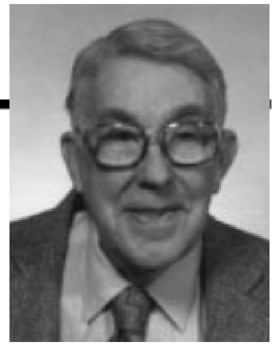
*Introduction*

The studies reported here have been co
a digital computer to behave in a way w
animals, would be described as involvin
this is not the place to dwell on the imp
cedures, or to discourse on the philosoph
very large amount of work, now done by
its demands on the intellect but does, ne
We have at our command computers wi
and with sufficient computational speed
techniques, but our knowledge of the ba
is still rudimentary. Lacking such know
methods of problem solution in minute ar
and costly procedure. Programming com
should eventually eliminate the need for
ming effort.

*Memoriam*

AI Magazine Volume 11 Number 3 (1990) (© AAAI)

# In Memoriam



## Arthur Samuel: Pioneer in Machine Learning

Arthur Samuel (1901–1990) was a pioneer of artificial intelligence research. From 1949 through the late 1960s, he did the best work in making computers learn from their experience. His vehicle for this work was the game of checkers.

Programs for playing games often fill the role in artificial intelligence research that the fruit fly Drosophila

Samuel was a modest man, and the importance of his work was widely recognized only after his retirement from IBM in 1966, in part because he didn't relish the politics that were required to have his research more vigorously followed up on. He was also realistic about the large difference between what had been accomplished in understanding intellectual mechanisms and what would be required to reach human-level intelligence.

Samuel's papers on machine learn-

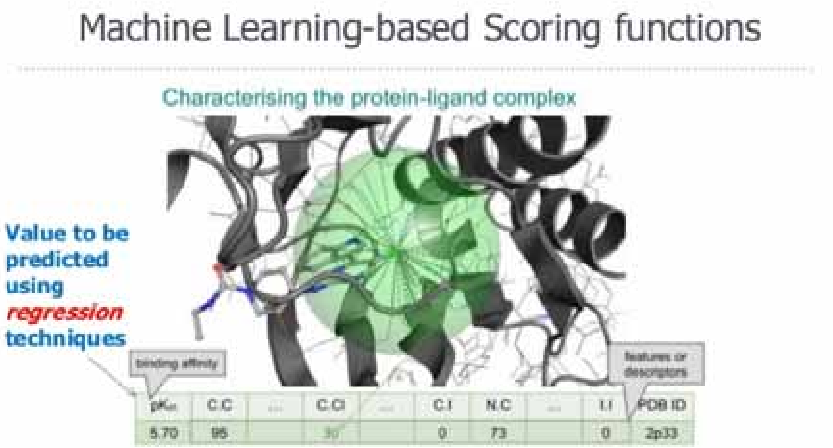
strate the power of electronic computers. He didn't finish the program while he was at the university of Illinois, perhaps because the computer wasn't finished in time.

In 1949, Samuel joined IBM's Poughkeepsie Laboratory, where he worked on IBM's first stored program

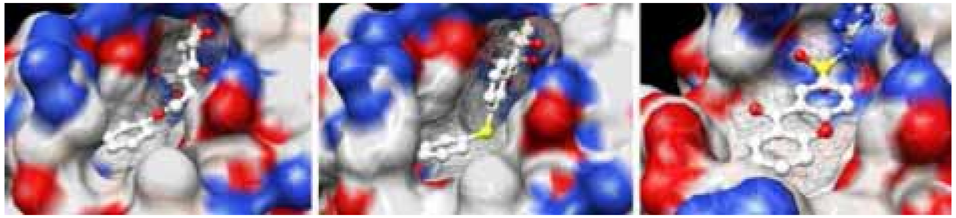
Mccarthy, J. & Feigenbaum, E. A. 1990. In Memoriam: Arthur Samuel: Pioneer in Machine Learning. AI Magazine, 11, (3), 10.

# 2015 everything is machine learning …

Takacs, G., Pilaszy, I., Nemeth, B., Tikk, D. & Acm 2008. Matrix Factorization and Neighbor Based Algorithms for the Netflix Prize Problem. Recsys'08: Proceedings of the 2008 ACM Conference on Recommender Systems, 267-274.

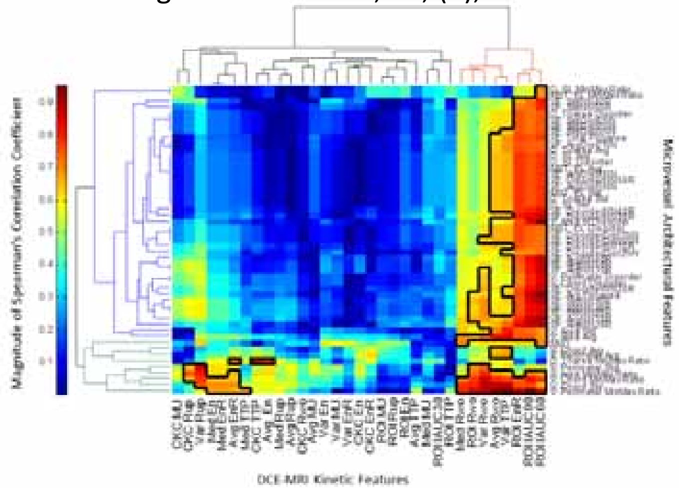



Ballester, P. J. & Mitchell, J. B. O. 2010. A machine learning approach to predicting protein–ligand binding affinity with applications to molecular docking. Bioinformatics, 26, (9), 1169-1175.



Khamis, M. A., Gomaa, W. & Ahmed, W. F. 2015. Machine learning in computational docking. Artificial Intelligence in Medicine, 63, 3,135-152


Schoenauer, M., Akrour, R., Sebag, M. & Souplet, J.-C. Programming by Feedback. Proceedings of the 31st International Conference on Machine Learning (ICML-14), 2014 Beijing. 1503-1511.




Singanamalli, A. et al 2013: A radiohistomorphometric approach. SPIE Medical Imaging, 867604-867604-14.

- most of it is automatic Machine Learning (aML)

- automatic Machine Learning (aML) := algorithms which interact with agents and can optimize their learning behaviour trough this interaction

# What is a best practice example of aML …


Dietterich, T. G. & Horvitz, E. J. 2015. Rise of concerns about AI: reflections and directions. Communications of the ACM, 58, (10), 38-40.

# Does this work here as well?

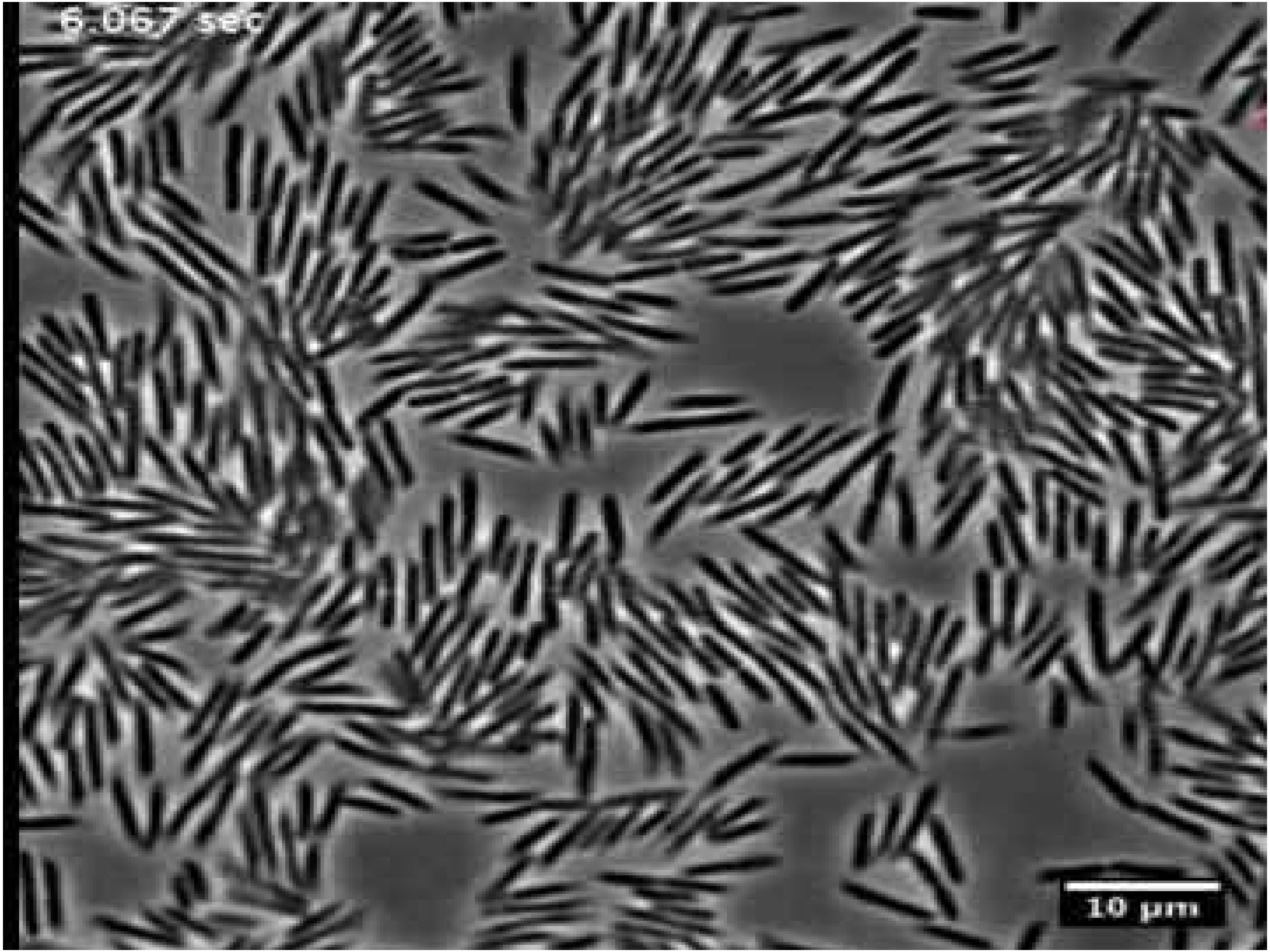
- Sometimes we **do not have "big data",** where aML-algorithms benefit.
- Sometimes we have
  - **Small amount of data sets**
  - Rare Events – **no training samples**
  - **NP-hard problems, e.g.**
    - Subspace Clustering,
    - Protein-Folding,
    - k-Anonymization,
    - Graph Coloring, Category Discovery, etc. etc.…

