Locksley Messam
Conor McAloon
Eleftherios Meletis

Diagnostic test evaluation with Bayesian latent class models

COST is supported by the EU Framework Programme Horizon 2020

HARMONY

Novel tools for test evaluation and disease prevalence estimation

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Examining the assumptions of the BLCA model for diagnostic test validation in more detail

COST is supported by the EU Framework Programme Horizon 2020

Locksley L. McV. Messam Dr. Med. Vet., PhD.
Lecturer in Veterinary Epidemiology
University College Dublin, School of Veterinary Medicine,
Section: Herd Health and Animal Husbandry

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Novel tools for test evaluation and disease prevalence estimation

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Context: Estimating Parameters I (Se, Sp)

- Estimating parameters (Se, Sp, P) - where R-tests applied to S-populations.
- Problems of degrees of freedom to estimate parameters (*"number of values in final calculation of a statistic that are allowed to vary").*
- If R tests – S populations: $(2^R - 1)S$ df. to estimate $(2R+1)S$ parameters
- R = S = 2 implies 6 df and 10 parameters: 4 Se, 4 Sp, 2 Prev.
- If Se and Sp constant across pops. then 2 Se, 2 Sp and 2 Prev. (6 df. and 6 parameters)

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Context: Estimating Parameters II (Prevalence)

- Could reduce df. by using one population ie Prev1 = Prev2

→ Biased estimates in the estimation procedure.

→ We need distinct prevalences

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Context: Estimating Parameters III (Conditional Dependence)

- Dependency is uncertainty. Model all uncertainty!!
- If tests are not correlated then no uncertainty to model
- If the tests are conditionally dependent then dependence is described by parameters (+ ? more parameters) → Not enough df.
- Issue of conditional dependence not immaterial

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What then are the assumptions?: Hui-Walter Paradigm

- Prevalences are different in the S populations (groups??)
- Sensitivities and specificities of the R tests are invariant across populations.
- Tests are conditionally independent (given the true disease status)

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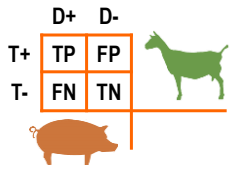
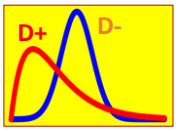
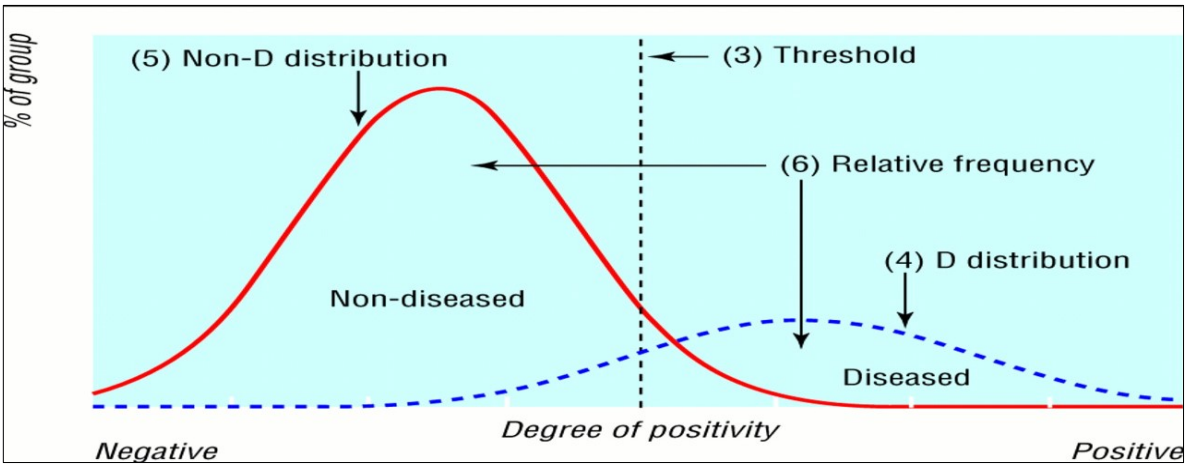


Diagnostic Tests: Diseased and Non-Diseased





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Different Prevalences in Pop 1 and Pop 2 (P1≠P2)

Implications: **Need a biologic (or subject matter) rationale!!**

- Different numbers of truly (D+) given fixed size (ie if n1 = n2).
- If P1 ≠ P2 distribution of individuals with disease D+ related characteristics different (spectrum) → if related to test target Se constant (potentially problematic)
- Potential solution - Distribution of individuals with D+- related characteristics different (but unrelated to test target)

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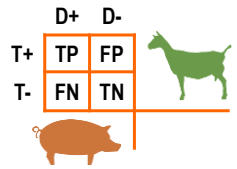

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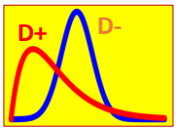

