

### Personal History

- Interest in Knowledge Representation
  - How do you write down in a computer real-world knowledge that is useful for
    - inference
    - learning
    - consistency checking
  - Special types of knowledge
    - Likelihood
    - Time
    - Space
    - Belief

# Artificial Intelligence in Medicine

Peter Szolovits Prof. of EECS, HST CSAIL Clinical Decision Making Group http://medg.csail.mit.edu

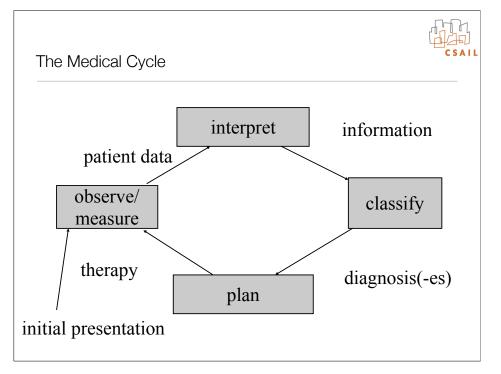
6.034 April 7, 2010

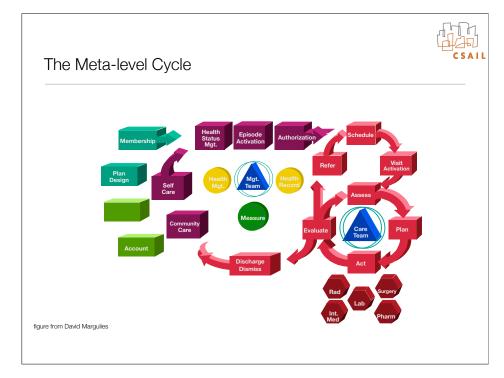


E E C S

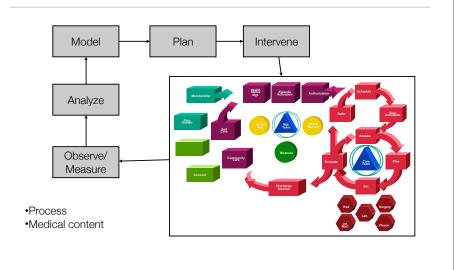
### What do Doctors do?

- Three classical medical tasks
  - diagnosis
    - abduction: reasoning from effects to causes
  - prognosis
    - predictive models
  - therapy
    - · choose actions, in light of diagnosis and prognosis
- Need to choose diagnostic tests makes it more like therapy
- Additional contemporary tasks
  - monitoring
  - prevention
  - public health and epidemiology
  - · biomedical research