# Sometimes we (still) need a human-in-the-loop

2
3
4
5
6

- interactive Machine Learning (iML) := algorithms which interact with agents*) and can optimize their learning behaviour trough this interaction
- *)**where the agents can be human**

Holzinger, A. 2015. Interactive Machine Learning (iML). Informatik Spektrum
DOI: 10.1007/s00287-015-0941-6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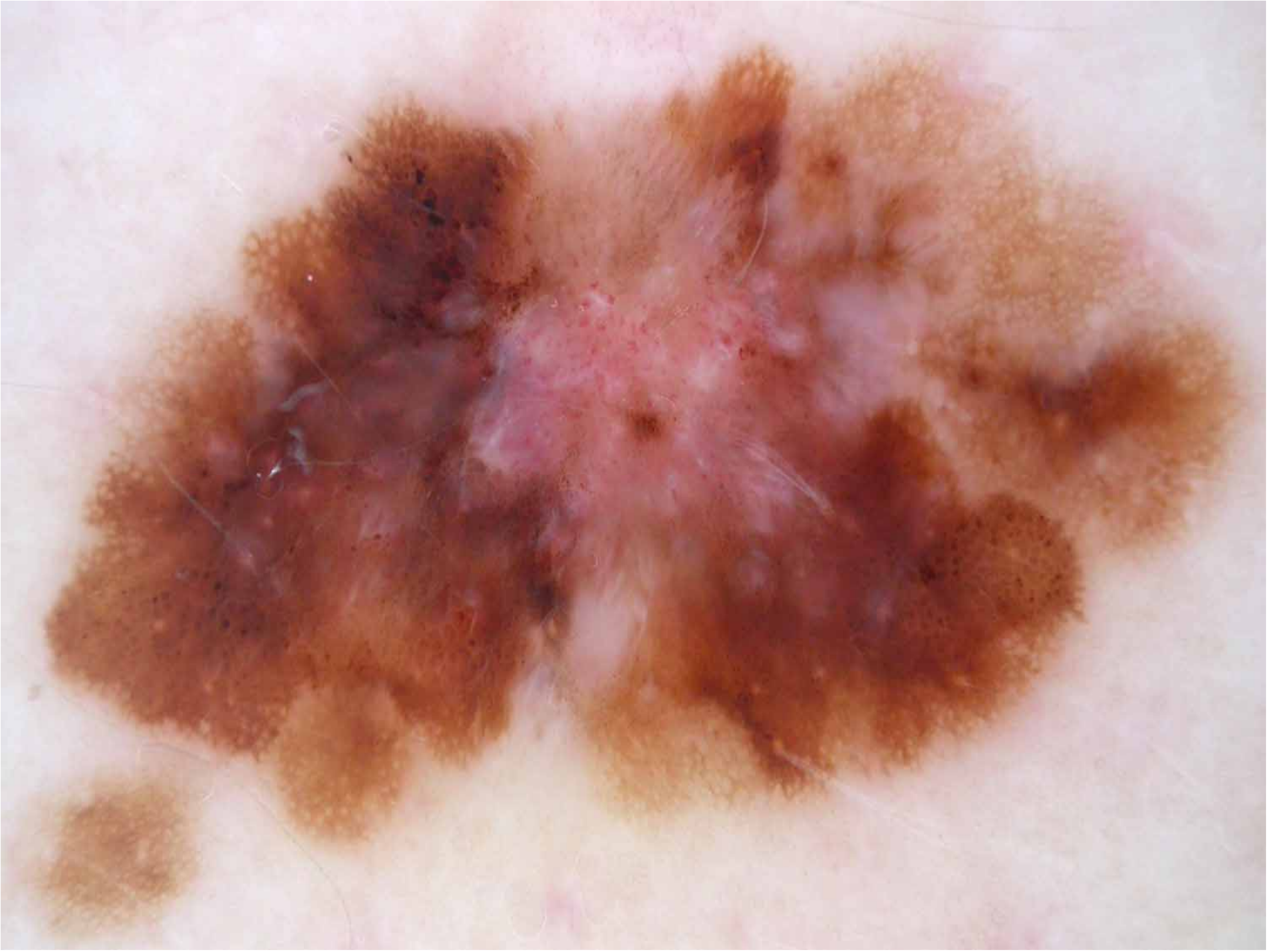
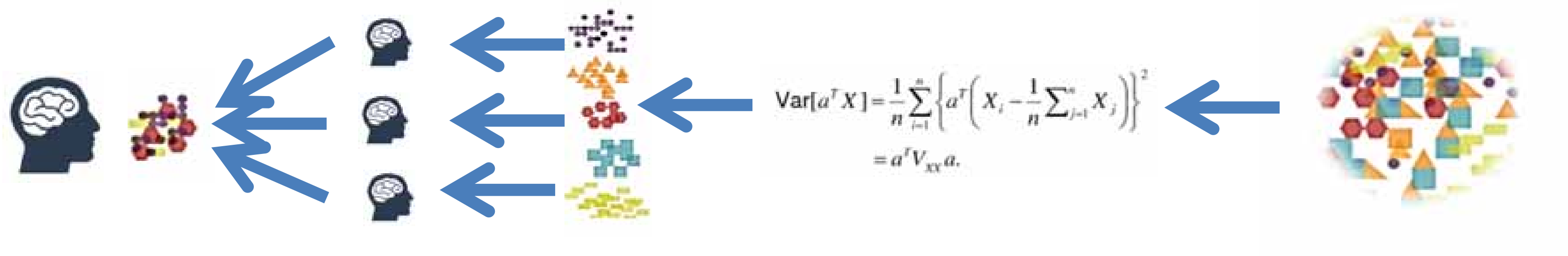
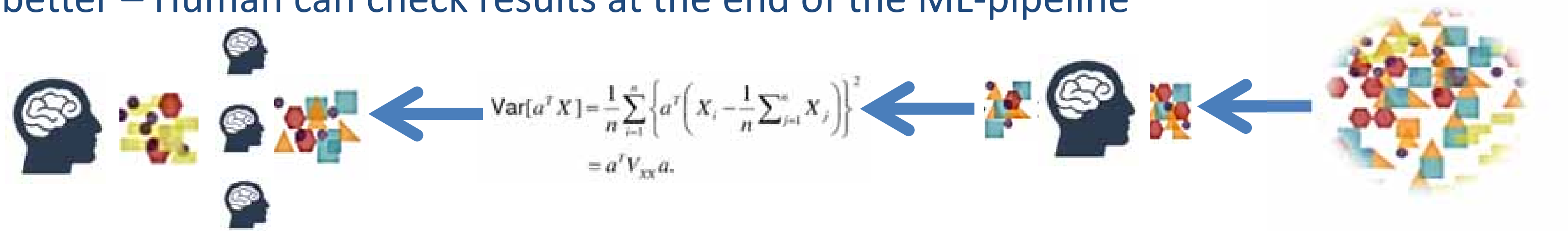


# aML: Unsupervised – Supervised – Semi-supervised

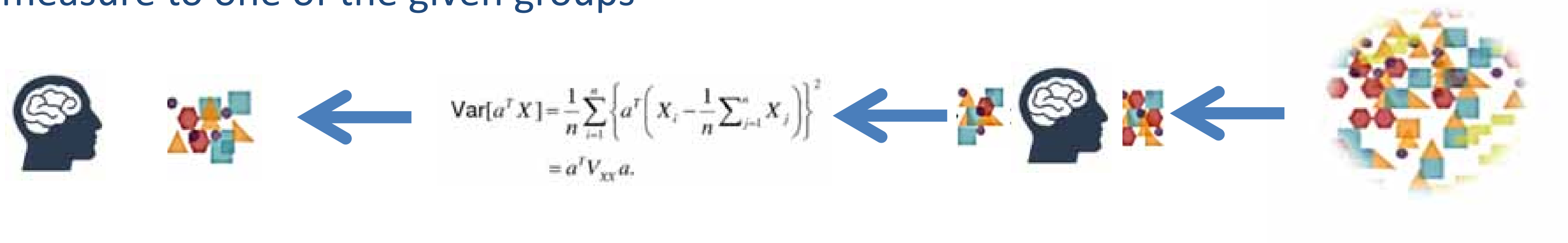
A) Unsupervised ML: Algorithm is applied on the raw data and learns fully automatic – Human can check results at the end of the ML-pipeline



