Using diagnostic tests to optimally control the spread of infectious diseases

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Background

- Farmer behaviour is an important factor in determining rates of disease transmission.
- How farmers manage disease through monitoring for its presence and controlling its spread has the potential to change the dynamics of disease spread.
- Sheep-scab is a parasitic mite disease which may give rise to clinical signs but also may be present in sheep which show no clinical signs. In order to determine the presence of scab in sub-clinical cases current tests employ a skin scraping test which has relatively low sensitivity.
- More recently Moredun Research Institute have developed an ELISA (blood) test to detect the presence of sheep-scab in sub-clinical cases.

Background

Background

- We develop a game theoretic model to investigate the circumstances under which farmer's would voluntarily adopt such a test taking into account both within and between flock transmission of the disease. In order to do this we first developed a two-farm meta-population model of within and between flock transmission of the disease without treatment or testing.
- We reformulated this in terms of a differential game model of diagnostic test adoption in which two farmers make strategic decisions as to whether or not to adopt the test.

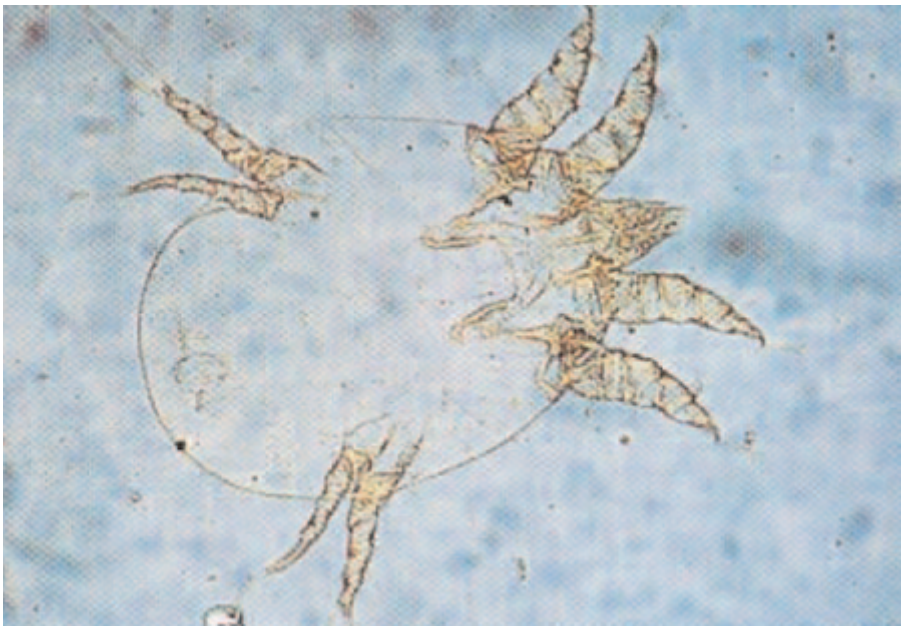

Figure 1: psoroptic mite

- We extend previous work by Bicknell et al. 1999 AJARE and Ceddia 2012 ERE to study diagnostic test adoption for sheep-scab in a competitive situation to farmer behaviour amongst sheep farmers. Previous bio-economic analyses of diagnostic tests include Bicknell et al. 1999 and Posner and Philipson 1993.

Economic epidemiology

- Seminal work: Posner, R. A. (1993). Private choices and public health: The AIDS epidemic in an economic perspective. Harvard University Press.
- Geoffard, P. Y., & Philipson, T. (1997). Disease eradication: private versus public vaccination. The American Economic Review, 222-230.
- Ceddia, M. G. (2012). Optimal disease eradication in sympatric metapopulations. Environmental and Resource Economics, 52(4), 499-530.

Economics of diagnostic testing

- Model of diagnostic test adoption Posner, R. A. (1993). Private choices and public health: The AIDS epidemic in an economic perspective. Harvard University Press.
- Bicknell, K. B., Wilen, J. E., & Howitt, R. E. (1999). Public policy and private incentives for livestock disease control. Australian Journal of Agricultural and Resource Economics, 43(4), 501-521.
- Hockstra, D. J. (1973). Partially Observable Markov Decision Processes with Applications (No. TR-156). STANFORD UNIV CALIF DEPT OF OPERATIONS RESEARCH.
- Hockstra, D. J., & Miller, S. D. (1976). Sequential games and medical diagnosis. Computers and Biomedical Research, 9(3), 205-215.
- Laking, G., Lord, J., & Fischer, A. (2006). The economics of diagnosis. Health economics, 15(10), 1109-1120.

