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Parameter identification for a PDE model representing scrapie transmission in a sheep flock

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Abstract— **In this paper a strategy for the identification of the parameters in a mathematical model which describes the dynamics of a scrapie outbreak in a sheep flock is proposed.**

Scrapie is a transmissible spongiform encephalopathy that affects sheep, characterised by a genetic susceptibility factor and a long incubation period. To represent the outbreak, demographic and epidemiological processes need to be taken into account in the model, as well as seasonality in breeding and scrapie transmission. The flock is hence structured according to scrapie status (susceptible or infected), genotype, time, age, and infection load (related to the incubation period), resulting into a PDE model.

We built a hierarchy of two aggregated models and take advantage of the hyperbolic structure of the PDEs to part the parameters of the model into three groups, which can theoretically be separately identified. The problem of identifiability and identification is addressed and tests with data from a natural scrapie outbreak are performed.

I. Introduction

Scrapie is a fatal and naturally occurring transmissible spongiform encephalopathy of sheep. The disease is associated with a conformationally abnormal form of the prion protein PrP. Polymorphism of the PrP gene encoding for this protein largely control the susceptibility and resistance of sheep to the disease. The epidemiology of scrapie and particularly the transmission mechanisms are still incompletely understood [1]. A previous study [2], conforted by experimental evidence (scrapie infectivity in placenta), provides strong support for the hypothesis of increased transmission during lambing periods via the ingestion of contaminated placental material.

The PDE model used in this paper was initially developed in [3] and has been used to study several outbreaks in Scottish sheep. In accordance with the study mentioned above, it incorporates here a seasonal pattern in breeding and transmission. We apply it to the Langlade experimental flock, in which a natural scrapie outbreak started in 1993 [4] and for which extensive demographic, genetic and scrapie case data are available.

The aim of this paper is to design a hierarchical method for the identification of the model parameters from the Langlade data. Many methods have been developed to identify the parameters of ODE models, in the linear and non linear cases [5]. However, there are only few studies that consider PDE-based models. The method we describe takes advantage of the hyperbolic structure of the PDEs [6], [7] to part the parameters of the model into three groups, so as to transform the identification problem into simplified subproblems.

First the complete PDE model is described, as well as the hierarchisation into three overlapping models used to address the identification problem. Then changes of variables and a cohort aggregation allows us to transform the original problem into subproblems on the upper level ODE models. The parameter identifiability and identification is then addressed and parameters are estimated from the Langlade data. Finally conclusions are drawn and future developments are discussed.

II. Model structure

The flock is structured according to scrapie status (susceptible S or infected I), PrP genotype $g \in \mathcal{G}$, sheep age a and, for the infected sheep only, infection load θ. When a susceptible sheep becomes infected, it is given an variable initial load, which is assumed to grow during the incubation period until a set maximum value corresponding the onset of clinical signs is reached; it is followed by the culling of the animal. The variable initial load thus allows for variable incubation periods. The resulting sheep population densities are $S_g(t,a)$ and $I_g(t,a,\theta)$, where

- time $t_0 \leqslant t \leqslant T$ (in years),
- age $0 \leqslant a \leqslant A$ (in years),
- and infection load $0 \leqslant \theta \leqslant 1$ (dimensionless)

are continuous variables.

The model incorporates the following components: seasonal breeding and routine culling, genetic susceptibility, a long and variable incubation period, and seasonal horizontal transmission. Hence, to represent the evolution through time of the population densities with respect to age and infection load, the model consists of a set of partial differential equations.

A. Formulation

We assume the following:

- age and load for genotype g grow with time, with dynamics

$$\frac{da}{dt} = 1, \qquad \frac{d\theta}{dt} = c_g\theta;$$

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- the routine culling rate $\mu(a)$ only depends on the age of the animal;
- the initial load is distributed according to the probability density function $\Theta(\theta)$ of a gamma distribution with parameters k and l;
- only horizontal transmission occurs (no in utero transmission), hence $I_g(t,0,\theta) = 0$, so all newborns are susceptible;
- birth and transmission are seasonal and occur each year during the same period $[d_1, d_2]$ $(0 < d_1 < d_2 < 1)$, the length of which is approximately one month ($d_2 - d_1 \simeq \frac{1}{12}$);
- the infectiousness, i.e. the relative capacity of an infected animal to contaminate a susceptible one, is constant during the incubation period;
- the transmission rate is proportional to the total infected population $I(t) = \sum_{g'} \int_0^1 \int_0^A I_{g'}(t,a',\theta')da'd\theta'$ and the relative genetic susceptibility $\sigma_g \in [0,1]$ of the sheep being infected, with coefficient K;
- once the end of the incubation period is reached ($\theta = 1$), the animals are euthanized immediately.

