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Optimal combinations of acute phase proteins for detecting infectious disease in pigs

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Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

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Citation (APA):
Stockmarr, A. (2012). Optimal combinations of acute phase proteins for detecting infectious disease in pigs [2D/3D (physical products)]. Statistikseminar, Copenhagen, Denmark, 16/01/2012

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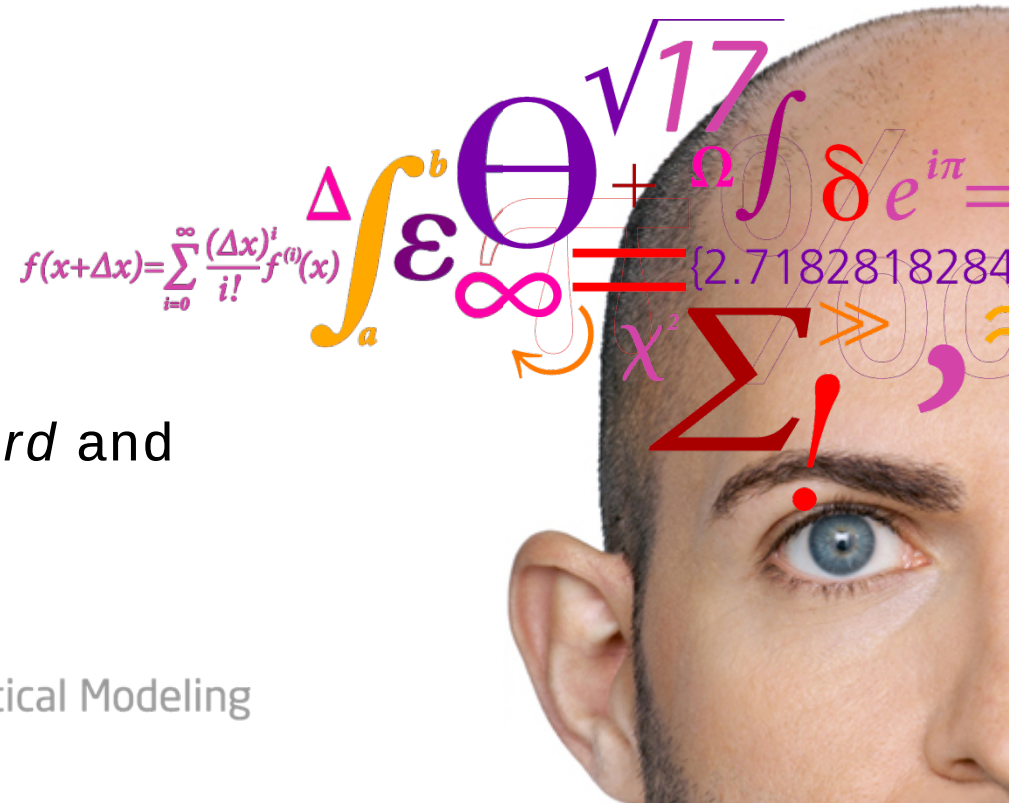
Optimal combinations of acute phase proteins for detecting infectious disease in pigs

Statistics group
Axelborg 16/01 2012

Anders Stockmarr,
DTU Data Analysis



Joint work with *Peter Heegaard* and *Nanna Skall Sørensen*

DTU Informatics
Department of Informatics and Mathematical Modeling

Acute Phase Proteins – APP's:

- Proteins whose plasma concentrations increase (positive acute phase proteins) or decrease (negative acute phase proteins) in response to inflammation.

- Altered plasma concentration varies with the type of infection that causes inflammation, with the time passed since infection happened, and among animals.

- Inflammations may not always be discovered, but APP levels found in routine blod samples etc. may reveal an inflammation and thus an infection of some, unknown, kind.

When APP levels indicate inflammation:

- We don’t know which kind of inflammation we are dealing with;
- We don’t know where in the corresponding disease progression we are;
- Response depend on the specific APP; some react better under specific infections but not so well under other types; but they still react;
- We thus cannot pair inflammation types with corresponding APP’s.

Working hypothesis:

APP levels can be established for a range of infection types and a disease progression length, such that:

- Critical levels of APP indicate inflammation irrespectively of the type of infection;
- and irrespectively of the length of the disease progression.

Experimental design

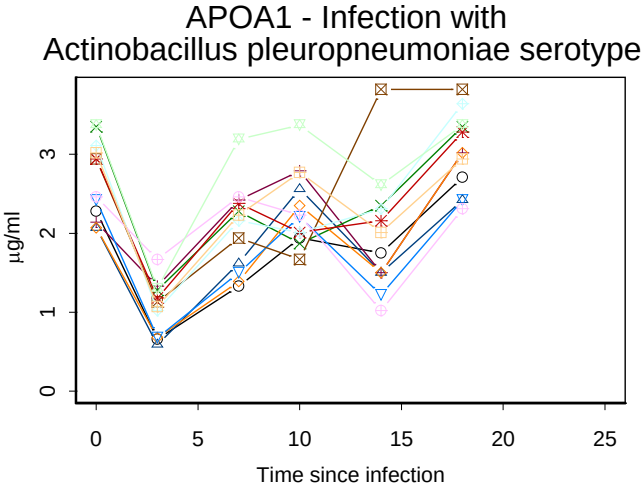
- A number of pigs were infected with one of a different number of very different agents;
- *Actinobacillus pleuropneumoniae, European Mycoplasma hyosynoviae*, *Porcine Reproductive and Respiratory Syndrome Virus* (PRRSV), *Streptococcus suis*, *Toxoplasma gondii*, Turpentine.

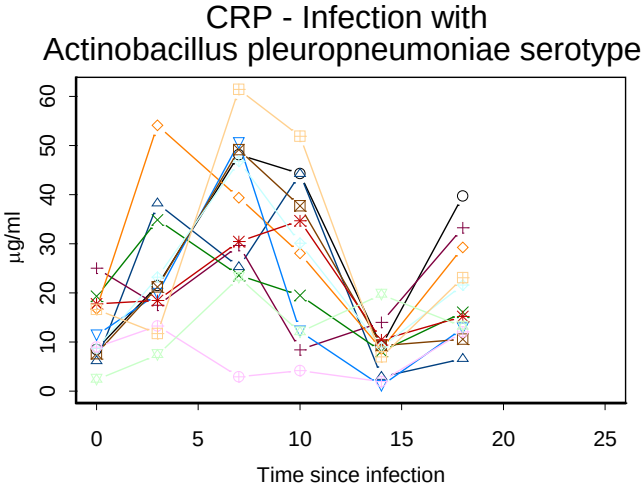
Different bacteria, virus, parasites and turpentine to mimic aseptic inflammation.

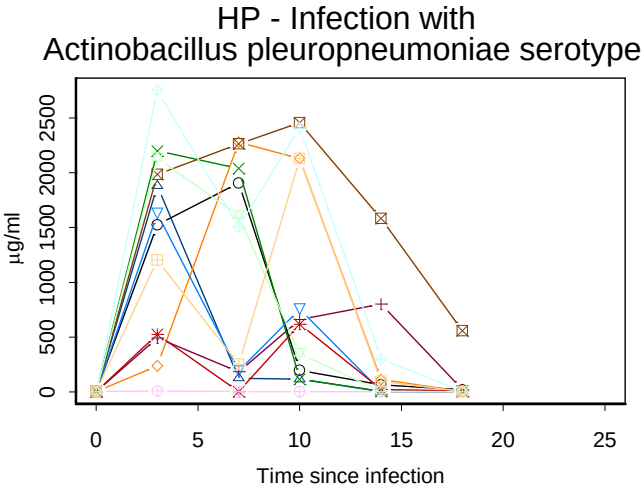
PRRSV was disregarded because too few pigs had recorded data.

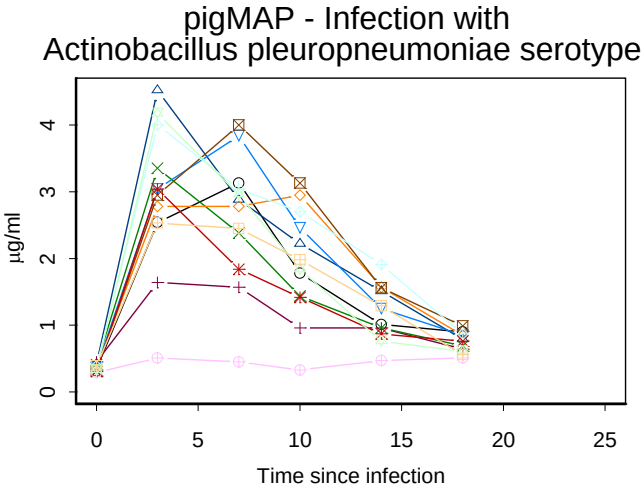
- 4 APP's were measured in a period before and after infection:
- Apolipoprotein A-1 (APOA1), C-reactive protein (CRP), Haptoglobin (HP) and pigMAP.

