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MATHEMATICAL ANALYSIS OF A PDE EPIDEMIOLOGICAL MODEL APPLIED TO SCRAPIE TRANSMISSION

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Abstract. The aim of this paper is to analyse a dynamic model which describes the spread of scrapie in a sheep flock. Scrapie is a transmissible spongiform encephalopathy, endemic in a few European regions and subject to strict control measures. The model takes into account various factors and processes, including seasonal breeding, horizontal and vertical transmission, genetic susceptibility of sheep to the disease, and a long and variable incubation period. Therefore the model, derived from a classical SI (susceptible-infected) model, also incorporates a discrete genetic structure for the flock, as well as a continuous infection load structure which represents the disease incubation. The resulting model consists of a set of partial differential equations which describe the evolution of the flock with respect to time and infection load. To analyse this model, we use the semigroup and evolution family theory, which provides a flexible mathematical framework to determine the existence and uniqueness of a solution to the problem. We show that the corresponding linear model has a unique classical solution and that the complete nonlinear model has a global solution.

1. **Introduction.** Scrapie is a transmissible spongiform encephalopathy (TSE) occurring naturally in sheep and goat flocks. TSEs are slowly progressive, fatal, neurodegenerative disorders that are characterised by the accumulation in the brain of a conformationally abnormal form of the prion protein PrP. Animal TSEs also include bovine spongiform encephalopathy (BSE, or "mad cow disease"), which started in the UK in 1985. Unlike BSE, there is no evidence that scrapie constitutes a human health risk. However, experimental studies have shown that BSE can infect sheep and produce similar clinical signs (only post-mortem tests on brain samples differ), even if no natural contamination has been observed in sheep[1]. Therefore, scrapie surveillance and eradication plans are implemented in Europe and a particular emphasis is put on the disease propagation studies.

Scrapie is a common pathology in European flocks, endemic in certain regions; the first mention of the disease dates back to the 18th century. It is associated with

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[1]The first BSE case in a goat, a French animal culled in 2002, was confirmed in January 2005.

a long incubation period (ca. 2 years) and polymorphisms of the PrP gene encoding for the prion protein largely control the susceptibility and resistance of sheep to the disease. However, the epidemiology of scrapie is still incompletely understood [6, 1], particularly the transmission processes.

Scrapie can widely spread in a flock. Vertical transmission, i.e. maternal transmission to lamb, is possible, but contamination may occur post-natally rather than in utero. Horizontal transmission is likely to occur by the oral route since the earliest detection of scrapie infectivity in naturally infected individuals is in the digestive tract. However, there may be other routes of entry (e.g. scarification). Presence of scrapie infectivity in the placenta suggests the possibility of increased transmission during lambing via the ingestion of contaminated placental material. This assumption is supported by a recent study by [13] based on a mathematical model of scrapie transmission dynamics.

A mathematical model of transmission dynamics is a valuable tool to explore biological hypotheses and to assess the efficiency of surveillance and control strategies. Such a model allows to combine epidemiological, demographic, genetic and management factors, which are essential to study diseases such as scrapie with long incubation periods relative to lifespan. The model we analyse in this paper is derived from a scrapie transmission model [12] in which the flock dynamics is represented by a set of nonlinear first order hyperbolic partial differential equations (PDE). It is an SI (susceptible–infected) model, with an additional discrete genotype structure for the population and a continuous infection load structure for the infected individuals. It is described in more details in the following section.

The mathematical analysis of such a PDE model is not standard. Its right-hand side is non autonomous with integro-differential nonlinear terms. Most epidemiological studies conducted on this or similar models are based on numerical analysis and simulations, for instance to assess the basic reproduction number [10, 5], or to estimate parameters and validate biological scenarios [9, 13]. Furthermore, to our knowledge this type of model is not encountered outside the epidemiology field. So a thorough mathematical analysis to determine the existence and validity of solutions for this PDE model is lacking. It is the aim of this paper. The mathematical framework chosen in this paper is the semigroup theory, which provides tools to investigate the solvability of the PDE model, by exploiting the properties of the operators constituting the associated Cauchy Problem [11, 4]. These techniques have been used to analyse other PDE models, such as a blood production model [2], an autonomous delay model with a physiological structure. In our model, we deal with a non autonomous system, so we had to extend these results using the evolution family theory.

After presenting the epidemiological model, we focus on the mathematical analysis and results, which are then discussed. To ease the understanding of the mathematical developments, Appendix A introduces basic definitions and theorems.

2. **Description of the model.**

The model used here to represent the scrapie spread within a flock is a deterministic SI (susceptible–infected) model, which is adapted to represent the disease characteristics. The initial model was elaborated for Scottish sheep flocks [12, 9] and further developed for a French outbreak in the Langlade flock [13]. Compared to these previous papers, the model here is simplified: the age variable is not retained; the infected population is not split into two groups according to the transmission route, i.e. the horizontally infected sheep

and the vertically infected sheep; the ram allele frequencies are supposed to be known at each breeding season.

The flock is structured according to scrapie status (susceptible S or infected I), PrP genotype $g \in \{1 \dots N_g\}$ (determined by the polymorphisms at codons 136, 154 and 171 of the gene encoding for the prion protein) and, for the infected sheep only, infection load $\theta \in [0, 1]$. In the Langlade flock [3], 4 alleles were identified: VRQ, ARQ, AHQ, ARR, from the most susceptible to the most resistant one, resulting in $N_g = 10$ genotypes: VRQ-VRQ, VRQ-ARQ, etc. When a susceptible sheep becomes infected, it is given an initial load, which is assumed to grow during the incubation period until the maximum value 1 corresponding to the onset of clinical signs is reached; the onset is followed by the culling of the animal. Variable initial loads allow for variable incubation periods. The resulting sheep population densities are $S_g(t)$ and $I_g(t, \theta)$, where t represents the time.

The model does not discriminate by gender; since only a small number of breeding rams are kept, only the population of ewes is considered. It incorporates the following components: seasonal breeding and routine culling, genetic susceptibility, a long and variable incubation period followed by culling, seasonal horizontal transmission and vertical transmission. Hence, to represent the evolution through time of the population densities with respect to infection load, the model consists of a set of partial differential equations. But first we will describe the model components and assumptions implied.

2.1. **Demographic processes.** There is no way to identify infected sheep, so all sheep are bred and culled independently from their scrapie status. Moreover, we assume that no genetic selection for disease resistance was performed on the ewes. Routine culling represents all sources of mortality for the ewes, scrapie excluded. So the culling rate μ is independent from the PrP genotype and is assumed to be constant.

