Analysis and calibration of a linear model for structured cell populations with unidirectional motion : Application to the morphogenesis of ovarian follicles

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ANALYSIS AND CALIBRATION OF A LINEAR MODEL FOR STRUCTURED CELL POPULATIONS WITH UNIDIRECTIONAL MOTION : APPLICATION TO THE MORPHOGENESIS OF OVARIAN FOLLICLES*

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Abstract. We analyze a multi-type age dependent model for cell populations subject to unidirectional motion, in both a stochastic and deterministic framework. Cells are distributed into successive layers; they may divide and move irreversibly from one layer to the next. We adapt results on the large-time convergence of PDE systems and branching processes to our context, where the Perron-Frobenius or Krein-Rutman theorem can not be applied. We derive explicit analytical formulas for the asymptotic cell number moments, and the stable age distribution. We illustrate these results numerically and we apply them to the study of the morphodynamics of ovarian follicles. We prove the structural parameter identifiability of our model in the case of age independent division rates. Using a set of experimental biological data, we estimate the model parameters to fit the changes in the cell numbers in each layer during the early stages of follicle development.

Key words. structured cell populations, multi-type age dependent branching processes, renewal equations, McKendrick-VonFoerster model, parameter calibration, structural identifiability

AMS subject classifications. 35L65, 60K15, 60J80, 92D25

1. Introduction. We study a multi-type age dependent model in both a deterministic and stochastic framework to represent the dynamics of a population of cells distributed into successive layers. The model is a two dimensional structured model: cells are described by a continuous age variable and a discrete layer index variable. Cells may divide and move irreversibly from one layer to the next. The cell division rate is age and layer dependent, and is assumed to be bounded below and above. After division, the age is reset and the daughter cells either remain within the same layer or move to the next one. In its stochastic formulation, our model is a multi-type Bellman-Harris branching process and in its deterministic formulation, it is a multi-type McKendrick-VonFoerster system.

The model enters the general class of linear models leading to Malthusian exponential growth of the population. In the PDE case, state-of-the-art-methods call to renewal equations system [6] or, to an eigenvalue problem and general relative entropy techniques [7, 9] to show the existence of an attractive stable age distribution. Yet, in our case, the unidirectional motion prevents us from applying the Krein-Rutman theorem to solve the eigenvalue problem. As a consequence, we follow a constructive approach and explicitly solve the eigenvalue problem. On the other hand, we adapt entropy methods using weak convergences in $\mathbf{L}^1$ to obtain the large-time behavior and lower bound estimates of the speed of convergence towards the stable age distribution. In the probabilistic case, classical methods rely on renewal equations [2] and martingale convergences [3]. Using the same eigenvalue problem as in the deterministic study, we derive a martingale convergence giving insight into the large-time fluctuations around the stable state. Again, due to the lack of reversibility in our model, we cannot apply the Perron-Frobenius theorem to study the asymptotic of the renewal equations. Nevertheless, we manage to derive explicitly the stationary

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solution of the renewal equations for the cell number moments in each layer as in [2]. We recover the deterministic stable age distribution as the solution of the renewal equation for the mean age distribution.

The theoretical analysis of our model highlights the role of one particular layer: the leading layer characterized by a maximal intrinsic growth rate which turns out to be the Malthus parameter of the total population. The notion of a leading layer is a tool to understand qualitatively the asymptotic cell dynamics, which appears to operate in a multi-scale regime. All the layers upstream the leading one may extinct or grow with a rate strictly inferior to the Malthus parameter, while the remaining, downstream ones are driven by the leading layer.

We then check and illustrate numerically our theoretical results. In the stochastic case, we use a standard implementation of an exact Stochastic Simulation Algorithm. In the deterministic case, we design and implement a dedicated finite volume scheme adapted to the non-conservative form and dealing with proper boundary conditions. We verify that both the deterministic and stochastic simulated distributions agree with the analytical stable age distribution. Moreover, the availability of analytical formulas helps us to study the influence of the parameters on the asymptotic proportion of cells, Malthus parameter and stable age distribution.

Finally, we consider the specific application of ovarian follicle development inspired by the model introduced in [1] and representing the proliferation of somatic cells and their organization in concentric layers around the germ cell. While the original model is formulated with a nonlinear individual-based stochastic formalism, we design a linear version based on branching processes and endowed with a straightforward deterministic counterpart. We prove the structural parameter identifiability in the case of age independent division rates. Using a set of experimental biological data, we estimate the model parameters to fit the changes in the cell numbers in each layer during the early stages of follicle development. The main interest of our approach is to benefit from the explicit formulas derived in this paper to get insight on the regime followed by the observed cell population growth.

Beyond the ovarian follicle development, linear models for structured cell populations with unidirectional motion may have several applications in life science modeling, as many processes of cellular differentiation and/or developmental biology are associated with a spatially oriented development (e.g. neurogenesis on the cortex, intestinal crypt) or commitment to a cell lineage or fate (e.g. hematopoiesis, acquisition of resistance in bacterial strains).

The paper is organized as follows. In section 2, we describe the stochastic and deterministic model formulations and enunciate the main results. In section 3, we give the main proofs accompanied by numerical illustrations. Section 4 is dedicated to the application to the development of ovarian follicles. We conclude in section 5. Technical details and classical results are provided in Supplementary materials.

2. Model description and main results.

2.1. Model description. We consider a population of cells structured by age $a \in \mathbb{R}_+$ and distributed into layers indexed from $j = 1$ to $j = J \in \mathbb{N}^*$. The cells undergo mitosis after a layer-dependent stochastic random time $\tau = \tau^j$, ruled by an age-and-layer-dependent instantaneous division rate $b = b_j(a) : \mathbb{P}[\tau^j > t] = e^{-\int_0^t b_j(a)da}$. Each cell division time is independent from the other ones. At division, the age is reset and the two daughter cells may pass to the next layer according to layer-dependent probabilities. We note $p_{2,0}^{(j)}$ the probability that both daughter cells remain

on the same layer, $p_{1,1}^{(j)}$ and $p_{0,2}^{(j)}$, the probability that a single or both daughter cell(s) move(s) from layer j to layer $j+1$, with $p_{2,0}^{(j)} + p_{1,1}^{(j)} + p_{0,2}^{(j)} = 1$. Note that the last layer is absorbing: $p_{2,0}^{(J)} = 1$. The dynamics of the model is summarized in Figure 1.

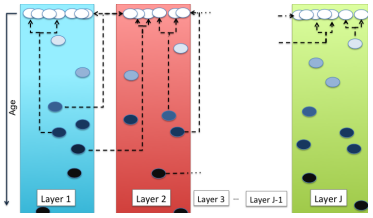


FIGURE 1. ***Model description.*** *Each cell ages until an age-dependent random division time τ^j. At division time, the age is reset and the two daughter cells may move only in an unidirectional way. When $j = J$, the daughter cells stay on the last layer.*

Stochastic model. Each cell in layer j of age a is represented by a Dirac mass $\delta_{j,a}$ where $(j,a) \in \mathcal{E} = [\![1,J]\!] \times \mathbb{R}^+$. Let $\mathcal{M}_P$ be the set of point measures on $\mathcal{E}$:

$$\mathcal{M}_P := \left\{ \sum_{k=1}^{N} \delta_{j_k,a_k}, N \in \mathbb{N}^*, \forall k \in [\![1,N]\!], (j_k,a_k) \in \mathcal{E} \right\}.$$

The cell population is represented for each time $t \geq 0$ by a measure $Z_t \in \mathcal{M}_P$:

$$Z_t = \sum_{k=1}^{N_t} \delta_{I_t^{(k)}, A_t^{(k)}}, \quad N_t := \ll Z_t, \mathbb{1} \gg = \sum_{j=1}^{J} \int_0^{+\infty} Z_t(dj, da). \tag{1}$$

N_t is the total number of cells at time t. On the probability space $(\Omega, \mathcal{F}, \mathbb{P})$, we define Q as a Poisson point measure of intensity $ds \otimes \#dk \otimes d\theta$, where ds and $d\theta$ are Lebesgue measures on $\mathbb{R}_+$ and $\#dk$ is a counting measure on $[\![1,J]\!]$. The dynamics of $Z = (Z_t)_{t\geq 0}$ is given by the following stochastic differential equation:

$$\begin{aligned}
Z_t &= \sum_{k=1}^{N_0} \delta_{I_0^{(k)}, A_0^{(k)}+t} + \int_{[0,t]\times\mathcal{E}} \mathbb{1}_{k\leq N_{s^-}} R(k,s,Z,\theta) Q(\mathrm{d}s, \mathrm{d}k, \mathrm{d}\theta) \\
&\text{where } R(k,s,Z,\theta) = (2\delta_{I_{s^-}^{(k)}, t-s} - \delta_{I_{s^-}^{(k)}, A_{s^-}^{(k)}+t-s}) \mathbb{1}_{0\leq\theta\leq m_1(s,k,Z)} \\
&+ (\delta_{I_{s^-}^{(k)}, t-s} + \delta_{I_{s^-}^{(k)}+1, t-s} - \delta_{I_{s^-}^{(k)}, A_{s^-}^{(k)}+t-s}) \mathbb{1}_{m_1(s,k,Z)\leq\theta\leq m_2(s,k,Z)} \\
&+ (2\delta_{I_{s^-}^{(k)}+1, t-s} - \delta_{I_{s^-}^{(k)}, A_{s^-}^{(k)}+t-s}) \mathbb{1}_{m_2(s,k,Z)\leq\theta\leq m_3(s,k,Z)} \\
&\text{and } m_1(s,k,Z) = b_{I_{s^-}^{(k)}}(A_{s^-}^{(k)}) p_{2,0}^{(I_{s^-}^{(k)})}, \\
&m_2(s,k,Z) = b_{I_{s^-}^{(k)}}(A_{s^-}^{(k)})(p_{2,0}^{(I_{s^-}^{(k)})} + p_{1,1}^{(I_{s^-}^{(k)})}), \quad m_3(s,k,Z) = b_{I_{s^-}^{(k)}}(A_{s^-}^{(k)}).
\end{aligned} \tag{2}$$

Deterministic model. The cell population is represented by a population density function $\rho := \left(\rho^{(j)}(t,a)\right)_{j\in[\![1,J]\!]} \in \mathbf{L}^1(\mathbb{R}_+)^J$ where $\rho^{(j)}(t,a)$ is the cell age density in layer j at time t. The population evolves according to the following system of partial differential equations:

$$\begin{cases}
\partial_t \rho^{(j)}(t,a) + \partial_a \rho^{(j)}(t,a) = -b_j(a)\rho^{(j)}(t,a) \\
\rho^{(j)}(t,0) = 2p_L^{(j-1)} \displaystyle\int_0^\infty b_{j-1}(a)\rho^{(j-1)}(t,a)da + 2p_S^{(j)} \int_0^\infty b_j(a)\rho^{(j)}(t,a)da \\
\rho(0,a) = \rho_0(a)
\end{cases} \tag{3}$$

where $\forall j \in [\![1, J-1]\!]$, $p_S^{(j)} = \frac{1}{2}p_{1,1}^{(j)} + p_{2,0}^{(j)}$, $p_L^{(j)} := \frac{1}{2}p_{1,1}^{(j)} + p_{0,2}^{(j)}$, $p_L^{(0)} = 0$ and $p_S^{(J)} = 1$. Here, $p_S^{(j)}$ is the probability that a cell taken randomly among both daughter cells, remains on the same layer and $p_L^{(j)} = 1 - p_S^{(j)}$ is the probability that the cell moves.