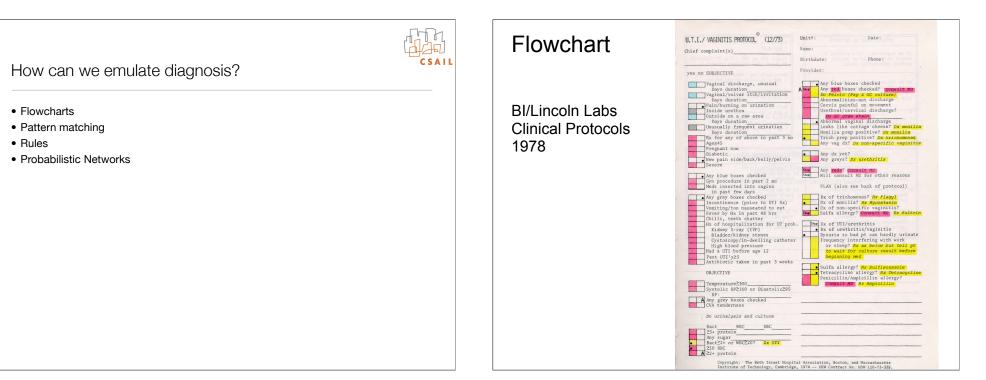




### The "Learning Health Care System"

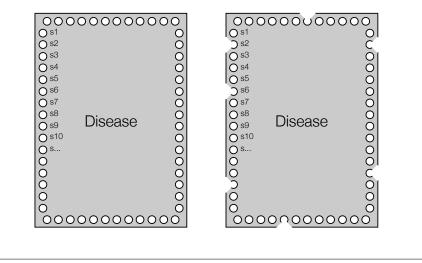


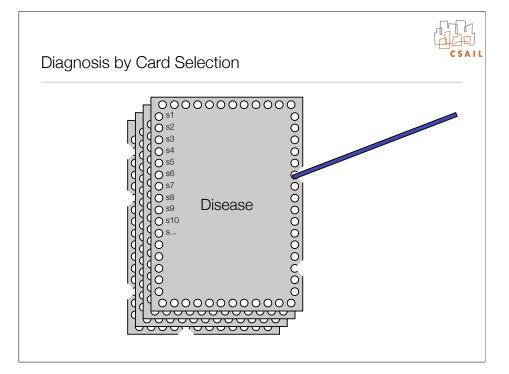
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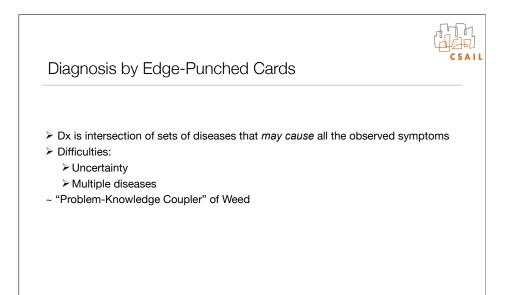


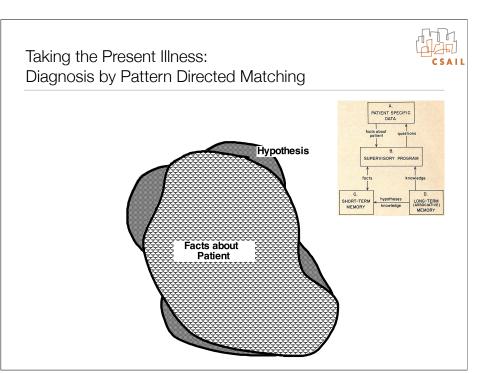
Simple Representation of Disease/Symptom Associations

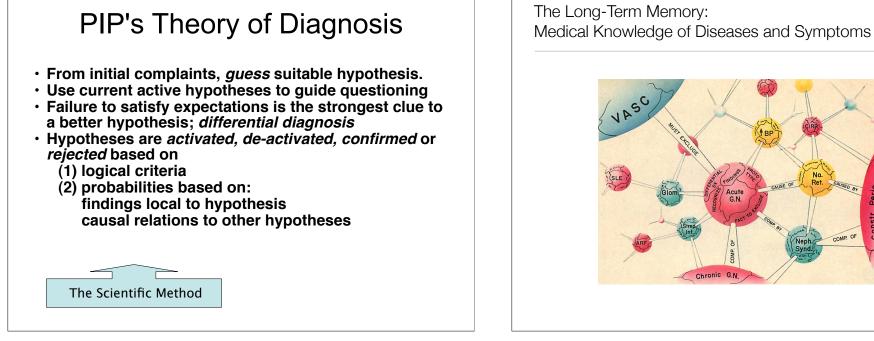




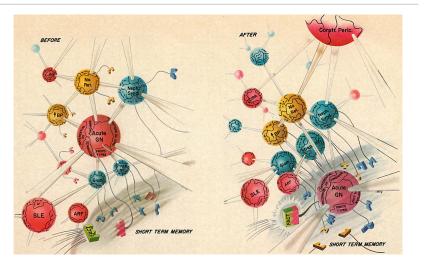


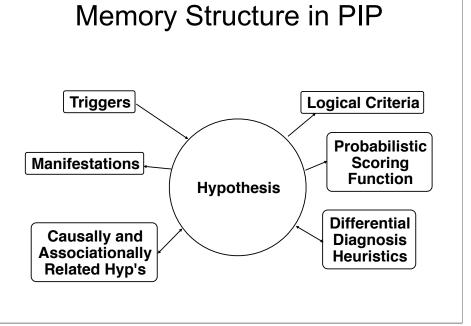
















# PIP's Model of Nephrotic Syndrome

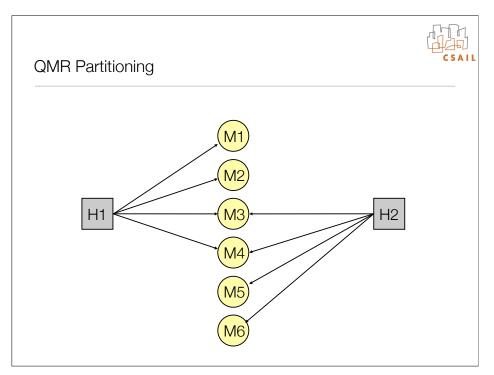
NEPHROTIC SYNDROME, a clinical state FINDINGS: 1\* Low serum albumin concentration 2. Heavy proteinuria 3\* >5 gm/day proteinuria 4\* Massive symmetrical edema 5\* Facial or peri-orbital symmetric edema 6. High serum cholesterol 7. Urine lipids present IS-SUFFICIENT: Massive pedal edema & >5 gm/day proteinuria MUST-NOT-HAVE: Proteinuria absent SCORING .... MAY-BE-CAUSED-BY: AGN, CGN, nephrotoxic drugs, insect bite, idiopathic nephrotic syndrome, lupus, diabetes mellitus MAY-BE-COMPLICATED-BY: hypovolemia, cellulitis MAY-BE-CAUSE-OF: sodium retention DIFFERENTIAL DIAGNOSIS:

neck veins elevated → constrictive pericarditis ascites present → cirrhosis pulmonary emboli present → renal vein thrombosis

