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PARAMETERS IDENTIFICATION FOR A MODEL OF T CELL HOMEOSTASIS

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Abstract. In this study, we consider a model of T cell homeostasis based on the Smith-Martin model. This nonlinear model is structured by age and CD44 expression. First, we establish the mathematical well-posedness of the model system. Next, we prove the theoretical identifiability regarding the up-regulation of CD44, the proliferation time phase and the rate of entry into division, by using the experimental data. Finally, we compare two versions of the Smith-Martin model and we identify which model fits the experimental data best.

1. **Introduction.** The size and composition of the T lymphocyte compartment is subject to strict homeostatic regulation and is remarkably stable throughout life, despite variable dynamics in cell production and death during T cell development and immune responses [13, 7].

Homeostasis refers to the tendency of the body to preserve its internal steady state, allowing it to return to a normal set point following perturbation. The term was first used by the American physiologist Walter Canon in his seminal work, Wisdom of the Body, in 1932 [5]. He emphasized the dynamic nature of homeostasis, stating that while it ensures stability of the organism, homeostasis does not imply something set and immobile, a stagnation. This dynamism is evident in the homeostasis of the adaptive immune system where rapid fluctuations in the number, diversity, and function of lymphocytes occur during immune responses. Yet, for the efficient function of the immune system, the population and activation states of T cells need to remain relatively stable in the long term [14]. The term lymphocyte homeostasis has been used to refer to the maintenance of lymphocyte numbers as well as the maintenance of lymphocyte diversity [20, 6].

T cells that have yet to encounter the antigen they recognise are termed naive as they have not been activated to respond. In normal case, the majority of naive T cells are non dividing and express low level of the surface phenotype (CD44 low). Under such conditions of T cell deficiency (eg. AIDS), naive T cells undergo

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cell division, termed homeostasic proliferation or lymphopenia induced proliferation (LIP). This regularization process can also be associated with acquisition of a memory phenotype (CD44 high), and such cells share both functional and molecular characteristics of conventional memory cells [11, 10].

In this context, a biologically reasonable specific model of cell division is given by Smith-Martin model [19]. Based on their quantitative study of the FLM (fraction of labelled mitoses) curves of dividing cell population in vitro, Smith and Martin [19] formulated a simple quantitative description for the process of cell division. In fact, this description is similar to the model proposed by Burns and Tannock [4]. Several authors have developed mathematical models based on Smith-Martin model in order to analyse their experimental data [17, 3, 22, 9, 15, 16, 2, 8]. This model divides the four phases (G0 or G1, S, G2, M) of the cell cycle into A-state (resting phase) and B-phase (proliferative phase). The A-state corresponds to the G0 or G1 phase where the cells are randomly activated to enter in B-phase (S, G2, M phase) with a rate λ. The B-phase has a fixed duration Δ. After completing the deterministic B-phase, a cell delivers two daughter cells into the stochastic A-state from which the cells may be recruited for another round of division. A-state and B-phase have death rates δ_A and δ_B respectively. The Smith-Martin model is summarized in Fig. 1.

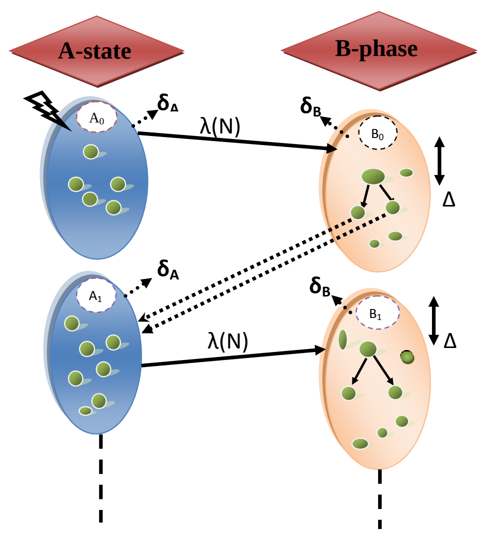

FIGURE 1. Model of T cell proliferation in vitro during the homoeostatic process. A_i and B_i are the number of T cells, having undergone i divisions in A-state and B-phase respectively. Δ is the duration of B-phase. The rate of entry into division (λ) is described by a function of the total cell number (N) and division number i, which is linked to all phases and all divisions [12].

Ayoub et al. [1] have extended the versions of Smith-Martin proposed by many authors [2, 9, 8, 22, 12]. They have taken into account the CD44 expression on the cell surface in the modelling of T cell homeostasis. This new criteria is a natural marker that represents the transition of T cells from naive (CD44 low) to memory (CD44 hight) phenotype during the homoeostatic process. The new version of

Smith-Martin proposed by [1] is written as follows

$$
\begin{cases}
\dfrac{dA_0(t,s)}{dt} = -\delta_A A_0(t,s) - \lambda(N)A_0(t,s), \\
\begin{cases}
for\ i = 1, ..., I \\
\dfrac{dA_i(t,s)}{dt} = 2\displaystyle\int_0^{\Delta} \mu(\tau)B_{i-1}(t,\tau,s)\ d\tau - \delta_A A_i(t,s) - \lambda(N)A_i(t,s),
\end{cases} \\
\begin{cases}
for\ i = 0, ..., I \\
\frac{\partial}{\partial t}B_i(t,\tau,s) + \frac{\partial}{\partial \tau}B_i(t,\tau,s) + \frac{\partial}{\partial s}[v_i(s).B_i(t,\tau,s)] \\
= -\left(\delta_B + \mu(\tau)\right) B_i(t,\tau,s),
\end{cases}
\end{cases}
\tag{1}
$$

where the variable $s \in [0, m]$ represents the intensity of CD44 presented on the cell's surface in A-state and B-phase, and $\tau \in [0, \Delta]$ depicts the age of cells in B-phase. The maximum intensity of CD44 is denoted by m. The number I depicts the maximum division number undergone by cells. In addition,

- $A_i(t,s)$ is the number of cells at time t having undergone i divisions in the resting phase (A_i phase), and having an intensity s of CD44 expression.
- $B_i(t,\tau,s)$ is the number of cells at time t having undergone i divisions, having spent time τ in the proliferative phase (B_i phase), and having an intensity s of CD44 expression.
- The total cell number is defined by

$$
N := N(t) := \sum_{i=0}^{I} \left(\int_0^m A_i(t,s)ds + \int_0^{\Delta} \int_0^m B_i(t,\tau,s)ds\, d\tau \right). \tag{2}
$$

- The recruitment rate from A-state into B-phase is denoted by $\lambda(N)$ which depends on the total number of cells $N := N(t)$.
- Function, $\mu(\tau)$, denotes the rate of cells which divided at age τ and have given rise to two daughter cells in the resting phase.
- The up-regulation of the CD44 expression on the T cell's surface is represented in (1) by a velocity v_i in each division. This function depends on variable s.

The boundary and initial distributions are

$$
\begin{cases}
B_i(t,0,s) = \lambda(N)A_i(t,s)\ and\ v_i(0)B_i(t,\tau,0) = 0\ for\ i = 0, ..., I \\
B_i(0,\tau,s) = 0,\ for\ i = 0, ..., I\ and\ A_i(0,s) = 0,\ for\ i = 1, ..., I \\
A_0(0,s) = A_{0,0}(s).
\end{cases}
\tag{3}
$$

In [1], the authors estimate numerically the velocity of up-regulation of CD44 (v_i) in order to understand the switch from naive (CD44 low) to memory (CD44 high) phenotype during the homeostatic process. However, this study did not show the analysis of System (1-3), such as the mathematical well-posedness of the model, the identifiability of the parameters, which validates the uniqueness of estimates in [1], and the model comparison to another model in the literature. In this study, we examined all these points. This work is organized as follows. In Sect. 2, we show some results that characterize the solution of System (1-3). Next, we prove the local existence and uniqueness of the solution by using the fixed point method, and then we conclude the global existence by using the maximal interval of existence. Sect. 3 is devoted to proving the theoretical identifiability of some parameters (v_i, $\lambda(N)$, Δ) by using the data of Hogan et al. [12]. In Sect. 4, we rewrite (1-3) as an age-structured model and we compare this system with another age-structured system used in several previous studies. We present the methodology and the criteria to compare the models. Finally, we show the parameters and the simulations that we obtain from the models and compare them to experimental data.

2. **Existence and uniqueness.** In this section, we are looking for the well-posedness of the mathematical model (1-3). We first state some notion of solution.