Breeding is seasonal. The birth rate $b(t)$ represents the number of offspring produced by a ewe per time unit during the lambing period; it is supposed to be the same for all ewes and it is zero outside this period. The birth rate determines the global inflow of lambs in the flock, but they need to be distributed among the different genotypes. Therefore, a breeding matrix $G(t) = (G_{gg'}(t))$ needs to be introduced, giving the proportion of lambs of genotype g born from dams with genotype g' (or the probability for ewes g' to give birth to lambs g) for $g, g' \in \{1 \dots N_g\}$. We assume the following: (i) the sire allele frequencies $f_a(t)$ are known; (ii) there is random mating between dams and sires. So for instance,

$$\begin{cases} g' = \text{VRQ-VRQ}, & g = \text{ARQ-ARR}, & \Rightarrow\ G_{gg'}(t) = 0, \\ g' = \text{VRQ-VRQ}, & g = \text{VRQ-ARQ}, & \Rightarrow\ G_{gg'}(t) = f_{ARQ}(t), \\ g' = \text{VRQ-ARQ}, & g = \text{ARQ-ARR}, & \Rightarrow\ G_{gg'}(t) = f_{ARR}(t)/2, \\ g' = \text{VRQ-ARQ}, & g = \text{VRQ-ARQ}, & \Rightarrow\ G_{gg'}(t) = (f_{VRQ}(t) + f_{ARQ}(t))/2, \end{cases}$$

etc., and so the breeding matrix is built.

A common control measure to eradicate scrapie is to apply genetic selection by using resistant rams. It is implemented in the French, British and Dutch scrapie plans, and is present in the EU recommendations. If only ARR-ARR rams are used in a flock, then $f_{ARR}(t) = 1$ and all other frequencies are zero.

2.2. **Epidemiological processes.** Note: In these paragraphs, a variable with a $'$ usually refers to the contaminating animal, and a variable without to the susceptible and yet to become infected sheep.

Scrapie transmission depends on the susceptibility of the yet to become infected sheep, the infectiousness of the contaminating animal and the season.

- For each genotype, the proportion of susceptible sheep exposed to scrapie and that become infected is taken to be proportional to their relative genetic susceptibility and to the force of infection, i.e. the sum of all infected animals weighted by their infectiousness. The relative genetic susceptibility $\sigma_g \in [0,1]$ is set to 0 if the genotype is fully resistant and to 1 for the most susceptible genotype.
- The infectiousness of a sheep is supposed to be a function of the infection load $\phi(\theta')$.
- As we assume that horizontal transmission mainly occurs during lambing periods, due to the ingestion of contaminated placental material, a seasonal function $s(t)$ is defined: $s(t) = 1$ during the lambing period and $0 \leqslant s(t) \ll 1$ otherwise.

So the horizontal transmission rate, which represents the ratio of susceptible sheep of genotype g infected by an infected sheep of infection load θ' is

$$\beta_g(t,\theta') \propto \sigma_g\, \phi(\theta')\, s(t).$$

By definition, vertical/maternal transmission only occurs during lambing. So the vertical transmission rate, defined as the proportion of lambs of genotype g contaminated by an infected dam of infection load θ', is

$$\gamma_g(\theta') \propto \sigma_g\, \phi(\theta'), \quad \gamma_g \in [0,1].$$

Newly infected individuals are given an initial infection load, according to a distribution $\Theta(\theta)$ (it verifies $\int_0^1 \Theta(\theta)d\theta = 1$, for example a beta distribution). During the incubation period, we assume that the infection load increases exponentially, at a rate c_g which only depends on the sheep genotype, as follows

$$\frac{d\theta}{dt} = c_g\, \theta.$$

At the end of the incubation period, when $\theta = 1$, the sheep start showing clinical signs and are culled. Hence, genotype-dependent distributions are obtained for the incubation period.

2.3. **Model equations.** Let us note $S_g(t)$ the number of susceptible sheep of genotype g at time t, and similarly $I_g(t,\theta)$ the density of infected sheep with infection load θ. The PDE model describing the evolution of these population densities according to the demographic and epidemiological processes described above, with respect to time and infection load, is the following:

$$\frac{dS_g(t)}{dt} = -\,\mu S_g(t) - S_g(t) \sum_{g'} \int_0^1 \beta_g(t,\theta') I_{g'}(t,\theta')\, d\theta' \tag{1}$$

$$+\, b(t) \sum_{g'} G_{gg'}(t) \left(S_{g'}(t) + \int_0^1 (1-\gamma_g(\theta')) I_{g'}(t,\theta')\, d\theta' \right), \tag{2}$$

$$\frac{\partial I_g(t,\theta)}{\partial t}+\frac{\partial c_g\theta I_g(t,\theta)}{\partial \theta}=-\mu I_g(t,\theta)+\Theta(\theta)\Bigg(S_g(t)\sum_{g'}\int_0^1 \beta_g(t,\theta')I_{g'}(t,\theta')\,d\theta' \quad (3)$$

$$+\,b(t)\sum_{g'}G_{gg'}(t)\int_0^1 \gamma_g(\theta')I_{g'}(t,\theta')\,d\theta'\Bigg). \quad (4)$$

Infected sheep need to have a positive infection load, otherwise their incubation period is infinite, so the associated boundary condition is

$$I_g(t,0)=0, \quad (5)$$

and the initial condition is given by

$$S_g(0)=S_{0g}, \qquad I_g(0,\theta)=I_{0g}(\theta). \quad (6)$$

In the following sections, "the model" will refer to equations (2-6) above. Unless stated otherwise, all parameters, variables and functions are non negative. Moreover, the following conditions are satisfied throughout the paper:

- μ is positive;
- the birth function is continuous, i.e. $b\in \mathrm{C}([0,+\infty))$;
- the components of the breeding matrix are integrable, i.e. $G_{gg'}\in \mathrm{L}^1([0,+\infty))$;
- the vertical transmission rate is integrable, i.e. $\gamma_g\in \mathrm{L}^1([0,1))$;
- the horizontal transmission rate is continuous with respect to θ, i.e. $\beta_g(t,\cdot)\in \mathrm{C}([0,1])$;
- the horizontal transmission rate is integrable with respect to time, i.e. $\beta_g(\cdot,\theta)\in \mathrm{L}^1([0,+\infty))$;
- the initial infection load distribution Θ verifies $\int_0^1\Theta(\theta)d\theta=1$, is continuous on $[0,1]$, positive for $\theta>0$ and $\Theta(0)=0$ (for example a beta distribution).

A further hypothesis can be set: it is verified when the birth function, breeding matrix and horizontal transmission rate are continuously differentiable with respect to time, i.e.

$$b,\ G_{gg'},\ \beta_g(\cdot,\theta)\in \mathrm{C}^1(0,+\infty). \quad (7)$$

We will now turn to the mathematical analysis of the PDE model.

