Surveillance analysis Tool for Outcome-based Comparison of the confidence of FREEdom

European Food Safety Authority

The STOC free model

Objectives, hypotheses and model overview

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https://www.stocfree.eu/

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Infectious diseases of cattle

Regulated diseases

- Public health threats

  e.g. Tuberculosis

- Economic impact

  e.g. Foot and mouth disease

- Legislation on how to perform surveillance in order to substantiate freedom from disease

- Every country performs surveillance in the same way $\rightarrow$ comparable output

$\Rightarrow$ **Input-based surveillance**

Infectious diseases of cattle

Non-regulated diseases

- A lot of important infectious diseases are not regulated but have regional / national control programmes in place

  e.g. BVD, paratuberculosis ...

  - No *legal* prescription on the way to perform surveillance
  - Important diversity in the design of surveillance programmes
  - The *free status* in one programme can have a different meaning than the *free status* in another programme

$\Rightarrow$ Creates difficulties when trading animals between herds enrolled in different programmes

$\Rightarrow$ **Output-based surveillance**: production of an output that is comparable regardless of the input surveillance data

A method for output-based surveillance

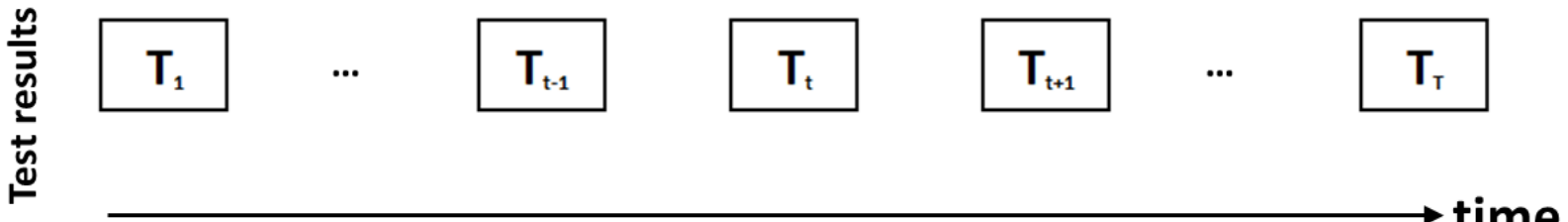
- Need for a method taking inputs from diverse surveillance programmes able to produce an output that is comparable
  - Structure of the method/model determined by what is common across surveillance programmes
  - Probability of freedom from infection estimated in a given programme from:
    - surveillance data available in the programme
    - relevant knowledge (e.g. test characteristics)

Control programmes

Common features

- *Control* programmes against cattle non-regulated diseases: prevalence > 0
- Objective: disease control or eradication
- Organised at regional or country level
- Rely on a surveillance component for the identification of infected herds or animals
- Detection of infection followed by control phase
- Surveillance performed in all participating herds
- Herd tested repeatedly over time

  $\Rightarrow$ Longitudinal data

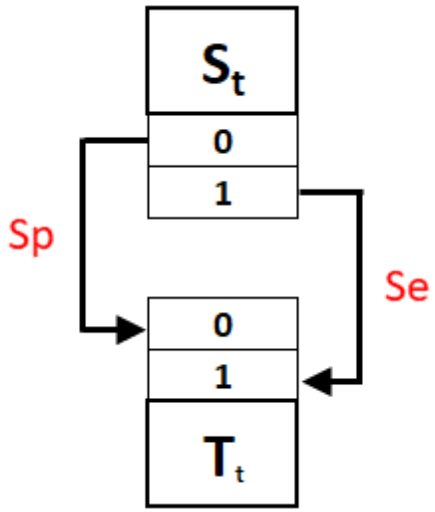


Control programmes

Common features

- Tests are imperfect
  - Sensitivity: $Se = p(T^+|D^+) < 1$
  - Specificity: $Sp = p(T^-|D^-) < 1$

$\Rightarrow$ Uncertainty in the true status of tested animals / herds



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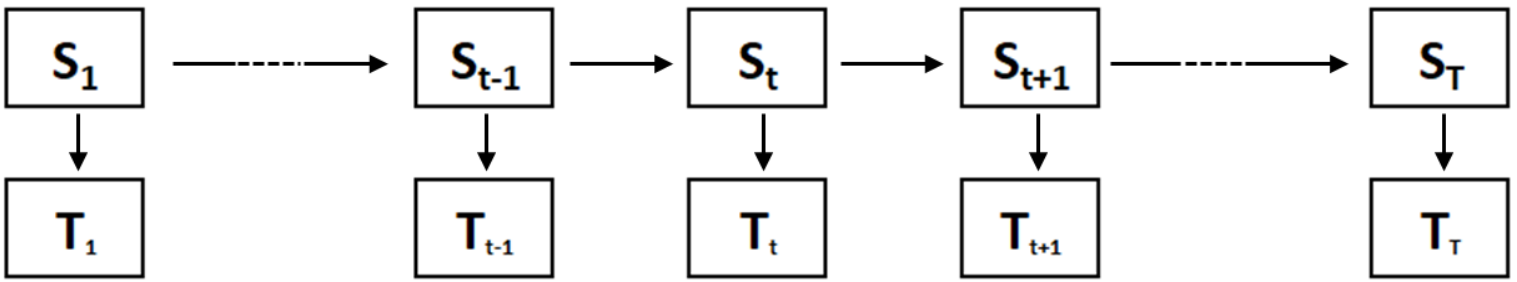
Modelling objectives

- Objective: Predict herd level probabilities of *(freedom from)* infection from longitudinal test data collected as part of surveillance programmes against endemic infectious diseases of cattle
- The modelling framework should:
  - Allow the use of longitudinal data i.e. account for the fact that sequences of test results are not random
  - Account for imperfect test information

Hidden Markov models

- Hidden Markov Models (**HMM**s) model a latent discrete variable with a Markovian dynamics, whose state at a given time determines the distribution of an observed variable
  - **discrete variable**: the variable of interest can be in 1 of k states. In the STOC free model, $k = 2$ (positive or negative status)
  - **latent variable**: this discrete variable is not directly observed. In the STOC free model, the **latent status** determines the probability of a negative or positive test result through test sensitivity and specificity
  - **Markovian dynamics**: the latent status is modelled in discrete time steps. The latent status at time t only depends on the status at time $t - 1$. The probabilities of transition between the k states between 2 time points are described by a k x k transition matrix.