Diagnostic testing

Assuming adoption sensitivity and specificity are calculated as follows:

	disease	No disease	
+ve	a	b (Type I)	a/(a+b)=PPV
-ve	c (Type II)	d	d/(c+d)=NPV
	a/(a+c) =Se	d/(b+d)=Sp	

perfect test corresponds to c=0 and b=0 no false negatives and no false positives.

In general not all sheep will be tested.

Tutorial on optimal control

- How do we manage a biological system through human action?
- Dynamic optimization problem:

$$\max_b \int_0^\infty U(\vec{x}, b) e^{-rt} dt$$

$$\dot{\vec{x}} = F(\vec{x}, b), \vec{x}(0) = \vec{x}_0$$

- Different approaches
- Calculus of variations (Euler-Lagrange)
- Dynamic programming (Hamilton-Jacobi-Bellman)
- Optimal Control (Pontryagin)

Pontryagin's Maximum Principle

Hamiltonian (current-value version:

$$H(\vec{x}, b, \vec{\lambda}) = U(\vec{x}, b) + \lambda F(\vec{x}, b)$$

First-order condition:

$$\frac{\partial H}{\partial b} = 0$$

$$\dot{\lambda} - r\lambda = -\frac{\partial H}{\partial x_i}, i = 1, \ldots, n$$

$$\dot{x_i} = \frac{\partial H}{\partial \lambda_i} = F_i(x_i, b), i = 1, \ldots, n$$

analytic solution of this system may not always be possible

Numerical optimal control

- Two approaches:
  - direct approach
  - indirect approach
- direct approach discretize the objective function and the control set.
- indirect approach discretize the resultant system of differential equations

The latter approach two main solutionmethods:

- (multiple) Shooting algorithm
- Collocation method

The model: set-up

- There is a single farm, sheep are assumed to homogeneously mix on the firm
- The farm consists of a sheep flock that is divided into five compartments:
  - susceptibles S
  - sub-clinically infective I_{sc}
  - clinically infective I_c
  - protected due to treatment P and
  - removed R due to death.
  - Infected animals that have reached the clinical stage are assumed to either die or recover at rate ρ.

Instantaneous farm profit

$$GM_i(N_i - I_{ci} - R_i - P_i) - GM_i D(I_{sci} + I_{ci})$$
$$-c_T T_i(N_i - R_i - P_i) - c_D(S_e + 1 - S_P)(N_i - I_{ci} - R_i - P_i)T_i$$

$$-c_D 0.5(N_i - I_{ci} - R_i - P_i)(1 - T_i)$$

- GM_i gross-margin for the i-th farm
- N_i flock size
- D damage parameter
- c_T marginal test cost
- c_D treatment (dipping) cost
- $T_i \in [0, \tau]$ treatment decision

The model

Farmers maximize the following

$$\max_{T\in[0,\tau]} \int_0^\infty \{GM(N - I_c - R - P) - GMDI_{sc}$$
$$-c_T T(N - I_c - R) - c_D(S_e S + (1 - S_p)I_{sc})T$$

$$-c_D 0.5(N - I_c - R - P)(1 - T)\} e^{-rt} dt$$

subject to the disease dynamics depicted on the following slides

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Disease dynamics

$$\frac{dS}{dt} = -\frac{\tilde{\beta}}{N - R} S(I_{sc} + \phi I_c)$$
$$-(1 - S_p)TS - 0.5S(1 - T) + \delta P, S_(0) = S_0$$

$$\frac{dI_{sc}}{dt} = \frac{\tilde{\beta}}{N - R} S(I_{sc} + \tilde{\phi} I_c)$$
$$-psiI_{sc} + \rho I_c - S_e T I_{sc} - 0.5 I_{sc}(1 - T), I_{sc}(0) = 0$$

$$\frac{dI_c}{dt} = \tilde{\psi} I_{sc} - \rho I_c - \mu I_c, I_c(0) = 0$$

Why 0.5? This has to do with Laplace principle of insufficient reason and the Ellsberg paradox. I am assuming there is no ambiguity in probabilities an alternative would be to build a model with ambiguity aversion.