3. **Mathematical analysis.** In this section, we aim at proving the existence and uniqueness of a solution to the model. The preliminary step consists in rewriting the model to obtain a standard abstract formulation, which is easier to handle. We can then tackle the mathematical analysis gradually. First, we consider the linear problem associated to the model and proceed in two steps: the autonomous problem, which corresponds to a population affected only by mortality, and which is treated thanks to the semigroup theory; the non autonomous problem, which corresponds to a population affected by mortality, birth and vertical transmission, and which is handled with the perturbation theory. Second, we consider the nonlinear problem: the horizontal transmission term is introduced; the existence of a local and then a global solution is investigated.

To ease the understanding of this mathematical analysis, which is detailed below, Appendix A provides some basic definitions and theorems.

3.1. **Abstract formulation.** The model (2-4) consists of a system of $2 \times N_g$ differential equations. The solution of the model is a vector $u(t,\cdot) = \begin{pmatrix} S(t) \\ I(t,\cdot) \end{pmatrix}$ of size $(2 \times N_g, 1)$, where

$$S(t) = \begin{pmatrix} S_1(t) \\ \vdots \\ S_{N_g}(t) \end{pmatrix} \in \mathbb{R}^{N_g} \quad \text{and} \quad I(t,\cdot) = \begin{pmatrix} I_1(t,\cdot) \\ \vdots \\ I_{N_g}(t,\cdot) \end{pmatrix} \in X_1$$

respectively represent the vector of susceptible sheep and the vector of infected sheep. X_1 is defined as the space of continuous functions on $[0,1]$ vanishing at 0 and with values in $\mathbb{R}^{N_g}$. So the boundary condition (5) is included in the definition of space X_1. The solution space is therefore $X = \mathbb{R}^{N_g} \times X_1$.

X_1 is endowed with the supremum norm $\|\cdot\|_\infty$, defined by

$$\|y\|_{X_1} = \|y\|_\infty = \sum_{i=1}^{N_g} \|y_i\|_\infty = \sum_{i=1}^{N_g} \sup_{x\in[0,1]} |y_i(x)|, \quad \text{for } y = (y_i)_{i=1,\dots,N_g} \in X_1.$$

$X = \mathbb{R}^{N_g} \times X_1$ is then endowed with the norm $\|\cdot\|$, defined by

$$\left\| \begin{pmatrix} x \\ y \end{pmatrix} \right\|_X = \left\| \begin{pmatrix} x \\ y \end{pmatrix} \right\| = \sum_{i=1}^{N_g} |x_i| + \sum_{i=1}^{N_g} \|y_i\|_\infty, \quad \text{for } \begin{cases} x = (x_i)_{i=1,\dots,N_g} \in \mathbb{R}^{N_g}, \\ y = (y_i)_{i=1,\dots,N_g} \in X_1. \end{cases}$$

To lighten the notations, in the following paragraphs and sections, we will write for every fixed t: $u(t,\cdot) = u(t)$, $I(t,\cdot) = I(\cdot) = I$ and $S(t) = S$.

In order to simplify the model formulation, we gather all equations in one and separate the linear and nonlinear terms. Let $u_0 = u(0)$ be the initial condition at $t = 0$, corresponding to equation (6). We can then formulate the abstract Cauchy problem associated to the model as follows:

$$\begin{cases} \dfrac{du(t)}{dt} = \mathcal{A}u(t) + \mathrm{V}(t)u(t) + \mathrm{H}(t,u(t)) \quad \text{for } t \geqslant 0, \\ u(0) = u_0. \end{cases} \tag{ACP}$$

The definition and interpretation of operators $\mathcal{A}$, $\mathrm{V}(t)$, and $\mathrm{H}(t,\cdot)$ are given below. Roughly, $\mathcal{A}$ corresponds to the non scrapie mortality process, V to the birth process, including vertical transmission, and H to horizontal transmission.

$\mathcal{A}$ is a matrix operator given by

$$\mathcal{A} = \begin{pmatrix} \mathcal{A}_S & 0 \\ 0 & \mathcal{A}_I \end{pmatrix},$$

with

$$\mathcal{A}_S = -\mu \mathbf{I_d},$$

$\mathbf{I_d}$ being the identity matrix, and

$$\begin{aligned} &\mathcal{A}_I : X_1 \longrightarrow X_1 \\ &\qquad \varphi \longmapsto \mathcal{A}_I\varphi(\cdot) = \left(-c_g \cdot \frac{\partial \varphi_g}{\partial \theta}(\cdot) - (\mu + c_g)\varphi_g(\cdot) \right)_{g=1,\dots,N_g}; \end{aligned}$$

$\mathcal{A}_S$ represents the mortality process related to the susceptible class and $\mathcal{A}_I$ the mortality plus the conservation law of the infected class.

The non autonomous operator V is defined as follows:

$$\mathrm{V}(t) = \begin{pmatrix} L(t) & M(t) \\ 0 & N(t) \end{pmatrix},$$

with:

$$L(t) : \mathbb{R}^{N_g} \longrightarrow \mathbb{R}^{N_g}$$

$$S \longmapsto L(t)S = \left(b(t) \sum_{g'=1}^{N_g} G_{gg'}(t) S_{g'} \right)_{g=1,\dots,N_g},$$

$$M(t) : X_1 \longrightarrow \mathbb{R}^{N_g}$$

$$I \longmapsto M(t)I = \left(b(t) \sum_{g'=1}^{N_g} G_{gg'}(t) \int_0^1 (1-\gamma_g(\theta'))I_{g'}(\theta')d\theta' \right)_{g=1,\dots,N_g},$$

$$N(t) : X_1 \longrightarrow X_1$$

$$I \longmapsto N(t)I(\cdot) = \left(\Theta(\cdot) b(t) \sum_{g'=1}^{N_g} G_{gg'}(t) \int_0^1 \gamma_g(\theta')I_{g'}(\theta')d\theta' \right)_{g=1,\dots,N_g},$$

where $L(t)$ represents the birth of susceptible lambs from susceptible ewes, $M(t)$ the birth of susceptible lambs from infected ewes, and $N(t)$ the birth of infected lambs from infected ewes, i.e. the vertical transmission.

