Log-linear modeling of dependence among diagnostic tests

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Background

- Many disease surveillance programs and practitioners use multiple tests in screening. Idea: more tests = more info on disease status.

- Typically dependence among tests not considered in test selection procedures by practitioners.

- Positive dependence among test results should be expected where tests measure similar biologic processes.

- Measures of pair-wise test dependence described in Gardner et al. (2000). Describing dependence among more than 2 tests requires consideration of all tests simultaneously.

Knowledge of conditional independence is useful

eg. Three binary tests: T_A, T_B, and T_C.

D is **Disease Status**.

$(D \perp T_C)|T_A, T_B$ tells us given T_A and T_B, D is independent of T_C.

• No more information on disease status from T_C once T_A and T_B are performed.

• Eliminates redundancy. Saves $$$.

• An approach to modeling dependence among several tests is the log-linear model.

Log-linear models

Log-linear model is ANOVA-type model for cross-classified data.

- Generalization of logit-model.

- Log of expected cell counts are modeled as sum of parameters indexed by factor levels in table.

- Presence of interaction terms indicates a specific dependence among factors in the table.

- Log-linear model doesn't care if diseased and non-diseased totals are fixed. Can do retrospective (case-control) study.

Two-test situation

X_{ijk} is cell count in contingency table:

Diseased ($D+$)

		T_B +	T_B −	Totals
T_A	+	X_{111}	X_{112}	$X_{11\bullet}$
	−	X_{121}	X_{122}	$X_{12\bullet}$
	Totals	$X_{1\bullet 1}$	$X_{1\bullet 2}$	$n_1 = X_{1\bullet\bullet}$

Non-diseased ($D-$)

		T_B +	T_B −	Totals
T_A	+	X_{211}	X_{212}	$X_{21\bullet}$
	−	X_{221}	X_{222}	$X_{22\bullet}$
	Totals	$X_{2\bullet 1}$	$X_{2\bullet 2}$	$n_2 = X_{2\bullet\bullet}$

Examples:

- $\log(E(X_{ijk})) = u_{DA(ij)} + u_{DB(ik)}$
  - $(T_A \perp T_B)|D$
  - Conditional independence
  - Both tests are needed
- $\log(E(X_{ijk})) = u_{D(i)} + u_{A(j)} + u_{B(k)}$
  - $D \perp T_A \perp T_B$
  - Neither test is useful
  - Should never fit given reasonable tests
- $\log(E(X_{ijk})) = u_{DB(ik)} + u_{AB(jk)}$
  - $(D \perp T_A)|T_B$
  - T_A is redundant given T_B; T_A gives no add'l info for diagnosis

Swine Brucellosis

Ferris et al. (1995) compared the sensitivities and specificities of 6 tests:

- particle concentration fluorescence immunoassay (PCFIA)
- automated complement fixation assay (ACF)
- card test
- buffered acidified plate antigen assay (BAPA)
- standard tube test (STT)
- rivanol

Details

- 221 swine from 39 naturally-infected herds; sample prevalence was 21%.

- Bacteriologic culture is “gold-standard”.

- Most pairs of test had high positive dependence in both sensitivity and specificity; expect redundancy among tests.

- Only 5-6 swine from each herd: assume herd effect negligible so have roughly multinomial sampling as did Ferris et al. (1995) and Gardner et al. (2000)

- Used same cut-offs as original authors for indication of presence of disease.

Log-linear modeling approach

- Fit model implies $(D \perp A, B, C, S)|R, P$. Given the results of the Rivanol and PCFIA tests, the other tests provide no additional information about the disease status of an animal.

- Using graphical modeling techniques can also surmise simpler interpretations. For example $(D \perp S)|P$; given PCFIA, the tube test gives no add'l info on disease.

- Can verify results by looking at empirical estimates of sensitivity and specificity for two most common multiple test paradigms: series and parallel testing.

Test	Sens.	(95% CI)
P	0.79	(0.65,0.91)
R	0.58	(0.44,0.72)
$P \cup R$	0.79	(0.65,0.91)
$C \cup P \cup A \cup B \cup R \cup S$	0.81	(0.70,0.91)
$P \cap R$	0.58	(0.44,0.72)
$C \cap P \cap A \cap B \cap R \cap S$	0.51	(0.37,0.65)

Test	Spec.	(95% CI)
P	0.89	(0.84,0.93)
R	0.95	(0.91,0.98)
$P \cup R$	0.89	(0.91,0.98)
$C \cup P \cup A \cup B \cup R \cup S$	0.61	(0.54,0.69)
$P \cap R$	0.95	(0.91,0.98)
$C \cap P \cap A \cap B \cap R \cap S$	0.96	(0.92,0.99)

- Extreme dependence among tests.

- PCFIA test alone has a sensitivity of 0.79, very close to maximum sensitivity possible of *all 6 tests interpreted in parallel* at 0.81.

- Rivanol alone has a specificity of 0.95, very close to the maximum specificity possible of *all 6 tests in series* at 0.96.

Main points

- Ignoring test dependence leads to unnecessary cost and effort.

- Log-linear model describes dependency structure among several tests and disease.

- Log-linear modeling picks out subset of tests that contains all information on disease status.

- Two other diseases looked at: swine toxoplasmosis and bovine paratuberculosis. Found similar redundancies among tests.