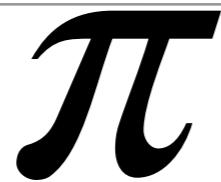




Differential Diagnosis

March 14, 2019



“Diagnosis is the identification of the nature and cause of a certain phenomenon”

“differential diagnosis is the distinguishing of a particular **disease** or condition from others that present similar clinical features”

—Wikipedia



Massachusetts
Institute of
Technology

Guyton's Model of Cardio-vascular Dynamics

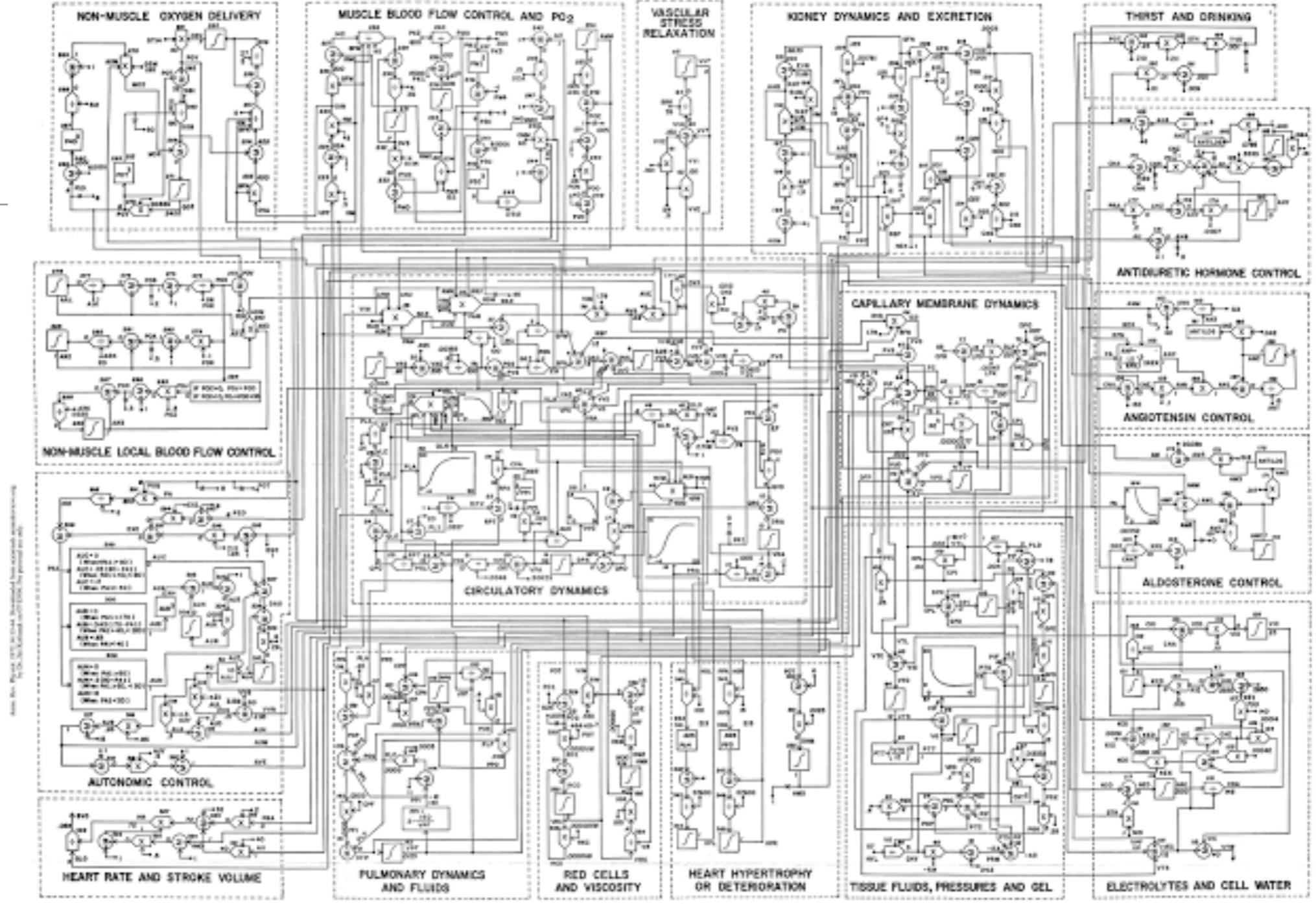


Figure 1. Block diagram of Guyton's model of cardiovascular dynamics. This figure is following: volume factors more important than pressure factors in determining arterial blood pressure is mathematical necessity; arterial factors are arbitrary; arterial blood pressure is assumed to be constant; but however, a value of 100 mmHg is assumed. Arterial blood pressure one place on the tree represents the major factor.

This following is a list of the important assumptions and simplifications made in the analysis to make it feasible:

1. Most variables are present for purposes of reference but probably have no biological significance.

2. Only variables present for purposes of reference are used.

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Models for Diagnostic Reasoning

- Flowcharts
- Based on associations between diseases and {signs, symptoms}
 - “*manifestations*” covers all observables, including lab tests, bedside measurements, ...
- Single disease vs. multiple diseases
- Probabilistic vs. categorical
- Utility theoretic
- Rule-based
- Pattern matching

Sign: Any objective evidence of disease, as opposed to a **symptom**, which is, by nature, subjective. For example, gross blood in the stool is a sign of disease; it is evidence that can be recognized by the patient, physician, nurse, or someone else. **Abdominal pain** is a symptom; it is something only the patient can perceive.

<https://www.medicinenet.com/script/main/art.asp?articlekey=5493>

Flowchart

- BI/Lincoln Labs Clinical Protocols

U.T.I./VAGINITIS PROTOCOL (12/73)

Chief complaint(s) _____

yes no SUBJECTIVE

<input type="checkbox"/>	Vaginal discharge, unusual Days duration _____
<input type="checkbox"/>	Vaginal/vulvar itch/irritation Days duration _____
<input checked="" type="checkbox"/>	Pain/burning on urination
<input type="checkbox"/>	Inside urethra
<input type="checkbox"/>	Outside on a raw area Days duration _____
<input type="checkbox"/>	Unusually frequent urination Days duration _____
<input type="checkbox"/>	Rx for any of above in past 3 mo
<input type="checkbox"/>	Age ≥ 45
<input type="checkbox"/>	Pregnant now
<input type="checkbox"/>	Diabetic
<input checked="" type="checkbox"/>	New pain side/back/belly/pelvis Severe

<input type="checkbox"/>	Any blue boxes checked
<input type="checkbox"/>	Gyn procedure in past 2 mo
<input type="checkbox"/>	Meds inserted into vagina in past few days
<input checked="" type="checkbox"/>	Any grey boxes checked
<input type="checkbox"/>	Incontinence (prior to UTI Sx)
<input type="checkbox"/>	Vomiting/too nauseated to eat
<input type="checkbox"/>	Fever by Hx in past 48 hrs
<input type="checkbox"/>	Chills, teeth chatter
<input type="checkbox"/>	Hx of hospitalization for UT prob.
<input type="checkbox"/>	Kidney X-ray (IVP)
<input type="checkbox"/>	Bladder/kidney stones
<input type="checkbox"/>	Cystoscopy/in-dwelling catheter
<input type="checkbox"/>	High blood pressure
<input type="checkbox"/>	Had a UTI before age 12
<input type="checkbox"/>	Past UTI's ≥ 3
<input type="checkbox"/>	Antibiotic taken in past 3 weeks

OBJECTIVE

<input type="checkbox"/>	Temperature ≥ 100 _____
<input type="checkbox"/>	Systolic BP ≥ 160 or Diastolic ≥ 95 BP: _____
<input checked="" type="checkbox"/>	Any grey boxes checked
<input type="checkbox"/>	CVA tenderness

Do urinalysis and culture

Bact	WBC	RBC
$\geq 3+$ protein	_____	_____
Any sugar	_____	_____
$\geq 2+$ or WBC $\geq 20?$	Dx UTI	_____
≥ 10 RBC	_____	_____
<input checked="" type="checkbox"/>	$\geq 2+$ protein	_____

Unit#: _____ Date: _____

Name: _____ Birthdate: _____ Phone: _____

Provider: _____

A Stop Any blue boxes checked
Any red boxes checked? Consult MD
Do Pelvic (Pap & GC culture)
Abnormalities-not discharge
Cervix painful on movement
Urethral/cervical discharge?
Do GC gram stain

Stop Any reds? Consult MD
Will consult MD for other reasons

PLAN (also see back of protocol)

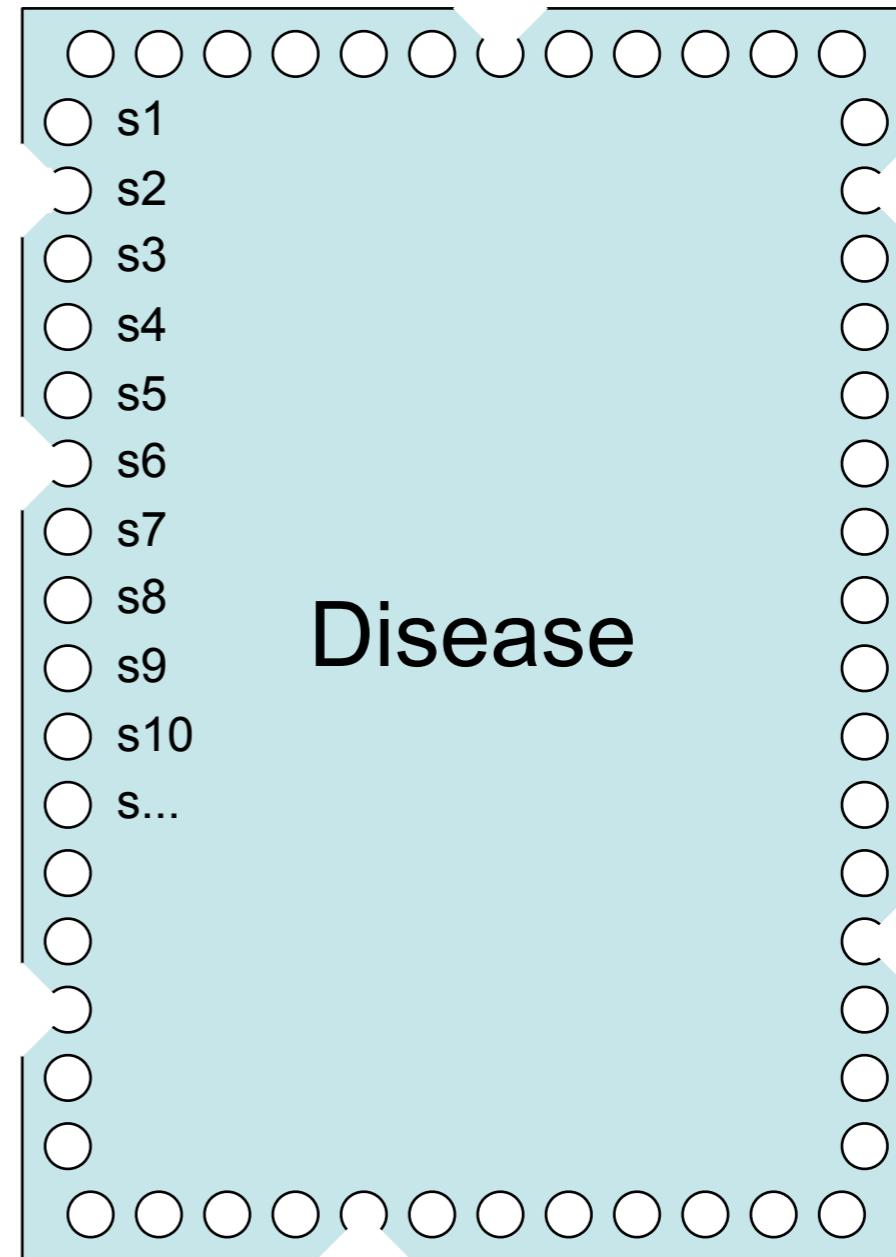
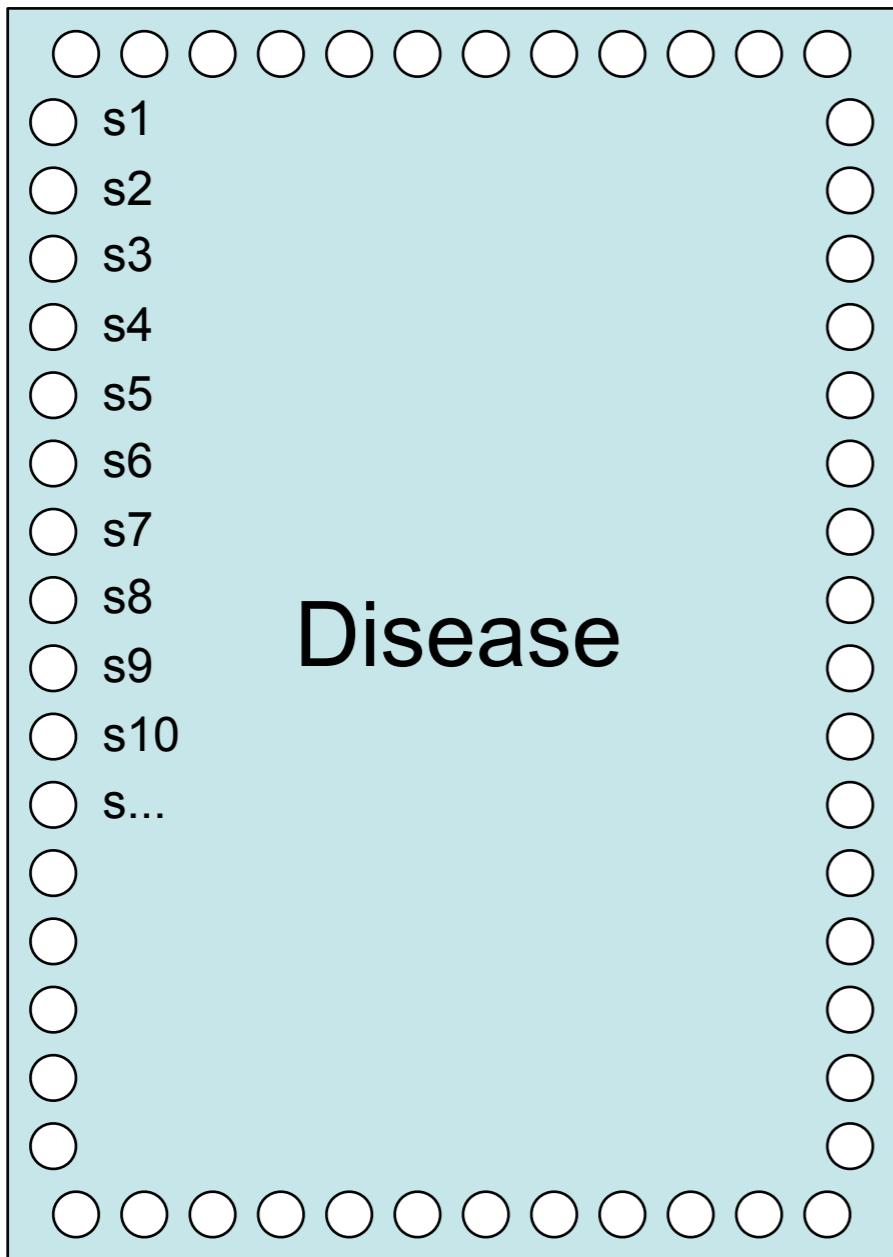
Stop Dx of trichomonas? Rx Flagyl
Dx of monilia? Rx Mycostatin
Dx of non-specific vaginitis?
Sulfa allergy? Consult MD Rx Sultrin

