

MATH364 Summer 2002 Exam Solutions

1. (a) ROC curve is a plot of sensitivity vs. specificity. Used to illustrate the behaviour of a diagnostic test based on a continuous measurement by plotting (sens, spec) at different cut-off values. The best cut-off values are those towards the top right of the plot.

[2 marks]

- (b) (i)

	Y	N
0-9	2	366
10+	24	493
Total	26	859

$$\text{Sensitivity} = 24/26 = 92\%.$$

$$\text{Specificity} = 366/859 = 43\%.$$

	Y	N
0-14	9	659
15+	17	200

$$\text{Sensitivity} = 17/26 = 65\%.$$

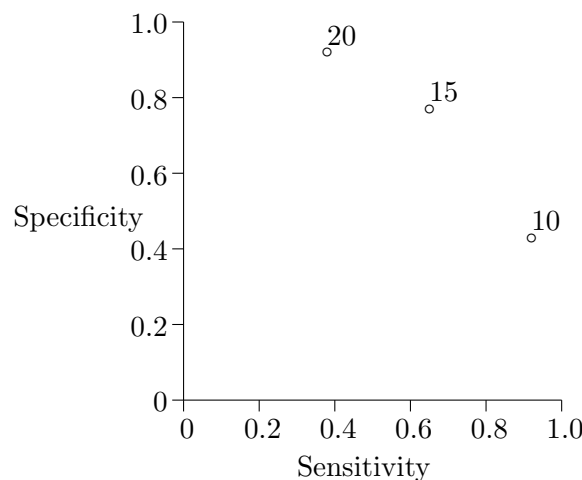
$$\text{Specificity} = 659/859 = 77\%.$$

	Y	N
0-19	16	789
20+	10	70

$$\text{Sensitivity} = 10/26 = 38\%.$$

$$\text{Specificity} = 789/859 = 92\%.$$

ROC curve:



[2 marks for using correct definitions of Sensitivity and Specificity;

5 marks for correctly computing all the values, with a mark lost for each mistake;

3 marks for the graph.]

- (ii) Best cut-off level is WBC count of 10, with sensitivity of 92% and 43%. Important to have high sensitivity, as bacteremia can have serious complications; not so important to have high specificity, since those who test positive are only being selected for further testing.

[2 marks]

(iii) For the sample, with cut-off value of 10, $ppv = 24/(24+493) = 4.64\%$. Prevalence
 $= 26/(26 + 859) = 2.94\%$.

[2 marks]

(iv) With population prevalence of 10%, cut-off value of 10,

$$ppv = \frac{\text{Prev} \times \text{Sens}}{\text{Prev} \times \text{Sens} + (1 - \text{Prev})(1 - \text{Spec})} = \frac{0.1 \times 0.92}{0.1 \times 0.92 + 0.9 \times 0.57} = 15.2\%$$

[2 marks for formula;