# A Case of a Middle-Aged Woman with Pedal Edema (swollen feet)

- PRESENTING PROBLEM: A MIDDLE AGED WOMAN WITH PEDAL EDEMA.
- THE CASE CAN BE SUMMARIZED AS FOLLOWS:
  - THIS IS A MIDDLE-AGED WOMAN, WHO HAS PEDAL EDEMA, WHICH IS NOT-PAINFUL, NOT-ERYTHEMATOUS, PITTING, SYMMETRICAL. 4+, WITHOUT-TEMPORAL-PATTERN, OCCASIONAL AND FOR-WEEKS. SHE DOES NOT HAVE DYSPNEA. SHE HAS HEAVY ALCOHOL CONSUMPTION. SHE HAS JAUNDICE. SHE HAS PAINFUL HEPATOMEGALY. SHE HAS SPLENOMEGALY. SHE HAS ASCITES. SHE HAS PALMAR ERYTHEMA. SHE HAS SPIDER ANGIOMATA. SHE DOES NOT HAVE PAROTID ENLARGEMENT. SHE HAS MODERATELY-ELEVATED. DIRECT-AND-INDIRECT BILIRUBIN. SHE HAS PROLONGED PROTHROMBIN TIME. SHE HAS MODERATELY-ELEVATED SGPT. SHE HAS MODERATELY-ELEVATED SGOT. SHE HAS MODERATELY-ELEVATED LDH. SHE HAS NOT-RECEIVED BLOOD TRANSFUSIONS. SHE HAS NOT-EATEN CLAMS. SHE DOES NOT HAVE ANOREXIA. SHE HAS MELENA. SHE DOES NOT HAVE HEMATEMESIS. SHE HAS LOW SERUM IRON. SHE HAS ESOPHAGEAL VARICES.
- DIAGNOSES THAT HAVE BEEN ACCEPTED ARE: ALCOHOLISM AND GI BLEEDING.
- THE LEADING HYPOTHESIS IS CIRRHOSIS.

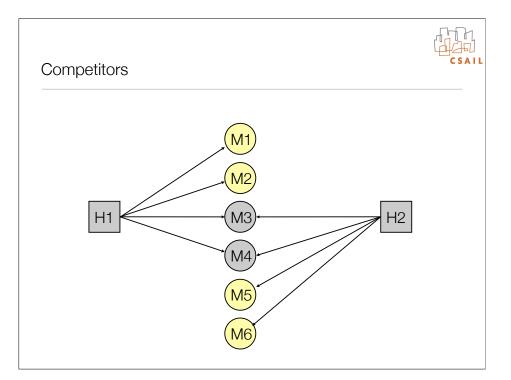
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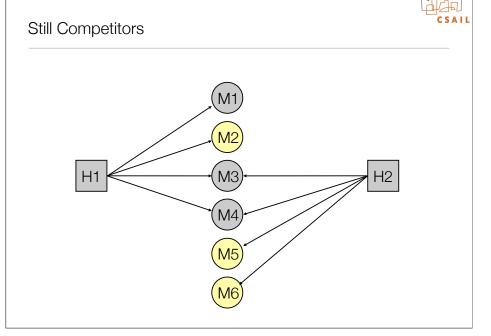


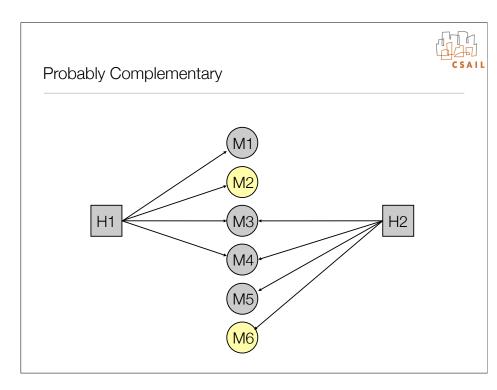
HYPOTHESES BEING CONSIDERED:

Case, continued

Hypothesis	fit of case to hypothesis	fraction of finding explained	average score
CIRRHOSIS	0.72	0.78	0.75
HEPATITIS PORTAL	0.75	0.30	0.53
HYPERTENSION	0.72	0.17	0.45
CONSTRICTIVE PERICARDITIS	0.17	0.13	0.15







