CLINICAL DECISION SUPPORT SYSTEMS AND DECISION SUPPORT MODELS

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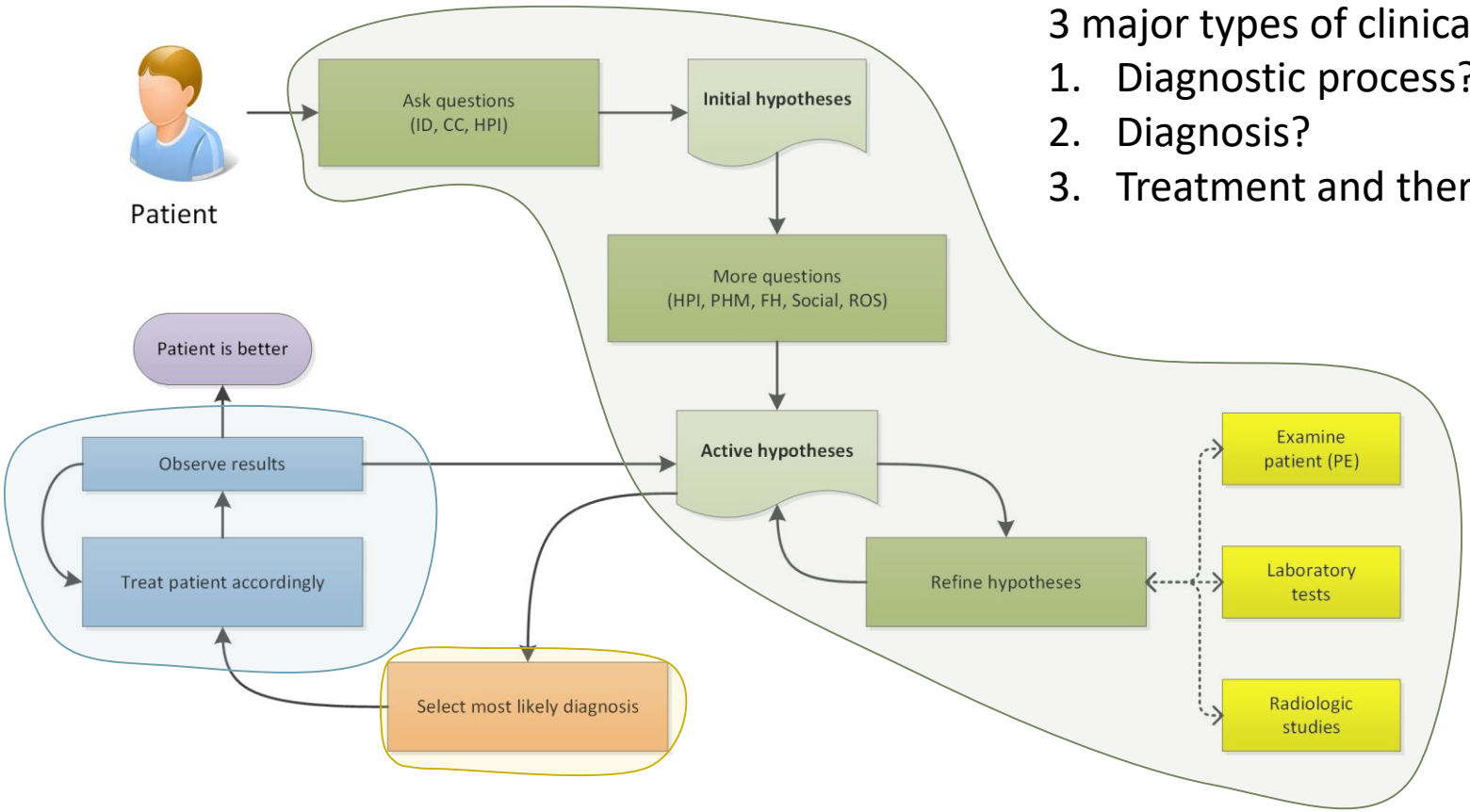
INTRODUCTION

Patient management process



3 major types of clinical decisions:

1. Diagnostic process?
2. Diagnosis?
3. Treatment and therapy?

Shortliffe, E.H. , Octo Barnett, G. (2014). Biomedical data: their acquisition, storage and use. In: Shortliffe, E.H., Cimino, J. (eds.): *Biomedical Informatics. Computer Applications in Health Care and Biomedicine*, Springer, 643-674.

Supporting clinical decisions

Making correct decisions requires:

1. Accurate and adequate data and information
2. Appropriate and current (up-to-date) knowledge
3. Problem solving skills (→ experience and ability to apply knowledge to data)

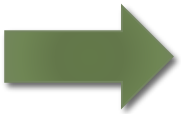
Clinical decision support (CDS) – the process that "provides clinicians with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care" [Osheroff et al., 2004]

Musen, M. , Middleton, B. , Greenes, R. A. (2014). Clinical decision support systems. In: Shortliffe, E.H., Cimino, J. (eds.): *Biomedical Informatics. Computer Applications in Health Care and Biomedicine*, Springer, 643-674.

Requirements for CDS tools

Factors determining successful deployment of CDS tools

1. Offering support as part of already adopted workflow
2. Providing suggestions covering the entire management process, not only diagnostic evaluation
3. Availability where and when necessary (at bed-side)
4. Implementation in form of a computer system



Clinical decision support systems (CDSS)

Kawamoto, K., Houlihan, C. A., Balas, E. A., & Lobach, D. F. (2005). Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *BMJ*, *330*(7494), 765.

Clinical decision support systems

CDSS is any computer system that helps healthcare providers (and patients…) make clinical decisions…

> *„In a sense, any computer system that deals with clinical data or knowledge is intended to provide decision support"* [Musen, Shahar, Shortliffe]

1. Systems for managing data, information and knowledge
2. Systems for focusing attention, reminding and alerting
3. Systems for providing patient-specific suggestions

CDSS do not replace healthcare providers in decision making, but support them!

CDSS characteristics

5 major categories and 26 axes to provide detailed description:

1. **Context** (setting, supported decisions, relation to point of care…)
2. **Knowledge and data source** (sources of clinical knowledge, sources and types of data, knowledge update mechanism…)
3. **Decision support** (reasoning method, *recommendation explicitness*, required user response…)
4. **Information delivery** (*delivery format*, *delivery mode*, explanation ability, action integration…)
5. **Workflow** (system user, target decision maker, workflow integration…)

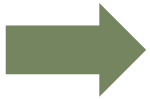
Berlin, A., Sorani, M., & Sim, I. (2006). A taxonomic description of computer-based clinical decision support systems. *Journal of Biomedical Informatics*, *39*(6), 656–67. http://doi.org/10.1016/j.jbi.2005.12.003

Recommendation explicitness

- **Indirect** recommendations
  - System delivers information or knowledge (including evidence-based resources, publications, guidelines…)
  - Ultimate decision is derived and made by the user
- **Direct** recommendations
  - System delivers possible decision options (e.g., possible diagnoses)
  - User selects and confirms one of the suggestions

Delivery format (for direct suggestions)

- **Consultation** – system delivers to the user possible decision options (established from available data)
- **Critique** – user enters their own suggestion, and the system evaluates it and proposes revisions (e.g., checking and revising drug orders to avoid interactions)



From the user's perspective, a better *subjective* control when critique format is used

Delivery mode

- **Passive** – user explicitly requests support from the system and provides all necessary data
- **Active** – system monitors available data and provides support appropriate for a given context

Problems with too “sensitive” active systems – too many alerts may decrease vigilance of the user

OVERVIEW OF DECISION MODELS

Scoring systems

- Evaluation of the patient state (or risk) using a simple additive value function

Asthma symptoms	PRAM Score			
	0	1	2	3
Suprasternal indrawing	absent		present	
Scalene retractions	absent		present	
Wheezing	absent	expiratory	inspiratory and expiratory	audible without stetoscope/ absent with no air entry
Air entry	normal	decreased at bases	widespread decrease	absent/minimal
Oxygen saturation	≥ 95%	92 - 95%	<92%	

- Usually based on regression models (logistic, linear, …) → simplified representation and calculations

Ducharme, F.M., Chalut, D., Plotnick, L. et al. (2006). The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr* 152(4), 476-480.

Example of a scoring system

Risk factor	Categories	Reference value (W_{ij})	β_i	$\beta_i(W_{ij} - W_{i\mathrm{REF}})$	$\mathrm{Points}_{ij} = \beta_1(W_{ij} - W_{i\mathrm{REF}})/B$
Age			0.0575		
	30–39	$34.5 = W_{1\mathrm{REF}}$		0	0
	40–49	44.5		0.5750	2
	50–59	54.5		1.1500	4
	60–69	64.5		1.7250	6
	70–79	74.5		2.3000	8
Sex			1.3078		
	Female	$0 = W_{2\mathrm{REF}}$		0	0
	Male	1		1.3078	5
Systolic blood pressure			0.0185		
	<120	107		−0.3330	−1
	120–129	$125 = W_{3\mathrm{REF}}$		0	0
	130–139	135		0.1850	1
	140–159	150		0.4625	2
	$\geqslant 160$	170		0.8325	3
Current smoker			0.9456		
	No	$0 = W_{4\mathrm{REF}}$		0	0
	Yes	1		0.9456	3

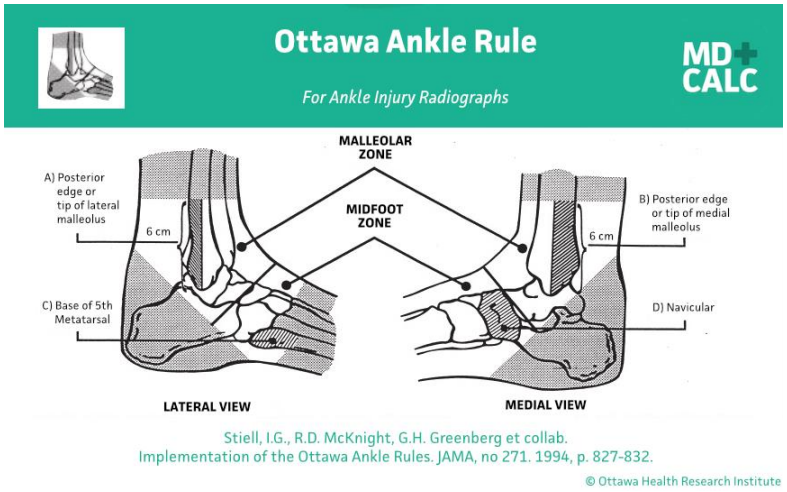
$$B = 5(0.0575) = 0.2875$$

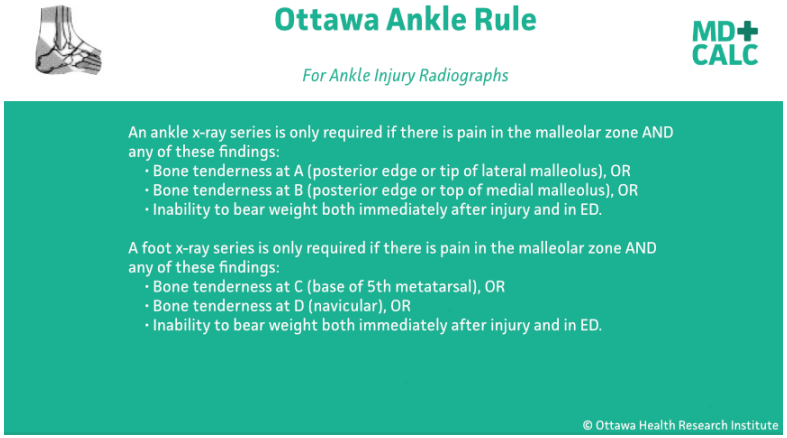
Number of “regression units” per one score point

Sullivan LM, Massaro JM, D’Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med*. 2004;23(10):1631–60.

Decision rules and trees

- Symbolic representation of domain knowledge
- Easy interpretation and possibility of application without a computer-based interpretation





Decision rules

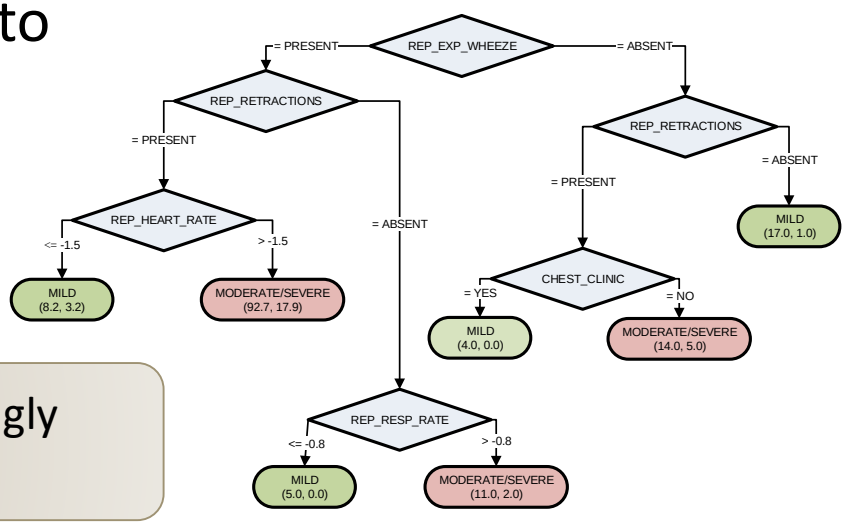
- **Classification-oriented** induction following *separate-and-conquer* principle
  - Construction of a minimal set of rules that separate positive from negative examples
  - Pruning of individual rules and an entire resulting set of rules
- **Discovery-oriented** induction following exhaustive search over the space of possible rules (additional requirements)

- Induction sometimes combined with additional techniques for dealing with inconsistent information, e.g., **rough set theory**
  - Approximations of sets (decision classes) representing certain and possible knowledge
  - Extension for multi-criteria analysis with preference-ordered decision classes and values of attributes

Decision trees

- Induction from data following *divide-and-conquer* principle
  - Greedy selection of the best splitting condition (into two or more subset)
  - Recursive partition of each of the obtained subsets
  - Pruning of resulting trees to avoid overfitting and to obtain a more general model
- Possibility of translating trees into rules
- *Forest* – a model composed of multiple trees

CART→ L. Breiman et al. (1984)
C4.5/C5.0 → R. Quinlan (1994)



Gradient boosting trees become increasingly popular in clinical applications

Naïve Bayesian classifier

$$P(C_i|X) \propto p(C_i)P(X|C_i) \quad \Rightarrow \quad P(C_i|X) \propto p(C_i)\prod_j p(x_j|C_i)$$

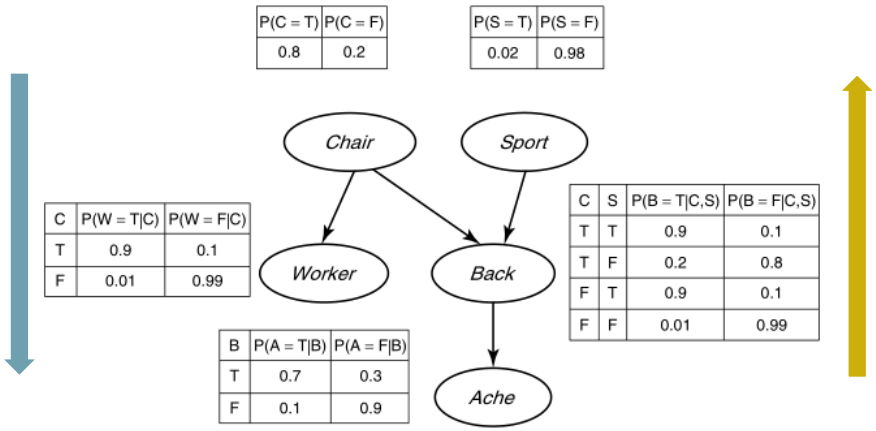
- Assumption about the independence of attributes – satisfactory practical performance despite its frequent violation
- Probabilities $p(x_j|C_i)$ are easy to establish and update
- Extensions for numerical attributes – Gaussian distribution (with parameters estimated from data) or kernel functions

One of the first decision models used in clinical decision support systems

Bayesian network

$$P(X_1, X_2, \ldots, X_n) = \prod_i p(X_i | \pi_i)$$

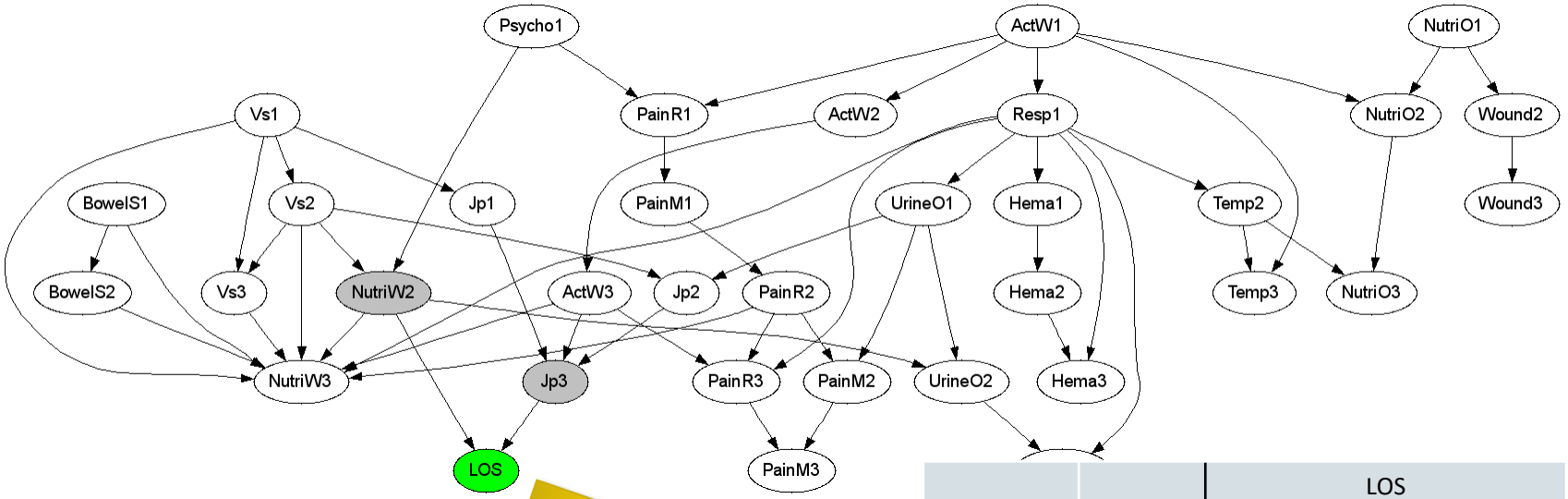
- **Graphical** model – acyclic directed graph with *dependencies* between variables and associated *probabilities*