Let us denote the horizontal transmission rates by the following matrix:

$$K(t,\cdot) = \begin{pmatrix} \beta_1(t,\cdot) & & 0 \\ & \ddots & \\ 0 & & \beta_{N_g}(t,\cdot) \end{pmatrix} \in X_1.$$

The nonlinear terms, representing the horizontal transmission process in the model, are gathered in the H operator defined by

$$\mathrm{H}(t,\cdot) : \quad X \longrightarrow X$$

$$\begin{pmatrix} S \\ I \end{pmatrix} \longmapsto \mathrm{H}\left(t, \begin{pmatrix} S \\ I \end{pmatrix}\right) = \begin{pmatrix} -\int_0^1 \sum_{g'=1}^{N_g} I_{g'}(\theta')K(t,\theta')d\theta'\, S \\ +\int_0^1 \sum_{g'=1}^{N_g} I_{g'}(\theta')K(t,\theta')d\theta'\, S\,\Theta \end{pmatrix}.$$

Hence, (ACP) is a non autonomous semilinear Cauchy problem, in which the linear non autonomous term $\mathrm{V}(t)$ represents the birth and the vertical transmission and the nonlinear term $\mathrm{H}(t,\cdot)$ represents the horizontal transmission. Because of this non linearity, we first study the linear problem associated to (ACP) and defined as follows:

$$\begin{cases} \dfrac{du(t)}{dt} = \mathcal{A}u(t) + \mathrm{V}(t)u(t) \quad \text{for } t \geqslant 0, \\ u(0) = u_0. \end{cases} \tag{ACPL}$$

Remark 1. There is no horizontal transmission in (ACPL). Biologically, it would be more realistic to neglect the vertical transmission term, which in a scrapie outbreak contributes far less to the disease spread than the horizontal term. However, the difficulties implied by the nonlinear operator make us start the analysis by the linear problem (ACPL). So for mathematical reasons, we first neglect the horizontal transmission term.

3.2. **Existence and uniqueness of a solution to the linear problem.** We propose to establish the existence and uniqueness of the solution to the linear problem (ACPL). A way to achieve this goal is first to treat the corresponding autonomous problem, and then to use a perturbation method to solve (ACPL). The semigroup theory is particularly well suited for the autonomous Cauchy problems and the evolution family for the non autonomous case.

3.2.1. *Study of the autonomous case.* Let us define the autonomous linear abstract Cauchy problem by

$$\begin{cases} \dfrac{du(t)}{dt} = \mathcal{A}u(t) \quad \text{for } t \geqslant 0, \\ u(0) = u_0. \end{cases} \tag{ACPL'}$$

where the domain of the operator $\mathcal{A}$ is defined as $D(\mathcal{A}) = D(\mathcal{A}_S) \times D(\mathcal{A}_I)$.

Lemma 3.1. *$\mathcal{A}$ is an infinitesimal generator of a strongly continuous semigroup with domain $D(\mathcal{A})$.*

Proof. $\mathcal{A}_S$ is an infinitesimal generator of a continuous semigroup defined on $D(\mathcal{A}_S) = \mathbb{R}^{N_g}$ and denoted by $T_{\mathcal{A}_S}(t) = e^{t\mathcal{A}_S} = \operatorname{diag}(e^{-\mu t})$.

Theorem A.7 given in Appendix A shows that the operator $\mathcal{A}_I$ defined on domain $D(\mathcal{A}_I) = \{f \in X_1 \cap C^1((0,1], \mathbb{R}^{N_g}) \mid \lim_{\theta \to 0} \theta f'(\theta) = 0\}$ generates a continuous semigroup denoted by $(T_{\mathcal{A}_I}(t))_{t \geqslant 0}$ and given by

$$T_{\mathcal{A}_I}(t)\varphi_g(\cdot) = \left(e^{-(\mu + c_g)t}\varphi_g(\cdot\, e^{-c_g t})\right)_{g=1,\ldots,N_g}.$$

$\mathcal{A}$ is a matrix operator with domain $D(\mathcal{A}) = D(\mathcal{A}_S) \times D(\mathcal{A}_I)$, thus it is also an infinitesimal generator of a continuous semigroup $(T_{\mathcal{A}}(t))_{t \geqslant 0}$ given by

$$T_{\mathcal{A}}(t) = \begin{pmatrix} T_{\mathcal{A}_S}(t) & 0 \\ 0 & T_{\mathcal{A}_I}(t) \end{pmatrix}, \quad \forall t \geqslant 0. \tag{8}$$

□

The generator $\mathcal{A}$ determines the semigroup $(T_{\mathcal{A}}(t))_{t \geqslant 0}$ uniquely. Therefore, the solution of (ACPL') exists, is given by $u(t) = T_{\mathcal{A}}(t)u_0$ and is unique. The semigroup theory also allows us to deduce the properties of the solution from the semigroup properties.

Lemma 3.2. *The semigroup $(T_{\mathcal{A}}(t))_{t \geqslant 0}$ is positive and exponentially stable.*

Proof. It is obvious by construction that $(T_{\mathcal{A}_S}(t))_{t \geqslant 0}$ and $(T_{\mathcal{A}_I}(t))_{t \geqslant 0}$ are positive semigroups. Let $\binom{S}{I} \in X$. As $c_g \geqslant 0$, we have

$$\left\| T_{\mathcal{A}}(t) \binom{S}{I} \right\| \leqslant e^{-\mu t} \sum_{i=1}^{N_g} |S_g| + e^{-\mu t} \sum_{i=1}^{N_g} \sup_{\theta \in [0,1]} |I_g(\theta e^{-c_g t})|.$$

As $c_g t \geqslant 0$, then $\theta e^{-c_g t} \in [0,1]$ and $\sup_{\theta \in [0,1]} |I_g(\theta e^{-c_g t})| = \sup_{\theta \in [0,1]} |I_g(\theta)|$. Hence,

$$\left\| T_{\mathcal{A}}(t) \binom{S}{I} \right\| \leqslant e^{-\mu t} \left\| \binom{S}{I} \right\|,$$

so

$$\|T_{\mathcal{A}}(t)\| \leqslant e^{-\mu t}.$$

As $\mu > 0$, $(T_{\mathcal{A}}(t))_{t \geqslant 0}$ is exponentially stable, i.e. the operator converges to zero when $t \to \infty$. □

Therefore, the solution of (ACPL') is positive for every positive initial condition and vanishes at infinity. Moreover, it has some regularity ($C^1(0,+\infty)$) because it is classical solution for $u_0 \in D(\mathcal{A})$.

So the model without birth and transmission admits a unique regular, positive solution which vanishes at infinity.

3.2.2. *Study of the non autonomous case.* We now return to the linear non autonomous problem (ACPL) to establish the same mathematical results. We introduce the birth term V as a perturbation of the autonomous problem (ACPL'). Using the evolution family theory again allows us to explicitly obtain the solution of the problem according to the evolution family and the initial condition. Consequently, the properties of the evolution family induce those of the solution.

