Diagnosability

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Outline

1. Introduction
   - Binomial Model of Prevalence
   - Confidence Interval for Population Prevalence
   - Influence of n on Confidence Interval
2. Diagnosability
   - Basic Concepts of diagnostic instrument
   - Estimation of Basic Concepts from Study on Diagnostic Instrument
3. Meta study Diagnosing Dementia by MMSE
4. Receiver Operating Characteristic curve
   - Example Radiologist

Defining Binomial Model of Prevalence

Experiment consists of

1. n independent trials (Disease or Healthy)
2. per trial outcome Disease (=1) and Healthy (=0)
3. probability of Disease p identical for each trial (diagnosis)

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$$P(X = x) = \binom{n}{x} p^x (1 - p)^{n-x}$$

- $X = x$ event that x diseased persons occur out of n
- $\binom{n}{x} = \frac{n!}{x!(n-x)!}$ number of ways x diseased out of n
- $p^x(1 - p)^{n-x}$ prob. x consecutive diseased and $n - x$ healthy
- mean ($\mu = np$) is number of diseased persons to expect
- variance $\sigma^2 = np(1 - p)$ measures variability

For a more extensive explanations, see

- `https://www.youtube.com/watch?v=NaDZ0zVTyXQ`
- `https://www.youtube.com/watch?v=tFWsuO9f74o`

Model for Prevalence of 10%

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$$P(X = 2) = \binom{20}{2} 0.1^2 (1-0.1)^{20-2} = 190 \cdot 0.1^2 0.9^{18} = 0.2851$$

$$\begin{aligned} P(1 \leq X < 5) &= \sum_{x=1}^{4} \binom{20}{x} \cdot 0.1^x 0.9^{20-x} \\ &= 0.2701 + 0.2851 + 0.1901 + 0.0897 = 0.8352 \end{aligned}$$

- Probability that $(1 \leq X < 5)$ have disease is large
- Demo of distribution during lecture!
- Normal approximation works well, if p away from 0 and 1 and n large

Confidence Interval for Population Prevalence

A startup: https://www.youtube.com/watch?v=tFWsuO9f74o
Prevalence: Probability to have a disease $P(D) = p$.
Problem: Compute $100(1-\alpha)\%$ confidence interval for unknown p.
Solution: by CLT

$$Z = \frac{X - np}{\sqrt{np(1-p)}} = \frac{\hat{P} - p}{\sqrt{\frac{p(1-p)}{n}}} \rightarrow N(0,1) \Rightarrow$$

$$P\left(-z_{\alpha/2} \leq \frac{\hat{P} - p}{\sqrt{\frac{p(1-p)}{n}}} \leq z_{1-\alpha/2}\right) \simeq 1 - \alpha$$

after a little math

$$\hat{p} - z_{\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} \leq p \leq \hat{p} + z_{1-\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$$

- large sample $100(1-\alpha)\%$ CI for p
- $z_{1-\alpha/2}$ upper $\alpha/2$ percentile point of standard normal

Prevalence study

Experiment: $n = 20$, $x = 2$.
Problem: Summarize uncertainty in Confidence Interval.
Solution: Note that $\hat{p} = 2/20$, so

$$\hat{p} - z_{\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} \leq p \leq \hat{p} + z_{1-\alpha/2}\sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$$

$$0.10 - 1.96\sqrt{\frac{0.10(1-0.10)}{20}} \leq p \leq 0.10 + 1.96\sqrt{\frac{0.10(1-0.10)}{20}}$$

$$0.0175 \leq p \leq 0.3310$$

Conclusion: We are 95% certain that true prevalence belongs to interval $(0.0175; 0.3310)$

Influence of n on Confidence Interval

Let's repeat foregoing with several n:

Table: CI for various n

n	x	$\hat{p}$	**CI**	
10	1	0.10	0.0052	0.4588
20	2	0.10	0.0175	0.3310
50	5	0.10	0.0374	0.2259
100	10	0.10	0.0516	0.1803
1000	100	0.10	0.0824	0.1206
10000	1000	0.10	0.0942	0.1060

- Conclusion: CI becomes smaller as n increases.
- Remark: n small, then CI may pass 0 or 1! (Use e.g. exact methods)