- Predictive (top-down) and diagnostic (bottom-up) reasoning
- Automatic construction from data (e.g., K2 algorithm) or based on expert knowledge

Ben-Gal I., Bayesian Networks, in Ruggeri F., Faltin F. & Kenett R., Encyclopedia of Statistics in Quality & Reliability, Wiley & Sons (2007)

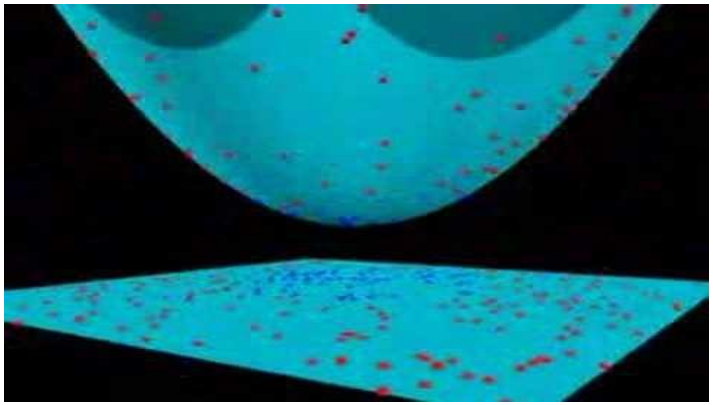
Example of Bayesian network



		LOS	
NutriW2	*Jp3*	Normal	Delayed
Liquid	None	0.4	0.6
Liquid	Small	0.3	0.7
Liquid	Medium	0.2	0.8
Liquid	Large	0.1	0.9
Regular	None	0.7	0.3
Regular	Small	0.6	0.4
Regular	Medium	0.5	0.5
Regular	Large	0.5	0.5

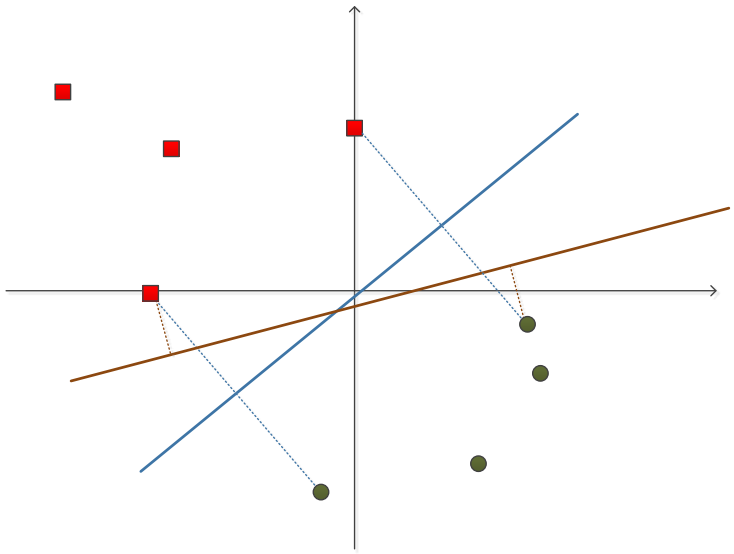
Support vector machines

- Model for binary classification
  - Separation of objects from different classes with a hyperplane – optimization (maximization) of the boundary margin
  - In case of poor linear separability transition to a space with a larger number of dimensions



- In case of multi-class problems construction of multiple models – *one-versus-all* or *one-versus-one*

Support vector machines



$$max: W(\alpha) = -\alpha^T \mathbf{1} + \frac{1}{2}\alpha^T H \alpha$$
$$st: \alpha^T = 0, 0 \leq \alpha \leq C\mathbf{1}$$

$$H_{ij} = y_i y_j \left(\phi(\boldsymbol{x}_i)\phi(\boldsymbol{x}_j)\right)$$

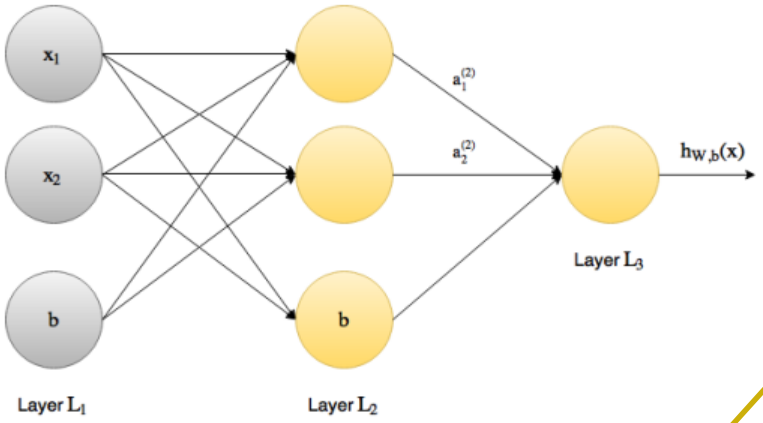
$$K(\boldsymbol{x}_i, \boldsymbol{x}_j) = \phi(\boldsymbol{x}_i)\phi(\boldsymbol{x}_j)$$

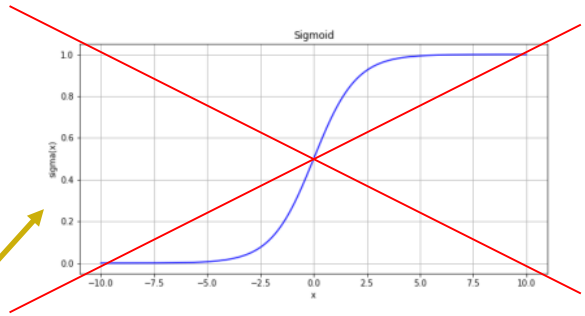
$$K(\boldsymbol{x}_i, \boldsymbol{x}_j) = \exp\left(-\frac{\|\boldsymbol{x}_i - \boldsymbol{x}_j\|^2}{2\sigma^2}\right)$$

Kernel trick → application of a kernel function to get a vector product in a new space (selection of a specific kernel function and its parameters for a given problem)

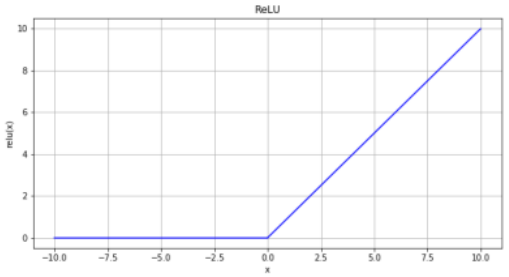
Boswell D., Introduction to support vector machines. 2002.

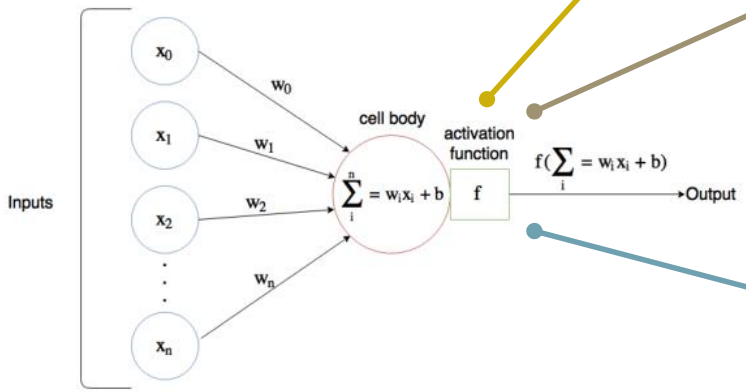
Neural networks



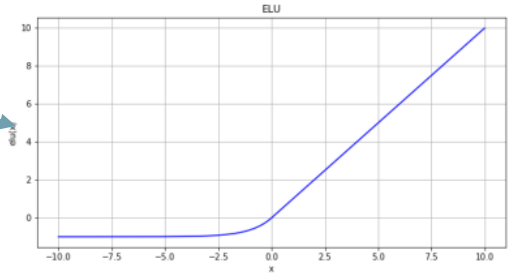


ReLU = rectified linear unit





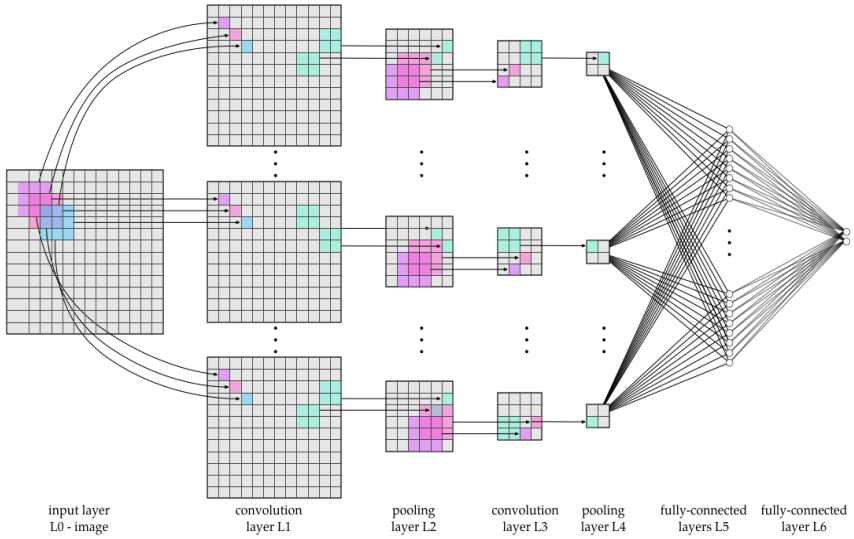
ELU = exponential linear unit

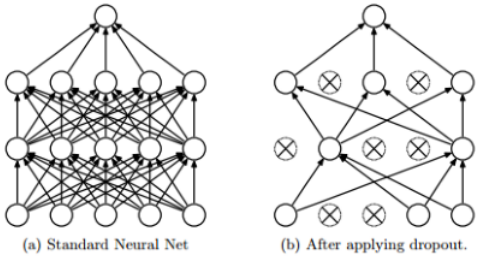


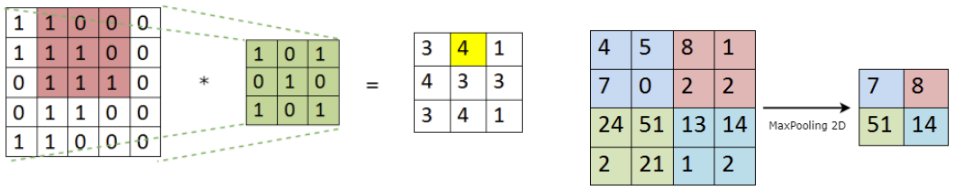
Drawings: Szymon Tuzel, master thesis, PP 2017

Deep neural networks

- Multiple hidden layers
- Feature selection and construction
  - *Convolution* layers
  - *Pooling* layers
  - *Dropout* technique
- Classification using newly constructed features (*fully-connected* layers)







Example of deep neural network

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December 13, 2016

Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs

Varun Gulshan, PhD[1]; Lily Peng, MD, PhD[1]; Marc Coram, PhD[1]; et al

» Author Affiliations | Article Information

JAMA. 2016;316(22):2402-2410. doi:10.1001/jama.2016.17216

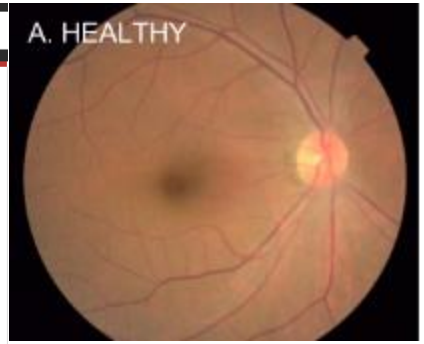
Editorial Comment

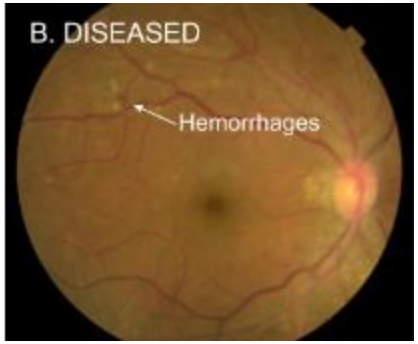
Key Points

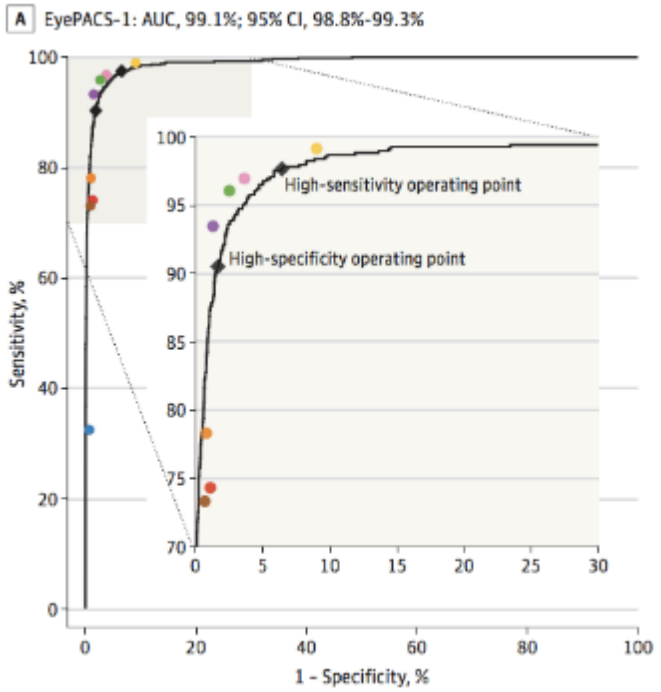
Question How does the performance of an automated deep learning algorithm compare with manual grading by ophthalmologists for identifying diabetic retinopathy in retinal fundus photographs?

Finding In 2 validation sets of 9963 images and 1748 images, at the operating point selected for high specificity, the algorithm had 90.3% and 87.0% sensitivity and 98.1% and 98.5% specificity for detecting referable diabetic retinopathy, defined as moderate or worse diabetic retinopathy or referable macular edema by the majority decision of a panel of at least 7 US board-certified ophthalmologists. At the operating point selected for high sensitivity, the algorithm had 97.5% and 96.1% sensitivity and 93.4% and 93.9% specificity in the 2 validation sets.

Meaning Deep learning algorithms had high sensitivity and specificity for detecting diabetic retinopathy and macular edema in retinal fundus photographs.







Automatic diagnosis of diabetic retinopathy

mp.pl OKULISTYKA

Znajdź leka

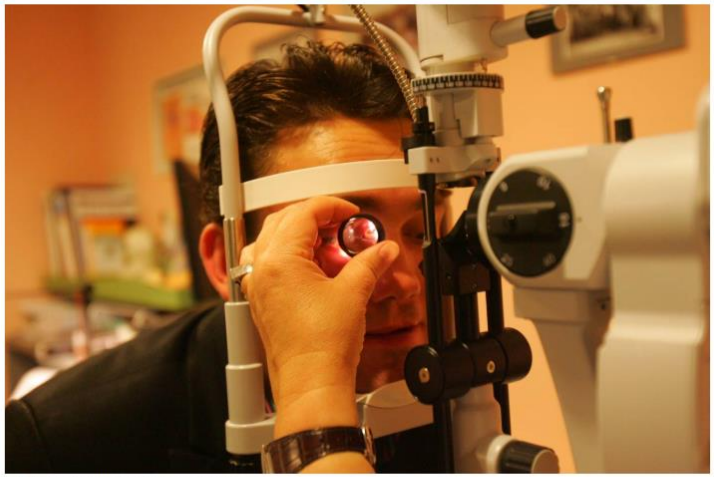
Zdrowe Oczy Wady wzroku Objawy Choroby Badania Inne zagadnienia Lekarze odpowia

Okulistyka ▸ Aktualności ▸ Oprogramowanie skuteczne jak okulista

Oprogramowanie skuteczne jak okulista

Jerzy Dziekoński
Kurier MP

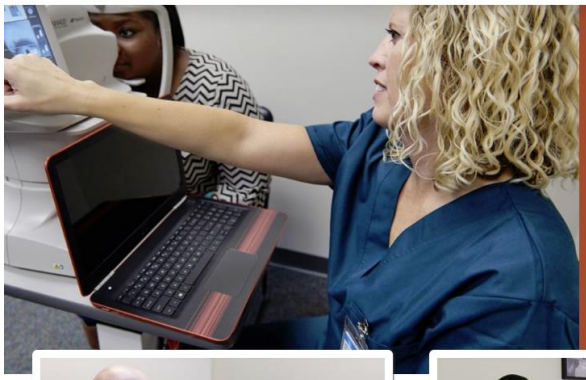
Udział sztucznej inteligencji w screeningu retinopatii cukrzycowej jest nieodzowny – uważa prof. Andrzej Grzybowski, kierownik Instytutu Okulistycznych Badań Naukowych w Poznaniu, który od lat prowadzi badania przesiewowe w tym kierunku. Za jego opinią przemawiają też liczby – wyłowienie chorych z powikłaniami ocznymi spośród blisko 3 mln osób z cukrzycą staje się realne, jeśli sojusznikiem jest skuteczne oprogramowanie.



Fot. Mieczysław Michalak / Agencja Gazeta

Prof. nadzw. dr hab. Andrzej Grzybowski, kierownik Katedry Okulistyki Uniwersytetu Warmińsko-Mazurskiego oraz kierownik Instytutu Okulistycznych Badań Naukowych w Poznaniu, jest założycielem i prezesem fundacji Okulistyka 21. Organizacja od kilku lat prowadzi badania z zakresu retinopatii cukrzycowej. Rokrocznie w Poznaniu przeprowadzano screening chorujących na cukrzycę pod kątem wspomnianych powikłań. Podobnie w bieżącym roku, jednak różnica polega na tym, że tym razem do pomocy zaprzęgnięto sztuczną inteligencję.