Stop Dx of UTI/urethritis
Dx of urethritis/vaginitis
Dysuria so bad pt can hardly urinate
Frequency interfering with work
or sleep? Rx as below but tell pt
to wait for culture result before
beginning med

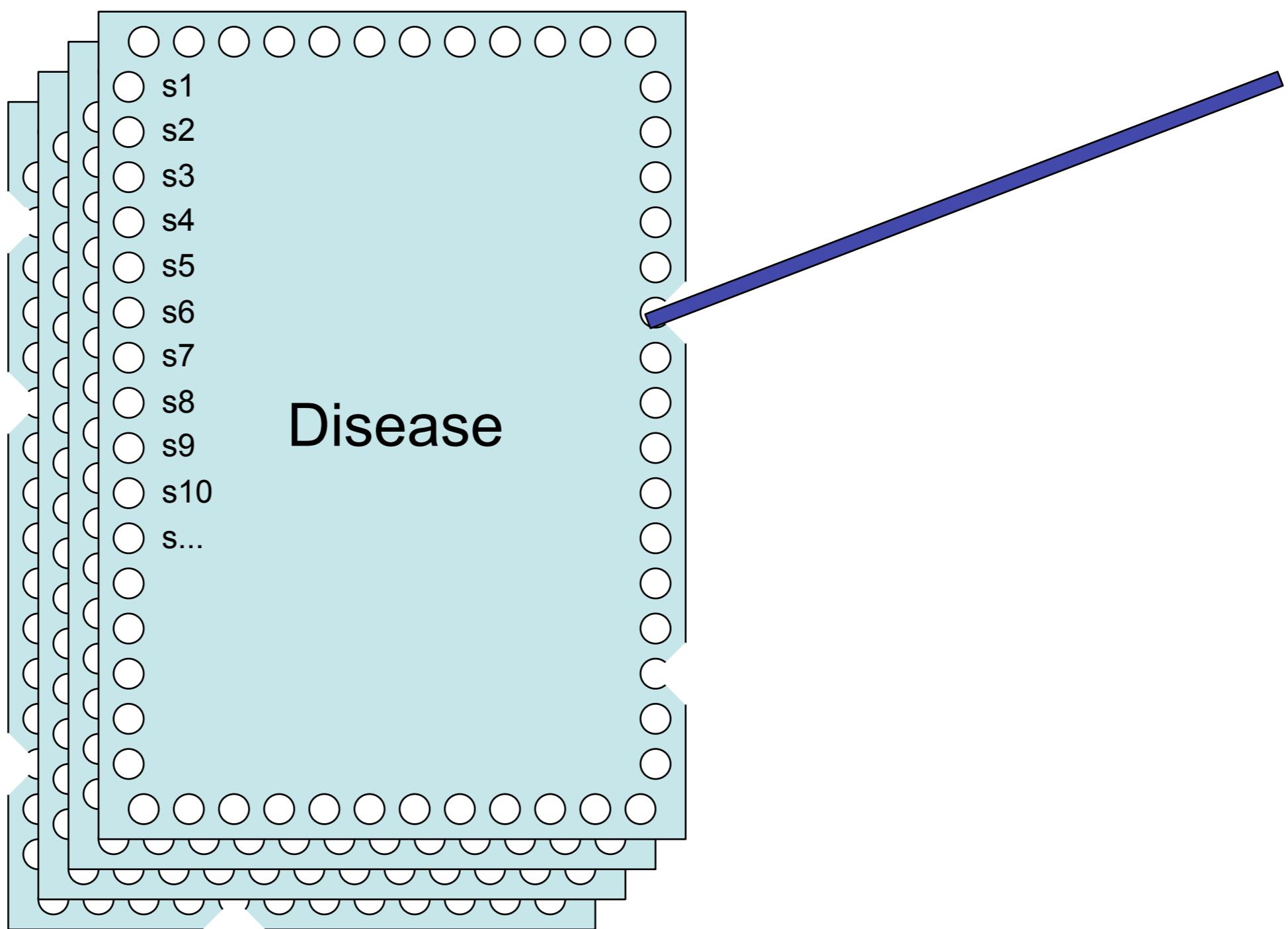
Stop Sulfa allergy? Rx Sulfisoxazole
Tetracycline allergy? Rx Tetracycline
Penicillin/Ampicillin allergy?
Consult MD Rx Ampicillin

Copyright: The Beth Israel Hospital Association, Boston, and Massachusetts Institute of Technology, Cambridge, 1974 -- HEW Contract No. HSM 110-73-335.

Disease = {signs & symptoms}

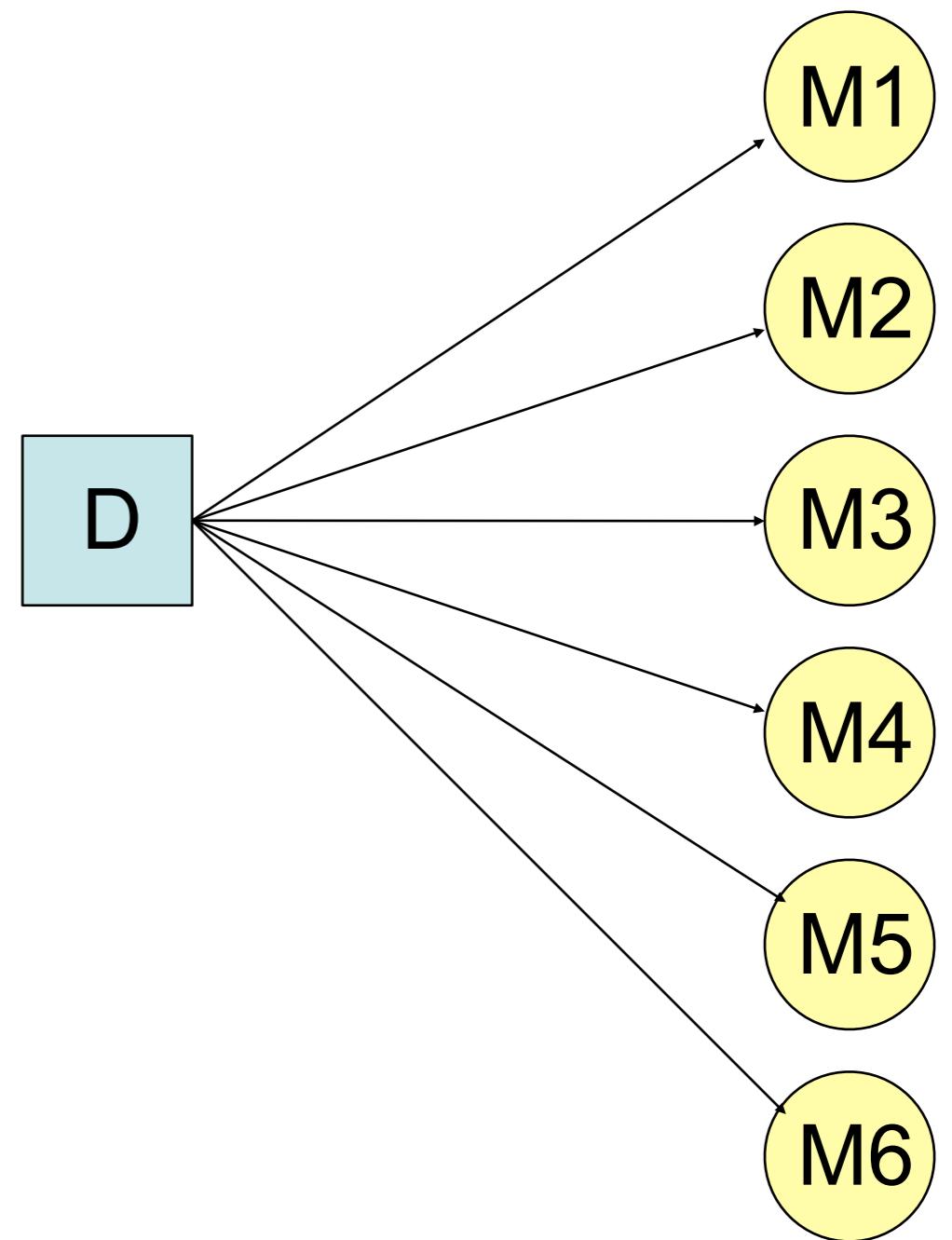


Diagnosis by Card Selection

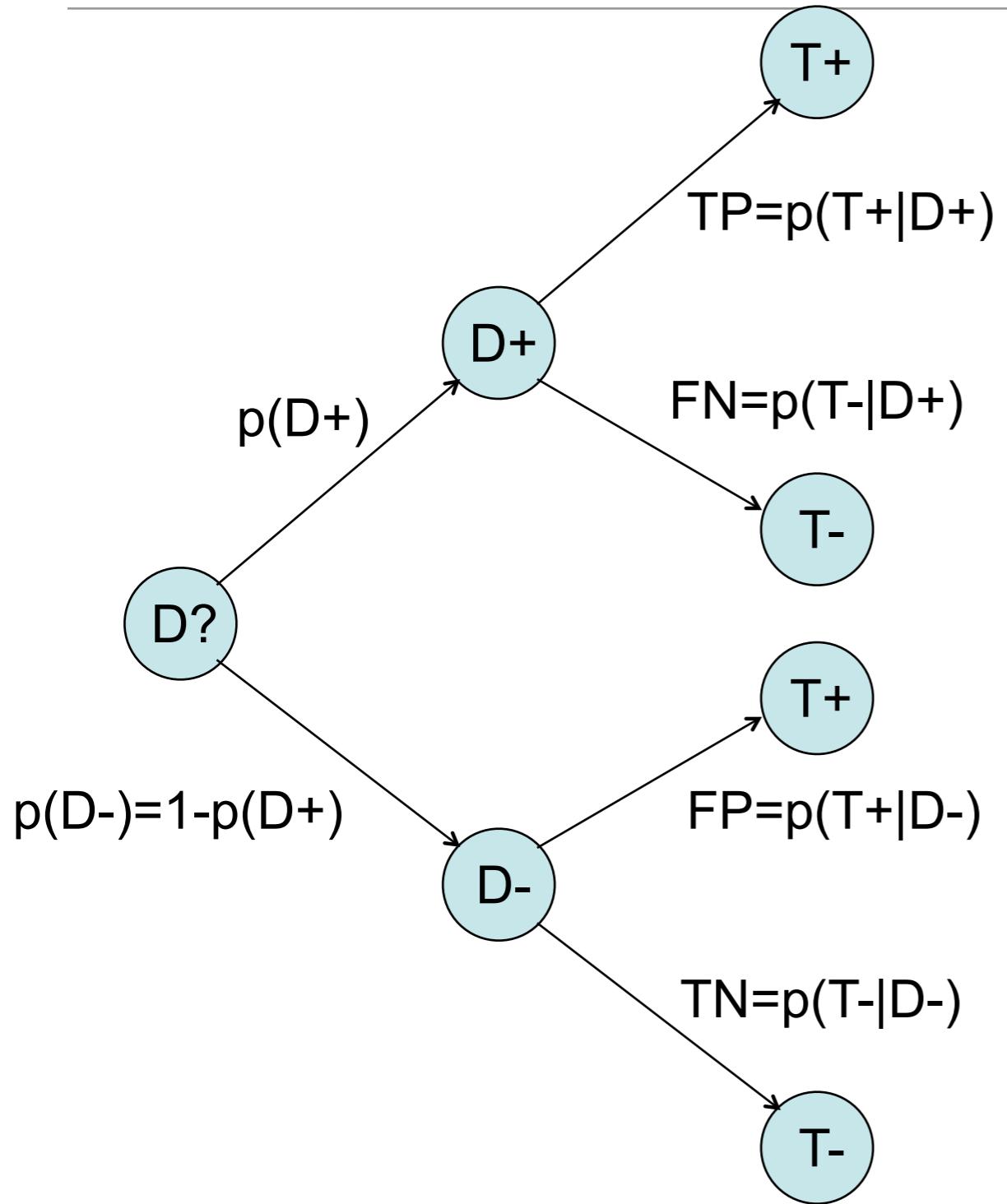


Naïve Bayes

- **Exhaustive and Mutually Exclusive** disease hypotheses (1 and only 1)
- **Conditionally independent** observables (manifestations)
- $P(D_i)$, $P(M_{ij}|D_i)$



How certain are we after a test?