Representation of surveillance programmes as HMMs



- S_t: latent status of interest at time t , from $t = 1$ to $t = T$
- T_t: test result at time t

Representation of surveillance programmes as HMMs

Status dynamics

- Time steps of equal duration

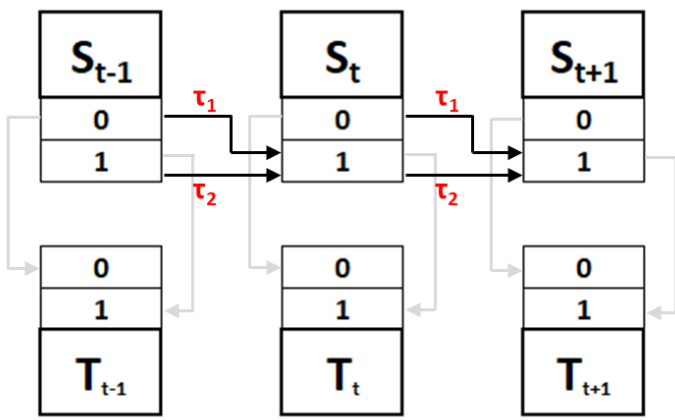
  (Discrete-time model)

- Herd status at time t depends on herd status at time t_1

  (Markovian property)

$$S_t \sim Bernoulli(\pi_t)$$

$$\pi_t = \begin{cases} \tau_1 & \text{if } S_{t-1} = 0 \\ \tau_2 & \text{if } S_{t-1} = 1 \end{cases}$$

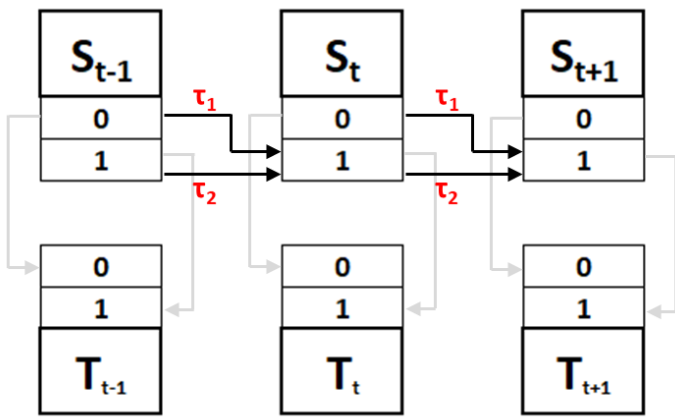


Representation of surveillance programmes as HMMs

Status dynamics

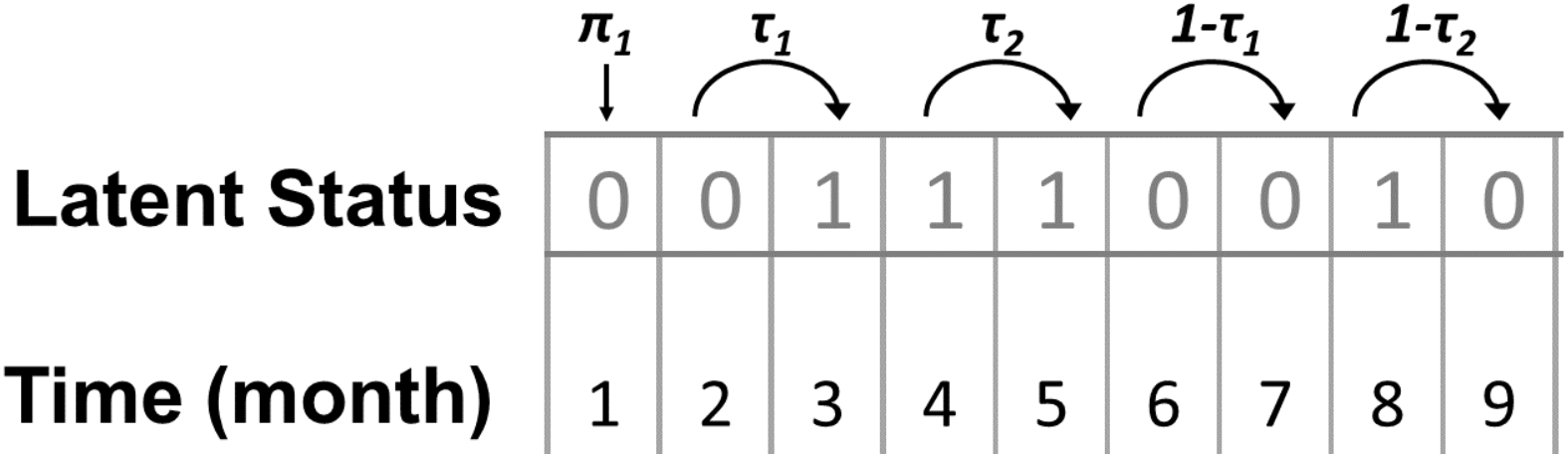
- Herd level probability of new infection (τ_{1t}) modelled as a function of one or several risk factors (X_t) using logistic regression

$$ln(\frac{\tau_{1t}}{1-\tau_{1t}}) = X_t\theta$$



Representation of surveillance programmes as HMMs

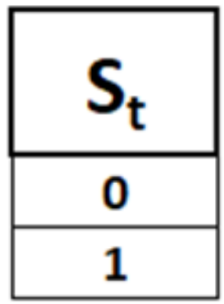
Status dynamics



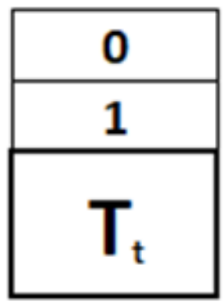
Representation of surveillance programmes as HMMs

Test results

- Herd status at time t is either negative (0) OR positive (1)



- Test result at time t is either negative (0) OR positive (1)