Results, AP4

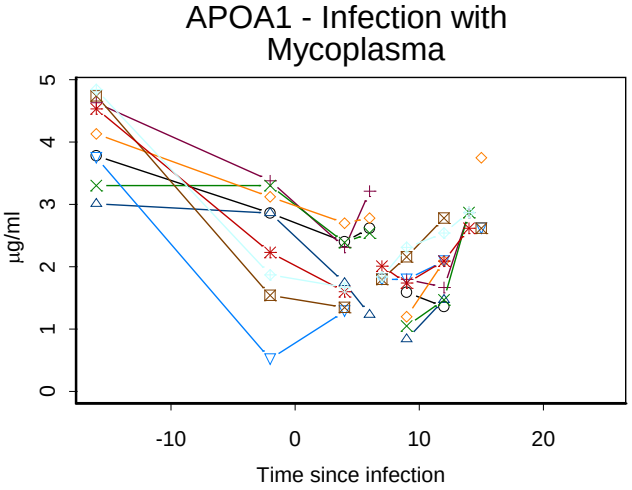

APOA1 - Infection with
Actinobacillus pleuropneumoniae serotype 4
µg/ml
0
1
2
3
0
5
10
15
20
25
Time since infection

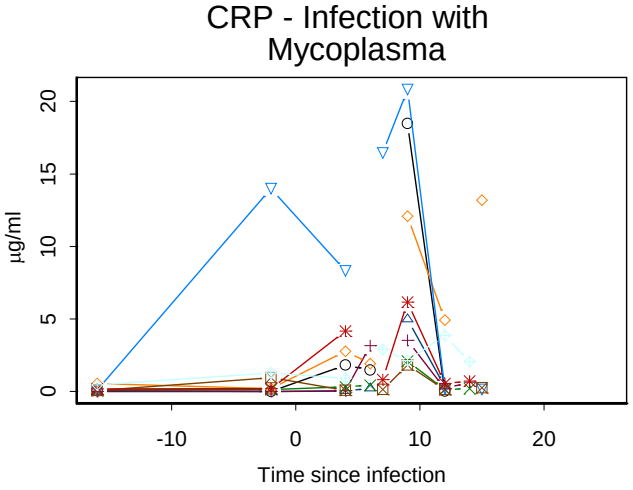

CRP - Infection with
Actinobacillus pleuropneumoniae serotype 4
µg/ml
0
10
20
30
40
50
60
0
5
10
15
20
25
Time since infection

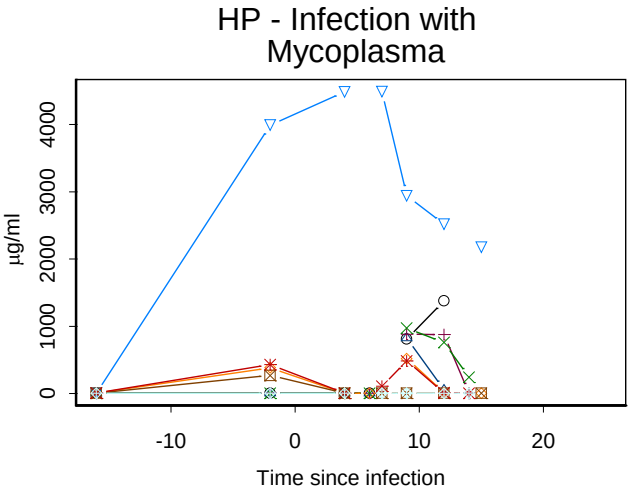

HP - Infection with
Actinobacillus pleuropneumoniae serotype 4
µg/ml
0
500
1000
1500
2000
2500
0
5
10
15
20
25
Time since infection

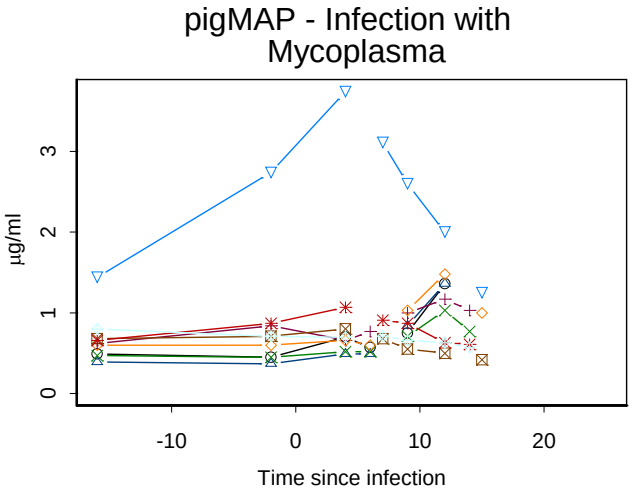

pigMAP - Infection with
Actinobacillus pleuropneumoniae serotype 4
µg/ml
0
1
2
3
4
0
5
10
15
20
25
Time since infection