Protection

$$\frac{dP}{dt} = (1 - S_p)TS + S_eTI_{sc}$$

$$+0.5(S + I_{sc})(1 - T) - \delta P, P(0) = 0$$

$$\frac{dR}{dt} = \mu I_c, R(0) = 0$$

and

$$N = S + I_{sc} + I_c + R + P$$

Hamiltonian

$H = GM(N-I_c-R-P)-GMDI_{sc}-c_TTest(N-I_c-R)-c_D(S_eS+(1-S_p)I_{sc})Test-c_D0.5(N-I_c-R-P)(1-Te$

To implement in R define the Hamiltonian as an expression:

```
H1 <- expression( GM * (N - Ic - R - P) - GM * D * Isc - cT*Test*(N
-Ic- R)- cD*(Se*S+(1-Sp)*Isc)*Test -cD*0.5*(N-Ic - R - P)*(1-Test)
+ L1*(- (beta/(N - R)) * S * (Isc + phi * Ic) - Se * S *Test - (1
- Test)*05*S + delta * P) + L2 * (beta/(N - R) * S * (Isc + phi *
Ic)- psi * Isc + rho * Ic - (1-Sp) * Isc* Test - (1-Test)*0.5*Isc)
+ L3 * (psi * Isc - rho * Ic - mu * Ic) + L4 * ((1-Sp) * Test * S
+ Se * Test * Isc + (1-Test)*0.5*(N - Ic - R - P) - delta * P) +
L5 * (mu * Ic) )
```

Symbolic algebra in R

- some packages Ryacas, RSymPy these don't suit our purpose however
- Use the native differentiation operator in R: D(expression,"Test")
- Need to automate algebra. How to do this?
- Use gsub(), paste() and cat() to write to file

- Example:

```
ex6<-c("dL1 <- r * L1","-","(",D(H1,"S"),")") ex6[4]<-gsub("Test",adopt,ex6[4])
cat(paste(ex6[1],ex6[2],ex6[3],ex6[4],ex6[5]),"\n",file="control-pmp-input.R",append=
TRUE) cat("\n",file="control-pmp-input.R",append=TRUE)
```

- Skipping writing to file: non-standard evaluation in the Meta-programming chapter, see Wickham, H. (2014). Advanced R. CRC Press (Thanks to Daniel for this suggestion).

Bang-bang solution

$$\frac{\partial \tilde{H}}{\partial T} = -c_T(N - R - P) - c_D(S_e S + (1 - S_p)I_{sc}) + c_D 0.5(N - I_c - R - P)$$
$$-\lambda_1(1 - S_p)S_- \lambda_2 S_e I_{sc} + \lambda_4((1 - S_p)S + S_e I_{sc}) > 0$$

then farmers will choose to test.

- Farmer's either test to the maximum or don't test.
- Test decisions vary with prevalence
- solution determines optimal timing of test adoption

Numerical challenges

- Two point-boundary value problem
- High-dimensionality (typical of compartmental models) creates additional challenges
- Solution procedure employs the shooting algorithm bvpshoot in the R package bvpSolve
- Bang-bang solution presents some additional challenges but these are easily resolvable