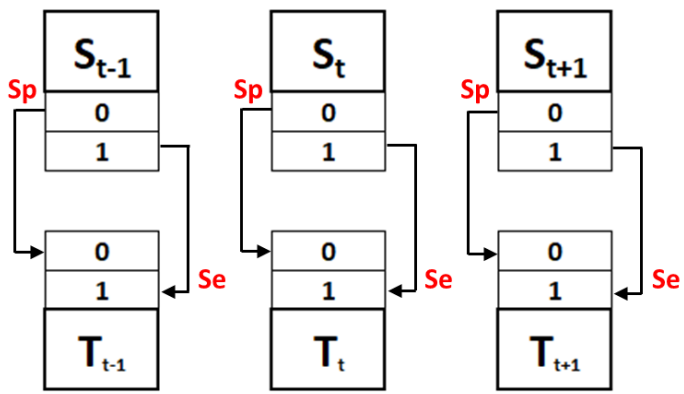


Representation of surveillance programmes as HMMs

Test results

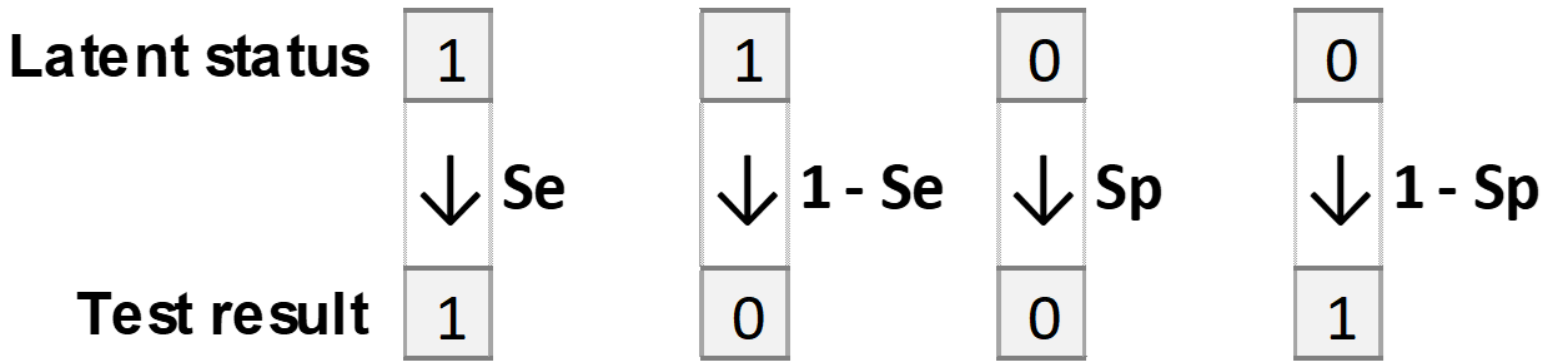
- Test results at the herd level
- Test results depend on the latent status through sensitivity and specificity

$$p(T_t = 1) = \begin{cases} 1 - Sp & \text{if } S_t = 0 \\ Se & \text{if } S_t = 1 \end{cases}$$



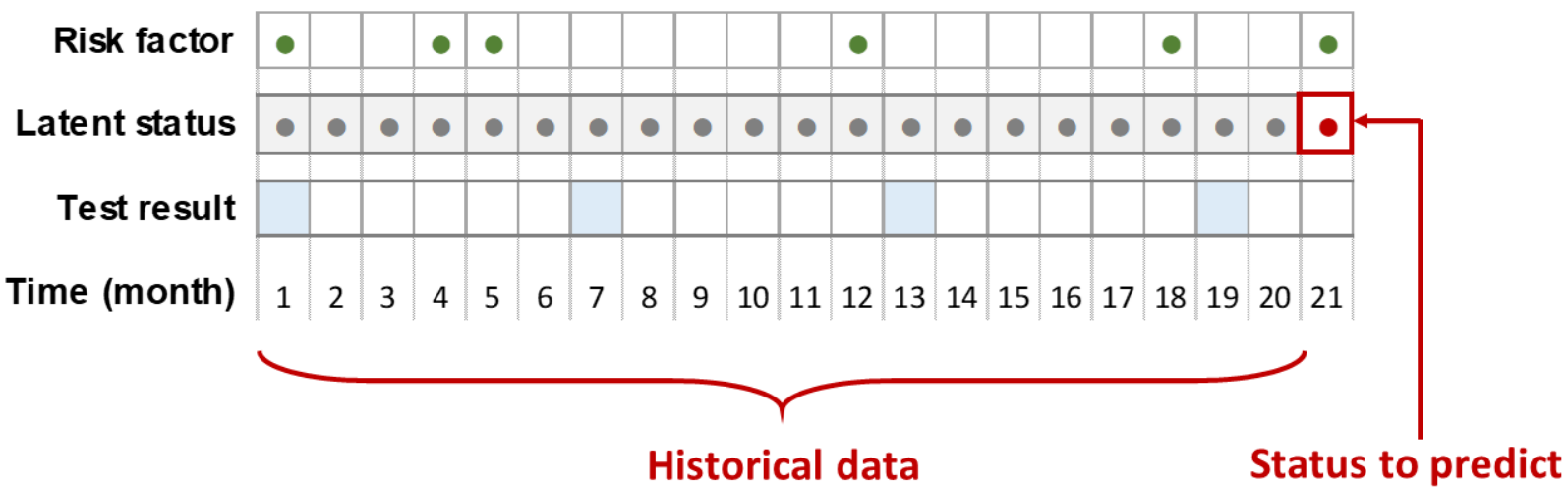
Representation of surveillance programmes as HMMs

Test results



Predictions

- The model predicts a herd level probability of being status positive at time T
- All the data available up to T are used for paremeter estimation



Summary of the different model parameters

- π_1: probability of being status positive on the first test month
- τ_1: probability of becmoing status positive between 2 months
- $\theta_1, \theta_2 \ldots$: coefficients of the logistic regression for the probability of becoming status positive
- τ_2: probability of remaining status positive between 2 months
- Se: herd-level test sensitivity
- Sp: herd-level test specificity

The complete model - no risk factor

$$S_1 \sim Bernoulli(\pi_1)$$

$$S_t \sim Bernoulli(\pi_t) \quad \forall t > 1$$

$$\pi_t = \begin{cases} \tau_1 & \text{if } S_{t-1} = 0 \\ \tau_2 & \text{if } S_{t-1} = 1 \end{cases}$$

$$T_t \sim Bernoulli(p(T_t))$$

$$p(T_t) = \begin{cases} 1 - Sp & \text{if } S_t = 0 \\ Se & \text{if } S_t = 1 \end{cases}$$

The complete model - with risk factors

$$S_1 \sim Bernoulli(\pi_1)$$

$$S_t \sim Bernoulli(\pi_t) \quad \forall t > 1$$

$$\pi_t = \begin{cases} \tau_{1t} & \text{if } S_{t-1} = 0 \\ \tau_2 & \text{if } S_{t-1} = 1 \end{cases}$$

$$ln(\frac{\tau_{1t}}{1 - \tau_{1t}}) = X_{ht}\theta$$

$$T_t \sim Bernoulli(p(T_t))$$

$$p(T_t) = \begin{cases} 1 - Sp & \text{if } S_t = 0 \\ Se & \text{if } S_t = 1 \end{cases}$$

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Data, hypotheses and parameters

- Data: test results, risk factors
- What we need to know: probability of infection on the current month
- What we know (more or less): test characteristics, characteristics of infection dynamics ...
- The modelling framework needs to be able to predict herd level probabilities of infection from test results and knowledge about test characteristics
- Chosen approach: Bayesian inference