We observe the following:

- the total population size $P_g(t,a)$ at each time t;
- the inflow of susceptible newborns at each time t, denoted as $S_g(t,0) = S_{0g}(t)$;
- the scrapie incidence $y_g(t,a) = c_g I_g(t,a,1)$, i.e. the outflow of infected animals dying of scrapie per unit of time and age;
- the outflow of routinely culled animals per unit of time and age.

Moreover, we consider that the initial condition $S_g(0,a)$ and $I_g(0,a,\theta)$ is known.

The model's equations are therefore

$$\begin{aligned} \partial_t S_g + \partial_a S_g &= -\mu(a) S_g - K\sigma_g s(t) I(t) S_g \\ S_g(t,0) &= S_{0g}(t) \\ \partial_t I_g + \partial_a I_g + \partial_\theta(c_g \theta I_g) &= -\mu(a) I_g \\ &\quad + \Theta(\theta) K \sigma_g s(t) I(t) S_g \\ I_g(t,0,\theta) &= I_g(t,a,0) = 0 \end{aligned} \tag{1}$$

where

$$\begin{aligned} S_g(t,a) = 0 \text{ and } I_g(t,a,\theta) = 0 &\quad \text{for } a < 0 \text{ or } a > A \\ I_g(t,a,\theta) = 0 &\quad \text{for } \theta < 0 \text{ or } \theta > 1 \\ \mu(a) = \kappa\lambda(\lambda a)^{\kappa-1} & \\ \Theta(\theta) = \frac{l(l\theta)^{k-1}e^{-l\theta}}{\Gamma(k)} & \\ s(t) = \begin{cases} 1 & \text{if } d_1 < t - [t] < d_2 \\ 0 & \text{otherwise} \end{cases} & \end{aligned}$$

$[t]$ denoting the integer part of t.

B. Hierarchisation

The set of parameters to be determined in model (1), namely $\{(c_g)_{g\in\mathcal{G}}, \kappa, \lambda, K, (\sigma_g)_{g\in\mathcal{G}}, l, k\}$ can be parted into three groups.

The first one is the "low level" group $\{(c_g)_{g\in\mathcal{G}}, k, l\}$: these parameters describe the detailed process of contamination at the elementary level, since they model the incubation process and the incubation time distribution.

1) Contact transmission model: They disappear when formulating a higher level model where for a given age and time, the density of the infected is integrated over the infection load θ. Setting $\mathbf{I_g}(t,a) = \int_0^1 I_g(t,a,\theta)d\theta$, the resulting model is

$$\begin{aligned} \partial_t S_g + \partial_a S_g &= -(\mu(a) + K\sigma_g s(t) I(t)) S_g \\ S_g(t,0) &= S_{0g}(t) \\ \partial_t \mathbf{I_g} + \partial_a \mathbf{I_g} &= -y_g - \mu(a)\mathbf{I_g} + K\sigma_g s(t) I(t) S_g \\ \mathbf{I_g}(t,0) &= 0. \end{aligned} \tag{2}$$

Hence the behaviour of system (2) still depends on k, l and c_g through variable y_g, but as it is a measured quantity, identification of the other parameters can be performed without knowing k, l and c_g.

From (2), we see that parameters $(K,\ (\sigma_g)_{g\in\mathcal{G}})$ form a higher level group, modelling global contact transmission.