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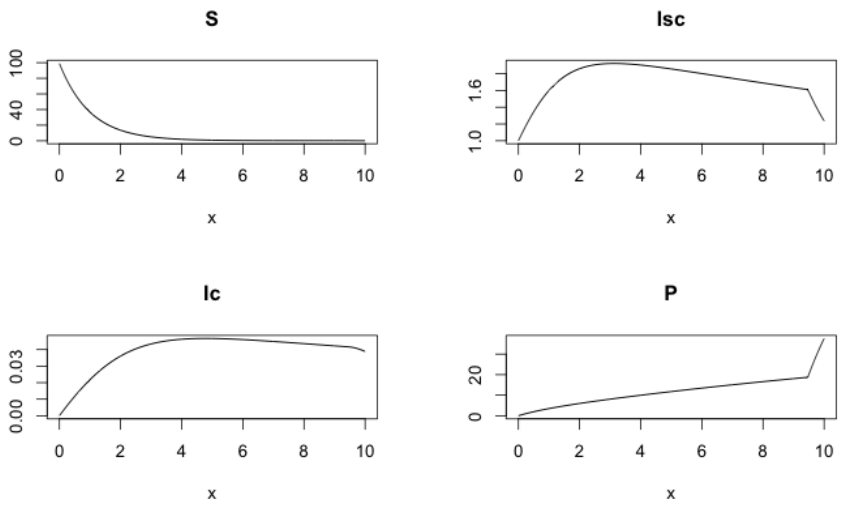


Figure 2: Disease dynamics

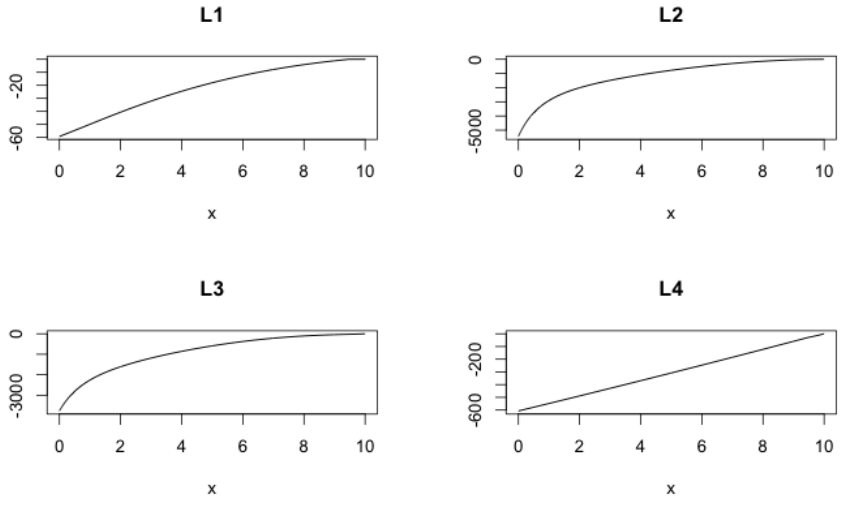


Figure 3: Co-state dynamics

Some results

Note boundary conditions are satisifed!

Plot of Switching Functions

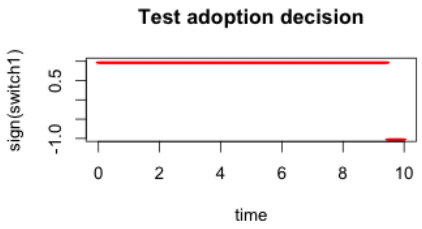


Figure 4: Discount rate 3%

sign of switching function changes over time.

So we have a behavioural feedback.

Impulse control

- Impulse control modifies the decisions to adopt the test so that they only occur at certain times.
- Need to define time of test adoption BUT also time of treatment when tests are not adopted (This is an added complication you will soon see why).

- Two approaches in the literature to impulse control
- Vind, K. (1967). Control systems with jumps in the state variables. Econometrica: Journal of the Econometric Society, 273-277.
- Blaquiére, A. (1985). Impulsive optimal control with finite or infinite time horizon. Journal of Optimization Theory and Applications, 46(4), 431-439.

Impulse control problem

$$\max_{v_i \in [0,\bar{\tau}]} \int_0^\infty \{GM(N - I_c - R - P) - GMDI_{sc}$$

$$\} e^{-rt} dt$$

$$+e^{-r\tau_i} \sum_{i=0}^{N} GM(N - I_c - R - P) - GMDI_{sc}(1 - (1 - S_p)v_i) - c_T v_i(N - R) -$$

$$c_D v_i((1 - S_p)S + S_e I_{sc}) - e^{-r\tau_j} \sum_{j=1}^{M} c_D 0.5(N - I_c - R - P), i \neq j$$

$$\bar{\tau}$$

is the maximal proportion of animals tested.

