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An inverse problem in cell dynamics: Recovering an initial distribution of telomere lengths from measurements of senescence times

Jules Olayé[†]

Abstract

Telomeres are repetitive sequences situated at both ends of the chromosomes of eukaryotic cells. At each cell division, they are eroded until they reach a critical length that triggers a state in which the cell stops to divide: the senescent state. In this work, we are interested in the link between the initial distribution of telomere lengths and the distribution of senescence times. We propose a method to retrieve the initial distribution of telomere lengths, using only measurements of senescence times. Our approach relies on approximating our models with transport equations, which provide natural estimators for the initial telomere lengths distribution. We investigate this method from a theoretical point of view by providing bounds on the errors of our estimators, pointwise and in all Lebesgue spaces. We also illustrate it with estimations on simulations, and discuss its limitations related to the curse of dimensionality.

Keywords: Inverse problem, integro-differential equation, transport equation, telomere lengths, cell division

1 Introduction

Biological motivation. Linear chromosomes of eukaryotic cells have repeated sequences of nucleotides called telomeres at their ends. These regions are non-coding, and prevent fusion between chromosomes, thus ensuring the integrity of chromosomes. At each cell division, half of the telomeres are slightly shortened because the enzyme responsible for the DNA replication is unable to copy the last nucleotides of the DNA. This phenomenon is called the *end-replication problem* [53, 54]. As telomeres progressively shorten, a cell may eventually reach a critical threshold in which telomeres are not long enough to protect the coding regions of DNA from degradation. To prevent this issue, when the shortest telomere of a cell attains a certain length, which is around 27 base pairs for the yeast [41], the cell enters a state called *senescence* [1, 7, 19, 30, 55]. This state is characterised by the fact that the cell stops dividing, thus avoiding the loss of coding DNA. Understanding this phenomenon may help to understand how cancer cells can emerge. The main reason is that cancer cells have mutated to be able to lengthen their telomeres, preventing them from senescence and allowing them to proliferate [43]. The study of telomere shortening has therefore gained in interest in the last years, and recent advances in microfluidics have opened new doors in its understanding. Specifically, microfluidic experiments have simplified the tracing of cell lineages, thus providing better experimental data at the microscopic level [56].

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Presentation of the problem. Since the criterion for a cell to become senescent is given by the lengths of its telomeres, initial telomere lengths distribution and fate of cell lineages/population are deeply connected. In [41], this link was studied with the following approach: how do the initial telomere lengths influence the fate of cell lineages/populations? Specifically, the authors investigated how the parameters of the initial distribution affect the population half-life time (the time at which the number of cells is halved) and the evolution of the average telomere length. In the current paper, we aim at understanding this link on lineages and by asking the opposite question: can we obtain information on the initial distribution of telomere lengths, knowing the fate of cell lineages? To answer this question, we propose to solve the following inverse problem: recovering the initial distribution of telomere lengths when only the senescence times distribution of several lineages is observed.

Informal description of the models. To address the issue presented above, we model telomere shortening with deterministic models, which correspond to integro-differential equations. These models can be seen as a counterpart of the stochastic models developed and studied in recent years [2, 5, 6, 7, 17, 27, 30, 35, 41]. Two models are considered in this study. The first model is a toy model for mathematical investigations, representing the evolution of cell lineages with a single telomere, see (2.3). In this model, cells are structured according to the length of their telomere $x \in \mathbb{R}_+$. The second model is a more biologically relevant one, representing cell lineages with several telomeres, see (2.8). Each chromosome in a cell has two telomeres, one at each end. Thus, denoting by $k \in \mathbb{N}^*$ the number of chromosomes of the species we study, the cells are structured by the length of their telomeres $x \in \mathbb{R}_+^{2k}$. In each of these models, the quantities modelled by our equations are the telomere lengths density over time, and the senescence times distribution. We assume that cells divide at a constant rate, and that at each division, the telomere (in the model on \mathbb{R}_+) or half of the telomeres (in the model on \mathbb{R}_+^{2k}) are shortened. We model senescence by a cemetery state, and assume that cells enter this state when one of their telomeres has a length below a threshold. This threshold is set to 0 for simplicity, as any other threshold value is equivalent to 0 by translation of the trait space. These give us that the telomere lengths densities and the senescence times distribution satisfy a system of two integro-differential equations, including the deterministic equation of a jump process as a first equation, and the rate this process reaches 0 as a second equation.

Difficulty. The main difficulty in solving this problem is that we work with integro-differential equations, which are non-local equations. This non-locality implies that we lose information about the telomere lengths distribution when only the senescence times are observed. This results in a non-injectivity of the operator linking the lengths distribution at a given time $t \geq 0$, and the senescence times distribution at this time t , see Remark 2.2. It is thus not possible to obtain information about the lengths distribution by inverting this operator. It also implies that it is very difficult to ensure identifiability for our inverse problem.

Estimation strategy. The estimation strategy we use allows us to manage the issues presented in the above paragraph. It consists in adapting the estimation strategy developed in [3, 13] to our setting. For this strategy, we first assume that the telomere shortening values are small and that the cell division rate is high. This assumption is biologically relevant because the ratio between the average telomere shortening and the average initial telomere length is small, see the discussion about the assumptions p. 13. Then, we use this assumption to obtain approximations of our models by transport equations absorbed by a cemetery when one coordinate of the trait reaches 0. This allows us, at the cost of working with a slightly different model, to recover locality and injectivity properties. Thereafter, we construct estimators of

the initial distribution that work on these approximated models. We do this here by using the characteristics of the transport equations, which provide a simple link between the distribution of entry times to the cemetery and the initial distribution. Finally, we apply the previously constructed estimators to the original models, and verify that they remain accurate. We check this here by obtaining bounds on their estimation errors, and then testing the inference method on simulations.

Review of the literature. Inverse problems in cell biology have been widely studied over the last few years. In general, the quantity to recover is the cell division rate or, equivalently, the cell cycle distribution [10, 11, 12, 14, 21, 34]. Other quantities have also been estimated, such as the fragmentation kernel of growth-fragmentation equations [11, 20], and the initial distribution of polymer sizes in protein depolymerisation [3, 13]. Our work is in line with this last example. Although the biological motivation is different, we work with a comparable model and within a similar setting. Indeed, as in [3, 13], we have here a trait that progressively degrades over time until it reaches the boundary of the trait space. We also observe the density of individuals at the boundary of the space, and we aim to retrieve the same quantity, the initial distribution of the trait.