Imagine $P(D+) = .001$ (it's a rare disease)
Accuracy of test = $P(T+|D+) = P(T-|D-) = .95$

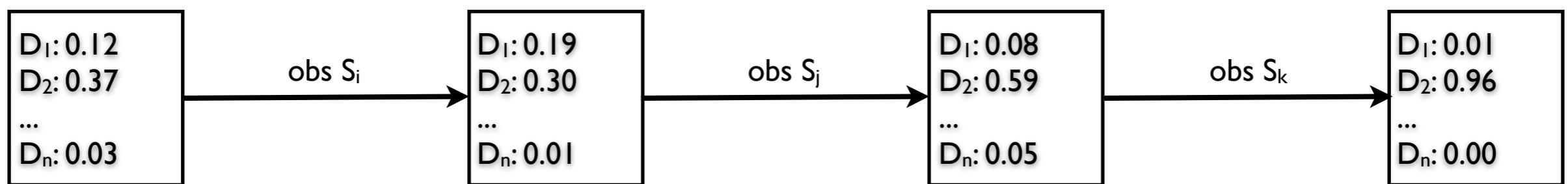


Bayes' Rule:

$$P_{i+1}(D_j) = \frac{P_i(D_j)P(S|D_j)}{\sum_{k=1}^n P_i(D_k)P(S|D_k)}$$

Diagnostic Reasoning with Naive Bayes

- Exploit assumption of conditional independence among symptoms
$$P(S_1, S_2, \dots, S_n | D_i) = P(S_1 | D_i)P(S_2 | D_i)P(S_n | D_i)$$
- Sequence of observations of symptoms, S_i , each revise the distribution via Bayes' Rule



- After the j -th observation,

$$P^j(D_i | S_1, \dots, S_j) = \frac{P^{j-1}(D_i)P(S_j | D_i)}{\sum_{i=0}^n P^{j-1}(D_i)P(S_j | D_i)}$$

Odds-Likelihood

- In gambling, “3-to-1” odds means 75% chance of success

$$O = P/(1 - P) = P/\neg P$$

- $P = 0.5$ means $O=1$
- Likelihood ratio
- Odds-likelihood form of Bayes rule

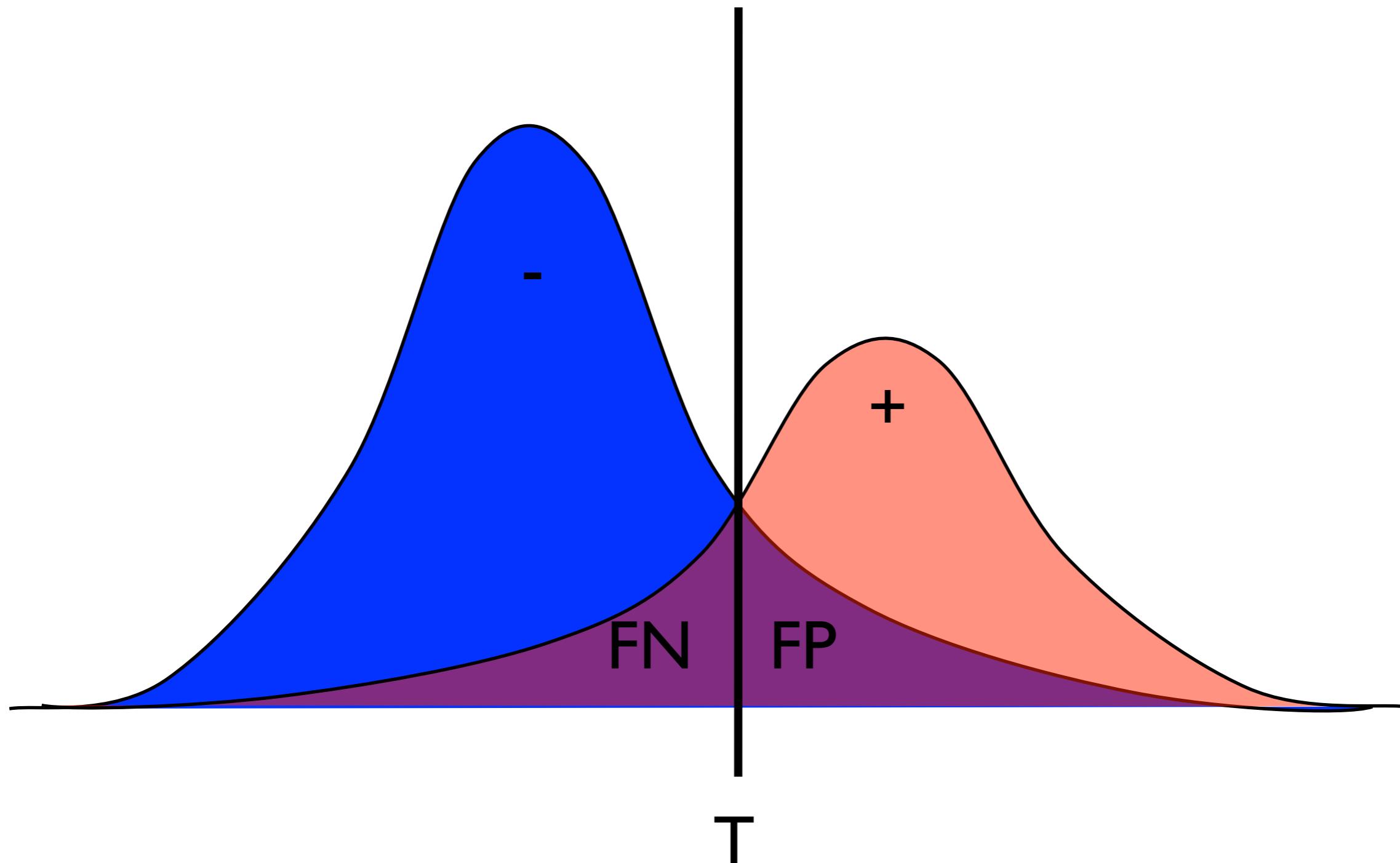
$$L(S|D) = P(S|D)/P(S|\neg D)$$

- Log transform

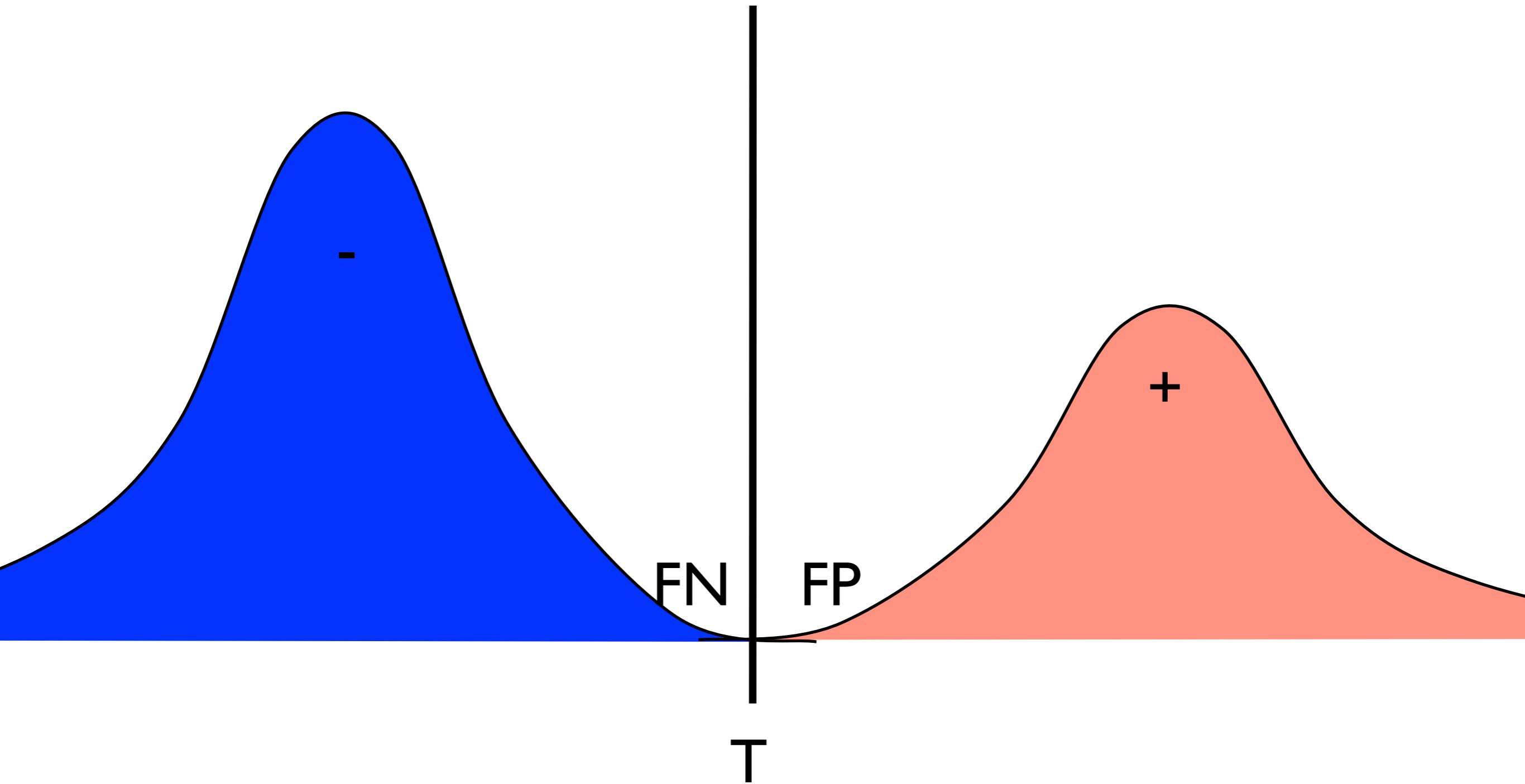
$$O(D|S_1, \dots, S_n) = O(D)L(S_1|D) \dots L(S_n|D)$$

$$\begin{aligned}\log O(D|S_1, \dots, S_n) &= \log[O(D)L(S_1|D) \dots L(S_n|D)] \\ &= \log[O(D)] + \log[O(S_1|D)] + \dots + \log[O(S_n|D)] \\ &= W(D) + W(S_1|D) + \dots + W(S_n|D)\end{aligned}$$