2.2. Hypotheses.

Hypothesis 2.1. $\forall j \in [\![1, J-1]\!]$, $p_S^{(j)}, p_L^{(j)} \in (0, 1)$

Hypothesis 2.2. For each layer j, b_j is continuous bounded below and above:

$$\forall j \in [\![1, J]\!], \quad \forall a \in \mathbb{R}_+, \quad 0 < \underline{b}_j \leq b_j(a) \leq \overline{b}_j < \infty\,.$$

DEFINITION 2.3. *$\mathcal{B}_j$ is the distribution function of τ^j ($\mathcal{B}_j(x) = 1 - e^{-\int_0^x b_j(a)da}$) and $d\mathcal{B}_j$ its density function ($d\mathcal{B}_j(x) = b_j(x)e^{-\int_0^x b_j(a)da}$).*

Hypothesis/Definition 2.4. (Intrinsic growth rate) The intrinsic growth rate λ_j of layer j is the solution of

$$d\mathcal{B}_j^*(\lambda_j) := \int_0^\infty e^{-\lambda_j s} d\mathcal{B}_j(s)ds = \frac{1}{2p_S^{(j)}}\,.$$

Remark 2.5. *$d\mathcal{B}_j^*$ is the Laplace transform of $d\mathcal{B}_j$. It is a strictly decreasing function and $]-\underline{b}_j, \infty[\subset Supp(d\mathcal{B}_j^*) \subset]-\overline{b}_j, \infty[$. Hence, $\lambda_j > -\overline{b}_j$. Moreover, note that $d\mathcal{B}_j^*(0) = \int_0^\infty d\mathcal{B}_j(x)dx = 1$. Thus, $\lambda_j < 0$ when $p_S^{(j)} < \frac{1}{2}$; $\lambda_j > 0$ when $p_S^{(j)} > \frac{1}{2}$ and $\lambda_j = 0$ when $p_S^{(j)} = \frac{1}{2}$. In particular, $\lambda_J > 0$ as $p_S^{(J)} = 1$.*

Remark 2.6. *In the classical McKendrick-VonFoerster model (one layer), the population grows exponentially with rate λ_1 ([16], Chap. IV). The same result is shown for the Bellman-Harris process in [2] (Chap. VI).*

Hypothesis/Definition 2.7 (Malthus parameter). *The Malthus parameter λ_c is defined as the unique maximal element taken among the intrinsic growth rates (λ_j, $j \in [\![1, J]\!]$) defined in (2.4). The layer such that the index $j = c$ is the leading layer.*

According to remark 2.5, λ_c is positive. We will need auxiliary hypotheses on λ_j parameters in some theorems.

Hypothesis 2.8. All the intrinsic growth rate parameters are distinct.

Hypothesis 2.9. $\forall j \in [\![1, J]\!]$, $\lambda_j > -\liminf_{a\to+\infty} b_j(a)$.

Hypothesis 2.9 implies additional regularity for $t \mapsto e^{-\lambda_j t} d\mathcal{B}_j(t)$ (see proof in SM1.1):

COROLLARY 2.10. *Under hypotheses 2.2, 2.4 and 2.9, $\forall j \in [\![1, J]\!]$, $\forall k \in \mathbb{N}$, $\int_0^\infty t^k e^{-\lambda_j t} d\mathcal{B}_j(t)dt < \infty$.*

Stochastic initial condition. We suppose that the initial measure $Z_0 \in \mathcal{M}_P$ is deterministic. $(\mathcal{F}_t)_{t\in\mathbb{R}_+}$ is the natural filtration associated with $(Z_t)_{t\in\mathbb{R}_+}$ and Q.

Deterministic initial condition. We suppose that the initial population density ρ_0 belongs to $\mathbf{L}^1(\mathbb{R}_+)^J$.

2.3. Notation.

Let $f, g \in \mathbf{L}^1(\mathbb{R}_+)^J$, we use for the scalar product:

- on $\mathbb{R}_+^J$, $f^T(a)g(a) = \sum_{j=1}^J f^{(j)}(a)g^{(j)}(a)$,
- on $\mathbf{L}^1(\mathbb{R}_+)$, $\langle f^{(j)}, g^{(j)}\rangle = \int_0^\infty f^{(j)}(a)g^{(j)}(a)da$, for $j \in [\![1, J]\!]$,
- on $\mathbf{L}^1(\mathbb{R}_+)^J$, $\ll f, g \gg = \sum_{j=1}^J \int_0^\infty f^{(j)}(a)g^{(j)}(a)da$.

For a martingale $M = (M_t)_{t\geq 0}$, we note $\langle M, M\rangle_t$ its quadratic variation. We also introduce

$$B(a) = diag(b_1(a), ..., b_J(a)), \quad [K(a)]_{i,j} = \begin{cases} 2p_S^{(j)} b_j(a), & i = j, \quad j \in [\![1, J]\!] \\ 2p_L^{(j-1)} b_{j-1}(a), & i = j-1, \quad j \in [\![2, J]\!] \end{cases}$$

We define the primal problem (P) as

$$\text{(P)} \qquad \begin{cases} \mathcal{L}^P \hat{\rho}(a) = \lambda \hat{\rho}(a),\ a \geq 0 \\ \hat{\rho}(0) = \displaystyle\int_0^\infty K(a)\hat{\rho}(a)da \quad , \quad \mathcal{L}^P \hat{\rho}(a) = \partial_a \hat{\rho}(a) - B(a)\hat{\rho}(a), \\ \ll \hat{\rho}, \mathbb{1} \gg = 1 \text{ and } \hat{\rho} \geq 0 \end{cases}$$

and the dual problem (D) is given by

$$\text{(D)} \qquad \begin{cases} \mathcal{L}^D \phi(a) = \lambda \phi(a),\ a \in \mathbb{R}_+^* \\ \ll \hat{\rho}, \phi \gg = 1 \text{ and } \phi \geq 0 \end{cases} \quad , \quad \mathcal{L}^D \phi(a) = \partial_a \phi(a) - B(a)\phi + K(a)^T \phi(0).$$

2.4. Main results.

2.4.1. Eigenproblem approach.

THEOREM 2.11 (Eigenproblem). *Under hypotheses 2.1, 2.2, 2.4, 2.7 and 2.9, there exists a first eigenelement triple $(\lambda, \hat{\rho}, \phi)$ solution to equations (P) and (D) where $\hat{\rho} \in \mathbf{L}^1(\mathbb{R}_+)^J$ and $\phi \in \mathcal{C}_b(\mathbb{R}_+)^J$. In particular, λ is the Malthus parameter λ_c given in Definition 2.7, and $\hat{\rho}$ and ϕ are unique.*

Beside the dual test function ϕ, we introduce other test functions to prove large-time convergence. Let $\hat{\phi}^{(j)}$, $j \in [\![1, J]\!]$ be a solution of

$$\partial_a \hat{\phi}^{(j)}(a) - (\lambda_j + b_j(a))\hat{\phi}^{(j)}(a) = -2p_S^{(j)} b_j(a)\hat{\phi}^{(j)}(0), \quad \hat{\phi}^{(j)}(0) \in \mathbb{R}_+^* \,. \tag{4}$$

THEOREM 2.12. *Under hypotheses 2.1, 2.2, 2.4, 2.7 and 2.9, there exist polynomials $(\beta_k^{(j)})_{1\leq k\leq j\leq J}$ of degree at most $j-k$ such that*

$$\left\langle \left| e^{-\lambda_c t}\rho^{(j)}(t,\cdot) - \eta\hat{\rho}^{(j)} \right|, \hat{\phi}^{(j)} \right\rangle \quad \leq \quad \sum_{k=1}^{j} e^{-\mu_j t}\beta_k^{(j)}(t) \left\langle \left| \rho_0^{(k)} - \eta\hat{\rho}^{(k)} \right|, \hat{\phi}^{(k)} \right\rangle, \tag{5}$$

where $\eta := \ll \rho_0, \phi \gg$, $\mu_j := \lambda_c - \lambda_j > 0$ when $j \in [\![1, J]\!] \setminus \{c\}$ and $\mu_c := \underline{b}_c$. In particular, there exist a polynomial β of degree at most $J-1$ and constant μ such that

$$\ll \left| e^{-\lambda_c t}\rho(t,\cdot) - \eta\hat{\rho} \right|, \hat{\phi} \gg \leq\ \beta(t)e^{-\mu t} \ll \left| \rho_0 - \eta\hat{\rho} \right|, \hat{\phi} \gg \,.$$

Using martingale techniques [3], we also prove a result of convergence for the stochastic process Z with the dual test function ϕ.

THEOREM 2.13. *Under hypotheses 2.1, 2.2, 2.4 and 2.7, $W_t^\phi = e^{-\lambda_c t} \ll \phi, Z_t \gg$ is a square integrable martingale that converges almost surely and in $\mathbf{L}^2$ to a non-degenerate random variable W_∞^ϕ.*

2.4.2. Renewal equation approach. Using generating function methods developed for multi-type age dependent branching processes (see [2], Chap. VI), we write a system of renewal equations and obtain analytical formulas for the two first moments. We define $Y_t^{(j,a)} := \langle Z_t, \mathbb{1}_{j,\leq a}\rangle$ as the number of cells on layer j and of age

less or equal than a at time t, and $m_i^a(t)$ its mean starting from one mother cell of age 0 on layer 1:

$$m_j^a(t) := \mathbb{E}[Y_t^{(j,a)} | Z_0 = \delta_{1,0}]\,. \tag{6}$$

THEOREM 2.14. *Under hypotheses 2.1, 2.2, 2.7, 2.8 and 2.9, for all $a \geq 0$,*

$$\forall j \in [\![1, J]\!], \quad m_j^a(t) e^{-\lambda_c t} \to \widetilde{m}_j(a), \quad t \to \infty, \tag{7}$$

where $\widetilde{m}_j(a) =$

$$\begin{cases} 0, & j \in [\![1, c-1]\!], \\ \dfrac{\int_0^a \hat{\rho}^{(c)}(s)ds}{2p_S^{(c)}\hat{\rho}^{(c)}(0)\int_0^\infty s d\mathcal{B}_c(s)e^{-\lambda_c s}ds}, & j = c, \\ \dfrac{\int_0^a \hat{\rho}^{(j)}(s)ds}{2p_S^{(c)}\hat{\rho}^{(c)}(0)\int_0^\infty s d\mathcal{B}_c(s)e^{-\lambda_c s}ds} \displaystyle\prod_{k=1}^{c-1} \frac{2p_L^{(k)} d\mathcal{B}_k^*(\lambda_c)}{1 - 2p_S^{(k)} d\mathcal{B}_k^*(\lambda_c)}, & j \in [\![c+1, J]\!]. \end{cases}$$

2.4.3. Calibration. We now consider a particular choice of the division rate:

Hypothesis 2.15 (Age-independent division rate). $\forall\,(j,a) \in \mathcal{E}$, $b_j(a) = b_j$.

We also consider a specific initial condition with $N \in \mathbb{N}^*$ cells:

Hypothesis 2.16 (First layer initial condition). $Z_0 = N\delta_{1,0}$.