2) Global population model: Finally, we can sum the dynamic equations in (2), and over the genotypes. We set

$$\begin{aligned} P(t,a) &= \sum_{g\in\mathcal{G}} (S_g(t,a) + \mathbf{I_g}(t,a)) = S(t,a) + I(t,a), \\ y(t,a) &= \sum_{g\in\mathcal{G}} y_g(t,a) \end{aligned}$$

and we get

$$\begin{aligned} \partial_t P + \partial_a P &= -y - \mu(a) P \\ P(t,0) &= P_0(t) = S_0(t), \end{aligned} \tag{3}$$

where only high level parameters κ and λ explicitly appear in μ and quantity $P(t,a)$ is measured.

III. Model transformation

The relationship between time and age ($\frac{da}{dt} = 1$) results in a first order hyperbolic structure for the linear part of the global contact transmission model (2) and the global population model (3). This suggests the use of the characteristic method [6], [7] to find for each model a suitable change of variables leading to a simpler form and a simpler identification subproblem.

Moreover, as birth occurs periodically during a short season, it seems adequate to aggregate population densities in birth cohorts.

A. Change of variables

1) Contact transmission model: To transform the global contact transmission model (2), we use the change of variable $(t,a) \to (\tau,\delta)$, where $t = \tau$ and $a = \tau - \delta$; δ is the time of

birth. We obtain a "δ-parametrised" ODE system:

$$\frac{d}{d\tau}S_g(\tau,\delta) = -(\mu(\tau-\delta) + K\sigma_g s(\tau)I(\tau))S_g(\tau,\delta) \quad (4a)$$

$$S_g(\delta,\delta) = S_{0g}(\delta) \quad (4b)$$

$$\frac{d}{d\tau}\mathbf{I_g}(\tau,\delta) = -y_g(\tau,\delta) - \mu(\tau-\delta)\mathbf{I_g}(\tau,\delta) + K\sigma_g s(\tau)I(\tau)S_g(\tau,\delta) \quad (4c)$$

$$\mathbf{I_g}(\delta,\delta) = 0. \quad (4d)$$

Note that initial conditions (4b) and (4d) are valid only when $\delta \geqslant t_0$, where t_0 is the time at which computation starts, otherwise it has to be replaced by initial values at time t_0 $S_g(t_0,\delta)$ and $\mathbf{I_g}(t_0,\delta)$.

2) Global population model: To transform the global population model (3), we use the change of variable $(t,a) \to (\delta,\alpha)$, where $a = \alpha$ and $t = \alpha + \delta$. We obtain a "δ-parametrised" ODE problem again:

$$\frac{d}{d\alpha}P(\delta,\alpha) = -y(\delta,\alpha) - \mu(\alpha)P(\delta,\alpha) \quad (5a)$$

$$P(\delta,0) = P_0(\delta) = S_0(\delta). \quad (5b)$$

Again, initial condition (5b) is valid only when $\delta \geqslant t_0$, otherwise it has to be replaced by initial values at time t_0 $P(\delta, t_0-\delta)$.

B. Cohort aggregation

1) Global population model: Let us first concentrate on the global population model (5). As birth in the flock is seasonal, it is interesting to integrate (5a) over δ on intervals of the form $[n_1,n_2] = [n+d_1,\ n+d_2]$ ($n \in \mathbb{N}$), outside which $P(\delta,\alpha) = 0$. It is easy to check that

$$C_n(\alpha) = \int_{n_1}^{n_2} P(\delta,\alpha)d\delta$$

and

$$y_n(\alpha) = \int_{n_1}^{n_2} y(\delta,\alpha)d\delta$$

are respectively the total number of animals in cohort number n (born between n_1 and n_2) that have reached age α and the number of animals in cohort number n dying of scrapie at age α per unit of age. We get

$$\frac{d}{d\alpha}C_n(\alpha) = -y_n(\alpha) - \mu(\alpha)C_n(\alpha).$$

As the flock is only represented on the time interval $[t_0,T]$, initial conditions C_{ni} (age $\alpha = 0$) are taken to be the newborns $C_n(0)$ if $n_1 \geqslant t_0$ or $C_n(t_0-n_1)$ if $n_1 < t_0$.