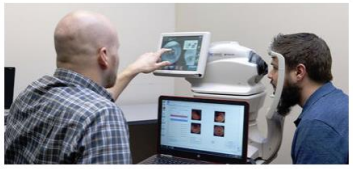
IDx About IDx-DR Pipeline News Contact Us



Autonomous AI that instantly detects disease

Increase patient access to early disease detection

Learn More



IDx-DR

The first ever autonomous AI system cleared by the FDA to provide a diagnostic decision

How to test for DR in primary care

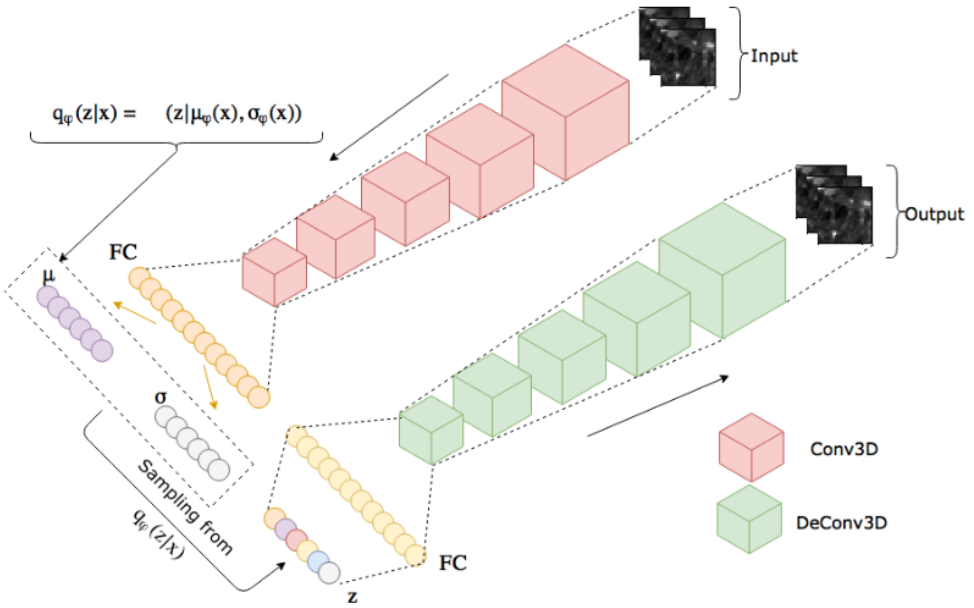
Download our white paper on the pros and cons of telmedicine and AI solutions

87% Sensitivity
90% Specificity
96% Imageability

Endpoints Exceeded By A Wide Margin

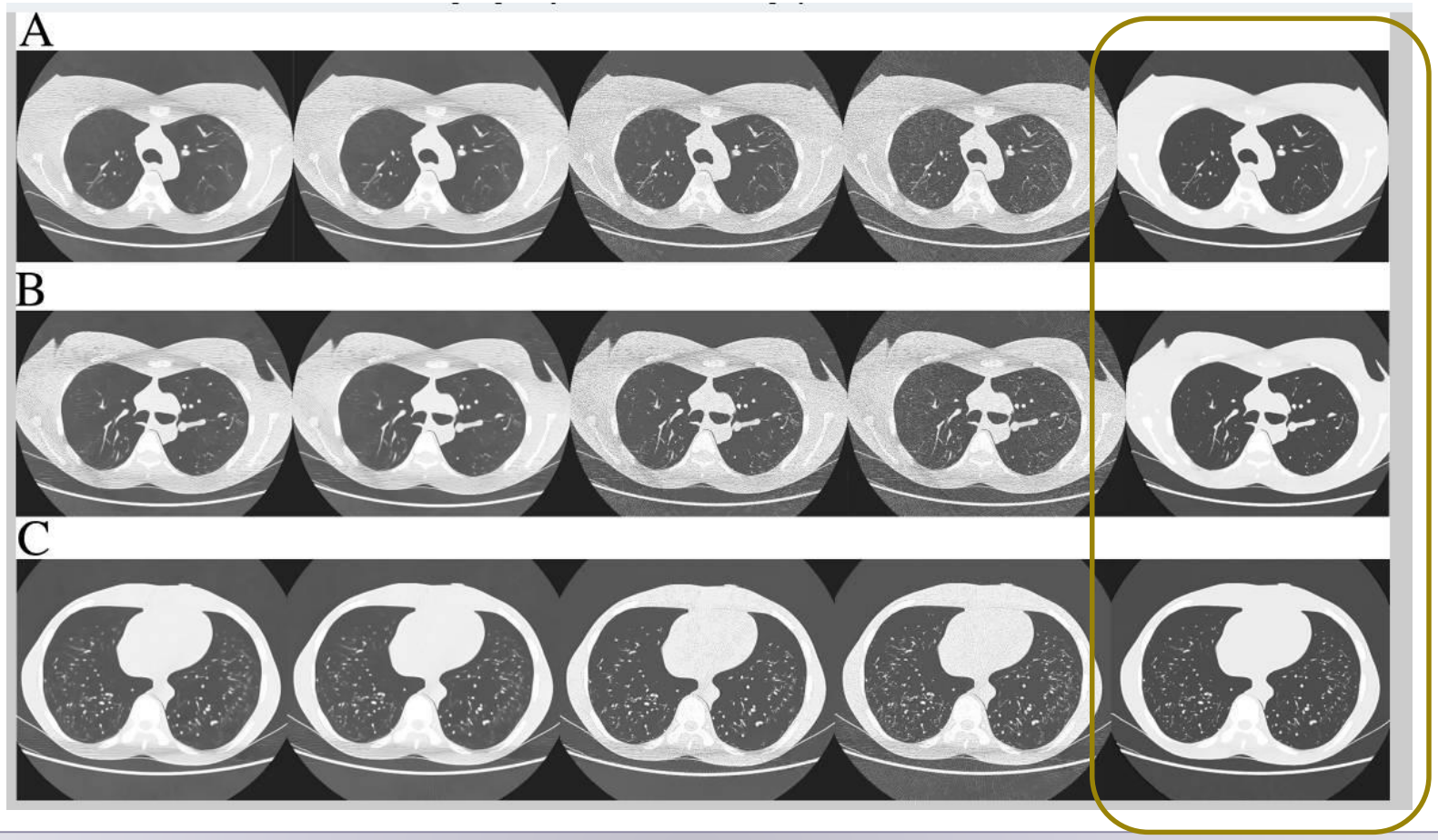
Autoencoders

- Convolution networks that reconstruct an input patter (image)
- Data compression – transformation of input to a reduced set of values (neurons on the hidden layer)
- Using information captured by hidden layer for further processing (e.g., dimensionality reduction for other classification models)
- *Variational* autoencoders → possible applications for one-class decision problems



Sample application of autoencoders

Improving the quality of CT scans



Nishio, M., Nagashima, C., Hirabayashi, S., Ohnishi, A., Sasaki, K., Sagawa, T., … Yamashita, T. (2017). Convolutional auto-encoders for image denoising of ultra-low-dose CT. *Heliyon*, *3*(8).

HANDLING IMBALANCED DATA

Difficulty factors in clinical data

- Challenges for data mining from clinical data
  - Missing and imprecise values, inconsistent examples
  - Uneven distribution of patients across decision classes

Minority class (usually critical) vs. **majority** classes → **class imbalance**

- Class imbalance deteriorates performance of classifiers learned from data (especially for the minority class!)
- Three groups of approaches to address this problem
  - *Data-level* methods – preprocessing before learning (more prevalent)
  - *Algorithm-level* methods – specialized learning algorithms
  - *Cost-based* methods – methods that consider costs of misclassifications (at different times)

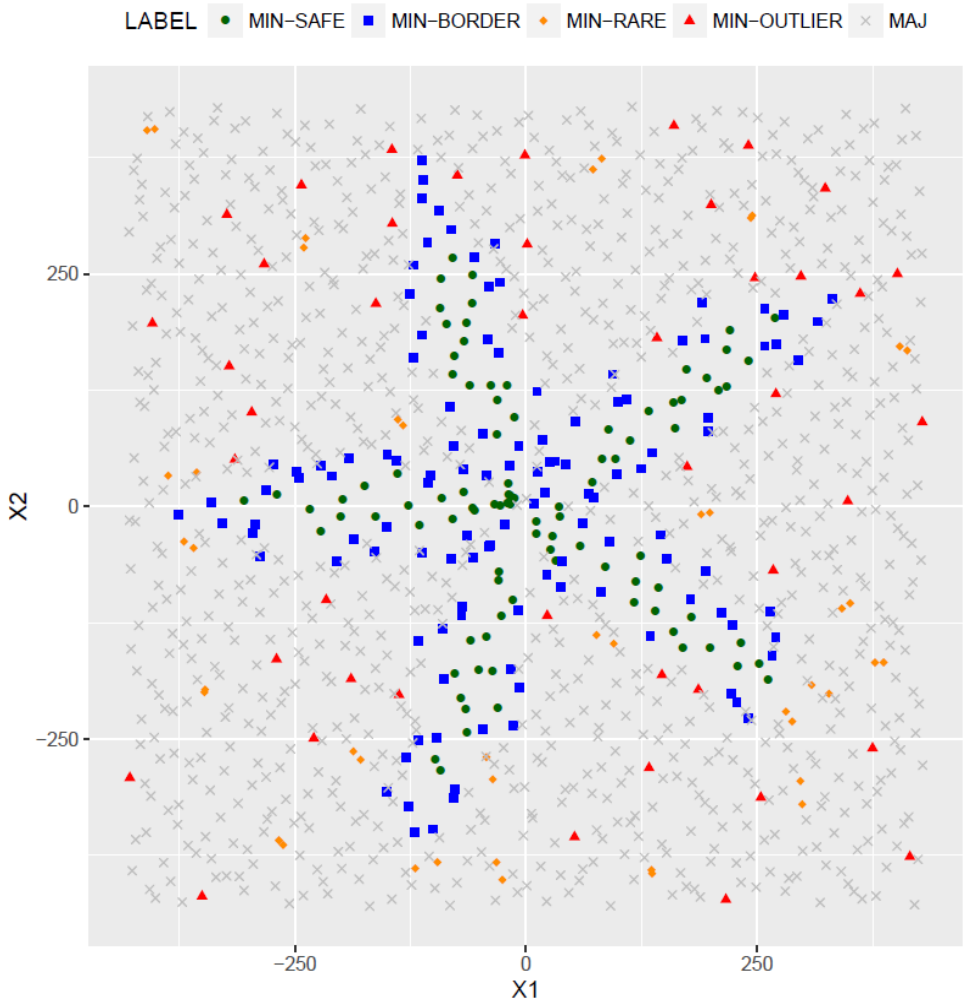
Dealing with imbalanced data

Class imbalance is not the only or main problem…

- Other data difficulty factors (affecting the minority class)
  - Overlapping regions between classes
  - Rare sub-concepts (→ *small disjuncts*) in the minority class and "outliers" thrown into the majority classes
- Identification of difficulty factors – tagging examples based on their local neighborhood [Napierała and Stefanowski, 2015]

Safe vs. *unsafe* (→ borderline, rare and outlier)

Types of examples capturing difficulty factors



Goal and research questions

Goal: evaluate and compare combinations of preprocessing methods and classifiers on clinical data

1. What are the data difficulty factors encountered in the analyzed clinical data sets?
2. How do the preprocessing methods improve the performance of obtained classifiers?
3. What are the best combinations of preprocessing methods and classifiers?

Special focus on the minority class

- Real-life clinical data sets collected in the ED at CHEO
- Common or relevant pediatric presentations
- Minority class indicates patients requiring quick care and significant resources

Wilk S., Stefanowski J., Wojciechowski S., Farion K.J., Michalowski W. (2016) Application of Preprocessing Methods to Imbalanced Clinical Data: An Experimental Study. In: Information Technologies in Medicine. ITiB 2016. Advances in Intelligent Systems and Computing, vol 471. Springer, Cham

Considered data sets

Data set	Clinical problem	# examples (minority)	Imbalance ratio	# attributes (numeric)
AP	Abdominal pain	457 (48)	0.11	13 (3)
HP	Hip pain	412 (46)	0.11	20 (4)
SP	Scrotal pain	409 (56)	0.14	14 (3)
AE1	Asthma exacerbations (2004)	362 (59)	0.16	32 (11)
AE2	Asthma exacerbations (2007)	240 (21)	0.09	42 (9)

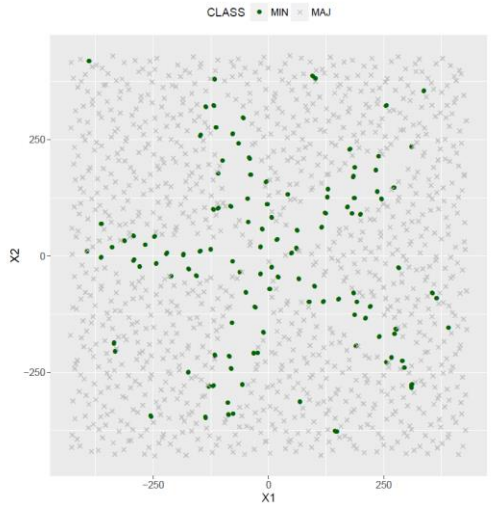
- Data collected retrospectively (HP, SP and AE1) and prospectively (AP and AE2)
- Removal of attributes with ≥ 50% of missing values (15 in SP, 10 in AE1)
- All non-critical classes combined into a single majority class

Experimental design

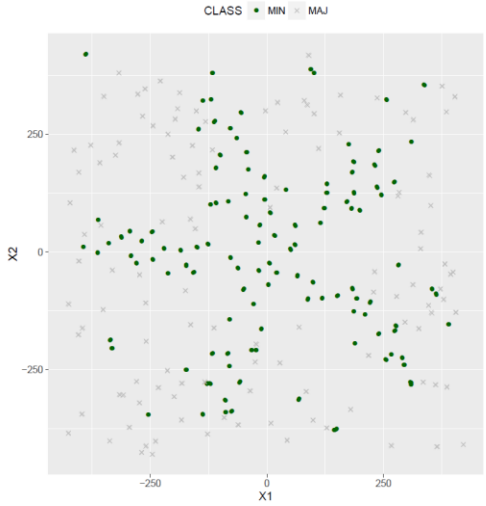
1. Identifying data difficulty factors in the data sets (by tagging examples with their types)
2. Evaluating the performance of selected combinations of preprocessing methods and classifiers on the data sets
   - Sensitivity, specificity and their geometric mean (G-mean, GM)
   - Stratified 10-fold cross validation repeated 10 times for reduced variance
   - Friedman test ($\alpha = 0.05$) to compare the performance of multiple combinations of preprocessing methods and classifiers over multiple data sets

Illustration of Preprocessing Methods

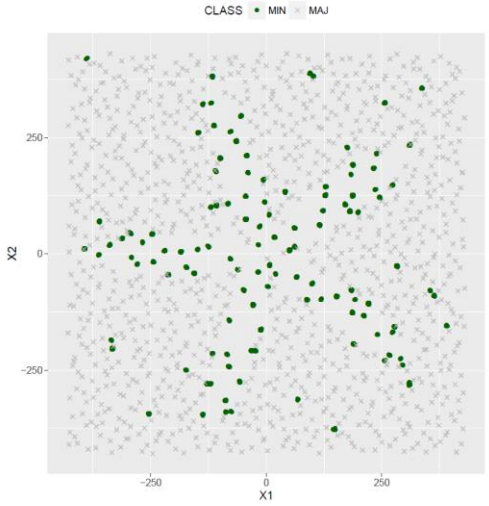
None



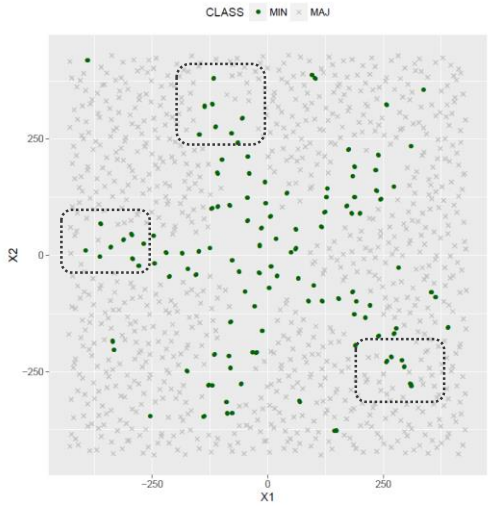
RU



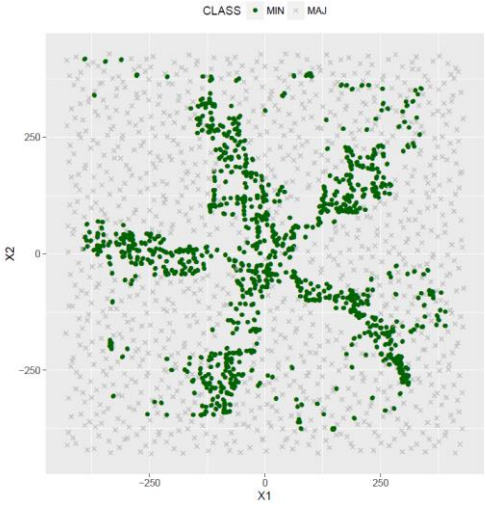
RO



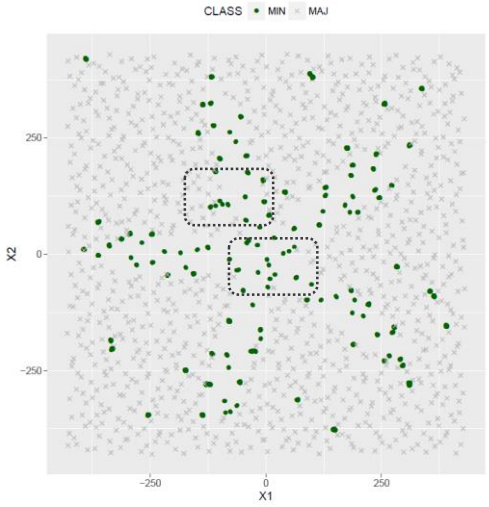
NCR



SM



SP2



Encountered Data Difficulty Factors

Data set	% Safe	% Borderline	% Rare	% Outlier
AP	29	38	8	25
HP	7	28	15	50
SP	4	53	11	32
AE1	2	63	10	25
AE2	14	24	10	52

- Large portion of unsafe (esp. borderline and outlier) examples
- Very small portion of safe examples

Observed sensitivity

AP	None	RU	RO	SM	NCR	SP2
1NN	0.4300	0.7500	0.4300	0.5220	0.5635	0.5005
3NN	0.4385	0.7390	0.6495	0.5365	0.5330	0.6230
C45	0.3680	0.7610	0.5140	0.5005	0.5455	0.5710
PART	0.4375	0.7595	0.5170	0.5255	0.5340	0.5325
NB	0.7160	0.7990	0.7875	0.6770	0.7490	0.8135
RBF	0.5130	0.7860	0.7645	0.6535	0.6685	0.7405
SVM	0.5020	0.7935	0.7880	0.6150	0.5770	0.7640