Then, integrating the deterministic PDE system (3) with respect to age or differentiating the renewal equation system (see (39)) on the mean number M, we obtain:

$$\begin{cases} \frac{d}{dt}M(t) = AM(t) \\ M(0) = (N, 0, ..., 0) \in \mathbb{R}^J \end{cases}, \quad [A]_{i,j} := \begin{cases} (2p_S^{(j)} - 1)b_j, & i = j, \quad j \in [\![1, J]\!], \\ 2p_L^{(j-1)} b_{j-1}, & i = j-1, \quad j \in [\![2, J]\!]. \end{cases} \tag{8}$$

We prove the structural identifiability of the parameter set $\mathbf{P} := \{N, b_j, p_S^{(j)}, j \in [\![1, J]\!]\}$ when we observe the vector $M(t; \mathbf{P})$ at each time t.

THEOREM 2.17. *Under hypotheses 2.1, 2.15 and 2.16 and complete observation of system (8), the parameter set $\mathbf{P}$ is identifiable.*

We then perform the estimation of the parameter set $\mathbf{P}$ from experimental cell number data retrieved on four layers and sampled at three different time points (see Table 1a). To improve practical identifiability, we embed biological specifications used in [1] as a recurrence relation between successive division rates:

$$b_j = \frac{b_1}{1 + (j-1) \times \alpha}, \; j \in [\![1, 4]\!], \; \alpha \in \mathbb{R}. \tag{9}$$

We estimate the parameter set $\mathbf{P}_{exp} = \{N, b_1, \alpha, p_S^{(1)}, p_S^{(2)}, p_S^{(3)}\}$ using the D2D software [12] with an additive Gaussian noise model (see Figure 2 and Table 1b). An analysis of the profile likelihood estimate shows that all parameters except $p_S^{(2)}$ are practically identifiable (see Figure SM1b).

3. Theoretical proof and illustrations.

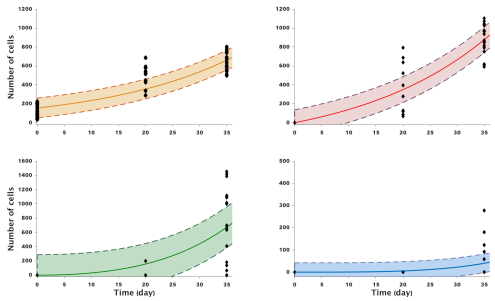


FIGURE 2. ***Data fitting with model (8).*** *Each panel illustrates the changes in the cell number in a given layer (top-left: Layer 1, top-right: Layer 2, bottom-left: Layer 3, bottom-right: Layer 4). The black diamonds represent the experimental data, the solid lines are the best fit solutions of (8) and the dashed lines are drawn from the estimated variance. The parameter values (Table 1b) are estimated according to the procedure described in section SM2.2.*

3.1. Eigenproblem. We start by solving explicitly the eigenproblem (P)-(D) to prove theorem 2.11.

Proof of theorem 2.11. According to definition 2.3, any solution of (P) in $\mathbf{L}^1(\mathbb{R}_+)^J$ is given by, $\forall j \in [\![1, J]\!]$,

$$\hat{\rho}^{(j)}(a) = \hat{\rho}^{(j)}(0) e^{-\lambda a} (\mathbb{1} - \mathcal{B}_j)(a)\,. \tag{10}$$

The boundary condition of the problem (P) gives us a system of equations for λ and $\hat{\rho}^{(j)}(0)$, $j \in [\![1, J]\!]$:

$$\hat{\rho}^{(j)}(0) \times (1 - 2p_S^{(j)} d\mathcal{B}_j^*(\lambda)) = 2p_L^{(j-1)} d\mathcal{B}_{j-1}^*(\lambda) \times \hat{\rho}^{(j-1)}(0)\,. \tag{11}$$

This system is equivalent to

$$C(\lambda)\hat{\rho}(0) = 0, \quad [C(\lambda)]_{i,j} = \begin{cases} 1 - 2p_S^{(j)} d\mathcal{B}_j^*(\lambda), & i = j, \quad j \in [\![1, J]\!], \\ 2p_L^{(j-1)} d\mathcal{B}_{j-1}^*(\lambda), & i = j-1, \quad j \in [\![2, J]\!]. \end{cases}$$

Let $\Lambda := \{\lambda_j, j \in [\![1, J]\!]\}$. The eigenvalues of the matrix $C(\lambda)$ are $1 - 2p_S^{(j)} d\mathcal{B}_j^*(\lambda)$, $j \in [\![1, J]\!]$. Thus, if $\lambda \notin \Lambda$, according to hypothesis 2.4, 0 is not an eigenvalue of $C(\lambda)$ which implies that $\hat{\rho}(0) = 0$. As $\hat{\rho}$ satisfies both (10) and the normalization $\ll \hat{\rho}, \mathbb{1} \gg = 1$, we obtain a contradiction. So, necessary $\lambda \in \Lambda$.
We choose $\lambda = \lambda_c$ the maximum element of Λ according to hypothesis 2.7. Then, using (11) when $j = c$, we have:

$$\hat{\rho}^{(c)}(0) \times (1 - 2p_S^{(c)} d\mathcal{B}_c^*(\lambda_c)) = 2p_L^{(c-1)} d\mathcal{B}_{c-1}^*(\lambda_c) \times \hat{\rho}^{(c-1)}(0)\,.$$

Note that $1 - 2p_S^{(c)} d\mathcal{B}_c^*(\lambda_c) = 0$, so $\hat{\rho}^{(c-1)}(0) = 0$ and by backward recurrence using (11) from $j = c - 1$ to 1, it comes that $\hat{\rho}^{(j)}(0) = 0$ when $j < c$. By hypothesis 2.7, $\max(\Lambda)$ is unique. Thus, when $j > c$, $\lambda_j \neq \lambda_c$ and $1 - 2p_S^{(j)} d\mathcal{B}_j^*(\lambda_c) \neq 0$. Solving (11) from $j = c + 1$ to J, we obtain:

$$\hat{\rho}^{(j)}(0) = \hat{\rho}^{(c)}(0) \times \prod_{k=c+1}^{j} \frac{2p_L^{(k-1)} d\mathcal{B}_{k-1}^*(\lambda_c)}{1 - 2p_S^{(k)} d\mathcal{B}_k^*(\lambda_c)}, \quad \forall j \in [\![c+1, J]\!]\,.$$

We deduce $\hat{\rho}^{(c)}(0)$ from the normalization $\ll \hat{\rho}, \mathbb{1} \gg = 1$. Hence, $\hat{\rho}$ is uniquely determined by (10) together with the following boundary value:

$$\hat{\rho}^{(j)}(0) = \begin{cases} 0, & j \in [\![1, c-1]\!], \\ \dfrac{1}{\sum_{j=c}^{J} \int_0^\infty \hat{\rho}^{(j)}(a)da \prod_{k=c+1}^{j} \frac{2p_L^{(k-1)} d\mathcal{B}^*_{k-1}(\lambda_c)}{1-2p_S^{(k)} d\mathcal{B}^*_k(\lambda_c)}}, & j = c, \\ \hat{\rho}^{(c)}(0) \prod_{k=c+1}^{j} \frac{2p_L^{(k-1)} d\mathcal{B}^*_{k-1}(\lambda_c)}{1-2p_S^{(k)} d\mathcal{B}^*_k(\lambda_c)}, & j \in [\![c+1, J]\!]. \end{cases} \tag{12}$$

For the ODE system (D), any solution is given by, for $j \in [\![1, J]\!]$,

$$\phi^{(j)}(a) = \left[\phi^{(j)}(0) - 2\big(\phi^{(j)}(0)p_S^{(j)} + \phi^{(j+1)}(0)p_L^{(j)}\big) \int_0^a e^{-\lambda_c s} d\mathcal{B}_j(s)ds\right] e^{\int_0^a \lambda_c + b_j(s)ds}.$$

As $\int_0^a b_j(s)e^{-\int_0^s \lambda_c + b_j(u)du}ds$ is equal to $d\mathcal{B}_j^*(\lambda_c) - \int_a^\infty b_j(s)e^{-\int_0^s \lambda_c + b_j(u)du}ds$, we get

$$\begin{aligned} \phi^{(j)}(a) = \Bigg[&\phi^{(j)}(0)\left(1 - 2p_S^{(j)} d\mathcal{B}_j^*(\lambda_c) + 2p_S^{(j)} \int_a^{+\infty} b_j(s)e^{-\int_0^s \lambda_c + b_j(u)du}ds\right) \\ &-\phi^{(j+1)}(0)\left(2p_L^{(j)} d\mathcal{B}_j^*(\lambda_c) - 2p_L^{(j)} \int_a^{+\infty} b_j(s)e^{-\int_0^s \lambda_c + b_j(u)du}ds\right)\Bigg] e^{\int_0^a \lambda_c + b_j(s)ds}. \end{aligned}$$

Searching for $\phi \in \mathcal{C}_b(\mathbb{R}_+)^J$, it comes that

$$\forall j \in [\![1, J]\!], \quad \phi^{(j)}(0)\left(1 - 2p_S^{(j)} d\mathcal{B}_j^*(\lambda_c)\right) - \phi^{(j+1)}(0) 2p_L^{(j)} d\mathcal{B}_j^*(\lambda_c) = 0. \tag{13}$$

According to definition 2.4, when $j = c$ in (13) we get $\phi^{(c+1)}(0) = 0$. Recursively, $\phi^{(j)}(0) = 0$ when $j > c$. Solving (13) from $j = 1$ to $c-1$, we get

$$\forall j \in [\![1, c-1]\!], \quad \phi^{(j)}(0) = \phi^{(c)}(0) \times \prod_{k=j}^{c-1} \frac{2p_L^{(k-1)} d\mathcal{B}^*_{k-1}(\lambda_c)}{1 - 2p_S^{(k)} d\mathcal{B}^*_k(\lambda_c)}. \tag{14}$$

Again, we deduce $\phi^{(c)}(0)$ from the normalization $1 = \ll \hat{\rho}, \phi \gg = \langle \hat{\rho}^{(c)}, \phi^{(c)} \rangle$. Using corollary 2.10, we apply Fubini theorem:

$$\phi^{(c)}(0) = \frac{1}{2\hat{\rho}^{(c)}(0)p_S^{(c)} \int_0^\infty \big(\int_a^{+\infty} e^{-\lambda_c s} d\mathcal{B}_c(s)ds\big)da} = \frac{1}{2\hat{\rho}^{(c)}(0)p_S^{(c)} \int_0^\infty s e^{-\lambda_c s} d\mathcal{B}_c(s)ds}. \tag{15}$$

Hence, the dual function ϕ is uniquely determined by

$$\phi^{(j)}(a) = 2\left[p_S^{(j)}\phi^{(j)}(0) + p_L^{(j)}\phi^{(j+1)}(0)\right] \int_a^{+\infty} b_j(s)e^{-\int_a^s \lambda_c + b_j(u)du}ds. \tag{16}$$

together with the boundary value (14) and (15) (ϕ is null on the layers upstream the leading layer). ∎

From theorem 2.11, we deduce the following bounds on ϕ (see proof in SM1.1).