Setting $\alpha_{ni} = \max(t_0-n_1,0)$, we obtain the following expression for $C_n(\alpha)$

$$C_n(\alpha) = C_{ni}e^{-\int_{\alpha_{ni}}^{\alpha}\mu(\alpha')d\alpha'} - \int_{\alpha_{ni}}^{\alpha} e^{-\int_{\alpha'}^{\alpha}\mu(\alpha'')d\alpha''}y_n(\alpha')d\alpha'.$$

As $\int_0^\alpha \mu(\alpha')d\alpha' = (\lambda\alpha)^\kappa$, it can be rewritten as

$$C_n(\alpha) = C_{ni}e^{-((\lambda\alpha)^\kappa-(\lambda\alpha_{ni})^\kappa)} - \int_{\alpha_{ni}}^{\alpha} e^{-((\lambda\alpha)^\kappa-(\lambda\alpha')^\kappa)}y_n(\alpha')d\alpha'. \quad (6)$$

Noting $\alpha_{nf} = \min(T-n_2, A)$, this expression is valid for age $\alpha \in [\alpha_{ni},\alpha_{nf}]$ and we use it for parameter identification.

2) Contact transmission model: In a similar way, integrating system (4) over δ on intervals $[n_1,\ n_2]$ and setting

$$S_{gn}(\tau) = \int_{n_1}^{n_2} S_g(\tau,\delta)d\delta$$

$$I_{gn}(\tau) = \int_{n_1}^{n_2} \mathbf{I_g}(\tau,\delta)d\delta$$

$$y_{gn}(\tau) = \int_{n_1}^{n_2} y_g(\tau,\delta)d\delta$$

we get

$$\frac{d}{d\tau}S_{gn} = -\int_{n_1}^{n_2}\mu(\tau-\delta)S_g(\tau,\delta)d\delta - K\sigma_g s(\tau)I(\tau)S_{gn}$$

$$\frac{d}{d\tau}I_{gn} = -y_{gn} - \int_{n_1}^{n_2}\mu(\tau-\delta)\mathbf{I_g}(\tau,\delta)d\delta + K\sigma_g s(\tau)I(\tau)S_{gn}.$$

As the lambing period is short, $n_2-n_1 = d_2-d_1$ is small. Assuming moreover that birth are symmetrically distributed during the lambing season, we can make the following approximation for S_g

$$\int_{n_1}^{n_2}\mu(\tau-\delta)S_g(\tau,\delta)d\delta \simeq \mu(\tau-n_{\frac{1}{2}})S_{gn},$$

where we set $n_{\frac{1}{2}} = \frac{n_1+n_2}{2}$. The same holds for I_g, leading to

$$\frac{d}{d\tau}S_{gn} = -\mu(\tau-n_{\frac{1}{2}})S_{gn} - K\sigma_g s(\tau)I(\tau)S_{gn} \quad (7a)$$

$$\frac{d}{d\tau}I_{gn} = -y_{gn} - \mu(\tau-n_{\frac{1}{2}})I_{gn} + K\sigma_g s(\tau)I(\tau)S_{gn} \quad (7b)$$

$$\frac{d}{d\tau}P_{gn} = -y_{gn} - \mu(\tau-n_{\frac{1}{2}})P_{gn} \quad (7c)$$

where

$$I(\tau) = \sum_{g\in\mathcal{G}}\sum_{\tau-A\leqslant n\leqslant\tau} I_{gn}(\tau) \quad \text{and} \quad P_{gn} = S_{gn} + I_{gn}.$$

We can easily consider that the initial time t_0 does not occur during a lambing period. To compute the initial condition (S_{gni}, I_{gni}) for cohort n such that $n_1 \geqslant t_0$, the shortness of the lambing period and the symmetry assumption also allows us to consider that all the animals are born at the same time $n_{\frac{1}{2}}$, so

$$S_{gni} = S_{gn}(n_{\frac{1}{2}}) = \int_{n_1}^{n_2} S_{0g}(\delta)d\delta$$

$$I_{gni} = I_{gn}(n_{\frac{1}{2}}) = 0;$$

whereas for cohorts such that $n2 < t_0$, we replace this by initial values at time t_0

$$S_{gni} = S_{gn}(t_0) = \int_{n_1}^{n_2} S_g(t_0, \delta) d\delta$$
$$I_{gni} = I_{gn}(t_0) = \int_{n_1}^{n_2} \mathbf{I_g}(t_0, \delta) d\delta.$$

The transformed system (7) is now under the well known "SI" bilinear form, with non constant total population.