Bayes' theorem

- What is a conditional probability?
  - Probability of an event given that another event has already happened

Sensitivity = probability of a positive test result (T^+) given that ($|$) an individual is diseased (D^+)

$$Se = p(T^+|D^+)$$

Positive predictive value = probability that an individual is diseased given a positive test result

$$PPV = p(D^+|T^+)$$

Bayes' theorem

- What is Bayes' theorem?
  - A simple formula that relates $p(B|A)$ to $p(A|B)$

$$p(B|A) = \frac{p(A|B)p(B)}{p(A)}$$

Bayes' theorem

- Bayes' theorem applied to determining the probability of disease given a positive test result
  - Usually we know test sensitivity, and we would like to know the probability that disease is present given test result

$$p(D^+|T^+) = \frac{p(T^+|D+)p(D^+)}{p(T^+)}$$

- $p(D^+|T^+)$: Positive predictive value
- $p(T^+|D+)$: Test sensitivity
- $p(D^+)$: Disease prevalence
- $p(T^+)$: Probability of a positive test

Bayes' theorem

- Bayes' theorem applied to determining the probability of disease given a positive test result

$$p(D^+|T^+) = \frac{p(T^+|D+)p(D^+)}{p(T^+)}$$

Bayes' theorem

- Bayes' theorem applied to determining the probability of disease given a positive test result

$$p(D^+|T^+) = \frac{p(T^+|D+)p(D^+)}{p(T^+)}$$

$$p(D^+|T^+) = \frac{p(T^+|D+)p(D^+)}{p(T^+|D+)p(D^+) + p(T^+|D^-)p(D^-)}$$

Bayes' theorem

- Bayes' theorem applied to determining the probability of disease given a positive test result

$$p(D^+|T^+) = \frac{p(T^+|D+)p(D^+)}{p(T^+)}$$

$$p(D^+|T^+) = \frac{p(T^+|D+)p(D^+)}{p(T^+|D+)p(D^+) + p(T^+|D^-)p(D^-)}$$

$$p(D^+|T^+) = \frac{Se\pi}{Se\pi + (1 - Sp)(1 - \pi)}$$

Bayes' theorem

Bayes' theorem applied to statistical inference

- We have some data (y) and a model, we would like to know what is the probability of the model parameter (θ) values given these data

$$p(\theta|y) = \frac{p(y|\theta)p(\theta)}{p(y)}$$

$p(\theta|y)$ Probability of parameters given data $\rightarrow$ **Posterior distribution**

$p(y|\theta)$ Probability of data given parameters $\rightarrow$ **Likelihood function**

$p(\theta)$ Parameter prior distributions$\rightarrow$ **priors**

$p(y)$ **Normalising constant**

Bayes' theorem

Bayes' theorem applied to statistical inference

- Bayesian inference is a way to estimate model parameters incorporating:
  - data
  - prior knowledge/hypotheses about the model parameters

Bayes' theorem

Bayes' theorem applied to statistical inference

- The normalising constant $p(y)$:
  - is an integral that cannot be readily computed, except in simple cases
  - makes the area under the posterior density curve sum to 1
  - is a constant

$$p(y) = \int p(y|\theta)p(\theta)d\theta$$

Bayes' theorem

Bayes' theorem applied to statistical inference

- Because in most cases the normalising constant cannot be computed, we need estimation methods that do no need to compute it for the estimation of the full posterior density

$$p(\theta|y) \propto p(y|\theta)p(\theta)$$

- Solution: draw many samples from likelihood x prior distribution using Markov Chain Monte Carlo

Markov Chain Monte Carlo

- **Monte Carlo**: draw random samples (θ) from statistical distributions
- **Markov Chain**: the next random values drawn depend on the values of the current ones