Let $L^1((0,\Delta),(0,m);\mathbb{R}^n)$ be the Banach space of equivalence classes of Lebesgue integrable functions, from $(0,\Delta)\times(0,m)$ in $\mathbb{R}^n$ with norm

$$\|u\|_{L^1((0,\Delta)\times(0,m))}=\int_0^{\Delta}\int_0^{m}|u(\tau,s)|d\tau ds.$$

Let $T>0$. One defines two spaces L_T and H_T respectively by setting

$$\begin{array}{rcl} L_T & := & L^\infty(0,T,L^1((0,\Delta)\times(0,m))) \\ & = & \{u(t,.,.)\in L^1((0,\Delta)\times(0,m))\ ,\ \sup\limits_{0\leqslant t\leqslant T}\|u(t,.,.)\|_{L^1((0,\Delta)\times(0,m))}<+\infty\}, \\ H_T & := & L^\infty(0,T,L^1((0,m))) \\ & = & \{q(t,.)\in L^1((0,m))\ ,\ \sup\limits_{0\leqslant t\leqslant T}\|q(t,.)\|_{L^1((0,m))}<+\infty\}. \end{array}$$

By using Lagrange method, one obtains an implicit solution of A_i

$$\begin{array}{rcl} A_0(t,s) & = & A_{0,0}(s)\ e^{-\int_0^t(\delta_A+\lambda(N(u)))du},\ \textit{and for } i\in\mathbb{N}_I^*:=\{1,...,I\} \\ A_i(t,s) & = & 2\displaystyle\int_0^t\int_0^{\Delta} e^{-\displaystyle\int_r^t(\delta_A+\lambda(N(q)))dq}\mu(\tau)B_{i-1}(r,\tau,s)d\tau\ dr. \end{array} \tag{4}$$

Now, we consider the following differential equations:

$$\left\{\begin{array}{l} \frac{ds_i^1(t)}{dt}=v_i(s_i^1(t)) \\ \\ s_i^1(t_0)=s_{i,0}^1\geqslant 0 \end{array}\right.,\quad \left\{\begin{array}{l} \frac{ds_i^2(\tau)}{d\tau}=v_i(s_i^2(\tau)) \\ \\ s_i^2(\tau_0)=s_{i,0}^2\geqslant 0. \end{array}\right. \tag{5}$$

where $s_i^1(t;t_0;s_{i,0}^1)$ and $s_i^2(\tau;\tau_0;s_{i,0}^2)$ are the curves which goes through $(t_0,s_{i,0}^1)$ and $(\tau_0,s_{i,0}^2)$ respectively. The curves, $Z_i^1(t):=s_i^1(t;0;0)$ and $Z_i^2(\tau):=s_i^2(\tau;0;0)$ are the characteristic through the origin. The solution of (5) is given by the following equations

$$s_i^1(t)=s_{i,0}^1+\int_{t_0}^t v_i(s_i^1(z))dz,\ \ s_i^2(\tau)=s_{i,0}^2+\int_{\tau_0}^{\tau}v_i(s_i^2(r))dr.$$

Integrating along the characteristic curve the PDE of System (1-3), one gets for all $i\in\mathbb{N}_{\mathbb{I}}:=\{0,...,I\}$

$$B_i(t,\tau,s)=\left\{\begin{array}{ll} 0 & t\leq\tau,\ Z_i^1(t)<s \\ \\ \frac{\lambda(N(t-\tau))A_i(t-\tau,\zeta_i)\,v_i(\zeta_i)}{v_i(s)}\,f(\tau) & 0\leq\tau<t,\ Z_i^2(\tau)<s \\ \\ 0 & s\leq Z_i^1(t),\ s\leq Z_i^2(\tau) \end{array}\right. \tag{6}$$

where $\zeta_i=s-Z_i^2(\tau)$ and $f(\tau):=e^{-\int_0^{\tau}(\delta_B+\mu(r))dr}$.

Definition 2.1. For all $T>0$ and $i\in\mathbb{N}_I$. (A_i, B_i) is called a global solution of System (1-3) (in the sense of the expressions (4)-(6)), if it belongs to $L^\infty(0,T,L^1(0,m))$ and $L^\infty(0,T,L^1((0,\Delta)\times(0,m)))$ respectively and it satisfies (4) and (6) respectively.

2.1. **Local existence and uniqueness of solution.** In this subsection we shall discuss the local existence of the solution of System (4)-(6) under the following assumption.

Assumption 2.1. - *Natural mortalities rates δ_A and δ_B are non-negative constants.*
- *Function $\mu(.)$ is bounded, non-negative and satisfies the following inequality*

$$0\le \underline{\mu}\le \mu(\tau)\le \bar{\mu},\ \forall\ \tau\in[0,\Delta].$$

- *Function $\lambda(N)$ is non-negative, bounded and Lipschitz continuous with constant k*

$$|\lambda(N)-\lambda(N^*)|\leqslant k|N-N^*|,\qquad N\geqslant 0,\quad N^*\geqslant 0.$$

- *Function v_i is bounded, non-negative for all $i\in\mathbb{N}_I$, satisfies the condition*

$$v_i(0)=0,\ \text{and}\ 0<\underline{v_i}\le v_i(s)\le \bar{v}_i,\ \forall s\in(0,m],$$

and continuously differentiable with respect to the variable s. In addition, there exists a positive constant d_{v_i}, $\forall\ i\in\mathbb{N}_I$, such that

$$|\frac{\partial v_i}{\partial s}|\leqslant d_{v_i},\quad \forall\ s\in(0,m].$$

- *Initial condition $A_{0,0}(.)$ is non-negative and belongs to $L^1_+((0,m))$.*

Remark 1. The integral formulation (6) rewrites as

$$\begin{aligned}B_i(t,\tau,s)=&\lambda(N(t-\tau))A_i(t-\tau,\zeta_i)\,f(\tau)\,e^{-\int_{\zeta_i}^{s}\frac{\partial v_i(\sigma)}{\partial\sigma}\frac{1}{v_i(\sigma)}d\sigma},\\ &\forall\ 0\le\tau<t\ \text{and}\ Z_i^2(\tau)<s.\end{aligned}$$

Using (6) and Assumption 2.1, one obtains

$$\|B_i(t,.,.)\|_{L^1((0,\Delta)\times(0,m))}\le\int_0^t\int_{Z_i^2(\tau)}^m \lambda(N(t-\tau))|A_i(t-\tau,s-Z_i^2(\tau))|e^{\frac{d_{v_i}Z_i^2(\tau)}{\underline{v_i}}}ds\,d\tau.$$

Using $Z_i^2(\tau):=\int_0^\tau v_i(s_i^2(r))dr$, one deduces the following estimate

$$\|B_i(t,.,.)\|_{L^1((0,\Delta)\times(0,m))}\le\int_0^t\int_{Z_i^2(\tau)}^m \lambda(N(t-\tau))|A_i(t-\tau,s-Z_i^2(\tau))|e^{C_{v_i}\tau}ds\,d\tau, \tag{7}$$

where $C_{v_i}:=\frac{d_{v_i}\bar{v}_i}{\underline{v_i}}$.

In what follows in this subsection, we shall use the following convention

$$\sum_j^i=0,\quad \prod_j^i=1\quad \textit{and}\quad \|.\|_\infty^{i-j}=1\qquad \textit{if } j>i.$$

Before studying local existence of a solution, we give the following preliminary result.

Lemma 2.2. *Let Assumption 2.1 be satisfied. For $T > 0$ and $t \in [0, T]$, any solution $((A_0, B_0), ..., (A_I, B_I))$ of (4)-(6) in the sense of Definition 2.1, satisfies $\forall\ i \in \mathbb{N}_I$*

$$\|A_i\|_{H_T} \leqslant \frac{2^i \bar{\mu}^i \|\lambda\|_\infty^i R_{A_0}}{\delta_A^i \left(\prod_{j=0}^{i-1} C_{v_j}\right)} \left(1 - e^{-\delta_A T}\right)^i \left[\prod_{j=0}^{i-1} \left(e^{C_{v_j} T} - 1\right)\right] := R_{A_i}, \quad (8)$$

and,

$$\|B_i\|_{L_T} \leqslant \frac{2^i \bar{\mu}^i \|\lambda\|_\infty^{i+1} R_{A_0}}{\delta_A^i \left(\prod_{j=0}^{i} C_{v_j}\right)} \left(1 - e^{-\delta_A T}\right)^i \left[\prod_{j=0}^{i} \left(e^{C_{v_j} T} - 1\right)\right] := R_{B_i}, \quad (9)$$

where $R_{A_0} := e^{-\delta_A T} \|A_{0,0}\|_{L^1((0,m))}$.

Proof. We proceed by induction.