Proposition 1. *$(\mathcal{A}+\mathrm{V}(t))_{t\geqslant 0}$ generates an evolution family.*

Proof. $\mathrm{V}(t)$ is bounded operator and is strongly continuous, hence by using the perturbation theory [11] and Lemma 3.1, we deduce the result above. □

Let $(U(t,s))_{t\geqslant s\geqslant 0}$ be the evolution family generated by $\mathcal{A}+\mathrm{V}(t)$. $T_{\mathcal{A}}(t))_{t\geqslant 0}$ being the semigroup defined in (8), the solution of problem (ACPL) is given by

$$u(t) = U(t,0)u_0, \qquad \text{with: } U(t,0) = T_{\mathcal{A}}(t) + \int_0^t T_{\mathcal{A}}(t-s)\mathrm{V}(s)U(s,0)ds.$$

We deduce the following theorem.

Theorem 3.3. *For all $u_0 = \binom{S_0}{I_0}$ with $S_0 \in \mathbb{R}^{N_g}$ and $I_0 \in X_1$, there exists a unique mild solution $u(\cdot)$ to (ACPL). This solution is continuous and satisfies*

$$u(t) = T_{\mathcal{A}}(t)u_0 + \int_0^t T_{\mathcal{A}}(t-s)\mathrm{V}(s)u(s)ds. \tag{9}$$

Moreover, if assumption (7) is satisfied and $I_0 \in D(\mathcal{A}_I)$, then u is a classical solution to (ACPL).

Remark 2. A mild solution of the initial value problem (ACPL) is a continuous solution of the integral equation (9). If the solution is continuously differentiable, it is a classical solution.

The solution obtained satisfies positivity and stability properties given by the following proposition.

Proposition 2. *The evolution family $(U(t,0))_{t\geqslant 0}$ is positive and if $\|\mathrm{V}\| < \mu$ then it is exponentially stable.*

Proof. In equation (9), we obtain an implicit formulation of the solution to (ACPL), which doesn't allow us to deduce any positivity result. Another way to express this solution is to use the Dyson-Phillips series

$$U(t) = \sum_{n=0}^{+\infty} U_n(t,0),$$

where the sequence $(U_n(t,0))_{n\in\mathbb{N}}$ is defined for all $x \in X$ by

$$U_0(t,0) = T_{\mathcal{A}}(t),$$

$$U_{n+1}(t,0)x = \int_0^t T_{\mathcal{A}}(t-s)\mathrm{V}(s)U_n(s,0)xds.$$

From Lemma 3.2, we know that $(T_{\mathcal{A}}(t))_{t\geqslant 0}$ is positive, so $U_0(t,0)_{t\geqslant 0}$ is positive as well. Let $x \in X$, x positive, and assume that $U_n(t,0)_{t\geqslant 0}$ is positive. V is positive by construction, so

$$T_{\mathcal{A}}(t-s)\mathrm{V}(s)U_n(s,0)x \geqslant 0 \qquad \forall s \geqslant 0,$$

$$\int_0^t T_{\mathcal{A}}(t-s)\mathrm{V}(s)U_n(s,0)x\,ds \geqslant 0 \qquad \forall s \in [0,t].$$

It follows that $U_{n+1}(t,0)_{t\geqslant 0}$ is positive. Hence, $U_n(t,0)_{t\geqslant 0}$ is positive for all $n \in \mathbb{N}$.

From Lemma 3.2, we also have that $(T_{\mathcal{A}}(t))_{t\geqslant 0}$ is exponentially stable, so we deduce that

$$U_0(t,0) \leqslant e^{-\mu t} \quad \text{and} \quad \|U_n(t,0)\| \leqslant e^{-t(\mu-\|\mathrm{V}\|)}\frac{\|\mathrm{V}\|^{n-1}t^{n-1}}{(n-1)!},$$

which implies that $U(t) = \sum_{n=0}^{+\infty} U_n(t,0)$ is convergent.

$$\sum_{n=0}^{+\infty} U_{n+1}(t,0) = \sum_{n=0}^{+\infty}\int_0^t T_{\mathcal{A}}(t-s)\mathrm{V}(s)U_n(s,0)ds = \int_0^t T_{\mathcal{A}}(t-s)\mathrm{V}(s)U(s)ds,$$

$$\text{so} \quad U(t) = \sum_{n=0}^{+\infty} U_n(t,0) = T_{\mathcal{A}}(t) + \int_0^t T_{\mathcal{A}}(t-s)\mathrm{V}(s)U(s)ds.$$

This shows that $U(t) = U(t,0)$ which implies that $U(t,0)_{t\geqslant 0}$ is positive.

From equation (9), we deduce that

$$\|U(t,0)x\| \leqslant e^{-\mu t}\|x\| + \int_0^t e^{-\mu(t-s)}\|\mathrm{V}\|\,\|U(s,0)\|ds\,\|x\|,$$

$$\text{so} \quad \|U(t,0)\| \leqslant e^{-\mu t} + \int_0^t e^{-\mu(t-s)}\|\mathrm{V}\|\,\|U(s,0)\|ds.$$

The Gronwall-Bellman inequality, given by Lemma A.6 in Appendix A, leads to

$$\|U(t,0)\| \leqslant e^{-t(\mu-\|\mathrm{V}\|)},$$

hence the result. □

Remark 3. Under assumption $\|\mathrm{V}\| < \mu$, the evolution family $(U(t,0))_{t\geqslant 0}$ is exponentially stable. So the solution to (ACPL), thus the population, does not explode and tends to zero in infinite time. This result is quite obvious: if birth, including vertical transmission, is lower than mortality in the flock, we expect the population to become extinct.

Having established the existence and uniqueness of the solution to the linear problem (ACPL) and having given some results on the asymptotic behaviour of the solution, we are now interested in establishing similar results for the nonlinear problem (ACP).

3.3. **Existence and uniqueness of the solution to the nonlinear problem.** In general, studying semilinear abstract Cauchy problems is not obvious, as the handling of their nonlinear part, which is non autonomous and depends on the solution, presents serious difficulties. This type of problem is, to our knowledge, only addressed by Pazy [11]. There, if the nonlinear term can be considered as a Lipschitz perturbation of the generator of a strongly continuous semigroup in the autonomous case, or of an evolution family in the non autonomous one, some results apply. First, the existence and uniqueness of a solution can be proved on a finite

time interval: solutions are local. Furthermore, if one can show that the solution is bounded, then the upper limit of the time interval is infinite and the local solution becomes a global solution defined on $[0, +\infty)$. These results are summarised in Theorem A.8 in Appendix A.

In this section, we first look for a local solution to (ACP), defined on a time interval $[0, t_{max})$. In the second part of this section, we determine conditions that ensure $t_{max} = +\infty$, or in other words that the solution is global. Lemmas and proofs are given in Appendix B.