We mention that in [13], the approximation used to construct their estimator is more refined than ours: the model is approximated by a transport-diffusion equation (second-order approximation) instead of a transport equation (first-order approximation). This second-order approximation provides more information, leading to a better estimation when solving the inverse problem. The actual work is thus more in line with [3] in which a first-order approximation is done to construct the estimator, using results from previous articles to justify it [25, 28, 45, 50]. This justification was reinforced in [13], where an alternative proof for the first-order approximation of the model in L^2 -norm is provided, even though it deals with the second order. In our case, it is also possible to do a second-order approximation to construct an estimator for the model in one dimension. This study has been conducted by the author of the current paper, and will be presented in an upcoming article.

Integro-differential equations such as those described by our models, see (2.3) and (2.8), have been well-studied in the literature [4, 16, 24, 29, 46] and are often referred to as *Volterra integro-differential equations*. However, the theoretical study of mathematical models representing telomere shortening is very recent, and still quite unexplored. The main articles we can cite are [5, 6] or [35]. In these works, the question of the existence of a stationary profile was addressed for telomere shortening models with both discrete and continuous state spaces. Prior to this, studies were conducted more from a biomathematical perspective [2, 17, 27, 36, 39, 40, 51] or from a numerical perspective [7, 30, 41, 55]. In some of these works, model approximations have already been studied. Notably, an approximation of a telomere shortening model by a transport-diffusion equation is done in [39], and approximations by both transport and transport-diffusion equations are considered in [51]. The approximations have been properly justified from a modelling perspective in these articles, but not from a theoretical one. To the best of our knowledge, theoretical results on the approximation of telomere shortening models with transport or transport-diffusion equations have not yet been obtained in the literature.

Main contributions. Our first contribution is to provide qualitative bounds for the approximation errors of our models and the errors of our estimators, pointwise and in all Lebesgue spaces. Specifically, we show that if the first and second derivatives of the initial distribution are bounded by an exponential, then the approximation and estimation errors decrease exponentially fast after a certain length and a certain time. This completes the approximation result obtained in [13], in a discrete model similar to ours. In their work, a result in L^2 -norm for the

approximation error was obtained under more general assumptions, with a bound increasing linearly with the time. However, obtaining a precise bound was not their primary focus. Our main idea to obtain these new bounds is to rewrite the approximation errors of the first lines of our systems of integro-differential equations as the integral of several sub-errors, see (3.19). This integral representation allows us to highlight for all $0 \leq s \leq t$ how the error generated at time s still influences the error at time t . Then, thanks to a maximum principle, we show that this error dissipates exponentially fast, which gives us exponential bounds. These bounds are then transferred to the approximation errors of the second lines of our systems, and to the errors done by our estimators. For more information, we refer to Sections 3 and 4.

Our second contribution concerns the extension of the estimation to a multidimensional setting, i.e., to the case where cells have several telomeres. From a theoretical point of view, we show that the estimator is less straightforward to obtain, as it requires a careful control over the rate at which cells remain outside the cemetery. From a practical point of view, we highlight the difficulties related to the curse of dimensionality and extreme value theory: a large amount of data is required to obtain a reliable estimate, and the approximation error increases with the dimension. We discuss these problems and suggest different approaches to solve them.

Our third contribution is the thorough study of how the noise related to sampling affects the quality of our estimators. This noise is a consequence of the fact that in practice, we only have a finite number of data, so we only observe an approximation of the senescence times density, and not its true value. The usual way to approximate this density is to do a kernel density estimation [37, 44], but this method gives a poor estimation of the density near 0, see Section D. We show in this work that doing a log-transform kernel density estimation [8, 33], instead of a classical one, solves this problem. We also obtain theoretical results on how the estimation errors decrease with the number of data.

Our final contribution, which follows on from the first one, is to provide theoretical results justifying that telomere shortening models can be approximated by transport equations. In particular, we complete the study done in [51], which have justified this approximation from a modelling perspective. We believe that the approximation results obtained in this work can be reused in applications other than solving this inverse problem. For example, they can be useful for studies related to [39, 51].

Organisation of the paper. The paper is organised as follows. First, in Section 2, we present the models and the estimators we use, and state the main result of this work. Then, we prove the main result for the model with one telomere and the model with several telomeres, in Sections 3 and 4 respectively. Thereafter, we illustrate in Section 5 the quality of our estimators on simulations and data. Finally, we discuss the limits and the prospects of our work in Section 6. Complements and auxiliary statements are presented in the Appendix.

2 Presentation of the models and the main result

This section is devoted to the presentation of the notations and the results of the paper. First, in Section 2.1, we define the two models that we study in this work. Then, in Section 2.2, we introduce our estimators, and give the assumptions and the main result of this work. Finally, in Section 2.3, we discuss our choice of modelling and assumptions. We mention that the proof of the well-posedness of the integro-differential equations introduced in this section is left to Appendix A.1, as this is relatively classical.

2.1 The models

Let us start by presenting in detail the models under consideration. The goal is to have models representing the microfluidic experiments done in [56], as this experimental framework has inspired our study. In these experiments, cell lineages are tracked over time in microcavities until the last cell of these lineages becomes senescent. At the end, biologists observe for each lineage the generation and the time of senescence of the last cell of the lineage. We therefore need models which describe the evolution of telomere lengths in cell lineages over time, as well as the times at which the last cell of these lineages becomes senescent.