For $i = 0$

Let $T > 0$ and $t \in [0, T]$. By using (4), let us integrate A_0 from 0 to m

$$\|A_0(t,.)\|_{L^1((0,m))} = \int_0^m |A_{0,0}(s)|\ e^{-\int_0^t (\delta_A + \lambda(N(u)))du} ds \leqslant e^{-\delta_A t} \|A_{0,0}\|_{L^1((0,m))},$$

that implies $\|A_0\|_{H_T} \leqslant R_{A_0}$. From (7), one has

$$\begin{aligned} &\|B_0(t,.,.)\|_{L^1((0,\Delta)\times(0,m))} \\ &\leq \int_0^t \int_{Z_0^2(\tau)}^m \lambda(N(t-\tau))|A_0(t-\tau, s - Z_0^2(\tau))|\ e^{C_{v_0}\tau} ds\ d\tau. \end{aligned}$$

Performing the change of variables $\sigma = s - Z_0^2(\tau)$ and $a = t - \tau$, one obtains

$$\|B_0(t,.,.)\|_{L^1((0,\Delta)\times(0,m))} \leq \int_0^t \int_0^m \lambda(N(a))|A_0(a,\sigma)|\ e^{C_{v_0}(t-a)} d\sigma\ da,$$

and one gets

$$\|B_0\|_{L_T} \leq \frac{\|\lambda\|_\infty}{C_{v_0}} \left(e^{C_{v_0} T} - 1\right) \|A_0\|_{H_T},$$

that implies $\|B_0\|_{L_T} \leq \frac{\|\lambda\|_\infty R_{A_0}}{C_{v_0}} \left(e^{C_{v_0} T} - 1\right)$. Then, inequalities (8) and (9) hold for $i = 0$.

For $i \in \mathbb{N}_I^*$

Assuming that inequalities (8) and (9) hold for i, let us show they still hold for $i + 1$. Integrating A_{i+1} over (0, m), one has

$$\|A_{i+1}(t,.)\|_{L^1((0,m))} \leqslant 2\bar{\mu} \int_0^m \int_0^t \int_0^\Delta e^{-\int_r^t (\delta_A + \lambda^i(N(q)))dq} |B_i(r,\tau,s)| d\tau\ dr\ ds.$$

Inequality (9) holds for i. Therefore, by using Fubini's theorem, one can write

$$\begin{aligned}
\|A_{i+1}\|_{H_T} &\leqslant \frac{2\bar{\mu}}{\delta_A}\left(1-e^{-\delta_A T}\right)\|B_i\|_{L_T} \\
&\leqslant \frac{2^{i+1}\bar{\mu}^{i+1}\|\lambda\|_\infty^{i+1}R_{A_0}}{\delta_A^{i+1}\left(\prod_{j=0}^{i}C_{v_j}\right)}\left(1-e^{-\delta_A T}\right)^{i+1}\left[\prod_{j=0}^{i}\left(e^{C_{v_j}T}-1\right)\right].
\end{aligned} \tag{10}$$

Now, let us integrate the solution B_{i+1} along the characteristic. Then one finds

$$\|B_{i+1}\|_{L_T} \leqslant \frac{\|\lambda\|_\infty}{C_{v_{i+1}}}\left(e^{C_{v_{i+1}}T}-1\right)\|A_{i+1}\|_{H_T}.$$

By using the inequality in (10), one eventually gets

$$\|B_{i+1}\|_{L_T} \leqslant \frac{2^{i+1}\bar{\mu}^{i+1}\|\lambda\|_\infty^{i+2}R_{A_0}}{\delta_A^{i+1}\left(\prod_{j=0}^{i+1}C_{v_j}\right)}\left(1-e^{-\delta_A T}\right)^{i+1}\left[\prod_{j=0}^{i+1}\left(e^{C_{v_j}T}-1\right)\right].$$

Then, inequalities (8) and (9) holds for $i+1$. □

Notation $(A_i, B_i; A_{0,0})$ stands for a solution (A_i, B_i) with initial condition $A_{0,0}$.

Lemma 2.3. *Let Assumption 2.1 be satisfied. Let $T>0$ and $t\in[0,T]$. For any two solutions $(A_i, B_i; A_{0,0})$ and $(A_i^*, B_i^*; A_{0,0}^*)$ of (4)-(6) in the sense of Definition 2.1, the following set of inequalities hold $\forall\ i \in \mathbb{N}_I := \{0, ..., I\}$,*

$$\begin{aligned}
\|A_i - A_i^*\|_{H_T} &\leq \alpha^i e^{-\delta_A T}\|A_{0,0}-A_{0,0}^*\|_{L^1((0,m))} + k\beta_A^i \sup_{0\leqslant t\leqslant T}|N(t)-N^*(t)|, \\
\|B_i - B_i^*\|_{L_T} &\leq \frac{\alpha^i\|\lambda\|_\infty\left(e^{C_{v_i}T}-1\right)}{C_{v_i}}e^{-\delta_A T}\|A_{0,0}-A_{0,0}^*\|_{L^1((0,m))} \\
&+ k\beta_B^i \sup_{0\leqslant t\leqslant T}|N(t)-N^*(t)|,
\end{aligned}$$

where

$$\alpha^i = \left[\frac{2\bar{\mu}\left(1-e^{-\delta_A T}\right)}{\delta_A}\right]^i \|\lambda\|_\infty^i \prod_{j=0}^{i-1}\frac{e^{C_{v_j}T}-1}{C_{v_j}},$$

$$\begin{aligned}
\beta_A^i = &\left[\frac{2\bar{\mu}\|\lambda\|_\infty\left(1-e^{-\delta_A T}\right)}{\delta_A}\right]^i\left[\prod_{j=0}^{i-1}\frac{\left(e^{C_{v_j}T}-1\right)}{C_{v_j}}\right]Te^{-\delta_A T}\|A_{0,0}\|_{L^1((0,m))} \\
&+\sum_{j=0}^{i-1}\left(\left[\frac{2\bar{\mu}\left(1-e^{-\delta_A T}\right)}{\delta_A}\right]^{i-j}\|\lambda\|_\infty^{i-j-1}\left[\prod_{k=j+1}^{i-1}\frac{\left(e^{C_{v_k}T}-1\right)}{C_{v_k}}\right]\right. \\
&\left.\left(R_{A_j^*}\frac{\left(e^{C_{v_0}T}-1\right),}{C_{v_0}}+TR_{B_j}\right)\right)
\end{aligned} \tag{11}$$

$$\beta_B^i = \|\lambda\|_\infty \left[\frac{2\bar{\mu}\|\lambda\|_\infty \left(1-e^{-\delta_A T}\right)}{\delta_A}\right]^i \left[\prod_{j=0}^{i} \frac{\left(e^{C_{v_j} T}-1\right)}{C_{v_j}}\right] T e^{-\delta_A T}\|A_{0,0}\|_{L^1((0,m))},$$
$$+\sum_{j=0}^{i}\left[\frac{2\bar{\mu}\|\lambda\|_\infty \left(1-e^{-\delta_A T}\right)}{\delta_A}\right]^{i-j}\left[\prod_{k=j}^{i}\frac{\left(e^{C_{v_k} T}-1\right)}{C_{v_k}}\right] R_{A_j^*}$$
$$+\sum_{j=0}^{i-1}\left[\frac{2\bar{\mu}\|\lambda\|_\infty \left(1-e^{-\delta_A T}\right)}{\delta_A}\right]^{i-j}\left[\prod_{k=j+1}^{i}\frac{\left(e^{C_{v_k} T}-1\right)}{C_{v_k}}\right] T R_{B_j} \tag{12}$$

and R_{A_i}, R_{B_i} are given in the previous Lemma 2.2.

Proof. As in the previous proof, we proceed by induction.

For $i = 0$

Let us integrate the difference between A_0 and A_0^* over $(0, m)$

$$\begin{aligned}\|A_0(t,.) - A_0^*(t,.)\|_{L^1((0,m))}& \\ \leqslant e^{-\delta_A t}\int_0^m |A_{0,0}^*(s)||e^{-\int_0^t \lambda(N(u))du} - e^{-\int_0^t \lambda(N^*(u))du}|\, ds& \\ +e^{-\delta_A t}\int_0^m |A_{0,0}(s) - A_{0,0}^*(s)|e^{-\int_0^t \lambda(N(u))du}\, ds.&\end{aligned}$$

Note that function $x \longrightarrow e^{-x}$ is Lipschitz continuous on $[0, +\infty)$ with constant 1. Then by using Assumption (2.1), one obtains

$$\begin{aligned}\|A_0 - A_0^*\|_{H_T} &\leqslant e^{-\delta_A T}\|A_{0,0} - A_{0,0}^*\|_{L^1((0,m))} \\ &+ k\underbrace{T e^{-\delta_A T}\|A_{0,0}^*\|_{L^1((0,m))}}_{=\beta_A^0}\sup_{0\leqslant t\leqslant T}|N(t) - N^*(t)|.\end{aligned}$$