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Basic Concepts

A start up: `https://www.youtube.com/watch?v=LCndoLgoPVk`

Test	Status D	H
T_+	t_+	f_+
T_-	f_-	t_-

- Status of person is Disease (D) or Healthy (H)
- Outcome of test is $+$ indicating D or negative indicating H
- Test is **correct** for
  - true positives t_+ (Disease detected)
  - true negatives t_- (Healthy detected)
- Test is **incorrect** for
  - false positives f_+ (D indicated for H)
  - false negatives f_- (H indicated for D)
- Prevalence = probability of having disease $P(D)$ property of population

Properties of Test

Test	Status D	H
T_+	t_+	f_+
T_-	f_-	t_-

- Sensitivity = probability of positive test having disease $P(T_+|D)$
- Specificity = probability of negative test being healthy $P(T_-|H)$

$$\text{Likelihood ratio positve } LR(+) = \frac{P(T_+|D)}{P(T_+|H)} \text{(larger = better)}$$

$$\text{Likelihood ratio negative } LR(-) = \frac{P(T_-|D)}{P(T_-|H)} \text{ (smaller = better)}$$

$$\text{diagnostic odds ratio } DOR = \frac{LR(+)}{LR(-)} \text{ (larger = better)}$$

See also

- `https://www.youtube.com/watch?v=2cI7TtcEZxE`
- `https://www.youtube.com/watch?v=TzPvCSFZUSQ`

Predictive Value of the Test

Test	Status D	H
T_+	t_+	f_+
T_-	f_-	t_-

Perspective of patient

- Positive Predictive Value $P(D|T_+)$: probability of having D given a positive test outcome
- Negative Predictive Value $P(H|T_-)$: probability of H given a negative test outcome

$$P(D|T_+) = \frac{P(T_+|D) \cdot P(D)}{P(T_+)}$$

Predictive Value Positive depends upon Sensitivity, probability of D, probability of T_+.

Estimation from the 2 by 2 frequency table

Test	Status D	H
T_+	t_+	f_+
T_-	f_-	t_-

$$P(D) \approx \frac{t_+ + f_-}{t_+ + f_+ + f_- + t_-}; \quad P(H) \approx \frac{f_+ + t_-}{t_+ + f_+ + f_- + t_-}$$

$$\text{sensitivity} = P(T_+|D) \approx \frac{t_+}{t_+ + f_-}; \quad \text{specificity} = P(T_-|H) \approx \frac{t_-}{f_+ + t_-}$$

$$PPV = P(D|T_+) \approx \frac{t_+}{t_+ + f_+}; \quad NPV = P(H|T_-) \approx \frac{t_-}{f_- + t_-}$$

$$LR(+) \approx \frac{\text{sensitivity}}{1 - \text{specificity}}; \quad LR(-) \approx \frac{1 - \text{sensitivity}}{\text{specificity}}$$

See also

- https://www.youtube.com/watch?v=mYWN685SrU0
- https://www.youtube.com/watch?v=7fLohSQOsNs

Diabetes in Population 1 (Bouter, 2005, p264)

Test	Status D	H	
T_+	$t_+ = 225$	$f_+ = 225$	450
T_-	$f_- = 25$	$t_- = 525$	550
	250	750	1000

$$P(D) \approx \frac{250}{1000} = 0.25; \quad P(H) \approx \frac{750}{1000} = 0.75$$

$$PPV = P(D|T_+) \approx \frac{225}{450} = 0.50; \quad NPV = P(H|T_-) \approx \frac{525}{550} = 0.95$$

$$LR(+) \approx 3(\text{CI } 2.67; 3.37); \; LR(-) \approx 0.14(\text{CI } 0.10; 0.21)$$

- Prevalence: Probability of having diabetes is 0.25
- Probability of diabetes given test positive is 0.50
- sensitivity 0.9 (95% CI 0.86 0.93); correctly diagnosed having *D*
- specificity 0.7 (95% CI 0.67; 0.73); correctly diagnosed *H*

Diabetes in Population 2 (Bouter, 2005, p266)

Test	Status D	Status H	
T_+	$t_+ = 225$	$f_+ = 29925$	30150
T_-	$f_- = 25$	$t_- = 69825$	69850
	250	99750	1000000

$$P(D) \approx \frac{250}{1000000} = 0.0025; \quad P(H) \approx \frac{99750}{1000000} = 0.9975$$

$$PPV = P(D|T_+) \approx \frac{225}{30150} = 0.0075; \; NPV = P(H|T_-) \approx \frac{69825}{69850} = 0.9$$

$$LR(+) \approx 3\,(\text{CI}2.88; 3.13); \; LR(-) \approx 0.14\,(\text{CI } 0.10; 0.21)$$