In both of our models, we assume that cell division times are distributed according to an exponential law with parameter $\tilde{b} > 0$. We denote by ∂ the senescence state, which can be seen as a cemetery reached when one telomere of a cell has a length below 0. We also consider $\tilde{\delta} > 0$ the maximum shortening value, $\tilde{g} : [0, \tilde{\delta}] \rightarrow \mathbb{R}_+$ a probability density function representing the distribution of telomere shortening values at each division, and for all $x \geq 0$

$$\tilde{G}(x) := \int_0^{\min(x, \tilde{\delta})} \tilde{g}(s) ds \quad (2.1)$$

its associated cumulative distribution function. We assume that \tilde{g} has finite first and second moments, and write for $i \in \{1, 2\}$

$$\tilde{m}_i := \int_0^{\tilde{\delta}} u^i \tilde{g}(u) du. \quad (2.2)$$

We finally consider a non-negative function $n_0 \in W^{2,1}(\mathbb{R}_+) \cap L_{\text{loc}}^\infty(\mathbb{R}_+)$ such that $\|n_0\|_{L^1(\mathbb{R}_+)} = 1$. This function represents the initial telomere length distribution in the model with one telomere, and the initial length distribution for each individual telomere in the model with several telomeres. The goal of this paper is, thus, to infer this initial distribution knowing the distribution of senescence times.

Model with one telomere. In the first model, we assume that each cell has only one telomere. This is not biologically realistic because a cell has always several telomeres, since each chromosome of a cell has two of them. However, this model helps us to gain mathematical intuition, and it is discussed in Section 2.3 how this model can be used in practice.

Cells are structured according to their telomere length that belongs to \mathbb{R}_+ . We consider the density of telomere with length $x \geq 0$ at time $t \geq 0$ when several lineages are tracked, denoted $n^{(1)}(t, x)$. We also consider the rate at which cell lineages enters senescence at time $t \geq 0$, denoted $n_\partial^{(1)}(t)$. In fact, $n_\partial^{(1)}$ can also be seen as the senescence times distribution because it is a probability density function by Proposition A.5. In this model, each cell divides at a rate \tilde{b} , and at each cell division, the telomere of the dividing cell is shortened by a random value distributed according to \tilde{g} . If after this shortening, its telomere length is still greater than 0, then the cell remains in the dynamics. Otherwise, the cell goes to the cemetery, i.e. becomes senescent. Thus, 0 acts here as a threshold to determine if a cell becomes senescent. Recalling that n_0 is the initial distribution of telomere length, we then consider the following system of integro-differential equations

$$\begin{cases} \partial_t n^{(1)}(t, x) = \tilde{b} \int_0^{\tilde{\delta}} n^{(1)}(t, x+v) \tilde{g}(v) dv - \tilde{b} n^{(1)}(t, x), & \forall t \geq 0, x \geq 0, \\ n_\partial^{(1)}(t) = \tilde{b} \int_0^{\tilde{\delta}} n^{(1)}(t, y) (1 - \tilde{G}(y)) dy, & \forall t \geq 0, \\ n^{(1)}(0, x) = n_0(x), & \forall x \geq 0. \end{cases} \quad (2.3)$$

This system corresponds to the above description, and is our first model for telomere shortening. It is in fact similar to the one obtained in [35, Theo. 2.6], which studies a branching jump process

with the same biological motivation. The term $\tilde{b} \int_0^{\tilde{\delta}} n^{(1)}(t, x+v) \tilde{g}(v) dv$, in the first line of (2.3), corresponds to the rate at which cells with a telomere length greater than x at time t divide to become a cell with telomere length x after shortening. The term $-\tilde{b} n^{(1)}(t, x)$, on the same line, corresponds to the division of cells with telomere length x at time t . In the second line of (2.3), we have $n_{\partial}(t) = \tilde{b} \int_0^{\tilde{\delta}} n^{(1)}(t, y) (1 - \tilde{G}(y)) dy$, because at each division, the probability that the length $y \geq 0$ of the telomere of the dividing cell becomes negative after shortening is $\int_{\min(y, \tilde{\delta})}^{\tilde{\delta}} \tilde{g}(v) dv = 1 - \tilde{G}(y)$. When we study this model, our aim is to estimate n_0 when $n_{\partial}^{(1)}$ is observed.

Remark 2.1. *We have conservation of the number of individuals. Formally, for any $t \geq 0$, we first integrate the first line of (2.3) in the variable x , and put the term $-\tilde{b} n^{(1)}(t, x)$ into the integral in view of the fact that g is a probability density function. Then, we apply Fubini's theorem to switch the order of integration, and simplify the integrals in dx . We obtain*

$$\begin{aligned} \frac{d}{dt} \left[\int_0^{+\infty} n^{(1)}(t, x) dx \right] &= \tilde{b} \int_0^{+\infty} \int_0^{\tilde{\delta}} \left[n^{(1)}(t, x+v) - n^{(1)}(t, x) \right] \tilde{g}(v) dv dx \\ &= -\tilde{b} \int_0^{\tilde{\delta}} \left[\int_0^v n^{(1)}(t, x) dx \right] \tilde{g}(v) dv. \end{aligned}$$

Now, we apply a second time Fubini's theorem, and use the second line of (2.3) to develop the expression of $n_{\partial}(t)$. The following comes to end the proof, for all $t \geq 0$,

$$\begin{aligned} \frac{d}{dt} \left[\int_0^{+\infty} n^{(1)}(t, x) dx + \int_0^t n_{\partial}^{(1)}(s) ds \right] &= -\tilde{b} \int_0^{\tilde{\delta}} n^{(1)}(t, x) (1 - \tilde{G}(x)) dx \\ &\quad + \tilde{b} \int_0^{\tilde{\delta}} n^{(1)}(t, v) (1 - \tilde{G}(v)) dv = 0. \end{aligned} \tag{2.4}$$

Remark 2.2. *One can easily see that the operator $\Psi : L^1(\mathbb{R}_+) \mapsto \mathbb{R}_+$ defined for all $F \in L^1(\mathbb{R}_+)$ as $\Psi(F) = \tilde{b} \int_0^{\tilde{\delta}} F(y) (1 - \tilde{G}(y)) dy$ is not injective, and therefore not invertible. Hence, by the second line of (2.3), it is impossible to retrieve qualitative information about $n^{(1)}(t, \cdot)$ from $n_{\partial}^{(1)}(t)$, at a fixed $t \geq 0$. This difficulty is what motivates us to obtain a model approximation.*

Model with $2k$ telomeres. We now create a model which takes into account the fact that a cell has several telomeres. We denote by $k \in \mathbb{N}^*$ the number of chromosomes of the species we study. Each chromosome has 2 ends, so each cell has $2k$ telomeres. Hence, we use the space \mathbb{R}_+^{2k} to represent telomere lengths in our second model. For all $i \in \llbracket 1, k \rrbracket$, the i -th and the $(i+k)$ -th coordinates of a vector in \mathbb{R}_+^{2k} represent telomeres on the same chromosome (the chromosome i). At each cell division, for all $i \in \llbracket 1, k \rrbracket$, we have the following biological constraint:

- Either the telomere linked to the coordinate i is shortened and the telomere linked to the coordinate $i+k$ stays unchanged, with probability $1/2$,
- Or the telomere linked to the coordinate $i+k$ is shortened and the telomere linked to the coordinate i is unchanged, with probability $1/2$.