SP	None	RU	RO	SM	NCR	SP2
1NN	0.2743	0.6307	0.2743	0.3950	0.4743	0.2793
3NN	0.2440	0.6590	0.5553	0.5240	0.4617	0.5513
C45	0.3990	0.6203	0.5523	0.3950	0.4550	0.5883
PART	0.3893	0.6637	0.5487	0.3597	0.4683	0.5760
NB	0.4343	0.7797	0.7203	0.4077	0.5187	0.7220
RBF	0.3913	0.6977	0.4920	0.4070	0.4743	0.5220
SVM	0.3293	0.6597	0.3813	0.3350	0.4163	0.3947

GM – consistent with sensitivity (RU + NB)
Specificity – deteriorated (worst for RU)

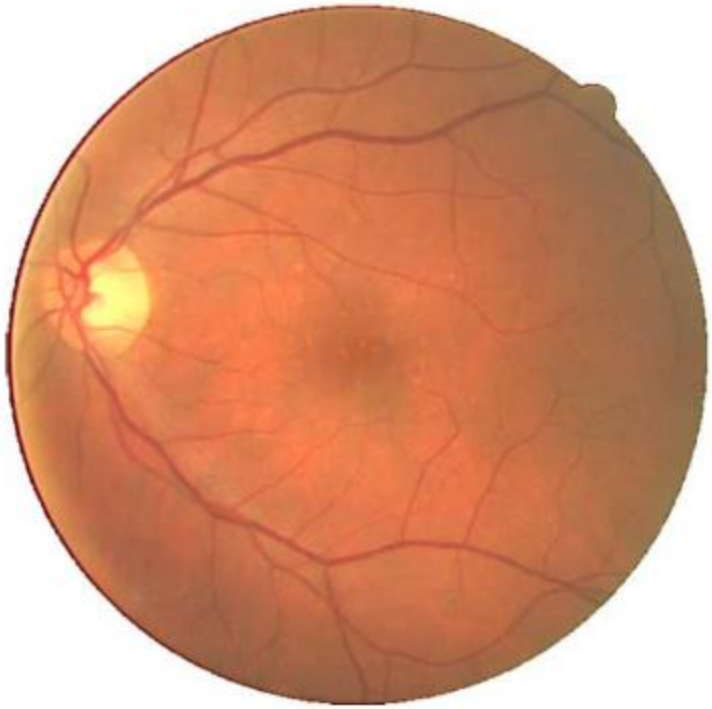
HP	None	RU	RO	SM	NCR	SP2
1NN	0.2035	0.6035	0.2035	0.3315	0.3040	0.2035
3NN	0.1205	0.6025	0.4300	0.3630	0.2095	0.4280
C45	0.2690	0.7170	0.4965	0.3865	0.3365	0.4780
PART	0.2875	0.6955	0.5115	0.3585	0.3370	0.4840
NB	0.7535	0.8480	0.8510	0.5645	0.7660	0.8615
RBF	0.5475	0.7920	0.7145	0.4245	0.5865	0.6840
SVM	0.5100	0.7210	0.4985	0.4445	0.5340	0.4970

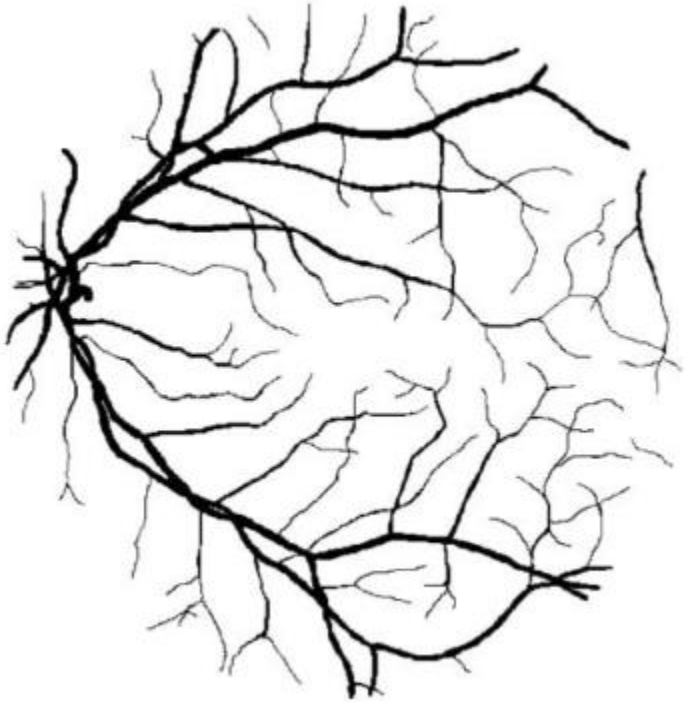
AE1	None	RU	RO	SM	NCR	SP2
1NN	0.2743	0.5903	0.2743	0.4570	0.3957	0.2760
3NN	0.1623	0.6327	0.5097	0.5277	0.3163	0.4860
C45	0.1847	0.6080	0.3910	0.2913	0.3097	0.3617
PART	0.2553	0.6330	0.3723	0.2823	0.3497	0.3953
NB	0.4897	0.7143	0.6833	0.4680	0.5803	0.7167
RBF	0.4343	0.6940	0.6683	0.4763	0.5203	0.7080
SVM	0.3217	0.6170	0.3147	0.3583	0.4080	0.3720

AE2	None	RU	RO	SM	NCR	SP2
1NN	0.1000	0.5867	0.1000	0.3217	0.1317	0.1000
3NN	0.0900	0.7133	0.4200	0.4417	0.1500	0.3750
C45	0.1733	0.6733	0.3933	0.1500	0.2683	0.3300
PART	0.2617	0.6767	0.3767	0.2817	0.3483	0.3400
NB	0.7117	0.7967	0.7267	0.2400	0.7467	0.7533
RBF	0.5317	0.7917	0.7367	0.2500	0.6800	0.7533
SVM	0.4117	0.5950	0.3200	0.3433	0.3533	0.2900

Another study – deep neural networks

Problem: blood vessel segmentation in fundus images





Liskowski P, Krawiec K. Segmenting Retinal Blood Vessels with Deep Neural Networks. *IEEE Trans Med Imaging*. 2016;35(11):2369-2380.

Another study – deep neural networks

Application of simple (random) undersampling → even distribution of classes

TABLE III
PERFORMANCE OF MODELS (POINT ESTIMATES FOR DRIVE, AVERAGES WITH .95 CONFIDENCE INTERVALS FOR STARE)

	DRIVE						STARE					
	AUC	Acc	Acc*	Kappa	Sens	Spec	AUC	Acc	Acc*	Kappa	Sens	Spec
PLAIN	.9683	.9479	.9473	.7653	.7417	.9804	.9767±.0053	.9559±.0071	.9551±.0072	.7477±.0451	.7495±.0721	.9788±.0081
GCN	.9708	.9487	.9475	.7708	.7550	.9792	.9787±.0049	.9571±.0064	.9572±.0064	.7573±.0394	.7620±.0656	.9789±.0072
ZCA	.9719	.9485	.9472	.7756	.7819	.9748	.9783±.0062	.9563±.0064	.9562±.0066	.7598±.0317	.7718±.0490	.9783±.0055
AUGMENT	.9663	.9466	.9453	.7610	.7447	.9784	.9744±.0048	.9527±.0068	.9512±.0069	.7306±.0431	.7376±.0720	.9769±.0086
BALANCED	.9738	.9230	.9251	.7193	.9160	.9241	.9820±.0045	.9309±.0107	.9620±.0051	.7021±.0305	.9307±.0274	.9304±.0133
NO-POOL	.9720	.9495	.9486	.7781	.7763	.9768	.9785±.0066	.9566±.0082	.9568±.0081	.7622±.0415	.7867±.0698	.9754±.0099

INTERPRETABILITY OF DECISION MODELS

Interpretability of decision model

A possibility of "looking into" a decision model and its outcomes
(→ **explainable AI**)

- **Transparency** – ability to understand an entire model (before it can be applied in practice)
- **Post-hoc interpretability** – ability to explain a decision suggestion for a specific case (a given patient)
- Significant challenge for non-symbolic classifiers – construction of auxiliary decision models for providing explanations

GDPR and ISO/IEC 27001 – a possibility to make the results re-traceable on demand

Lipton, Z. C. (2018). The Mythos of Model Interpretability. Acmqueue, 16(3). https://doi.org/10.1016/j.apmr.2007.10.023.
Holzinger, A., Biemann, C., Pattichis, C. S., & Kell, D. B. (2017). What do we need to build explainable AI systems for the medical domain?, (Ml), 1–28. Retrieved from http://arxiv.org/abs/1712.09923

Explaining decisions in neural networks

Introduction of a *global average pooling layer* to identify relevant regions on the image (→ **class activation map**)

http://cnnlocalization.csail.mit.edu/

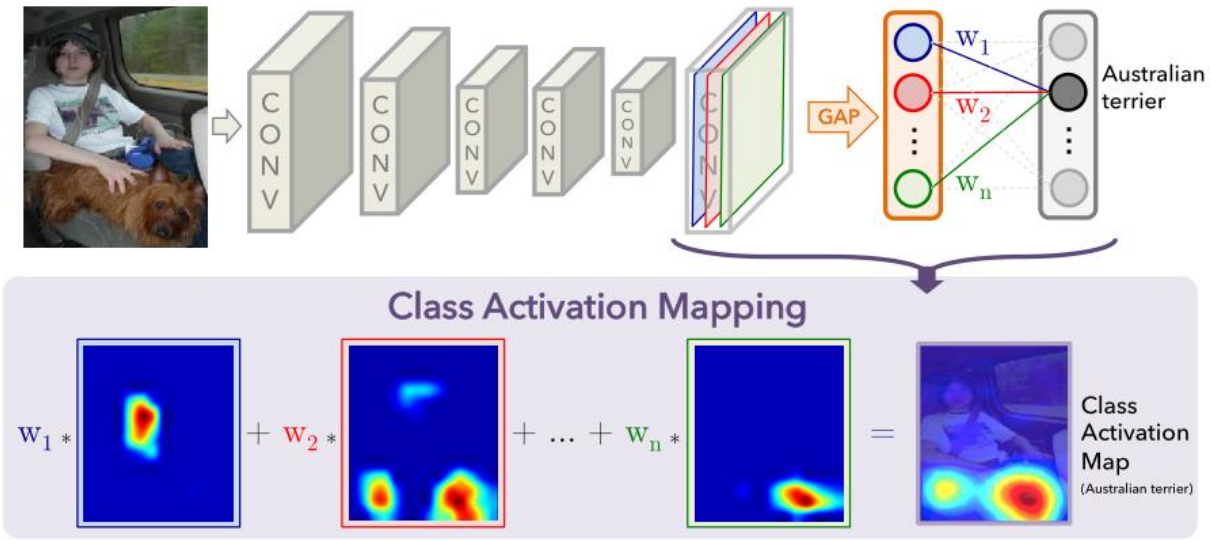
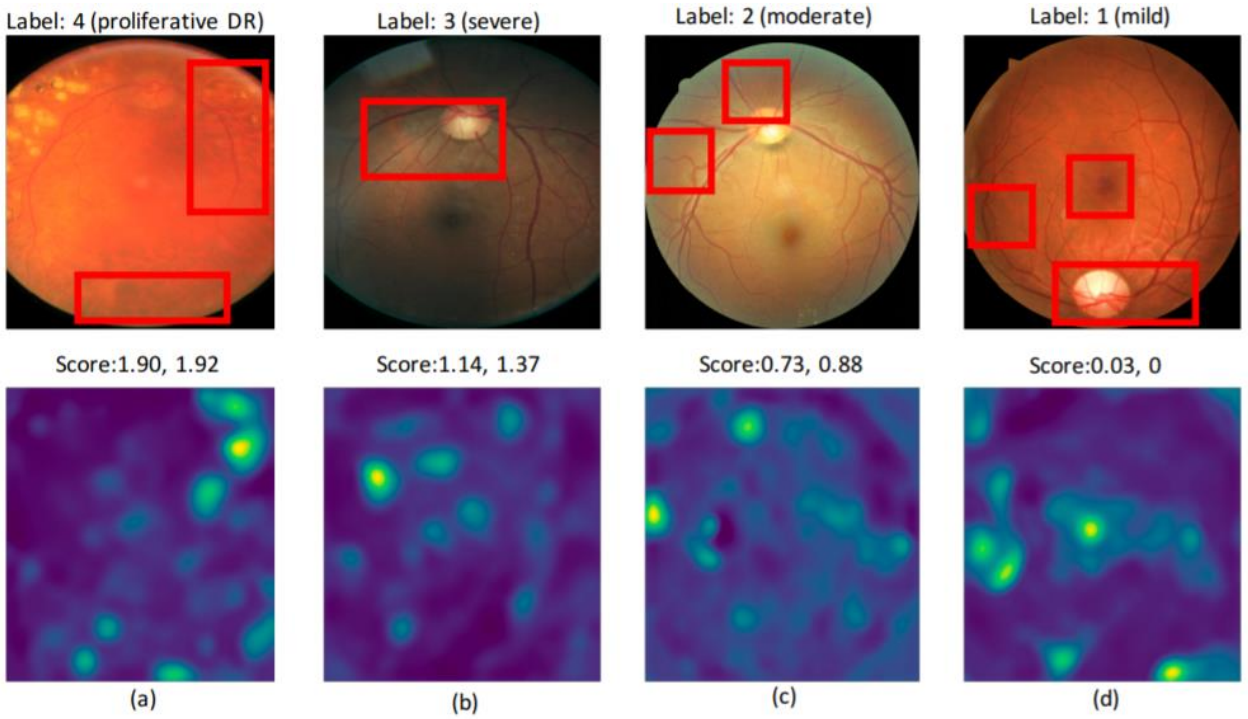


Figure 2. Class Activation Mapping: the predicted class score is mapped back to the previous convolutional layer to generate the class activation maps (CAMs). The CAM highlights the class-specific discriminative regions.

Zhou B, Khosla A, Lapedriza A, Oliva A, Torralba A. Learning Deep Features for Discriminative Localization. In: 2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR). 2016, 2921-2929.

Explaining decisions in neural networks

Similar solution for regression (→ **regression activation map**)



Wang Z., Yang J. (2017). „Diabetic Retinopathy Detection via Deep Convolutional Networks for Discriminative Localization and Visual Explanation". https://arxiv.org/abs/1703.10757.

LIME – Local Interpretable Model-Agnostic Explanations

- Constructs explainable model for a specific case
- Selects relevant cases that give global understanding of how a black model works (submodular pick)

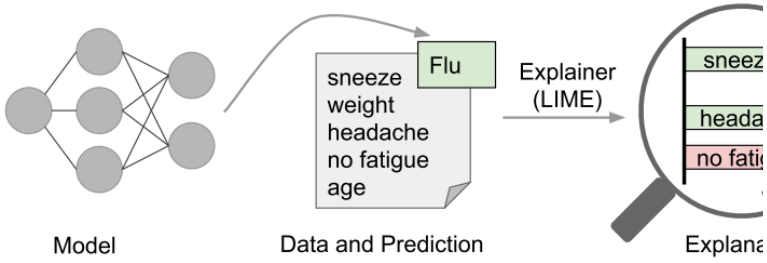


Figure 1: Explaining individual predictions. A model predicts that a
the symptoms in the patient's history that led to the prediction.
contributing to the "flu" prediction, while "no fatigue" is evidence ag
an informed decision about whether to trust the model's prediction.

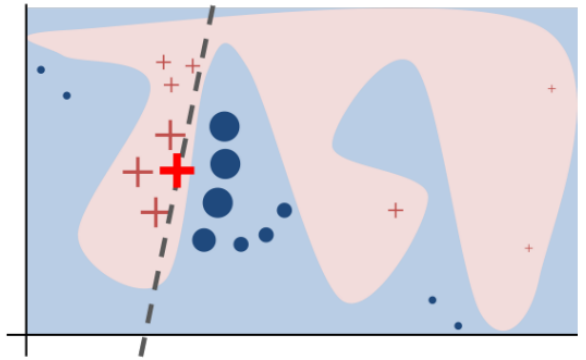


Figure 3: Toy example to present intuition for LIME. The black-box model's complex decision function f (unknown to LIME) is represented by the blue/pink background, which cannot be approximated well by a linear model. The bold red cross is the instance being explained. LIME samples instances, gets predictions using f, and weighs them by the proximity to the instance being explained (represented here by size). The dashed line is the learned explanation that is locally (but not globally) faithful.

Ribeiro, M. T., Singh, S., & Guestrin, C. (2016). "Why Should I Trust You?": Explaining the Predictions of Any Classifier. https://doi.org/10.18653/v1/N16-3020

BETA – Black Box Explanations through Transparent Approximations

- Constructs an interpretable white-box decision model
- Aimed at optimizing the *fidelity* to the original model and *interpretability* of the explanation (also complexity)
- Two-level decision rules – *neighborhood description* and *decision logic*

If Age <50 **and** Male =Yes:

If Past-Depression =Yes **and** Insomnia =No **and** Melancholy =No, **then** Healthy

If Past-Depression =Yes **and** Insomnia =Yes **and** Melancholy =Yes **and** Tiredness =Yes, **then** Depression

If Age ≥ 50 **and** Male =No:

If Family-Depression =Yes **and** Insomnia =No **and** Melancholy =Yes **and** Tiredness =Yes, **then** Depression

If Family-Depression =No **and** Insomnia =No **and** Melancholy =No **and** Tiredness =No, **then** Healthy

Default:

If Past-Depression =Yes **and** Tiredness =No **and** Exercise =No **and** Insomnia =Yes, **then** Depression

If Past-Depression =No **and** Weight-Gain =Yes **and** Tiredness =Yes **and** Melancholy =Yes, **then** Depression

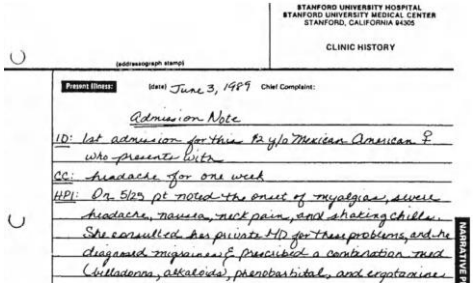
If Family-Depression =Yes **and** Insomnia =Yes **and** Melancholy =Yes **and** Tiredness =Yes, **then** Depression

Lakkaraju, H., Kamar, E., Caruana, R., & Leskovec, J. (2017). Interpretable & Explorable Approximations of Black Box Models. Retrieved from http://arxiv.org/abs/1707.01154

DATA FUSION

Heterogeneity of clinical data

- Text data – “free text” with unformal codes and expressions
- Numerical data
- Omics data (various representations)
- Drawings – hand-made sketches, markings on diagrams (dentistry)
- Signals (numerical time series)
- Images and videos


STANFORD UNIVERSITY HOSPITAL
STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

CLINIC HISTORY

Present Illness (date) June 3, 1989 Chief Complaint:

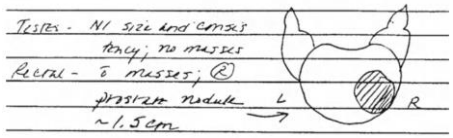
Admission Note

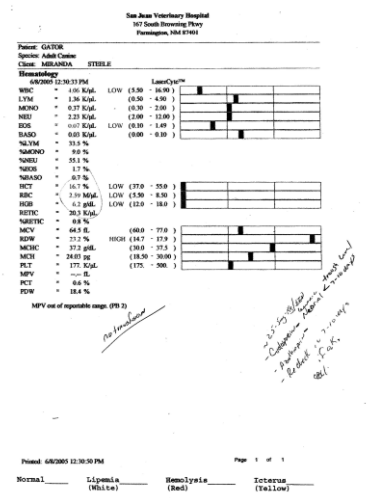
ID: 1st admission for this 32 y/o Mexican American F who presents with

CC: headache for one week

HPI: On 5/25 pt noted the onset of myalgias, severe headache, nausea, neck pain, and shaking chills. She consulted her private MD for these problems, and he diagnosed migraines & prescribed a combination med (belladonna, alkaloids), phenobarbital, and ergotamine.