COROLLARY 3.1. *According to hypotheses 2.2, 2.4 and 2.7,*

$$\forall j \in [\![1, J]\!], \quad \frac{\underline{b}_j}{\lambda_c + \bar{b}_j} \leq \frac{\phi^{(j)}(a)}{2[p_S^{(j)}\phi^{(j)}(0) + p_L^{(j)}\phi^{(j+1)}(0)]} \leq 1. \tag{17}$$

To conclude this section, we also solve the additional dual problem on isolated layers which is needed to obtain the large-time convergence (see proof in SM1.1).

LEMMA 3.2. *According to hypotheses 2.2, 2.4 and 2.9, any solution $\hat{\phi}$ of (4) satisfies*

$$\forall j \in [\![1, J]\!], \quad \hat{\phi}^{(j)}(a) = 2p_S^{(j)}\hat{\phi}^{(j)}(0)\int_a^{+\infty} b_j(s)e^{-\lambda_j s - \int_a^s b_j(u)du}ds \tag{18}$$

and, $\forall a \in \mathbb{R}_+ \cup \{+\infty\}$, $\frac{\underline{b}_j}{\lambda_j + \overline{b}_j} \leq \frac{\hat{\phi}^{(j)}(a)}{2p_S^{(j)}\hat{\phi}^{(j)}(0)} < +\infty$.

In all the sequel, we fix

$$\hat{\phi}^{(c)}(0) = \phi^{(c)}(0), \quad \forall j \in [\![1, c-1]\!] \quad \hat{\phi}^{(j)}(0) = \phi^{(j)}(0) + \frac{p_L^{(j)}}{p_S^{(j)}}\phi^{(j+1)}(0). \tag{19}$$

A first consequence is that $\hat{\phi}^{(c)} = \phi^{(c)}$ and moreover, from corollary 3.1 and lemma 3.2, we have

$$\phi^{(j)}(a) \leq \frac{\lambda_j + \overline{b}_j}{\underline{b}_j}\hat{\phi}^{(j)}(a)\,. \tag{20}$$

3.2. Asymptotic study for the deterministic formalism. Adapting the method of characteristic, it is classical to construct the unique solution in $\mathcal{C}^1\big(\mathbb{R}_+, \mathbf{L}^1(\mathbb{R}_+)^J\big)$ of (3) ([16], Chap. I). Let ρ the solution of (3), $\hat{\rho}$ and ϕ given by theorem 2.11 and $\eta = \ll \rho_0, \phi \gg$. We define h as

$$h(t,a) = e^{-\lambda_c t}\rho(t,a) - \eta\hat{\rho}(a), \quad (t,a) \in \mathbb{R}_+ \times \mathbb{R}_+\,. \tag{21}$$

Following [7], we first show a conservation principle (see proof in SM1.1).

LEMMA 3.3 (Conservation principle). *The function h satisfies the conservation principle*

$$\ll h(t,\cdot), \phi \gg = 0\,.$$

Secondly, we prove that h is solution of the following PDE system (see proof in SM1.1).

LEMMA 3.4. *h is solution of*

$$\begin{cases} \partial_t\big|h(t,a)\big| + \partial_a\big|h(t,a)\big| + (\lambda_c + B(a))\,\big|h(t,a)\big| = 0, \\ \big|h(t,0)\big| = \big|\int_0^{+\infty} K(a)h(t,a)da\big|. \end{cases} \tag{22}$$

Together with the above lemmas 3.2, 3.3 and 3.4, we now prove the following key estimates required for the asymptotic behavior.

LEMMA 3.5. *$\forall j \in [\![1, J]\!]$, the component $h^{(j)}$ of h verifies the inequality*

$$\partial_t\left\langle\big|h^{(j)}(t,\cdot)\big|, \hat{\phi}^{(j)}\right\rangle \leq \alpha_{j-1}\left\langle|h^{(j-1)}(t,\cdot)|, \hat{\phi}^{(j-1)}\right\rangle - \mu_j\left\langle\big|h^{(j)}(t,\cdot)\big|, \hat{\phi}^{(j)}\right\rangle + r_j(t)\,, \tag{23}$$

where $\alpha_0 := 0$, for $j \in [\![1, J]\!]$, $\alpha_j := \frac{p_L^{(j)}}{p_S^{(j)}}\frac{\overline{b}_j}{\underline{b}_j}\frac{\hat{\phi}^{(j+1)}(0)}{\hat{\phi}^{(j)}(0)}(\lambda_j + \overline{b}_j)$ and

$$\mu_j = \begin{cases} \lambda_c - \lambda_j, & j \neq c \\ \underline{b}_c, & j = c \end{cases}, \; r_j(t) := \begin{cases} 0, & j \neq c \\ \displaystyle\sum_{j=1}^{c-1}\frac{\lambda_j + \overline{b}_j}{\underline{b}_j}\left\langle\big|h^{(j)}(t,\cdot)\big|, \hat{\phi}^{(j)}\right\rangle, & j = c\,. \end{cases}$$

Proof of lemma 3.5. Remind that $p_L^{(0)} = 0$ so that all the following computations are consistent with $j = 1$. Multiplying (22) by $\hat{\phi}$ and using (4), it comes for any j

$$\begin{cases} \partial_t |h^{(j)}(t,a)|\hat{\phi}^{(j)}(a) + \partial_a |h^{(j)}(t,a)|\hat{\phi}^{(j)}(a) = -2p_S^{(j)}\hat{\phi}^{(j)}(0) b_j(a) |h^{(j)}(t,a)| + [\lambda_j - \lambda_c]|h^{(j)}(t,a)|\hat{\phi}^{(j)}(a), \\ |h^{(j)}(t,0)|\hat{\phi}^{(j)}(0) = \hat{\phi}^{(j)}(0)|2p_S^{(j)} \langle b_j, h^{(j)}(t,\cdot)\rangle + 2p_L^{(j-1)} \langle b_{j-1}, h^{(j-1)}(t,\cdot)\rangle|. \end{cases} \tag{24}$$

As $\rho(t,\cdot)$ and $\hat{\rho}$ belong to $\mathbf{L}^1(\mathbb{R}_+)^J$ and $\hat{\phi}$ is a bounded function (from lemma 3.2) we deduce that $\ll h(t,\cdot), \hat{\phi} \gg < \infty$. Integrating (24) with respect to age, we have

$$\begin{aligned} \partial_t \left\langle |h^{(j)}(t,\cdot)|, \hat{\phi}^{(j)} \right\rangle &= \hat{\phi}^{(j)}(0) \left[|h^{(j)}(t,0)| - 2p_S^{(j)} \left\langle |h^{(j)}(t,\cdot)|, b_j \right\rangle \right] \\ &\quad + (\lambda_j - \lambda_c) \left\langle |h^{(j)}(t,\cdot)|, \hat{\phi}^{(j)} \right\rangle . \end{aligned} \tag{25}$$

We deal with the first term in the right hand-side of (25). When $j \neq c$, using first the boundary value in (24), a triangular inequality and lemma 3.2, we get

$$\begin{aligned} \hat{\phi}^{(j)}(0) \left(|h^{(j)}(t,0)| - 2p_S^{(j)} \left\langle |h^{(j)}(t,\cdot)|, b_j \right\rangle \right) &\leq 2p_L^{(j-1)} \hat{\phi}^{(j)}(0) \left\langle |h^{(j-1)}(t,\cdot)|, b_{j-1} \right\rangle \\ &\leq \alpha_{j-1} \left\langle |h^{(j-1)}(t,\cdot)|, \hat{\phi}^{(j-1)} \right\rangle . \end{aligned}$$

Thus, for $j \neq c$,

$$\partial_t \left\langle |h^{(j)}(t,\cdot)|, \hat{\phi}^{(j)} \right\rangle \leq \alpha_{j-1} \left\langle |h^{(j-1)}(t,\cdot)|, \hat{\phi}^{(j-1)} \right\rangle - \mu_j \left\langle |h^{(j)}(t,\cdot)|, \hat{\phi}^{(j)} \right\rangle .$$

When $j = c$, using the boundary value in (24) and a triangular inequality, we get

$$\begin{aligned} \partial_t \left\langle |h^{(c)}(t,\cdot)|, \hat{\phi}^{(c)} \right\rangle &\leq 2p_S^{(c)} \hat{\phi}^{(c)}(0) \left[\left| \left\langle h^{(c)}(t,\cdot), b_c \right\rangle \right| - \left\langle |h^{(c)}(t,\cdot)|, b_c \right\rangle \right] \\ &\quad + 2p_L^{(c-1)} \hat{\phi}^{(c)}(0) \left| \left\langle h^{(c-1)}(t,\cdot), b_{c-1} \right\rangle \right| . \end{aligned} \tag{26}$$

To exhibit a term $\left\langle |h^{(c)}(t,\cdot)|, \hat{\phi}^{(c)} \right\rangle$ in the right hand-side of (26), we need a more refined analysis. According to the conservation principle (lemma 3.3), for any constant γ (to be chosen later), we obtain

$$\begin{aligned} 2p_S^{(c)} \hat{\phi}^{(c)}(0) \left| \left\langle h^{(c)}(t,\cdot), b_c \right\rangle \right| &= \left| 2p_S^{(c)} \hat{\phi}^{(c)}(0) \left\langle h^{(c)}(t,\cdot), b_c \right\rangle - \gamma \ll h(t,\cdot), \phi \gg \right| \\ &\leq \left| \left\langle h^{(c)}(t,\cdot), 2p_S^{(c)} \hat{\phi}^{(c)}(0) b_c - \gamma \phi^{(c)} \right\rangle \right| + \gamma \textstyle\sum_{j=1}^{c-1} \left\langle |h^{(j)}(t,\cdot)|, \phi^{(j)} \right\rangle . \end{aligned} \tag{27}$$

where we used a triangular inequality in the latter estimate. Moreover, according to (20), we have

$$\forall j \in [\![1, c-1]\!], \quad \left\langle |h^{(j)}(t,\cdot)|, \phi^{(j)} \right\rangle \leq \frac{\lambda_j + \bar{b}_j}{\underline{b}_j} \left\langle |h^{(j)}(t,\cdot)|, \hat{\phi}^{(j)} \right\rangle , \tag{28}$$

and according to corollary 3.1,

$$\phi^{(c)}(a) \leq \frac{2p_S^{(c)} \phi^{(c)}(0)}{\underline{b}_c} b_c(a). \tag{29}$$

We want to find at least one constant γ such that for all $a \geq 0$, $2p_S^{(c)} \hat{\phi}^{(c)}(0) b_c(a) - \gamma \phi^{(c)}(a) > 0$. From (29), we choose $\gamma = \underline{b}_c$, and deduce from (27) and (28)

$$\begin{aligned} 2p_S^{(c)} \hat{\phi}^{c}(0) \left| \left\langle h^{(c)}(t,\cdot), b_c \right\rangle \right| \leq & \; 2p_S^{(c)} \hat{\phi}^{(c)}(0) \left\langle |h^{(c)}(t,\cdot)|, b_c \right\rangle - \underline{b}_c \left\langle |h^{(c)}(t,\cdot)|, \phi^{(c)} \right\rangle \\ & + \; \underline{b}_c \textstyle\sum_{j=1}^{c-1} \frac{\lambda_j + \bar{b}_j}{\underline{b}_j} \left\langle |h^{(j)}(t,\cdot)|, \hat{\phi}^{(j)} \right\rangle . \end{aligned} \tag{30}$$

As before, using lemma 3.2, we obtain

$$2p_L^{(c-1)}\hat{\phi}^{(c)}(0)\left|\left\langle h^{(c-1)}(t,\cdot),b_{c-1}\right\rangle\right| \leq \alpha_{c-1}\left\langle\left|h^{(c-1)}(t,\cdot)\right|,\hat{\phi}^{(c-1)}\right\rangle .$$

Combining the latter inequality with (30) and (26), we deduce (23) for $j=c$. ∎

We now have all the elements to prove theorem 2.12.

