FMDV IMMUNITY
ESTIMATION OF ANTIBODY DYNAMICS

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In the problem of simulate the dynamics of antibody levels for Foot and Mouth Disease we consider a Markov Process with Probability matrix given by

$$P(t \mid \boldsymbol{\theta}) = \begin{pmatrix} P_{\mathrm{l}}(t \mid t_0 = 0) & P_{\mathrm{h}}(t \mid t_0 = 0) \\ P_{\mathrm{l}}(t \mid t_0 = 1) & P_{\mathrm{h}}(t \mid t_0 = 1) \end{pmatrix}$$

where $P_{\mathrm{h}}(t) = \Pr\{\text{High antibody levels at time } t\}$ and $P_{\mathrm{l}}(t) = \Pr\{\text{Low antibody levels at time } t\}$ and $\boldsymbol{\theta}$ is a vector of parameters. In a simplified form, we denote the random walk associated with the transition probability as

$$P_{Y,Z}(t \mid \theta) = \Pr\left\{X(s+t) = Z \mid X(s) = Y\right\} .$$

Our focus relies in the fact that antibody levels among the different SAT can be interpreted as a random walk within an individual. Thus, we can consider the dynamics of antibody levels within a cohort of animals as multiple random walks. Each individual random walk is then defined through the following distribution

$$f(x, \mathbf{t}) = \prod_{j=2}^{T} P_{x_{j-1},x_j}(t_j - t_{j-1} \mid \boldsymbol{\theta})$$

Hence for a sample $X_1, \ldots, X_n$ of water buffaloes, where the antibody dynamics are independent identically distributed through the distribution $f(x, \mathbf{t})$ above, we have that the likelihood of this arbitrary sample is given by

$$L(\boldsymbol{\theta} \mid \mathbf{x}, \mathbf{t}) = \prod_{i=1}^{n} \prod_{j=2}^{T_i} P_{x_{i,j-1},x_{i,j}}(t_{i,j} - t_{i,j-1} \mid \boldsymbol{\theta}) \tag{1}$$

The transition probabilities are governed through the following system of differential equations

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} P_{\mathrm{h}}(t) &= -\lambda_{\mathrm{h}}(t) P_{\mathrm{h}}(t) + \lambda_{\mathrm{l}}(t) P_{\mathrm{l}}(t) \\ \frac{\mathrm{d}}{\mathrm{d}t} P_{\mathrm{l}}(t) &= -\lambda_{\mathrm{l}}(t) P_{\mathrm{l}}(t) + \lambda_{\mathrm{h}}(t) P_{\mathrm{h}}(t) \end{aligned}$$

where $\lambda_{\mathrm{l}}(t)$ =hazard of moving from low to high and $\lambda_{\mathrm{h}}(t)$ =hazard of moving from high to low. Since $P_{\mathrm{l}}(t) = 1 - P_{\mathrm{h}}(t)$ and $\dfrac{\mathrm{d}}{\mathrm{d}t}(P_{\mathrm{h}} + P_{\mathrm{l}})(t) = 0$ the system above can be reduced to the ordinary differential equation

$$\frac{\mathrm{d}}{\mathrm{d}t} P_{\mathrm{h}}(t) = \lambda_{\mathrm{l}}(t) - (\lambda_{\mathrm{l}}(t) + \lambda_{\mathrm{h}}(t)) P_{\mathrm{h}}(t) = \eta(t) - \gamma(t) P_{\mathrm{h}}(t)$$

Let us notice that the ODE above can be solved analytically given that $\lambda_{\mathrm{l}}(t)$ and $\lambda_{\mathrm{h}}(t)$ are determined integrable functions, where the solution is then given by

$$P_{\mathrm{h}}(t) = \left(\int_{t_0}^{t} \exp\left\{ \int_{t_0}^{s} \gamma(\tau) d\tau \right\} \eta(s) ds - P_{\mathrm{h}}(t_0) \right) \exp\left\{ - \int_{t_0}^{t} \gamma(s) ds \right\}$$

From the solution above we can observe that the time dependency of the hazard functions play a critical role in the evolution of the antibody dynamics. Therefore, we need to assess if such functions are time dependent or not according to the experimental measurements. We thus compare the following two models:

Model	$\lambda_{\mathrm{l}}(t)$	$\lambda_{\mathrm{h}}(t)$
Model 1	a	b
Model 2	$\left(\frac{\alpha-\beta}{t_{end}-t_{start}}\right)t+\left(\frac{\alpha-\beta}{t_{end}-t_{start}}t_{start}+\alpha\right)=ct+d$	e