### Multi-Hypothesis Diagnosis

- Set aside complementary hypotheses
- $\succ\ldots$  and manifestations predicted by them
- Solve diagnostic problem among competitors
- > Eliminate confirmed hypotheses and manifestations explained by them
- $\succ$  Repeat as long as there are coherent problems among the remaining data

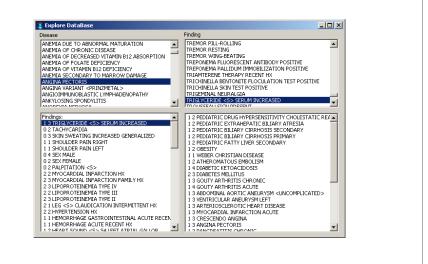


### Internist/QMR

### Knowledge Base:

- ≻956 hypotheses
- >4090 manifestations (about 75/hypothesis)
- ➤ Evocation like P(H|M)
- ➤ Frequency like P(M|H)
- >Importance of each M
- Causal relations between H's
- Diagnostic Strategy:
  - ➤Scoring function
  - ➢Partitioning
  - ➤Several questioning strategies

### QMR Database





### **QMR** Scoring

- Positive Factors
  - Evoking strength of observed Manifestations
  - Scaled Frequency of causal links from confirmed Hypotheses
- Negative Factors
  - > Frequency of predicted but absent Manifestations
  - > Importance of unexplained Manifestations
- Various scaling parameters (roughly exponential)

Exan	nple Case			CSAI
	💈 Internist Data Summary		_ 🗆 🗵	
	Internist Reconstruction Data Manifestations PRESENT:	Summary	Diagnose	
	ABDOMEN DISTENTION ABDOMEN LIDU WAVE AGE GTR. THAN SS ALXALINE MOSPHATASE BLOOD GTR. THAN 2 TIMES NORMAL AMMOREVIA ANOREVIA ASCHTIC FULID PROTEIN 3 GRAM <s> PER DL OR LESS ASCHTIC FULID ROTEIN 3 GRAM <s> PER DL OR LESS ASCHTIC FULID ROTEIN 3 GRAM <s> PER DL OR LESS BLIRUEN RUDOD CONJUGATED INCREASED BLIRUEN RUDOP FRESENT CHEST PAIN LATERAL SAVARP DEPRESSION HK DYSPAFA ARRUPT ONSFT</s></s></s>	Remove Present	1	
	Manifestations ABSENT: ALCOHUSM CHRONICL HX ASCITIC FULID OWNLASE INCREASED ASCITIC FULID OWNLASE INCREASED SACITIC FULID UCH GTR THAN 500 DIARHEA CHRONIC ESOPHAUS BARIUM MEAL VARICES FECES BLACK TARRY FEVER HEMATOCRIT BLOOD LESS THAN 35 PRESSURE VENUGS CERVICAL INCREASED ON INSPECTION STOMACH BARIUM MEAL LUCER CRATER <5> T3 RESIN UFFAIL INCREASED 14 FREE BLOOD INCREASED UREA NITROGEN BLOOD 30 TO 59 UREC ACID BLOOD INCREASED	Proven Abarah	1	
		Remove Absent		



### Initial Solution

Diagnostic Results	
oblem: -914 HEPATTHECHRONIC ACTIVE -914 HEPATTHECHRONIC ACTIVE -136 MARCY CHRONIC ACTIVE -136 MIARY CHRONIS FRIMARY -178 HEDIATRIC BILLARY CHRHOSIS FRIMARY -178 HEDIATRIC BILLARY CHRHOSIS FRIMARY	Complementary: 1439 MICCONCOAL CLORENOSIS <laennecs> 142 HEPATITIS ACUTE VIRAL 170 CHOLANGIOCARCINOMA <intrahepatic hilar="" non=""> 178 HEPATIC AMYLOIDOSIS</intrahepatic></laennecs>
	Shelf: ABDOMEN DISTENTION
xplaned: AGE GTR THAN 55 ALKAINE PHOSPHATASE BLOOD GTR THAN 2 TIMES NORMAL MOREXIA BILIRIBIN RING PROSENT BILIRIBIN RING PROSENT FROST LIGHT COLORED HADD C3> PAMMAR ERVITEMA	ARTHRUITS HX CHEST PAIN LATERAL EXACEBBATION WITH BREATHING CHEST PAIN LATERAL SHARP FECES QUALAC TEST POSITIVE PLEURAL FRICTION RUB WEIGHT INCREASE RECENT HX
MMUNOELECTROPHORESIS SERUM IGA INCREASED MMI INOFLECTROPHORESIS SERUM IGG INCREASED sent:	Askable:
JARRHEA CHRONIC EVER MEMATOCRIT BLOOD LESS THAN 35	ABDOMEN PAIN CHRONIC ABDOMEN PAIN CHRONIC ABDOMEN PAIN PERGASTRUM ABDOMEN PAIN PERGASTRUM INRELIEVED BY ANTACID ABDOMEN PAIN POINT CALL AND A ANTACID ABDOMEN PAIN NON COLICKY ABDOMEN PAIN NON COLICKY
nexplained:	ABDOMEN PAIN RIGHT UPPER QUADRANT
ABDOMEN DISTENTION BBDOMEN FLUDD WAVE MRYNONIA BLOOD INCERASED ARTHRITIS HX SICITIC FLUID PROTEIN 3 GRAM <s> PER DL OR LESS SICITIC FLUID WEC 100 TO 500</s>	ABDOMEN TENDERNESS PRESENT ABDOMEN TENDERNESS SICHT UPPER QUADRANT ACTIVATED PARTIAL THROMBOPLASTIN TIME INCREASED AGE 16 TO 25 AGE 26 TO 55 ALBUMIN SERUIN DECREASED ALBUMIN SERUIN DECREASED ALBUMIN SERUIN DECREASED ALBUMIN SERUIN DECREASED