NARRATIVE




San Juan Veterinary Hospital
567 South Browning Pkwy
Farmington, NM 87401

Patient: GATOR
Species: Adult Canine
Client: MIRANDA STEELE

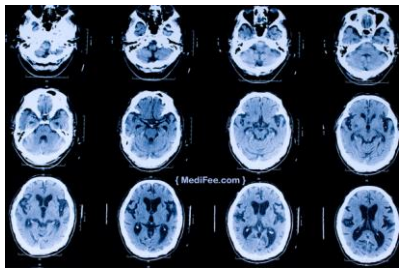
Hematology
6/8/2005 12:30:33 PM

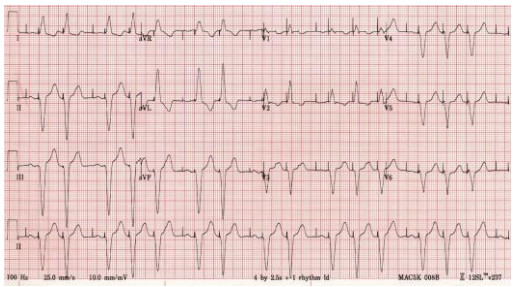
				LaserCyte™
WBC	4.06 K/µL	LOW	(5.50 - 16.90)	
LYM	1.36 K/µL		(0.50 - 4.50)	
MONO	0.37 K/µL		(0.30 - 2.00)	
NEU	2.23 K/µL		(2.00 - 12.00)	
EOS	0.07 K/µL	LOW	(0.30 - 1.49)	
BASO	0.03 K/µL		(0.00 - 0.10)	
%LYM	33.5 %			
%MONO	9.0 %			
%NEU	55.1 %			
%EOS	1.7 %			
%BASO	0.7 %			
HCT	36.7 %	LOW	(37.0 - 55.0)	
RBC	3.39 M/µL	LOW	(5.50 - 8.50)	
HGB	6.3 g/dL	LOW	(12.0 - 18.0)	
RETIC	20.3 K/µL			
%RETIC	0.8 %			
MCV	64.5 fL		(60.0 - 77.0)	
RDW	23.2 %	HIGH	(14.7 - 17.9)	
MCHC	37.2 g/dL		(30.0 - 37.5)	
MCH	24.03 pg		(18.50 - 30.00)	
PLT	177. K/µL		(175. - 500.)	
MPV	--- fL			
PCT	0.6 %			
PDW	18.4 %			

MPV out of reportable range. (Pft 2)

Printed: 6/8/2005 12:30:50 PM

Normal____ Lipemia____ Hemolysis____ Icterus____
(White) (Red) (Yellow)





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3658435    145    CHROMOSOME_I    1    0    100M    CHROMOSOME_II    2716898    0
GCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCT
AAGCCT
@CCC?:CCCCC@CCCEC>AFDFDBEGHEAHCIGIHHGIGEGJGGIIIHFHIHGF@HGGIGJJJJJIJJJJJJJJJJJJJJJJJJJJJHHHHHFF
FFFCCC    RG:Z:1    NH:i:1    NM:i:0