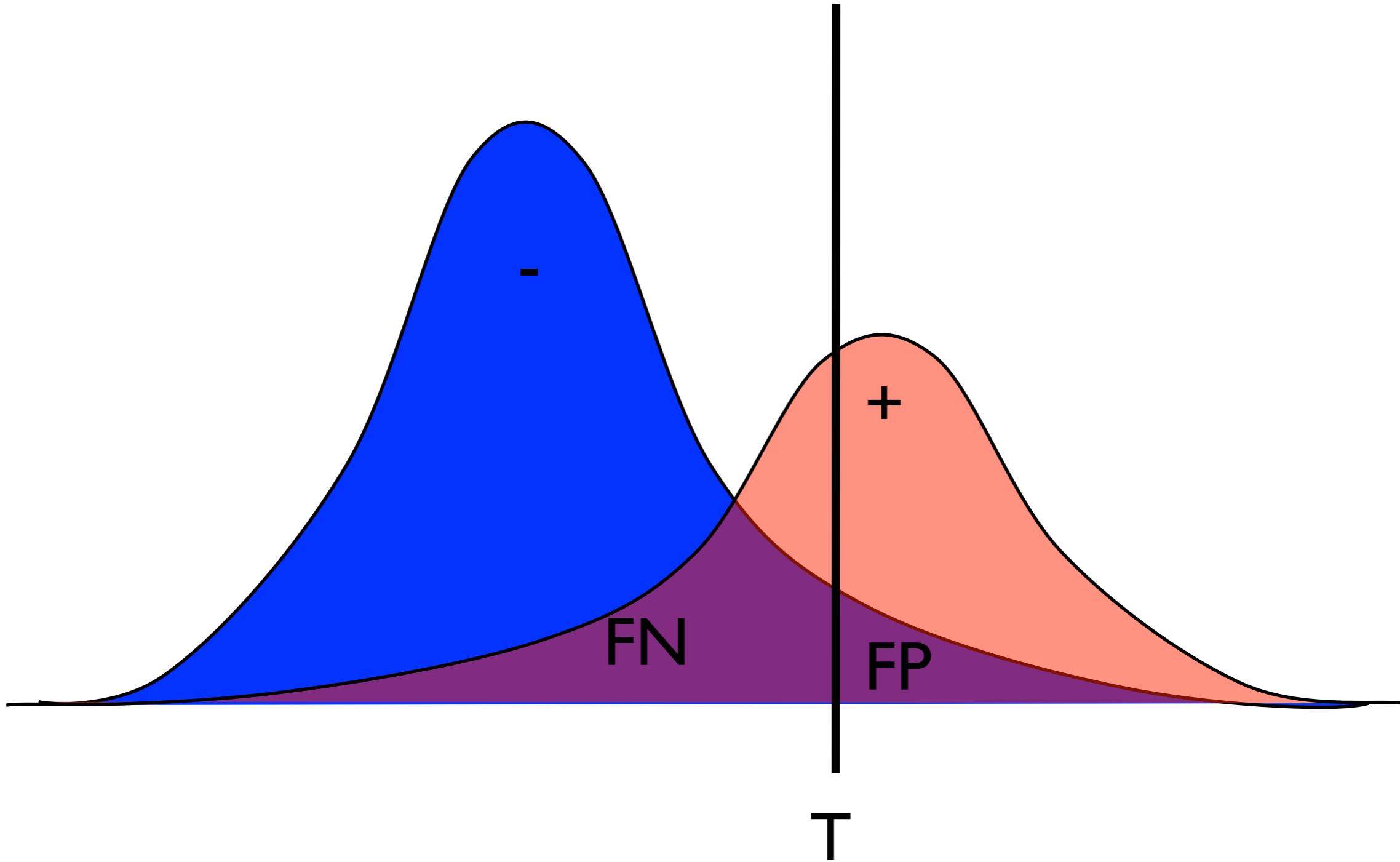
Test Thresholds



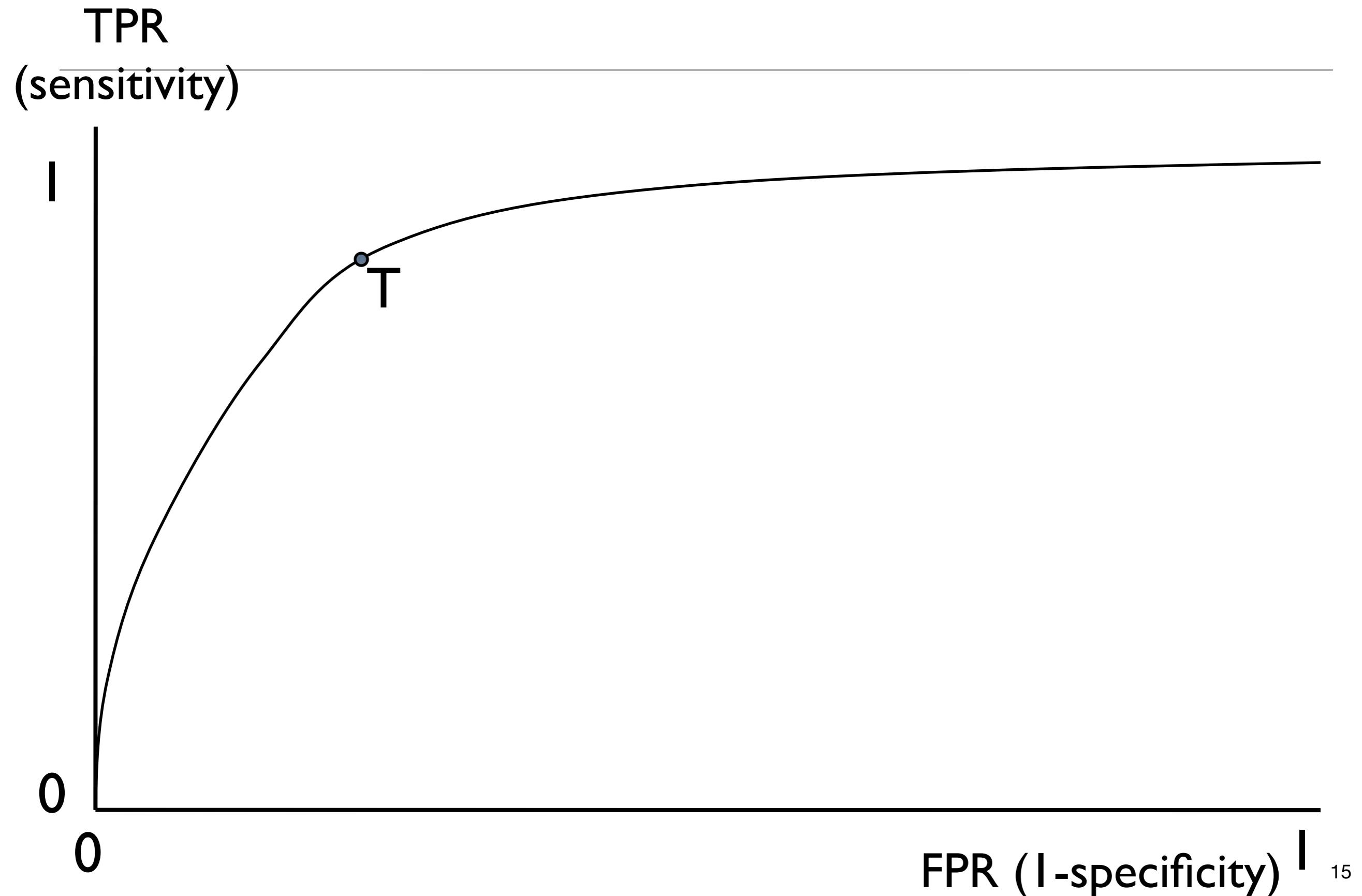
Wonderful Test



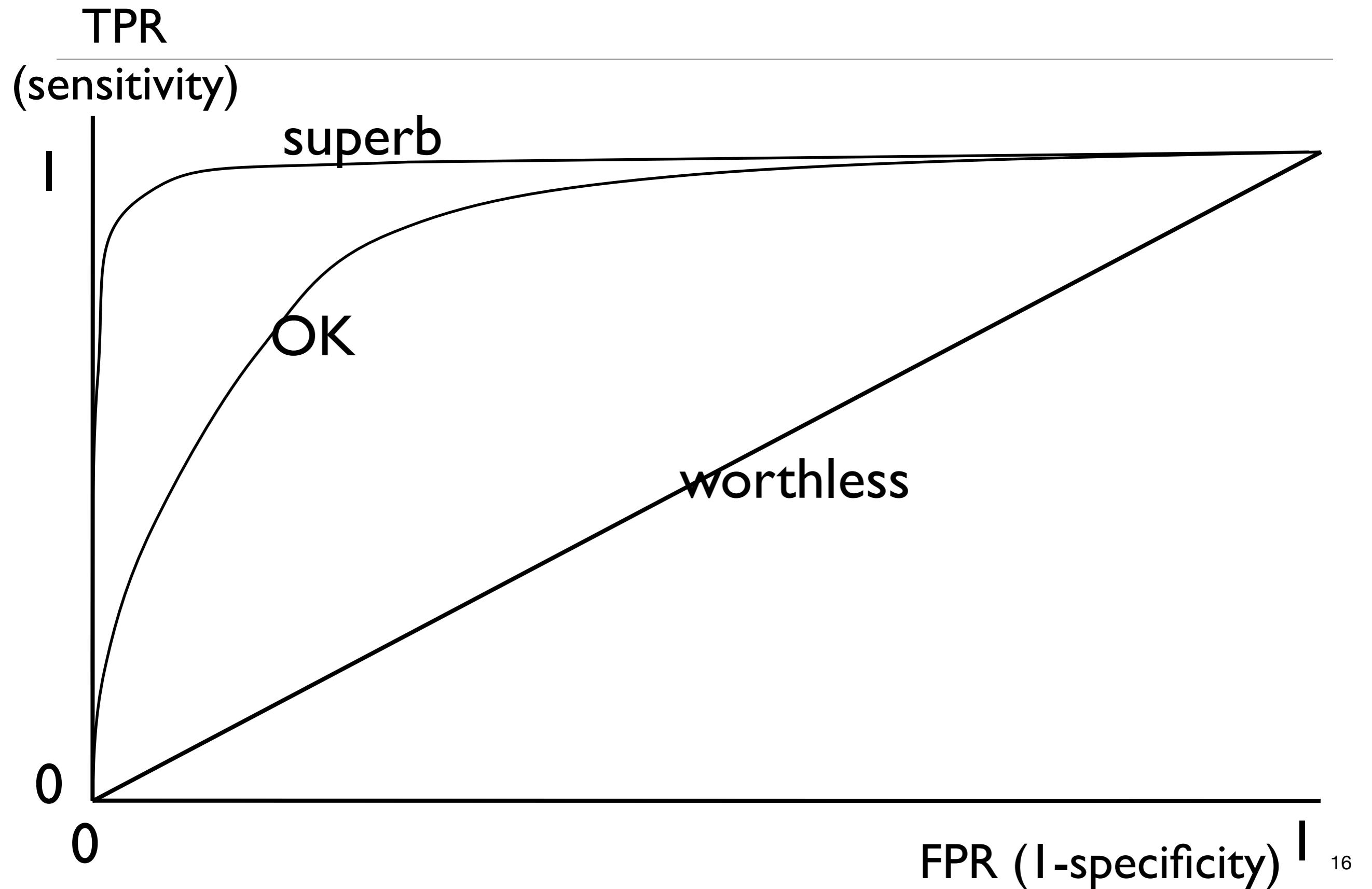
Test Thresholds Change Trade-off between Sensitivity and Specificity



Receiver Operator Characteristic (ROC) Curve



What makes a better test?



Rationality

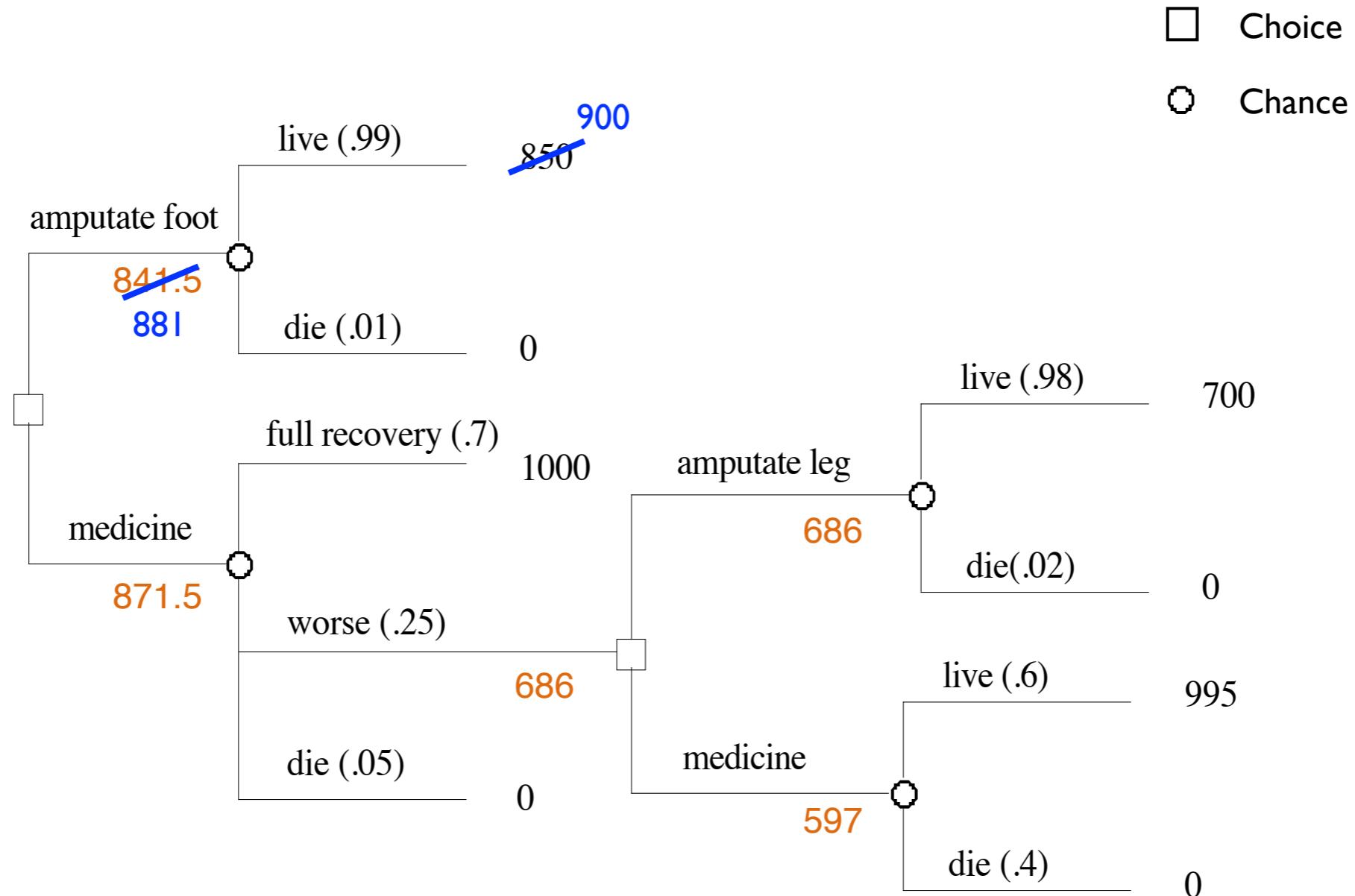
- Every action has a cost
- Principle of rationality
 - Act to maximize expected utility – *homo economicus*
 - Or minimize loss
- Utility measures the value (“goodness”) of an outcome, e.g.,
 - Life vs. death
 - Quality-adjusted life years (QALYs)

Case of a Man with Gangrene

- From Pauker's "Decision Analysis Service" at New England Medical Center Hospital, late 1970's.
- Man with gangrene of foot
- Choose to amputate foot or treat medically
- If medical treatment fails, patient may die or may have to amputate whole leg.
- What to do? How to reason about it?

Decision Tree for Gangrene Case

(Different sense of “Decision Tree” from ML/Classification!)



“Folding back” a Decision Tree

- The value of an outcome node is its utility
- The value of a chance node is the expected value of its alternative branches; i.e., their values weighted by their probabilities
- The value of a choice node is the maximum value of any of its branches

Where Do Utilities Come From?

- Standard gamble
 - Would you prefer (choose one of the following two):
 1. I chop off your foot
 2. We play a game in which a fair process produces a random number r between 0 and 1
 - If $r > 0.8$, I kill you; otherwise, you live on, healthy
 - If you're indifferent, that's the value of living without your foot!
 - I vary the 0.8 threshold until you are indifferent.
- Alas, difficult ascertainment problems!
 - Clearly depends on the individual
 - Not stable

Acute Renal Failure Program

- Differential Diagnosis of Acute Oliguric Renal Failure
 - “stop peeing”
- 14 potential causes, exhaustive and mutually exclusive
- 27 tests/questions/observations relevant to differential
 - “cheap”; therefore, ordering based on expected information gain
- 3 invasive tests (biopsy, retrograde pyelography, renal arteriography)
 - “expensive”; ordering based on (very naive) utility model
- 8 treatments (conservative, IV fluids, surgery for obstruction, steroids, antibiotics, surgery for clots, antihypertensive drugs, heparin)
 - expected outcomes are “better”, “unchanged”, “worse”

- Gorry, G. A., Kassirer, J. P., Essig, A., & Schwartz, W. B. (1973). Decision analysis as the basis for computer-aided management of acute renal failure. *The American Journal of Medicine*, 55(3), 473–484.

Question 5—What is the kidney size on plain film of the abdomen?

1. Small
2. Normal
3. Large
4. Very Large

Reply: 3

The current distribution is

<u>Disease</u>	<u>Probability</u>
OBSTR	0.80
FARF	0.12
PYE	0.04

Question 6—Was there a large fluid loss preceding the onset of oliguria?

Reply: No

The current distribution is

<u>Disease</u>	<u>Probability</u>
OBSTR	0.88
PYE	0.05
FARF	0.03

Figure 1. Typical interactive dialogue between the physician and the phase I computer program. The final diagnosis, which was arrived at after eight questions were asked, was urinary tract obstruction.