# Symptom Clustering for Multi-Disorder Diagnosis



**CSAI** 

HKN

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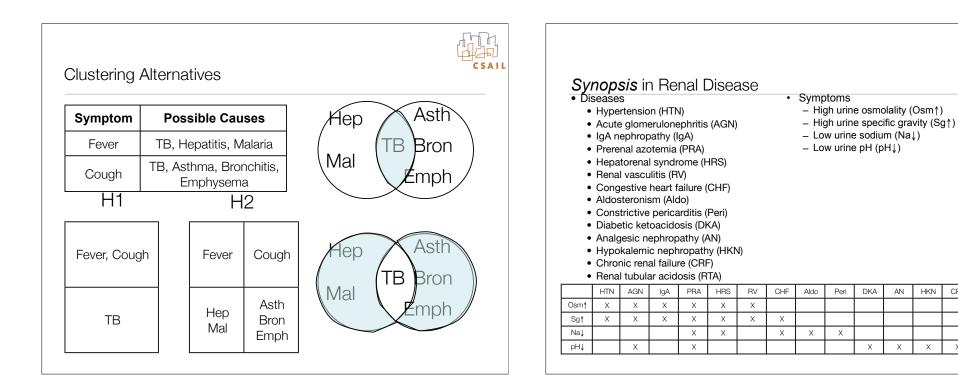
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RTA

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### — Tom Wu, Ph.D. 1991 Assume a bipartite graph representation of diseases/symptoms Given a set of symptoms, how to proceed? d1 ► s1 If we could "guess" an appropriate clustering of the symptoms so that each cluster has a single cause ... d2 s2 (s2, s3, s7) (s1) (s5, s9) s3 dk d3 d5 d1 d7 d6 d2 sn d8 d4 d9 ... then the solution is (d5, d6) x (d3, d7, d8, d9) x (d1, d2, d4)



40

CSAIL

## After Osm↑

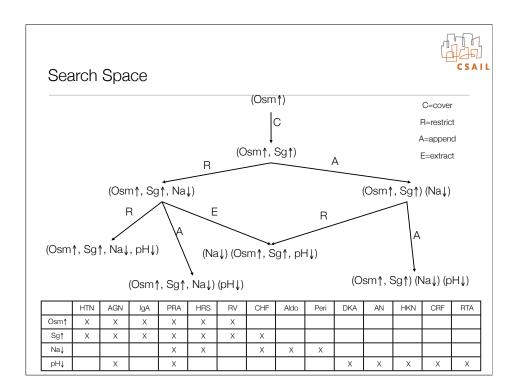


Add Sg↑

	Osm↑													
	HTN AGN IgA PRA HRS RV													
	HTN	AGN	lgA	PRA	HRS	RV	CHF	Aldo	Peri	DKA	AN	HKN	CRF	RTA
Osm↑	HTN X	AGN X	lgA X	PRA X	HRS X	RV X	CHF	Aldo	Peri	DKA	AN	HKN	CRF	RTA
Osm† Sg†							CHF X	Aldo	Peri	DKA	AN	HKN	CRF	RTA
	Х	х	Х	х	х	Х		Aldo	Peri X	DKA	AN	HKN	CRF	RTA

### Cover Osm↑, Sg↑ HTN AGN ΙgΑ PRA HRS RV HTN AGN lgA PRA HRS RV CHF Aldo Peri DKA AN HKN CRF RTA Osm∱ Х Х Х Х Х Х Х Sg† Х Х Х Х Х Х Na↓ Х Х Х Х Х Х pH↓ Х Х Х Х Х Х