Results – *Mycoplasma*

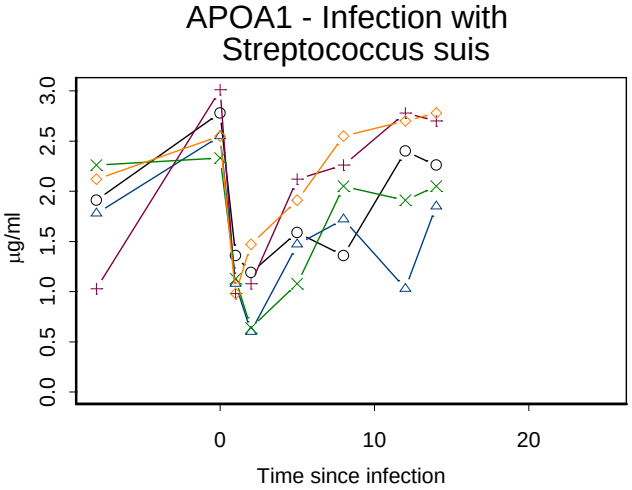


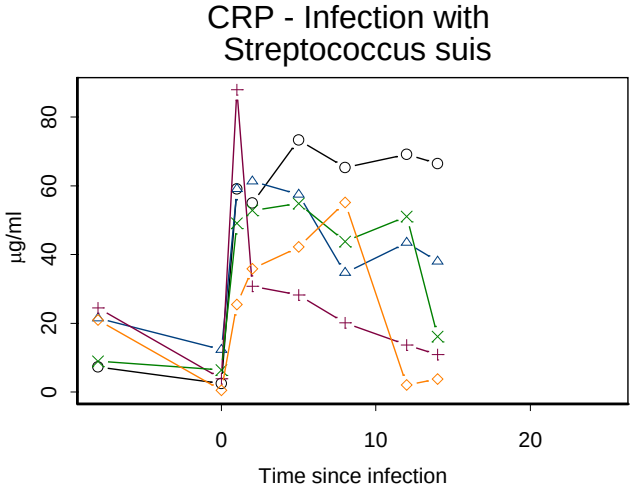


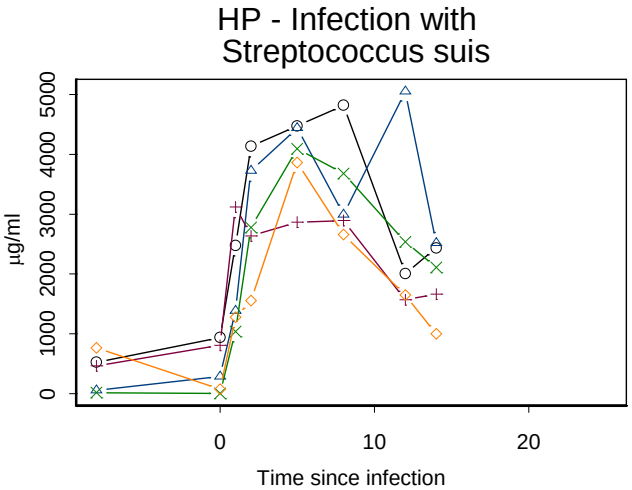


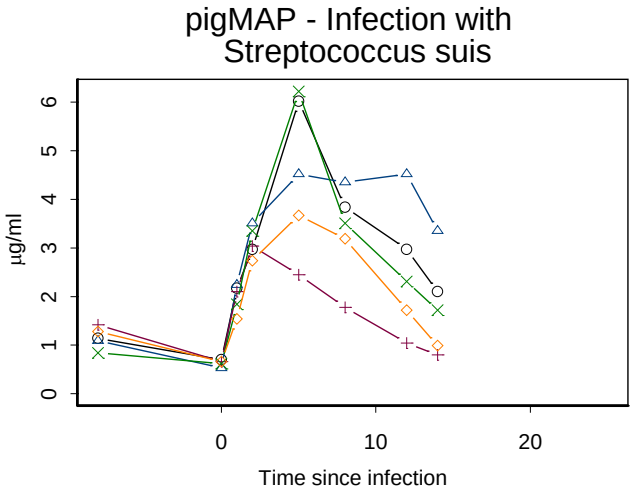


Results – *Streptococcus suis*

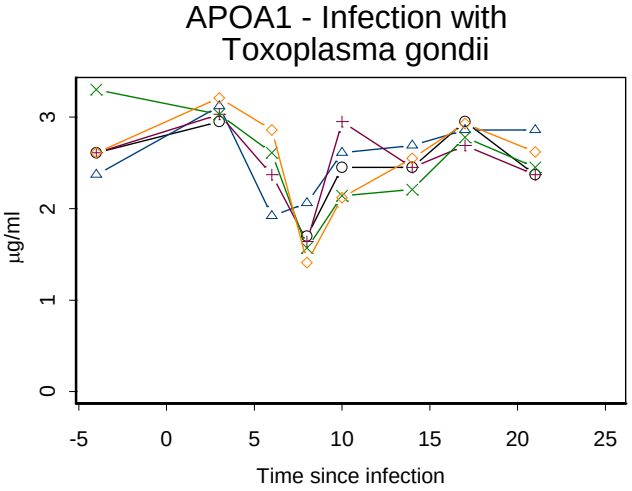


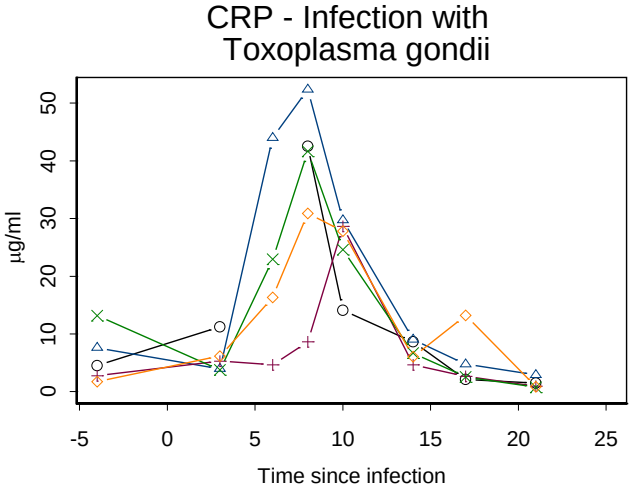