5482659    65    CHROMOSOME_I    1    0    100M    CHROMOSOME_II    11954696    0
GCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCTAAGCCT
AAGCCT
CCCFFFFFHHHGHGJJGIHIJIJJJJJJIJJJJJIJJGIJJJJJIIJIIJFJJJJJFIJJJJIIIIGIIJHHHHDEEFFFEEEEEDDDDCDCCCA
AA?CC:    RG:Z:1    NH:i:1    NM:i:0
```

Problem statement

Focus on a single data modality may be insufficient to construct a comprehensive and accurate clinical decision model

- Most of the developed clinical decision model rely on a single data modality (e.g., “traditional” data or image data)
- **Data fusion** may be used address the above limitation

Data fusion

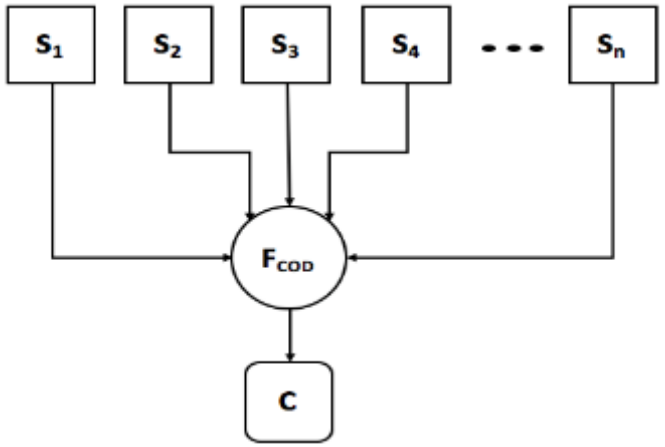
Integration of data and knowledge from multiple sources of diversified format and structure

- Human perception system → extended angular vision is obtained by the combination of percepts from each eye
- Human brain → fusion on information collected through all the senses and previous memory to generate orderly action
- Other application areas – multi-sensor networks, surveillance systems, imaging studies

Data fusion techniques

Combination of data (COD)

- Aggregation of data from various sources into a single space
- Construction of a decision model using aggregated space

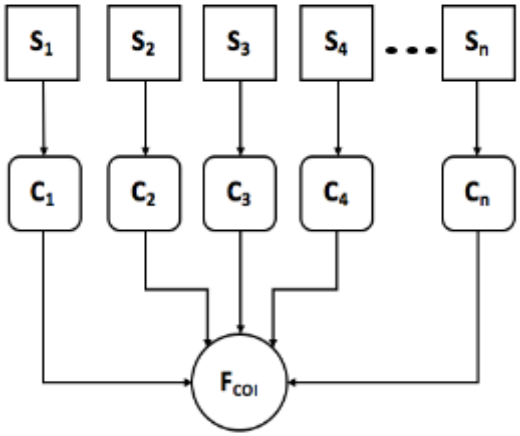


- Drawback: course of dimensionality

Data fusion techniques

Combination of interpretations (COI)

- Construction of decision models from each data source
- Combination of outcomes of obtained models by a combiner to produce a single decision (→ stacking)

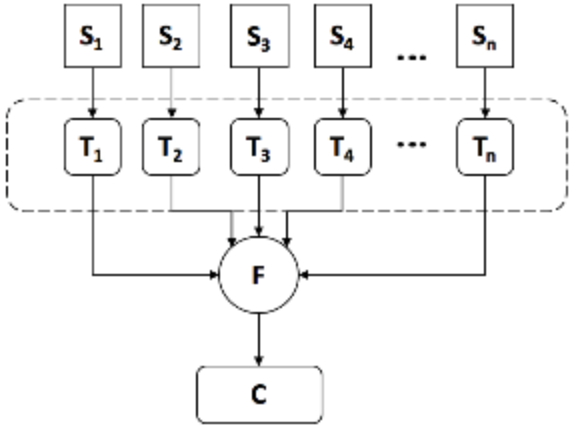


- Drawback: Inability to handle inter-source dependencies

Data fusion techniques

General fusion framework (GFF)

- Brining data into a homogeneous space through a series of simple and complex transformations
  - Simple: data pre-processing (feature selection, transformation)
  - Complex: construction of "intermediary" classifiers
- Construction of the final classifier from the homogeneous space



- Drawback: selecting transformations and their sequence

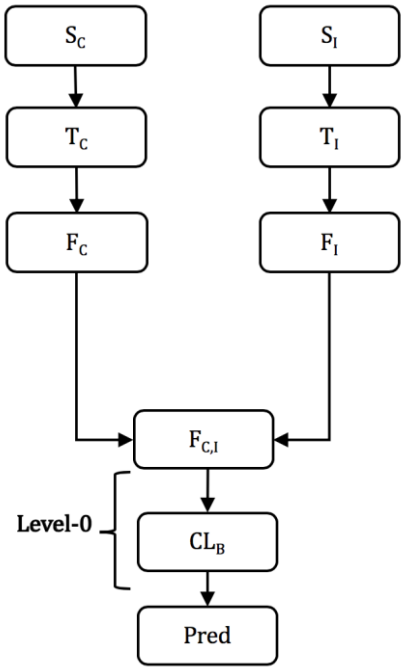
G. Lee, A. Madabhushi: A knowledge representation framework for integration, classification of multi-scale imaging and non-imaging data: Preliminary results in predicting prostate cancer recurrence by fusing mass spectrometry and histology. *IEEE International Symposium on Biomedical Imaging: From Nano to Macro*, 2009.

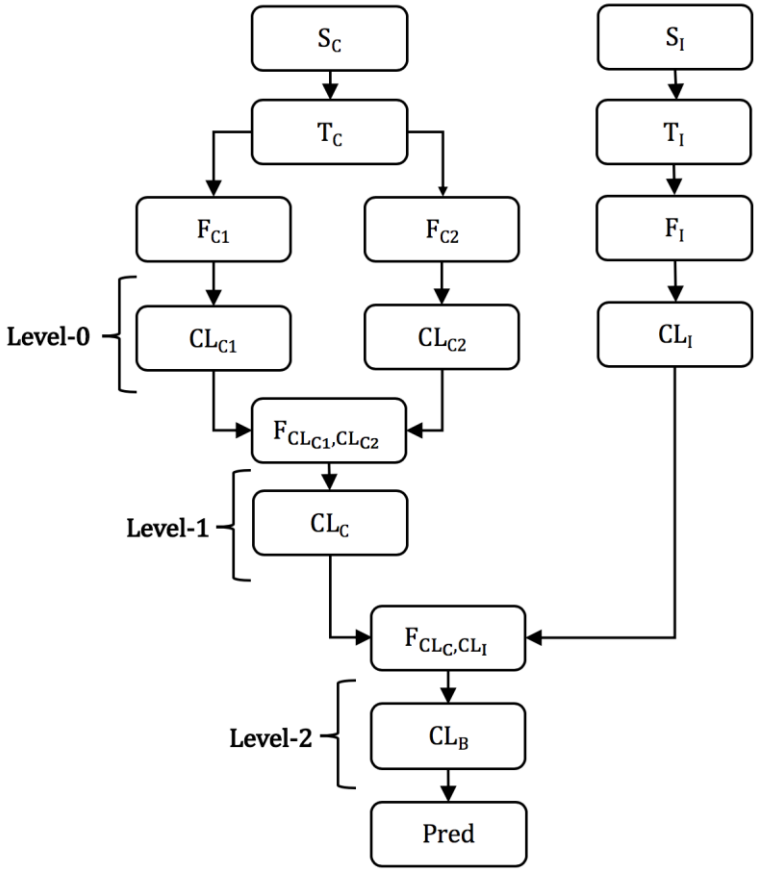
Predicting treatment for fractures

- Prediction of the type of treatment in patients with fractures – surgical vs. non-surgical
- Non-image data (demographics, results of examinations and lab tests) and image data (X-ray)
- 210 patients extracted from a repository of educational cases hosted by the WCT telemedical platform
- Comparison of COD and COI approaches (of varying complexity)

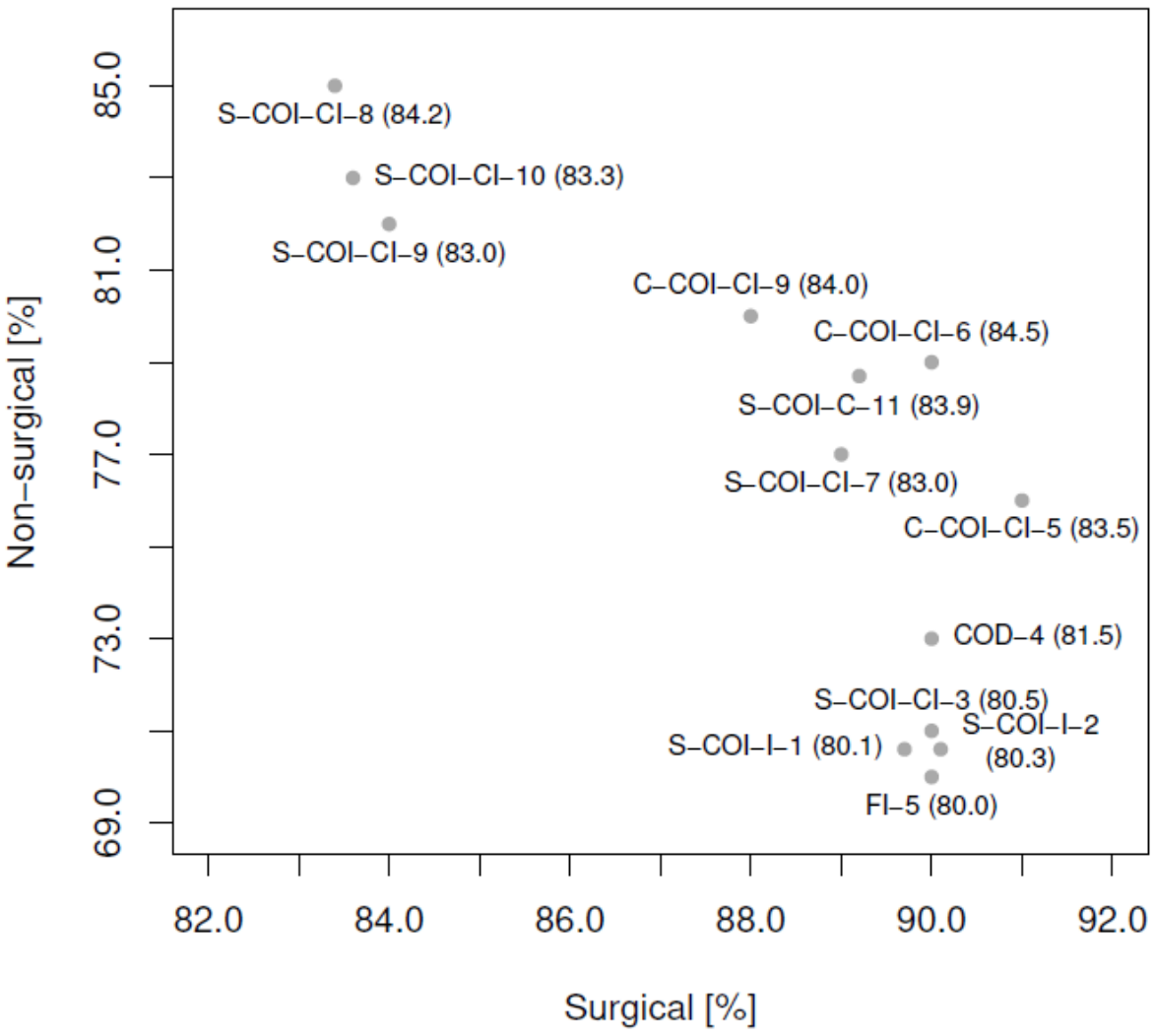
A. Haq, Sz. Wilk, A. Abelló: Fusion of clinical data: A case study to predict the type of treatment of bone fractures. AMC 29 (1), 2019.

Example fusion models





Results


S–COI–CI–8 (84.2)
S–COI–CI–10 (83.3)
S–COI–CI–9 (83.0)
C–COI–CI–9 (84.0)
C–COI–CI–6 (84.5)
S–COI–C–11 (83.9)
S–COI–CI–7 (83.0)
C–COI–CI–5 (83.5)
COD–4 (81.5)
S–COI–CI–3 (80.5)
S–COI–I–2
(80.3)
S–COI–I–1 (80.1)
FI–5 (80.0)
85.0
81.0
77.0
73.0
69.0
Non–surgical [%]
82.0
84.0
86.0
88.0
90.0
92.0
Surgical [%]

Application of deep learning

npj | Digital Medicine

www.nature.com/npjdigitalmed

ARTICLE OPEN

Scalable and accurate deep learning with electronic health records

Alvin Rajkomar[1,2], Eyal Oren[1], Kai Chen[1], Andrew M. Dai[1], Nissan Hajaj[1], Michaela Hardt[1], Peter J. Liu[1], Xiaobing Liu[1], Jake Marcus[1], Mimi Sun[1], Patrik Sundberg[1], Hector Yee[1], Kun Zhang[1], Yi Zhang[1], Gerardo Flores[1], Gavin E. Duggan[1], Jamie Irv… Kurt Litsch[1], Alexander Mossin[1], Justin Tansuwan[1], De Wang[1], James Wexler[1], Jimbo Wilson[1], Dana Ludwig[2], Samu… Katherine Chou[1], Michael Pearson[1], Srinivasan Madabushi[1], Nigam H. Shah[4], Atul J. Butte[2], Michael D. Howell[1], Greg S. Corrado[1] and Jeffrey Dean[1]

Predictive modeling with electronic health record (EHR) data is anticipated to drive personalized medicine and in… quality. Constructing predictive statistical models typically requires extraction of curated predictor variables from … data, a labor-intensive process that discards the vast majority of information in each patient's record. We propose a represe… of patients' entire raw EHR records based on the Fast Healthcare Interoperability Resources (FHIR) format. We demonstra… deep learning methods using this representation are capable of accurately predicting multiple medical events from multiple centers without site-specific data harmonization. We validated our approach using de-identified EHR data from two US academic medical centers with 216,221 adult patients hospitalized for at least 24 h. In the sequential format we propose, this volume of EHR data unrolled into a total of 46,864,534,945 data points, including clinical notes. Deep learning models achieved high accuracy for tasks such as predicting: in-hospital mortality (area under the receiver operator curve [AUROC] across sites 0.93–0.94), 30-day unplanned readmission (AUROC 0.75–0.76), prolonged length of stay (AUROC 0.85–0.86), and all of a patient's final discharge diagnoses (frequency-weighted AUROC 0.90). These models outperformed traditional, clinically-used predictive models in all cases. We believe that this approach can be used to create accurate and scalable predictions for a variety of clinical scenarios. In a case study of a particular prediction, we demonstrate that neural networks can be used to identify relevant information from the patient's chart.

npj Digital Medicine (2018)1:18 ; doi:10.1038/s41746-018-0029-1

216,221 patients,
46,864,534,945 data points
(tokens)

Application of deep learning

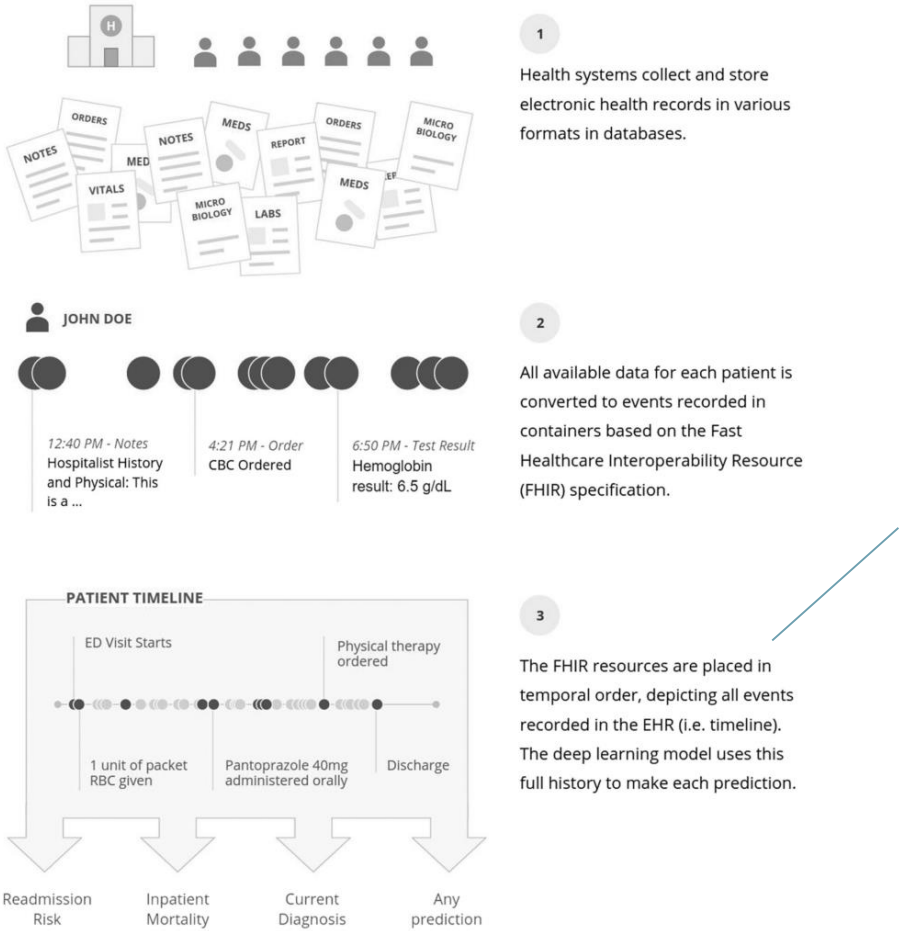


Fig. 4 Data from each health system were mapped to an appropriate FHIR (Fast Healthcare Interoperability Resources) resource and placed in temporal order. This conversion did not harmonize or standardize the data from each health system other than map them to the appropriate resource. The deep learning model could use all data available prior to the point when the prediction was made. Therefore, each prediction, regardless of the task, used the same data

An ensemble of 3 “time-aware” deep neural networks

Rajkomar, A., Oren, E., Chen, K., Dai, A. M., Hajaj, N., Liu, P. J., … Dean, J. (2018). Scalable and accurate deep learning for electronic health records. *Npj Digital Medicine*, (March), 1–10.

Integration of textual and non-textual data

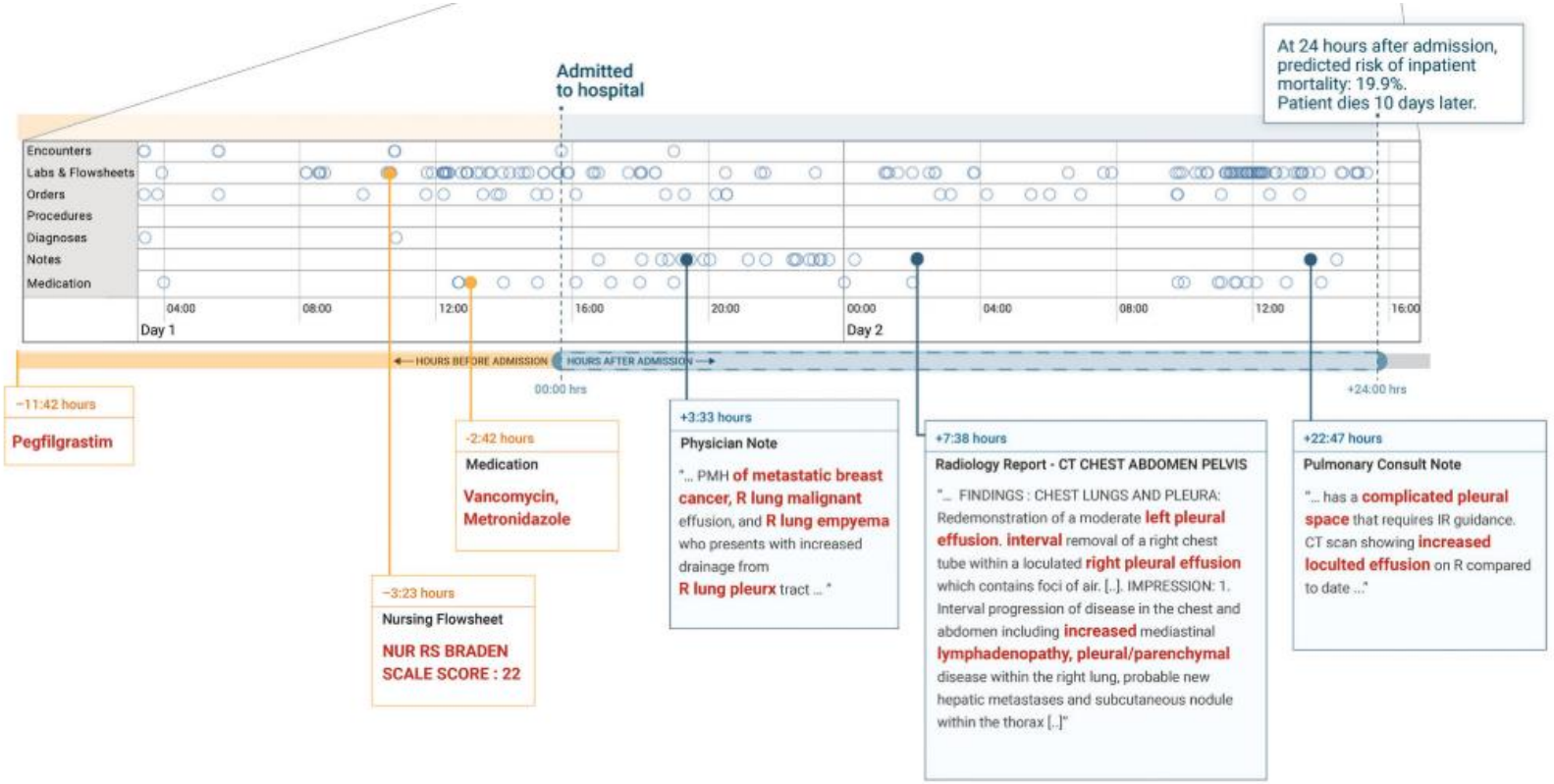
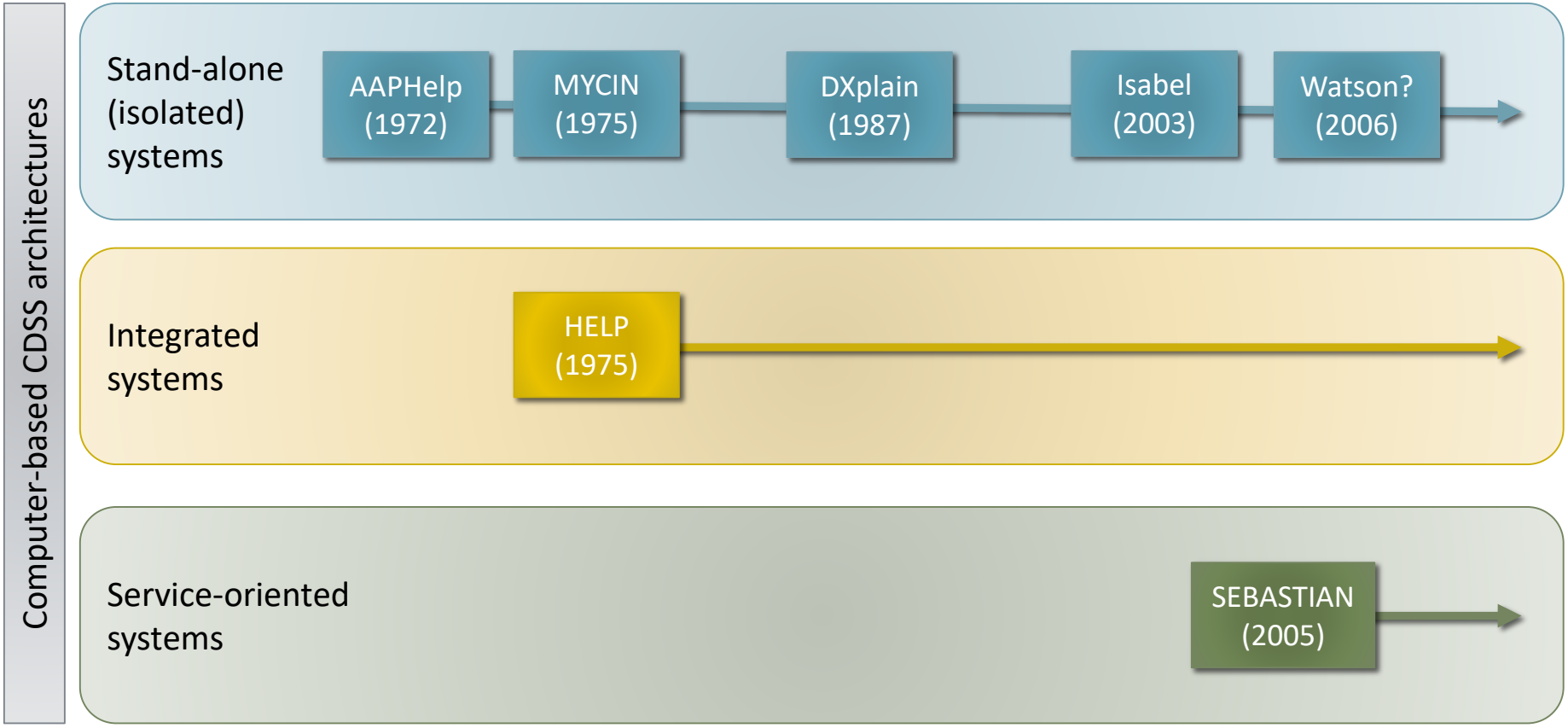


Fig. 3 The patient record shows a woman with metastatic breast cancer with malignant pleural effusions and empyema. The patient timeline at the top of the figure contains circles for every time-step for which at least a single token exists for the patient, and the horizontal lines show the data type. There is a close-up view of the most recent data points immediately preceding a prediction made 24 h after admission. We trained models for each data type and highlighted in red the tokens which the models attended to—the non-highlighted text was not attended to but is shown for context. The models pick up features in the medications, nursing flowsheets, and clinical notes relevant to the prediction

CDSS ARCHITECTURES AND EXAMPLES

CDSS architectures and history



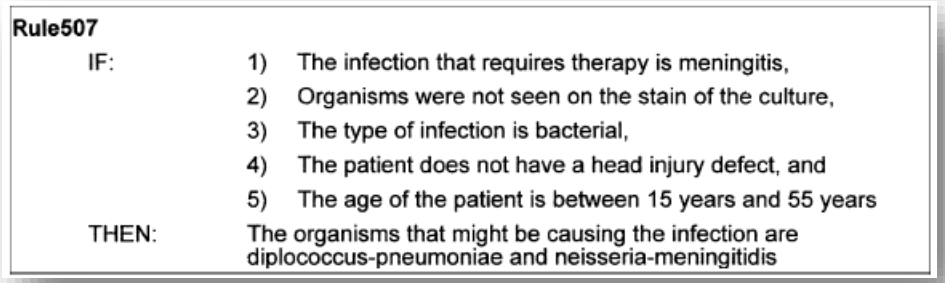
Wright, A., Sittig, D.F. (2008). A four-phase model of the evolution of clinical decision support architectures. *International Journal of Medical Informatics*, *77 (10)*, 641-649.

AAPHelp (1972 – 2004)

- System for abdominal pain diagnosis (7 possible diagnostic options, including appendicitis)
- Decision model employing a naïve Bayesian classifier, conditional probabilities established from historical data
- Very promising results in initial tests (309 cases)
  - Much higher diagnostic accuracy than for clinicians (91% ↔ 65-80%)