We note $t_{ni} = \max(n_{\frac{1}{2}}, t_0)$ and $t_{nf} = \max(n_{\frac{1}{2}}, t_0)$. We notice that (7a) can be integrated and gives for $\tau \in [t_{ni}, t_{nf}]$

$$\frac{S_{gn}(\tau)}{S_{gn}(t_{ni})} = e^{-\int_{t_{ni}}^{\tau} \mu(\tau' - n_{\frac{1}{2}}) d\tau'} e^{-K\sigma_g \int_{t_{ni}}^{\tau} sI(\tau') d\tau'}. \quad (8)$$

Let $P_{gn}(\tau) = S_{gn}(\tau) + I_{gn}(\tau)$ be the total population in the cohort at time τ, $Y_{gn}(\tau) = \int_{t_{ni}}^{\tau} y_{gn}(\tau') d\tau'$ the number of animals that died from scrapie between t_{ni} and τ, and $M_{gn}(\tau) = \int_{t_{ni}}^{\tau} \mu(\tau' - n_{\frac{1}{2}}) P_{gn}(\tau') d\tau'$ the number of animals that died for another reason between t_{ni} and τ. Integrating (7a)+(7b) between t_{ni} and τ yields

$$P_{gn}(\tau) - P_{gn}(t_{ni}) = -Y_{gn}(\tau) - M_{gn}(\tau). \quad (9)$$

Combining (8) and (9) and setting

$$A_{gn}(\tau) = S_{gn}(t_{ni}) e^{-\int_{t_{ni}}^{\tau} \mu(\tau' - n_{\frac{1}{2}}) d\tau'}$$

we obtain

$$e^{-K\sigma_g \int_{t_{ni}}^{\tau} sI(\tau') d\tau'} = \frac{P_{gn}(t_{ni}) - (I_{gn} + Y_{gn} + M_{gn})(\tau)}{A_{gn}(\tau)}$$

From this we get, provided that $\sigma_g \neq 0$, an expression of the ratio of genetic susceptibilities from two cohorts with date of birth and genotype respectively $n_{\frac{1}{2}}$, g and $n'_{\frac{1}{2}}$, g'.

$$\frac{\sigma_{g'}}{\sigma_g} = \frac{\ln(\frac{P_{gn}(t_{ni}) - (I_{gn} + Y_{gn} + M_{gn})(\tau)}{A_{gn}(\tau)})}{\ln(\frac{P_{g'n'}(t_{ni}) - (I_{g'n'} + Y_{g'n'} + M_{g'n'})(\tau)}{A_{g'n'}(\tau)})}. \quad (10)$$

IV. Identification

A. The data

A natural scrapie outbreak started in the Langlade experimental sheep flock[1] in 1993 (see Fig. 1) and has been studied ever since. It is probable that the disease was introduced in the flock by animals from a particular cohort involved in parasitological experiments, although no formal association could be found between the parasites and the onset of scrapie [4]. It constitutes a remarkable scrapie cluster: this cohort was the first to show scrapie clinical signs and all individuals had been removed by August 1993.

Extensive data are available, including: sex, breed, pedigree (sire and dam identification), date of birth, date of death, reason for death (including scrapie), and PrP genotypes. Genetic susceptibility to scrapie is determined by polymorphisms of the PrP gene. Four alleles were identified in the flock: VRQ, ARQ, AHQ and ARR. Cases have been observed in eight of the ten resulting genotypes (all except AHQ/ARR and ARR/ARR), but the majority of cases occur within the three most susceptible genotypes: VRQ/VRQ, ARQ/VRQ and ARQ/ARQ.

[1]The Langlade experimental sheep fbck is managed by the Station d'Am´elioration G´en´etique des Animaux, INRA Toulouse, France

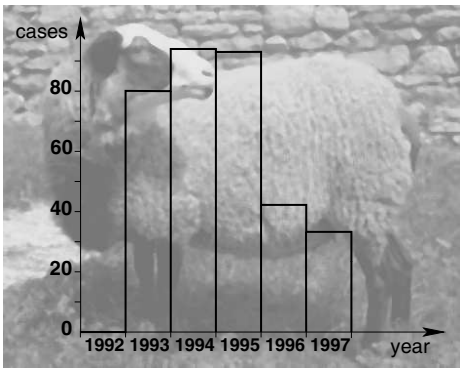

Fig. 1. Scrapie outbreak in the Langlade fbck: number of cases per year.