Let us notice that whenever $\alpha=\beta$ in Model 2 we reduce to Model 1; this allows us to compare this nested models by using the Maximum Likelihood Estimator (MLE) and design the following hypothesis test

$$H_0: \quad \alpha=\beta \qquad \text{v.s.} \qquad H_1: \alpha\neq\beta$$

We thus find the following point estimators by using the likelihood (1)

SAT	$\hat{a}_{MLE}$	$\hat{b}_{MLE}$	$\hat{\alpha}_{MLE}$	$\hat{\beta}_{MLE}$	$\hat{e}_{MLE}$
SAT1	0.450635794734879	0.0932094146241297	0.669900541887672	0.146555991721188	0.0891200968121728
SAT2	0.337941760897452	0.208302701098458	0.273348379072234	0.383014679455082	0.206566595621934
SAT3	0.275879222040706	0.363338860591964	0.381970336932573	0.178230483666068	0.36247553412567

Through the use of the Likelihood Ratio Test (LRT) we can conclude that there is strong statistical evidence to reject the null hypothesis for the cases of SAT1 and SAT2; whilst the test is inconclusive for SAT2. This is further confirmed through the use of the Akaike Information Criterion (AIC)

SAT	LRT	AIC Model 1	AIC Model 2	AIC comparison $\left(1-\exp\left(-\frac{\lvert AIC1-AIC2\rvert}{2}\right)\right)$
SAT1	0.992295837730399	593.816025975106	588.715041451824	0.921956761148986
SAT2	0.560697237082864	843.150614568539	844.552511643543	0.50388550266813
SAT3	0.971803995705221	932.153980922522	929.337937989104	0.755373193056843

Therefore, we can conclude that the model that best fits for our experimental data is Model 2 where we have time dependency on one of the hazard functions ($\lambda_{\mathrm{l}}(t)$).

The analysis above relies on given deterministic functions and that the collected data is accurate. Nevertheless, this often is untrue or not completely reliable. Therefore, a Bayesian approach has been implemented. By assuming that Model 1 has parameters with uniform prior distributions and the likelihood given in (1) we sample the posterior distribution

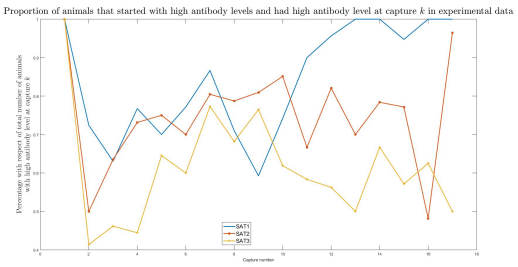
$$\pi(\boldsymbol{\theta}\mid \mathbf{x},\mathbf{t})\propto L(\boldsymbol{\theta}\mid \mathbf{x},\mathbf{t})$$

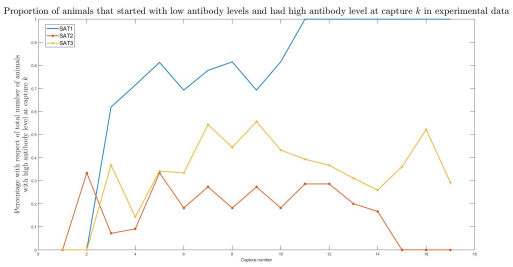
through a Metropolis-Hastings (M-H) algorithm. The results of this Markov Chain Monte Carlo method we obtain a histogram of the posterior distribution, the Maximum A Posteriori (MAP) estimator of both parameters a and b that define the hazard functions $\lambda_{\mathrm{l}}(t)$ and $\lambda_{\mathrm{h}}(t)$ respectively, and the 95% Credible intervals for these parameters.

SAT	$\hat{a}_{MAP}$	$\hat{b}_{MAP}$	Acceptance rate
SAT1	0.457494520560844	0.095045285534491	0.258433333333333
SAT2	0.342968101512515	0.211123981280086	0.222966666666667
SAT3	0.279533720894248	0.366114380812467	0.167566666666667

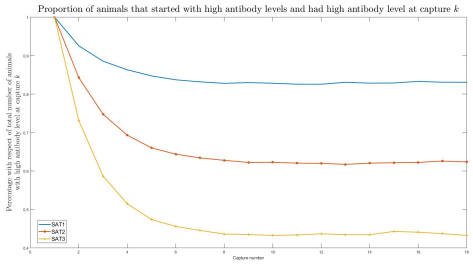
SAT	Credible interval a	Credible interval b
SAT1	(0.359614523621854,0.575163740647241)	(0.0702984658629116,0.125296240300929)
SAT2	(0.268534220168746,0.4322409462545)	(0.169627774260504,0.2600386418752)
SAT3	(0.224755918189966,0.344664924464384)	(0.299140253996511,0.449573780637181)

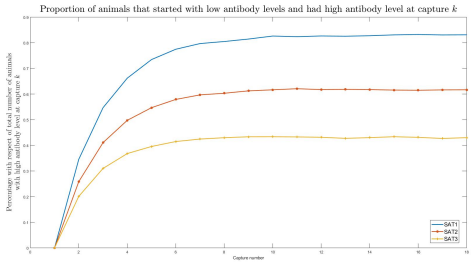
The following are some of the most representative graphical results of our different analyses. From the experimental data we have the following proportions of antibody dynamics among the different animals in the studied buffalo cohort.