On the other hand, integrating the difference between B_0 and B_0^* on $(0, \Delta) \times (0, m)$ one finds

$$\begin{aligned}&\|B_0(t,.,.) - B_0^*(t,.,.)\|_{L^1((0,\Delta)\times(0,m))} \\ &\leqslant \int_0^t \int_{Z_0^2(\tau)}^m e^{C_{v_0}\tau}\big[\lambda(N(t-\tau))\,|A_0(t-\tau,\zeta_0) - A_0^*(t-\tau,\zeta_0)| \\ &+|\lambda(N(t-\tau)) - \lambda(N^*(t-\tau))|\,|A_0^*(t-\tau,\zeta_0)|\big]\, ds\, d\tau.\end{aligned}$$

By using Lemma 2.2 and Assumption (2.1), one gets

$$\begin{aligned}&\|B_0 - B_0^*\|_{L_T} \leqslant \|\lambda\|_\infty \frac{\left(e^{C_{v_0}T}-1\right)}{C_{v_0}} e^{-\delta_A T}\|A_{0,0} - A_{0,0}^*\|_{L^1((0,m))} \\ &+k\underbrace{\frac{\left(e^{C_{v_0}T}-1\right)}{C_{v_0}}\left(\|\lambda\|_\infty T e^{-\delta_A T}\|A_{0,0}^*\|_{L^1((0,m))} + R_{A_0^*}\right)}_{=\beta_B^0}\sup_{0\leqslant t\leqslant T}|N(t) - N^*(t)|.\end{aligned}$$

Then, the inequalities in the statement of Lemma 2.3 are satisfied for $i = 0$.

For $i \in \mathbb{N}_I^*$

Assuming that the inequalities in the statement of Lemma 2.3 hold for i. Let us show they still hold for i+1.

$$\|A_{i+1}(t,.) - A^*_{i+1}(t,.)\|_{L^1((0,m))} \leqslant$$
$$2\bar{\mu}\int_0^m \int_0^t \int_0^\Delta e^{-\delta_A(t-r)} \Big[|e^{-\int_r^t \lambda(N(q))dq} - e^{-\int_r^t \lambda(N^*(q))dq}| \, |B_i(r,\tau,s)|$$
$$+e^{-\int_r^t \lambda(N^*(q))dq} \, |B_i(r,\tau,s) - B^*_i(r,\tau,s)|\Big] \; d\tau \; dr \; ds.$$

Therefore, using Lemma 2.2 and Assumption (2.1), one obtains

$$\begin{aligned}\|A_{i+1} - A^*_{i+1}\|_{H_T} &\leqslant 2\bar{\mu}\frac{\left(1-e^{-\delta_A T}\right)}{\delta_A}\|B_i - B^*_i\|_{L_T} \\ &+ \quad 2\bar{\mu}kTR_{B_i}\frac{\left(1-e^{-\delta_A T}\right)}{\delta_A}\sup_{0\leqslant t\leqslant T}|N(t)-N^*(t)|.\end{aligned}$$

By using the inductive hypothesis (i.e inequalities in the statement of Lemma 2.3 for i) , one gets

$$\|A_{i+1} - A^*_{i+1}\|_{H_T} \leqslant$$
$$\overbrace{2\bar{\mu}\alpha^i\|\lambda\|_\infty \frac{\left(1-e^{-\delta_A T}\right)}{\delta_A}\frac{\left(e^{C_{v_i}T}-1\right)}{C_{v_i}}}^{\alpha^{i+1}} e^{-\delta_A T}\|A_{0,0} - A^*_{0,0}\|_{L^1((0,m))}$$
$$+k\underbrace{\left[2\bar{\mu}\frac{\left(1-e^{-\delta_A T}\right)}{\delta_A}\beta^i_B + 2\bar{\mu}TR_{B_i}\frac{\left(1-e^{-\delta_A T}\right)}{\delta_A}\right]}_{\beta^{i+1}_A}\sup_{0\leqslant t\leqslant T}|N(t)-N^*(t)|, \quad (13)$$

where α^{i+1} and β^{i+1}_A are given in the statement of Lemma 2.3.

Also, one has

$$\|B_{i+1}(t,.,.) - B^*_{i+1}(t,.,.)\|_{L^1((0,\Delta)\times(0,m))} \leqslant$$
$$\int_0^t \int_{Z^2_{i+1}(\tau)}^m e^{C_{v_{i+1}}\tau}\big[|\lambda(N(t-\tau))| \, |A_{i+1}(t-\tau,\zeta_{i+1}) - A^*_{i+1}(t-\tau,\zeta_{i+1})|$$
$$+|\lambda(N(t-\tau)) - \lambda(N^*(t-\tau))| \, |A^*_{i+1}(t-\tau,\zeta_{i+1})|\big] \; ds \; d\tau.$$

Furthermore, using Lemma 2.2 and Assumption (2.1), one obtains

$$\begin{aligned}\|B_{i+1} - B^*_{i+1}\|_{L^T} &\leqslant \|\lambda\|_\infty\frac{\left(e^{C_{v_{i+1}}T}-1\right)}{C_{v_{i+1}}}\|A_{i+1} - A^*_{i+1}\|_{H_T} \\ &\quad +kR_{A^*_{i+1}}\frac{\left(e^{C_{v_{i+1}}T}-1\right)}{C_{v_{i+1}}}\sup_{0\leqslant t\leqslant T}|N(t)-N^*(t)|.\end{aligned}$$

Finally, using (13)

$$\|B_{i+1} - B^*_{i+1}\|_{L^T} \leqslant$$
$$\frac{\alpha^{i+1}\|\lambda\|_\infty\left(e^{C_{v_{i+1}}T}-1\right)}{C_{v_{i+1}}}e^{-\delta_A T}\|A_{0,0} - A^*_{0,0}\|_{L^1((0,m))}$$
$$+k\underbrace{\frac{\left(e^{C_{v_{i+1}}T}-1\right)}{C_{v_{i+1}}}\left(\|\lambda\|_\infty\beta^{i+1}_A + R_{A^*_{i+1}}\right)}_{\beta^{i+1}_B}\sup_{0\leqslant t\leqslant T}|N(t)-N^*(t)|.$$

This ends the proof of the Lemma 2.3. □

Now, we will state the main result of this subsection.

Theorem 2.4. *Under Assumption 2.1, System (4)-(6) admits a unique local solution in* $[0, T^*]$.

Proof. We set up a fixed point method.

At first, define an operator

$$\bigwedge : \ ((A_0, B_0), ..., (A_I, B_I)) \ \longmapsto \Big((\hat{A}_0, \hat{B}_0), ..., (\hat{A}_I, \hat{B}_I)\Big)$$

wherein

$$\begin{aligned}
\hat{A}_0(t,s) &= A_{0,0}(s)\ e^{-\int_0^t(\delta_A+\lambda(N(u)))du},\\
\hat{A}_{i\in\mathbb{N}_I^*}(t,s) &= 2\int_0^t\int_0^\Delta e^{-\displaystyle\int_r^t(\delta_A+\lambda^i(N(q)))dq}\mu(\tau)\hat{B}_{i-1}(r,\tau,s)d\tau\ dr,\\
\hat{B}_{i\in\mathbb{N}_I}(t,\tau,s) &= \begin{cases} 0 & t\le\tau,\ Z_i^1(t)<s\\ \frac{\lambda(N(t-\tau))\hat{A}_i(t-\tau,\zeta_i)\ v_i(\zeta_i)}{v_i(s)}\ f(\tau) & 0\le\tau<t,\ Z_i^2(\tau)<s\\ 0 & s\le Z_i^1(t),\ s\le Z_i^2(\tau)\end{cases}
\end{aligned}$$

where $N(t)$ is given by (1-3), $\zeta_i = s - Z_i^2(\tau)$ and $f(\tau) := e^{-\int_0^\tau(\delta_B+\mu(r))dr}$.

Let $M := (H_T \times L_T)^I$ and define a norm on M as follows

$$\|u\|_M = \sum_{i=0}^I \sup_{0\leqslant t\leqslant T}\left(\int_0^m |A_i(t,s)|\ ds + \int_0^\Delta\int_0^m |B_i(t,\tau,s)|\ ds\ d\tau\right), \qquad (14)$$

for all $u := ((A_0, B_0), ..., (A_I, B_I)) \in M$.

We shall show that the operator $\bigwedge$ is a map from M into M and it is strict contraction for T small enough.

(1) $\bigwedge : M \longmapsto M$

Let u and $\hat{u} := \Big((\hat{A}_0, \hat{B}_0), ..., (\hat{A}_I, \hat{B}_I)\Big)$ lie in M and satisfy (4)-(6). By using (14), one can write

$$\|\hat{u}\|_M = \sum_{i=0}^I\left(\|\hat{A}_i\|_{H_T} + \|\hat{B}_i\|_{L_T}\right).$$

Substituting (8) and (9) in the previous equality, one obtains

$$\|\hat{u}\|_M \le \sum_{i=0}^I\left(R_{\hat{A}_i} + R_{\hat{B}_i}\right).$$

Then for $T < +\infty$, one gets $\bigwedge$ maps M into M.