  - Less unnecessary surgeries for patients with appendicitis (6 ↔ 20)
- Results could not be confirmed in other settings/locations!
- Improvement of diagnostic accuracy associated with imposing of structured data collection (paper forms, batch processing)

MYCIN (1975)

- An expert system shell “loaded” with knowledge on diagnosing and treating bacterial infections
- A decision model employing rules defined by domain experts
- Advanced reasoning mechanism – backward reasoning (from hypotheses to evidence), chaining multiple rules
- Rules given in both machine and human-readable representations, ability to justify rule selection
- Confidence factors associated with rules and data to capture and consider possible uncertainty
- But it was never used in clinical practice!



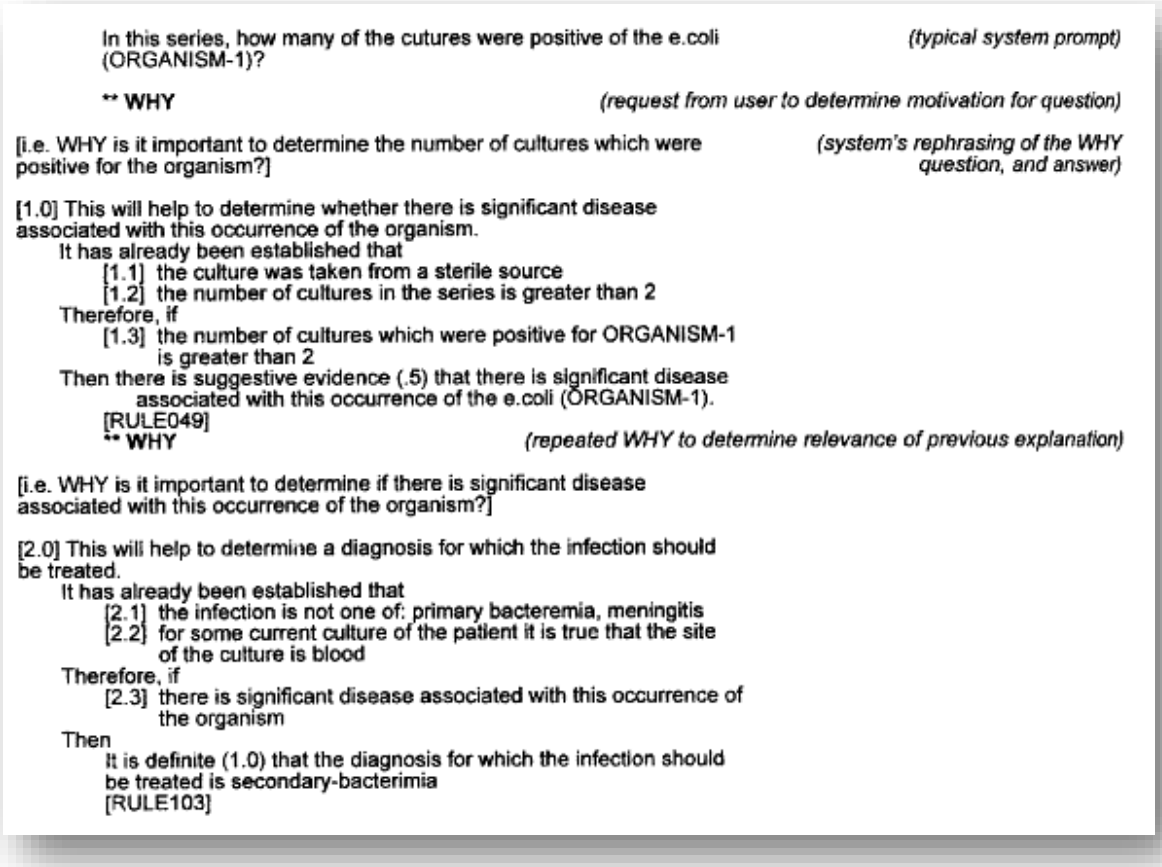
Rule507

IF:
1) The infection that requires therapy is meningitis,
2) Organisms were not seen on the stain of the culture,
3) The type of infection is bacterial,
4) The patient does not have a head injury defect, and
5) The age of the patient is between 15 years and 55 years

THEN: The organisms that might be causing the infection are diplococcus-pneumoniae and neisseria-meningitidis

Sample session in MYCIN

Possibility for QA interactions with the system



In this series, how many of the cutures were positive of the e.coli (ORGANISM-1)? *(typical system prompt)*

** WHY *(request from user to determine motivation for question)*

[i.e. WHY is it important to determine the number of cultures which were positive for the organism?] *(system's rephrasing of the WHY question, and answer)*

[1.0] This will help to determine whether there is significant disease associated with this occurrence of the organism.
It has already been established that
[1.1] the culture was taken from a sterile source
[1.2] the number of cultures in the series is greater than 2
Therefore, if
[1.3] the number of cultures which were positive for ORGANISM-1 is greater than 2
Then there is suggestive evidence (.5) that there is significant disease associated with this occurrence of the e.coli (ORGANISM-1).
[RULE049]
** WHY *(repeated WHY to determine relevance of previous explanation)*

[i.e. WHY is it important to determine if there is significant disease associated with this occurrence of the organism?]

[2.0] This will help to determine a diagnosis for which the infection should be treated.
It has already been established that
[2.1] the infection is not one of: primary bacteremia, meningitis
[2.2] for some current culture of the patient it is true that the site of the culture is blood
Therefore, if
[2.3] there is significant disease associated with this occurrence of the organism
Then
It is definite (1.0) that the diagnosis for which the infection should be treated is secondary-bacterimia
[RULE103]

Musen, M. , Shahar, Y. , Shortliffe, E. H. (2006). Clinical decision support systems. In: Shortliffe, E.H., Cimino, J. (eds.): *Biomedical Informatics. Computer Applications in Health Care and Biomedicine*, Springer, 698-736.

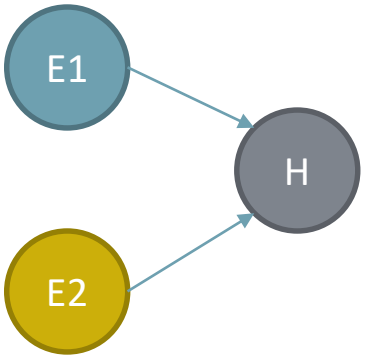
Confidence factors in MYCIN

- **Confidence factor** – change in confidence in the hypothesis *H* after assuming evidence $E - CF(H,E) \in [-1,+1]$
- Confidence factors also for data collected by the user

$$CF(H) = CF(H,E) \cdot CF(E)$$

- Confidence factors for more complex (parallel and sequential) reasoning patters

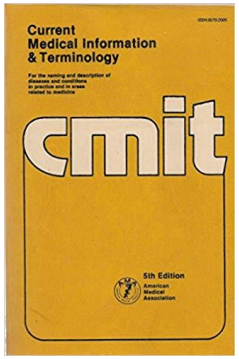
$$CF(H, E1 \wedge E2) = \begin{cases} CF(H,E1) + CF(H,E2) - CF(H,E1)CF(H,E2) & CF > 0 \\ CF(H,E1) + CF(H,E2) + CF(H,E1)CF(H,E2) & CF < 0 \\ \dfrac{CF(H,E1) + CF(H,E2)}{1 - \min\{|CF(H,E1)|, |CF(H,E2)|\}} & otherwise \end{cases}$$



$$CF(H,E1) = CF(H,E2) \cdot \max\{0, CF(E2,E1)\}$$

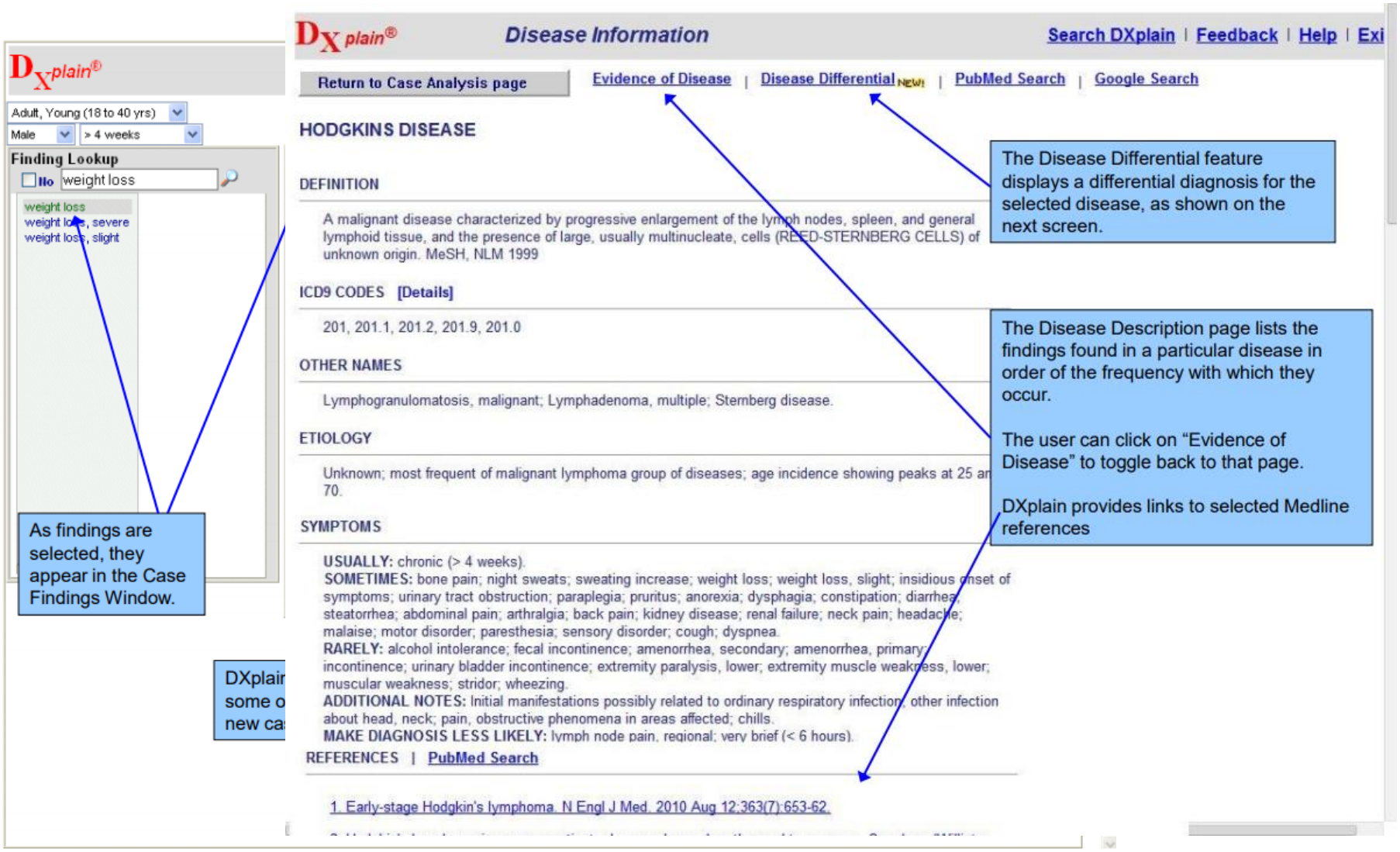
DXplain (1987 – now)

- System for supporting diagnostic decisions in various problems (2.4k diseases associated with 5k findings)
- Presents a list of possible diagnoses for a given patient, their descriptions and associated publications (e.g., from PubMed)
- Findings constitute a hierarchy (from least to most specific)
- Decision model takes into account *importance*, *frequency* (co-occurrence) and *evoking power* of reported findings
- Model parameters based on literature studies and expert knowledge (→ team of 13 researchers)
- System available for eligible users (medical students, physicians) as a web application and a service



http://www.mghlcs.org/projects/dxplain

Sample session in DXplain



ISABEL (2001 – now)

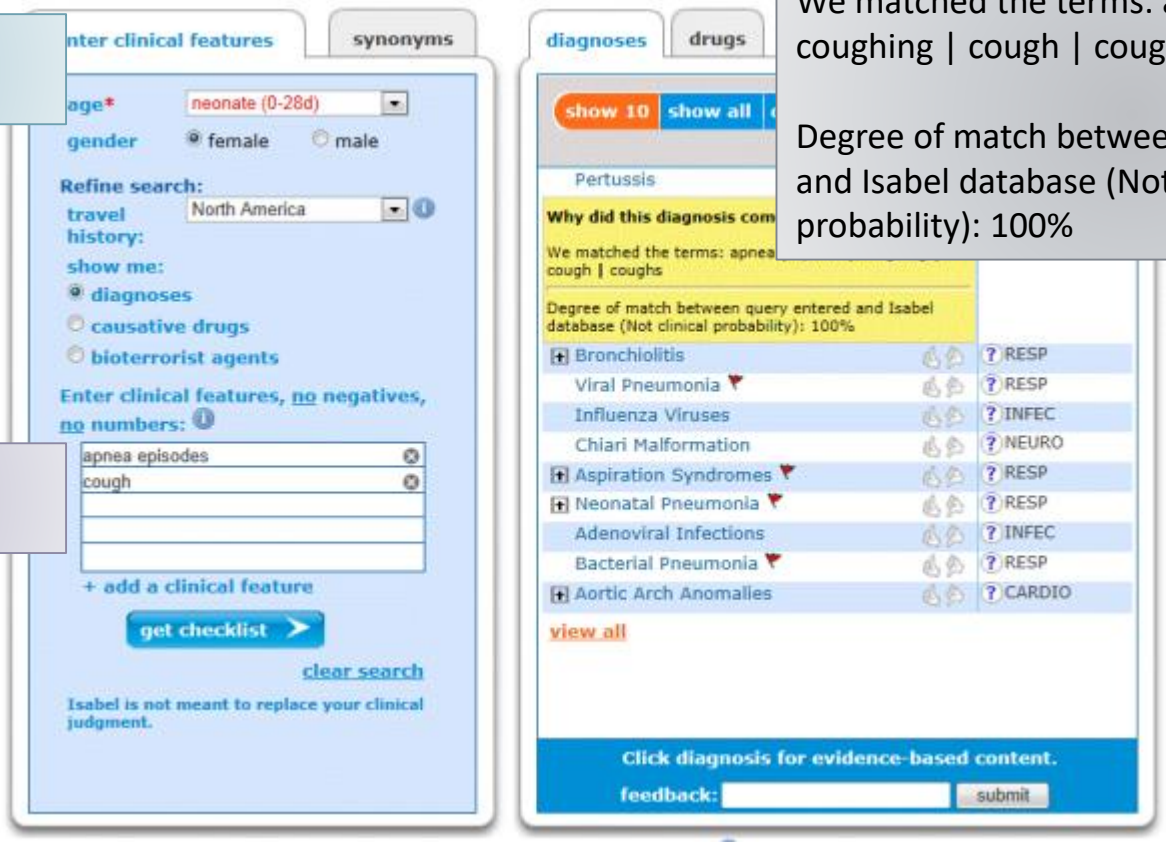
- System for supporting diagnostic decisions in various problems and adverse effects of drugs (11k diagnoses, 4k drugs)
- Expert knowledge comes for medical publications and textbooks → specialized indexing and search
- Presents a list of possible diagnosis with additional descriptions (excerpts from associated resources)
- Very promising results in preliminary tests (200 cases, accuracy between 91-95%)
- System available as web and mobile application and a service for medical users and for patients (simplified version)

http://www.isabelhealthcare.com

Sample session in ISABEL

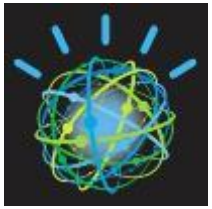
neonate (0-28d)
female

apnea episodes
cough



We matched the terms: apnea | apneic | coughing | cough | coughs

Degree of match between query entered and Isabel database (Not clinical probability): 100%



IBM Watson (2006 – now)

- Initially, general purpose system for answering questions in natural language → winner of Jeopardy (2011)
- Enthusiastic acceptance in American medical world (AMIA 2011: “return of AI to medicine…”)
- Based on Apache open-source projects (UIMA and Lucene) for processing of text resources
- Currently for analysis and visualization of poorly structured data (e.g., images, texts) using deep learning techniques → **cognitive computing**
- Special version for oncological problems → Watson for Oncology (searching for evidence, trials, treatment…)

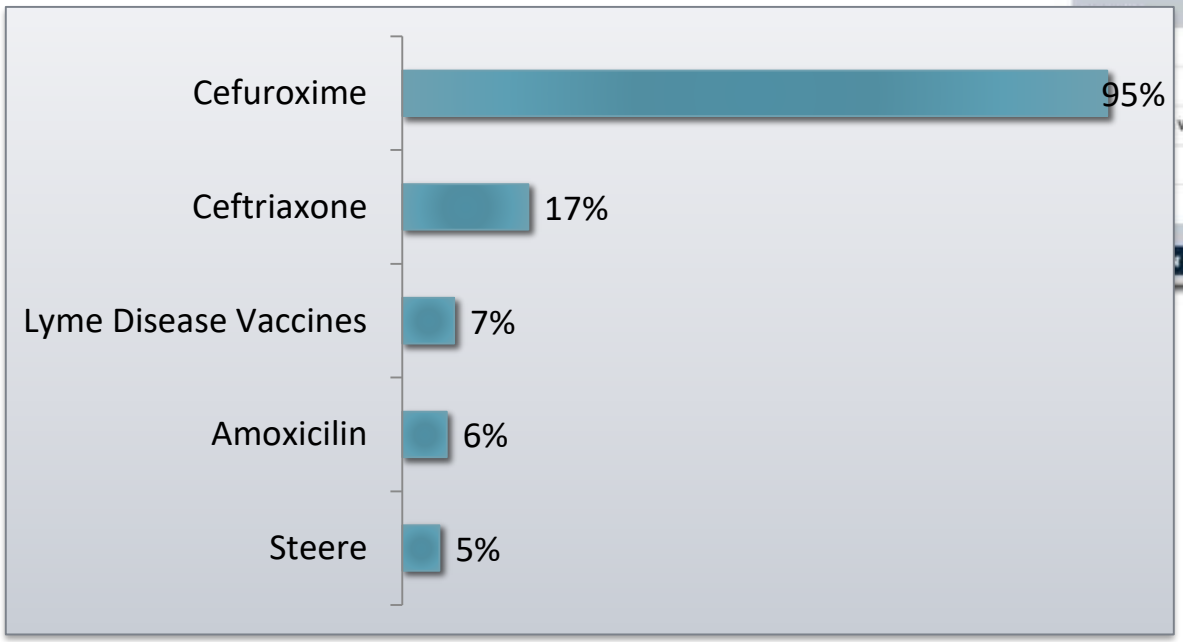
http://www.ibm.com/watson

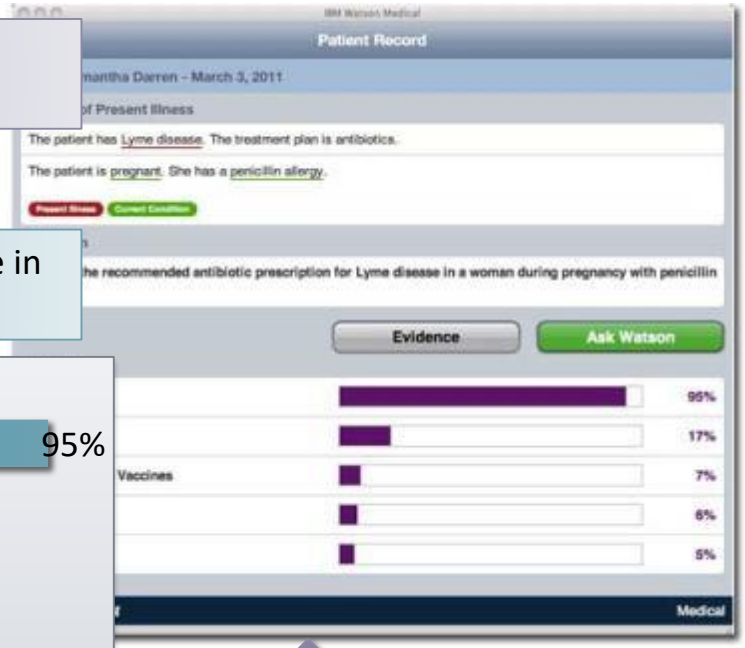
https://www.youtube.com/watch?v=338CIHlVi7A

Sample session in Watson

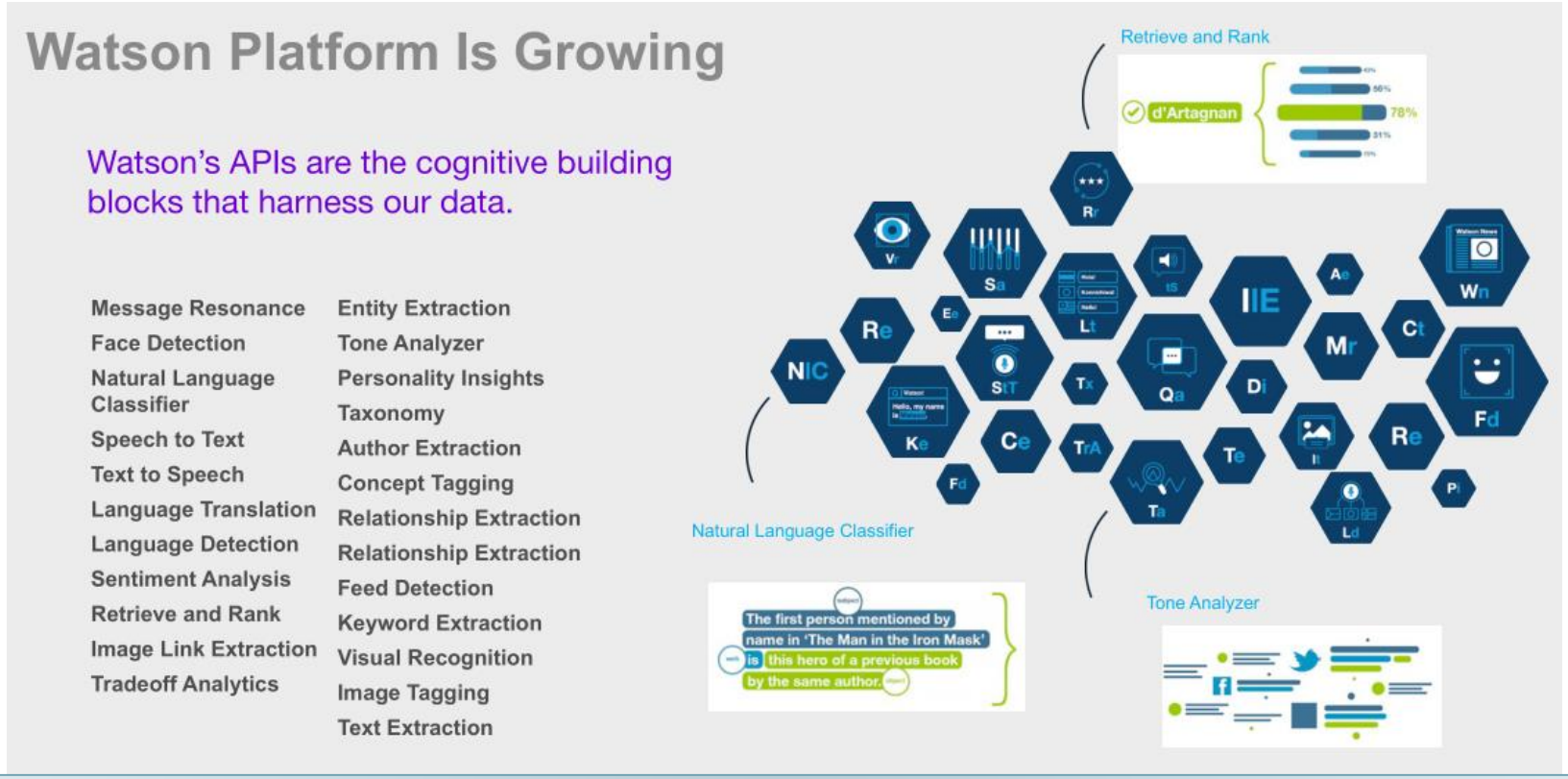
The patient has Lyme disease. The treatment plan is antibiotics.
The patient is pregnant. She has a penicillin allergy.

What is the recommended antibiotic prescription for Lyme disease in a woman during pregnancy with penicilin allergy?





IBM Watson – services



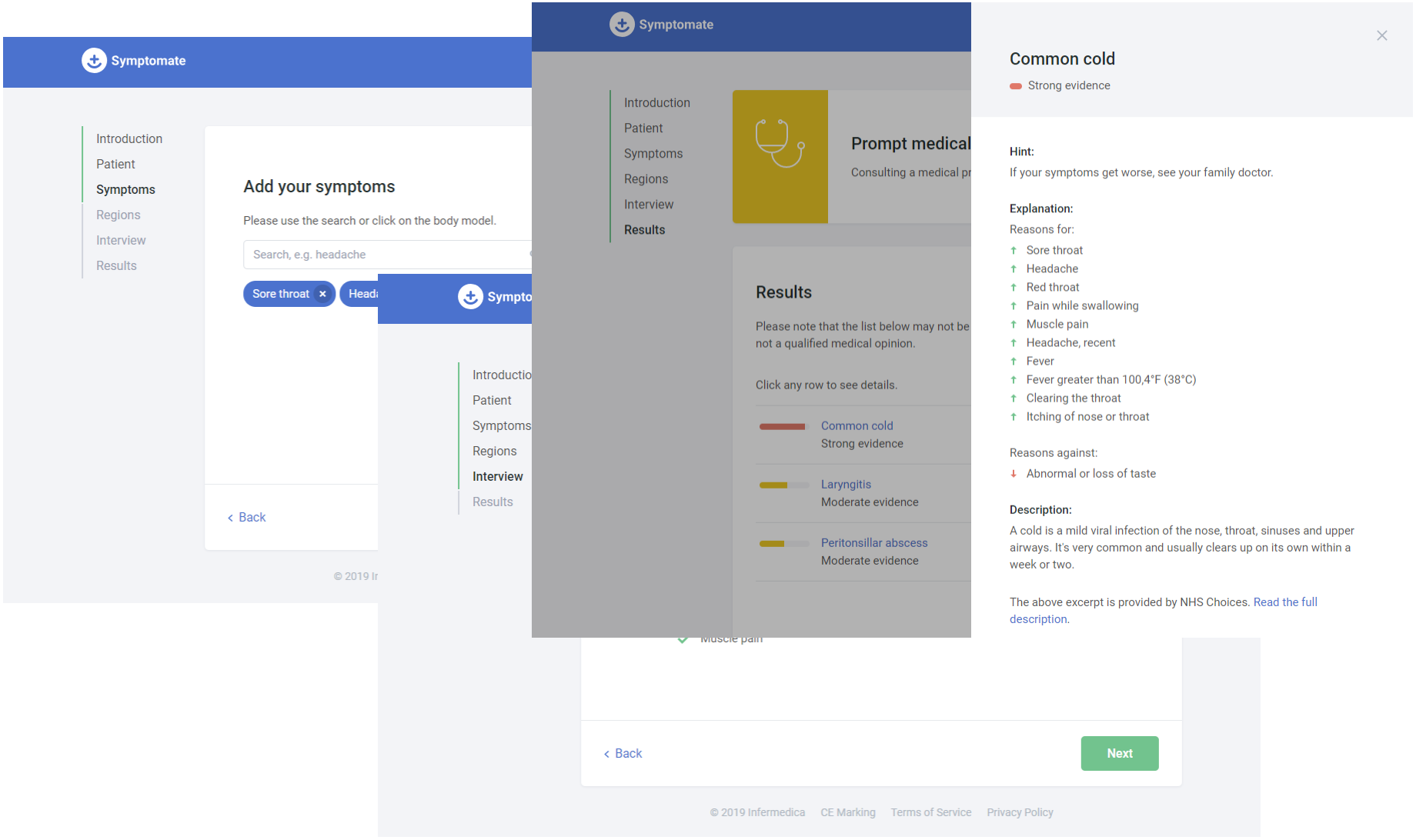
https://www.ibm.com/watson/developercloud/services-catalog.html
https://conversation-demo.mybluemix.net/
https://personality-insights-livedemo.mybluemix.net/
https://www.ibm.com/watson/developercloud/visual-recognition.html
https://natural-language-understanding-demo.mybluemix.net/

Symptomate (2013 – now)

- Polish (!) system for supporting diagnosis (→ symptom checker)
- Decision model based on Bayesian networks (10 models for major medical specialties)
- Additional expert rules to control the process of asking questions and collecting data
- Advanced algorithms for combining multiple Bayesian networks to simplify them and to ensure quick response time (1 sec.)
- System available as web and mobile application for non-medical users, also controlled through voice and chat-bot
- Diagnostic-oriented API available as a separate service

http://symptompate.com

Sample session in Symptomate



HELP (1975 – now)

- Active decision support functionality implemented within HIS
- Monitoring rules represented as **medical logic modules** (MLMs) → 1 rule = 1 module
  - Rules triggered by specific events (e.g., availability of new data)
  - Diversified actions – checking for drug interactions and displaying warnings, performing calculations, preparing results
- MLMs represented using a specialized and standardized (HL7) language – Arden Syntax
- MLMs have been adopted in other systems → knowledge portability, but possible "{} problem" with data models

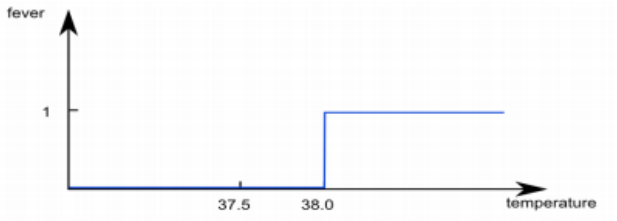
HELP

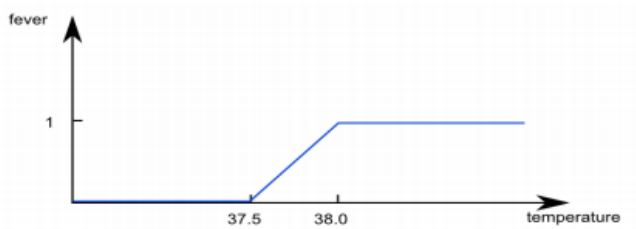
Sample MLM: warning about allergy to penicillin