$$p(\theta|y) \propto p(y|\theta)p(\theta)$$

Markov Chain Monte Carlo

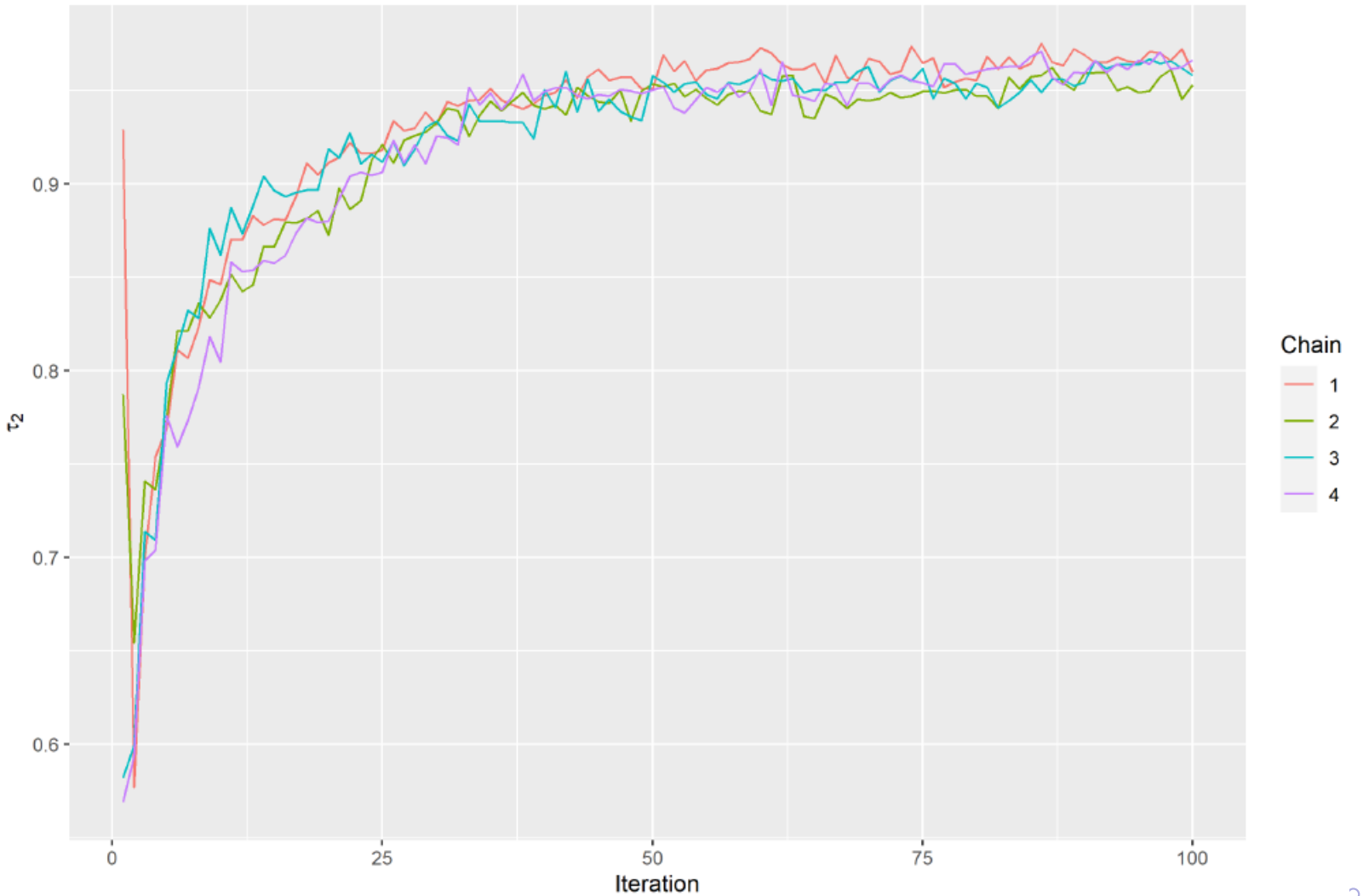
Principles of MCMC algorithms

- Start with some random initial values ($t = 1$)
- Use values at current iteration to sample values at next iteration (Markovian transition)
- The Markov Chain is constructed in such a way that it moves towards the target posterior probability distribution
- There is no way to be absolutely sure that the samples come from the target distribution
  - First iterations discarded $\Rightarrow$ burn in or warmup
  - Different simulations are run in parallel $\Rightarrow$ chains

Markov Chain Monte Carlo

Convergence

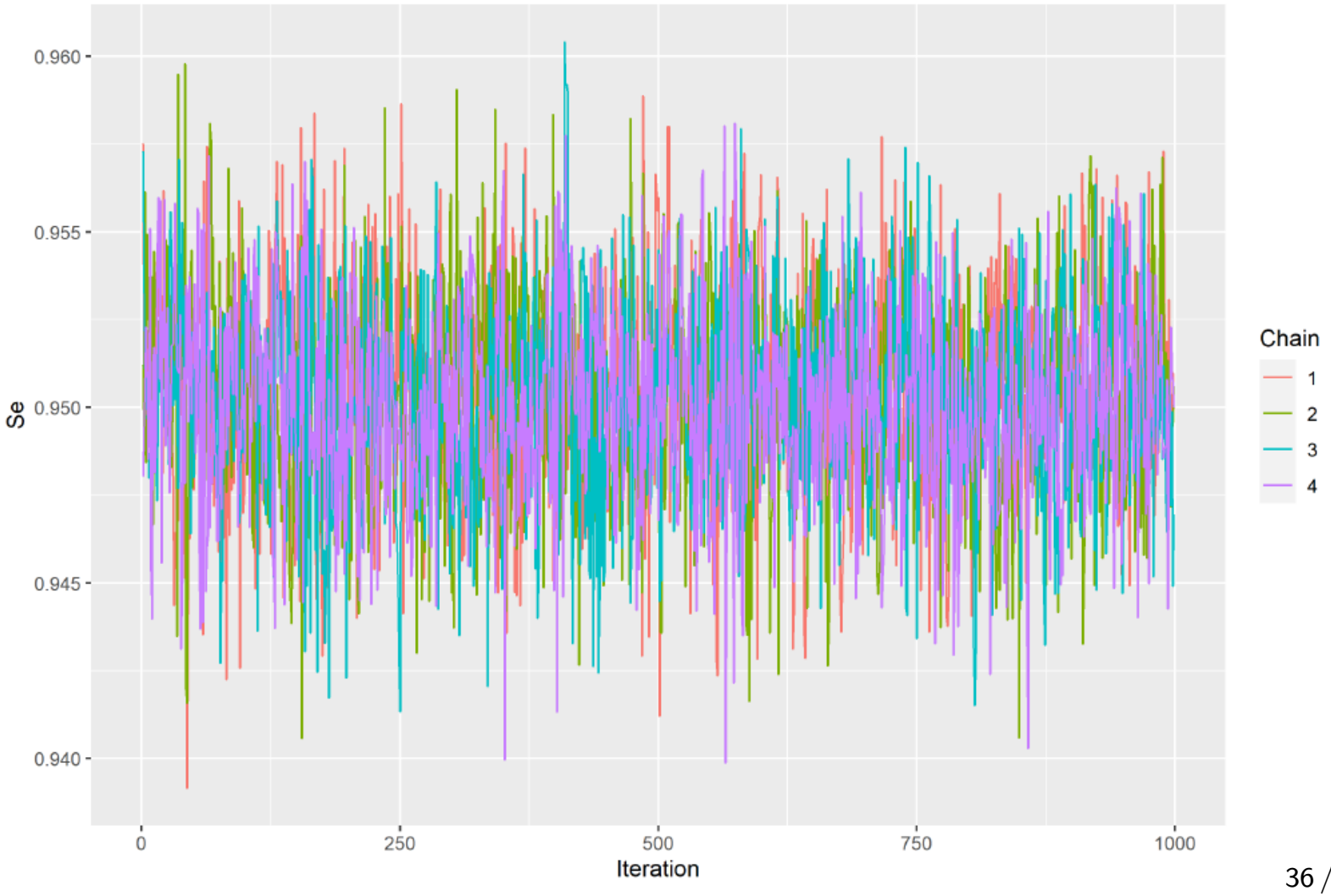
- Moving towards the target distribution