(2) It remains to show that $\bigwedge$ is a contraction for T small enough

Let u, $\hat{u}$, $\bar{u} := \big((\bar{A}_0, \bar{B}_0), ..., (\bar{A}_I, \bar{B}_I)\big)$ and $\bar{\hat{u}} := \Big((\bar{\hat{A}}_0, \bar{\hat{B}}_0), ..., (\bar{\hat{A}}_I, \bar{\hat{B}}_I)\Big)$ in M and satisfies (1-3).

Then, the norm in M of the difference between $\hat{u}$ and $\bar{\hat{u}}$ is

$$\|\hat{u} - \bar{\hat{u}}\|_M = \sum_{i=0}^I \|\hat{B}_i - \bar{\hat{B}}_i\|_{L_T} + \sum_{i=0}^I \|\hat{A}_i - \bar{\hat{A}}_i\|_{H_T}.$$

Solutions, $\hat{u}$ and $\hat{\bar{u}}$ having the same initial condition ($\hat{A}_{0,0} \equiv \hat{\bar{A}}_{0,0}$). Lemma 2.3 allows us to estimate the previous equality by

$$\begin{aligned} \|\hat{u} - \hat{\bar{u}}\|_M &\leqslant \Theta \sup_{0 \leqslant t \leqslant T} |N(t) - \bar{N}(t)| \\ &\leqslant \Theta \|u - \bar{u}\|_M, \end{aligned}$$

where

$$\Theta = \Theta(T) = k \sum_{i=0}^{I} \left(\beta_A^i + \beta_B^i\right).$$

Note that $\lim_{T \to 0} \Theta(T) = 0$ (see (11-12) for β_A^i and β_B^i). Then, there exists at least $T^* > 0$ where $\Theta(T^*) < 1$, which implies that $\bigwedge$ is a strict contraction.

This completes the local existence and uniqueness proof. □

2.2. Global existence.

Remark 2. If u is a solution of (1-3) in $[0, T]$ and $\hat{u}$ is a continuous extension of u in $[T, T + \hat{T}]$ such that $\forall\, i \in \mathbb{N}_I$

$$A_i(t, s) = \hat{A}_i(t - T, s), \quad \textit{and} \quad B_i(t, \tau, s) = \hat{B}_i(t - T, \tau, s),$$

then u is a solution in $[0, T + \hat{T}]$.

In the next, we introduce the maximum interval of existence of a solution.

Definition 2.5. The maximal interval of existence of a solution, denoted by $[0, T_{max}]$ is the interval with the property that there exists $u \in (H_T \times L_T)^I$, solution of (1-3) for each $T \in (0, T_{max})$.

Lemma 2.6. *Let Assumption 2.1 be satisfied and let u be a solution of System (1-3) in $[0, T_{max})$. If $T_{max} < \infty$, then $\forall\, i \in \mathbb{N}_I$*

$$\lim_{t \to T_{max}} \|A_i(t, .)\|_{L^1((0,m))} = \infty, \qquad \lim_{t \to T_{max}} \|B_i(t, ., .)\|_{L^1((0,\Delta) \times (0,m))} = \infty. \tag{15}$$

Proof. Assume there exists $r_1 > 0$ and $r_2 > 0$ such that $\|B_i(t, ., .)\|_{L^1((0,\Delta) \times [0,m])} \leqslant r_1$ and $\|A_i(t, .)\|_{L^1((0,m))} \leqslant r_2$ for all $t \in [0, T_{max})$, it suggests that there exists a sequence $(t_n)_{n \in \mathbb{N}}$ satisfying $\lim_{n \to \infty} t_n = T_{max}$. Then, one has

$$\begin{aligned} \sup_{n \in \mathbb{N}} \|B_i(t_n, ., .)\|_{L^1((0,\Delta) \times (0,m))} &\leqslant r_1, \\ \sup_{n \in \mathbb{N}} \|A_i(t_n, .)\|_{L^1((0,m))} &\leqslant r_2, \end{aligned}$$

such that u is a solution of (1-3) in $[0, t_n]$. From Remark 2, let u^{t_n} be a solution in $[t_n, t_n + \epsilon]$, $\forall\, \epsilon > 0$. According to local uniqueness, one gets a solution u on the larger interval $[0, T_{max} + \epsilon)$. It leads to a contradiction with the maximal interval $[0, T_{max})$. Therefore, (15) is hold. □

Obviously, we can state the global existence of the solution as follows

Theorem 2.7. *Let Assumption 2.1 be satisfied, there exists a unique solution of system (4-6) for all $T \in (0, \infty)$.*

Proof. Suppose that there exists a maximal interval $[0, T_{max})$ of the solution u. By the above lemma, $\lim_{t \longrightarrow T_{max}} \|A_i(t,.)\|_{L^1((0,m))} = \infty$ and $\lim_{t \to T_{max}} \|B_i(t,.,.) \|_{L^1((0,\Delta)\times(0,m))} = \infty$. In contrast, one has from Lemma 2.2 for $i = 0$

$$\begin{aligned}\|A_0(t,.)\|_{L^1((0,m))} &\leqslant e^{-\delta_A t}\|A_{0,0}\|_{L^1((0,m))},\\ \|B_0(t,.,.)\|_{L^1((0,\Delta)\times(0,m))} &\leqslant \frac{\|\lambda\|_\infty \left(e^{C_{v_0}}-1\right)}{C_{v_0} t}\left[e^{-\delta_A t}\|A_{0,0}\|_{L^1((0,m))}\right].\end{aligned}$$

That's mean for $t \longrightarrow T_{max}$:

$$\lim_t \|A_0(t,.)\|_{L^1((0,m))} < \infty \quad \textit{and} \quad \lim_t \|B_0(t,.,.)\|_{L^1((0,\Delta)\times(0,m))} < \infty.$$

It is a contradiction. Then the conclusion $T_{max} = \infty$ holds. □

3. Parameter identification.

An important step in using the mathematical approach is the estimation of model parameters using experimental data. In the literature, several types of data have been explored and used in the context of T cell proliferation through LIP (Lymphopenia Induced Proliferation). Using cell dyes, such as Carboxy Fluorescein diacetate Succinimidyl Ester (CFSE), is currently one of the most informative methods for characterizing the dynamics of cell division in the immune system. Following each division, CFSE divides equally between daughter cells, resulting in a two-fold decrease in the intensity of cellular fluorescence in each successive generation. This property of CFSE allows accurate tracking of the number of divisions that a given cell has undergone either in vitro or following transfer in vivo [18].

The Smith-Martin model has been applied widely to CFSE data [17, 3, 22, 9, 15, 16, 2, 8]. The duration of deterministic phase (B phase), the division rate and the probability of cell death have been estimated from experimental data mainly based on CFSE cell division profiles [9, 3, 8]. Hogan et al. [12] improved the technique and accuracy of the parameters estimations from the Smith-Martin model. The DNA binding dye, 7-Aminoactinomycin D (7AAD), was used with CFSE to distinguish the proliferating and non-proliferating cells, therefore enabling estimations of the rate of recruitment of cells from A phase into B phase.

Let us describe briefly the data used in this study.

Experimental data. Data were collected during a previously published study [12]. Indeed, the behavior of two different T cell clonotypes (OT-1 and F5) was studied in lymphopenic Rag1-/- mice by using CFSE, 7AAD dyes and CD44 expression measured by flow cytometry. Following adoptive transfer of T cells, cohorts of between three and five host mice were analysed at days 3, 5, 7, 10 and 12. At each time point, the number of T cells, the proportion of cells actively replicting their DNA as determined by 7AAD staining, and the intensity of expression of CD44 on the cell surface was measured for in each host and separated according to the number of divisions performed as assessed by CFSE labeling.

Ayoub et al. [1] have used this recent data of Hogan et al. [12] to estimate numerically the velocity of CD44 up-regulation. In this section, we are interested in the identifiability of some parameters by using the data stated in the previous paragraph.

3.1. **Identifiability.** Let us denote the experimental data of [12] by

$$N_i^{exp}(t,s) := \int_0^{\Delta} B_i(t,\tau,s)d\tau + A_i(t,s),$$

where $i \in \mathbb{N}_I$, $t \in [0,T]$, $s \in [0,m]$ and (A_i, B_i) is the solution of System (1-3).