Proof of theorem 2.12. We proceed by recurrence from the index $j=1$ to J. For $j=1$, we can apply Gronwall lemma in inequality (23) to get

$$\left\langle\left|h^{(1)}(t,\cdot)\right|,\hat{\phi}^{(1)}\right\rangle \leq e^{-\mu_1 t}\left\langle\left|h^{(1)}(0,\cdot)\right|,\hat{\phi}^{(1)}\right\rangle .$$

We suppose that for a fixed $2\leq j\leq J$ and for all ranks $1\leq i\leq j-1$, there exist polynomials $\beta_k^{(i)}$, $k\in[\![1,i]\!]$, of degree at most $i-k$ such that

$$\left\langle\left|h^{(i)}(t,\cdot)\right|,\hat{\phi}^{(i)}\right\rangle \quad\leq\quad \sum_{k=1}^{i}\beta_k^{(i)}(t)e^{-\mu_k t}\left\langle\left|h^{(k)}(0,\cdot)\right|,\hat{\phi}^{(k)}\right\rangle . \tag{31}$$

Applying this recurrence hypothesis in inequality (23) for j, there exist polynomials $\widetilde{\beta}_k^{(j)}(t)$ for $k\in[\![1,j-1]\!]$ (same degree than $\beta_k^{(j-1)}(t)$):

$$\partial_t\left\langle\left|h^{(j)}(t,\cdot)\right|,\hat{\phi}^{(j)}\right\rangle \leq \sum_{k=1}^{j-1}\widetilde{\beta}_k^{(j)}(t)e^{-\mu_k t}\left\langle\left|h^{(k)}(0,\cdot)\right|,\hat{\phi}^{(k)}\right\rangle - \mu_j\left\langle\left|h^{(j)}(t,\cdot)\right|,\hat{\phi}^{(j)}\right\rangle .$$

We get from a modified version of Gronwall lemma (see lemma SM1.1):

$$\left\langle\left|h^{(j)}(t,\cdot)\right|,\hat{\phi}^{(j)}\right\rangle \leq \sum_{k=1}^{j}\beta_k^{(j)}(t)e^{-\mu_k t}\left\langle\left|h^{(k)}(0,\cdot)\right|,\hat{\phi}^{(k)}\right\rangle .$$

where $\beta_j^{(j)}$ is a constant and for $k\in[\![1,j-1]\!]$, $\beta_k^{(j)}$ is a polynomial of degree at most $(j-1-k)+1=j-k$ (the degree only increases by 1 when $\mu_k=\mu_j$). This achieves the recurrence. ∎

3.3. Asymptotic study of the martingale problem. The existence and uniqueness of the SDE (2) is proved in a more general context than ours in [15]. Following the approach proposed in [15], we first derive the generator of the process Z solution of (2). In this part, we consider $F\in\mathcal{C}^1(\mathbb{R}_+,\mathbb{R}_+)$ and $f\in\mathcal{C}_b^1(\mathcal{E},\mathbb{R}_+)$.

THEOREM 3.6 (Infinitesimal generator of (Z_t)). *Under hypotheses 2.1 and 2.2, the process Z defined in (2) and starting from Z_0 is a Markovian process in the Skhorod space $\mathbb{D}([0,T],\mathcal{M}_P([\![1,J]\!]\times\mathbb{R}_+))$. Let $T>0$, Z satisfies*

$$\mathbb{E}\big[\sup_{t\leq T}N_t\big]<\infty,\quad \mathbb{E}\big[\sup_{t\leq T}\ll a,Z_t\gg\big]<\infty, \tag{32}$$

and its infinitesimal generator is

$$\begin{aligned}\mathcal{G}F[\ll f, Z\gg] =& \ll F'[\ll Z, f\gg]\partial_a f, Z\gg \\ &+\sum_{j=1}^{J}\int_0^\infty (F[\ll f, 2\delta_{j,0}-\delta_{j,a}+Z\gg]-F[\ll f, Z\gg])p_{2,0}^{(j)}b_j(a)Z(dj,da) \\ &+\sum_{j=1}^{J}\int_0^\infty (F[\ll f, \delta_{j,0}+\delta_{j+1,0}-\delta_{j,a}+Z\gg]-F[\ll f, Z\gg])p_{1,1}^{(j)}b_j(a)Z(dj,da) \\ &+\sum_{j=1}^{J}\int_0^\infty (F[\ll f, 2\delta_{j+1,0}-\delta_{j,a}+Z\gg]-F[\ll f, Z\gg])p_{0,2}^{(j)}b_j(a)Z(dj,da)\,.\end{aligned}$$

From this theorem, we derive the following Dynkin formula :

LEMMA 3.7 (Dynkin formula). *Let $T>0$. Under hypotheses 2.1 and 2.2, $\forall t\in[0,T]$,*

$$F[\ll f, Z_t\gg] = F[\ll f, Z_0\gg] + \int_0^t \mathcal{G}F[\ll f, Z_s\gg]ds + M_t^{F,f}$$

where $M^{F,f}$ is a martingale. Moreover,

$$\ll f, Z_t\gg = \ll f, Z_0\gg + \int_0^t \ll \mathcal{L}^D f, Z_s\gg ds + M_t^f \tag{33}$$

where $\mathcal{L}^D$ the dual operator in (D) and M^f is a $\mathbf{L}^2-$martingale defined by

$$\begin{aligned}M_t^f =& \int_0^t \ll B(\cdot)f(\cdot) - K(\cdot)^T f(0), Z_s\gg ds \\ &+\int\int_{[0,t]\times\mathcal{E}} \mathbb{1}_{k\le N_{s^-}} \ll f, 2\delta_{I_{s^-}^{(k)},0}-\delta_{I_{s^-}^{(k)},A_{s^-}^{(k)}}\gg \mathbb{1}_{0\le\theta\le m_1(s,k,Z)}Q(ds,dk,d\theta) \\ &+\int\int_{[0,t]\times\mathcal{E}} \mathbb{1}_{k\le N_{s^-}} \ll f, \delta_{I_{s^-}^{(k)},0}+\delta_{I_{s^-}^{(k)}+1,0}-\delta_{I_{s^-}^{(k)},A_{s^-}^{(k)}}\gg \mathbb{1}_{m_1(s,k,Z)\le\theta\le m_2(s,k,Z)}Q(ds,dk,d\theta) \\ &+\int\int_{[0,t]\times\mathcal{E}} \mathbb{1}_{k\le N_{s^-}} \ll f, 2\delta_{I_{s^-}^{(k)}+1,0}-\delta_{I_{s^-}^{(k)},A_{s^-}^{(k)}}\gg \mathbb{1}_{m_2(s,k,Z)\le\theta\le m_3(s,k,Z)}Q(ds,dk,d\theta)\end{aligned} \tag{34}$$

and

$$\begin{aligned}\left\langle M^f, M^f\right\rangle_t =& \int_0^t [\sum_{j=1}^{J}\int_{\mathbb{R}_+} [\ll f, 2\delta_{j,0}-\delta_{j,a}\gg]^2 b_j(a)p_{2,0}^{(j)}Z_s(dj,da) \\ &+\sum_{j=1}^{J}\int_{\mathbb{R}_+} [\ll f, \delta_{j,0}+\delta_{j+1,0}-\delta_{j,a}\gg]^2 b_j(a)p_{1,1}^{(j)}Z_s(dj,da) \\ &+\sum_{j=1}^{J}\int_{\mathbb{R}_+} [\ll f, 2\delta_{j+1,0}-\delta_{j,a}\gg]^2 b_j(a)p_{0,2}^{(j)}Z_s(dj,da)]ds\,.\end{aligned} \tag{35}$$

The proofs of theorem 3.6 and lemma 3.7 are classical and provided in SM1.2 for reader convenience. We now have all the elements to prove theorem 2.13.

Proof of theorem 2.13. We apply the Dynkin formula (33) with the dual test function ϕ and obtain $\ll \phi, Z_t\gg = \ll \phi, Z_0\gg + \lambda_c\int_0^t \ll \phi, Z_s\gg ds + M_t^\phi$. As ϕ is bounded, $\ll \phi, Z_t\gg$ has finite expectation for all time t according to (32). Thus,

$$\mathbb{E}\big[\ll \phi, Z_t\gg\big] = \mathbb{E}\big[\ll \phi, Z_0\gg\big] + \lambda_c\mathbb{E}\big[\int_0^t \ll \phi, Z_s\gg ds\big]. \tag{36}$$

Using Fubini theorem and solving equation (36), we obtain:

$$\mathbb{E}\big[\ll \phi, Z_t \gg \big] = e^{\lambda_c t}\mathbb{E}\big[\ll \phi, Z_0 \gg \big] \Rightarrow \mathbb{E}\big[e^{-\lambda_c t} \ll \phi, Z_t \gg \big] = \mathbb{E}\big[\ll \phi, Z_0 \gg \big].$$

Hence, $W_t^\phi = e^{-\lambda_c t} \ll \phi, Z_t \gg$ is a martingale. According to martingale convergence theorems (see Theorem 7.11 in [4]), W_t^ϕ converges to an integrable random variable $W_\infty^\phi \geq 0$, $\mathbb{P}-$p.s. when t goes to infinity. To prove that W_∞^ϕ is non-degenerated, we will show that the convergence holds in $\mathbf{L}^2$. Indeed, from the $\mathbf{L}^2$ and almost sure convergence, we deduce the $\mathbf{L}^1$ convergence. Then, applying the dominated convergence theorem, we have:

$$\mathbb{E}[W_\infty^\phi] := \mathbb{E}[\lim_{t\to\infty} W_t^\phi] = \lim_{t\to\infty} \mathbb{E}[W_t^\phi] = \mathbb{E}[W_0^\phi] > 0.$$

Consequently, W_∞^ϕ is non-degenerated. To show the $\mathbf{L}^2$ convergence, we compute the quadratic variation of W^ϕ. Applying Ito formula (see [10] p. 78-81) with $F(t, \ll \phi, Z_t \gg) = e^{-\lambda_c t} \ll \phi, Z_t \gg$, we deduce:

$$\begin{aligned}
W_t^\phi =& \ll \phi, Z_0 \gg + \int_0^t \Big[\int_{\mathcal{E}} e^{-\lambda_c s}(\partial_a \phi^{(j)}(a) - \lambda_c \phi^{(j)}(a)) Z_s(dj, da)\Big] ds \\
&+ \int\int_{[0,t]\times\mathcal{E}} \mathbb{1}_{k\leq N_{s^-}} e^{-\lambda_c s} \ll \phi, 2\delta_{I_{s^-}^{(k)},0} - \delta_{I_{s^-}^{(k)},A_{s^-}^{(k)}} \gg \mathbb{1}_{0\leq\theta\leq m_1(s,k,Z)} Q(ds, dk, d\theta) \\
&+ \int\int_{[0,t]\times\mathcal{E}} \mathbb{1}_{k\leq N_{s^-}} e^{-\lambda_c s} \ll \phi, \delta_{I_{s^-}^{(k)},0} + \delta_{I_{s^-}^{(k)}+1,0} - \delta_{I_{s^-}^{(k)},A_{s^-}^{(k)}} \gg \mathbb{1}_{m_1(s,k,Z)\leq\theta\leq m_2(s,k,Z)} Q(ds, dk, d\theta) \\
&+ \int\int_{[0,t]\times\mathcal{E}} \mathbb{1}_{k\leq N_{s^-}} e^{-\lambda_c s} \ll \phi, 2\delta_{I_{s^-}^{(k)}+1,0} - \delta_{I_{s^-}^{(k)},A_{s^-}^{(k)}} \gg \mathbb{1}_{m_2(s,k,Z)\leq\theta\leq m_3(s,k,Z)} Q(ds, dk, d\theta).
\end{aligned} \tag{371}$$