Impulse control problem

Subject to the disease dynamics given by the following system of ordinary differential equations:

$$\frac{dS}{dt} = -\frac{\tilde{\beta}}{N - R} S(I_{sc} + \tilde{\phi} I_c) + \delta P, S_1(0) = S_0$$

There will be jumps in the state of

$$S$$

at each test-treatment time

$$\tau_i$$

so that:

$$S(\tau_i+) - S(\tau_i-) = -(1 - S_p)v_i S, i = 1, ..., N$$

$$S(\tau_j+) - S(\tau_j-) = -0.5S$$

where

$$N$$

is the number of times that testing occurs.

Impulse control problem

$$\frac{dI_{sc}}{dt} = \frac{\tilde{\beta}}{N - R} S(I_{sc} + \tilde{\phi} I_c) - \tilde{\psi} I_{sc} + \rho I_c, I_{sc}(0) = 1$$

$$I_{sc}(\tau_i+) - I_{sc}(\tau_i-) = -S_e v_i I_{sc}$$

$$I_{sc}(\tau_j+) - I_{sc}(\tau_j-) = -0.5 I_{sc}$$

$$\frac{dI_c}{dt} = \tilde{\psi} I_{sc} - \rho I_c - \mu I_c, I_c(0) = 0$$

$$\frac{dP}{dt} = -\delta P, P(0) = 0$$

$$P(\tau_i+) - P(\tau_i-) = (1 - S_p)v_i S + S_e v_i I_{sc}$$

$$P(\tau_j+) - P(\tau_j-) = 0.5(N - I_c - R - P)$$

$$\frac{dR}{dt} = \mu I_c, R(0) = 0$$

Impulse Hamiltonians

Ordinary Hamiltonian:

$$H = GM(N - I_c - R - P) - GMDI_{sc} + \lambda_1(-\frac{\tilde{\beta}}{N-R}S(I_{sc} + \tilde{\phi}I_c) + \delta P)$$

$$+\lambda_2(\frac{\tilde{\beta}}{N-R}S(I_{sc} + \tilde{\phi}I_c) - \tilde{\psi}I_{sc} + \rho I_c)$$
$$+\lambda_3(\tilde{\psi}I_{sc} - \rho I_c - \mu I_c)$$
$$+\lambda_4(-\delta P)$$
$$+\lambda_5(\mu I_c)$$

Impulse Hamiltonian at Test adoption dates

$$IH^N = \sum_{i=0}^{N} GM(N - I_c - R - P) - GMDI_{sc}(1 - (1 - S_P)v_i) - c_T v_i(N - R) -$$

$$c_D v_i((1 - S_p)S + S_e I_{sc}) + \lambda_1(\tau_i+)(-(1 - S_P)S)$$
$$+\lambda_2(\tau_i+)(-S_e v_i I_{sc}) + \lambda_3(\tau_i+)((1 - S_p)v_i S + S_e v_i I_{sc})$$

Impulse Hamiltonian at treatment dates

$$IH^M = \sum_{j=1}^{M} c_D 0.5(N - I_c - R - P) + \lambda_1(-0.5S)$$
$$+\lambda_2(\tau_j+)(-0.5I_{sc}) + \lambda_3(\tau_j+)(0.5(N - I_c - R - P))$$

Blaquiére's maximum principle

The solution to this problem is given by Blaquiére's maximum principle:

$$\dot{\lambda_1} - r\lambda_1 = -\frac{\partial H}{\partial S}$$

$$\dot{\lambda_2} - r\lambda_2 = -\frac{\partial H}{\partial I_{sc}}$$

$$\dot{\lambda_3} - r\lambda_3 = -\frac{\partial H}{\partial I_c}$$

$$\dot{\lambda_4} - r\lambda_4 = -\frac{\partial H}{\partial P}$$

$$\dot{\lambda_5} - r\lambda_5 = -\frac{\partial H}{\partial R}$$

Blaquiére's maximum principle

at the impulse points we have

$$\frac{\partial IH}{\partial v_i}(v_i - v_i^*) \leq 0$$

Complementary slackness condition?