3.3.1. *Local solution.* We show in Lemma B.1 in Appendix B that the semilinear part $\mathrm{V}(t)\cdot+\mathrm{H}(t,\cdot)$ is a Lipschitz perturbation of the continuous semigroup $T_{\mathcal{A}}(t))_{t\geqslant 0}$ given by equation (8). Therefore, using Theorem A.8, also given in Appendix A, we can deduce the existence and uniqueness of a mild solution to problem (ACP). Hence we obtain the following theorem.

Theorem 3.4. *For all initial condition in X, there exists an interval of time $[0, t_{max})$ in which the problem (ACP) has a unique mild solution.*

We only obtain a local solution here, so we will now turn to the global existence of the solution.

3.3.2. *Global solution.* We are now interested to show that the local solution can become global, and this by showing that it is bounded. Let us set $t \in [0, t'] \subset [0, t_{max})$ such that $0 \leqslant t' < t_{max}$.

Let $P_g(t) = S_g(t) + \int_0^1 I_g(t,\theta)d\theta,\ g = 1, \ldots, N_g$ be the components of the total population vector $P(t)$. By integrating equation (4) over θ and summing it with equation (2), we obtain that

$$\frac{dP_g}{dt}(t) = -\mu P_g(t) + b(t) \sum_{g'=1}^{N_g} G_{gg'}(t) P_g(t) - c_g I_g(t,1).$$

We denote by c the diagonal matrix with coefficients c_g. Then P satisfies the following differential equation:

$$\frac{dP(t)}{dt} = (-\mu \mathbf{I_d} + b(t)G(t))P(t) - cI(t,1).$$

c and I being non negative, we have

$$\frac{dP(t)}{dt} \leqslant (-\mu \mathbf{I_d} + b(t)G(t))P(t),$$

which implies that

$$P(t) \leqslant \bar{P}(t) \quad \text{with: } \bar{P}(t) = \exp\left(-\mu t \mathbf{I_d} + \int_0^t b(\sigma)G(\sigma)d\sigma\right) P(0). \tag{10}$$

Remark 4. $\bar{P}(t)$ corresponds to the total population size without scrapie. It has to be larger than $P(t)$, the total population size with infection, as the presence of the disease increases the total mortality. Moreover, the following inequalities are verified: $S(t) \leqslant P(t) \leqslant \bar{P}(t)$ and $\int_0^1 I(t,\theta)d\theta \leqslant P(t) \leqslant \bar{P}(t)$.

Let us set $\bar{b} = \sup_{t\in[0,t_{max})} b(t)$ and $\bar{\beta}(t) = \max_{\theta\in[0,1]} \beta(t,\theta)$. Let us also note that all the components of G and the vertical transmission rate $\gamma_g(\cdot)$ are by definition

less than 1. Taking all this into consideration, equation (4) implies that

$$\frac{\partial I}{\partial t}(t,\theta) \leqslant -\frac{\partial c\theta I}{\partial \theta}(t,\theta) - \mu I(t,\theta) + \Theta(\theta)\left[\bar{\beta}(t)\bar{P}(t) + b(t)\mathbf{I_d}\right]\sum_{g'=1}^{N_g}\bar{P}_{g'}(t),$$

$$\leqslant \mathcal{A}_I I(t,\theta) + \Theta(\theta)\left[\bar{\beta}(t)\bar{P}(t) + b(t)\mathbf{I_d}\right]\sum_{g'=1}^{N_g}\bar{P}_{g'}(t).$$

Let us define

$$D(t)(\cdot) = \Theta(\cdot)\left[\bar{\beta}(t)\bar{P}(t) + b(t)\mathbf{I_d}\right]\sum_{g'=1}^{N_g}\bar{P}_{g'}(t).$$

As Θ is continuous on $[0,1]$, we can also define

$$\bar{D}(t) = \sup_{\theta\in[0,1]} D(t)(\cdot) \quad \text{and} \quad \bar{\Theta} = \sup_{\theta\in[0,1]}\Theta(\cdot).$$

We then have

$$D(t)(\cdot) \leqslant \bar{D}(t) = \bar{\Theta}\left[\bar{\beta}(t)\bar{P}(t) + b(t)\mathbf{I_d}\right]\sum_{g'=1}^{N_g}\bar{P}_{g'}(t).$$

Applying Lemma B.2 given in Appendix B to the previous inequality, we deduce that

$$I(t,\cdot) \leqslant T_{\mathcal{A}_I}(t)I_0(\cdot) + \int_0^t T_{\mathcal{A}_I}(t-s)D(s)(\cdot)ds.$$

Since the function $\theta \longmapsto I(t,\theta)$ is continuous on $[0,1]$, for all $t \in [0, t_{max})$

$$\|I(t,\cdot)\|_\infty \leqslant |T_{\mathcal{A}_I}(t)| \sup_{\theta\in[0,1]}|I_0(\theta)| + \int_0^t |T_{\mathcal{A}_I}(t-s)|\,|\bar{D}(s)|ds.$$

then

$$\begin{aligned}\|u(t)\| &= |S(t)| + \|I(t,\cdot)\|_\infty,\\ &\leqslant |\bar{P}(t)| + |T_{\mathcal{A}_I}(t)| \sup_{\theta\in[0,1]}|I_0(\theta)| + \int_0^t |T_{\mathcal{A}_I}(t-s)|\,|\bar{D}(s)|ds.\end{aligned} \tag{11}$$

We denote by $f(t)$ the right-hand side of this inequality. Taking into account that b, $\beta(\cdot,\theta)$, $\bar{\beta}$ and by construction $\bar{P}$ are continuous functions from $[0,+\infty)$ to $[0,+\infty)$, we deduce that f is also a continuous function from $[0,+\infty)$ to $[0,+\infty)$. Particularly, for all $t \in [0,t']$ with $0 \leqslant t' < +\infty$, $f(t)$ is continuous and bounded. Consequently, $\|u(t)\|$ is bounded for t in bounded intervals, which means that $\|u(t)\|$ cannot be infinite in bounded time intervals. By using Theorem A.8, we deduce that $t_{max} = +\infty$.

We have shown by Theorem A.8 that the solution $u(t)\binom{S}{I}$ of the nonlinear problem (ACP) is a local mild solution. We have proved that this local solution is bounded on bounded time intervals. Then Theorem A.8 allows us to conclude that the maximum time interval on which the solution exists is infinite. In other words the mild solution is a global solution.

Remark 5. In this general case, the initial value problem (ACP) has a solution for all $t \in [0,+\infty)$. A particular case is when we have $\bar{b} \leqslant \mu$ which corresponds to a situation when we impose in the flock a rate of mortality larger than birth. The solution is in this case asymptotically becomes extinct in the course of the time.