Assumption 3.1. - *Functions* $(v_0, ..., v_I)$ *are defined in the space* $K = (C_+^{\bar{u}})^I$ *where*

$$C_+^{\bar{u}} = \{u \in C^0([0,m]),\ u(0) = 0,\ 0 < u(s) \leqslant \bar{u}\ ,\ \forall\ s \in (0,m]\}.$$

- *Initial condition* $A_{0,0}(s) > 0$ *for all* $s \in (0,m]$.

Lemma 3.1. *Let Assumptions 2.1 and 3.1 be satisfied. The velocity* v_i *is identifiable for all* $i \in \mathbb{N}_I := \{0, ..., I\}$.

Proof. Let's fix $(v_0, ..., v_I) \in K$ and consider a second parameter $(\bar{v}_0, ..., \bar{v}_I) \in K$ wherein

$$N_i^{exp}(t,s;v_i) = N_i^{exp}(t,s;\bar{v}_i),\ \forall\ i \in \mathbb{N}_I, \tag{16}$$

and $(\bar{A}_i(t,s), \bar{B}_i(t,\tau,s))$ is the solution relative to $\bar{v}_i$.

By integrating and summing (16) over s and i respectively, one gets

$$N(t) = \bar{N}(t). \tag{17}$$

By using the implicit solution (4), one obtains

$$A_0(t,s) = \bar{A}_0(t,s)\ \forall\ s \in [0,m]. \tag{18}$$

From (16), one gets $\int_0^{\Delta} B_0(t,\tau,s)d\tau = \int_0^{\Delta} \bar{B}_0(t,\tau,s)d\tau$.

Furthermore by induction, if we prove $v_{i-1}(s) = \bar{v}_{i-1}(s)$, $\forall\ i \in \mathbb{N}_I^*$ and $s \in [0,m]$, one obtains $A_i(t,s) = \bar{A}_i(t,s)$ and then from (16), one gets $\int_0^{\Delta} B_i(t,\tau,s)d\tau = \int_0^{\Delta} \bar{B}_i(t,\tau,s)d\tau$. Therefore, the problem returns to the proof of the identifiability of v_i through the following system

$$\begin{cases} \frac{\partial}{\partial t}B_i(t,\tau,s) + \frac{\partial}{\partial \tau}B_i(t,\tau,s) + \frac{\partial}{\partial s}\left[v_i(s)B_i(t,\tau,s)\right] = -\left(\delta_B + \mu(\tau)\right)B_i(t,\tau,s), \\ \\ B_i(0,\tau,s) = 0;\ B_i(t,0,s) = \lambda(N(t))A_i(t,s);\ v_i(0)B_i(t,\tau,0) = 0. \end{cases} \tag{19}$$

Let $\tilde{B}_i := B_i - \bar{B}_i$ and $\tilde{v}_i := v_i - \bar{v}_i$. B_i and $\bar{B}_i$ are the solution given by (19) relative to v_i and $\bar{v}_i$ respectively. Then, one has

$$\begin{cases} \frac{\partial}{\partial t}\tilde{B}_i(t,\tau,s) + \frac{\partial}{\partial \tau}\tilde{B}_i(t,\tau,s) + \frac{\partial}{\partial s}\left[\tilde{v}_i(s)B_i(t,\tau,s) + \bar{v}_i(s)\tilde{B}_i(t,\tau,s)\right] \\ = -f(\tau)\tilde{B}_i(t,\tau,s), \\ \\ \tilde{B}_i(0,\tau,s) = 0;\ \tilde{B}_i(t,0,s) = 0;\ \tilde{v}_i(0)B_i(t,\tau,0) = 0, \\ \\ Observation:\ \int_0^{\Delta}\tilde{B}_i(t,\tau,s)d\tau = 0, \end{cases} \tag{20}$$

where $f(\tau) := \delta_B + \mu(\tau)$.

Now, we define the following Lagrangian formulation related to System (20).

$$\begin{aligned} &\mathscr{L}(\tilde{B}_i, \tilde{v}_i, \tilde{q}_i) = \\ &\int_\Omega [\frac{\partial}{\partial t}\tilde{B}_i(t,\tau,s) + \frac{\partial}{\partial \tau}\tilde{B}_i(t,\tau,s) + \frac{\partial}{\partial s}\left[\tilde{v}_i(s)B_i(t,\tau,s) + \bar{v}_i(s)\tilde{B}_i(t,\tau,s)\right] \\ &+f(\tau)\tilde{B}_i(t,\tau,s)]\tilde{q}_i(t,\tau,s)d\Omega + \int_\Omega \tilde{B}_i(t,\tau,s)d\Omega, \end{aligned}$$

where $\Omega = [0,T] \times [0,\Delta] \times [0,m]$, $d\Omega = dt\, d\tau\, ds$ and $\tilde{q}_i$ corresponds to the dual variable. The first derivative of the Lagrangian $\mathscr{L}$ with respect to $\tilde{B}_i$, gives us the adjoint equation.

$$\begin{cases} \frac{\partial}{\partial t}\tilde{q}_i(t,\tau,s) + \frac{\partial}{\partial \tau}\tilde{q}_i(t,\tau,s) + \frac{\partial}{\partial s}\left[\bar{v}_i \tilde{q}_i(t\tau,s)\right] = F(\tau)\tilde{q}_i(t\tau,s) + 1, \\ \\ \tilde{q}_i(T,\tau,s) = \tilde{q}_i(t,\Delta,s) = \tilde{q}_i(t,\tau,m) = 0. \end{cases} \tag{21}$$

Multiplying (21) by $\tilde{B}_i(t,\tau,s)$ and integrating over Ω, one obtains

$$\int_\Omega \left(\tilde{B}_i(t,\tau,s) - \left[\frac{\partial \tilde{v}_i(s) B_i(t,\tau,s)}{\partial s}\right] \tilde{q}_i(t,\tau,s)\right) d\Omega = 0.$$

Using the observation in (20), one gets

$$\frac{\partial}{\partial s}\left[\tilde{v}_i(s) B_i(t,\tau,s)\right] = 0.$$

Replacing the above equality in (20), one has

$$\begin{cases} \frac{\partial}{\partial t}\tilde{B}_i(t,\tau,s) + \frac{\partial}{\partial \tau}\tilde{B}_i(t,\tau,s) + \frac{\partial}{\partial s}\left[\bar{v}_i(s)\tilde{B}_i(t,\tau,s)\right] = -f(\tau)\tilde{B}_i(t,\tau,s), \\ \\ \tilde{B}_i(0,\tau,s) = 0;\ \tilde{B}_i(t,0,s) = 0;\ \bar{v}_i(0)\tilde{B}_i(t,\tau,0) = 0. \end{cases} \tag{22}$$

Integrating along the characteristic curve the PDE of the above system, one obtains $\forall\ (t,\tau,s) \in \Omega$ and $i \in \mathbb{N}_I$

$$\tilde{B}_i(t,\tau,s) = 0, \ \textit{and then}\ B_i(t,\tau,s) = \bar{B}_i(t,\tau,s). \tag{23}$$

If $\bar{Z}_i^2(\tau) = Z_i^2(\tau) + c_i(\tau)$ where $c_i(\tau) > 0$ for all $\tau \in (0,\Delta]$ and $i \in \mathbb{N}_I$. Then for a fixed $i_0 \in \mathbb{N}_I$ and $s = \bar{Z}_{i_0}^2(\tau) > Z_{i_0}^2(\tau)$, one obtains $\bar{B}_{i_0}(t,\tau,s) = 0$ and $B_{i_0}(t,\tau,s) = \frac{\lambda(N(t-\tau)) A_{i_0}(t-\tau,\zeta_{i_0})\, v_{i_0}(\zeta_{i_0})}{v_{i_0}(s)} f(\tau)$ from (6). Using (23), one gets

$$A_{i_0}(t-\tau, c_{i_0}(\tau)) v_{i_0}(c_{i_0}(\tau)) = 0\ \forall\ 0 < \tau < t\ \textit{and}\ c_{i_0}(\tau) > 0.$$

Using the implicit solution of A_{i_0} (4), one remarks that the previous equality leads to a contradiction with Assumptions 2.1 and 3.1 (specifically $A_{0,0}(s) > 0$ and $v_{i_0}(s) > 0$ for all $s \in (0,m]$). Therefore, one deduces

$$Z_i^2(\tau) = \bar{Z}_i^2(\tau)\ \forall\ 0 \le \tau < t\ \textit{and}\ i \in \mathbb{N}_I.$$

Using (23) and (6), one gets for all $s > Z_i^2(\tau)$ and $0 < \tau < t$

$$\frac{v_i(s - Z_i^2(\tau))}{v_i(s)} = \frac{\bar{v}_i(s - Z_i^2(\tau))}{\bar{v}_i(s)}. \tag{24}$$