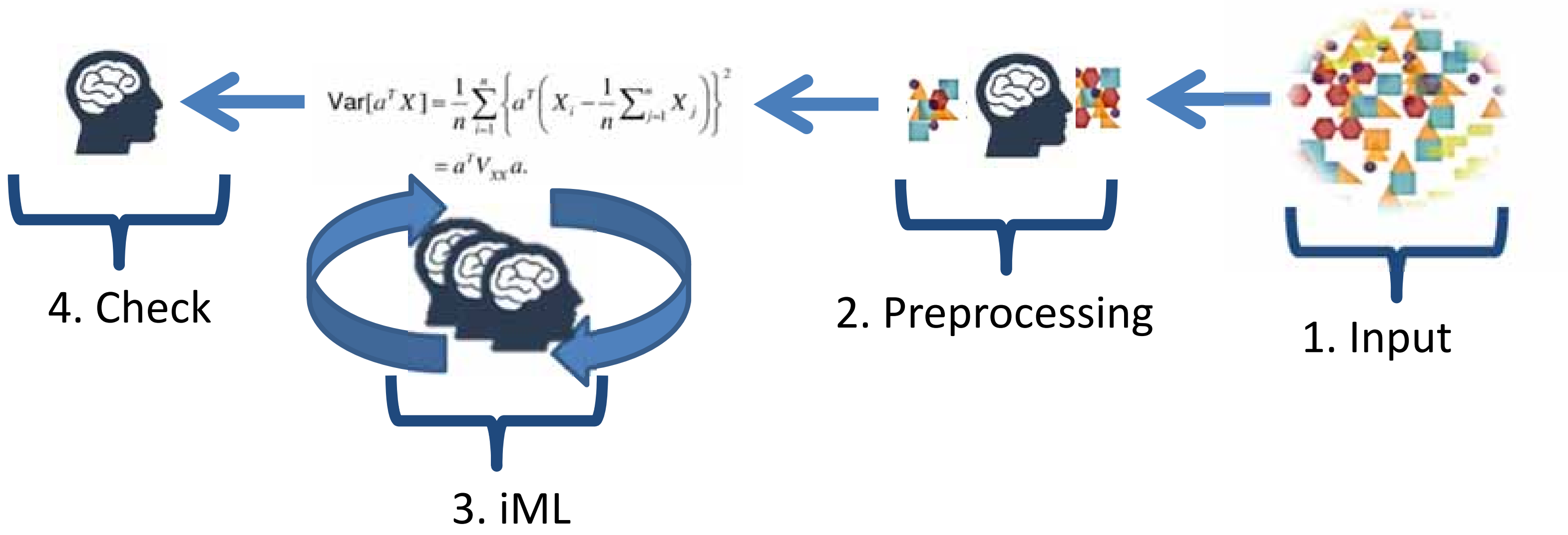

B) Supervised ML: Humans are providing the labels for the training data and/or select features to feed the algorithm to learn – the more samples the better – Human can check results at the end of the ML-pipeline




C) Semi-Supervised Machine Learning: A mixture of A and B – mixing labeled and unlabeled data so that the algorithm can find labels according to a similarity measure to one of the given groups



D) **Interactive Machine Learning:** Human is seen as an agent involved in the actual learning phase, step-by-step influencing measures such as distance, cost functions …




**Constraints** of humans: Robustness, subjectivity, transfer?

**Open Questions:** Evaluation, replicability, …


Holzinger, A. 2016. Interactive Machine Learning for Health Informatics: When do we need the human-in-the-loop? Springer Brain Informatics (BRIN), 3, http://link.springer.com/article/10.1007/s40708-016-0042-6

Holzinger, A. 2016. Interactive Machine Learning (iML). Informatik Spektrum, 39, (1), 64-68.

- Example 1: k-Anonymity
- Example 2: Protein Folding
- Example 3: Subspace Clustering

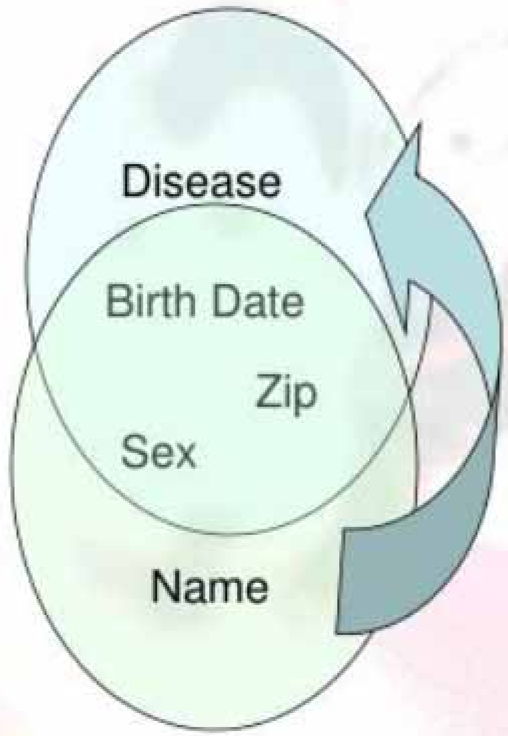
## 87 % of the population in the USA can be uniquely re-identified by Zip-Code, Gender and date of birth

**Hospital Patient Data**

| Birthdate | Sex | Zipcode | Disease |
|---|---|---|---|
| 1/21/76 | Male | 53715 | Flu |
| 4/13/86 | Female | 53715 | Hepatitis |
| 2/28/76 | Male | 53703 | Brochitis |
| 1/21/76 | Male | 53703 | Broken Arm |
| 4/13/86 | Female | 53706 | Sprained Ankle |
| 2/28/76 | Female | 53706 | Hang Nail |

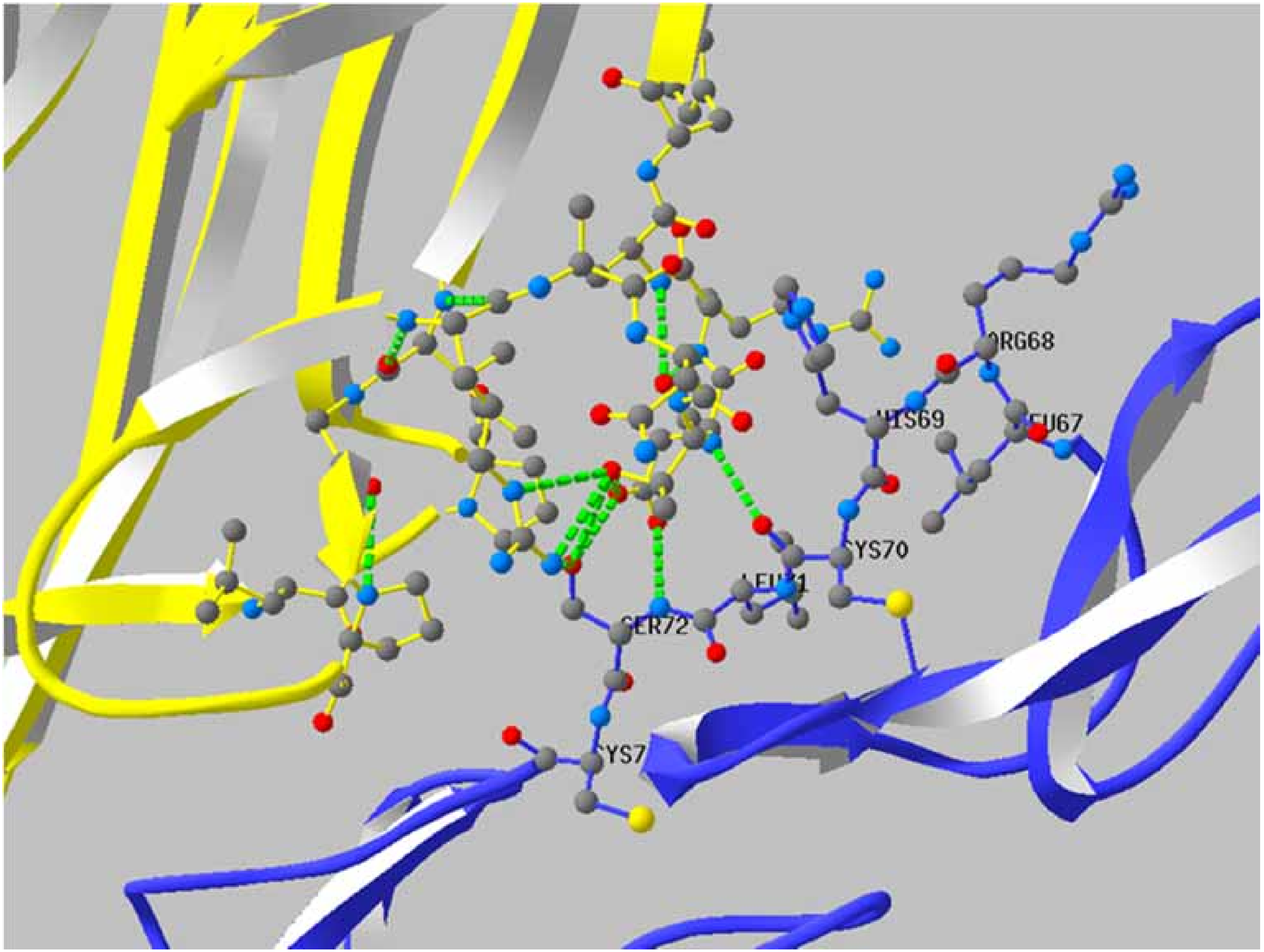
**Voter Registration Data**

| Name | Birthdate | Sex | Zipcode |
|---|---|---|---|
| Andre | 1/21/76 | Male | 53715 |
| Beth | 1/10/81 | Female | 55410 |
| Carol | 10/1/44 | Female | 90210 |
| Dan | 2/21/84 | Male | 02174 |
| Ellen | 4/19/72 | Female | 02237 |