Question 7—What is the degree of Proteinuria?

1. 0
2. trace to 2+
3. 3+ to 4+

Reply: 1

The current distribution is

<u>Disease</u>	<u>Probability</u>
OBSTR	0.94
FARF	0.03
PYE	0.03

Question 8—Is there a history of prolonged hypotension preceding the onset of oliguria?

Reply: No

The current distribution is

<u>Disease</u>	<u>Probability</u>
OBSTR	0.96
PYE	0.03

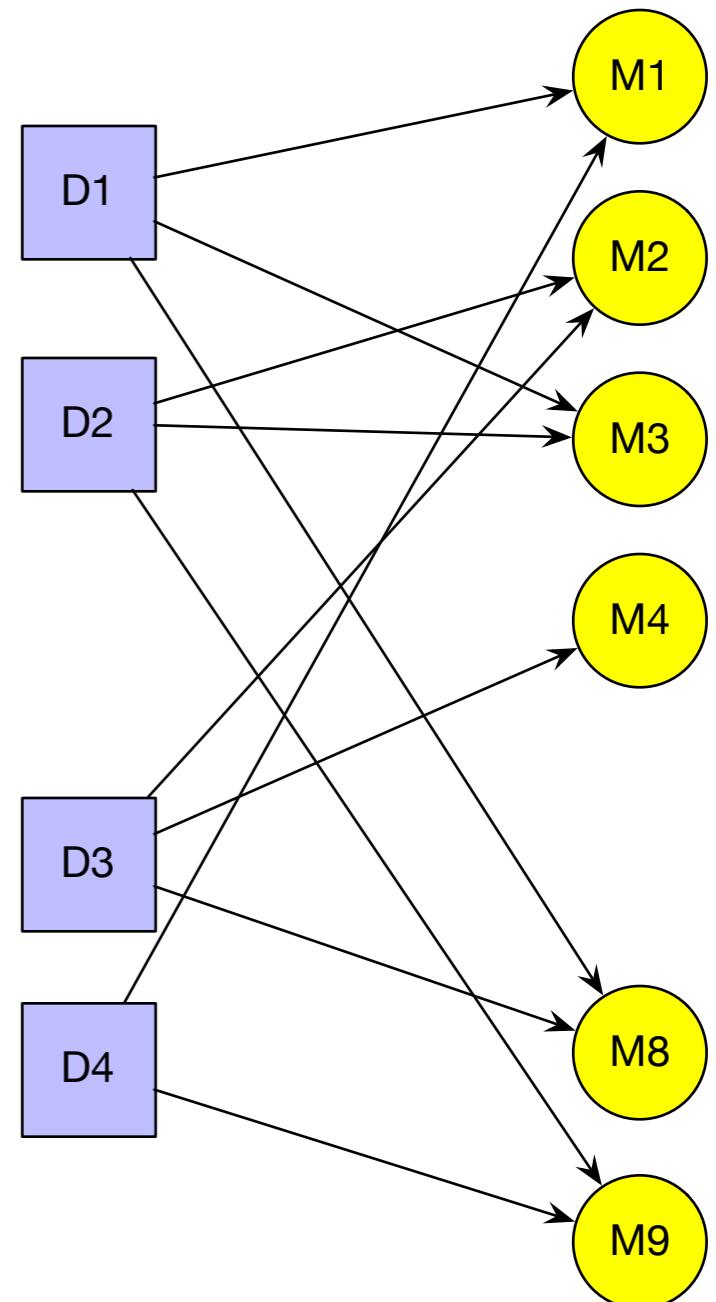
Demo of Acute Renal Failure Program

- Only the diagnostic portion
 - Original program also solved the decision analysis problem of what to do next
 - BADLY!
- 1990s GUI instead of 1970s terminal interface

“It thinks just the way I do!”

Bipartite Graph Model

- Multiple diseases
 - Diseases are independent
 - Manifestations depend only on which diseases are present
 - Thus, they are conditionally independent
-
- This is a type of Bayes Network
 - Computationally intractable
 - Complexity exponential in number of undirected cycles



Dialog/Internist/QMR ~1982

- ~500 diseases
 - (est. 70-75% of major diagnoses in internal medicine)
 - ~3,500 manifestations
 - (~15 man-years)
-
- By 1997, commercialized QMR had 766 Dx and 5498 Mx

Table 4. A Sample Manifestations List.*

Data in QMR

- For each Dx
 - List of associated Mx
 - with Evoking strength & Frequency
 - ~75 Mx per Dx
- For each Mx
 - Importance

**DISPLAY WHICH MANIFESTATION LIST?
ALCOHOLIC HEPATITIS**

AGE 16 TO 25 ... 0 1
AGE 26 TO 55 ... 0 3
AGE GTR THAN 55 ... 0 2
ALCOHOL INGESTION RECENT HX ... 2 4
ALCOHOLISM CHRONIC HX ... 2 4
SEX FEMALE ... 0 2
SEX MALE ... 0 4
URINE DARK HX ... 1 3
WEIGHT LOSS GTR THAN 10 PERCENT ... 0 3
ABDOMEN PAIN ACUTE ... 1 2
ABDOMEN PAIN COLICKY ... 1 1
ABDOMEN PAIN EPIGASTRIUM ... 1 2
ABDOMEN PAIN NON COLICKY ... 1 2
ABDOMEN PAIN RIGHT UPPER QUADRANT ... 1 3
ANOREXIA ... 0 4
DIARRHEA ACUTE ... 1 2
MYALGIA ... 0 3
VOMITING RECENT ... 0 4
ABDOMEN BRUIT CONTINUOUS RIGHT UPPER
QUADRANT ... 1 2
ABDOMEN BRUIT SYSTOLIC RIGHT UPPER QUADRANT ... 1 2
ABDOMEN TENDERNESS RIGHT UPPER QUADRANT ... 2 4
CONJUNCTIVA AND/OR MOUTH PALLOR ... 1 2
FECES LIGHT COLORED ... 1 2
FEVER ... 0 4
HAND(S) DUPUYTRENS CONTRACTURE(S) ... 1 2
JAUNDICE ... 1 3
LEG(S) EDEMA BILATERAL SLIGHT OR MODERATE ... 1 2
LIVER ENLARGED MASSIVE ... 1 2
LIVER ENLARGED MODERATE ... 1 3
LIVER ENLARGED SLIGHT ... 1 2
PAROTID GLAND(S) ENLARGED ... 1 2

Data in QMR

Frequency (Fr)	
1	Mx occurs rarely in Dx
2	Mx occurs in a substantial minority of cases of Dx
3	Mx occurs in roughly half of cases of Dx
4	Mx occurs in a substantial majority of cases of Dx
5	Mx occurs in essentially all cases of Dx

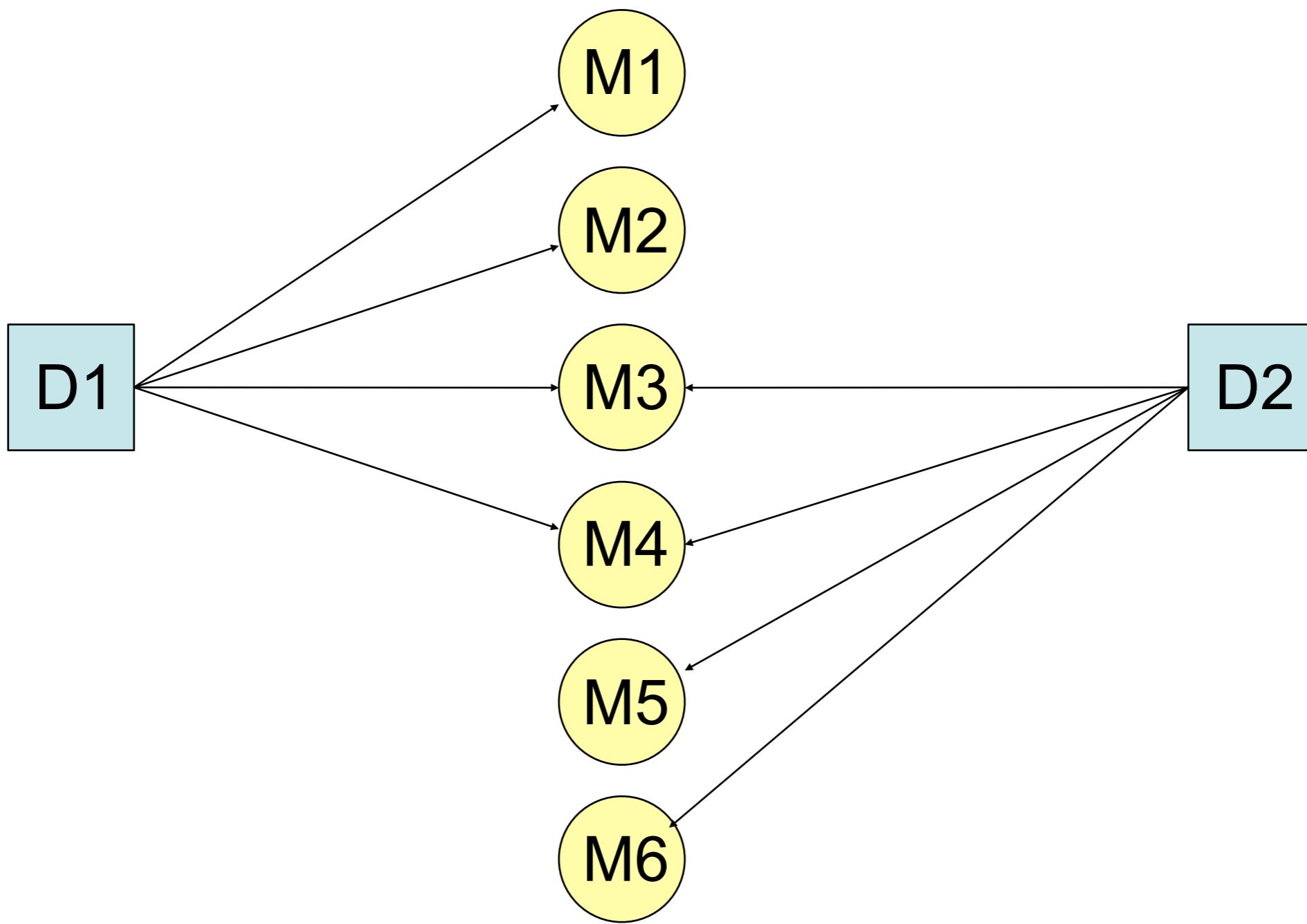
Evoking Strength (Ev)	
0	Nonspecific
1	Dx is a rare or unusual cause of Mx
2	Dx causes a substantial minority of instances of Mx
3	Dx is the most common but not overwhelming cause of Mx
4	Dx is the overwhelming cause of Mx
5	Mx is <i>pathognomonic</i> for Dx

Importance (Im)	
1	Usually unimportant; occurs often in normal patients
2	May be important but can often be ignored
3	Medium importance, but unreliable indicator of disease
4	High importance, rarely disregarded
5	Absolutely must be explained by final diagnosis

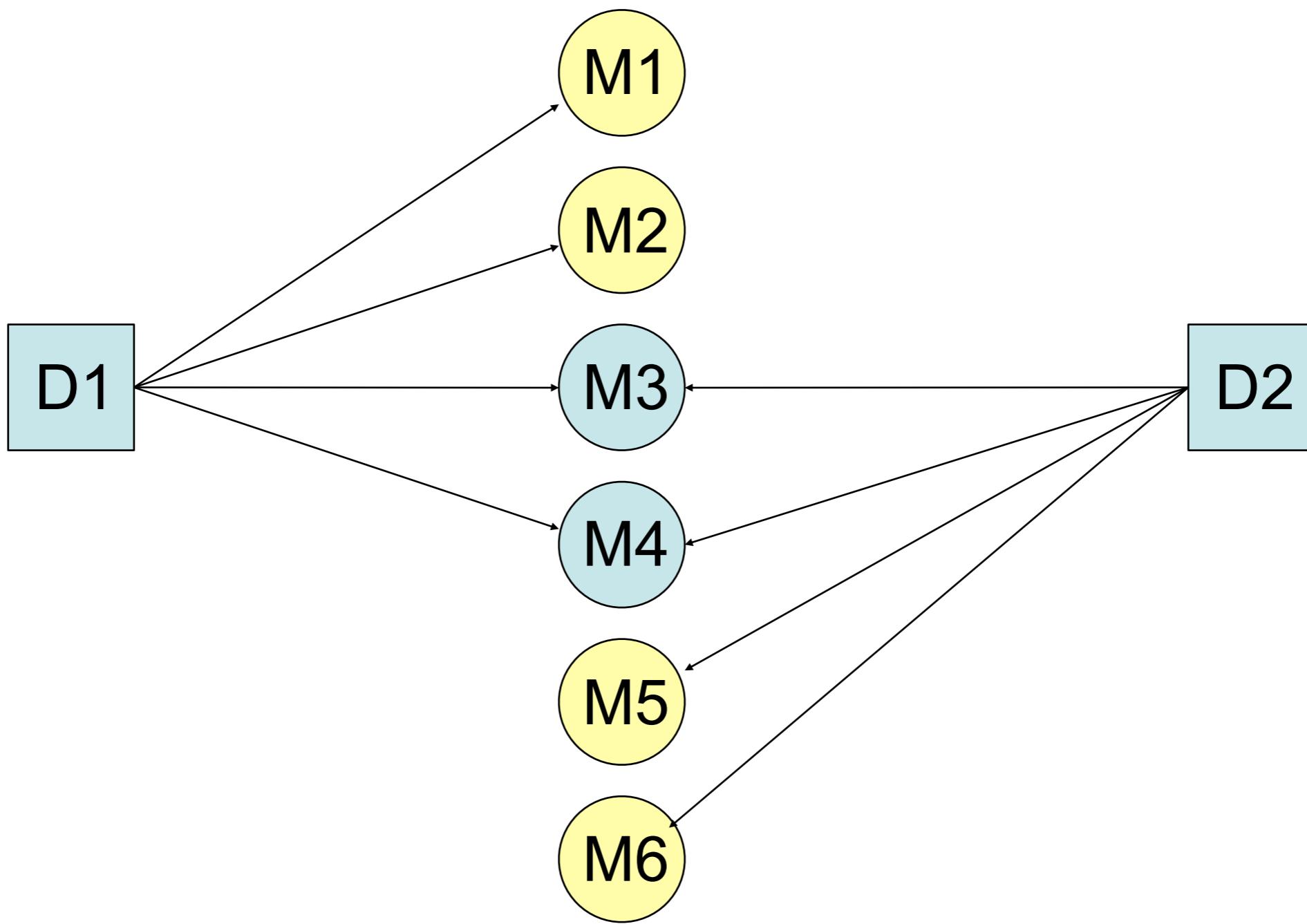
Abductive Logic in QMR

- List Mx of a case
 - Many demonstrated on NEJM Clinico-Pathological Conference cases
 - These are quite complex and challenging to doctors
- Evoke Dx's with high evoking strengths from Mx's
- Score Dx's
 - Positive:
 - Evoking strength of observed Manifestations
 - Scaled Frequency of causal links from confirmed Hypotheses
 - Scaling roughly exponential
 - Negative:
 - Frequency of predicted but absent Manifestations
 - Importance of unexplained Manifestations
- Form a differential around highest-scoring Dx