Indeed, under the condition $\bar{b} \leqslant \mu$ we deduce from (10) that $\bar{P}(t) \to 0$ and from (11) that $\|u(t)\| \to 0$ when $t \to \infty$, as $(T_{\mathcal{A}_I}(t))_{t \geqslant 0}$ is exponentially stable.

4. **Discussion.** The aim of this paper was to perform a mathematical analysis of a PDE model applied to the within-flock transmission of scrapie.

The model is based on a realistic model that has been applied to Scottish and French flocks, with a few simplifying hypotheses: no age structure is introduced, the animals infected by the vertical or the horizontal route are not distinguished. The latter simplification is not restrictive, as within a flock the route of infection of an animal cannot be determined; separating the infected sheep by route is mainly useful to test the efficiency of control strategies targeting a particular route. Adding a continuous age structure to the flock would be more interesting, as the flock management and possibly the transmission are age-dependent. The model also considers the ram allele frequencies as an exogenous input (G is a function of t) unlinked to the flock allele frequencies; as artificial insemination is frequently used and as scrapie plans in Europe impose genetic selection for scrapie resistance in scrapie-affected farms (mainly implemented by ram selection), this assumption is reasonable.

After formulating the model in terms of an abstract Cauchy problem, the mathematical analysis was done in two stages: first, the linear case was treated, which corresponds to the initial model without horizontal transmission; then the complete nonlinear model was studied. Using classical tools of the semigroup and evolution family theory, we have shown that the linear model admits a unique, positive and regular solution. The handling of the nonlinear case was less obvious: to our knowledge, very few works have been published on this type of semilinear, non autonomous, integro-differential model. We have shown that the model has a unique global solution. We were able to show that a local solution and is in addition a global solution. We have mentioned a fairly restrictive case, corresponding roughly to a situation in which birth is lower than mortality: in this case, we have also shown that the population is bounded and becomes extinct, which can logically be expected.

A further study, which exceeds the scope of this paper, would be necessary to analyse more in depth the asymptotic behaviour of the model; global attractors a positive equilibrium could possibly exist for certain levels of infection. From a control point of view, the birth and culling function could be used to stabilise the model; in a flock, this is actually how the population is set. Our future work includes this type of study.

Furthermore, it would be interesting to produce similar results under more general conditions, in particular when adding a continuous age structure to the model. We would then need to adapt the semigroup/evolution family approach to treat the semilinear problem with non autonomous boundary conditions arising from this more general model. We are also interested in carrying on in this direction.

Finally, we would like to point out that although this model is derived from the scrapie epidemiology, it is fairly general and would be relevant for diseases with long incubation periods relative to lifespan, genetic susceptibility factors, and for the more general model, age susceptibility factors. The analysis performed in this paper only requires very loose conditions on the various components of the model, such as the birth function, the transmission rate, etc.

Appendix A. **Definitions and theorems.** The following definitions can be found in [11] or [4], the Gronwall-Bellman inequality in [7].

Definition A.1 (Semigroup)**.** A family $(T(t))_{t\geqslant 0}$ of bounded linear operators on a Banach space X is called a strongly continuous semigroup if the functional equation

$$\begin{cases} T(t+s) = T(t)T(s) & \text{for all } t \geqslant 0 \\ T(0) = I \end{cases}$$

holds and the orbit maps

$$\xi_x : t \mapsto \xi_x(t) = T(t)x$$

are continuous from $[0, +\infty)$ into X for every $x \in X$.

Definition A.2 (Generator)**.** The generator $\mathcal{A} : D(\mathcal{A}) \subseteq X \to X$ of a strongly continuous semigroup $(T(t))_{t\geqslant 0}$ on a Banach space X is the operator

$$\mathcal{A}x = \dot{\xi}_x(0) = \lim_{h\downarrow 0} \frac{1}{h}(T(t)x - x)$$

defined on every x in its domain

$$D(\mathcal{A}) = \{x \in X : \xi_x \text{ is differentiable}\}.$$

Definition A.3 (Evolution family)**.** A family of bounded operators $(U(t,s))_{t,s\in\mathbb{R},\, t\geqslant s}$ on a Banach space X is called an evolution family if

(i) $U(t,s) = U(t,r)U(r,s)$ and $U(s,s) = \mathbf{I_d}$ for $t \geqslant r \geqslant s$ and $t, r, s \in \mathbb{R}$; and
(ii) the mapping $\{(\tau,\sigma) \in \mathbb{R}^2 : \tau \geqslant \sigma\} \ni (t,s) \mapsto U(t,s)$ is strongly continuous.

Let us consider the following semilinear initial value problem:

$$\begin{cases} \dfrac{du(t)}{dt} = \mathcal{A}u(t) + f(t,u(t)), \quad t > 0, \\ u(0) = u_0 \end{cases} \tag{P}$$

where $\mathcal{A}$ is the generator of a strongly continuous semigroup $T(t), t \geqslant 0$ on a Banach space X and $f : [0,T] \times X \to X$ is continuous in t and satisfies a Lipschitz condition in u.
The corresponding linear homogeneous problem is defined by

$$\text{(P)} \quad \text{with } f = 0. \tag{P'}$$

Definition A.4 (Classical solution)**.** A function $u : [0, +\infty) \to X$ is called a classical solution of (P') if u is continuously differentiable with respect to t, $u(t) \in D(A)$ for all $t \geqslant 0$ and (P') holds.

Definition A.5 (Mild solution)**.** Let $f : [0,T] \times X \to X$ be continuous in t and satisfy a Lipschitz condition in u, and let $\mathcal{A}$ be the generator of a strongly continuous semigroup $T(t), t \geqslant 0$. We call a mild solution of (P) a continuous solution $u : [0, +\infty) \to X$ satisfying the integral equation

$$u(t) = T(t)u_0 + \int_0^t T(t-s)f(s,u(s))ds.$$

Lemma A.6 (Gronwall-Bellman inequality from [7])**.** *Let y and λ be continuous real functions on $[a,b]$ and let μ be a continuous and non negative function on $[a,b]$. If*

$$y(t) \leqslant \lambda(t) + \int_a^t \mu(s)y(s)ds$$

is satisfied for $t \in [a,b]$, then on the same interval

$$y(t) \leqslant \lambda(t) + \int_a^t \lambda(s)\mu(s) \exp\left(\int_s^t \mu(\tau)d\tau\right) ds.$$

Theorem A.7 (from [8]). *Let X_1 be the space $\{f \in C([0,1],\mathbb{C}) | f(0) = 0\}$ with the supremum norm. We consider the following initial value problem of a partial differential equation:*

$$\begin{cases} \dfrac{\partial u}{\partial t} = \gamma x \dfrac{\partial u}{\partial x} + h(x) \\ u(0,x) = f(x) \end{cases}$$

where $\gamma < 0$, $h \in C([0,1],\mathbb{C})$ and $f \in X_1$. Then the solution semigroup $\{T_t\}_{t\geqslant 0}$ $((T_t f(x) = \exp(\int_0^t h(e^{\gamma(t-s)}x)ds) f(e^{\gamma t}))$ to the partial differential equation is a strongly continuous semigroup on X_1.