- Prevalence: Probability of having diabetes is 0.0025
- Probability of diabetes given test positive is 0.0075 (!)
- sensitivity 0.9 (95% CI 0.86 0.93); correctly diagnosed having *D*
- specificity 0.7 (95% CI 0.7; 0.7); correctly diagnosed *H*

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33 Diagnostic Studies by MMSE on Dementia

The diagnostic instrument MMSE to detect mild cognitive impairment. (Mitchell, A. (2009). A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. Journal of Psychiatric Research, 43, 411431.)

	TP	FN	FP	TN
1	66	4	240	870
2	118	12	10	110
3	48	20	64	990
⋮	⋮	⋮	⋮	⋮
33	78	34	46	376

- Demonstration during lecture UsingR for forest plots of: Sensitivities, Specificities, posLR, negLR, DOR
- Warning: meta analysis of sensitivities can be misleading...

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Receiver Operating Characteristic curve

ROC curve

- plot of sensitivity against 1- specificity of screening test.
- different points on curve correspond to different cut-off points used to designate test positive
- sensitivity = (estimated) probability that symptom is present given that person has disease
- specificity = (estimated) probability that symptom is *not* present given that person does *not* have disease

See also

- `https://www.youtube.com/watch?v=1Ha1UYAxGxs`
- `https://www.youtube.com/watch?v=WO8Re7YqnP0`

Computed Tomographic (CT) images (Rosner, 2000, Fundamentals of Biostatistics)

Predictor	Normal	Abnormal
Definitely Normal 1	33	3
Probably normal 2	6	2
Questionable 3	6	2
probably abnormal 4	11	11
Definitely Abnormal 5	2	33
Sum	58	51

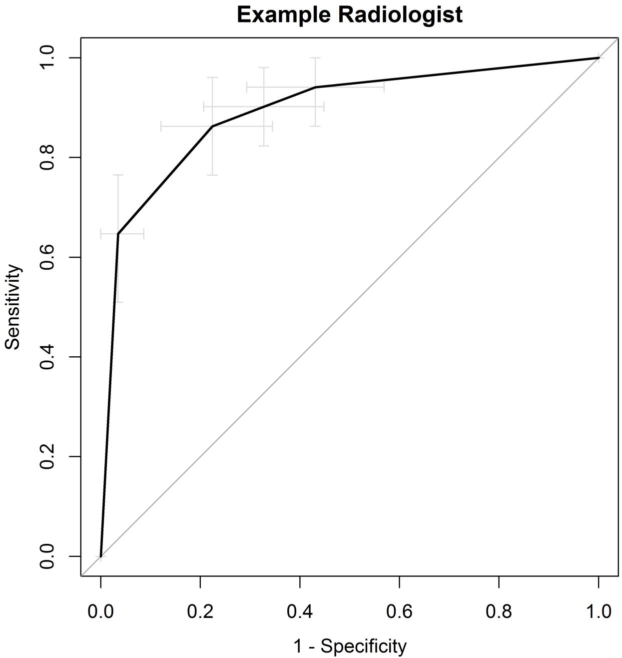
sensitivity 4+ = Prob symptom given disease = $\frac{11+33}{51} = 0.86$
specificity 4+ = Prob no symptom given normal = $\frac{33+6+6}{58} = 0.78$
sensitivity 5+ = Prob symptom given disease = $\frac{33}{51} = 0.65$
specificity 5+ = Prob no symptom given normal = $\frac{33+6+6+11}{58} = 0.97$

Continuation Example Radiologist

Predictor	Nor.	Ab.	Sensitivity	Specificity	1 - Specificity
Def. Nor. 1+	33	3	1	0	1
Pro. Nor. 2+	6	2	.94	.57	.43
Quest. 3+	6	2	.90	.67	.33
Prob. Ab. 4+	11	11	.86	.78	.22
Def. Ab. 5+	2	33	.65	.97	.03
6+			0	1	0

ROC is Graph with

- horizontally 1 - Specificity
- vertically Sensitivity


Example Radiologist
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0