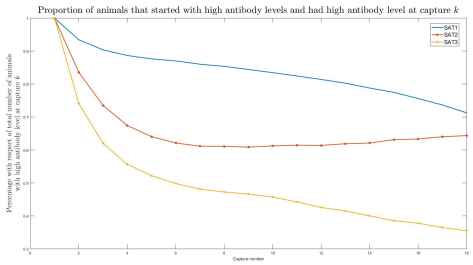


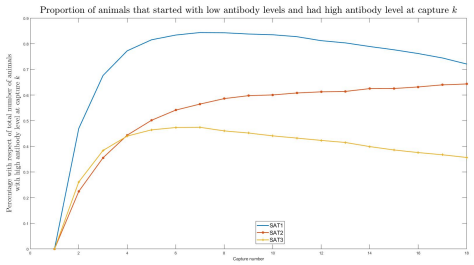
Simulating data through Model 1, by using the MLE estimator given above we obtain the following



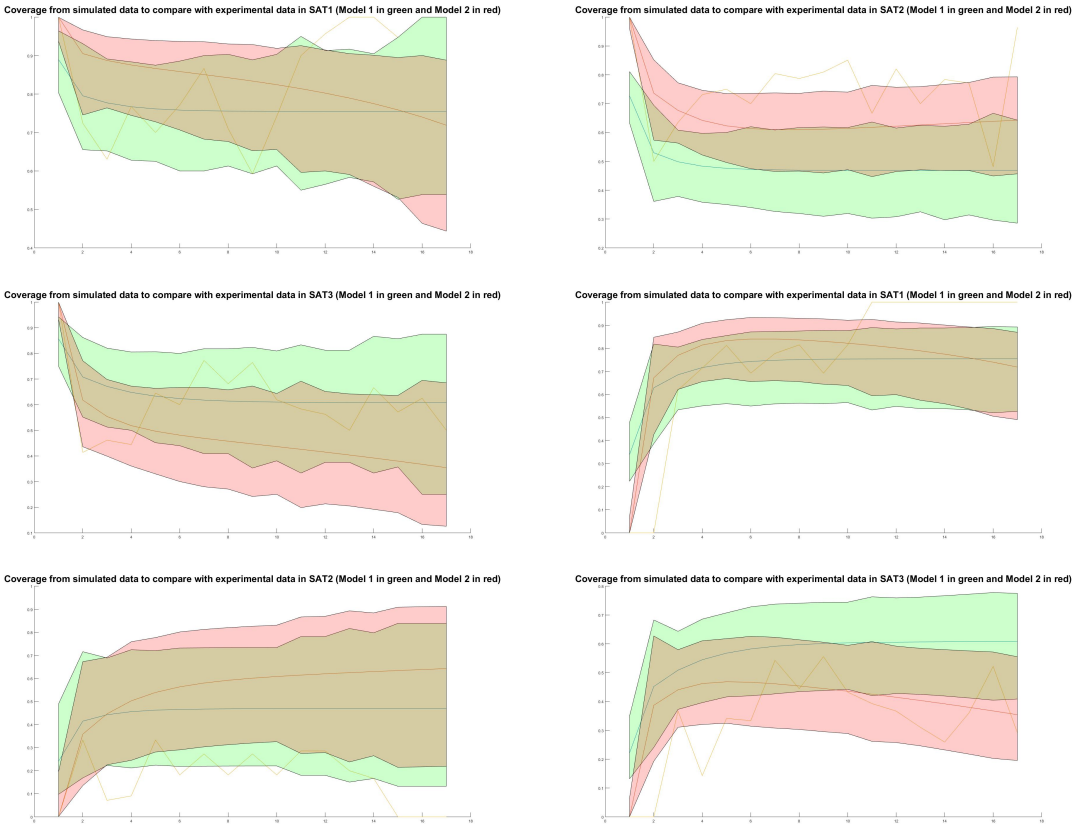


In contrast with the simulated data through Model 2

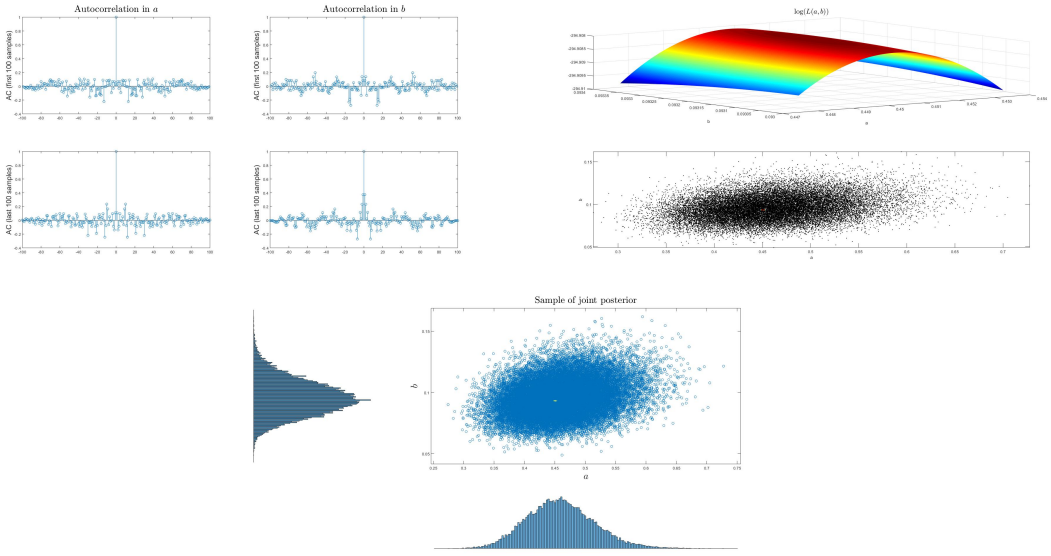




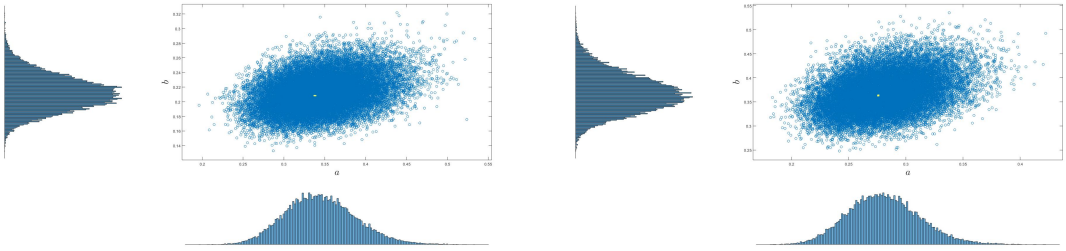