Theorem A.8 (from [11]). *Let $f : [0,\infty) \times X \to X$ be continuous in t for $t \geqslant 0$ and locally Lipschitz-continuous in u, uniformly in t on bounded intervals. If A is the generator of a strongly continuous semigroup $T(t)$ on X, then for every $u_0 \in X$ there is a $t_{max} \leqslant \infty$ such that the initial value problem (P) has a unique mild solution u on $[0, t_{max})$. Moreover, if $t_{max} < \infty$ then*

$$\lim_{t \to t_{max}} \|u(t)\| = \infty.$$

Appendix B. Proofs of lemmas.

Lemma B.1. *For all $t \geqslant 0$, the nonlinear term $f(t,\cdot) = \mathrm{V}(t)\cdot + \mathrm{H}(t,\cdot)$ is locally Lipschitz-continuous.*

Proof. The function $(t,\cdot) \longmapsto \mathrm{V}(t)\cdot$ is continuous in t and thus uniformly continuous in each bounded time interval. It is also linear in the second variable, so it is uniformly Lipschitz-continuous. Hence, we only need to prove the result above for $\mathrm{H}(t,\cdot)$.

Let us set $t' \geqslant 0$ and $\omega \geqslant 0$. For all $t \in [0,t']$ and all $u, v \in X$ with $\|u\| \leqslant \omega$ and $\|v\| \leqslant \omega$, we want to show that there exists a constant $R(t',\omega)$ such that:

$$\|\mathrm{H}(t,u) - \mathrm{H}(t,v)\| \leqslant R(t',\omega)\|u - v\|.$$

Let $u = \binom{x}{y}$ and $v = \binom{p}{q}$. Noting $\langle \mathbf{1}, I(\theta')\rangle = \sum_{g'=1}^{N_g} I_g(\theta')$, we have

$$\begin{aligned}
&\|\mathrm{H}(t,u) - \mathrm{H}(t,v)\| \\
&\quad = \left\| \begin{pmatrix} -\int_0^1 \langle \mathbf{1}, y(\theta')\rangle K(t,\theta')d\theta'\, x + \int_0^1 \langle \mathbf{1}, q(\theta')\rangle K(t,\theta')d\theta'\, p \\ \left(\int_0^1 \langle \mathbf{1}, y(\theta')\rangle K(t,\theta')d\theta'\, x - \int_0^1 \langle \mathbf{1}, q(\theta')\rangle K(t,\theta')d\theta', p\right)\Theta(\cdot) \end{pmatrix} \right\| \\
&\quad = \left| \int_0^1 \langle \mathbf{1}, y(\theta')\rangle K(t,\theta')d\theta'\, x - \int_0^1 \langle \mathbf{1}, q(\theta')\rangle K(t,\theta')d\theta'\, p \right| \\
&\qquad + \left\| \left(\int_0^1 \langle \mathbf{1}, y(\theta')\rangle K(t,\theta')d\theta'\, x - \int_0^1 \langle \mathbf{1}, q(\theta')\rangle K(t,\theta')d\theta'\, p \right)\Theta(\cdot) \right\| \\
&\quad = (1 + \|\Theta\|_\infty) \left| \int_0^1 \langle \mathbf{1}, y(\theta')\rangle K(t,\theta')d\theta'\, x - \int_0^1 \langle \mathbf{1}, q(\theta')\rangle K(t,\theta')d\theta'\, p \right|.
\end{aligned}$$

Let

$$E = \left| \int_0^1 \langle \mathbf{1}, y(\theta')\rangle K(t,\theta')d\theta' x - \int_0^1 \langle \mathbf{1}, q(\theta')\rangle K(t,\theta')d\theta' p \right|.$$

Then

$$E = \left| \int_0^1 \langle \mathbf{1}, y(\theta') - q(\theta') \rangle K(t,\theta') d\theta' \, x - \int_0^1 \langle \mathbf{1}, q(\theta') \rangle K(t,\theta') d\theta' \, (p-x) \right|$$
$$= \|y-q\|_\infty \left| \int_0^1 K(t,\theta') d\theta' \right| |x| + \|q\|_\infty \left| \int_0^1 K(t,\theta') d\theta' \right| |p-x|.$$

We have $|x| \leqslant \|u\| \leqslant \omega$ and $\|q\|_\infty \leqslant \|v\| \leqslant \omega$. So

$$E \leqslant \omega \left| \int_0^1 K(t,\theta') d\theta' \right| (|p-x| + \|y-q\|_\infty) \leqslant \omega \left| \int_0^1 K(t,\theta') d\theta' \right| \|u-v\|,$$

and finally

$$\|\mathrm{H}(t,u) - \mathrm{H}(t,v)\| \leqslant \omega \, (1 + \|\Theta\|_\infty) \left| \int_0^1 K(t,\theta') d\theta' \right| \|u-v\|.$$

□

Lemma B.2. *Let $\mathcal{A}$ be the generator of a positive semigroup $T(\cdot)$ on a Banach lattice E. Let φ and ψ be two functions in $C([0,t'),E)$, with $t_{max} \geqslant 0$, such that $\varphi(t) \in D(\mathcal{A})$ for all $t \in [0,t')$ and φ is differentiable. If*

$$\begin{cases} \dfrac{d}{dt}\varphi(t) \leqslant \mathcal{A}\varphi(t) + \psi(t), \quad \text{for } t \in [0,t') \\ \varphi(0) = x_0 \end{cases} \tag{Q}$$

is verified, then $\varphi(t) \leqslant T(t)x_0 + \int_0^t T(t-s)\psi(s)ds$ for $t \in [0,t')$.

Proof. For $t \in [0,t')$, let us consider the function v defined on $[0,t]$ by $v(s) = T(t-s)\varphi(s)$. v is differentiable and satisfies

$$\frac{d}{ds}v(s) = T(t-s)\frac{d}{ds}\varphi(s) - T(t-s)\mathcal{A}\varphi(s), \quad 0 \leqslant s < t.$$

Hence, from (Q) and the positivity of the semigroup $T(\cdot)$ it follows that

$$\frac{d}{ds}v(s) \leq T(t-s)\psi(s).$$

By integrating this inequality between 0 and t, we obtain the result above. □

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