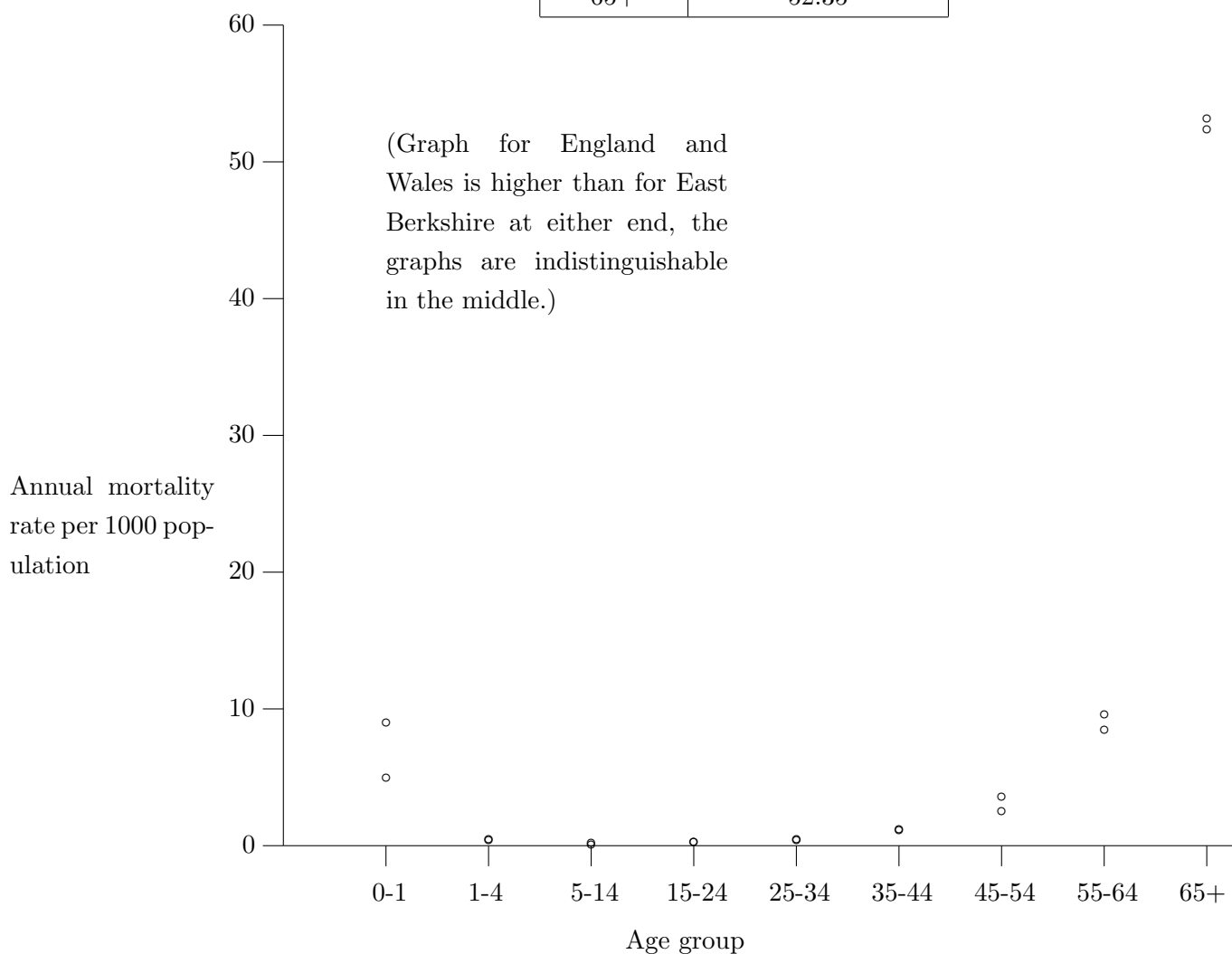
2 marks for correct calculation of value.]

2. (a) Standardisation is important as different geographical areas will have different age and sex structures, which will affect the mortality rate, so need to take into account age and sex to see if there seem to be other factors affecting mortality rates.

[2 marks]

- (b) (i) Female annual mortality rates in East Berkshire:

Age group	Death rate per 1000
0-1	5
1-4	0.51
5-14	0.08
15-24	0.28
25-34	0.42
35-44	1.11
45-54	2.50
55-64	8.45
65+	52.35



Comment: The rates for East Berkshire are all lower than those for England and Wales, except in age group 1-4. However, with the exception of age group 0-1,

the differences are all quite small.

[2 marks for calculation of rates;

3 marks for graph;

1 mark for comment.]

(ii) Expected numbers of female deaths in East Berkshire:

Age group	Expected deaths
0-1	21.6
1-4	3.96
5-14	4.82
15-24	8.55
25-34	12.95
35-44	29.16
45-54	73.44
55-64	185.28
65+	1335.32

Total expected deaths $E = 1675.08$. Total observed deaths $O = 1593$.

$SMR = 1593/1675.08 = 95.1\%$.