In other words, for any chromosome of the cell, one and only one end of the chromosome is shortened at each cell division. To take into account this, we introduce the following set

$$\mathcal{I}_k = \left\{ I \in \mathcal{P}(\llbracket 1, 2k \rrbracket) \mid \#I = k, \forall (i, j) \in I^2 : i \neq j \implies i \bmod k \neq j \bmod k \right\}, \tag{2.5}$$

where $\mathcal{P}(\llbracket 1, 2k \rrbracket)$ is the power set of $\llbracket 1, 2k \rrbracket$, i.e. the set that contains all subsets of $\llbracket 1, 2k \rrbracket$. The set \mathcal{I}_k contains all the possible combinations of telomeres that can be shortened at each division. In particular, the condition

$$\forall (i, j) \in I^2 : i \neq j \implies i \bmod k \neq j \bmod k$$

represents the fact that only one end of the chromosome is shortened at each division. At each cell division, we draw one set $I \in \mathcal{I}_k$ uniformly to know the indices where there is a shortening for the daughter cell we follow.

Example 2.3. When $k = 2$, we have

$$\mathcal{I}_2 = \{\{1, 2\}, \{1, 4\}, \{2, 3\}, \{3, 4\}\}.$$

If at a cell division, we draw $\{1, 4\} \in \mathcal{I}_2$ (probability 1/4 that this happens) as a set where indices are shortened, then there is a shortening in the coordinates 1 and 4, and the coordinates 2 and 3 stay unchanged.

We also introduce the following measure for all $I \in \mathcal{I}_k$

$$d\tilde{\mu}^{(I)}(v) := \left[\prod_{i \in I} \tilde{g}(v_i) dv_i \right] \left[\prod_{i \in \llbracket 1, 2k \rrbracket \setminus I} \delta_0(dv_i) \right]. \quad (2.6)$$

This measure represents the distribution of how telomeres are shortened at a division, knowing the fact that the telomeres that are shortened are those in I . Dirac measures represent the fact that the coordinates in $\llbracket 1, 2k \rrbracket \setminus I$ are unchanged, and the measure $\tilde{g}(v)dv$ that there is a shortening for the coordinates in I .

Finally, we consider

$$d\tilde{\mu}(v) := \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} d\tilde{\mu}^{(I)}(v). \quad (2.7)$$

This measure represents how telomeres are shortened at each division, taking into account all the possible combinations of telomeres that can be shortened at a division. The term 2^k comes from the fact that $\#\mathcal{I}_k = 2^k$, see Lemma A.7. Intuitively, this is because, at each division, for each chromosome, we do a choice between its two ends to know the one that is shortened. Additional results concerning the cardinals of subsets of \mathcal{I}_k are given in Section A.2.

We now have everything to write our model. We denote by $n^{(2k)}(t, x)$ the density of telomere with lengths $x \in \mathbb{R}_+^{2k}$ at time $t \geq 0$. We also denote by $n_\delta^{(2k)}(t)$ the density of senescence times at time $t \geq 0$. We assume that at each division, telomeres of the dividing cell are shortened by a random value distributed according to $\tilde{\mu}$, and that the dividing cell becomes senescent if one of its telomere has a length below 0. Then, the probability that a cell with length $y \in \mathbb{R}_+^{2k}$ becomes senescent after division is $\tilde{\mu}(\{v \in \mathbb{R}_+^{2k} \mid y - v \notin \mathbb{R}_+^{2k}\})$. We also assume that the initial distribution of telomere lengths is $n(0, x) = \prod_{i=1}^{2k} n_0(x_i)$, and refer to Remark 2.4 for more details about this choice. Adapting what we have explained for the single-telomere model to the above dynamics, we have that our second model is the following system of integro-differential equations

$$\begin{cases} \partial_t n^{(2k)}(t, x) = \tilde{b} \int_{\mathbb{R}_+^{2k}} n^{(2k)}(t, x + v) d\tilde{\mu}(v) - \tilde{b} \cdot n^{(2k)}(t, x), & \forall t \geq 0, x \in \mathbb{R}_+^{2k}, \\ n_\delta^{(2k)}(t) = \tilde{b} \int_{\mathbb{R}_+^{2k}} n^{(2k)}(t, y) \tilde{\mu}(\{v \in \mathbb{R}_+^{2k} \mid y - v \notin \mathbb{R}_+^{2k}\}) dy, & \forall t \geq 0, \\ n^{(2k)}(0, x) = \prod_{i=1}^{2k} n_0(x_i), & \forall x \in \mathbb{R}_+^{2k}. \end{cases} \quad (2.8)$$

Again, our aim is to estimate n_0 when $n_\delta^{(2k)}$ is observed.

Remark 2.4. We have assumed that the initial telomere lengths distribution is given by the product $\prod_{i=1}^{2k} n_0(x_i)$ for all $x \in \mathbb{R}_+^{2k}$. This means that the initial length distributions of two different telomeres are independent. We have no theoretical or simulation-based result that the latter is true for the moment. Further studies will be conducted in this regard. The reader should see this as a first mathematical simplification.