As $\mathcal{L}^D\phi = \lambda_c\phi$, we have

$$\int_{\mathcal{E}} (\partial_a \phi^{(j)}(a) - \lambda_c \phi^{(j)}(a)) Z_s(dj, da) = \ll B(\cdot)\phi(\cdot) - K^T(\cdot)\phi(0), Z_s \gg .$$

Consequently, from (34), we deduce

$$W_t^\phi = \ll \phi, Z_0 \gg + \int_0^t e^{-\lambda_c s} dM_s^\phi . \tag{37}$$

where dM_s^ϕ is defined as $M_t^\phi = \int_0^t dM_s^\phi$. According to (35) and (37), we get

$$\begin{aligned}
\langle W_\cdot^\phi, W_\cdot^\phi \rangle_t &= \int_0^t e^{-2\lambda_c s} d\langle M^\phi, M^\phi \rangle_s \, ds \\
&= \int_0^t e^{-2\lambda_c s} \Big[\int_{\mathcal{E}} \Big(p_{2,0}^{(j)}[\ll \phi, 2\delta_{j,0} - \delta_{j,a} \gg]^2 + p_{1,1}^{(j)}[\ll \phi, \delta_{j,0} + \delta_{j+1,0} - \delta_{j,a} \gg]^2 \\
&\qquad + p_{0,2}^{(j)}[\ll \phi, 2\delta_{j+1,0} - \delta_{j,a} \gg]^2 \Big) b_j(a) Z_s(dj, da) \Big] ds .
\end{aligned}$$

Since, ϕ and b are bounded, there exists a constant $K > 0$ such that

$$\langle W^\phi, W^\phi \rangle_t \leq K \int_0^t e^{-2\lambda_c s} \left[\int_{\mathcal{E}} Z_s(dj, da) \right] ds .$$

Taking the expectation and using moment estimate (32), we get $\mathbb{E}[\langle W^\phi, W^\phi \rangle_t] < \infty$. Thanks to the Burkholder-Davis-Gundy inequality (see Theorem 48, [10]), we deduce that $\mathbb{E}[\sup_{t\leq T} \left(W_t^\phi\right)^2] < \infty$, and thus the $\mathbf{L}^2$ convergence of W^ϕ. □

3.4. Asymptotic study of the renewal equations. We now turn to the study of renewal equations associated with the branching process Z. Following [2] (Chap. VI), we introduce generating functions that determine the cell moments. In all this subsection, we consider $a \in \mathbb{R}_+ \cup \{+\infty\}$. We recall that $Y_t^{(j,a)} = \langle Z_t, \mathbb{1}_j \mathbb{1}_{\leq a} \rangle$ and $Y_t^a = (Y_t^{(j,a)})_{j \in [\![1,J]\!]}$. For $\mathbf{s} = (s_1, ..., s_J) \in \mathbb{R}^J$ and $\mathbf{j} = (j_1, ..., j_J) \in \mathbb{N}^J$, we use classical vector notation $\mathbf{s}^{\mathbf{j}} = \prod_{i=1}^J s_i^{j_i}$.

DEFINITION 3.8. *We define* $F^a[\mathbf{s};t] = (F^{(i,a)}[\mathbf{s};t])_{i \in [\![1,J]\!]}$ *where* $F^{(i,a)}$ *is the generating function associated with* Y_t^a *starting with* $Z_0 = \delta_{i,0}$*:*

$$F^{(i,a)}[\mathbf{s};t] := \mathbb{E}[\mathbf{s}^{Y_t^a} | Z_0 = \delta_{i,0}] \,.$$

We obtain a system of renewal equations for F and $M^a(t) := (\mathbb{E}[Y_t^{(j,a)} | Z_0 = \delta_{i,0}])_{i,j \in [\![1,J]\!]}$.

LEMMA 3.9 (Renewal equations for F). *For* $i \in [\![1,J]\!]$, $F^{(i,a)}$ *satisfies:*

$$\forall i \in [\![1,J]\!], \quad F^{(i,a)}[\mathbf{s};t] = (s_i \mathbb{1}_{t \leq a} + \mathbb{1}_{t>a})(1 - \mathcal{B}_i(t)) + f^{(i)}(F^a[\mathbf{s},.]) * d\mathcal{B}_i(t) \tag{38}$$

where $f^{(i)}$ *is given by* $f^{(i)}(\mathbf{s}) := p_{2,0}^{(i)} s_i^2 + p_{1,1}^{(i)} s_i s_{i+1} + p_{0,2}^{(i)} s_{i+1}^2$.

LEMMA 3.10 (Renewal equations for M). *For* $(i,j) \in [\![1,J]\!]^2$, $M_{i,j}^a$ *satisfies:*

$$M_{i,j}^a(t) = \delta_{i,j}(1 - \mathcal{B}_i(t)) \mathbb{1}_{t \leq a} + 2p_S^{(i)} M_{i,j}^a * d\mathcal{B}_i(t) + 2p_L^{(i)} M_{i+1,j}^a * d\mathcal{B}_i(t) \,. \tag{39}$$

The proofs of lemma 3.9 and 3.10 are given in SM1.2.

THEOREM 3.11. *Under hypotheses 2.1, 2.2, 2.7, 2.8 and 2.9,*

$$\forall i \in [\![1,J]\!], \quad \forall k \in [\![0, J-i]\!], \quad M_{i,i+k}^a(t) \sim \widetilde{M}_{i,i+k}(a) e^{\lambda_{i,i+k} t}, \quad t \to \infty \tag{40}$$

where $\lambda_{i,i+k} = \max_{j \in [\![i,i+k]\!]} \lambda_j$,

$$\widetilde{M}_{i,i}(a) = \frac{\int_0^a (1 - \mathcal{B}_i(t)) e^{-\lambda_i t} dt}{2p_S^{(i)} \int_0^\infty t d\mathcal{B}_i(t) e^{-\lambda_i t} dt} \tag{41}$$

and, for $k \in [\![1, J-i]\!]$

$$\widetilde{M}_{i,i+k}(a) = \begin{cases} \dfrac{2p_L^{(i)} d\mathcal{B}_i^*(\lambda_{i,i+k})}{1 - 2p_S^{(i)} d\mathcal{B}_i^*(\lambda_{i,i+k})} \widetilde{M}_{i+1,i+k}(a), & \text{if } \lambda_{i,i+k} \neq \lambda_i \; (i) \\ \dfrac{2p_L^{(i)} d\mathcal{B}_i^*(\lambda_i)}{2p_S^{(i)} \int_0^\infty t d\mathcal{B}_i(t) e^{-\lambda_i t} dt} \displaystyle\int_0^\infty M_{i+1,i+k}^a(t) e^{-\lambda_i t} dt, & \text{if } \lambda_{i,i+k} = \lambda_i (ii). \end{cases} \tag{42}$$

Proof. Let the mother cell index $i \in [\![1,J]\!]$. As no daughter cell can move upstream to its mother layer, the mean number of cells on layer $j < i$ is null (for all $t \geq 0$ and for $j < i$, $M_{i,j}^a(t) = 0$). We consider the layers downstream the mother one ($j \geq i$) and proceed by recurrence:

$$\mathcal{H}^k : \quad \forall i \in [\![1, J-k]\!], \;\; M_{i,i+k}^a(t) \sim \widetilde{M}_{i,i+k}(a) e^{\lambda_{i,i+k} t}, \text{ as } t \to \infty \,.$$

We first deal with $\mathcal{H}^0$. We consider the solution of (39) for $j = i$:

$$\forall t \in \mathbb{R}_+, \quad M^a_{i,i}(t) = (1 - \mathcal{B}_i(t))\, \mathbb{1}_{t\le a} + 2p_S^{(i)} M^a_{i,i} * d\mathcal{B}_i(t)\,. \tag{43}$$

We recognize a renewal equation as presented in [2](p.161, eq.(1)) for $M_{i,i}$, which is similar to a single type age-dependent process. The main results on renewal equations are recalled in SM1.3. Here, the mean number of children is $m = 2p_S^{(i)} > 0$ and the life time distribution is $\mathcal{B}_i$. From hypothesis 2.2, we have

$$\int_0^\infty (1 - \mathcal{B}_i(t))\, \mathbb{1}_{t\le a} e^{-\lambda_i t} dt \le \frac{1}{\bar{b}_i} \int_0^\infty \mathbb{1}_{t\le a} d\mathcal{B}_i(t) e^{-\lambda_i t} dt \le \frac{1}{\bar{b}_i} \int_0^\infty d\mathcal{B}_i(t) e^{-\lambda_i t} dt < \infty$$

according to hypothesis 2.4. Thus, $t \mapsto \mathbb{1}_{t\le a}\,(1 - \mathcal{B}_i(t))\, e^{-\lambda_i t}$ is in $\mathbf{L}^1(\mathbb{R}_+)$. Using hypotheses 2.4 and 2.9, we apply corollary 2.10 and lemma SM1.4 (see lemma 2 of [2],p.161) and obtain:

$$M^a_{i,i}(t) \sim \widetilde{M}_{i,i}(a) e^{\lambda_i t}, \text{ as } t \to \infty, \text{ where } \widetilde{M}_{i,i}(a) = \frac{\int_0^a (1 - \mathcal{B}_i(t)) e^{-\lambda_i t} dt}{2p_S^{(i)} \int_0^\infty t d\mathcal{B}_i(t) e^{-\lambda_i t} dt}\,.$$

Hence, $\mathcal{H}^0$ is verified. We then suppose that $\mathcal{H}^{k-1}$ is true for a given rank $k - 1 \ge 0$ and consider the next rank k. According to (39), $M^a_{i,i+k}$ is a solution of the equation:

$$M^a_{i,i+k}(t) = 2p_S^{(i)} M^a_{i,i+k} * d\mathcal{B}_i(t) + 2p_L^{(i)} M^a_{i+1,i+k} * d\mathcal{B}_i(t)\,. \tag{44}$$

We distinguish two cases : $\lambda_{i,i+k} \neq \lambda_i$ and $\lambda_{i,i+k} = \lambda_i$. We first consider $\lambda_{i,i+k} = \lambda_i$ and show that $f(t) = M^a_{i+1,i+k} * d\mathcal{B}_i(t) e^{-\lambda_i t}$ belongs to $\mathbf{L}^1(\mathbb{R}_+)$. Let $R > 0$. Using Fubini theorem, we deduce that:

$$\int_0^R f(t)dt = \int_0^R \left[\int_u^R e^{-\lambda_i (t-u)} M^a_{i+1,i+k}(t-u) dt \right] e^{-\lambda_i u} d\mathcal{B}_i(u) du\,.$$