CSAIL



Add Na↓

	Re	estri	ct				Append								
	Osm†, Sg†, Na↓						Osm∱, Sg↑				Na↓				
		PRA HRS			or		HTN AGN IgA RV				Aldo CHF Peri				
	HTN	AGN	lgA	PRA	HRS	RV	CHF	Aldo	Peri	DKA	AN	HKN	CRF	RTA	
Osm↑	Х	Х	Х	Х	Х	Х									
Sg↑	Х	Х	Х	Х	Х	Х	Х								
Na↓				Х	Х		Х	Х	Х						
pH↓		Х		Х						X	Х	Х	Х	Х	



## Symptom Clustering is Efficient

- Like in any "planning island" approach, reducing an exponential problem to several smaller exponential problems vastly improves efficiency, if it captures some insight into the problem.
- Wu's algorithm (SYNOPSIS) will keep a compact encoding even if it overgenerates slightly.
  - E.g., suppose that of the set of diseases represented by (d5, d6) x (d3, d7, d8, d9) x (d1, d2, d4), d6 x d8 x d1 is not a candidate. To represent this precisely would require enumerating the 23 valid candidates. Instead, the factored representation is kept.
- In a diagnostic problem drawn from a small subset of the Internist database,
- it is a power of 3 faster and a power of 5 more compact than standard symptom clustering.
- Guide search via probabilities, if we have a reasonable model(!)

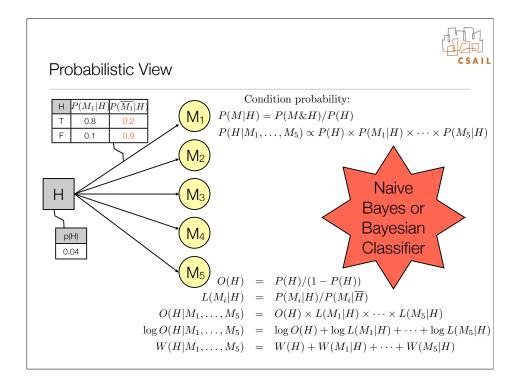
### **Reasoning Using Rules**

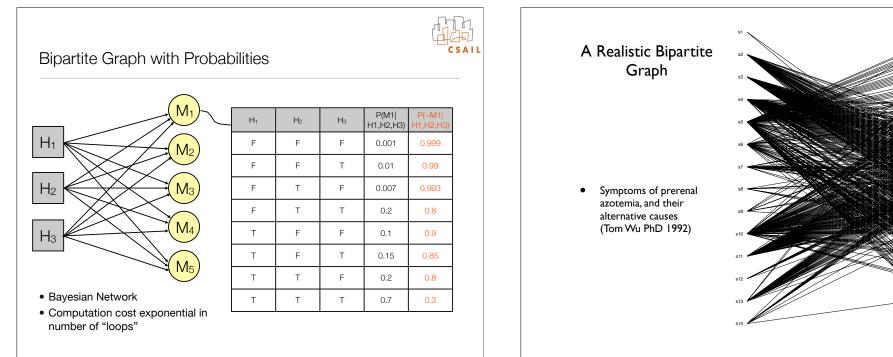
- Mycin used *backward chaining* (from conclusions back to facts) with a collection of <1000 rules
  - Domain: bacterial infections
- E.g., RULE037
  - If the organism
    - stains grampos
    - has coccus shape
    - grows in chains
  - Then there is suggestive evidence (.7) that it is streptococcus.

### How Mycin Works

- To find out a fact
  - If there are rules that can conclude it, try them
  - Ask the user
- To "run" a rule
  - Try to find out if the facts in the premises are true
  - If they all are, then assert the conclusion(s), with a suitable certainty
- Backward chaining from goal to given facts
- ▲ Dynamically traces out behavior of (what might be) a flowchart
  - Information used everywhere appropriate
  - ▲ Single expression of any piece of knowledge

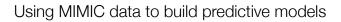






### What to do with Tons of Data?

- Partners Healthcare has ~4M records of previously-treated patients
- Mayo Clinic has ~60M discharge summaries
- We have 30K detailed records on patients in the ICU (Intensive Care Unit)
- Surely, these must be useful for *something*!
- State<sub>k</sub>(patient<sub>i</sub>)=f<sub>k</sub>(features<sub>patienti</sub>)
  - We can learn  $f_k$  from data
  - Use it to predict Statek for future patients
- What are useful Statek?
  - Death
  - Specific diseases
  - Effectiveness of particular therapies
  - Optimal timing of various interventions
  - ...