$$\lambda_1(\tau_i^*+) - \lambda_1(\tau_i^*-) = -\frac{\partial IH^N}{\partial S}$$

$$\lambda_2(\tau_i^*+) - \lambda_2(\tau_i^*-) = -\frac{\partial IH^N}{\partial I_{sc}}$$

$$\lambda_3(\tau_i^*+) - \lambda_3(\tau_i^*-) = -\frac{\partial IH^N}{\partial P}$$

$$\lambda_1(\tau_j^*+) - \lambda_1(\tau_j^*-) = -\frac{\partial IH^M}{\partial S}$$

$$\lambda_2(\tau_j^*+) - \lambda_2(\tau_j^*-) = -\frac{\partial IH^M}{\partial I_{sc}}$$

$$\lambda_3(\tau_j^*+) - \lambda_3(\tau_j^*-) = -\frac{\partial IH^M}{\partial P}$$

Noting that

$$i \neq j$$

.

Blaquiére's maximum principle

In addition

$$H(\tau_i+) - H(\tau_i-) - (\frac{\partial G}{\partial \tau} - rG)$$
$$-\lambda(\tau_i+)\frac{\partial g}{\partial \tau}$$
$$\begin{cases} \geq 0 & \tau_i^* = 0 \\ = 0 & \tau_i^* \in (0,T) \\ \leq 0 & \tau_i^* = T \end{cases}$$

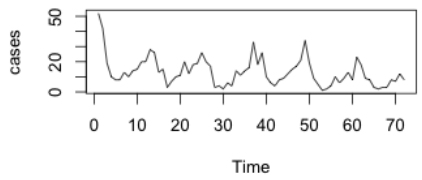
$$H(\tau_j+) - H(\tau_j-) - (\frac{\partial G}{\partial \tau} - rG)$$
$$-\lambda(\tau_j+)\frac{\partial g}{\partial \tau}$$
$$\begin{cases} \geq 0 & \tau_j^* = 0 \\ = 0 & \tau_j^* \in (0,T) \\ \leq 0 & \tau_j^* = T \end{cases}$$

Note: This version of Blaquiére's maximum principle is non-scalar (this is not a problem some versions of BMP have addressed the non-scalar case) and involves multiple time-scales (this is an issue, it is easy to see the generalization but this case has not been studied and a proof is probably needed) for impulses so it is more general than Blaquiére's original version.

The Flexible Modelling Environment (FME) package in R and inverse modelling with data

- Let's say we have some time-series data for cases
- We would like to fit parameter values for our partially observed system to what data we have
- FME allows us to do this (some caveats)
- This process is referred to in the differential equations literature as inverse modelling
- The idea is to compare simulated model outputs against the observed data and then update the model outputs to fit the data.

The data



Example: a UK level disease dynamics model for sheep-scab

This is a seasonally forced model so time dependent dynamics.

$$C = Ic/c$$

$$\frac{dS}{dt} = (-S\beta cos(\theta Z)(I_{sc} + cC\phi)/(N - R))$$

$$\frac{dI_{sc}}{dt} = (cC\rho - I_{sc}\psi + S\beta cos(\theta Z)(I_{sc} + cCphi)/(N - R))$$

$$\frac{dI_c}{dt} = (I_{sc}\psi - cC\mu - cC\rho)$$

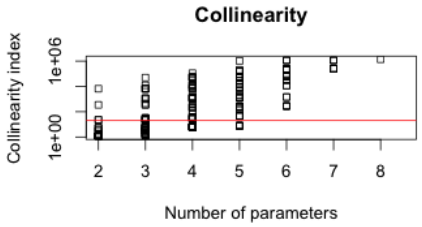
$$\frac{dR}{dt} = cC\mu$$

$$\frac{dC}{dt} = (I_{sc}\psi - cC\mu - cC\rho)/c$$

$$\frac{dZ}{dt} = 1$$

Parameter identification

- Not all parameters can necessarily be identified because of collinearities
- Need to estimate sub-sets on non-collinear parameters



Extending to a differential game

- Differential game results with shooting algorithm are suggesting we are using poor starting values.
- So use the initial conditions from the optimal control problem as starting values for the shooting algorithm.
- Do this assuming no spread between farms and then gradually increase the spread.
- Why this will work? Because optimal control problems are special cases of games

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Thanks for listening!

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