Female death rate in East Berkshire is estimated to be 95.1% of the national average, once age structure is taken into account.

[3 marks for expected numbers;

2 marks for SMR value;

1 mark for interpretation.]

(iii) 95% CI for SMR is

$$95.1 \pm 1.96 \times \frac{95.1}{\sqrt{1593}} = (90.43, 99.77)$$

Quite confident that the female death rate for East Berkshire is between 90.4% and 99.8% of the national average. This interval excludes 100% (though only just), so there is significant evidence that the East Berkshire female death rate is lower than the national rate.

[3 marks for correct formula for CI;

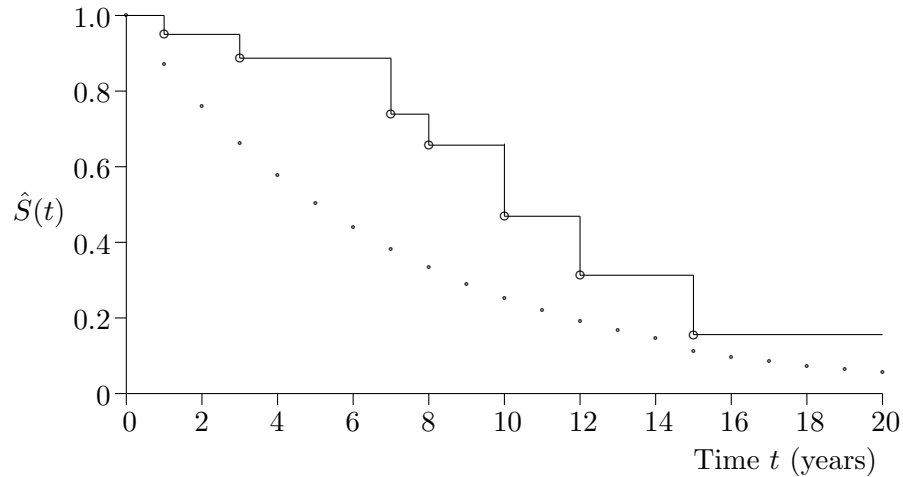
1 mark for correct calculation of CI;

2 marks for interpretation.]

3. (a)

$t_{(i)}$	n_i	d_i	$1 - (d_i/n_i)$	$S(t_i+)$
1	20	1	19/20	0.950
3	15	1	14/15	0.887
7	12	2	10/12	0.739
8	9	1	8/9	0.657
10	7	2	5/7	0.469
12	3	1	2/3	0.313
15	2	1	1/2	0.156

Kaplan-Meier estimate and Exponential survivor function from part (b):



[3 marks for t , n , d values;

3 marks for $S(t)$ values;

4 marks for K-M graph.]

(b) Mean of all values is $1/\hat{\lambda} = 146/20 = 7.3$, so that $\hat{\lambda} = 0.1370$.

Exponential survival function is $S(t) = \exp(-\lambda t)$.

[2 marks for $\hat{\lambda}$;

1 mark for $S(t)$;

2 marks for graph.]

(c) The exponential curve lies well below the Kaplan-Meier estimate. This is as one would expect, because treating censored observations as uncensored will lead to under-estimation of the survival probability. The value of a censored observation is always less than the true death time for that individual.

Would prefer the Kaplan-Meier estimate, because the Exponential model (i) doesn't seem to fit terribly well; (ii) imposes a survival time distribution which may not be correct; and (ii) treats censored observations in a way which leads to bias.

[2 marks for comparison between K-M and Exponential;

3 marks for explaining preference for K-M.]