Mortality

### Caleb Hug, PhD 2009 http://dspace.mit.edu/handle/1721.1/46690

- Comparison to SAPS II
- Stationary Daily Acuity Score
- Daily Acuity Scores (one for each day *n* of ICU stay)
- Real-time Acuity Scores
- Secondary Outcomes
  - Weaning from Vasopressors
  - Weaning from Intraortic Balloon Pump
  - Onset of Septic Shock
  - Acute Kidney Injury
  - Weaning from Mechanical Ventilator
  - Tracheotomy Insertion
  - First response to Vasopressor Reduction





Arterial Base Excess

5 10 15 20 25

Hours Between Art BE Me

### Cleaning the data-half the research time

### • Missing values

- Some values are not measured for some clinical situations
- Failures in data capture process
- Episodically measured variables
- Unclear/undefined clinical states
- Imprecise timing of meds, ...
- Partially measured i/o
- Proxies: e.g., which ICU⇒what disease
- Derived variables: integrals, slopes, ranges, frequencies, etc.
- Transformed variables: square root, log, etc.
- Select subset of data with enough data!

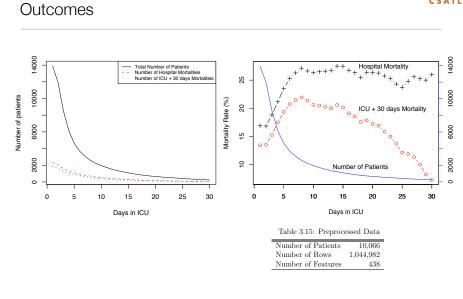




Table 4.1: SAPS II Variables	
Variable	Max Points
Age	18
Heart rate	11
Systolic BP	13
Body temperature	3
PaO2:FiO2 (if ventilated or continuous	11
positive airway pressure)	
Urinary output	11
Serum urea nitrogen level	10
WBC count	12
Serum potassium	3
Serum sodium level	5
Serum bicarbonate level	6
Bilirubin level	9
Glasgow Coma Score <sup>a</sup>	26
Chronic diseases	17
Type of admission	8

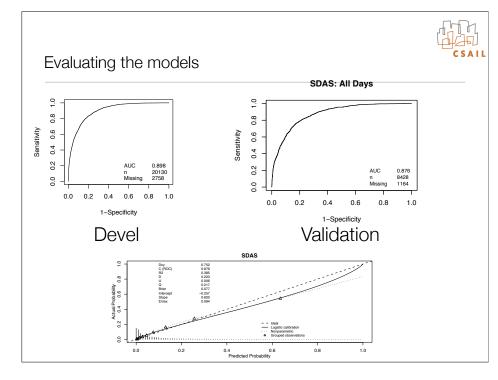
 $^a\mathrm{If}$  the patient is sedated, the estimated GCS prior to sedation