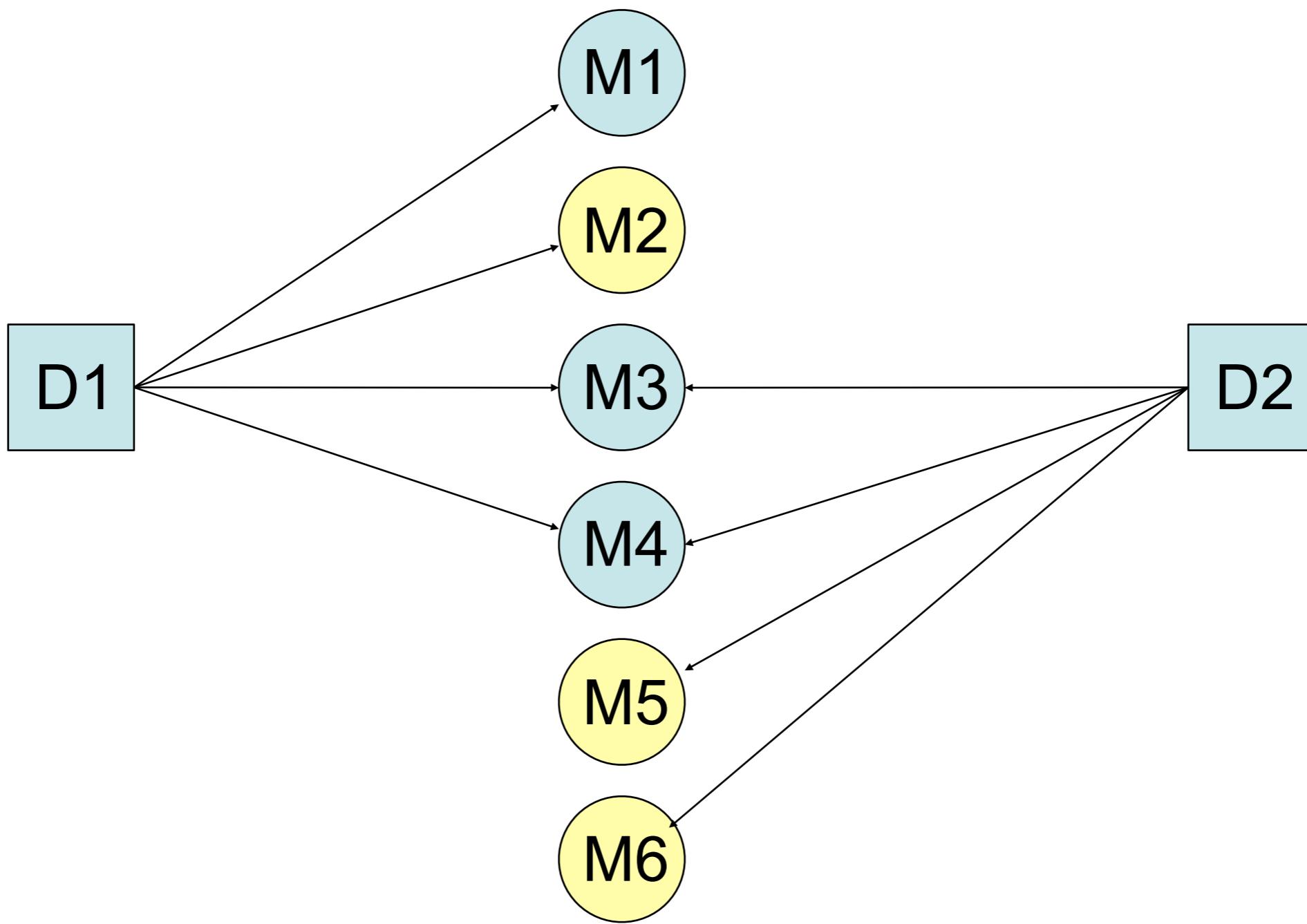
QMR Partitioning



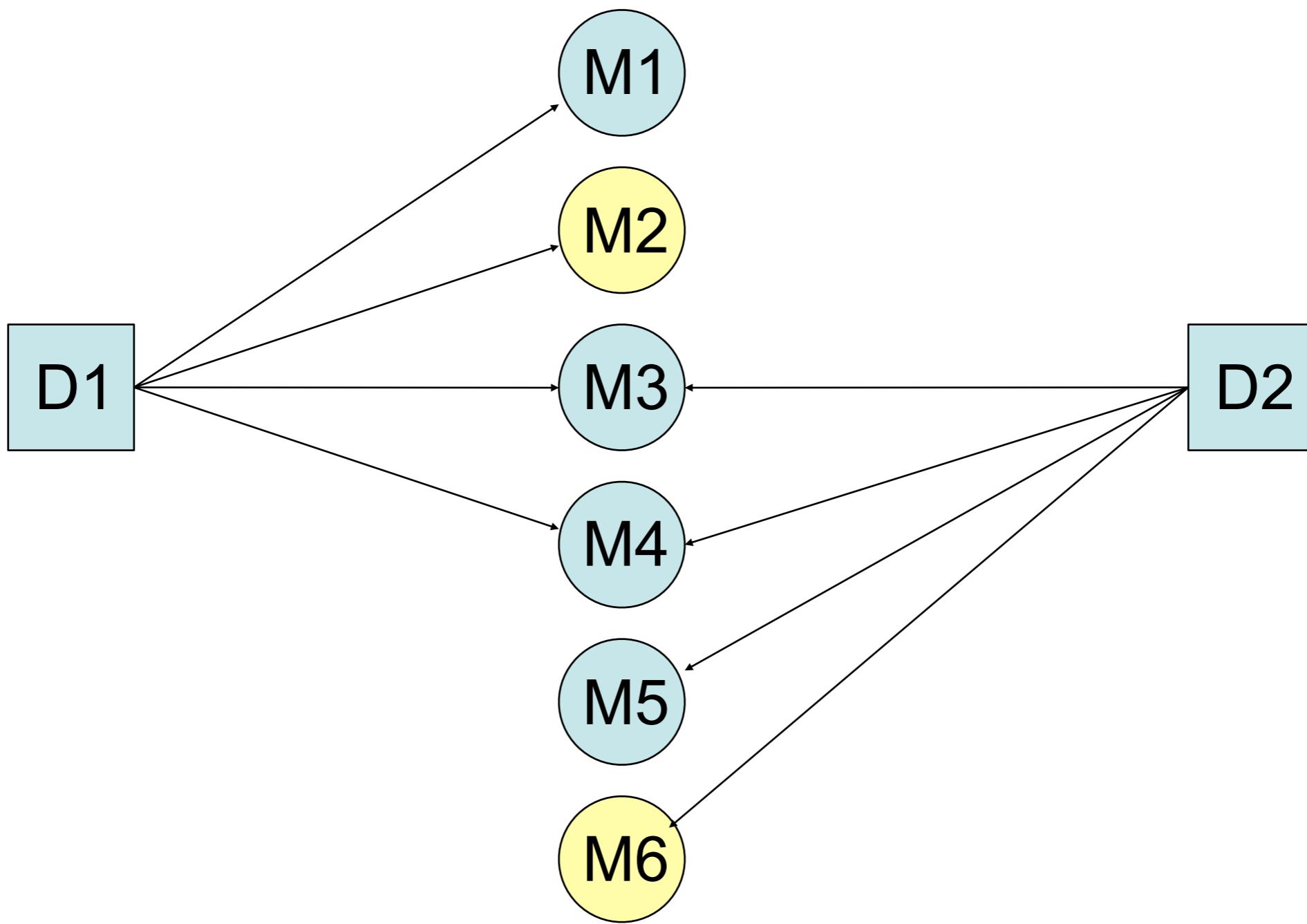
Competitors



Still Competitors



Probably Complementary



Multi-Hypothesis Diagnosis

- Set aside complementary hypotheses
 - ... and manifestations predicted by them
- Solve diagnostic problem among competitors
 - differential determines questioning strategy: *pursue, rule-out, differentiate, ...*
- Eliminate confirmed hypotheses and manifestations explained by them
- Repeat as long as there are coherent problems among the remaining data

Table 5. Summary of Results for Major Diagnoses in 19 Cases
Used in the INTERNIST-I Evaluation.

CATEGORY	INTERNIST-I	CLINICIANS	DISCUSSANT
			<i>no. of instances</i>
<i>Total possible diagnoses</i>	43	43	43
Definitive, correct	17	23	29
Tentative, correct	8	5	6
Failed to make correct diagnosis	18	15	8
Definitive, incorrect	5	8	11
Tentative, incorrect	6	5	2
Total no. of incorrect diagnoses	11	13	13
Total no. of errors in diagnosis	29	28	21

1990s Evaluation of Diagnostic Systems

- Evaluate: QMR, DXplain, Iliad, Meditel
- 105 cases (based on actual patients) created by 10 experts
- Results:
 - Coverage — fraction of real diagnoses included in program's KB
 - Correct — fraction of program's dx considered correct by experts
 - Rank — rank order of correct dx in program's list
 - Relevance — fraction of program's dx considered worthwhile by experts
 - Comprehensiveness — number of experts' dx included in program's top 20
 - Additional — “value added” dx by program

Table 1. Performance Scores of the Computer-Based Diagnostic Systems.

VARIABLE AND SAMPLE USED*	DXPLAIN	ILIAD	MEDITEL	QMR	OVERALL ANALYSIS OF VARIANCE	P VALUE	SIGNIFICANT PAIRWISE COMPARISONST
							mean (95 percent confidence interval)
Diagnosis in Knowledge Base	0.91 (0.86–0.97)	0.76 (0.68–0.85)	0.85 (0.78–0.92)	0.73 (0.65–0.82)	$\chi^2 = 20.32$	<0.001	D vs. I, D vs. Q, M vs. Q
Correct Diagnosis							
105 cases	0.69 (0.60–0.78)	0.61 (0.52–0.70)	0.71 (0.62–0.79)	0.52 (0.43–0.62)	$\chi^2 = 11.58$	0.009	D vs. Q, M vs. Q
63 cases	0.79 (0.69–0.90)	0.76 (0.65–0.87)	0.89 (0.81–0.97)	0.71 (0.60–0.83)	$\chi^2 = 7.06$	0.070	—
Rank‡							
Diagnosis in program studied§	12.4 (9.5–15.3)	10.4 (8.0–12.8)	13.3 (10.5–16.1)	6.6 (3.0–10.3)	—	—	—
Diagnosis in all four programs¶	11.7 (8.3–15.1)	10.2 (7.5–12.9)	12.0 (8.8–15.3)	5.4 (3.7–7.1)	—	—	—
Relevance							
105 cases	0.24 (0.21–0.26)	0.19 (0.16–0.21)	0.22 (0.20–0.24)	0.37 (0.31–0.42)	F = 15.80	<0.001	Q vs. D, Q vs. M, Q vs. I, D vs. I, M vs. I
63 cases	0.26 (0.23–0.29)	0.21 (0.17–0.24)	0.23 (0.20–0.26)	0.46 (0.39–0.54)	F = 16.45	<0.001	Q vs. D, Q vs. M, Q vs. I, D vs. I
Comprehensiveness							
105 cases	0.38 (0.34–0.43)	0.25 (0.21–0.29)	0.38 (0.33–0.43)	0.28 (0.23–0.32)	F = 13.99	<0.001	D vs. I, D vs. Q, M vs. I, M vs. Q
63 cases	0.38 (0.33–0.44)	0.27 (0.22–0.32)	0.39 (0.32–0.46)	0.30 (0.25–0.35)	F = 5.05	0.004	D vs. I, D vs. Q, M vs. I, M vs. Q
Additional Diagnoses							
105 cases	2.3 (1.8–2.7)	2.0 (1.6–2.4)	2.1 (1.8–2.4)	1.8 (1.4–2.2)	F = 1.65	0.182	—
63 cases	2.6 (2.0–3.1)	2.2 (1.7–2.8)	2.2 (1.8–2.5)	2.0 (1.4–2.5)	F = 1.02	0.392	—

*The analyses of 105 cases were based on all cases included in the test, whereas the analyses of 63 cases were limited to the cases whose diagnoses were included in the knowledge base of all four programs.

†D denotes Dxplain, I Iliad, Q QMR, and M Meditel.

‡This variable could not be tested for significance because the sample varied in size according to the program used.

§This analysis included variable numbers of cases (72 for Dxplain, 64 for Iliad, 74 for Meditel, and 55 for QMR).

¶This analysis included variable numbers of cases (50 for Dxplain, 48 for Iliad, 56 for Meditel, and 45 for QMR).