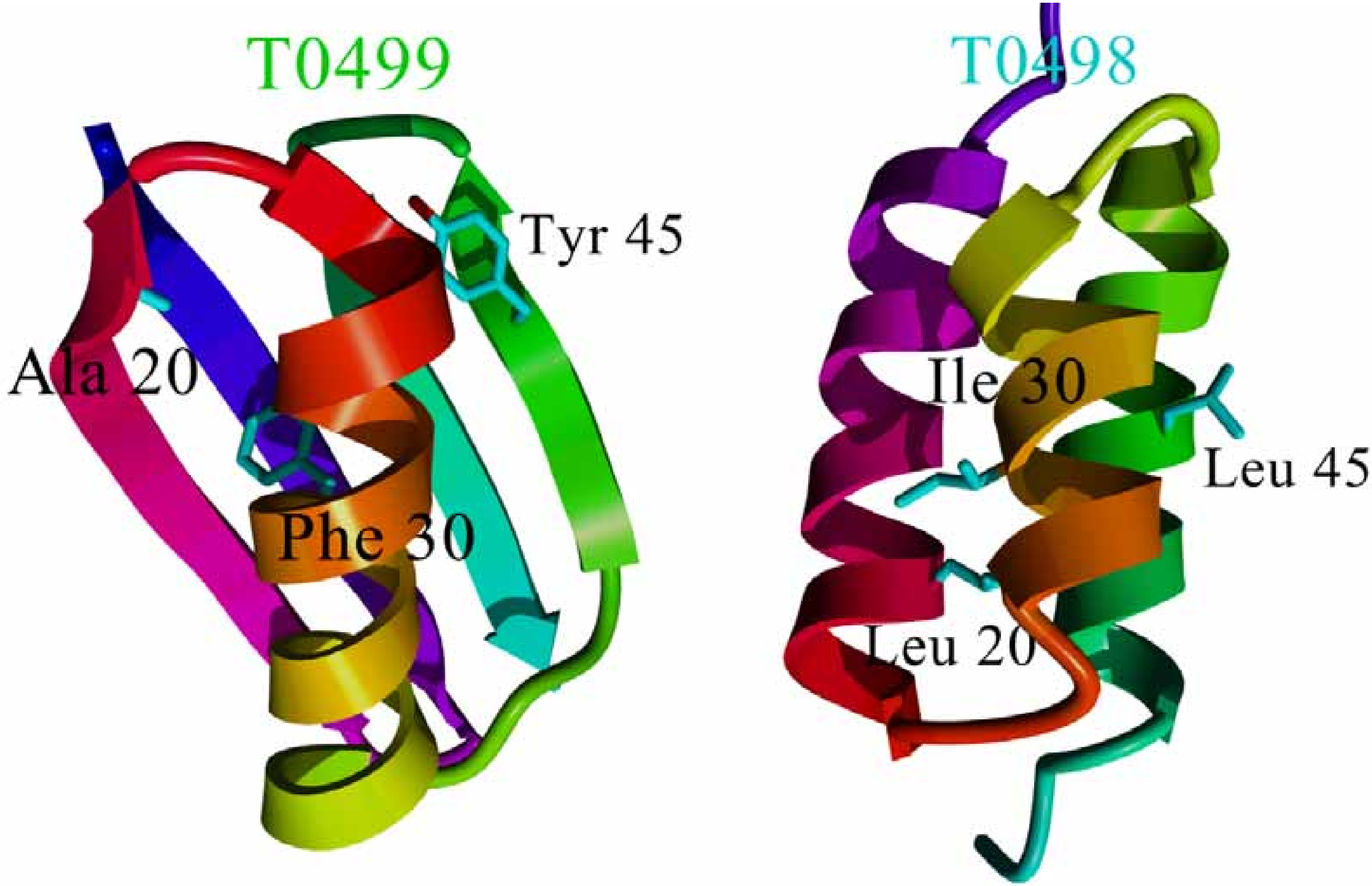

Sweeney, L. 2002. Achieving k-anonymity privacy protection using generalization and suppression. International Journal of Uncertainty, Fuzziness and Knowledge-Based Systems, 10, (05), 571-588.

# Proteins are the building blocks of life …



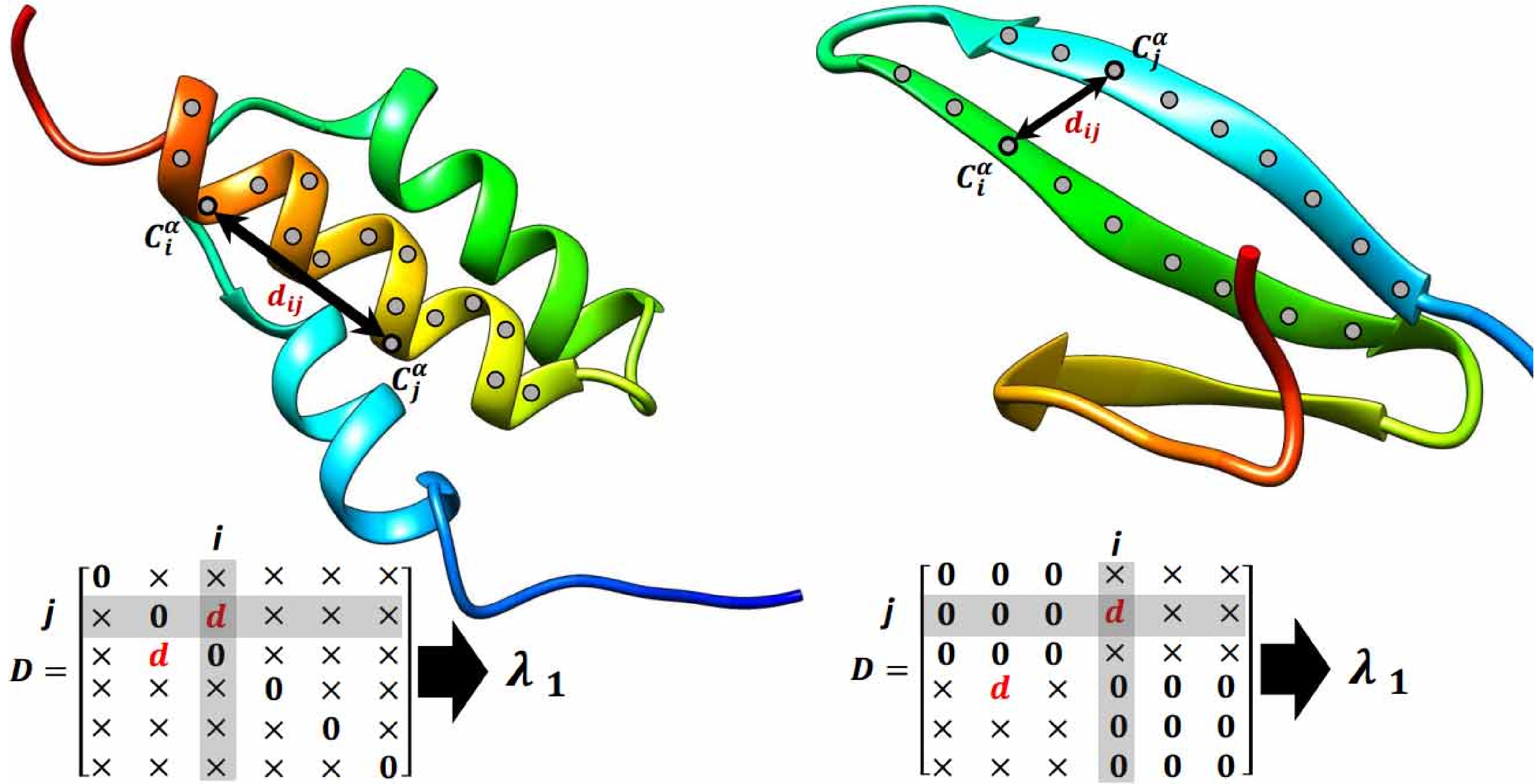

Wiltgen, M., Holzinger, A. & Tilz, G. P. (2007) Interactive Analysis and Visualization of Macromolecular Interfaces Between Proteins. In: *Lecture Notes in Computer Science (LNCS 4799). Berlin, Heidelberg, New York, Springer, 199-212.*

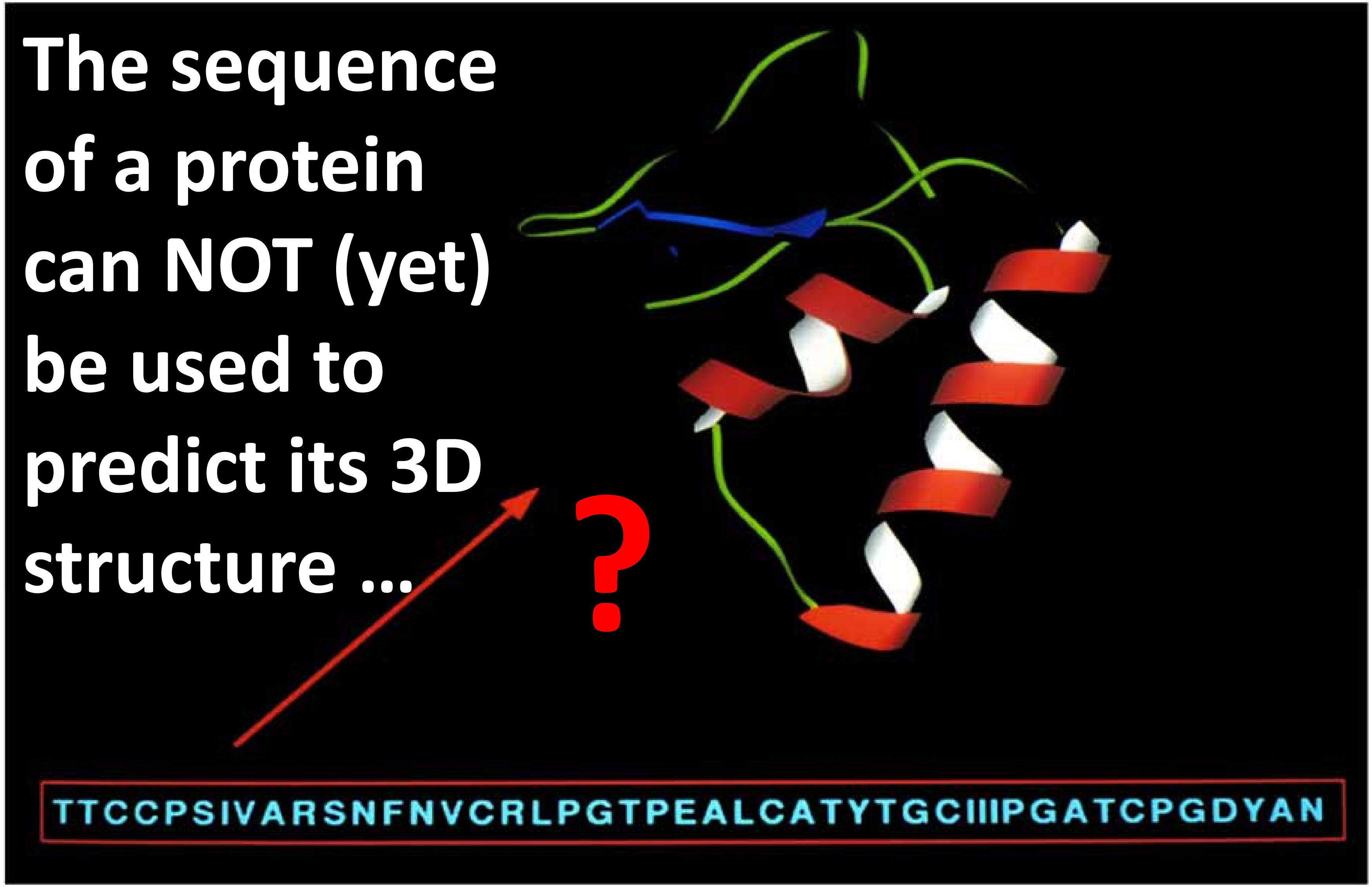
He, Y., Chen, Y., Alexander, P., Bryan, P. N. & Orban, J. (2008) NMR structures of two designed proteins with high sequence identity but different fold and function. Proceedings of the National Academy of Sciences, 105, 38, 14412.




```
T0499   TTYKLILNLKQAKEEAIKEAVDAGTAEKYFKLIANAKTVEGVWTYKDEIKTFTVTE
        |||||||||||||||||||X|||||||||X||||||||||||||X|||||||||||
T0498   TTYKLILNLKQAKEEAIKELVDAGTAEKYIKLIANAKTVEGVWTLKDEIKTFTVTE
```