Remark 2.5. As for the model with one telomere, we have conservation of the number of individuals, i.e. that for all $t \geq 0$

$$\frac{d}{dt} \left[\int_{x \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x) dx + \int_0^t n_{\partial}^{(2k)}(s) ds \right] = 0, \quad \text{and} \quad \int_{x \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x) dx = \int_t^{+\infty} n_{\partial}^{(2k)}(s) ds. \quad (2.9)$$

Here are the steps to obtain this. First, integrate the first line of (2.8) in the variable x . Then, apply the Fubini's theorem and simplify the integrals in dx . Finally, apply another time the Fubini's theorem. It comes the following, which is exactly the left-hand side of (2.9), for all $t \geq 0$,

$$\begin{aligned} \frac{d}{dt} \left[\int_{x \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x) dx \right] &= -\tilde{b} \int_{v \in \mathbb{R}_+^{2k}} \left[\int_{x \in \mathbb{R}_+^{2k}, \exists i \in [1, 2k] : x_i < v_i} n^{(2k)}(t, x) dx \right] d\tilde{\mu}(v) \\ &= -\tilde{b} \int_{x \in \mathbb{R}_+^{2k}} \tilde{\mu} \left(\left\{ v \in \mathbb{R}_+^{2k} \mid x - v \notin \mathbb{R}_+^{2k} \right\} \right) n^{(2k)}(t, x) dx = -n_{\partial}^{(2k)}(t). \end{aligned}$$

Integrating both sides of the above, in view of Corollary A.6, then gives the right-hand side of (2.9).

2.2 Assumptions and main result

The main result of this work is the construction of estimators for the initial distribution of telomere lengths for both models, with their respective errors of estimation. We begin by presenting the main hypothesis of this work and some notations.

Assumptions. The assumptions for our main result are the following. They are verified for example when n_0 is the density of an Erlang distributions. This case is widely studied in our numerical study, see Section 5.

(H_1) : There exist $N > 0$ (large), $\delta > 0$, $g : [0, \delta] \rightarrow \mathbb{R}_+$ a probability density function and $b > 0$ such that

$$\tilde{\delta} = \frac{\delta}{N}, \quad \forall x \in [0, \tilde{\delta}] : \tilde{g}(x) = Ng(Nx), \quad \text{and} \quad \tilde{b} = bN.$$

(H_2) : There exist $\lambda > 0$, $C_\lambda > 0$ and $C'_\lambda > 0$ such that for all $x \in \mathbb{R}_+$

$$|n''_0(x)| \leq C_\lambda \exp(-\lambda x), \quad \text{and} \quad |n'_0(x)| \leq C'_\lambda \exp(-\lambda x).$$

(H_3) : There exists $D_\lambda \geq 1$ such that for all $x \in \mathbb{R}_+$

$$n_0(x) \leq D_\lambda \lambda \exp(-\lambda x).$$

(H_4) : There exist $\omega \geq \lambda$, $f_\omega : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ non-decreasing, and $D_\omega \in (0, 1]$ such that for all $x \geq 0$

$$n_0(x) \geq \frac{D_\omega f_\omega(x) \exp(-\omega x)}{\int_0^{+\infty} f_\omega(y) \exp(-\omega y) dy}.$$

The above assumptions are further discussed in Section 2.3, notably the biological relevance of the first one. We only mention the following point, that is crucial to understand the end of this subsection: in (H_1) , N is assumed to be large. Then, when a result is stated, one needs to imagine that N tends to infinity to understand it.

Notations. First, we denote the equivalents of $(\tilde{m}_i)_{i \in \{1,2\}}$ and \tilde{G} for g :

$$\forall i \in \{1, 2\} : m_i := \int_0^\delta u^i g(u) du, \quad \text{and} \quad \forall x \in \mathbb{R}_+ : G(x) := \int_0^{\min(x, \delta)} g(s) ds.$$

Then, we introduce the equivalents of $(\tilde{\mu}^{(I)})_{I \in \mathcal{I}_k}$ and $\tilde{\mu}$ for g :

$$\forall I \in \mathcal{I}_k : d\mu^{(I)}(v) := \left[\prod_{i \in I} g(v_i) dv_i \right] \left[\prod_{i \in \llbracket 1, 2k \rrbracket \setminus I} \delta_0(dv_i) \right], \quad \text{and} \quad d\mu(v) := \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} d\mu^{(I)}(v). \quad (2.10)$$

Thereafter, for all $d \in \mathbb{N}^*$ and ξ finite measure on \mathbb{R}_+^d , we consider $\mathcal{L}(\xi)$ the Laplace transform of ξ , defined for all $\beta \geq 0$ as:

$$\mathcal{L}(\xi)(\beta) := \int_{u \in \mathbb{R}_+^d} \exp\left(-\beta \sum_{i=1}^d u_i\right) \xi(du).$$

Finally, we define the two following constants:

$$\lambda_N := \frac{N}{m_1} \left[1 - \mathcal{L}(g)\left(\frac{\lambda}{N}\right) \right], \quad \lambda'_N := \frac{N}{km_1} \left[1 - \left(\mathcal{L}(g)\left(\frac{\lambda}{N}\right) \right)^k \right]. \quad (2.11)$$

In view of the fact that $\mathcal{L}(g)(0) = \int_0^\delta g(u) du = 1$ and the definition of the derivative, we have that $\lim_{N \rightarrow +\infty} \lambda_N = -\frac{\lambda(\mathcal{L}(g))'(0)}{m_1} = \lambda$. By the formula of the derivative of the power of a function, we also have that $\lim_{N \rightarrow +\infty} \lambda'_N = \lambda$. Then, as N is supposed large, λ_N and λ'_N correspond to approximations of λ .