Applying a change of variable and using that $M^a_{i+1,i+k}(t) \ge 0$ for all $t \ge 0$, we have:

$$\int_u^R e^{-\lambda_i (t-u)} M^a_{i+1,i+k}(t-u) dt \le \int_0^R e^{-\lambda_i t} M^a_{i+1,i+k}(t) dt\,.$$

According to $\mathcal{H}^k$, we know that $M^a_{i+1,i+k}(t) \sim \widetilde{M}_{i+1,i+k}(a) e^{\lambda_{i+1,i+k} t}$ as $t \to \infty$. Then,

$$\begin{aligned}\int_0^R e^{-\lambda_i t} M^a_{i+1,i+k}(t) dt &= \int_0^R e^{-\lambda_{i+1,i+k} t} M^a_{i+1,i+k}(t) e^{-(\lambda_i - \lambda_{i+1,i+k})t} dt \\ &\le K \int_0^R e^{-(\lambda_i - \lambda_{i+1,i+k})t} dt \quad < \infty\end{aligned}$$

when $R \to \infty$, as $\lambda_i = \lambda_{i,i+k} > \lambda_{i+1,i+k}$. Moreover, $\int_0^R e^{-\lambda_i u} d\mathcal{B}_i(u) du \le d\mathcal{B}_i^*(\lambda_i) < \infty$ according to hypothesis 2.7. Finally, we obtain an estimate for $\int_0^R f(t)dt$ that does not depend on R. So, f is integrable. We can apply lemma SM1.4 and deduce $M^a_{i,i+k}(t) \sim \widetilde{M}_{i,i+k}(a) e^{\lambda_{i,i+k} t}$, as $t \to \infty$, with $\widetilde{M}_{i,i+k}(a)$ given in (42)(ii).
We now consider the case $\lambda_{i,i+k} \neq \lambda_i$ and introduce the following notations :

$$\widehat{M}^a_{i,i+k}(t) = M^a_{i,i+k}(t) e^{-\lambda_{i,i+k} t}, \quad \widehat{d\mathcal{B}_i}(t) = \frac{d\mathcal{B}_i(t)}{d\mathcal{B}_i^*(\lambda_{i,i+k})} e^{-\lambda_{i,i+k} t}\,.$$

In this case, $\lambda_{i,i+k} > \lambda_i$, so that $2p_S^{(i)} d\mathcal{B}_i^*(\lambda_{i,i+k}) < 2p_S^{(i)} d\mathcal{B}_i^*(\lambda_i) = 1$. We want to apply lemma SM1.5 (see lemma 4 of [2], p.163). We rescale (44) by $e^{-\lambda_{i,i+k}t}$ and obtain the following renewal equation for $\widehat{M}^a_{i,i+1}$:

$$\widehat{M}^a_{i,i+k}(t) = 2p_S^{(i)} d\mathcal{B}_i^*(\lambda_{i,i+k}) \widehat{M}^a_{i,i+k} * \widehat{d\mathcal{B}_i}(t) + 2p_L^{(i)} M^a_{i+1,i+k} * d\mathcal{B}_i(t) e^{-\lambda_{i,i+k}t}\,.$$

We compute the limit of $f(t) = M^a_{i+1,i+k} * d\mathcal{B}_i(t) e^{-\lambda_{i,i+k}t}$:

$$f(t) = \int_0^\infty \mathbb{1}_{[0,t]}(u) M^a_{i+1,i+k}(t-u) e^{-\lambda_{i,i+k}(t-u)} e^{-\lambda_{i,i+k}u} d\mathcal{B}_i(u) du\,.$$

According to $\mathcal{H}^{k-1}$, $M^a_{i+1,i+k}(t) \sim e^{-\lambda_{i+1,i+k}t} \widetilde{M}_{i+1,i+k}(a)$. As $\lambda_{i,i+k} \neq \lambda_i$, we have $\lambda_{i,i+k} = \lambda_{i+1,i+k}$. Hence, $M^a_{i+1,i+k}(t) e^{-\lambda_{i,i+k}t}$ is dominated by a constant K such that $\int_0^\infty K e^{-\lambda_{i,i+k}u} d\mathcal{B}_i(u) du < \infty$. We apply the Lebesgue dominated convergence theorem and obtain $\lim_{t\to\infty} f(t) = \widetilde{M}_{i+1,i+k}(a) d\mathcal{B}_i^*(\lambda_{i,i+k})$. Applying lemma SM1.5, we obtain that:

$$\lim_{t\to\infty} \widehat{M}^a_{i,i+k}(t) = \frac{2p_L^{(i)} \widetilde{M}_{i+1,i+k}(a) d\mathcal{B}_i^*(\lambda_{i,i+k})}{1 - 2p_S^{(i)} d\mathcal{B}_i^*(\lambda_{i,i+k})} = \widetilde{M}_{i,i+k}(a),$$

and the recurrence is proved. ∎

We have now all the elements to prove theorem 2.14.

Proof of theorem 2.14. According to theorem 3.11, we have:

$$\forall j \in [\![1, J]\!], \quad m_j^a(t) \sim \widetilde{M}_{1,j}(a) e^{\lambda_{1,j}t}, \quad \text{as } t \to \infty. \tag{45}$$

When $j < c$, we deduce directly from (45) that $\widetilde{m}_j(a) = 0$. We then consider the leading layer $j = c$. For $k \in [\![1, c-1]\!]$, $\lambda_{k,c} \neq \lambda_k$ so, $\widetilde{M}_{k,c}(a)$ is related to $\widetilde{M}_{k+1,c}(a)$ by (42)(i). Thus, we obtain:

$$\widetilde{m}_c(a) = \prod_{m=1}^{c-1} \frac{2p_L^{(m)} d\mathcal{B}_m^*(\lambda_c)}{1 - 2p_S^{(m)} (d\mathcal{B}_m^*)(\lambda_c)} \widetilde{M}_{c,c}(a)\,. \tag{46}$$

$\widetilde{M}_{c,c}(a)$ is given by (41) and we deduce $\widetilde{m}_c(a)$. We turn to the layers $j > c$. For $k \in [\![1, c-1]\!]$, we have $\lambda_c = \lambda_{k,j} \neq \lambda_k$. We obtain from (42)(i)

$$\widetilde{m}_j(a) = \prod_{m=1}^{c-1} \frac{2p_L^{(m)} d\mathcal{B}_m^*(\lambda_c)}{1 - 2p_S^{(m)} (d\mathcal{B}_m^*)(\lambda_c)} \widetilde{M}_{c,j}(a). \tag{47}$$

Then, as $\lambda_c = \lambda_{c,j}$, we use (42)(ii) and obtain:

$$\widetilde{M}_{c,j}(a) = \frac{2p_L^{(c)} d\mathcal{B}_c^*(\lambda_c)}{2p_S^{(c)} \int_0^\infty t e^{-\lambda_c t} d\mathcal{B}_c(t) dt} \int_0^\infty M^a_{c+1,j}(t) e^{-\lambda_c t} dt. \tag{48}$$

Then, we apply the Laplace transform to (39) for $\alpha = \lambda_c$. Theorem 3.11 and the fact that $\lambda_c = \lambda_{c,j}$ guarantee that we can apply the Laplace transform to (39) (see details in SM1.3). We obtain:

(49)
$$\int_0^\infty M^a_{c+1,j}(t)e^{-\lambda_c t}dt = \prod_{k=c+1}^{j-1} \frac{2p_L^{(k)} d\mathcal{B}_k^*(\lambda_c)}{1-2p_S^{(k)} d\mathcal{B}_k^*(\lambda_c)} \times \frac{\int_0^a \hat{\rho}^{(j)}(s)ds}{(1-2p_S^{(j)} d\mathcal{B}_j^*(\lambda_c)) \times \hat{\rho}^{(j)}(0)}.$$

Combining (47), (48) and (49) and the value of $\hat{\rho}^{(j)}(0)$ given in (12), we obtain $\widetilde{m}_j(a)$.□

We also study the asymptotic behavior of the second moment in SM1.3 (see theorem SM1.8).

Remark 3.12. These results can be extended in a case when the mother cell is not necessary of age 0 (for the one layer case, see [2], p.153).

Remark 3.13. Using the same procedure as in theorem 3.11, we can obtain a better estimate for the convergence of the deterministic solution ρ than that in theorem 2.12. Indeed, we can consider the study of $h(t,x) = e^{-\lambda_{1,j}t}\rho(t,x) - \eta\hat{\rho}_{1,j}(x)$ where $\hat{\rho}_{1,j}$ is the eigenvector of the sub-system composed of the j-th first layer, and find the proper function $\phi_{1,j}$.

3.5. Numerical illustration. We perform a numerical illustration with age independent division rates (which satisfy hypothesis 2.2). Figure 3a illustrates the exponential growth of the number of cells, either for the original solution of the model (2) (left panel) or the renormalized solution (right panel), checking the results given in theorems 2.14 and SM1.8. Figure 3b instantiates the effect of the parameters b_1 and $p_S^{(1)}$ on the leading layer (left panel) and the asymptotic proportion of cells (right panel). Note that the layer with the highest number of cells is not necessary the leading one. As can be seen in Figure 4, the renormalized solutions of the SDE (2) and PDE (3) match the stable age distribution $\hat{\rho}$ (see theorems 2.11 and 2.14). Asymptotically, the age distribution decreases with age, which corresponds to a proliferating pool of young cells, and is consistent with the fact that $\hat{\rho}^{(j)}$ is proportional to $e^{-\lambda_c a}\mathbb{P}[\tau^{(j)} > a]$. The convergence speeds differ between layers (here, the leading layer is the first one and the stable state of each layer is reached sequentially), corroborating the inequality given in theorem 2.12.

4. Parameter calibration. Throughout this part, we will work under hypotheses 2.1, 2.15 and 2.16. As a consequence, the intrinsic growth rate per layer can be computed easily:

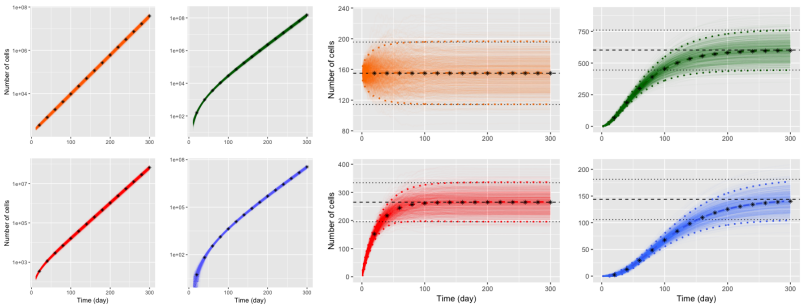
(50) $$\lambda_j = (2p_S^{(j)} - 1)b_j \in]-b_j, b_j[, \text{when } j < J\,.$$

4.1. Structural identifiability. We prove here the structural identifiability of our system following [8]. We start by a technical lemma.