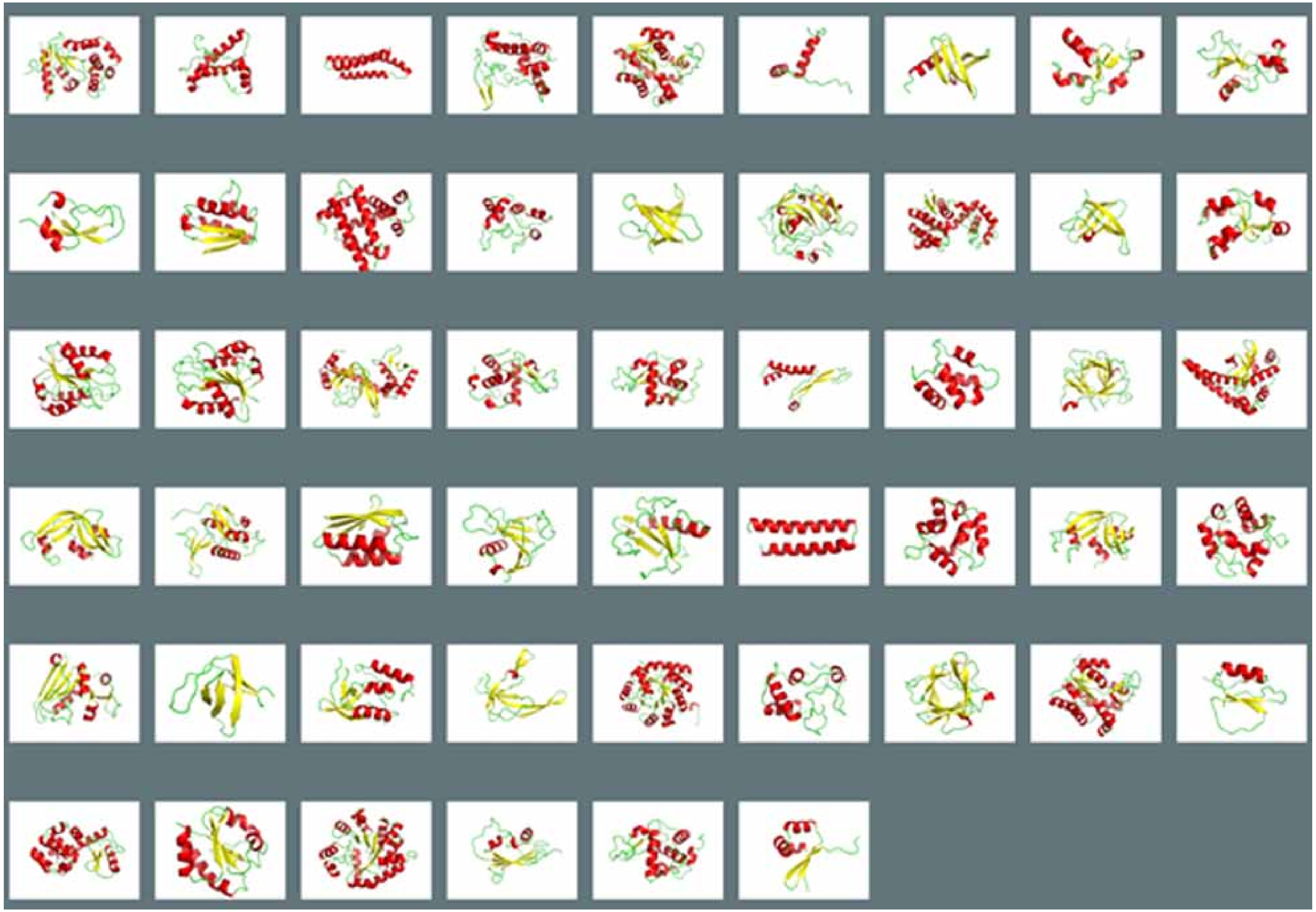
# Johnston et al (2015)





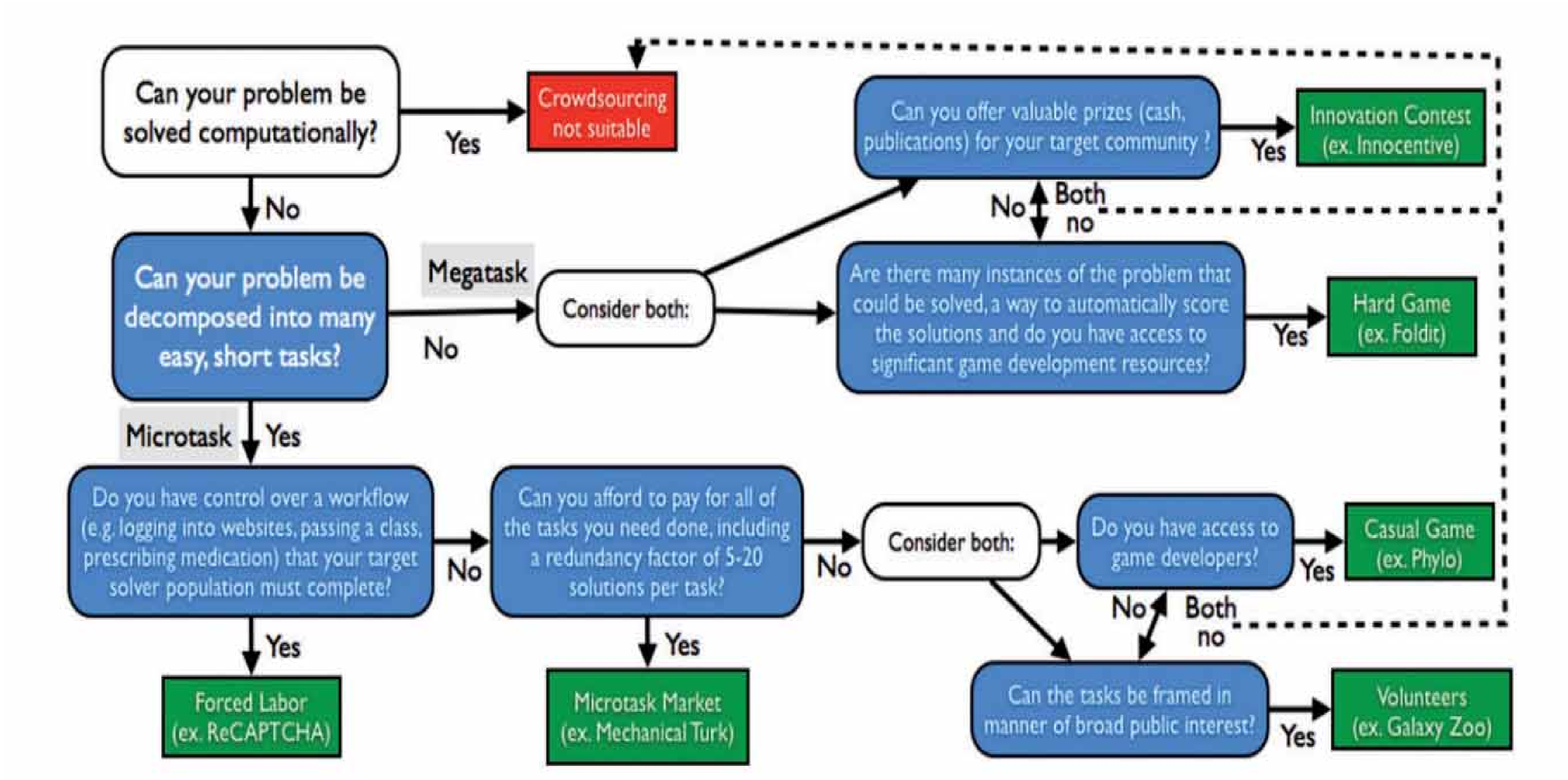

Anfinsen, C. B. **1973.** Principles that Govern the Folding of Protein Chains. Science, 181, (4096), 223-230.

# State-of-2015: aML still is not able to help sufficiently …



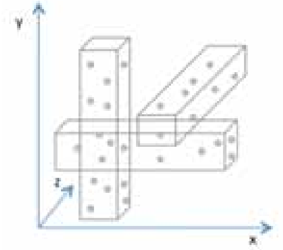
Jia, L., Yarlagadda, R. & Reed, C. C. 2015. Structure Based Thermostability Prediction Models for Protein Single Point Mutations with Machine Learning Tools. Plos One, 10, (9).