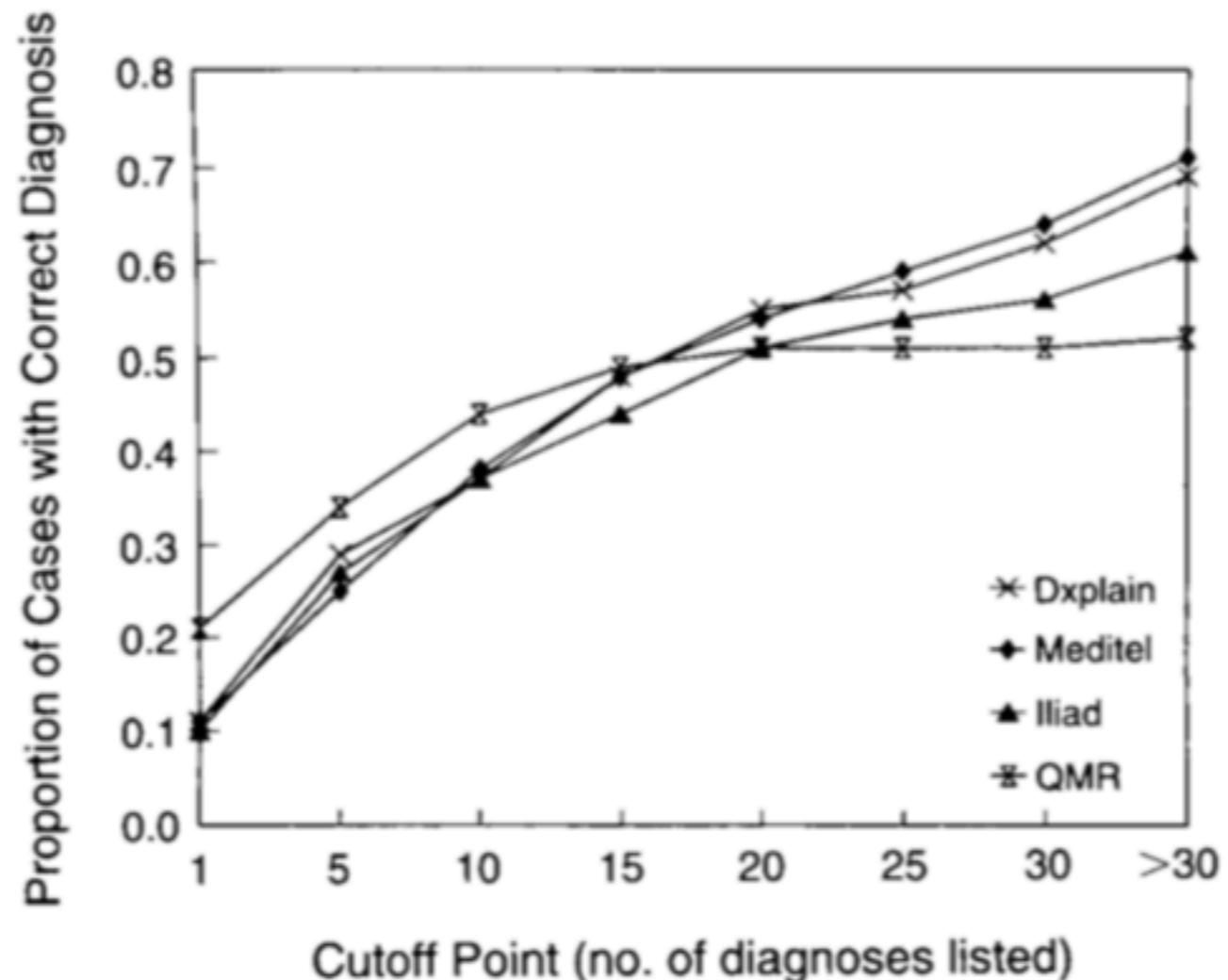


Figure 1. Proportion of Cases with a Correct Diagnosis in the Computer, According to the Cutoff Point Establishing the Numbers of Diagnoses Listed.

Evaluation Bottom Line

- ... long lists of potential diagnoses. ... many that a knowledgeable physician would regard as not being particularly helpful
- ... each program suggested some diagnoses, though not highly likely ones, that the experts later agreed were worthy of inclusion in the differential diagnosis
- None performed consistently better or worse on all the measures
- Although the sensitivity and specificity ... were not impressive, the programs have additional functions not evaluated
 - interactive display of signs and symptoms associated with diseases
 - relative likelihood of each dx (study only used ranking)
- Need to study effect of such programs on {physician, computer} team

QMR Database

 Explore DataBase

Disease

- ANEMIA DUE TO ABNORMAL MATURATION
- ANEMIA OF CHRONIC DISEASE
- ANEMIA OF DECREASED VITAMIN B12 ABSORPTION
- ANEMIA OF FOLATE DEFICIENCY
- ANEMIA OF VITAMIN B12 DEFICIENCY
- ANEMIA SECONDARY TO MARROW DAMAGE
- ANGINA PECTORIS**
- ANGINA VARIANT <PRINZMETAL>
- ANGIOIMMUNOBLASTIC LYMPHADENOPATHY
- ANKYLOSING SPONDYLITIS
- ANOREXIA NERVOSEA

Finding

- TREMOR PILL-ROLLING
- TREMOR RESTING
- TREMOR WING-BEATING
- TREPONEMA FLUORESCENT ANTIBODY POSITIVE
- TREPONEMA PALLIDUM IMMobilIZATION POSITIVE
- TRIAMTERENE THERAPY RECENT HX
- TRICHINELLA BENTONITE FLOCUlATION TEST POSITIVE
- TRICHINELLA SKIN TEST POSITIVE
- TRIGEMINAL NEURALGIA
- TRIGLYCERIDE <S> SERUM INCREASED**
- TRIGLYCERIDE <S> SERUM PRESENT

Findings:

- 1 3 TRIGLYCERIDE <S> SERUM INCREASED**
- 0 2 TACHYCARDIA
- 0 3 SKIN SWEATING INCREASED GENERALIZED
- 1 1 SHOULDER PAIN RIGHT
- 1 1 SHOULDER PAIN LEFT
- 0 4 SEX MALE
- 0 2 SEX FEMALE
- 0 2 PALPITATION <S>
- 2 2 MYOCARDIAL INFARCTION HX
- 2 3 MYOCARDIAL INFARCTION FAMILY HX
- 2 3 LIPOPROTEINEMIA TYPE IV
- 2 2 LIPOPROTEINEMIA TYPE III
- 2 3 LIPOPROTEINEMIA TYPE II
- 2 1 LEG <S> CLAUDICATION INTERMITTENT HX
- 2 2 HYPERTENSION HX
- 1 1 HEMORRHAGE GASTROINTESTINAL ACUTE RECENT
- 1 1 HEMORRHAGE ACUTE RECENT HX
- 1 2 HEART SOUND <S> 54 LEFT ATRIAL CALLUS

- 1 2 PEDIATRIC DRUG HYPERSENSITIVITY CHOLESTATIC REA
- 1 2 PEDIATRIC EXTRAHEPATIC BILIARY ATRESIA
- 1 2 PEDIATRIC BILIARY CIRRHOsis SECONDARY
- 1 2 PEDIATRIC BILIARY CIRRHOsis PRIMARY
- 1 2 PEDIATRIC FATTY LIVER SECONDARY
- 1 2 OBESITY
- 1 1 WEBER CHRISTIAN DISEASE
- 1 2 ATHEROMATOUS EMBOLISM
- 1 4 DIABETIC KETOACIDOSIS
- 2 3 DIABETES MELLITUS
- 1 3 GOUTY ARTHRITIS CHRONIC
- 1 4 GOUTY ARTHRITIS ACUTE
- 1 3 ABDOMINAL AORTIC ANEURYSM <UNCOMPLICATED>
- 1 3 VENTRICULAR ANEURYSM LEFT
- 1 3 ARTERIOSCLEROTIC HEART DISEASE
- 1 3 MYOCARDIAL INFARCTION ACUTE
- 1 3 CRESCENDO ANGINA
- 1 3 ANGINA PECTORIS
- 1 2 PANCREATITIS CHRONIC

Example Case

 Internist Data Summary

Internist Reconstruction -- Data Summary

Manifestations PRESENT:

- ABDOMEN DISTENTION
- ABDOMEN FLUID WAVE
- AGE GTR THAN 55
- ALKALINE PHOSPHATASE BLOOD GTR THAN 2 TIMES NORMAL
- AMMONIA BLOOD INCREASED
- ANOREXIA
- ARTHRITIS HX
- ASCITIC FLUID PROTEIN 3 GRAM <5> PER DL OR LESS
- ASCITIC FLUID WBC 100 TO 500
- ASTERIXIS
- BILIRUBIN BLOOD CONJUGATED INCREASED
- BILIRUBIN URINE PRESENT
- CHEST PAIN LATERAL EXACERBATION WITH BREATHING
- CHEST PAIN LATERAL SHARP
- DEPRESSION HX
- DYSPIA ARRIFT ONSET

Manifestations ABSENT:

- ALCOHOLISM CHRONIC HX
- ASCITIC FLUID AMYLASE INCREASED
- ASCITIC FLUID CYTOLOGY POSITIVE
- ASCITIC FLUID LDH GTR THAN 500
- DIARRHEA CHRONIC
- ESOPHAGUS BARIUM MEAL VARICES
- FECES BLACK TARRY
- FEVER
- HEMATOCRIT BLOOD LESS THAN 35
- PRESSURE VENOUS CERVICAL INCREASED ON INSPECTION
- STOMACH BARIUM MEAL ULCER CRATER <5>
- T3 RESIN UPTAKE INCREASED
- T4 FREE BLOOD INCREASED
- UREA NITROGEN BLOOD 30 TO 59
- URIC ACID BLOOD INCREASED

Initial Solution

 Diagnostic Results

Problem:

- 94 HEPATITIS CHRONIC ACTIVE
- 119 PEDIATRIC HEPATITIS CHRONIC ACTIVE
- 136 MACRONODAL CIRRHOSIS <POSTNECROTIC>
- 158 BILIARY CIRRHOSIS PRIMARY
- 178 PEDIATRIC BILIARY CIRRHOSIS PRIMARY

Complementary:

- 143 MICRONODAL CIRRHOSIS <LAENNECS>
- 162 HEPATITIS ACUTE VIRAL
- 170 CHOLANGIOCARCINOMA <INTRAHEPATIC NON HILAR>
- 178 HEPATIC AMYLOIDOSIS

Shelf:

- ABDOMEN DISTENTION
- ARTHROSIS HX
- CHEST PAIN LATERAL EXACERBATION WITH BREATHING
- CHEST PAIN LATERAL SHARP
- FECES GUAIAC TEST POSITIVE
- PLEURAL FRICTION RUB
- WEIGHT INCREASE RECENT HX

Explained:

- AGE GTR THAN 55
- ALKALINE PHOSPHATASE BLOOD GTR THAN 2 TIMES NORMAL
- ANOREXIA
- BILIRUBIN BLOOD CONJUGATED INCREASED
- BILIRUBIN URINE PRESENT
- FECES LIGHT COLORED
- HAND <S> PALMAR ERYTHEMA
- IMMUNOELECTROPHORESIS SERUM IGA INCREASED
- TMMI INOFECTROPHORESTS SFRIUM TGG INCREASED

Absent:

- DIARRHEA CHRONIC
- FEVER
- HEMATOCRIT BLOOD LESS THAN 35

Unexplained:

- ABDOMEN DISTENTION
- ABDOMEN FLUID WAVE
- AMMONIA BLOOD INCREASED
- ARTHRITIS HX
- ASCITIC FLUID PROTEIN 3 GRAM <S> PER DL OR LESS
- ASCITIC FLUID WBC 100 TO 500

Askable:

- ABDOMEN PAIN CHRONIC
- ABDOMEN PAIN EPIGASTRIUM
- ABDOMEN PAIN EPIGASTRIUM UNRELIEVED BY ANTACID
- ABDOMEN PAIN EXACERBATION WITH MEAL <S>
- ABDOMEN PAIN NON COLICKY
- ABDOMEN PAIN PRESENT
- ABDOMEN PAIN RIGHT UPPER QUADRANT
- ABDOMEN TENDERNESS PRESENT
- ABDOMEN TENDERNESS RIGHT UPPER QUADRANT
- ACTIVATED PARTIAL THROMBOPLASTIN TIME INCREASED
- AGE 16 TO 25
- AGE 26 TO 55
- ALBUMIN SERUM DECREASED
- AL KAL TNF PHOSPHATASE BLOOD INCREASED NOT OVER 2 TIMES NORMA

QMR-DT

- Interpret QMR data as a BN, with assumptions
 - Bipartite graph: marginal independence of D_x , conditional independence of M_x
 - Binary D_x and M_x
 - “Causal independence”—leaky *noisy-OR*
 - No distinction between M_x that predispose to a D_x and those that are a consequence of the D_x
 - Priors on D_x estimated from health statistics
 - problem of mapping QMR D_x names to ICD-9-CM
 - QMR treats age and gender as M_x , but QMR-DT conditions priors on them
 - No Evoking strengths are used
 - Estimate “leak” for each M_x from Importance values
- Use iterative diagnosis similar to QMR’s setting aside competitors, with D_x - D_x links altering priors on successive rounds
- Likelihood weighting to estimate posteriors

QMR-DT interpretation of Frequency and Importance

Table 1 A mapping between QMR frequencies and probabilities.

Frequency	$P(f^+ \text{only } d_i^+)$
1	0.025
2	0.20
3	0.50
4	0.80
5	0.985

Table 2 A mapping between QMR imports and the probability that one or more significant diseases causes a finding f given that f is present.

Import	Fitted ^a $P(D_f f)$	Std. Error $P(D_f f)$
1	0.39	0.071
2	0.52	0.081
3	0.65	0.101
4	0.79	0.083
5	0.92	0.106

^aThe fitted $P(D_f | f)$ values were calculated by regressing the assessed values of $P(D_f | f)$ on the import values of the respective finding.

QMR-DT performance on Scientific American Medicine cases

Table 2 Ranks assigned to the reference diagnosis of the 23 SAM cases.