Using (24) and the definition of $Z_i^2(\tau)$ and $\bar{Z}_i^2(\tau)$, one obtains

$$\int_0^\tau v_i(s(r)) \left[\frac{\bar{v}_i(s(r) - Z_i^2(r))}{v_i(s(r) - Z_i^2(r))} - 1\right] dr = 0.$$

By deriving the above equation with respect to τ, one gets

$$v_i(s)\left[\frac{\bar{v}_i(s - Z_i^2(\tau))}{v_i(s - Z_i^2(\tau))} - 1\right] = 0,$$

where $s := s(\tau)$. Therefore, one concludes $v_i(s) = \bar{v}_i(s)$, $\forall\ s \in [0,m]$ and $i \in \mathbb{N}_I$. $\square$

Theorem 3.2. *Let Assumptions 2.1 and 3.1 be satisfied. The parameters $v_i(s)$, $\lambda(N(t))$ and Δ are identifiable for all $i \in \mathbb{N}_I$, $s \in [0,m]$ and $t \in (0,T]$.*

Proof. Let's fix $\theta = [(v_0, ..., v_I) \in K, \lambda, \Delta]$ and consider a second parameters $\bar{\theta} = \big[(\bar{v}_0, ..., \bar{v}_I) \in K, \bar{\lambda}, \bar{\Delta}\big]$ wherein $\forall\ t \in [0, T]$ and $s \in [0, m]$,

$$A_i(t, s; \theta) + \int_0^{\Delta} B_i(t, \tau, s; \theta) d\tau = \bar{A}_i(t, s; \bar{\theta}) + \int_0^{\bar{\Delta}} \bar{B}_i(t, \tau, s; \bar{\theta}) d\tau,\ \forall\ i \in \mathbb{N}_I\,, \quad (25)$$

where $(A_i(., .; \theta), B_i(., ., .; \theta))$ and $\big(\bar{A}_i(., .; \bar{\theta}), \bar{B}_i(., ., .; \bar{\theta})\big)$ are the solutions of System (1-3), and are related to the parameters θ and $\bar{\theta}$ respectively.

If $\bar{\Delta} \leq \Delta$, we consider

$$\bar{B}_i^*(t, \tau, s) := \begin{cases} \bar{B}_i(t, \tau, s) & if \quad \tau \in [0, \bar{\Delta}], \\ 0 & if \quad \tau \in (\bar{\Delta}, \Delta]. \end{cases}$$

Using the integral formulation of (6), one gets for all $\tau \in (0, \Delta]$

$$B_0(t, \tau, s) = \bar{B}_0^*(t, \tau, s) = 0\ \forall\ s \leq \min(Z_0^2(\tau), \bar{Z}_0^2(\tau)).$$

Replacing the previous equality in (25), one obtains for all $\tau \in (0, \Delta]$

$$A_0(t, s) = \bar{A}_0(t, s)\ \forall\ s \leq \min(Z_0^2(\tau), \bar{Z}_0^2(\tau)).$$

Using the implicit solution (4), one obtains

$$\int_0^t \big(\lambda(N(u)) - \bar{\lambda}(\bar{N}(u))\big)\, du = 0. \quad (26)$$

Deriving the previous equality with respect to t,

$$\lambda(N(t)) = \bar{\lambda}(\bar{N}(t)).$$

By integrating and summing (25) over s and i respectively, one gets

$$N(t) = \bar{N}(t). \quad (27)$$

Then, one deduces $\lambda(N(t)) = \bar{\lambda}(N(t))$ for all $t \in (0, T]$.

Using Lemma 3.1, one deduces $v_i(s) = \bar{v}_i(s)$ for all $s \in [0, m]$ and $i \in \mathbb{N}_I$. Therefore, one has

$$\int_0^{\Delta} B_0(t, \tau, s) d\tau = \int_0^{\bar{\Delta}} B_0(t, \tau, s) d\tau.$$

Since $\bar{\Delta} \leq \Delta$, then the previous equality can be written as

$$\int_{\bar{\Delta}}^{\Delta} B_0(t, \tau, s) d\tau = 0.$$

Under Assumptions 2.1 and 3.1, one has $B_0(t, \tau, s) > 0$ for all $s > Z_0^2(\tau)$, $\tau \in [\bar{\Delta}, \Delta]$ and t large enough ($t > \Delta$). Therefore, one deduces $\bar{\Delta} = \Delta$ from the previous equality. □

4. **Comparison of two versions of Smith-Martin model.** Bernard et al. [2] and Ganusov et al. [9] have formulated the Smith-Martin model in terms of PDEs. Next, several studies have been made in order to improve the prediction of this model to the experimental data. For example, Yates et al. [22] and Hogan et al. [12] have modified the Smith-Martin model by considering that the rate of entry in B-phase (λ) depends on the time evolution (t) [22] and the total cell number ($N(t)$) [12]. Their results show that the modified Smith-Martin model provides a

good description of the observed response by T cells to lymphopenia. This version of Smith-Martin is written as follows

$$(SM_1)\quad \begin{cases} \frac{dA_0}{dt} = -(\lambda(N) + \delta_A)A_0(t),\ \{A_0(0) > 0\} \\ \frac{dA_i}{dt} = 2B_{i-1}(t,\Delta) - (\lambda(N) + \delta_A)A_i(t),\ \{A_i(0) = 0\},\ i = 1, ..., I \\ \begin{cases} \frac{\partial}{\partial t}B_i(t,\tau) + \frac{\partial}{\partial \tau}B_i(t,\tau) = -\delta_B B_i(t,\tau),\ i = 0, ..., I \\ B_i(t,0) = \lambda(N)A_i(t),\ B_i(0,\tau) = 0 \end{cases} \end{cases}$$

where $(t,\tau) \in [0,T] \times [0,\Delta]$. $A_i(t)$ is the number of cells at time t having undergone i divisions in A-state. $B_i(t,\tau)$ is the number of cells at time t having undergone i divisions and having spent time τ in B-phase. The total cell number in SM_1 model is defined by

$$N = N(t) := \sum_{i=0}^{I} \left(A_i(t) + \int_0^\Delta B_i(t,\tau)d\tau \right).$$

In the general case, cells are triggered from A-state to enter the proliferative B-phase. They spend a time $\tau \in [0,\Delta]$ to divide in B-phase. Proliferative cell divides into two daughter cells only when it completes the process of mitosis (Δ is approximately the time to finish the process). More specifically, when a cell divides, it disappears from the B-phase.

In SM_1 model, the Smith-Martin model describes the dynamics of cells that we have discussed in the previous paragraph, but the mother cells are not removed from the B-phase after dividing (see the right side of the PDE in SM_1 model) that is because their age become larger than Δ. Since the age (τ) is defined between 0 and Δ, the mother cells with an age more than Δ, are not counted in the dynamic, but in fact, they stay in B-phase. This means that Δ is not really the maximum age of cells in B-phase, as it is defined in SM_1 model.

In contrast, Ayoub et al. [1] have considered another strategy of modelling for the dividing cells. They have introduced a function $\mu(\tau)$ to remove cells after dividing (see System (1-3)).

Integrating System (1-3) with respect to the variable s (CD44 expression), we derive an age-structured system as SM_1 model but with additional parameter $\mu(.)$. It reads

$$(SM_2)\quad \begin{cases} \frac{dA_0}{dt} = -(\lambda(N) + \delta_A)A_0(t),\ \{A_0(0) > 0\} \\ \frac{dA_i}{dt} = 2\int_0^\Delta \mu(\tau)B_{i-1}(t,\tau)d\tau - (\lambda + \delta_A)A_i(t),\ \{A_i(0) = 0\},\ i = 1, ..., I \\ \begin{cases} \frac{\partial}{\partial t}B_i(t,\tau) + \frac{\partial}{\partial \tau}B_i(t,\tau) = -(\delta_B + \mu(\tau))B_i(t,\tau),\ i = 0, ..., I \\ B_i(t,0) = \lambda(N)A_i(t),\ B_i(0,\tau) = 0 \end{cases} \end{cases}$$

where $A_i(t) := \int_0^m \tilde{A}_i(t,s)ds$, $B_i(t,\tau) := \int_0^m \tilde{B}_i(t,\tau,s)ds$ and $(\tilde{A}_i, \tilde{B}_i)$, $\forall\ i \in \mathbb{N}_I$ are the state variable of System (1-3).

Note that if a cell divides only when its age is close to Δ, the function μ can be approximated by a non-negative rectangular function with a mean value 1. Ayoub et al. [1] have assumed that a cell divides only when its age is close to Δ, precisely

$[\Delta - h, \Delta]$ where $0 < h << \Delta$.

$$\mu(\tau) = \begin{cases} \frac{1}{h} & \text{if } \Delta - h \leqslant \tau \leqslant \Delta, \\ 0 & \text{else,} \end{cases}$$

Recruitment of cells from A-state into the B-phase occurs at a rate λ. As the cellular population increases, the amount of resources per cell is decreasing and the recruitment rate is reduced. A smaller division rate corresponds to the smaller transfer rate λ of the model [12]. Then, the recruitment rate can be defined by

$$\lambda = \lambda(N(t)) = \lambda_0 \, e^{-\eta \, N(t)}, \tag{28}$$

where $\lambda_0 > 0$ represents the ability of each clonotype to respond to an unlimited resource, and $\eta > 0$ determines the size of the reduction caused by increasing number of competing cells (N) [12].