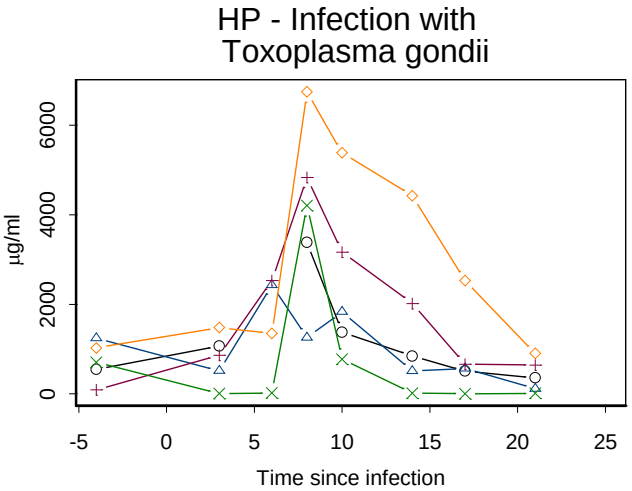


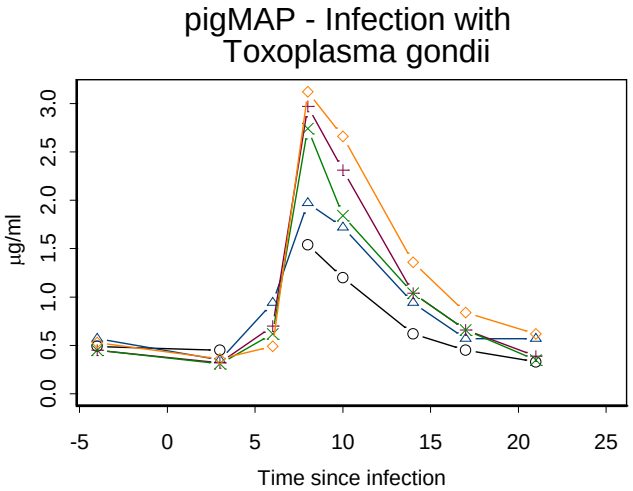


Results – Toxoplasma

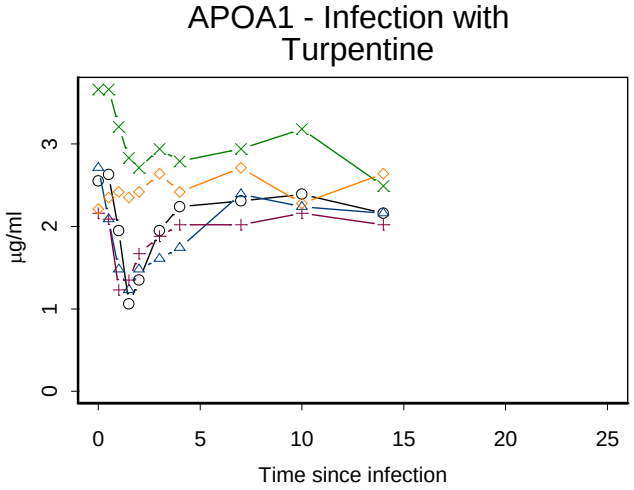


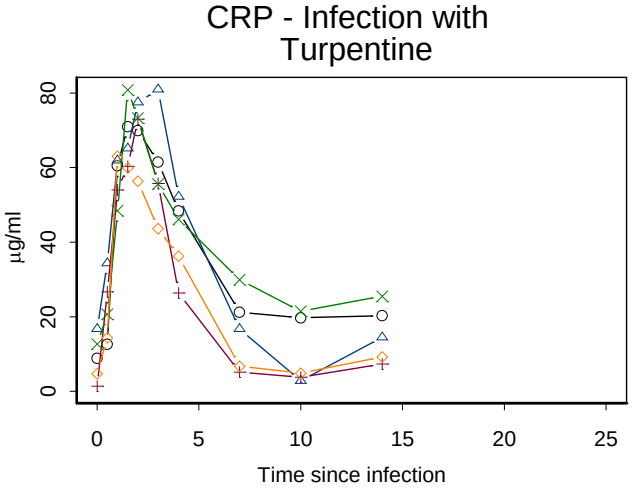


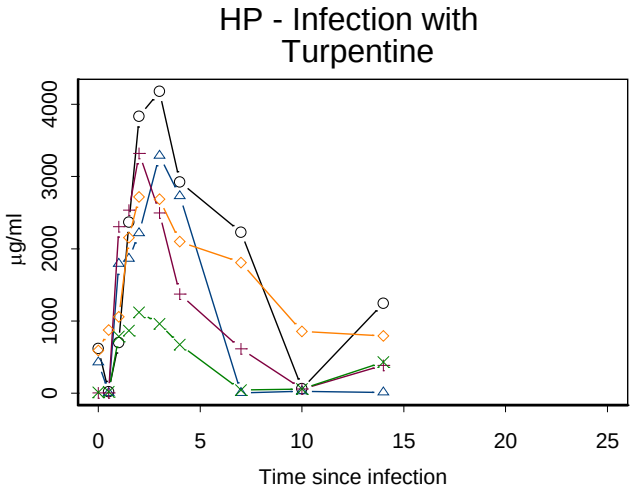


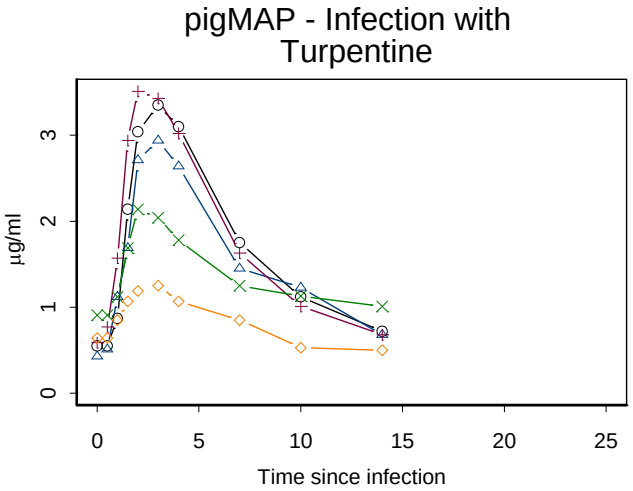


Results – Turpentine