4. (a) For no treatment, $\mu_N = 0.24$, $\sigma_N = 0.02$,

$$\begin{aligned}\alpha_N &= \frac{0.24^2 \times 0.76}{0.02^2} - 0.24 = 109.44 - 0.24 = 109.2 \\ \alpha_N + \beta_N &= \frac{0.24 \times 0.76}{0.02^2} - 1 = 455, \text{ so } \beta_N = 455 - 109.2 = 345.8\end{aligned}$$

For treatment, $\mu_T = 0.2$, $\sigma_T = 0.04$,

$$\begin{aligned}\alpha_T &= \frac{0.2^2 \times 0.8}{0.04^2} - 0.2 = 20 - 0.2 = 19.8 \\ \alpha_T + \beta_T &= \frac{0.2 \times 0.8}{0.04^2} - 1 = 99, \text{ so } \beta_T = 99 - 19.8 = 79.2\end{aligned}$$

[1 mark each for $\alpha_N, \beta_N, \alpha_T, \beta_T$.]

(b) Prior beliefs:

$$\begin{aligned}\log(\theta_N / (1 - \theta_N)) &\sim N\left(\log\left(\frac{109.2 - 0.5}{345.8 - 0.5}\right), \frac{1}{109.2} + \frac{1}{345.8}\right) \\ &\sim N(\log(0.3148), 0.01205) \sim N(-1.156, 0.01205) \\ \log(\theta_T / (1 - \theta_T)) &\sim N\left(\log\left(\frac{19.8 - 0.5}{79.2 - 0.5}\right), \frac{1}{19.8} + \frac{1}{79.2}\right) \\ &\sim N(\log(0.2452), 0.06313) \sim N(-1.406, 0.06313) \\ \log(\text{OR}) &\sim N(-0.25, 0.07518)\end{aligned}$$

Hence 95% CI for $\log(\text{OR})$ is

$$-0.25 \pm 1.96\sqrt{0.07518} = (-0.787, 0.287)$$

and 95% CI for the odds ratio is (0.455, 1.332).

[3 marks for distribution of $\log(\text{OR})$;

2 marks for CI for log odds ratio;

1 mark for CI for odds ratio.]

(c) $r_N = 4$, $n_N = 20$, $r_T = 1$, $n_T = 20$, so posterior distribution of log odds ratio has

$$\begin{aligned}\mu &= \log\left(\frac{(19.8 + 1 - 0.5)(345.8 + 16 - 0.5)}{(109.2 + 4 - 0.5)(79.2 + 19 - 0.5)}\right) \\ &= \log\left(\frac{20.3 \times 361.3}{112.7 \times 97.7}\right) = \log(0.6661) = -0.4063 \\ \sigma^2 &= \frac{1}{109.2 + 4} + \frac{1}{345.8 + 16} + \frac{1}{19.8 + 1} + \frac{1}{79.2 + 19} \\ &= 0.008834 + 0.002764 + 0.048077 + 0.010183 = 0.06986\end{aligned}$$

Hence posterior 95% CI for $\log(\text{OR})$ is

$$-0.4063 \pm 1.96\sqrt{0.06986} = (-0.9243, 0.1117)$$

and posterior 95% CI for the odds ratio is (0.3968, 1.1182).

[4 marks for distribution of $\log(\text{OR})$;

1 mark for CI for log odds ratio;

1 mark for CI for odds ratio.]

(d) Posterior CI for OR includes 1, so it's plausible that the treatment has no effect. The prior CI for OR also included 1. However, in the sample data, the death rate among non-treated patients was 4 times that among treated patients, suggesting treatment is effective. Problem is that the trial was very small, with only 40 patients altogether. Also very dependent upon the prior beliefs of a single expert, who believed the treatment to have some effect, but not very much.

[2 marks for comment on posterior vs prior and sample;

2 marks for comment on design.]