We then observe the coverage of these two models to the experimental data



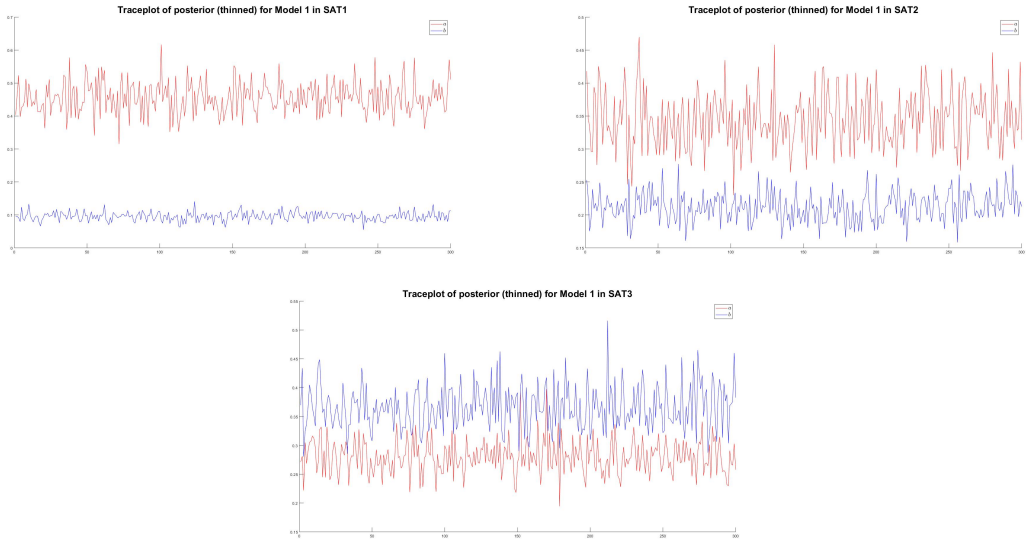
For SAT1 we have the following results of our MCMC simulations



the histogram of the posterior for SAT2 and SAT3



the traceplot of the Markov chain among the different serotypes.



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