### Many univariate analyses

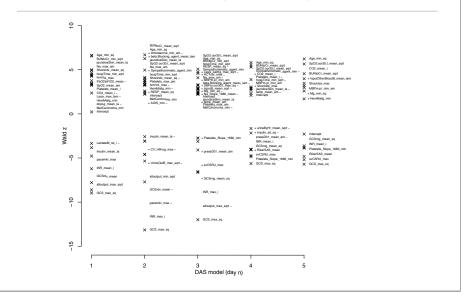
Obs Max Deriv Model	IR. df.	P C	Dxv	Obs Max Deriv Model L.R.	d.f. P	С	Dxy
	15.11 30	0 0.893	0.785	20130 3e-10 5619.28	35 0	0.898	0.797
Gamma Tau-a	R2 Brier	0 0.095	0.765	Gamma Tau-a R2	Brier		
	0.439 0.076			0.798 0.177 0.456	0.074		
0.787 0.176	0.439 0.076						
					Coef S.E. -0.0064668 5.032e-04	Wald Z P	
	Coef S.E.	Wald Z P		GCS_max_sq INR mean i	-0.0064668 5.032e-04 -1.8734049 1.458e-01		
NR_mean_i	-1.795e+00 1.423e-01			pacemkr max	-0.9337190 1.179e-01		
CS_max_sq	-7.485e-03 6.000e-04			svCSRU max	-0.9137522 1.250e-01		
lutputB_60_mean_sqrt	-6.561e-02 6.885e-03			RikerSAS_mean	-0.3430971 5.151e-02		
acemkr_max	-1.084e+00 1.183e-01	-9.16 0.0000		Platelets_Slope_1680_min	-5.8856843 8.839e-01	-6.66 0.0000	
vCSRU_max	-9.516e-01 1.208e-01			urineByHr_mean_sqrt	-0.0584113 9.453e-03	-6.18 0.0000	
CSrdv_mean	-1.138e-01 1.528e-02	-7.45 0.0000		GCSrdv_mean	-0.0902717 1.552e-02		
ressD01_mean_am	-2.774e+00 3.893e-01	-7.13 0.0000		GCSrng_min_am	-0.0812232 1.459e-02		
latelets_Slope_1680_min	-5.493e+00 8.615e-01	-6.38 0.0000		pressD01_mean_am	-1.6132643 3.005e-01		
ressD01_sd_sq	-5.085e+00 8.678e-01	-5.86 0.0000		CV_HRrng_max Insulin_sd_sq	-0.0061979 1.216e-03 -2.1686950 4.372e-01		
edatives_mean_sq	-4.375e-01 8.455e-02			alloutput_max_la	-0.0890330 2.265e-02		
al24 max	-4.493e-05 1.222e-05	-3.68 0.0002		MetCarcinoma min	0.4468763 1.567e-01		
V_HRrng_max	-3.267e-03 1.083e-03	-3.02 0.0026		WBC_mean_am	0.0147036 5.149e-03		
intercept	4.292e-01 4.085e-01	1.05 0.2934		AIDS_min	0.5954305 1.991e-01	2.99 0.0028	
	4.292e=01 4.085e=01 3.523e+00 1.113e+00	3.17 0.0015		Intercept	1.5314512 4.529e-01	3.38 0.0007	
lilrinone_perKg_min_sq				MBPm.pr_min_am	1.4601630 3.518e-01		
.OSBal_max	2.247e-05 5.703e-06	3.94 0.0001		HemMalig_min	0.6032027 1.212e-01		
rmVA_max	3.410e-01 6.767e-02	5.04 0.0000		RESP_mean_sq	0.0006615 1.324e-04		
BPm.pr_min_am	1.904e+00 3.711e-01	5.13 0.0000		hrmVA_max Pa02toFi02 mean	0.3520834 6.823e-02 0.2672376 4.336e-02		
lg_min_sq	1.067e-01 1.798e-02	5.93 0.0000		Na mean am	0.2672376 4.336e=02 0.0549066 8.506e=03		
eta.Blocking_agent_mean_la		6.11 0.0000		Mg_min_sq	0.1173220 1.815e-02		
a_mean_am	5.214e-02 8.415e-03	6.20 0.0000		ShockIdx max	0.5742182 8.853e-02	6.49 0.0000	
echVent_mean_sq	7.183e-01 1.047e-01	6.86 0.0000		Platelets_mean_i	24.0719462 3.560e+00	6.76 0.0000	
ESP_mean_sq	9.226e-04 1.293e-04	7.13 0.0000		hospTime_min_sqrt	0.0057514 8.158e-04	7.05 0.0000	
latelets_mean_i	2.512e+01 3.512e+00	7.15 0.0000		day_min_sq	0.0170075 2.372e-03		
asix max lam	2.550e-01 3.457e-02	7.38 0.0000		jaundiceSkin_mean_la	0.1469141 2.045e-02		
02_mean_i	2.038e+01 2.741e+00	7.43 0.0000		CO2_mean_i	19.3845272 2.682e+00		
aundiceSkin_mean_la	1.523e-01 2.014e-02	7.56 0.0000		Lasix_max_lam beta.Blocking_agent_mean_lam	0.2523702 3.444e-02		
cospTime_min_sqrt	6.860e-03 7.939e-04	8.64 0.0000		Sympathomimetic_agent_min	0.2918077 3.923e=02 0.8576883 9.254e=02		
ressorSum.std_mean_sqrt	7.758e-01 7.225e-02	10.74 0.0000		Sp02.oor30.t mean sort	0.4059329 4.128e-02		
pD2.oor30.t_mean_sqrt	4.929e-01 4.095e-02	12.04 0.0000		BUNtoCr_min_sqrt	0.2829088 2.348e-02		
	4.929e-01 4.095e-02 2.867e-01 2.323e-02	12.34 0.0000		Age_min_sq	0.0002601 1.495e-05	17.40 0.0000	
UNtoCr_min_sqrt .ge_min_sq	2.258e-04 1.450e-05						

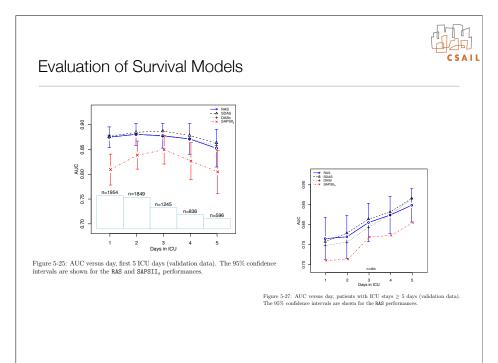


CSAL



### Selected features for each day of ICU stay





### "There's Gold in Them Thar Hills"



• Federal investment of ~\$45B in healthcare IT

• Strong pressures to make healthcare more efficient



CSAII