Estimators and main result. To estimate n_0 from the observations of $n_\partial^{(1)}$ or $n_\partial^{(2k)}$, we use the estimators $\hat{n}_0^{(1)}$ and $\hat{n}_0^{(2k)}$ respectively, defined for all $x \geq 0$ as

$$\hat{n}_0^{(1)}(x) := \frac{1}{\tilde{b}\tilde{m}_1} n_\partial^{(1)}\left(\frac{x}{\tilde{b}\tilde{m}_1}\right), \quad \hat{n}_0^{(2k)}(x) := \frac{1}{k\tilde{b}\tilde{m}_1} \frac{n_\partial^{(2k)}\left(\frac{2x}{\tilde{b}\tilde{m}_1}\right)}{\left(\int_{\frac{2x}{\tilde{b}\tilde{m}_1}}^\infty n_\partial^{(2k)}(s) ds\right)^{1-\frac{1}{2k}}}. \quad (2.12)$$

Let us briefly explain how the expression of these estimators is obtained. The estimator on the left comes from the approximation of the pair $(n^{(1)}, n_\partial^{(1)})$ by a transport equation with drift $-bm_1$ and absorbed at $x = 0$, see Section 3. Thanks to this approximation, we have by using the characteristics of the transport equation that $n_\partial^{(1)}(t)$ is close to $bm_1 n_0(bm_1 t)$ for all $t \geq 0$ (see the right-hand side of (3.6)). Therefore, by first taking $t = \frac{x}{bm_1}$, then dividing both terms by bm_1 , and finally using the following equality that comes from the change of variable $u' = \frac{u}{N}$ and (H_1) :

$$bm_1 = b \int_0^\delta u g(u) du = bN^2 \int_0^{\frac{\delta}{N}} u' g(Nu') du' = \tilde{b}\tilde{m}_1, \quad (2.13)$$

we obtain that $\frac{1}{b\tilde{m}_1}n_{\partial}^{(1)}\left(\frac{x}{b\tilde{m}_1}\right)$ is close to $n_0(x)$ for all $x \geq 0$.

The estimator on the right of (2.12) also comes from an approximation of $(n^{(2k)}, n_{\partial}^{(2k)})$, see Section 4. This time, the approximated model is a transport equation with drift $-\frac{bm_1}{2}$ in each coordinate, and absorbed when one coordinate reaches 0. Compared to $\hat{n}_0^{(1)}$, it requires more steps to obtain the expression of $\hat{n}_0^{(2k)}$ from this approximation. First, by the conservation of the number of individuals stated in (2.9), our model approximation, and the characteristics of the equation, we have that $\int_t^{+\infty} n_{\partial}^{(2k)}(s)ds$ is close to $\left(\int_{\frac{bm_1 t}{2}}^{+\infty} n_0(s)ds\right)^{2k}$ for all $t \geq 0$ (see Remark 4.3). Then, by taking both terms to the power $\frac{1}{2k}$ and differentiating, we have that $\frac{1}{2k}n_{\partial}^{(2k)}(t)\left(\int_t^{+\infty} n_{\partial}^{(2k)}(s)ds\right)^{\frac{1}{2k}-1}$ is approximately equal to $\frac{bm_1}{2}n_0\left(\frac{bm_1 t}{2}\right)$ for all $t \geq 0$. Finally, by taking $t = \frac{2x}{bm_1}$, then multiplying by $\frac{2}{bm_1}$, we have that $\frac{1}{kbm_1}n_{\partial}^{(2k)}\left(\frac{2x}{bm_1}\right)\left(\int_{\frac{2x}{bm_1}}^{+\infty} n_{\partial}^{(2k)}(s)ds\right)^{\frac{1}{2k}-1}$ is close to $n_0(x)$ for all $x \geq 0$. This last result justifies the expression of the estimator on the right of (2.12) because bm_1 and $\tilde{b}\tilde{m}_1$ are equals, see (2.13).

The steps to obtain our estimators presented above are detailed more rigorously in Sections 3 and 4. In particular, after completing them, we obtain the following result, which provides upper bounds on the errors between the estimators presented in (2.12) and n_0 . It is the main result of the paper.

Theorem 2.6 (Main result). *We recall the constants λ_N and λ'_N defined in (2.11). The following statements hold.*

(a) *Assume $(H_1) - (H_2)$. Then, there exists $c_1 > 0$ such that for all $x \geq 0$*

$$\left|\hat{n}_0^{(1)}(x) - n_0(x)\right| \leq \frac{c_1}{N}(x+1)\exp(-\lambda_N x),$$

where c_1 depends only on $g, C_{\lambda}, C'_{\lambda}$ and D_{λ} .

(b) *Assume $(H_1) - (H_4)$. Then, there exists $d_1 > 0$ such that for all $x \geq 0$*

$$\left|\hat{n}_0^{(2k)}(x) - n_0(x)\right| \leq \frac{d_1}{N}\left(\frac{D_{\lambda}}{D_{\omega}}\right)^{2k}(k^2 x + k + 1)\exp[-(2k+1)\lambda'_N x + 2k\omega x],$$

where d_1 depends only on $g, \delta, \lambda, C_{\lambda}, C'_{\lambda}, D_{\lambda}$, and D_{ω} .

Notice that the pointwise errors tend to zero when $N \rightarrow +\infty$. Then, as N is assumed to be large, we have that $\hat{n}_0^{(1)}(x)$ and $\hat{n}_0^{(2k)}(x)$ estimate accurately $n_0(x)$, for all $x \geq 0$. The benefit of having a pointwise error is that it provides guarantees on the *local error* of the estimator, i.e. on any subset of \mathbb{R}_+ . It also provides information on where the estimation is the most and least reliable.

Let us comment on the dependence on x of the bounds in Theorem 2.6. First, assume that $(2k+1)\lambda'_N > 2k\omega$. Then, for each of the estimators, the bound contains a term corresponding to a linear growth in x , and a term corresponding to an exponential decay in x . The linear growth is related to the accumulation of errors during the model approximation: for all $s < t$, the error present at time s still affects the value at time t . The exponential decay is related to the fact that the influence of past errors dissipates over time at an exponential rate: the larger $t - s$ is, the less the error at time s influences the error at time t . In the case where $(2k+1)\lambda'_N \leq 2k\omega$, there is no exponential decay for $\hat{n}_0^{(2k)}$. This is because the denominator term of $\hat{n}_0^{(2k)}$, which tends

to 0 exponentially fast, compensates for the dissipation and leads to an exponential growth of the error (linear in the critical case $(2k+1)\lambda'_N = 2k\omega$). This is a problem because it means that the quality of the estimator declines very quickly.