SAM case number	QMR	TB	ITB	S	S/UD	S/UL
1	6	1	1	1	1	1
6	2	2	1	2	2	2
15	1	1	1	2	2	1
20	1	1	1	1	1	1
22	1	1	1	1	2	1
23†	-(1)	5(1)	20(1)	103(1)	4(1)	216(1)
25	3	1	2	1	2	6
27	1	1	3	1	1	1
28	1	2	1	1	1	1
29	3	4	11	9	6	106
30	5	2	3	7	17	36
31	12	9	11	24	166	255
33	2	2	17	2	1	1
34	1	6	12	4	4	445
35	1	1	3	1	2	2
37	2	17	2	2	7	8
40	1	1	1	1	1	352
42	4	1	3	2	2	1
46	1	1	1	1	1	1
47	1	1	1	1	1	1
50	1	1	2	1	1	1
51	2	2	5	57	22	30
53	3	1	1	1	1	1

Key:

— Reference diagnosis not ranked

† In case 23, we identified retrospectively an intermediate pathophysiologic state of malabsorption. The rank of malabsorption appears in parentheses for each algorithm.

Symptom Checkers

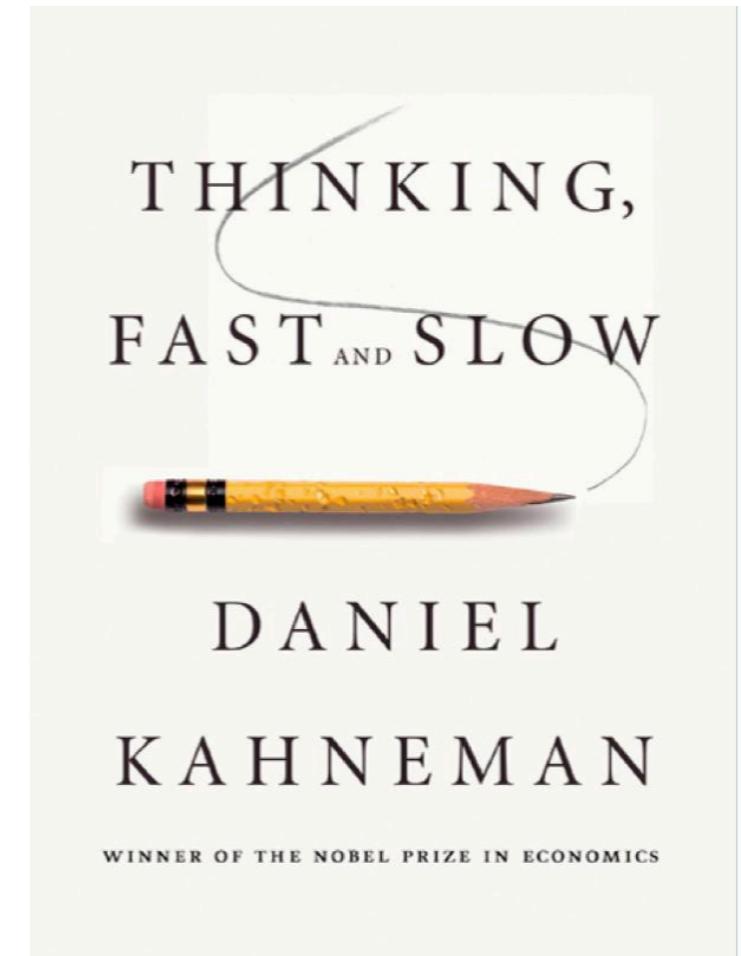
- Demo *K Health*
- BMJ article, 2015
 - 23 symptom checkers
 - 45 standardized patient vignettes
 - 3 levels of urgency:
 - emergent care needed: e.g., pulmonary embolism
 - non-emergent care reasonable: e.g., otitis media (ear ache)
 - self-care reasonable: e.g., viral infection
 - Goals
 - if diagnosis given, is right answer within top 20 (n=770)
 - if triage given, is it the right level of urgency (n=532)
 - Correct dx first in 34% of cases, within top 20 in 58%
 - Correct triage in 57% (80% in emergent, 55% non-emergent, 33% self-care)
 - different systems ranged from 33% to 78% average accuracy

Symptom Checkers: BMJ conclusions

- The public is increasingly using the internet for self diagnosis and triage advice, and there has been a proliferation of computerized algorithms called symptom checkers that attempt to streamline this process
- Despite the growth in use of these tools, their clinical performance has not been thoroughly assessed
- Our study suggests that symptom checkers have deficits in both diagnosis and triage, and their triage advice is generally risk averse

Rationality under Resource Constraints

- Utility comes not only from the ultimate “patient” but from reasoning about the computational process
- McGyver’s utilities drop suddenly under deadline constraints
- Partial computation
 - Any-time algorithms
 - Simplify model
 - Approximate
- Kahneman
 - Fast: reflex, rules
 - Slow: deliberative

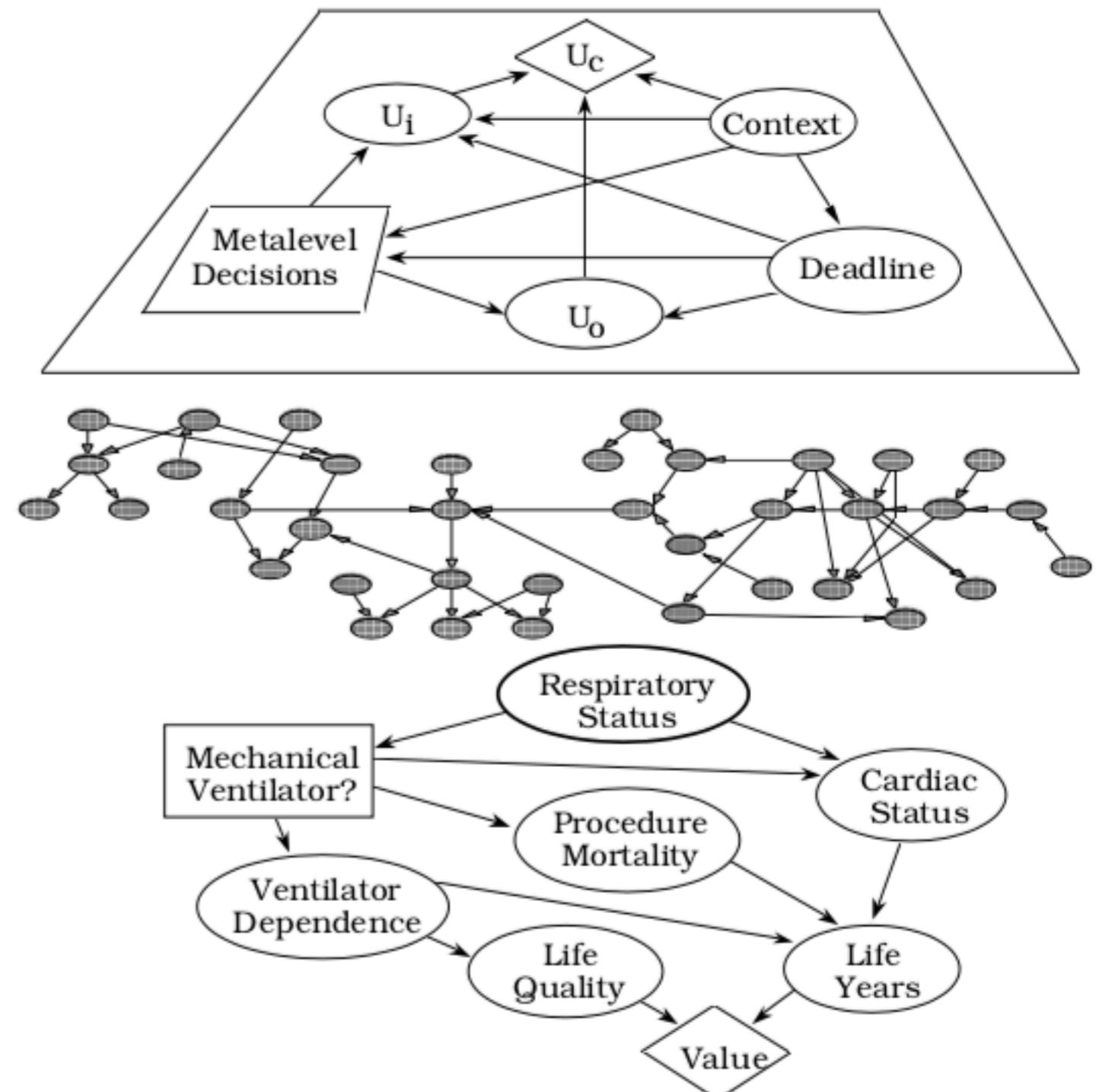


Meta-level Reasoning about How to Reason

- “the expected value of computation as a fundamental component of reflection about alternative inference strategies”
 - alternative methods (e.g., QMR’s question-asking strategies)
 - degree of refinement (e.g., incremental algorithms can stop early)
- Value of information, value of computation, value of experimentation

A Time-Pressured Decision Problem

- decision-theoretic metareasoning
- belief network representing propositions and dependencies in intensive care physiology
- close-up on “Respiratory Status” node and its relationship to current decision problem
 - “A 75yo woman in ICU has sudden breathing difficulties”
 - Should we start mechanical ventilation?



Reinforcement Learning for Speeding up Diagnosis

- Rather than heuristics, use MDP formulation and RL
- State space: set of positive and negative findings
- Action space: ask about a finding, or conclude a diagnosis
- Reward: correct or incorrect (**single**) diagnosis
- Finite horizon imposed by limit on number of questions
- Discount factor encourages short question sequences
- Standard q-learning framework, using double-deep NN strategy
- Magic sauce:
 - Encourage asking questions likely to have positive answers because of sparsity, by *reward shaping*: add extra reward; policy still optimal
 - Identify reduced finding space by *feature rebuilding*.

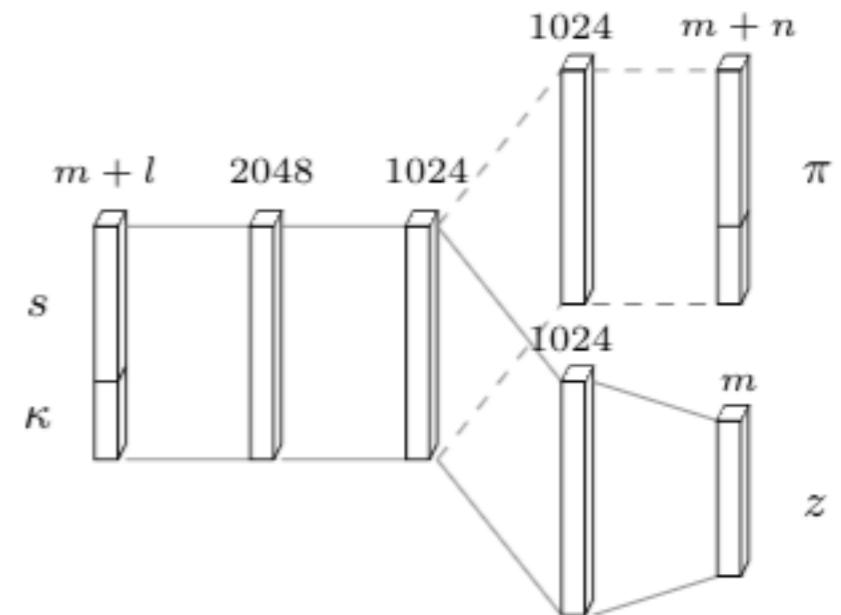


Figure 1: Dual neural network architecture. The upper branch is the policy π of an agent. The lower branch is the feature rebuilding part of sparse features.

REFUEL Performance

- Simulated data: 650 diseases and 376 symptoms

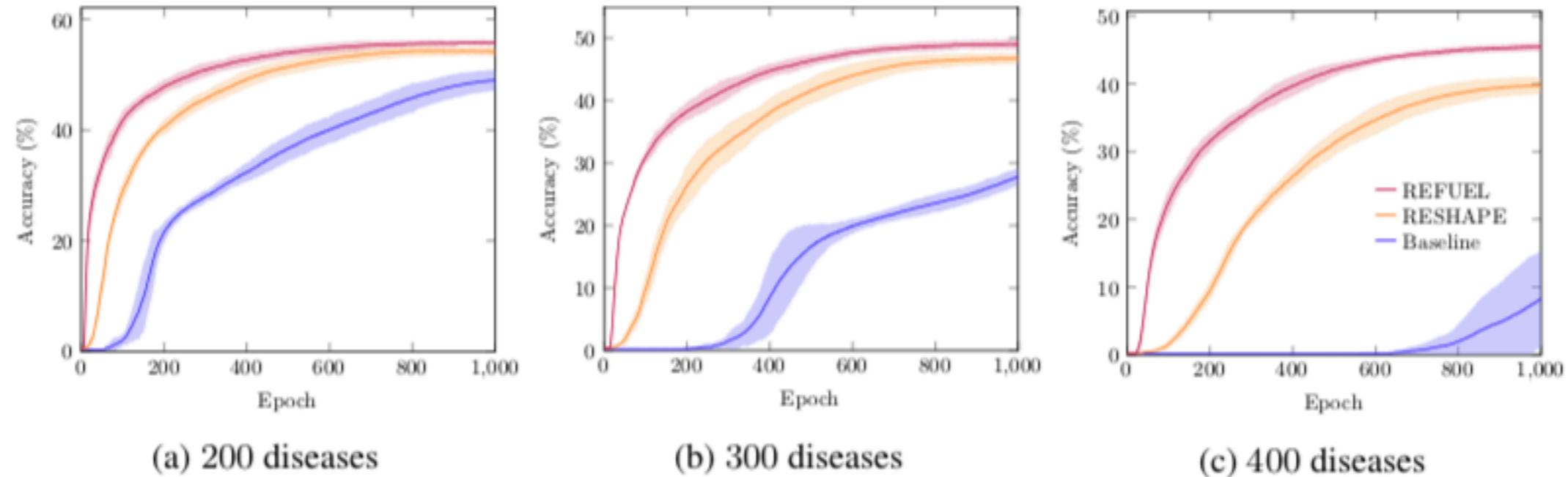


Figure 2: Experiments on 3 datasets of different disease numbers. The curves show the training accuracy of three methods. REFUEL (red line) uses reward shaping and feature rebuilding; RESHAPE (yellow line) only uses reward shaping; Baseline (blue line) adopts none of them. The solid line is the averaged result of 5 different random seeds. The shaded area represents two standard deviations.