5. (a) Pooled log odds ratio is positive, suggesting that over all trials, Octreotide produces a higher proportion of responses than the control treatment.
[2 marks]

(b)

Trial	a_i	b_i	c_i	d_i	OR	\hat{y}_i	w_i	$w_i(\hat{y}_p - \hat{y}_i)^2$
1	3	10	4	9	0.675	-0.393	1.259	2.178
2	6	4	2	8	6	1.792	0.960	0.726
3	34	40	18	32	1.511	0.413	7.081	1.838
4	19	2	3	17	53.833	3.986	1.058	9.934
5	16	4	6	14	9.333	2.234	1.816	3.123
6	22	1	5	15	66	4.190	0.762	8.136
7	16	2	12	1	0.667	-0.405	0.608	1.071
8	5	12	7	9	0.536	-0.624	1.861	4.451

So $Q = 31.46$. From tables, $\chi^2_7(0.0005) = 26.02$, so for the test for heterogeneity $p < 0.0005$. Very strong evidence of heterogeneity between trials. Not appropriate to use a pooled estimate of treatment effect.

[3 marks for \hat{y} values;

3 marks for w values;

2 marks for Q ;

2 marks for carrying out test and reporting conclusion;

1 mark for saying pooled estimate not appropriate.]

- (c) Subgroup analysis not a good idea because (i) the group sizes are small, so low power; (ii) multiple testing likely to lead to significant result even in the absence of an effect; (iii) not clear that there is any clinical reason to believe AIDS patients and post-chemotherapy patients would respond differently to Octreotide for refractory diarrhoea.

[3 marks]

- (d) *Publication bias* is the fact that trials which produce statistically significant results are more likely to get published than those which don't.

To investigate the possibility of publication bias, plot precision against treatment effect estimate for the 8 trials. In this case, treatment effect estimate is the log odds ratio \hat{y}_i and precision is $1/\text{s.d.}(\hat{y}_i)$. In the absence of bias, the plot should be symmetrical and funnel-shaped. If there is bias, the plot will be asymmetric.

[4 marks]

6. (a) A period effect is a systematic difference between the two periods of the trial, such as observations in the second period being generally higher than in the first period, irrespective of treatment. A carryover effect exists when the treatment effect in the first period carries over into the second period, so that the difference between the treatments depends on the order in which they are given.

[2 marks for period effect;

2 marks for carryover effect.]

(b)

Group 1			Group 2		
D	P	(D+P)/2	P	D	(D+P)/2
8	5	6.5	12	11	11.5
14	10	12	6	8	7
8	0	4	13	9	11
11	6	8.5	8	8	8
9	7	8	8	9	8.5
3	5	4	4	8	6
6	0	3	8	14	11
0	0	0	2	4	3
13	12	12.5			

For group 1, $\bar{x}_1 = 58.5/9 = 6.5$, $s_1^2 = ((6.5 - 6.5)^2 + \dots + (12.5 - 6.5)^2) / 8 = 139.5/8 = 17.4375$, $s_1 = 4.176$.

For group 2, $\bar{x}_2 = 66/8 = 8.25$, $s_2^2 = ((11.5 - 8.25)^2 + \dots + (3 - 8.25)^2) / 7 = 60/7 = 8.5714$, $s_2 = 2.928$.

Test for carryover using two-sample t -test, assuming equal variances.

$$\begin{aligned}
 s_p &= \sqrt{\frac{(n_1 - 1) s_1^2 + (n_2 - 1) s_2^2}{n_1 + n_2 - 2}} \\
 &= \sqrt{\frac{139.5 + 60}{15}} = \sqrt{13.3} = 3.647 \\
 T &= \frac{\bar{x}_1 - \bar{x}_2}{s_p \sqrt{(1/n_1) + (1/n_2)}} \\
 &= \frac{6.5 - 8.25}{3.647 \sqrt{(1/9) + (1/8)}} = -0.988
 \end{aligned}$$

Compare with t -distribution on 15 degrees of freedom. $t_{15}(0.2) = 0.8662$, $t_{15}(0.15) = 1.074$. So $0.3 < p < 0.4$, and there is no evidence of a carryover effect.

[1 mark each for $\bar{x}_1, \bar{x}_2, s_1^2, s_2^2$;

1 mark for formula for s_p ;

1 mark for calculation of s_p ;

2 marks for formula for T ;

1 mark for calculation of T ;

3 marks for carrying out test and reporting conclusion.]