Markov Chain Monte Carlo

Convergence

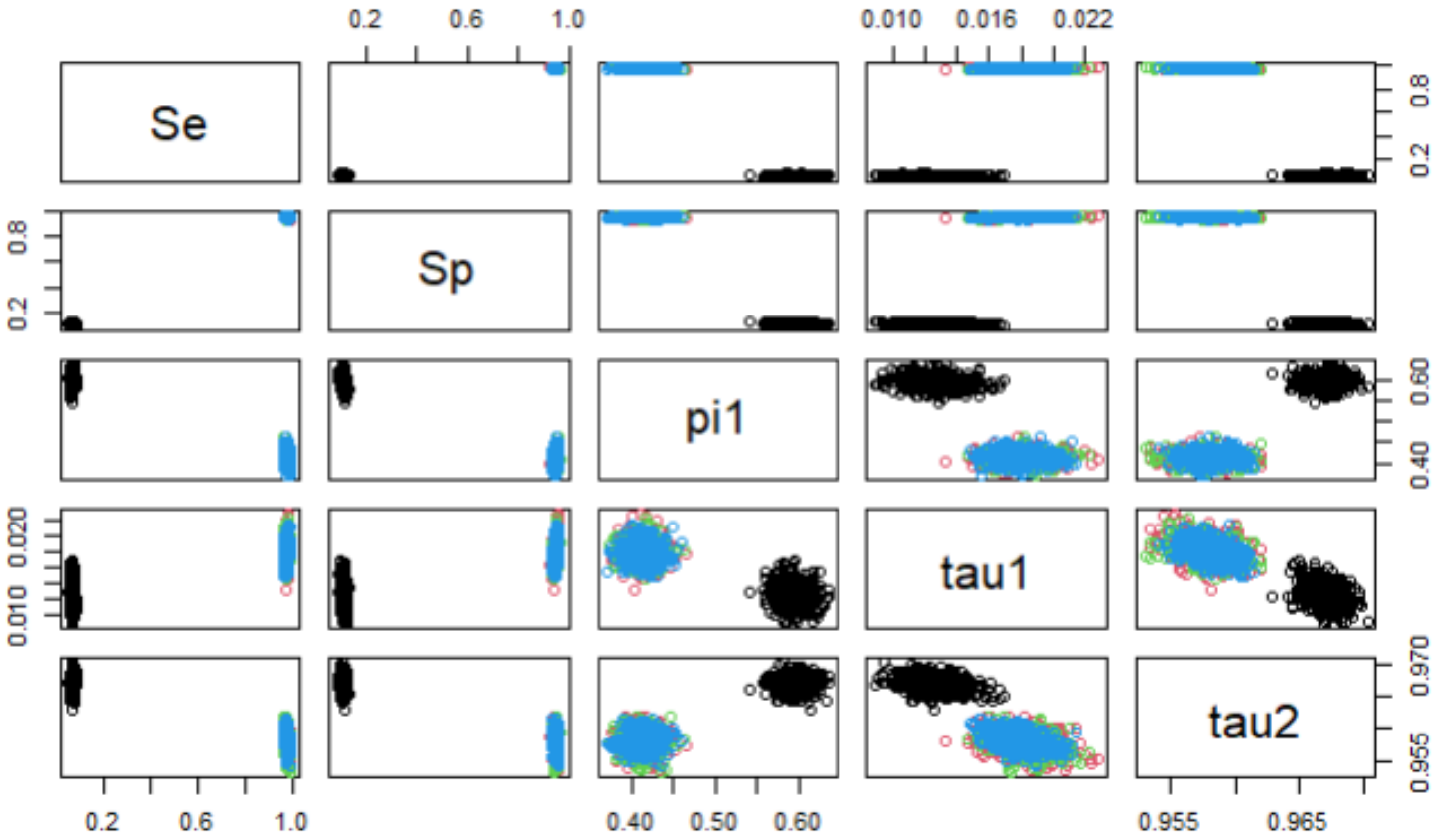
- All chains should converge to the same distribution → traceplot



Markov Chain Monte Carlo

Convergence

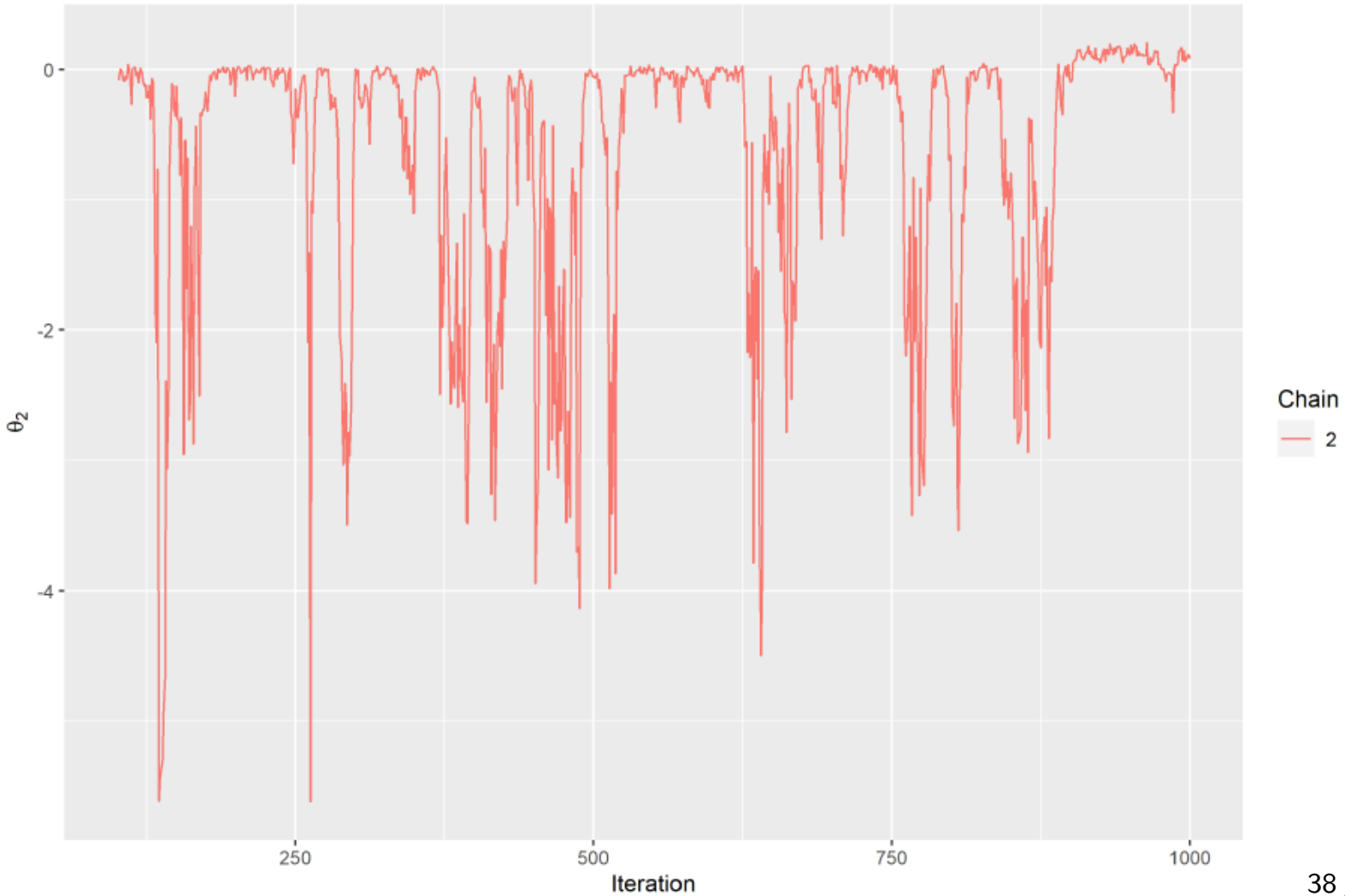
- Different chains can converge to different distributions
  - Model with 5 parameters / each color is a chain