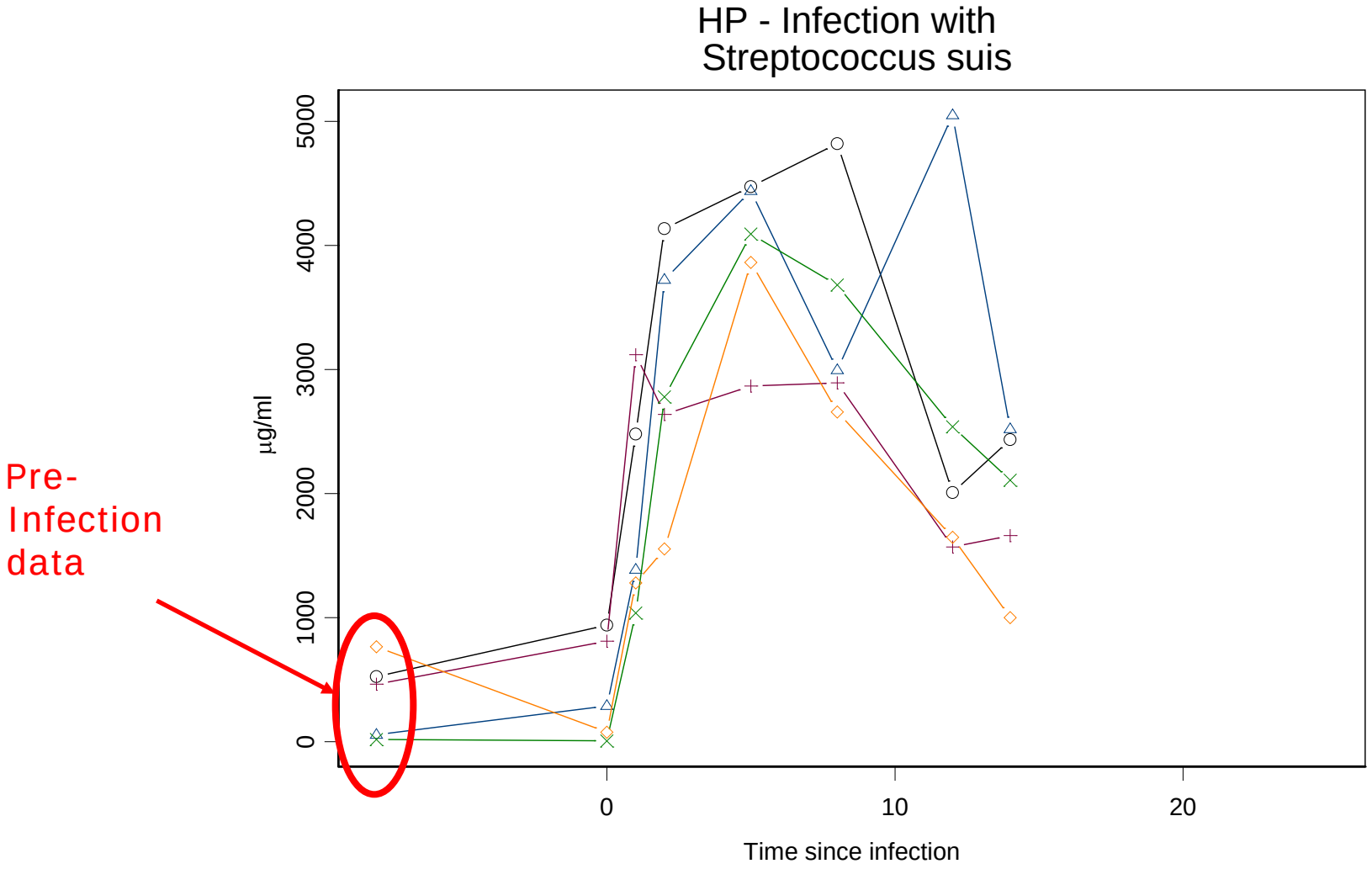




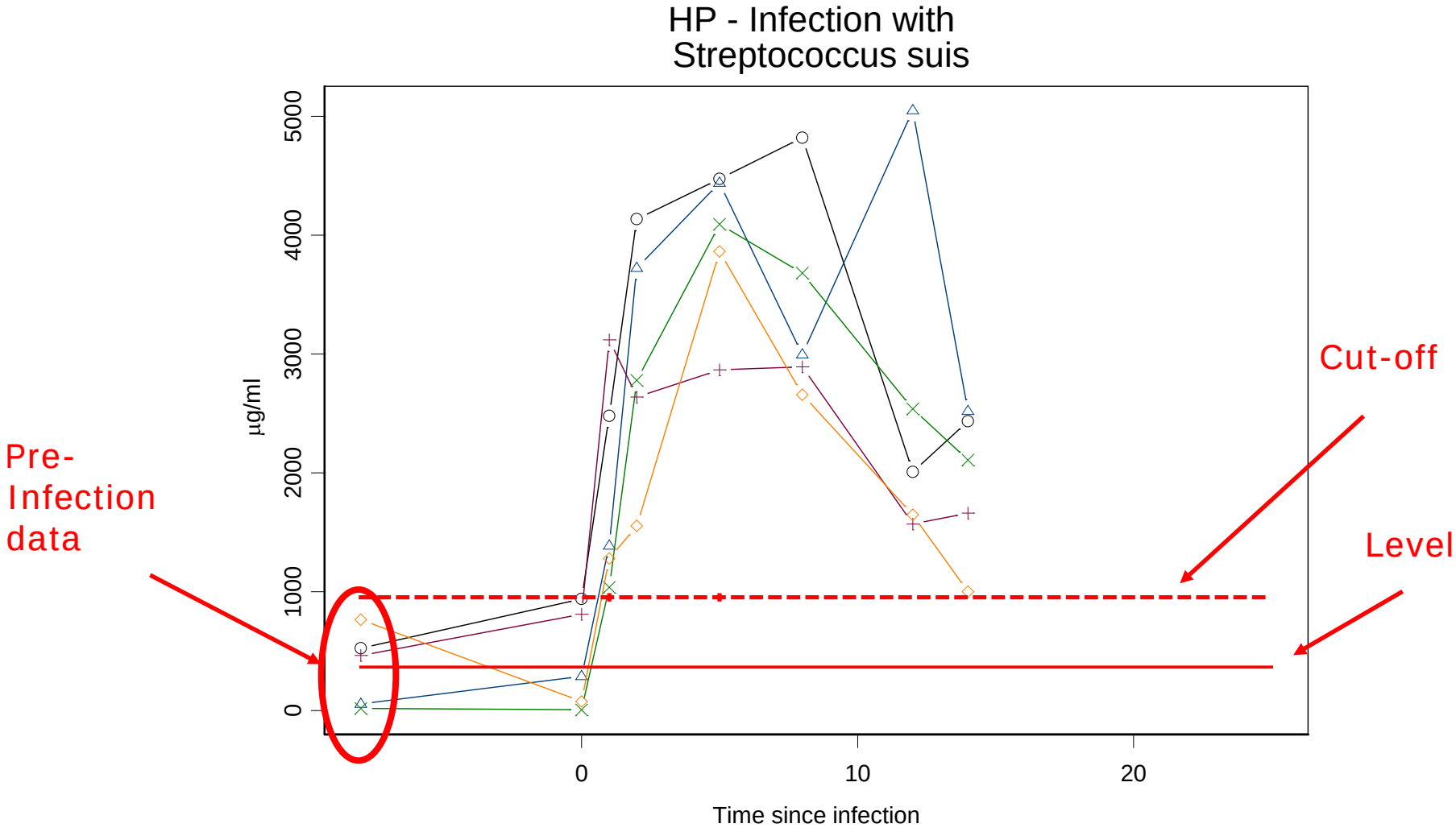




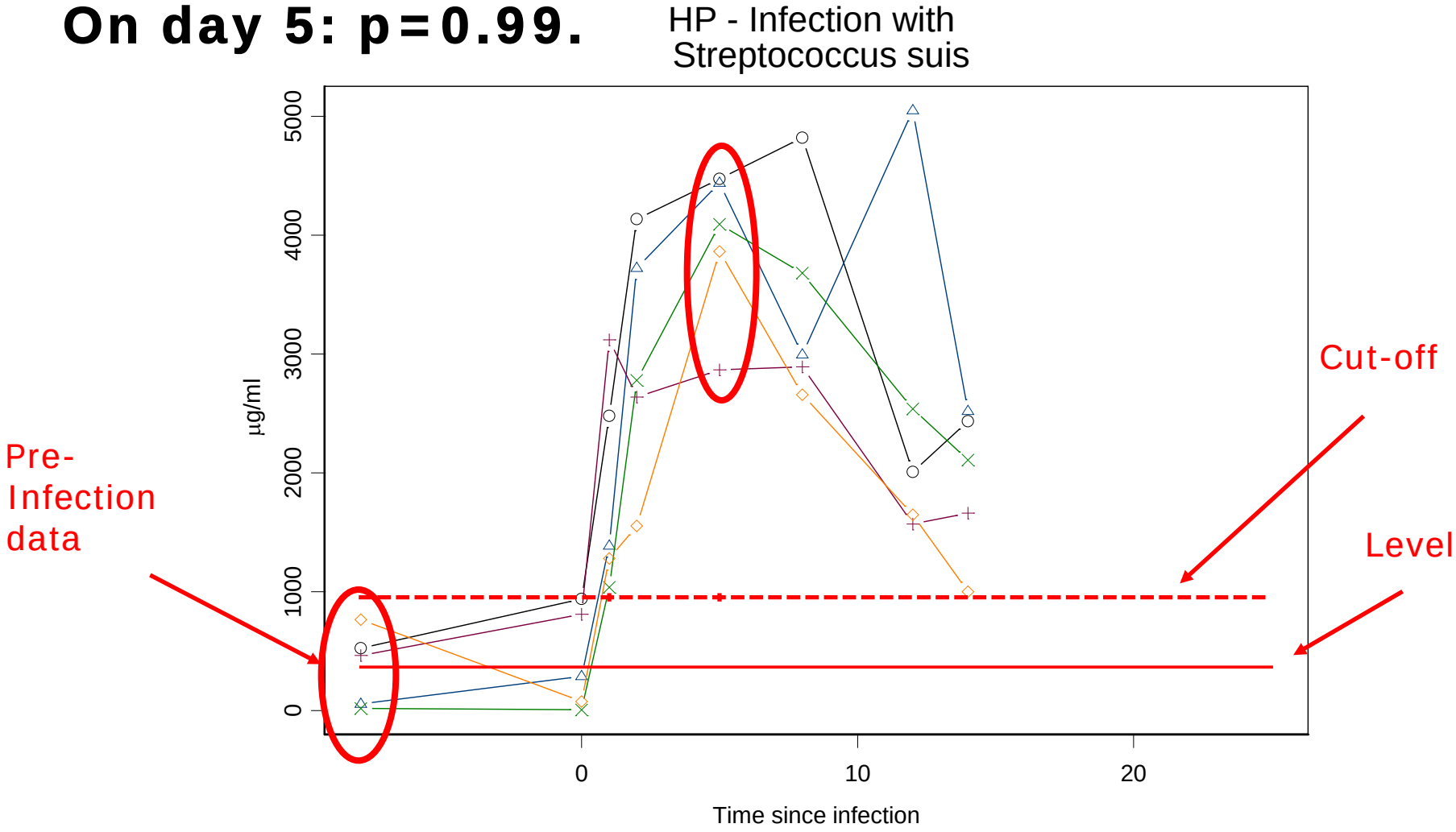
When is the APP level high enough to indikate presence of inflammation?



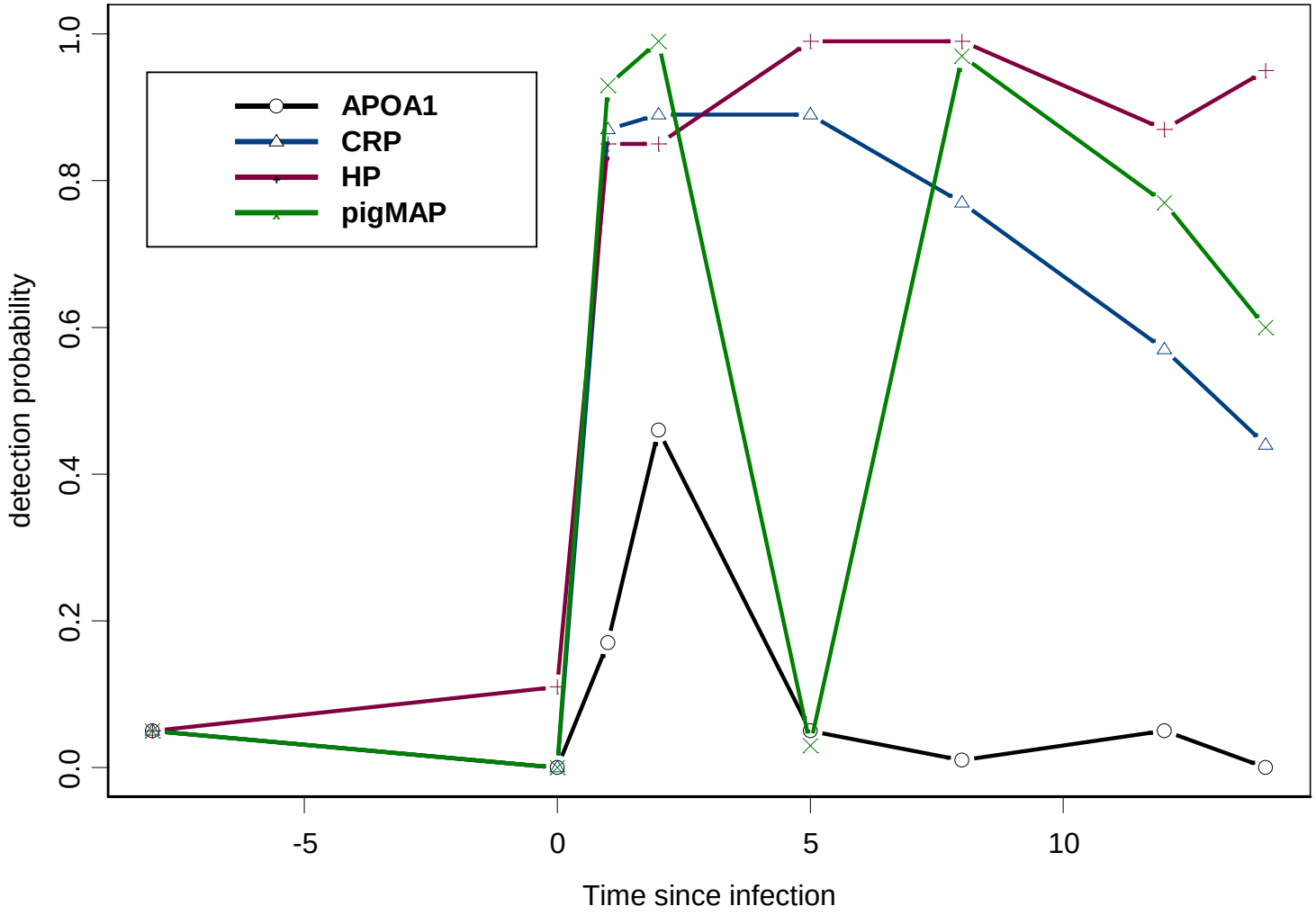
When is the APP level high enough to indikate presence of inflammation?