- (i) If no evidence of carryover, examine the evidence for a period effect. If no period effect, go on to perform a two-sample t -test on the differences between treatments

from the two groups to see if there is evidence of a difference in effectiveness between the treatments. If there is a significant period effect, need to consider whether the crossover trial was appropriate.

[2 marks]

- (ii) If evidence of carryover, restrict subsequent analysis to data from the first period only. Compare treatments (in terms of their first period effectiveness) via a two-sample t -test.

[2 marks]

7. (a) Logistic regression is used when we have a binary outcome variable depending upon covariates which may be a mixture of continuous and categorical variables. The model is

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1x_1 + \beta_2x_2 + \dots$$

where p is the probability of some event of interest, x_1, x_2, \dots are covariate values, and $\beta_0, \beta_1, \beta_2, \dots$ are parameters to be estimated.

Purposes of logistic regression analysis are (i) to describe the relationship between the outcome variable and explanatory variables; (ii) to predict future outcomes for given covariate values; (iii) to adjust for the effects of other covariates when examining the effect of one particular covariate.

Logistic regression appropriate for survival data if the main interest is in whether a particular event happened, rather than when it happened. For instance, if the event is rare and we have similar lengths of follow-up on all individuals in the study.

[2 marks for description of model;

3 marks for purposes;

1 mark for when it is appropriate.]

- (b) Variable selection used to decide which covariates should be included in the model. Important because if a variable has no significant effect, you don't want to waste time/effort including it, but if a variable does have a significant effect, that needs to be taken into account.

Methods (any two of):

Forwards selection: start with no covariates and add covariates in one at a time, adding in the one with the lowest p -value, stopping when the lowest p -value is not sufficiently low, for instance greater than 0.05.

Backwards selection: start with all the covariates, delete covariates one at a time, each time deleting the one with the highest p -value, stopping when the highest p -value becomes sufficiently low, for instance less than 0.05.

Stepwise: forwards selection, but after adding each new covariate, if any covariate has p -value greater than some threshold (eg 0.05), remove the covariate with the highest p -value.

All subsets: fit every possible combination of covariates, see which is 'best', in some sense.

[2 marks for explaining importance;

1 mark each for two methods.]

- (c) Denoting by p the survival probability, fitted model is

$$\ln(\hat{p}/(1-\hat{p})) = -2.354 + 0.5324(\text{haemoglobin}) - 0.4892(\text{bilirubin})$$

The odds ratio for survival is higher for infants with higher haemoglobin levels, lower for infants with higher bilirubin levels.

For each 1 g/100 ml increase in haemoglobin concentration, the odds ratio for survival increases by a factor of $\exp(0.5324) \approx 1.7$. A 95% CI for $\hat{\beta}_1$ is $0.5324 \pm 1.96 \times 0.1487 = (0.241, 0.824)$, so 95% CI for the factor by which the odds ratio increases is (1.27, 2.28).

For each 1 mg/100 ml increase in bilirubin concentration, the odds ratio for survival is multiplied by a factor of $\exp(-0.4892) \approx 0.61$. Odds of survival decrease as bilirubin concentration increases. A 95% CI for $\hat{\beta}_2$ is $-0.4892 \pm 1.96 \times 0.3448 = (-1.165, 0.187)$, so 95% CI for the factor by which the odds ratio is multiplied is (0.31, 1.21).

For bilirubin, the CI for odds ratio increase factor includes 1, and the given p -value is 0.167, so it seems that bilirubin concentration is not significant. Should take it out of the model and try fitting haemoglobin alone.

For haemoglobin, p -value is 0.001 (and CI excludes 1) so strong evidence of significance.

[1 mark for fitted model;

1 mark for saying odds of survival better for higher haemoglobin, lower for higher bilirubin;

1 mark for estimated effect of haemoglobin;

2 marks for CI for haemoglobin;

1 mark for estimated effect of bilirubin;

2 marks for CI for bilirubin;

2 marks for further analysis.]