```
penicillin_order :=
        event {medication_order
                        where class = penicillin};
    /* find allergies */
    penicillin_allergy :=
      read last {allergy
                where agent_class = penicillin};
    ;;
    evoke: penicillin_order ;;
    logic:
    If exist (penicillin_allergy) then conclude true;
    endif;
    ;;
    action:
    write
    "Caution, the patient has the following allergy to penicillin documented:"
    || penicillin_allergy ;;
```

Musen, M. , Shahar, Y. , Shortliffe, E. H. (2006). Clinical decision support systems. W: Shortliffe, E.H., Cimino, J. (red.): *Biomedical Informatics. Computer Applications in Health Care and Biomedicine*, Springer, 698-736.

Fuzzy rules in Arden Syntax





- **Usual** Arden Syntax

```
fever_limit := 38;
temperature := 37.9;

message := "patient has no fever";
IF temperature > fever_limit THEN
   message := "patient has fever";
END IF
```

  - Result message: "patient has no fever"
  - Borderline case is not detected

- **Fuzzy** Arden Syntax

```
fever_limit := FUZZY SET (37.5,0), (38,1);
temperature := 37.9;

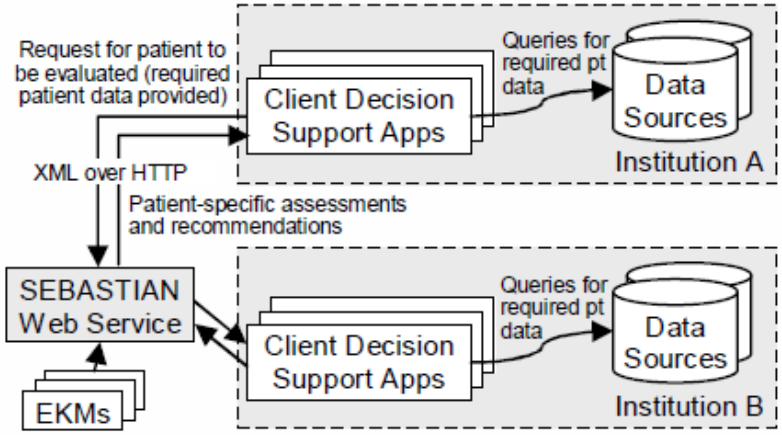
message := "patient has no fever";
IF temperature > fever_limit THEN
   message := "patient has fever";
END IF
```

  - Result message: "patient has fever" (with applicability 0.8)

SEBASTIAN (2005)

System for Evidence-Based Advice through Simultaneous Transaction with an Intelligent Agent across a Network

- Generic infrastructure based on web services allowing for constructing diversified CDSS

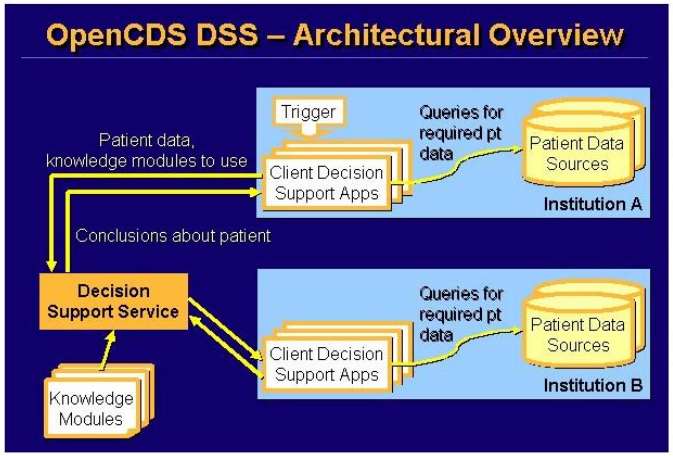


- Specific clinical knowledge embedded in **executable knowledge modules** *(*EKMs)
- Reliance on standards (HL7 RIM, UMLS)

- Continued as OpenCDS – an open implementation of the proposed infrastructure

Kawamoto, K. , Lobach, D. (2005). Design, implementation, use, and preliminary evaluation of SEBASTIAN, a standards-based Web service for clinical decision suport. *AMIA Annu Symp*, 380-384.

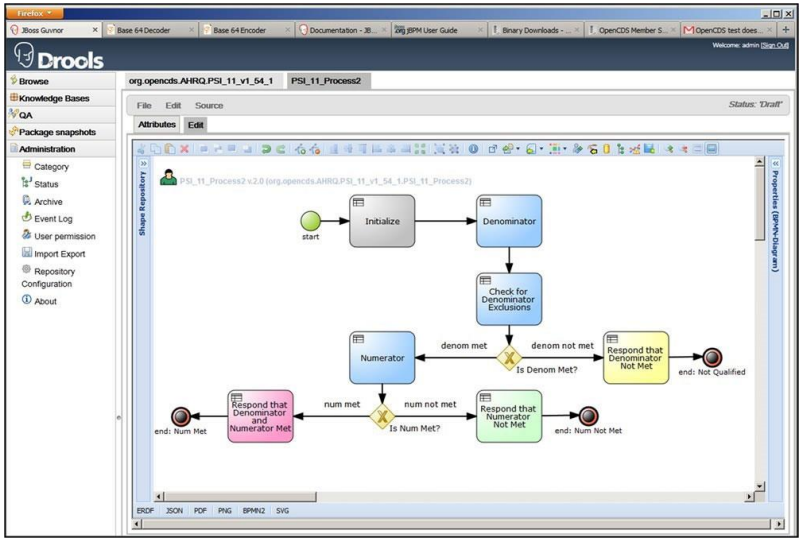
OpenCDS (2011 – now)



http://www.opencds.org

OpenCDS

- Relies on adopted standards tools
  - HL7/OMG DSS interface
  - HL7 vMR (*virtual medical record*) and FHIR
- Includes open tools to build specific EKMs
  - JBoss Drools – rule-based reasoning (forward, backward)
  - JBoss jBPM – workflow (BPMN) modeling and execution
  - Appleton DTS – terminology server



HL7/OMG DSS interface

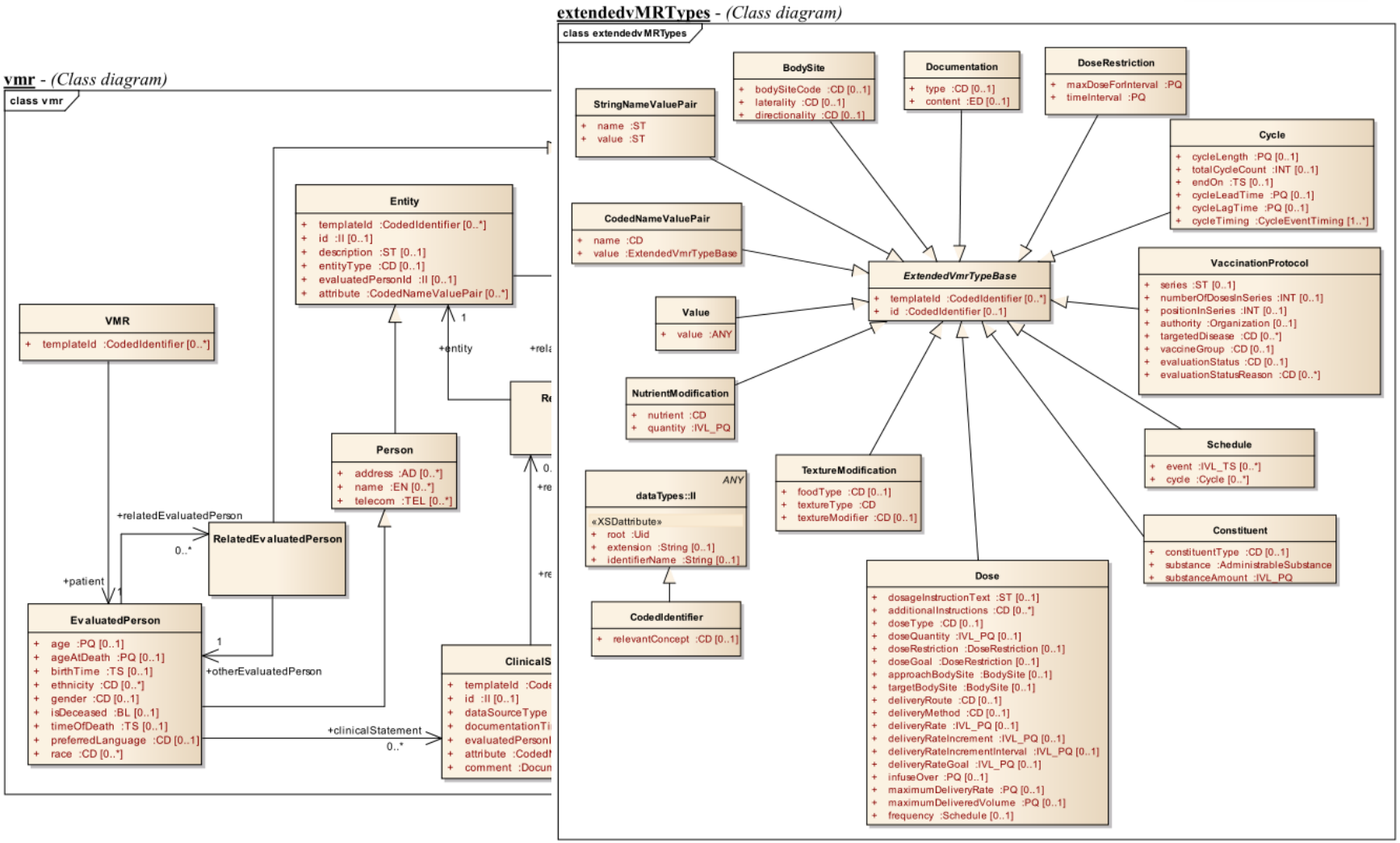
Web-based (SOAP) standard for decision support services

1. Metadata discovery (`listProfiles`, `describeProfile`, …)
   - Checking for available profiles and their descriptions
   - Profile determines what methods are available at lower levels
2. Query (`listKMs`, `findKMs`, `getKMDataRequirements`, …)
   - Checking for available EKMs and searching for specific EKMs
   - Checking input and output requirements of specific EKMs
3. Evaluation (`evaluate`, `evaluateInteractively`, …)
   - Applying a specific EKM to a given patient (establishing a suggestion)
   - May result final or intermediate results (iterative evaluation) with subsequent data requirements

HL7 Virtual Medical Record (vMR)

- Data model limited to elements relevant for clinical decision making and support (unifying view on data)
- Demographic and clinical data, decision suggestions
- Based on HL7 V3, with many simplifications
  - No structural attributes (`mood code`, `negation`) → specialized classes introduced instead (`AppointmentRequest`, `MissedAppointment`)
  - No nested structures, e.g., a problem and embedded observations confirming its appearance → flat data structures instead
  - No more `nullFlavor` – missing data are not recorded

HL7 vMR – selected class diagrams



PERSPECTIVES AND CHALLENGES FOR CDSS

Perspectives and challenges

- **Improve the human-computer interface**
- Use text data to drive decision support
- Summarize patient level information
- **Combine recommendations for patients with comorbidities**
- Mine large clinical databases to create new CDSSs
- Create an architecture for sharing executable CDSS modules and services
- Create internet-accessible clinical decision support repositories (this calls for standards for knowledge and data representation)

„A bit awkward to use at the bedside b/c I don't care to have my nose in the computer as I'm trying to interact with patients (for the same reason I don't take full notes during interaction; I write afterwards at the nursing station).

Sittig, D. F., Wright, A., Osheroff, J. A., Middleton, B., Teich, J. M., Ash, J. S., Campbell, E., et al. (2008). Grand challenges in clinical decision support. *J of Biomed Inform*, *41*(2), 387–392.