Markov Chain Monte Carlo

Autocorrelation

- Autocorrelation: within a chain, high correlation between consecutive MCMC samples



Markov Chain Monte Carlo

in pratcice

- Run several chains (> 2): allows checking that the samples obtained do not come from different distributions = convergence (traceplots , Gelman Rubin statistic)
- Initialise each chain with different values
- Discard the first n iterations = burn in, warmup
- If autocorrelation, use 1 out of k iterations (depending on autocorrelation) = thinning

Markov Chain Monte Carlo

Algorithms

- There exist many different MCMC algorithms:
  - Metropolis: first invented (1953)

    See an introduction here: Ben Lambert - An introduction to the Random Walk Metropolis algorithm
  - Metropolis Hastings
  - Gibbs sampling: BUGS, WinBUGS, JAGS
  - Hamiltonian Monte Carlo: Stan

Markov Chain Monte Carlo

Gibbs sampling

- First widely used algorithm for Bayesian inference
  - Not possible before the 1990s because computation intensive
  - First implementations:
    - BUGS = Bayesian Inference Using Gibbs Sampling
    - WinBUGS , OpenBUGS
  - Most recent implementations
    - JAGS: Just Another Gibbs Sampler
    - MultiBUGS

    $\Rightarrow$ Same principles, more efficient

Markov Chain Monte Carlo

Gibbs sampling

- All the programmes use the same language to code statistical models
- Easy to write the code from model specification
- Straightforward to translate the STOC free model equations into code

Markov Chain Monte Carlo

Hamiltonian Monte Carlo

- Implemented in Stan
- Much more efficient than Gibbs sampling
  - Exploration of the posterior distribution much more efficient
  - Less autocorrelation $\rightarrow$ requires less iterations
- Does not support latent discrete parameters
  - Not possible to code the STOC free model as simply as in JAGS

Markov Chain Monte Carlo

- For a visual comparison of different MCMC algorithms, see: The Markov-chain Monte Carlo Interactive Gallery by Chi-Feng

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JAGS model

- Easy to go from model equations to JAGS code
- On the following slides:
  - Simplified version in which test results assumed available for all months
  - The *real* model allows for missing test results with a complicated system of loops. Same idea but harder to read
  - When no test available, the dynamics drive status evolution

JAGS model

First status

```
model{
  ## loop over all herds
  ## t1 is the vector of indices for first month of test in each herd
  ## t2 is the vector of indices for second month of test in each herd
  ## tf is the vector of indices for last month of test in each herd
  for(i in 1:N_herds){

    ### First monthly status of each herd
    ## probability of being latent status positive for herd i at t1
    logit_pi1[i] ~ dnorm(logit_pi1_mean, logit_pi1_prec)

    ## latent status for herd i at time = 1
    Status[t1[i]] ~ dbern(ilogit(logit_pi1[i]))

    ## probability of being test positive given herd status
    p_test_pos[t1[i]] <- Se * Status[t1[i]] +
                         (1 - Sp) * (1 - Status[t1[i]])

    ## test result associated with first Status => data
    test_res[t1[i]] ~ dbern(p_test_pos[t1[i]])
...
```

JAGS model

Statuses 2 to last - 1

```
### Statuses 2 to  1 minus last
for(t in (t1[i] + 1):(tf[i] - 1)){

  # probability of new infection
  # logistic regression
  logit(tau1[t]) <- inprod(risk_factors[t,], theta)

  ## probability of being status positive given previous status,
  ## tau1 and tau2
  pi[t] <- (1 - Status[t - 1]) * tau1[t] +
           Status[t - 1] * tau2

  ## herd status at time t
  Status[t] ~ dbern(pi[t])

  ## probability of test positive at time t
  p_test_pos[t] <- Se * Status[t] + (1 - Sp) * (1 - Status[t])

  ## test result at time t  => data
  test_res[t] ~ dbern(p_test_pos[t])

}
```

JAGS model

Predicted statuses

```
  # probability of new infection
  logit(tau1[tf[i]]) <- inprod(risk_factors[tf[i],], theta)

  ## Predicted probability of infection for herd i on last month
  pi[tf[i]] <- tau1 * (1 - Status[tf[i] - 1]) +
               tau2 * Status[tf[i] - 1]
  # probability of infection updated with test result
  predicted_proba[tf[i]] <- test_res[tf[i]] * (
    Se * pi[tf[i]] / (Se * pi[tf[i]] + (1 - Sp) * (1 - pi[tf[i]]))
  ) + (1 - test_res[tf[i]]) * (
      (1 - Se) * test_res[tf[i]] /
        ((1 - Se) * pi[tf[i]]  + Sp * (1 - pi[tf[i]] ) )
    )

}
```

JAGS model

Priors

```
### Priors
## test characteristics
Se ~ dbeta(Se_beta_a, Se_beta_b)
Sp ~ dbeta(Sp_beta_a, Sp_beta_b)

## Status dynamics - sampling on the logit scale
logit_tau2 ~ dnorm(logit_tau2_mean, logit_tau2_prec)

## logit back to the probability scale
tau2 <- ilogit(logit_tau2)

## Logistic regression coefficients
for(i_rf in 1:n_risk_factors){

  theta[i_rf] ~ dnorm(theta_norm_mean[i_rf], theta_norm_prec[i_rf])

}

}
```

Stan model

- Stan implements Hamiltonian Monte Carlo which is expected to be more efficient at sampling from the full posterior distribution
- Stan does not support latent discrete parameters
- Translation of the model's equations not as easy as with JAGS
- Various HMM implementations in Stan described in a tutorial by Damiano et al. (2017)

Stan model

- Forward algorithm adapted from the tutorial
- Same model as the JAGS version, but estimation performed in a different way

Comparison of the JAGS and Stan implementations

- The JAGS and Stan implementations of the model were compared using data collected as part of BVDV control programme in France
  - Work under review with PCI Animal Science, available as a pre-print.
- The Stan implementation:
  - gives the same parameter estimates
  - is much faster
  - converges much better
  - returns predicted probabilities of infection that are easier to interpret