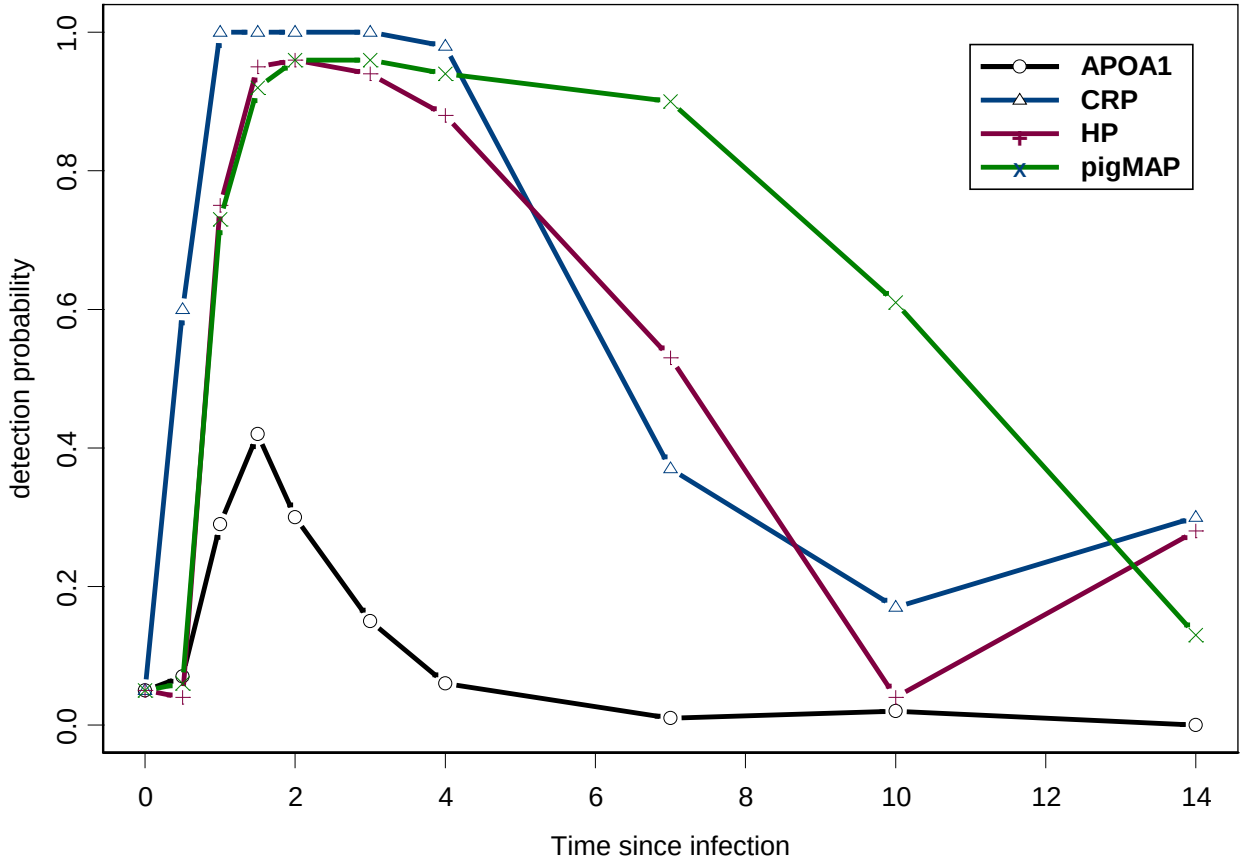
When is the APP level high enough to indikate presence of inflammation? On day 5: p=0.99.



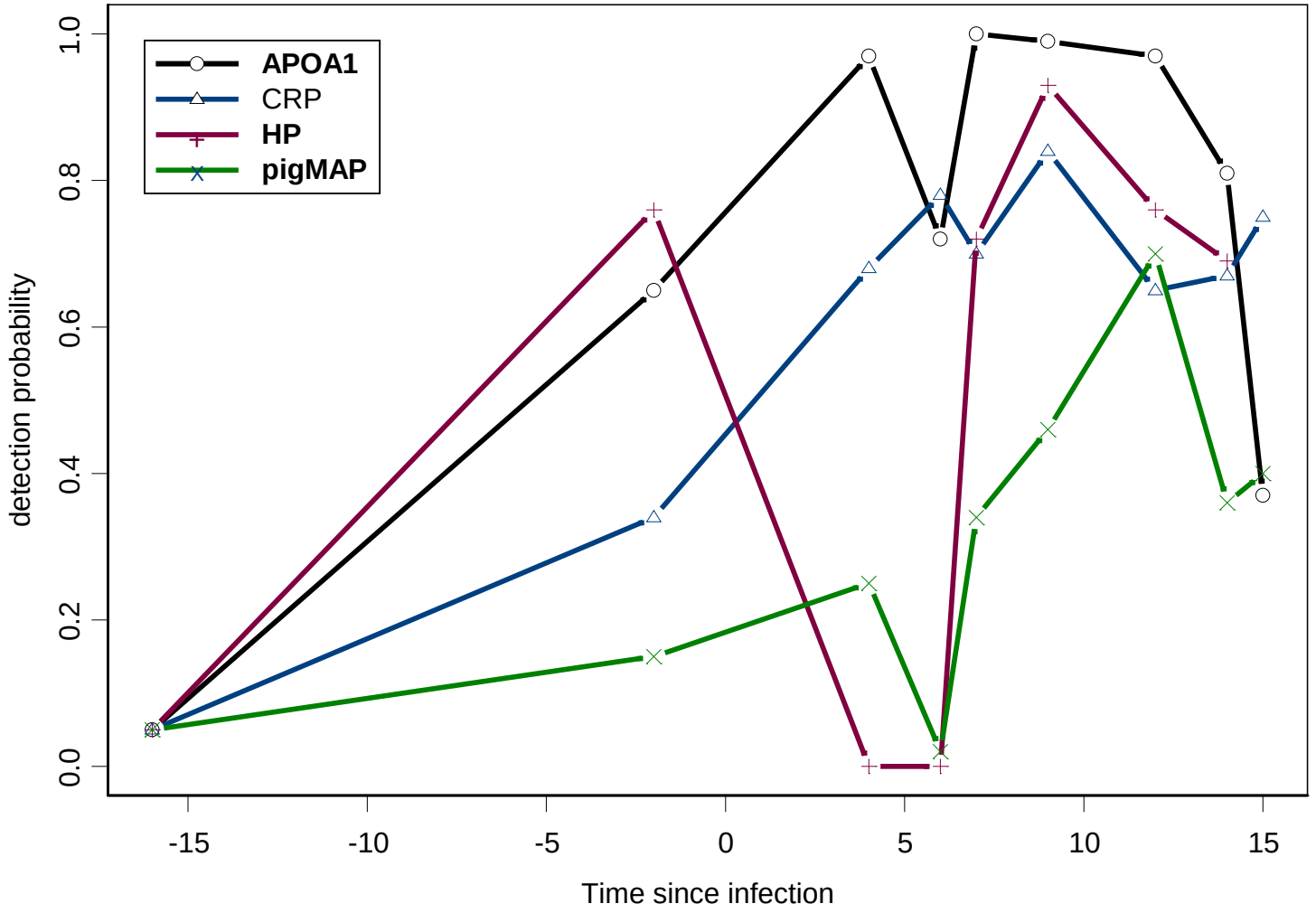
Detection probabilities, *Streptococcus suis* infection.



Detection probabilities, Toxoplasma infection



Detection probabilities, Mycoplasma infection



Other problems

- Detection probabilities are too low, and starts to decline too rapidly.

- The same APP cannot be used for all infections.

Solution:

- Utilize all the information from data, by looking at the APPs simultaneously. They may complement each other and combine power to detect infections.

Multivariate analysis

$$X = \begin{pmatrix} -X^{(APOA1)} \\ X^{(CRP)} \\ X^{(HP)} \\ X^{(pigMAP)} \end{pmatrix}$$

X not from infected animal $\Rightarrow X \sim N_4(\mu, \Sigma)$

where μ and Σ are determined from pre-infection data.