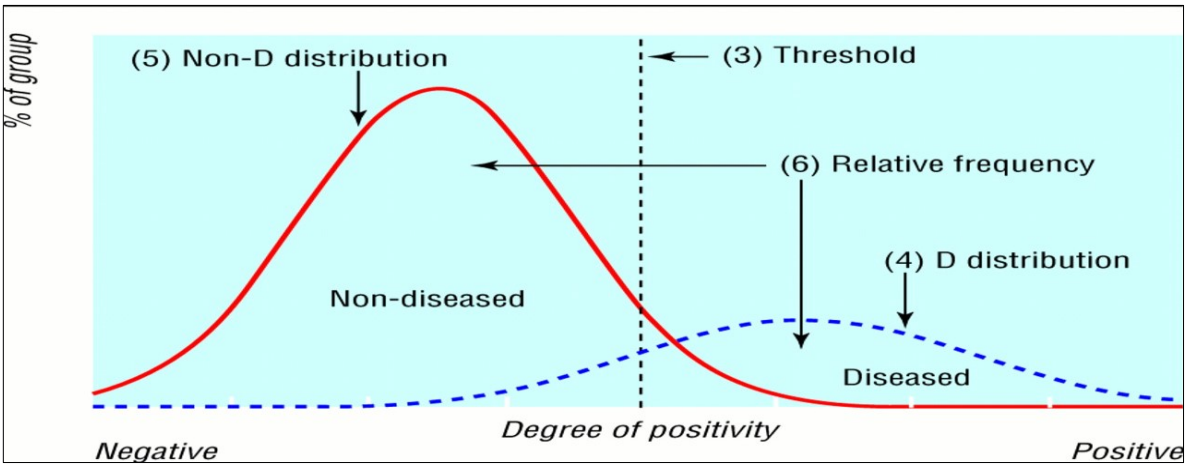

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Different Prevalences in Pop 1 and Pop 2 (P1≠P2)

Violations:

- Smaller the differences, poorer the precison of Se and Sp.
- If precision of Se (Sp) too low – issues of validity!!
- Precision of Se affected more than precision of Sp (Sp sample size always larger).
- Estimate P1 and P2 separately (with either or both tests) to check for evidence of P1≠P2

Toft et. al. (2005), PVM 68:19-33

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Constant Se and Sp across Pop 1 and Pop 2

Implications: Need a biological rationale!

- Distribution of individuals with D+ (and hence T+) - related characteristics same (Spectrum same) – while (P1≠P2)
- Easier for non-continuos tests (X-rays, uLtra sounds etc.).
- Conceptually easier for Sp (spectrum of cross-reacting reacting agents the same?) .

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Constant Se and Sp across Pop 1 and Pop 2

Violations

- If Se11 ≠ Se12 but Sp1 or Sp2 = 100% – Posterior of Se1 is weighted average of Se11 and Se12. [Weight is function of expected no. of D+ in pops]
- If Se11 ≠ Se12 but Sp1, Sp2 ≠ 100% – Posterior not necessarily a weighted average – Posterior of Se1 may even be larger than Se11 and Se12 (problematic)
- Similar results expected for Sp (to be verified).
- Do 2 tests in 1 pop to check for evidence of different Se and Sp

Gardner et. al. (2009), PVM 68:116-121

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Conditional Independence of T1 and T2

Definition:

- Two tests (T1 and T2)are conditionally independent when the Se (or Sp) of T2 does not depend on the results of T1 (or vice versa) for diseased and non-diseased individuals.

- P(T2+|T1+, D+) = P(T2+|T1-, D+) = P(T2+|D+) *for Se2*
- P(T2-|T1+, D-) = P(T2-|T1-, D-) = P(T2-|D-) *for Sp2*
- P(T1+|T2+, D+) = P(T1+|T2-, D+) = P(T1+|D+) *for Se1*
- P(T1-|T2+, D-) = P(T1-|T2-, D-) = P(T1-|D-) *for Sp1*

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Conditional dependence of T1 and T2

Definition: Dependence

- Conditional dependence occurs when sensitivities and specificities vary depending on the result of another test.

- P(T2+|T1+, D+) ≠ P(T2+|T1-, D+)
- P(T2-|T1+, D-) ≠ P(T2-|T1-, D-)
- P(T1+|T2+, D+) ≠ P(T1+|T2-, D+)
- P(T1-|T2+, D-) ≠ P(T1-|T2-, D-)

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Conditional dependence of T1 and T2

Definition: Dependence

- Conditional dependence occurs when sensitivities and specificities vary depending on the result of another test.

- P(T2+|T1+, D+) > P(T2+|T1-, D+) – **Positive dependence (most plausible, Se decreases among T1- individuals**
- P(T2-|T1+, D-) < P(T2-|T1-, D-) - **Positive dependence (most plausible, Sp increases among T1- individuals**
- P(T2+|T1+, D+) < P(T2+|T1-, D+) – Negative dependence (Se increases among T1- individuals)
- P(T2-|T1+, D-) > P(T2-|T1-, D-) – Negative dependence (Sp increases among T1+ individuals)

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Conditional independence of T1 and T2

Conditional Independence: Need a biological rationale!

- If tests are used jointly, dependence issues must be considered.
- Tests measuring similar biological processes likely dependent.
- Dependence of test Se does not imply dependence of test Sp.
- Dependence is a matter of degree
- Dependence means correlation

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Conditional independence of T1 and T2

Conditional dependence: Implications

- Increase in parameters to model
- Additional parameters depend on biological considerations (should)
- Must model or.... biased estimates of Se and Sp
- Options:
  - Model covariances (2 parameters – D+, D-), priors not easy to find
  - Model Correlations
  - Model transformations (priors?)
- Need better prior info on (tests)
- Run both models and compare

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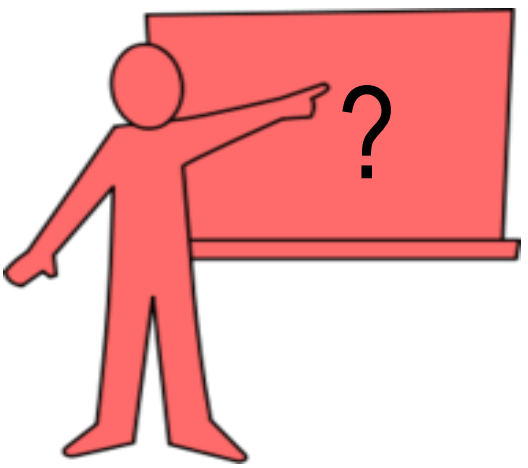

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