The purpose of this section is to estimate numerically the parameters (Δ, λ_0, η) of each model (SM_1 and SM_2). Therefore, we can evaluate the difference between SM_1 and SM_2 caused by the function $\mu(.)$ and identify which model fits better the data of Hogan et al. [12].

4.1. **Materials and methods.** Let $N^{exp}_{i,m}(t_k)$ be the data set given in [12] that represents the total cell number having undergone i divisions at time t_k in each mouse m. The parameters to estimate in SM_1 and SM_2 models are: $\vec{\theta} = (\lambda_0, \Delta, \eta)$. We used weighted sums of squared residuals ($SSRs$) for optimization with variance over observed cells with given i at given day as the measurement error function.

Criterion to compare the models. Comparison of the different models (SM_1 and SM_2) was done using a cross validation approach. The whole data set was separated into two parts each day of the experiment: a validation set with data for one given mouse, m, and a training set with the remaining data ($M - 1$) (M is the total number of mice).

Parameter values were obtained by minimizing the SSR with the training set.

$$SSR^{-m} = \sum_{i=0}^{I} \sum_{k=1}^{K} \sum_{\substack{j=1 \\ j \neq m}}^{M} \frac{\left(N_i(\vec{\theta}, t_k) - N^{exp}_{i,j}(t_k)\right)^2}{\sigma_i^2(t_k)}, \tag{29}$$

where

$$N_i(\vec{\theta}, t_k) = \Delta t \left(A_i(t_k) + \Delta\tau \sum_{s=1}^{N_\tau} B_i(t_k, \tau^s) \right)$$

are calculated from SM_1 and SM_2 models. $\sigma_i^2(t)$, Δt and $\Delta\tau$ are the variance and the mesh size of time and age respectively. The variable i stands for the number of divisions (total number $I = 8$), k is the number of sampling day (with total number $K = 5$), j is the number of mouse, M is the total number of mice in the experiment ($M = 20$).

Indeed, we use an optimization algorithm BCONF (see [21] for more details) based on the quasi-Newton method to solve (29).

At the next step, for each mouse m, the comparison reference value (CrV) criterion is calculated by using the estimated parameter values $\vec{\theta^*}$ using the validation set

$$CrV_m = \sum_{i=0}^{I}\sum_{k=1}^{K}\frac{\left(N_i(\vec{\theta},t_k) - N_{i,m}^{exp}(t_k)\right)^2}{\sigma_i^2(t_k)}.$$

The CrV_m was calculated for each experimental mouse m in the validation set. The final estimate of the cross validation was

$$CrV = \frac{1}{M}\sum_{m=1}^{M} CrV_m.$$

The lower value of CrV indicates the better model.

4.2. **Results.** In the experiment, CFSE-labeled OT-1 T cells were transferred to $Rag1^{-/-}$ recipients. Each mouse received 1.5×10^6 cells at the initial date (i.e $A_0(0) = 1.5 \times 10^6$), and the rate of cell death (δ_A or δ_B) observed was very close to zeros [12]. We therefore omitted δ_A and δ_B from SM_1 and SM_2 models. In addition, the time division (h) is supposed small ($h = 30$ mn) with respect to the age of cells in B phase (Δ is estimated in hours [12]).

Best-fit parameters (Table 1) for SM_1 and SM_2 models were determined by minimizing weighted SSR given in (29).

Model	η	Δ(hour)	λ_0 (/cell/hour)	CrV
SM_1	1.00000E-06	8.51000	3.764693E-02	109.902
SM_2	1.97568E-06	7.17858	3.768979E-02	48.0315

TABLE 1. Best-fit parameter estimations for SM_1 and SM_2 models.

Despite the constraining data sets, the parametrization in Table 1 (Δ, η and λ_0) of SM_1 model is close to those of the previous studies [12, 22]. From Fig 2, the SM_1 and SM_2 models were successful in describing lymphopenia induced proliferation (LIP) by T cell clonotype (OT-1) as apparent in the predicted division profiles. Also despite the differences between the parameterization of SM_1 and SM_2 models, specific estimates of η and λ_0 ($1.0E-06$ and $3.764693E-02$, respectively) of SM_1 were in close agreement with those of SM_2 ($1.97568E-06$ and $3.768979E-02$, respectively).

In contrast, the small difference in the parametrizations of SM_1 and SM_2 was captured with distinct values for the parameter Δ (the duration of B phase). The estimated value of Δ was higher for SM_1 (8.51 h) than SM_2 (7.17858 h). Then, the key parameter Δ is affected by taking into account the dynamic of the dividing cells. Therefore, it was important to compare SM_2 with SM_1 model. However, it was clear that LIP by OT-1 was better modeled with the SM_2 than SM_1 model, as reflected in the lower CrV for SM_2 model fit (Table 1), which is a measure of goodness of fit (low is better).

5. **Conclusion and remarks.** The present study examined a model of T cell homeostasis in vitro proposed by [1]. This model is a version of Smith-Martin model with additional structure like the CD44 expression on the surface of cells. At first, we analyse the mathematical well-posedness of the model System (1-3). Next, we interest in the theoretical identifiability of some parameters by using the data of CFSE and CD44 generated by Hogan et al. [12]. Typically, we found that

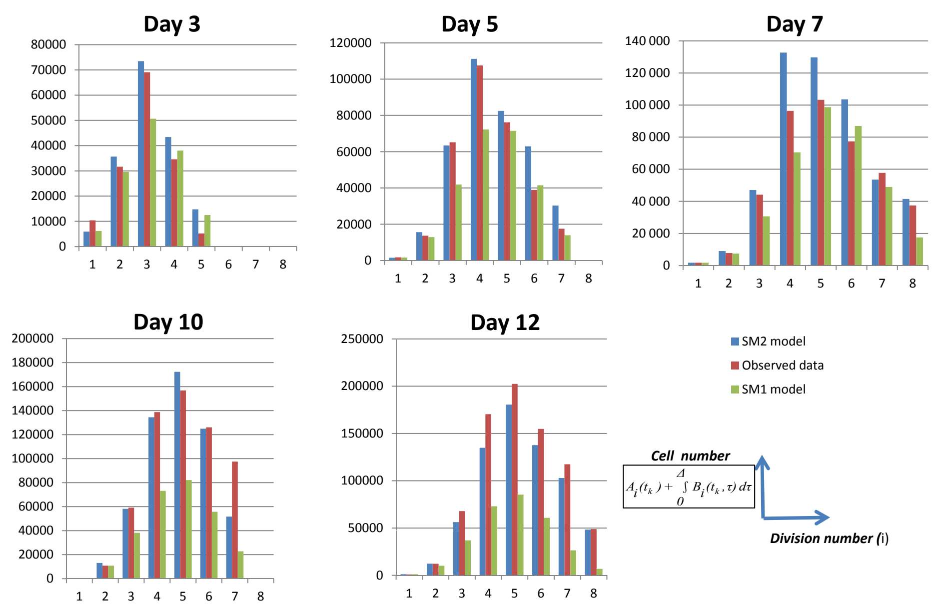

FIGURE 2. SM_2 model fits more the proliferation of OT-1 T cells than SM_1 model. Best-fit parameter estimates from SM_1 and SM_2 models (see Table 1) were used to predict the cell number in each division. At the indicated time points after transfer, data predicted by SM_1 (green) and SM_2 (blue) models were compared with experimental data for OT-1 cells (red).

the velocity of CD44 ($v_i(.)$), the duration of B-phase (Δ) and the rate of entry into division ($\lambda(N(.))$) are identifiable if Assumptions 2.1 and 3.1 are satisfied.

In the literature, the most mathematical models based on Smith-Martin model assume that the cells divide in B-phase exactly at age Δ. In contrast, System (1-3) takes into account the small variability in the time of division of the cells in B-phase, and eliminates the assumption of an immediate switch at time Δ. In this work, we interest to compare these two types of modelling by fitting SM_1 and SM_2 models to the data of OT-1 T cells. By taking into account the small variability in the time of division, we noticed that the duration of B-phase related to SM_2 model model becomes shorter than in the SM_1 model. Also, the rate of entry into division is approximately the same in these two models. Finally, we find that SM_2 model fits better the experimental data (CrV for SM2 is much less than SM1).

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