Let us now comment on the dependence on k of the bound obtained in Theorem 2.6-(b). We observe that two terms contribute to the k -dependence of the error. The first one is the term $\left(\frac{D_\lambda}{D_\omega}\right)^{2k}$. It implies that there is exponential growth in the error bound when the number of chromosomes increases. In fact, this growth is mainly related to the fact that our assumptions are not optimal, which leads to a non-optimal bound, and not to the fact that the error grows exponentially. To be more precise, the bounding of n_0 by the densities presented in (H₃) and (H₄) results in a loss of information about n_0 . This loss of information is multiplied when the dimension increases since we start from an initial condition $n(0, x) = \prod_{i=1}^{2k} n_0(x_i)$, see (2.8). Then, as the dimension increases, it is theoretically more difficult to obtain a reliable bound on the error. The only case for which we can handle this effectively is when n_0 corresponds to the density of an exponential distribution. The reason is that we can verify (H₃) – (H₄) with $D_\lambda = D_\omega = 1$, and thus obtain that $\left(\frac{D_\lambda}{D_\omega}\right)^{2k}$ does not increase with k . The second term that contributes to the k -dependence of the bound in the second statement of Theorem 2.6 is the term $k^2x + k + 1$. It is related to the fact that the size of the space \mathbb{R}_+^{2k} becomes larger when k increases, making the model more difficult to approximate. In fact, the dependence on k of the error poses problems when one is interested in species for which $2k$ is large, such as yeast cells ($2k = 32$) or human cells ($2k = 94$). This issue is further studied in Section 5.2.2.

Theorem 2.6 provides bounds on the pointwise error of each estimator. Despite the advantages it has, it is not sufficient to only study this error. Specifically, we need to ensure that the accumulation of the pointwise errors does not lead to an explosion of the global error. To verify this, we obtain from Theorem 2.6 by using that $\int_0^{+\infty} x^p e^{-\beta x} dx = \frac{\Gamma(p+1)}{\beta^{p+1}}$ for all $\beta \geq 0$ and $p > 0$, the following corollary. It provides an error in terms of norms for our estimators, in all the Lebesgue spaces.

Corollary 2.7 (Estimation errors in Lebesgue spaces). *We recall the constants λ_N and λ'_N defined in (2.11). Under (H₃), we also consider the constant $\beta'_N := (2k+1)\lambda'_N - 2k\omega$. The following statements hold.*

(a) *Assume (H₁) – (H₂). Then, for all $p > 0$ we have*

$$\left\| \widehat{n}_0^{(1)} - n_0 \right\|_{L^p(\mathbb{R}_+)} \leq \frac{c_1}{N} \left(\frac{\Gamma(p+1)^{\frac{1}{p}}}{(\lambda_N p)^{1+\frac{1}{p}}} + \frac{1}{(\lambda_N p)^{\frac{1}{p}}} \right),$$

where c_1 is the same constant as in Theorem 2.6-(a).

(b) *Assume (H₁) – (H₄), and that $\beta'_N > 0$. Then, for all $p > 0$, we have*

$$\left\| \widehat{n}_0^{(2k)} - n_0 \right\|_{L^p(\mathbb{R}_+)} \leq \frac{d_1}{N} \left(\frac{D_\lambda}{D_\omega} \right)^{2k} \left(\frac{k^2 \Gamma(p+1)^{\frac{1}{p}}}{(\beta'_N p)^{1+\frac{1}{p}}} + \frac{k+1}{(\beta'_N p)^{\frac{1}{p}}} \right),$$

where d_1 is the same constant as in Theorem 2.6-(a).

From the above, we have that if $(2k+1)\lambda'_N \leq 2k\omega$, then the accumulation of the pointwise errors for $\widehat{n}_0^{(2k)}$ is too large to get a result in norm, due to the exponential growth of the pointwise errors (linear when $(2k+1)\lambda'_N = 2k\omega$). Conversely, when $(2k+1)\lambda'_N > 2k\omega$, we have that the accumulation of the pointwise errors is finite, and tends to 0 when $N \rightarrow +\infty$.

2.3 Discussion about the models and the assumptions

We conclude this section by providing complements about our choice of modelling and our main result assumptions. First, we present possible extensions of our model. Then, we explain our choice of having a trait space in continuous state space and a model with only one telomere. Finally, we discuss more our assumptions.

Extensions of the current models. In the models presented in Section 2.1, the following points can be complexified to have a better biological reality.

- Cell lifetimes are modelled by an exponential distribution. However, this is not biologically relevant because lifetimes have a shifted modal distribution, see Section B.1. The memory-less property of the exponential law is also problematic. A first possible generalisation is thus to add an age structure to our equations to be able to model other cell cycle distributions [35, 38, 48].
- We have used a deterministic threshold for the entry into the senescence state. It seems more realistic to use a rate rather than a threshold for the entry in senescence, as done in [5]. However, recent results coming from parameters calibration of telomere shortening models seem to support the fact that a deterministic threshold is a good approximation [41].
- It is also possible to consider a time-discrete version of our model in which cells lineages are followed generation by generation, and in which we observe the senescence generation instead of the time generation. This model version is relevant because senescence generations are more often studied than senescence times, see [7, 17, 30, 56]. We have not made this choice here because we are more comfortable with continuous-time equations.

A continuous state space. In our models, we use a continuous state space while telomere lengths are usually measured with a discrete unit, i.e. the *base pairs*. As telomere length variation between two nucleotides is very small, and we have a lot of nucleotides, this approximation is reasonable. Indeed, as illustrated in Section B.2, we do not observe any gap when we plot the discretised versions of some telomere length densities, and the latter can be seen as a continuous curve. From a practical point of view, what we only have to do is to discretise the continuous initial distribution estimated by our method to get a discrete estimation.

Relevance of using a model with one telomere. As said in the presentation of the first model, up to our knowledge, there is no species with only one telomere. However, there are at least two good reasons to work with such a model.

- It is possible with experimental methods to place ourselves in a setting very similar to the study of cells with one telomere [57, p. 112].
- It has been deduced numerically that 60% of senescence times are signalled by the telomere that was the shortest at the beginning of the dynamics [7]. This suggests that the telomere that is shortest initially is the one that most frequently signals the distribution of senescence times. Therefore, even if the approximation is rough, we can assume that this is the shortest telomere at the beginning that signals senescence. This approximation allows us to simplify computations and to gain first insight. Under this approximation, it is sufficient to consider a single-telomere model.