The present work was conducted on a 4-year period, from January 1992 until December 1995, which covers the introduction of the first scrapie animals into the flock, to the time when breeding practices changed. During this period, the flock was composed of 600-800 ewes and was closed. The lambs culled under the age of 8 months were not included in this study, as it is assumed that they did not play a major role in the transmission of scrapie within the flock.

B. Global population parameters

To estimate the global population parameters, the data provide the daily population and its age structure, as well as the number of scrapie cases and their dates. So for each cohort n we know the initial number of sheep C_{ni} in the cohort and the number $C_n(\alpha)$ for each age $\alpha \in [\alpha_{ni}, \alpha_{nf}]$. The scrapie case data result in a Dirac structure for the incidence in cohort n, that we write

$$y_n(\alpha') = \sum_{j=1}^{Y_n} y_{nj}\, \delta_{\alpha_{nj}}(\alpha')$$

where $\{\alpha_{nj},\ 1 \leqslant j \leqslant Y_n\}$ are the Y_n distinct ages at which scrapie cases were detected in cohort n and y_{nj} is the number of cases that has been detected at age α_{nj}. Replacing this incidence in (6) we obtain

$$C_n(\alpha) = C_{ni} e^{-((\lambda\alpha)^\kappa - (\lambda\alpha_{ni})^\kappa)} - \sum_{1 \leqslant j \leqslant Y_n \ \&\ \alpha_{nj} \leqslant \alpha} y_{nj} e^{-((\lambda\alpha)^\kappa - (\lambda\alpha_{nj})^\kappa)}.$$

Summing over all cohorts, we then get

$$C(\alpha) = e^{-(\lambda\alpha)^\kappa} \Bigg(\sum_{t_0 - A \leqslant n \leqslant T \ \&\ \alpha_{ni} \leqslant \alpha} C_{ni} e^{(\lambda\alpha_{ni})^\kappa} - \sum_{1 \leqslant j \leqslant Y \ \&\ \alpha_j \leqslant \alpha} y_j e^{(\lambda\alpha_j)^\kappa} \Bigg) \quad (11)$$

where α_j, Y, and y_j are defined for all cohorts confounded in a way similar to the equivalent cohort-based parameters.

$C(\alpha)$ represents the number of animals that reached age α during the study period.

Parameters κ and λ were fitted to the data using equation (11) calculated at regular age intervals and a leastsquare criterion. the 95% confidence intervals were computed. The optimal values hence obtained are $\kappa = 1.47 \pm 0.06$ and $\lambda = 0.280 \pm 0.007$. The result is shown in Fig. 2.

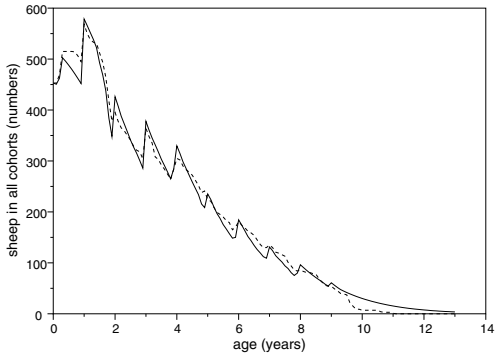

Fig. 2. Observed (dashed line) and simulated (solid line) number of sheep in all cohorts $C(\alpha)$ that have reached age α during the study period $[t_0, T]$; the simulated curve is defi ned in equation (11) with the optimal values $\kappa = 1.47$ and $\lambda = 0.280$.

C. Contact transmission model parameters

We normalise the σ_g coefficients by arbitrarily fixing $\sigma_g = 1$ for the greatest genetic susceptibility. Then K can be identified as the greatest $K\sigma_g$.

The genotypes g for which $\sigma_g = 0$ can easily be detected as their population P_g decreases according to the culling function μ and their incidence y_g is equal to zero.