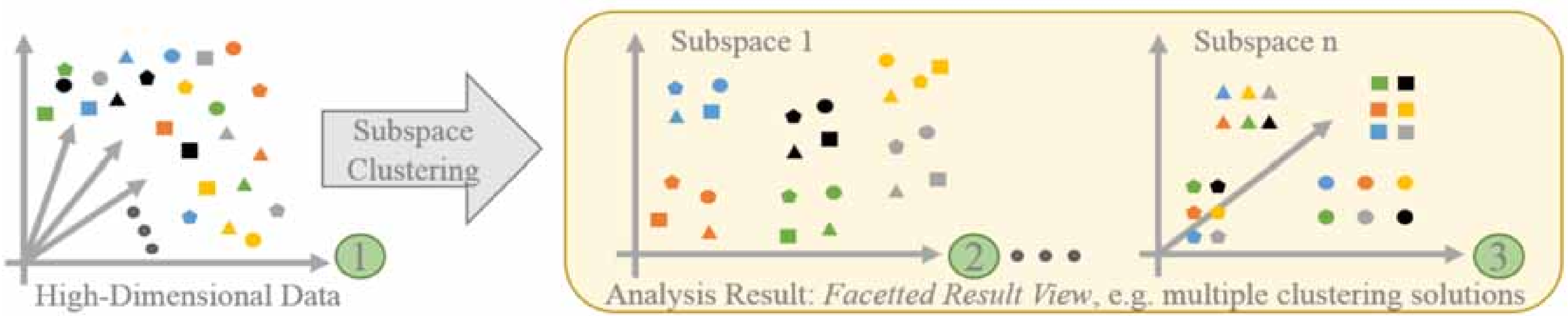
# Humans can help here: Crowdsourcing




Good, B. M. & Su, A. I. 2013. Crowdsourcing for bioinformatics. *Bioinformatics,* 29, (16), 1925-1933.

- Patterns may be found in subspaces (dimension combinations)
- Clustering and subset selection: Non-convex & NP-hard
- Real data are often noisy and corrupted
- Little prior knowledge about low-dim structures
- Data points in different subgroups can be very close



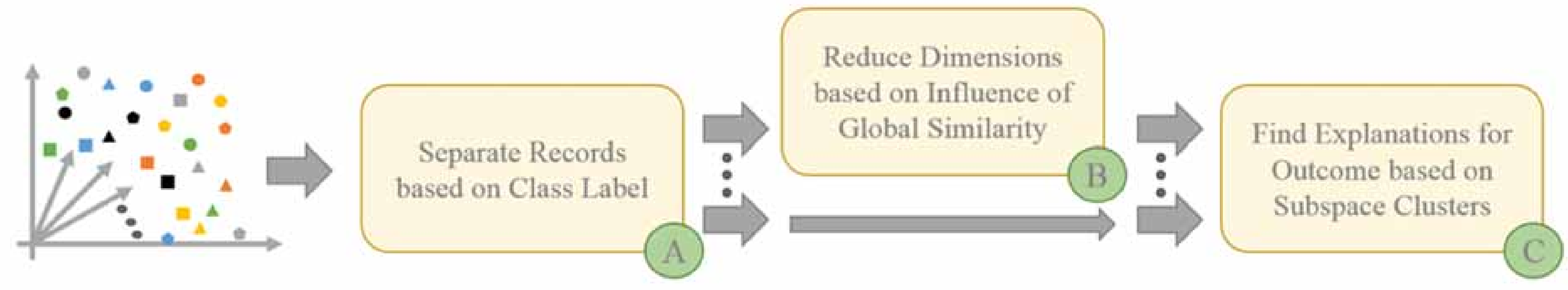



Hund, M., Sturm, W., Schreck, T., Ullrich, T., Keim, D., Majnaric, L. & Holzinger, A. 2015. Analysis of Patient Groups and Immunization Results Based on Subspace Clustering. In: Lecture Notes in Artificial Intelligence LNAI 9250, pp. 358-368.

| Nr. | Name | Type | missing | Description |
|---|---|---|---|---|
| 1 | age | numerical | 0 | age (years) |
| 2 | sex | binary | 0 | (M=Male, F=Female) |
| 3 | Hyper | binary | 0 | Hypertension (yes, no) |
| 4 | DM | nominal | 0 | Diabetes mellitus (yes, IGT=Impaired glucose tolerance, no) |
| 5 | F Glu | numerical | 0 | Fasting blood glucose (mmol/L) |
| 6 | HbA1c | numerical | 0 | Glycosilated Haemoglobin (%) (showing average blood glucose during last three months) |
| 7 | Chol | numerical | 0 | Total Cholesterol (mmol/L) |
| 8 | TG | numerical | 0 | Triglycerides (mmol/L) |
| 9 | HDL | numerical | 0 | HDL-cholesterol (mmol/L) |
| 10 | Statins | binary | 0 | Therapy with statins (yes,no) |
| 11 | Anticoag | binary | 1 | Therapy with anticoagulant/antiaggregant drugs (yes,no) |
| 12 | CVD | binary | 0 | Cardiovascular diseases (yes, no) (myocardial infarction, angina, history of revascularisation, stroke, transient ischaemic cerebral event, peripheral vascular disease) |
| 13 | BMI | numerical | 0 | Body Mass Index ($kg/m^2$) |
| 14 | w/h | numerical | 0 | Waist/hip ratio |
| 15 | Arm cir | numerical | 1 | Mid arm circumference (mm) |
| 16 | skinf | numerical | 0 | Triceps skinfold thickness (mm) |
| 17 | gastro | binary | 0 | Gastroduodenal disorders (yes,no) (gastritis, ulcer) |
| 18 | uro | binary | 1 | Chronic urinary tract disorders (yes,no) (recurrent cystitis in women, symptoms of prostatism in men) |
| 19 | COPB | binary | 0 | Chronic obstructive pulmonary disease (yes,no) |
| 20 | Aller d | binary | 0 | Allergy (Rhinitis and/or Asthma) (yes,no) |
| 21 | dr aller | binary | 0 | Drugs allergy (yes, no) |
| 22 | analg | binary | 0 | Therapy with analgetics/NSAR (yes,no) |
| 23 | derm | binary | 0 | Chronic skin disorders (yes,no) (chronic dermatitis, dermatomycosis) |
| 24 | neo | binary | 0 | Malignancy (yes,no) |
| 25 | OSP | binary | 18 | Osteoporosis (yes, no) |
| 26 | Psy | binary | 0 | Neuropsychiatric disorders (yes,no) (anxiety/depression, Parkinson‘s disease, cognitive impairments) |