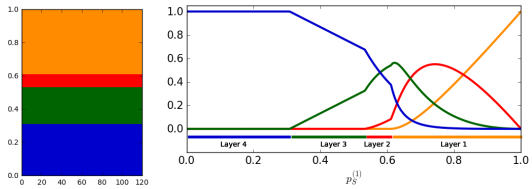
LEMMA 4.1. *Let M be the solution of (8). For any linear application $U : \mathbb{R}^J \to \mathbb{R}^J$, we have $[\forall t, M(t) \in \ker(U)] \Rightarrow [U = 0]$.*

Proof. Ad absurdum, if $U \neq 0$ and $M(t) \in \ker(U)$, for all t, then there exists a non-zero vector $u := (u_1, ..., u_J)$ such that for all t, $u^T M(t) = 0$. This last relation, evaluated at $t = 0$ and thanks to the initial condition of (8), implies $u_1 = 0$. Then, derivating M, solution of (8), we obtain:

$$\frac{d}{dt}\sum_{j=2}^{J} u_j M^{(j)}(t) = 0 \Rightarrow \qquad \sum_{j=2}^{J} u_j[(b_{j-1} - \lambda_{j-1})M^{(j-1)}(t) + \lambda_j M^{(j)}(t)] = 0\,.$$



(a) Exponential growth and asymptotic behavior



(b) Leading layer index and asymptotic proportion of cells

FIGURE 3. ***Exponential growth and asymptotic moments***. ***Figure 3a:*** *Outputs of 1000 simulations of the SDE (2) according to the algorithm SM1 with* $p_S^{(j)}$, b_j *given in Figure 1b,* $p_{1,1}^{(j)} = 0$ *and* $Z_0 = 155\delta_{1,0}$. ***Left panel:*** *the solid color lines correspond to the outputs of the stochastic simulations while the black stars correspond to the numerical solutions of the ODE (8) with the initial number of cells on the first layer* $N = 155$ *(orange: Layer 1, red: Layer 2, green: Layer 3, blue: Layer 4).* ***Right panel:*** *the color solid lines correspond to the renormalization of the outputs of the stochastic simulations by* $e^{-\lambda_c t}$. *The black stars are the numerical solutions of the ODE (8). The color and black dashed lines correspond to the empirical means of the simulations and the analytical asymptotic means* ($155\widetilde{m}_j(\infty)$, *theorem 2.14), respectively. The color and black dotted lines represent the empirical and analytical asymptotic* 95% *confidence intervals* ($1.96\sqrt{v_j(\infty)}$, *corollary SM1.10), respectively.* ***Figure 3b:*** *Leading layer index as a function of* b_1 *and* $p_S^{(1)}$ *(left panel) and proportion of cells per layer in asymptotic regime with respect to* $p_S^{(1)}$ *(right panel). In both panels, b satisfies (9) and* $p_S^{(j)} = -15 * p_L^{(1)} * (j-1)^2 - 110 * p_L^{(1)} * (j-1) + p_S^{(1)}$.

Again, at $t = 0$, we obtain $u_2(b_1 - \lambda_1) = 0$. Because $\lambda_1 \neq b_1$, $u_2 = 0$. Iteratively,

$$\forall j \in [\![2, J]\!], \quad u_j \prod_{k=1}^{j-1}(b_{k-1} - \lambda_{k-1}) = 0 \quad \Rightarrow u_j = 0\,.$$

We obtain a contradiction. □

We can now prove theorem 2.17.

Proof of theorem 2.17. According to [8], the system (8) is $\mathbf{P}$-identifiable if, for two sets of parameters $\mathbf{P}$ and $\widetilde{\mathbf{P}}$, $M(t;\mathbf{P}) = M(t;\widetilde{\mathbf{P}})$ implies that $\mathbf{P} = \widetilde{\mathbf{P}}$.

$$\begin{aligned} \forall t \geq 0, M(t;\mathbf{P}) = M(t;\widetilde{\mathbf{P}}) \Rightarrow & \quad \frac{d}{dt}M(t;\mathbf{P}) = \frac{d}{dt}M(t;\widetilde{\mathbf{P}}) \\ \Rightarrow & \quad A_{\mathbf{P}}M(t;\mathbf{P}) = A_{\widetilde{\mathbf{P}}}M(t;\widetilde{\mathbf{P}}) = A_{\widetilde{\mathbf{P}}}M(t;\mathbf{P}) \\ \Rightarrow & \quad (A_{\mathbf{P}} - A_{\widetilde{\mathbf{P}}})M(t;\mathbf{P}) = 0 \end{aligned}$$

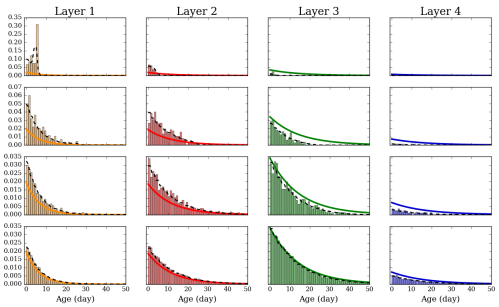


FIGURE 4. ***Stable age distribution per layer.*** *Age distribution at different times of one simulation of the SDE (2) and of the PDE (3) using the algorithms described in respectively SM1 and SM2.0.2. We use the same parameters as in Figure 3. From top to bottom: $t = 5$, 25, 50 and 100 days. The color bars represent the normalized stochastic distributions. The black dashed lines correspond to the normalized PDE distributions, the color solid lines to the stable age distributions $\hat{\rho}^{(j)}$, $j \in [\![1, 4]\!]$. The details of the normalization of each lines are provided in SM2.1.*

So, $M(t; \mathbf{P}) \in \ker(A_{\mathbf{P}} - A_{\widetilde{\mathbf{P}}})$ and, from lemma 4.1, we deduce that $A_{\mathbf{P}} = A_{\widetilde{\mathbf{P}}}$. Thus,

$$\begin{cases} (2p_S^{(j)} - 1)b_j = (2\widetilde{p}_S^{(j)} - 1)\widetilde{b}_j, & \forall j \in [\![1, J]\!], \\ 2p_L^{(j)} b_j = 2\widetilde{p}_L^{(j)}\widetilde{b}_j, & \forall j \in [\![1, J-1]\!]. \end{cases}$$

Using that $p_L^{(j)} = 1 - p_S^{(j)}$ and hypothesis 2.1, we deduce $\mathbf{P} = \widetilde{\mathbf{P}}$. ∎

4.2. Biological application. We now consider the application to the development of ovarian follicles.

4.2.1. Biological background. The ovarian follicles are the basic anatomical and functional units of the ovaries. Structurally, an ovarian follicle is composed of a germ cell, named oocyte, surrounded by somatic cells (see Figure 5). In the first stages of their development, ovarian follicles grow in a compact way, due to the proliferation of somatic cells and their organization into successive concentric layers starting from one layer at growth initiation up to four layers.

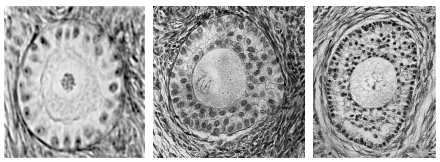


FIGURE 5. ***Histological sections of ovarian follicles in the compact growth phase.*** *Left panel: one-layer follicle, center panel: three-layer follicle, right panel: four-layer follicle. Courtesy of Danielle Monniaux.*

4.2.2. Dataset description. We dispose of a dataset providing us with morphological information at different development stages (oocyte and follicle diameter, total number of cells), and acquired from *ex vivo* measurements in sheep fetus [5]. In addition, from [14, 13], we can infer the transit times between these stages: it takes 15 days to go from one to three layers and 10 days from three to four layers. Hence (see Table 1a), the dataset consists of the total numbers of somatic cells at three time points.

	$t=0$	$t=20$	$t=35$
Data points (62)	34	10	18
Total cell number	113.89 ± 57.76	885.75 ± 380.89	2241.75 ± 786.26
Oocyte diameter (μm)	49.31 ± 8.15	75.94 ± 10.89	88.08 ± 7.43
Follicle diameter (μm)	71.68 ± 13.36	141.59 ± 17.11	195.36 ± 23.95

(a) **Summary of the dataset**

Layer j	$p_S^{(j)}$	b_j	λ_j
1	0.6806	0.1146	0.0414
2	0.4837	0.0435	-0.0014
3	0.9025	0.0354	0.0285
4	1	0.0324	0.0324

(b) **Estimated values of the parameters.**

TABLE 1

Experimental dataset and estimated values of the parameters. *Table 1b. The estimated value of α and the initial number of cells are respectively $\alpha = 1.633$ and $N \approx 155$. For $j \geq 2$, the b_j parameter values (in blue) were computed using formula (9). The λ_j values were computed using formula (50). The 95%-confidence intervals are $b_1 \in [0.0760; 0.1528]$, $\alpha \in [0.0231; 5.685]$, $N \in [126.4; 185.4]$, $p_S^{(1)} \in [0.6394; 0.7643]$, $p_S^{(2)} \in [0; 0.7914[$ and $p_S^{(3)} \in [0.6675; 0.9739]$.*

We next take advantage of the spheroidal geometry and compact structure of ovarian follicles to obtain the number of somatic cells in each layer. Spherical cells are distributed around a spherical oocyte by filling identical width layers one after another, starting from the closest layer to the oocyte. Knowing the oocyte and somatic cell diameter (respectively d_O and d_s) and, the total number of cells N^{exp}, we compute the number of cells on the jth layer according to the ratio between its volume V^j and the volume of a somatic cell V^s:

INITIALIZATION: $j \leftarrow 1, V^s \leftarrow \frac{\pi d_s^3}{6}, N \leftarrow N^{exp}$
While $N > 0$:
$V^j \leftarrow \frac{\pi}{6}\left[(d_O + 2 * j * d_s)^3 - (d_O + 2 * (j-1) * d_s)^3\right]$
$N_j \leftarrow \min(\frac{V^j}{V^s}, N), N \leftarrow N - N_j, j \leftarrow j + 1$
$J \leftarrow j - 1$

The corresponding dataset is shown on the four panels of Figure 2.

4.2.3. Parameter estimation. Before performing parameter estimation, we take into account additional biological specifications on the division rates. The oocyte produces growth factors whose diffusion leads to a decreasing gradient of proliferating chemical signals along the concentric layers, which results to the recurrence law (9) similar as that initially proposed in [1]. Considering a regression model with an additive gaussian noise, we estimate the model parameters to fit the changes in cell numbers in each layer (see SM2.2 for details). The estimated parameters are provided in Table 1b and the fitting curves are shown in Figure 2. We compute the profil likelihood estimates [11] and observe that all parameters are practically identifiable except $p_S^{(2)}$ (Figure SM1a). In contrast, when we perform the same estimation procedure on the total cell numbers, most of the parameters are not practicality identifiable (dataset in Table 1a, see detailed explanations in SM2.2).

5. Conclusion. In this work, we have analyzed a multi-type age-dependent model for cell populations subject to unidirectional motion, in both a stochastic and deterministic framework. Despite the non-applicability of either the Perron-Frobenius or Krein-Rutman theorem, we have taken advantage of the asymmetric transitions between different types to characterize long time behavior as an exponential Malthus growth, and obtain explicit analytical formulas for the asymptotic cell number moments and stable age distribution. We have illustrated our results numerically, and

studied the influence of the parameters on the asymptotic proportion of cells, Malthus parameter and stable age distribution. We have applied our results to a morphodynamic process occurring during the development of ovarian follicles. The fitting of the model outputs to biological experimental data has enabled us to represent the compact phase of follicle growth. Thanks to the flexibility allowed by the expression of morphodynamic laws in the model, we intend to consider other non-compact growth stages.

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