Post-mortem scrapie tests on culled animals are performed as part of active surveillance strategies and may detect preclinical infected sheep. If we had that information it would provide an estimate of μI_{gn}, from which we could deduct I_{gn}, then S_{gn}, and it would allow to identify K and σ_g from the contact model equations (7). Unfortunately, these tests were not performed at Langlade during the study period. The only measures available are y_{gn} and P_{gn}, linked by equation (7c). So, as long as the input y_g is not expressed as a function of σ_g, the relative genetic susceptibilities $(\sigma_g)_{g\in\mathcal{G}}$ are not identifiable from (7).

However, if we observe a few cohorts at the end of the outbreak, we can assume that there remains no infected sheep in the cohort, so we can use equation (10) to estimate the $\frac{\sigma_{g'}}{\sigma_g}$ ratios by setting $I_{gn} = 0$; P_{gn}, M_{gn}, and Y_{gn} are observed, A_{gn} can be computed. Thanks to the normalisation described above, all σ_g can be identified, but not K.

Actually, the option we chose was to approximate the σ_g by the proportion of scrapie cases within the culled (clinical scrapie and non scrapie) population of genotype g during the study period, and then normalise the values thus obtained. The idea is to link the incidence to the inflow of newly infected sheep; the non scrapie mortality of infected animals is then assumed to be negligible compared to the scrapie incidence, which is reasonable when the infection level is quite high, as in Langlade; moreover, incubation periods have to be similar between genotypes. The resulting relative genetic susceptibilities are shown in Table I. It is a sensible choice, as these parameters correctly rank the genotypes according to their relative susceptibility and satisfactory results are produced. Parameter K was fitted by least square, as well as k, l, and c_g on the complete PDE model (1). The fit we get for the genotype distribution of scrapie cases is rather good, as shown in Fig. 3.

TABLE I
RELATIVE GENETIC SUSCEPTIBILITIES

Genotype g	VRQ VRQ	ARQ VRQ	ARQ ARQ	AHQ AHQ	ARR VRQ
σ_g	1	0.755	0.502	0.156	0.097
Genotype g	AHQ ARQ	ARQ ARR	AHQ VRQ	AHQ ARR	ARR ARR
σ_g	0.077	0.036	0.025	0	0

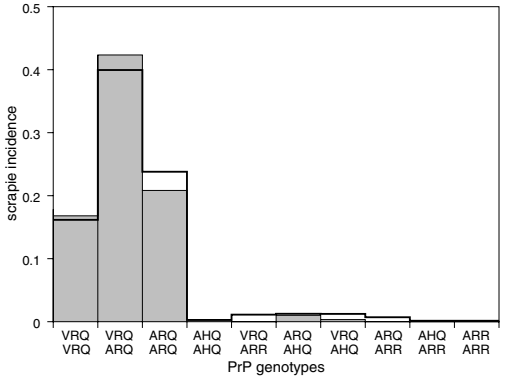

Fig. 3. Observed (grey bars) and simulated (thick line) genotype distribution of scrapie cases, with the relative genetic susceptibility values from Table I.

V. CONCLUSIONS AND FUTURE WORKS

We have presented a hierarchical identification procedure for a hyperbolic PDE model representing scrapie transmission in a sheep flock. On the upper level, the global population model allows us to identify the parameters of the routine culling function. At the intermediate contact transmission level, some work remains to be done, but we have shown that the genetic susceptibility parameters σ_g and the transmission coefficient K are not identifiable without introducing information from the lower level model, or making further assumptions. Moreover, alternative methods have been proposed to estimate the genetic susceptibilities.

Ongoing work for this study focuses on the intermediate level. The relationship between incidence and the genetic susceptibilities is being explored by means of a delay-differential model. This hierarchical approach could be applied to more general epidemiological models; for instance, adding a non constant infectiousness function would only increase the number of unknown parameters at the intermediate level.

In the future, a theoretical study of structural identifiability, especially for the low level parameters, is planned. We also plan to study the construction of observers (state estimators) taking advantage of results from surveillance data (pre-clinical tonsil biopsies and post-mortem tests); we are currently studying other flocks in which such data are available. This should for example allow reconstruction of the number of susceptible animals in a cohort and avoid approximations in the parameter identification procedure.

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