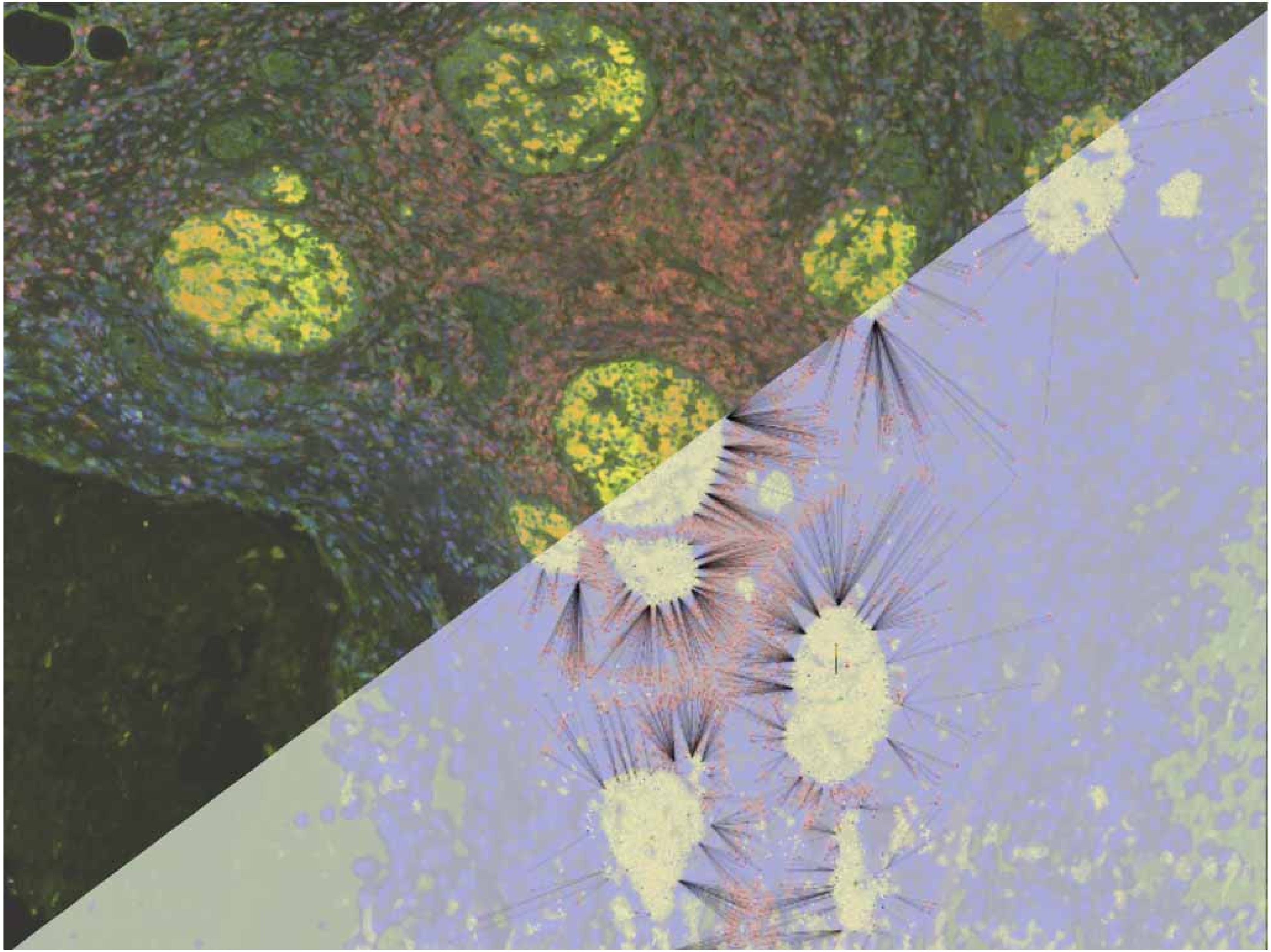
| | | | | |
|---|---|---|---|---|
| 27 | MMS | numerical | 0 | Mini Mental Score - test for screening on cognitive dysfunction Max Score=30 Score ¡24 indicates cognitive impairment |
| 28 | CMV | numerical | 0 | Cytomegalovirus specific IgG antibodies (IU/ml) |
| 29 | EBV | numerical | 0 | Epstein-Barr virus specific IgG (IU/ml) |
| 30 | HPG | numerical | 0 | Helicobacter pylori specific IgG (IU/ml) |
| 31 | HPA | numerical | 0 | Helicobacter pylori specific IgA (IU/ml) |
| 32 | LE | numerical | 0 | Leukocytes Number x$10^9$/L |
| 33 | NEU | numerical | 0 | Neutrophils $ in White Blood Cell differential |
| 34 | EO | numerical | 0 | Eosinophils % in White Blood Cell differential |
| 35 | MO | numerical | 0 | Monocytes % in White Blood Cell differential |
| 36 | LY | numerical | 0 | Lymphocytes % in White Blood Cell differential |
| 37 | CRP | numerical | 1 | C-reactive protein (mg/L) |
| 38 | E | numerical | 0 | Erythrocytes number x$10^{12}$/L |
| 39 | HB | numerical | 0 | Haemoglobin (g/L) |
| 40 | HTC | numerical | 0 | Haematocrite (erythrocyte volume blood fraction) |
| 41 | MCV | numerical | 0 | Mean cell Volume (fL) |
| 42 | FE | numerical | 0 | Iron (g/L) |
| 43 | PROT | numerical | 2 | Total serum proteins (g/L) |
| 44 | ALB | numerical | 0 | Serum albumin (g/L) |
| 45 | clear | numerical | 1 | Creatinine clearance (ml/s/1.73$m^2$) |
| 46 | HOMCIS | numerical | 0 | Homocistein ($\mu$mol/L) |
| 47 | ALFA1 | numerical | 0 | Serum protein electrophoresis (g/L) |
| 48 | ALFA2 | numerical | 0 | Serum protein electrophoresis (g/L) |
| 49 | BETA | numerical | 0 | Serum protein electrophoresis (g/L) |
| 50 | GAMA | numerical | 0 | Serum protein electrophoresis (g/L) |
| 51 | RF | numerical | 0 | Rheumatoid Factor level (IU/ml) |
| 52 | VITB12 | numerical | 0 | Vitamin B12 (pmol/L) |
| 53 | FOLNA | numerical | 0 | Folic acid (mM/L) |
| 54 | INS | numerical | 0 | Insulin ($\mu$IU/L) |
| 55 | CORTIS | numerical | 0 | Cortisol in the morning (nmol/L) |
| 56 | PRL | numerical | 0 | Prolactin in the morning (mIU/L) |
| 57 | TSH | numerical | 1 | Thyroid-stimulating hormone (IU/ml) |
| 58 | FT3 | numerical | 0 | Free triiodothyronine (pmol/L) |
| 59 | FT4 | numerical | 0 | Free thyroxine (pmol/L) |

# What did the “doctor-in-the-loop” do?




- **Positive** subspace clusters
  - One homogeneous cluster (healthy patients)
    - `hyper, CVD, neoplasm, psy.disorder, drug allergy`
    - No medications: `statins, anticoagulants, analgesics` and `clear` (preserved renal function)
- **Negative** subspace clusters
  - Cluster with obvious reasons for neg. outcome
    - Impairment of certain pathophysiologic mechanism increased `MCV`, decreased `VITB12, FOLNA, CORTIS`) despite no: `DM, drug allergy, Fglu, E/HB` (anaemia)

# Future Goal: Category Discovery



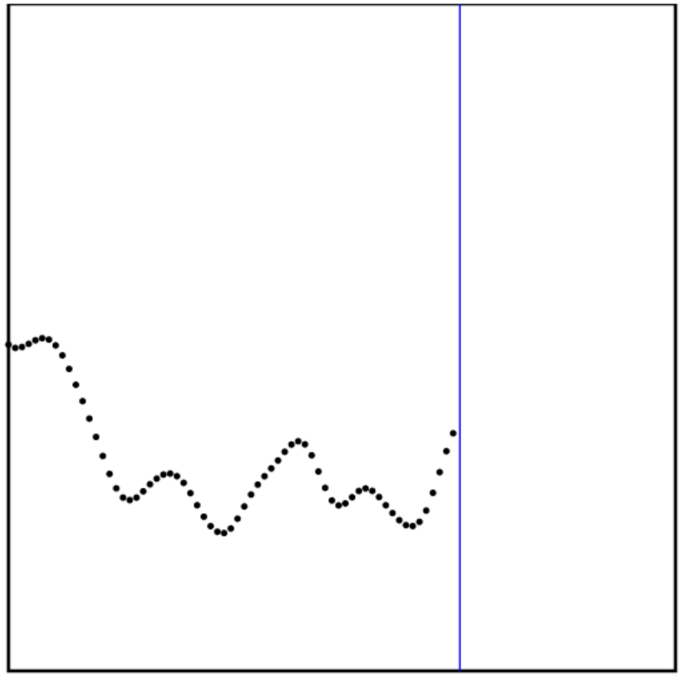
# Example: Human kernel …

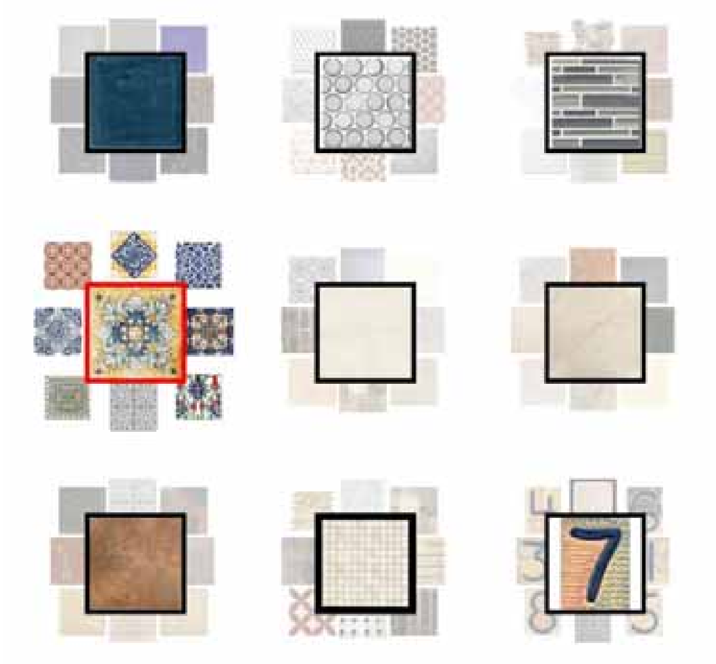
Judgment 1 out of 33

This is the first function from the system. Please try to predict the new points as well as you can based on the points you can see.

Please click along the blue line to say what you think the height of the point is for that location.

Once you have selected a position along the line, **hit the 's' key to submit the point**.

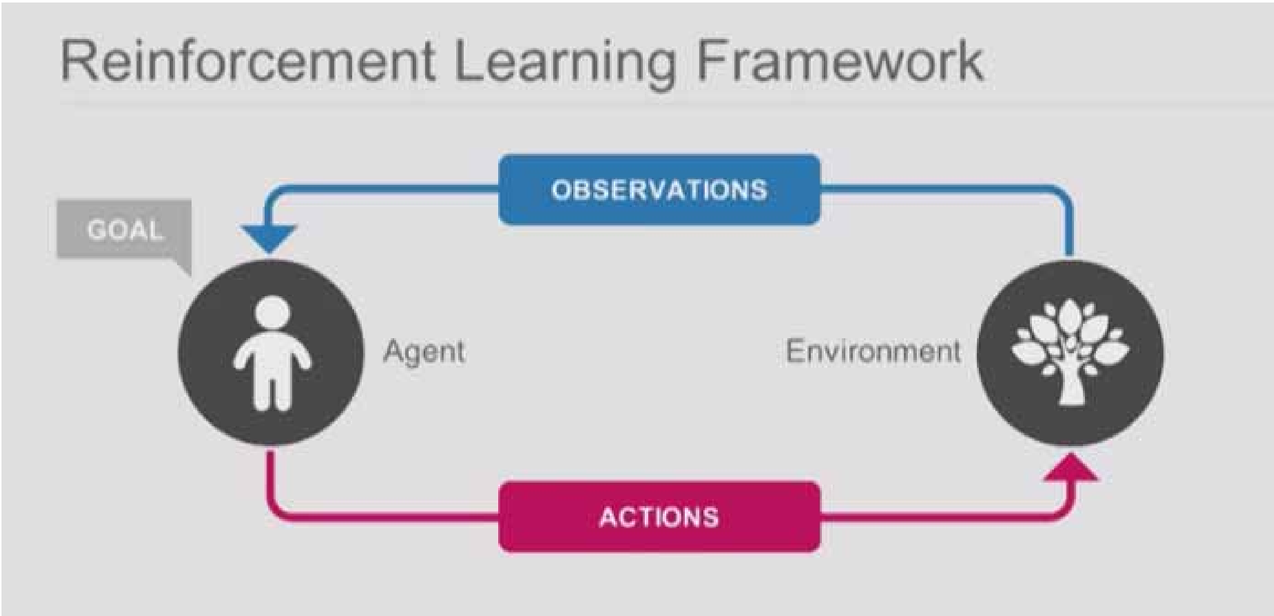




Wilson, A. G., Dann, C., Lucas, C. & Xing, E. P. The Human Kernel. Advances in Neural Information Processing Systems, 2015. 2836-2844.