The STOCfree R package

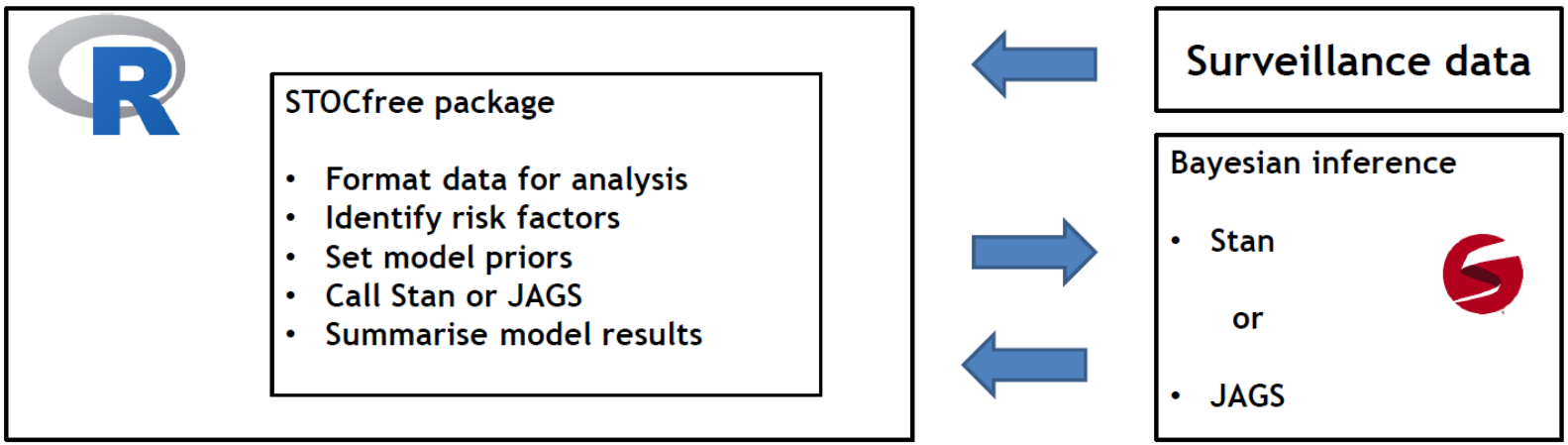
What is an R package?

- Programming environment for data manipulation and analysis
- Widely used
- Free

 package

- Set of functions gathered to perform specific tasks
- Users install a package and can use the functions they contain
- Packages are installed from the web (CRAN, GitHub...)

The STOCfree R package

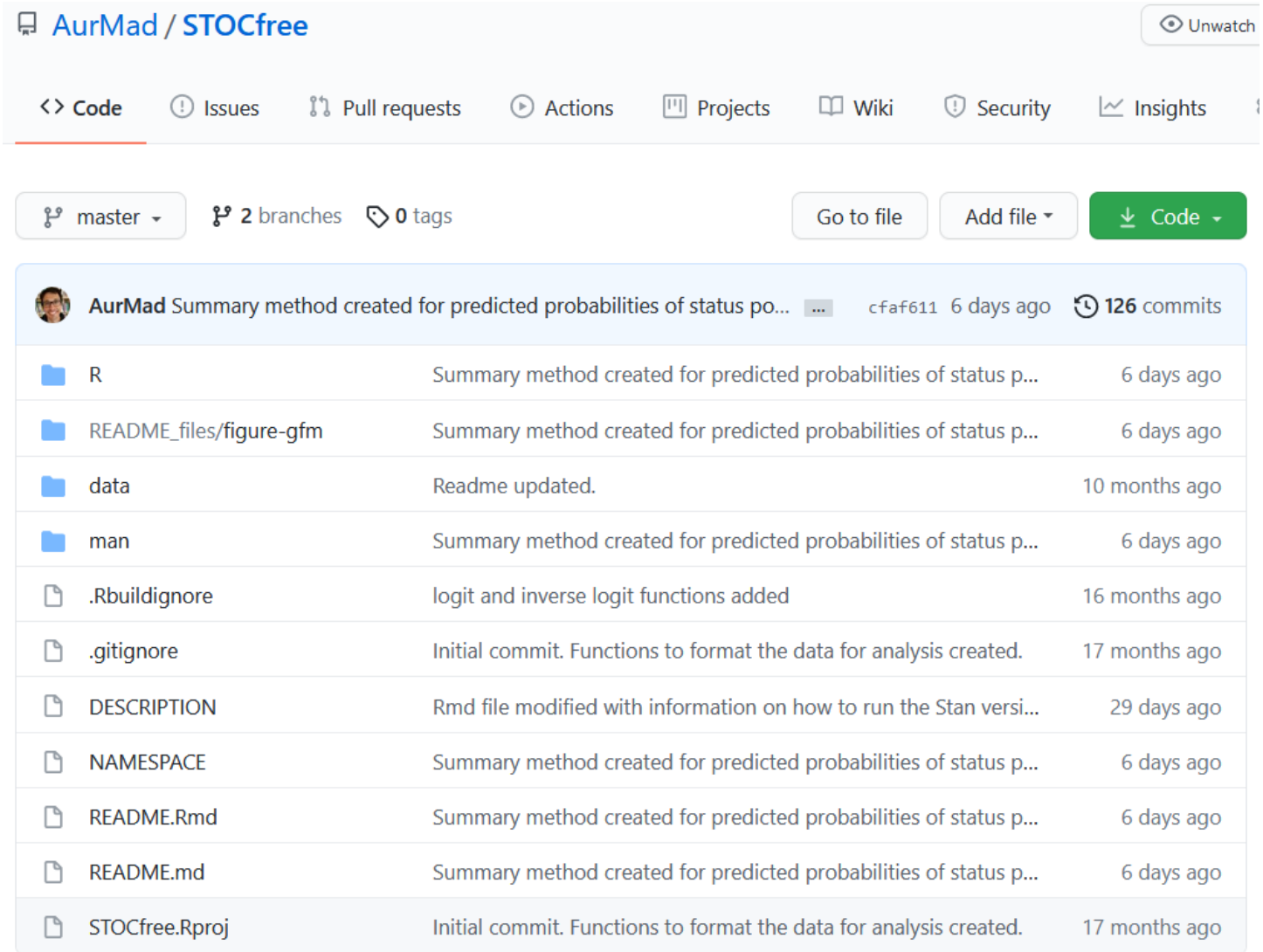


The STOCfree R package on Github

- The package is hosted on Github
  https://github.com/AurMad/STOCfree
- Github is a server hosting:
  - The package code
  - The package documentation
  - The history of development and different package versions, using the Git versioning programme

The STOCfree R package on Github

- All the code is in the `R` folder



The STOCfree R package on Github

- The documentation is at the bottom of the page

README.md

STOCfree: prediction of probabilities of freedom from infection from longitudinal data

Overview

The aim of the `STOCfree` package is to predict herd level probabilities of freedom from infection from

STOC free

efsa
European Food Safety Authority

Thank you for your attention

http://www.stocfree.eu/

This study was awarded a grant by EFSA and was co-financed by public organisations in the countries participating in the study.

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