Infection with *Streptococcus suis*:

$$\widehat{\mu} = \begin{pmatrix} 16.64 \\ 365.76 \\ -1.82 \\ 1.15 \end{pmatrix}, \widehat{\Sigma} = \begin{pmatrix} 62 & 548 & 2.33 & 1.22 \\ 548 & 102700 & 21 & 51 \\ 2.33 & 21 & 0.23 & 0.077 \\ 1.22 & 51 & 0.077 & 0.047 \end{pmatrix}$$

Correlation matrix: $\begin{pmatrix} 1 & 0.22 & 0.62 & 0.71 \\ 0.22 & 1 & 0.14 & 0.73 \\ 0.62 & 0.14 & 1 & 0.74 \\ 0.71 & 0.73 & 0.74 & 1 \end{pmatrix}$

Correlated data

Univariate versus multivariate data

- Post-infection data have higher values for some but not necessarily all APP.

- Obvious choice of a decision rule: Maximum of the 4 APP levels is ’high’.
- Problematic definition; APP levels for different pathogens do not have the same distribution, and they are correlated so that one level being high implies other levels likely to be high.
- Correct for both, while keeping the decision rule.

Removing correlations and creating independence for a given infection type:

$$Y_1 = X_1$$

$$Y_2 = X_2 - \Sigma_{2,1}/\Sigma_{1,1}(X_1 - \mu_1)$$

$$Y_3 = X_3 - \begin{pmatrix}\Sigma_{3,1} & \Sigma_{3,2}\end{pmatrix} \begin{pmatrix}\Sigma_{1,1} & \Sigma_{1,2} \\ \Sigma_{2,1} & \Sigma_{2,2}\end{pmatrix}^{-1} \begin{pmatrix}X_1 - \mu_1 \\ X_2 - \mu_2\end{pmatrix}$$

$$Y_4 = X_3 - \begin{pmatrix}\Sigma_{4,1} & \Sigma_{4,2} & \Sigma_{4,3}\end{pmatrix} \begin{pmatrix}\Sigma_{11} & \Sigma_{1,2} & \Sigma_{1,3} \\ \Sigma_{2,1} & \Sigma_{2,2} & \Sigma_{2,3} \\ \Sigma_{3,1} & \Sigma_{3,2} & \Sigma_{3,3}\end{pmatrix}^{-1} \begin{pmatrix}X_1 - \mu_1 \\ X_2 - \mu_2 \\ X_3 - \mu_3\end{pmatrix}$$

Streptococcus suis

$$\mathbb{Y} = \mathbb{X} - \Phi(\mathbb{X} - \mu)$$

$$\widehat{\Phi} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 5.34e-3 & 0 & 0 & 0 \\ 3.74e-2 & 5.34e-3 & 0 & 0 \\ 7.62e-3 & 4.08e-4 & 0.22 & 0 \end{pmatrix}$$

$$\mathbb{E}[\mathbb{Y}] = \mathbb{E}[\mathbb{X}] \text{ and } \mathbb{V}[Y] = (1-\Phi)\mathbb{V}[\mathbb{X}](1-\Phi)^T$$

Construction of multivariate cut-off values:

- Decision rule: Max of the Y_i's are big.
- Construct c_i such that

$$P\left(\frac{\mathbb{Y}_i - \mu_i}{\sqrt{\mathbb{V}(\mathbb{Y}_i)}} < c_i\right) = 0.95^{1/4}$$

- As the Y's are independent, it follows that

$$P\left(\max_{i=1,\ldots,4} \frac{\mathbb{Y}_i - \mu_i}{\sqrt{\mathbb{V}(\mathbb{Y}_i)}} - c_i < 0\right) = \prod_{i=1}^{4} P\left(\frac{\mathbb{Y}_i - \mu_i}{\sqrt{\mathbb{V}(\mathbb{Y}_i)}} < c_i\right)$$

$$= (0.95^{1/4})^4 = 0.95$$

- Cut-off for $\mathbb{Y}_i$: $\tilde{c}_i = c_i\sqrt{V(\mathbb{Y}_i)} + \mu_i$

Complications

- We DON'T know Σ! Thus, formally, we can't calculate the Y's!

- However, we can estimate Σ and use the estimated value.

- Consequence: The Y's are only approximately independent.

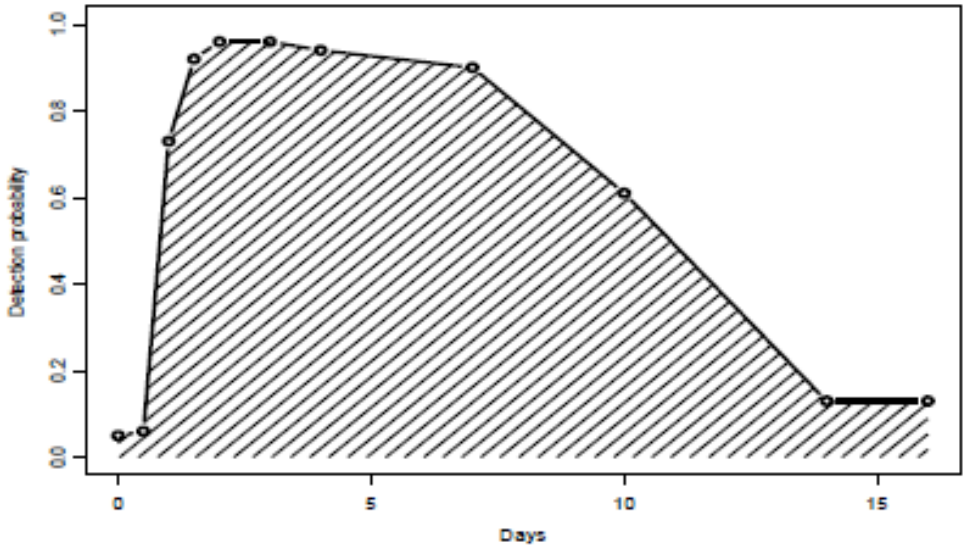
- Their distribution is non-standard, and we obtained results through simulation.

Corresponding technique for combinations of less than 4 APP's.

- 4 single APP's;
- 6 pairs of APP's;
- 4 three-combinations off APP's;
- 1 combination of all 4 APS's.

Which combination should be chosen, as the best to detect imflammations from all the infections in the design, relative to resources at hand?

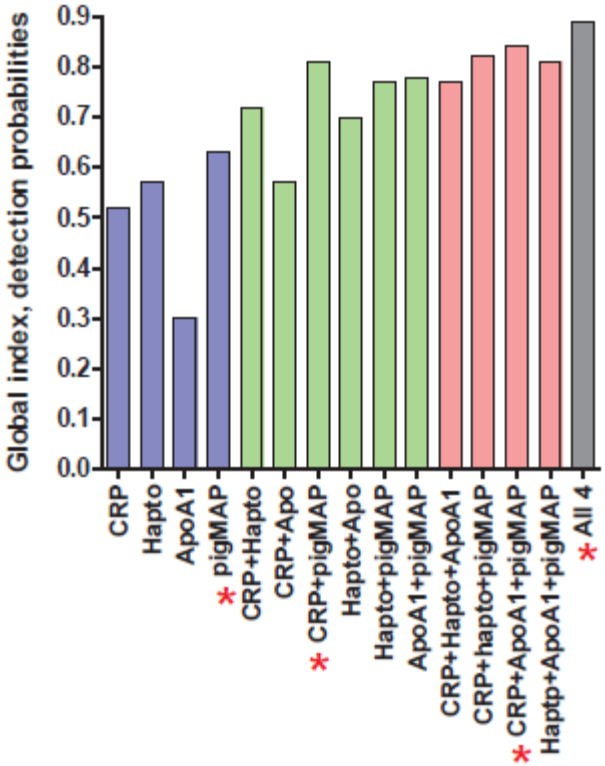
Creating a Detection Index



Combine over inflammation types and normalize:

$$I_A = \frac{1}{5} \sum_i \frac{1}{\ell_i} \int_0^{\ell_i} f_{A,i}(t)\, dt$$

Detection Index

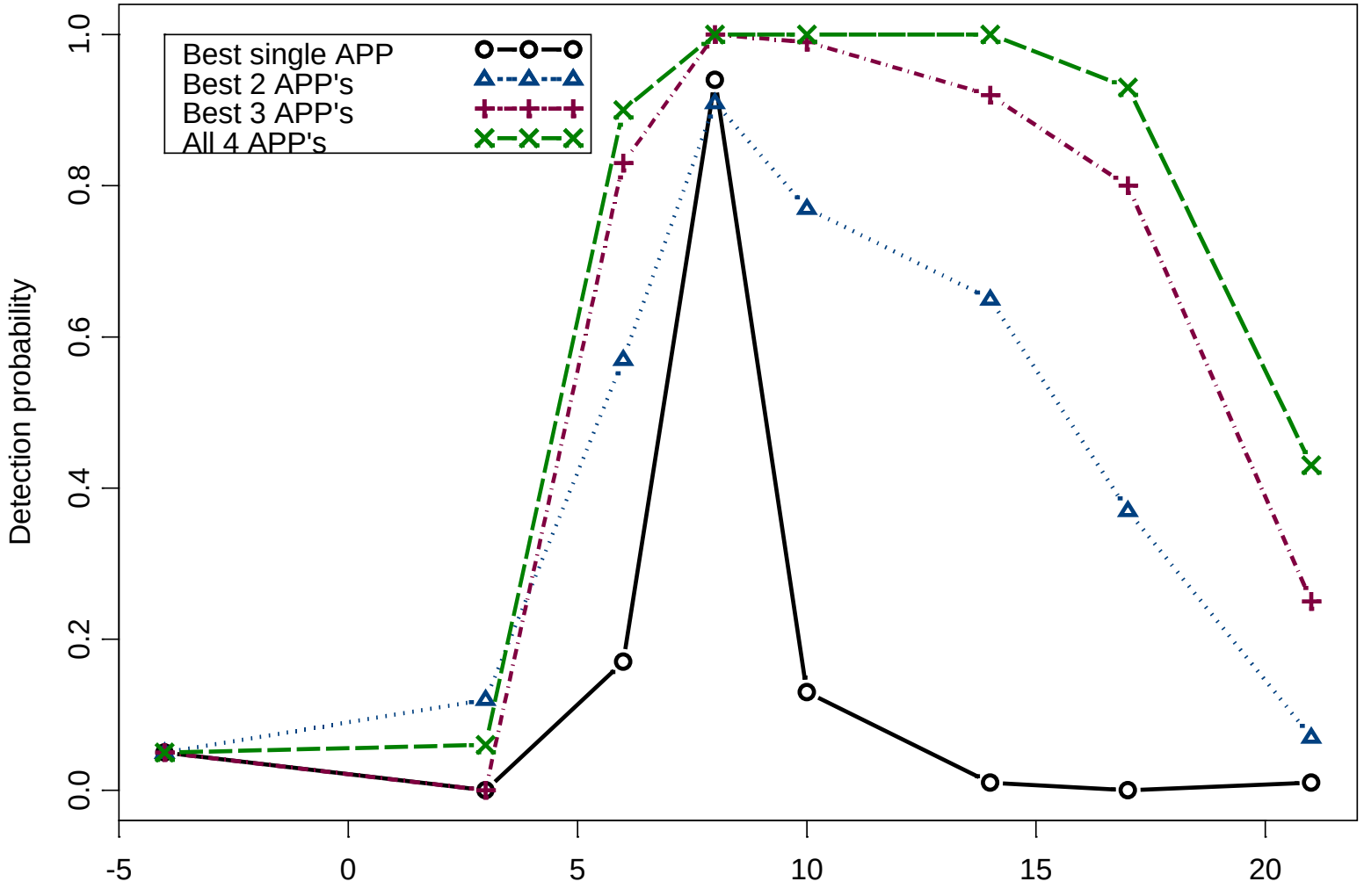


Stars indicate best possible combinations.

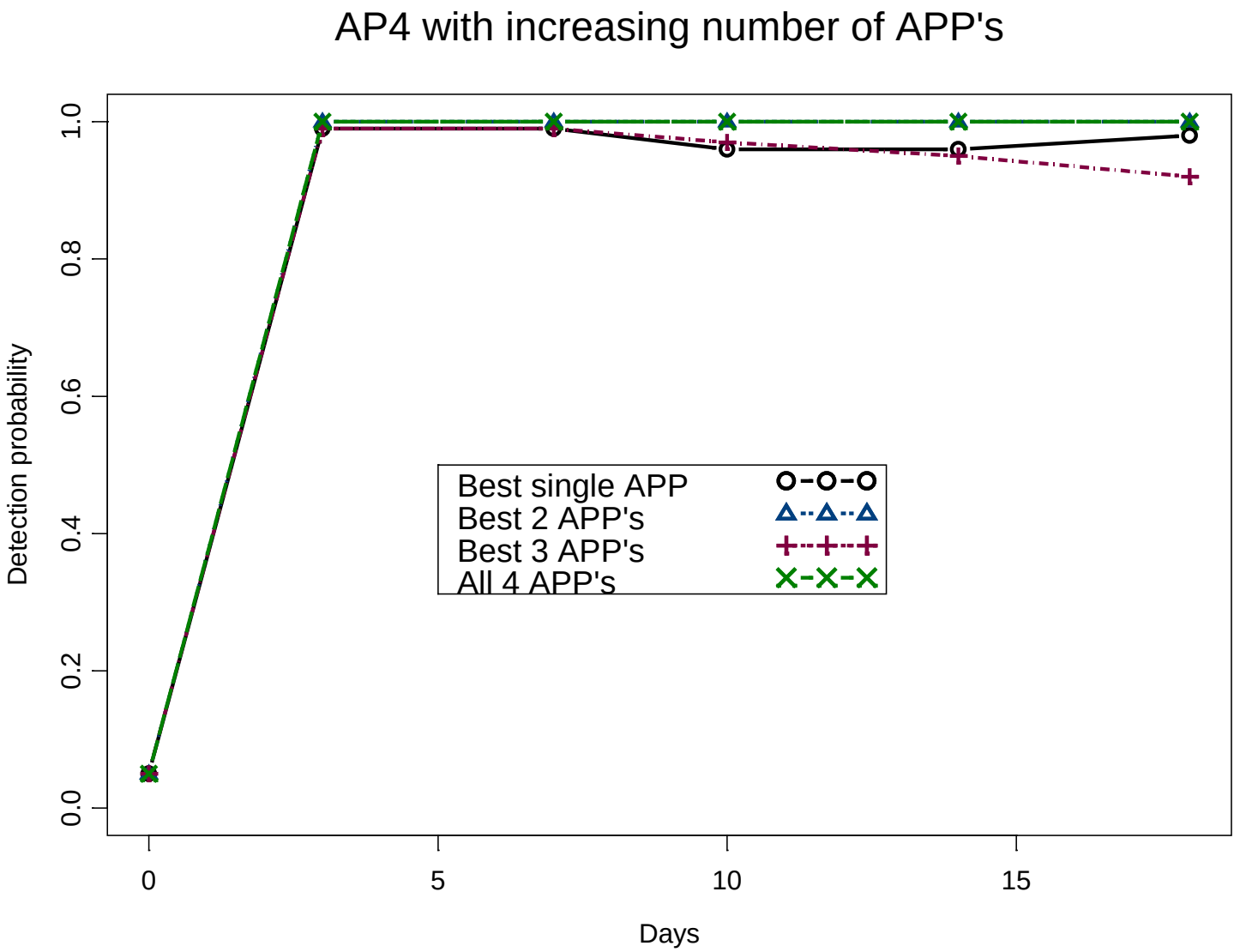
Maximum value for the index: 0.935.

Detection probabilities, Toxoplasma

Toxoplasma with increasing number of APP's



Detection probabilities, AP4



Conclusion

- We have developed a method that apparently allows detection of inflammation over a wide range of causes and a considerable part of the disease progression period.
- Cut-off values may be subject to local conditions and the number of animals included in the study and thus cannot be generalized.
- An obvious step is to apply the method to different animals, to assess the sensitivity of local conditions.
- Heegaard et al. Veterinary Research 2011, 42:50
- http://www.veterinaryresearch.org/content/42/1/50

Further work

- Expanding and validating a health index concept on a larger set of herds and a wider range of APP's;
- Defining a global set of APPs that is not limited to the data set which it is based on;
- Explore possibilities in herd welfare classification systems, as well as the use in efficient health surveillance in pig herds;

- Business partners a necessity.

- Current project group:

  – **Anders Stockmarr**, DTU Informatics, DTU Data Analysis
  – **Peter Heegaard**, DTU National Veterinary Institute
  – **Jens Peter Nielsen**, KU LIFE