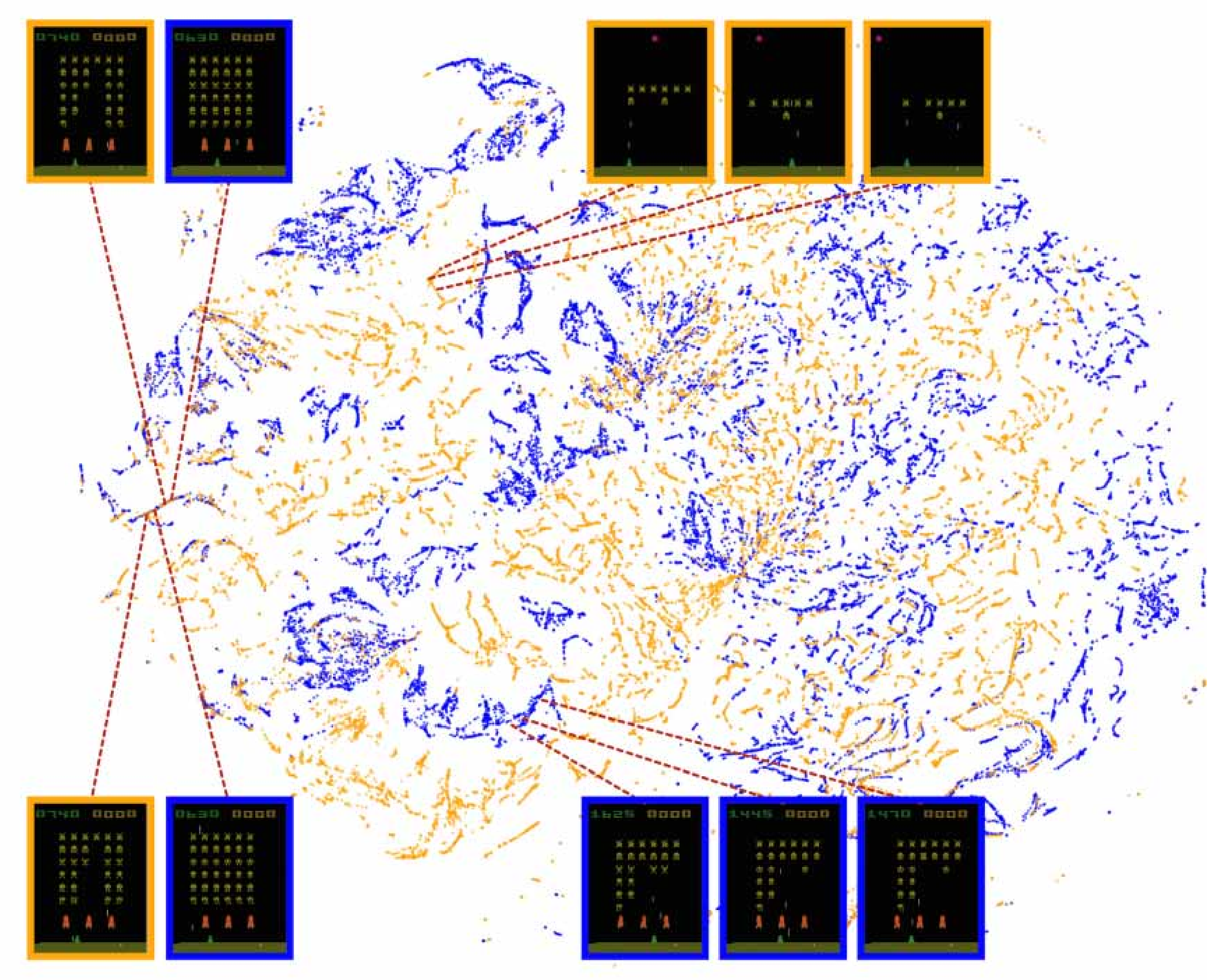
$$\hat{p}^{a}_{bc} = \frac{\mu + \delta_{ac}}{2\mu + \delta_{ab} + \delta_{ac}} \quad \text{and} \quad K_{ii} = 1,$$

- **Reinforcement Learning** (1950)
- **Preference Learning** (1987)
- **Active Learning** (1996)




Russell, S., Dietterich, T., Horvitz, E., Selman, B., Rossi, F., Hassabis, D., Legg, S., Suleyman, M., George, D. & Phoenix, S. 2015. Letter to the Editor: Research Priorities for Robust and Beneficial Artificial Intelligence: An Open Letter. *AI Magazine,* 36, (4).

# Deep Reinforcement Learning



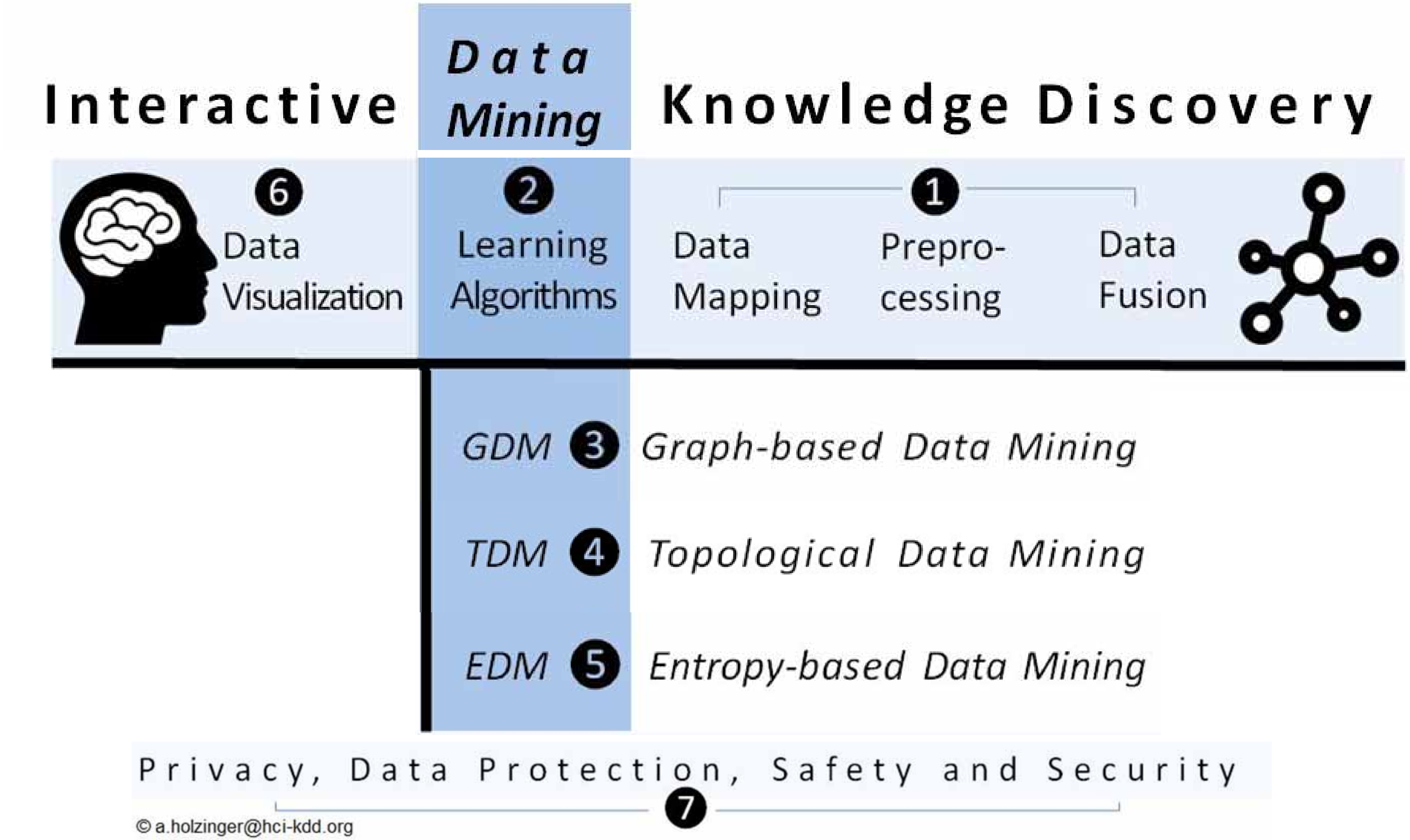
Mnih, V. et al. … Hassabis, D. 2015. Human-level control through deep reinforcement learning. Nature, 518, (7540), 529-533.

- 1 Heterogeneous data sources
  - need for data integration and data fusion
- 2 Complexity – reduction of search space
  - combining the best of Human & Computer
- 3 What is interesting? – and relevant!
  - need of effective mapping $\mathbb{R}^N \to \mathbb{R}^2$
- 4 Clinical time limits “5 Minutes”
  - need of efficient solutions

Holzinger, A. & Jurisica, I. 2014. Knowledge Discovery and Data Mining in Biomedical Informatics: The future is in Integrative, Interactive Machine Learning Solutions In: LNCS 8401. Heidelberg, Berlin: Springer, pp. 1-18.

- **Multi-Task Learning (MTL)**
  - for improving prediction performance, help to reduce catastrophic forgetting
- **Transfer learning (TL)**
  - is not easy: learning to perform a task by exploiting knowledge acquired when solving previous tasks:
  - a solution to this problem would have major impact to AI research generally and machine learning specifically.
- **Multi-Agent-Hybrid Systems (MAHS)**
  - To include swarm-intelligence and crowdsourcing

# ML needs a concerted effort …




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

concerted effort

international

without boundaries …


You
HCI-KDD

HCI-KDD

# Thank you!