Discussion about the assumptions. We now discuss the consequences of our assumptions, how they are useful in our proofs, and why we made them.

- (H_1) : This is the key assumption of this paper, as it allows us to justify that we can approximate our models by transport equations, see Sections 3.1 and 4.1. Since N is assumed to be large, this assumption means that the shortening value is small compared to the scale where telomere lengths are initially distributed. The assumption that the shortening value is small comes from the following biological reality:
 - The average telomere length of the budding yeast is of the order of 300 base pairs [47, 53], and the average shortening value is of the order of 7.5 base pairs [17]. The ratio between these is $\frac{7.5}{300} = \frac{1}{40} = 2.5\%$, which is small.
 - The average telomere length of the human is of the order of 12.5 kilobase pairs [47], and the average shortening value is of the order of 0.125 kilobase pairs [22]. The ratio between these is $\frac{0.125}{12.5} = \frac{1}{100} = 1\%$, which is small.

By the above explanation, we have that $N = 40$ when we study the budding yeast, and $N = 100$ when we study the human.

The assumption on the birth rate \tilde{b} means that we work on a time scale where division times occur very frequently. This allows us to compensate the fact that the shortening values are small, and to avoid to have senescence times that tend to infinity when $N \rightarrow +\infty$.

- (H_2) : Due to a Taylor's expansion of the second order, the approximation errors of our models are mainly given by the second derivative of n_0 , see Section 3.3. The inequality on the left-hand side of (H_2) allows us to have a control on it.

The inequality on the right-hand side, for its part, allows us to have a control on the variation of telomere length density close to 0. Controlling this is important because cells susceptible to become senescent have telomere lengths close to 0. For more information, we refer to Sections 3.4, 3.5 and 4.5.

- (H_3) : The error between the model with several telomeres and a transport equation depends on the first and the second derivative of n_0 , but also on n_0 itself. This assumption allows us to control it.
- (H_4) : This assumption allows us to obtain a lower bound for $\int_t^{+\infty} n_{\partial}^{(2k)}(s)ds$, for all $t \geq 0$. It is important to have such lower bound because the inverse of $\int_t^{+\infty} n_{\partial}^{(2k)}(s)ds$ appears in the expression of $\hat{n}_0^{(2k)}$, see (2.12), and tends to 0 when $t \rightarrow +\infty$. Therefore, if the decay of the function $t \mapsto \int_t^{+\infty} n_{\partial}^{(2k)}(s)ds$ is too fast, then $\hat{n}_0^{(2k)}(x)$ explodes when $x \rightarrow +\infty$.

3 The single-telomere model

To facilitate understanding, we begin by obtaining a bound on the error done by the estimator $\hat{n}_0^{(1)}$ used in the single-telomere model, i.e. we prove Theorem 2.6-(a). This statement follows almost directly from the approximation of the single-telomere model by a transport equation. We thus focus a large part of this section in obtaining bounds on the approximation errors of $n^{(1)}$ and $n_{\partial}^{(1)}$, after having explained how this approximation allows us to obtain Theorem 2.6-(a).

First, in Section 3.1, we successively rewrite (2.3) using the constants and functions introduced in (H_1) , explain how an approximation by a transport equation can be obtained from

this rewriting, and prove Theorem 2.6-(a) assuming that the approximation is true. Then, in Section 3.2, we present the auxiliary results necessary to obtain this approximation. Thereafter, in Sections 3.3 and 3.4, we prove these auxiliary statements. Finally, in Section 3.5, we prove the model approximation. Throughout this section, we assume that (H_1) holds.

3.1 Model approximation and proof of Theorem 2.6-(a)

To obtain a bound on the error of $\widehat{n}_0^{(1)}$, we first need to approximate (2.3). This approximation is obtained by letting the scaling parameter N , introduced in (H_1) , tend to infinity. To do so, we need to rewrite (2.3) using the quantities introduced in (H_1) to replace \tilde{b} and \tilde{g} . This will allow us to observe what happens when $N \rightarrow +\infty$. Let us start with the first line of (2.3). In this equation, we replace \tilde{b} with bN , then $\tilde{g}(v)$ with $Ng(Nv)$ for all $v \geq 0$, and finally $\tilde{\delta}$ with $\frac{\delta}{N}$. Thereafter, we do the change of variable $v' = Nv$, and place $n^{(1)}(t, x)$ inside the integral by using that g is a probability density function. We obtain the following, for all $t \geq 0, x \geq 0$,

$$\begin{aligned} \partial_t n^{(1)}(t, x) &= bN^2 \int_0^{\frac{\delta}{N}} n^{(1)}(t, x + v) g(Nv) dv - bN \cdot n^{(1)}(t, x) \\ &= bN \int_0^{\delta} \left[n^{(1)}\left(t, x + \frac{v'}{N}\right) - n^{(1)}(t, x) \right] g(v') dv'. \end{aligned} \quad (3.1)$$

Now, we rewrite the second line of (2.3). First observe that, by the change of variable $w' = \frac{w}{N}$, we have for all $v \in [0, \frac{\delta}{N}]$

$$G(Nv) = \int_0^{Nv} g(w) dw = N \int_0^v g(Nw') dw' = \int_0^v \tilde{g}(w') dw' = \tilde{G}(v). \quad (3.2)$$

In view of the above equality, in the second line of (2.3), we successively replace \tilde{b} with bN , $\tilde{G}(v)$ with $G(Nv)$ for all $v \geq 0$, and finally $\tilde{\delta}$ with $\frac{\delta}{N}$. Then, we do the change of variable $v' = Nv$. It comes the following rewriting, for all $t \geq 0$,

$$n_{\partial}^{(1)}(t) = bN \int_0^{\frac{\delta}{N}} n^{(1)}(t, v) (1 - G(Nv)) dv = b \int_0^{\delta} n^{(1)}\left(t, \frac{v'}{N}\right) (1 - G(v')) dv'. \quad (3.3)$$

By combining (3.1) and (3.3), we now have, below, a new expression for (2.3) in which N appears explicitly

$$\begin{cases} \partial_t n^{(1)}(t, x) = bN \int_0^{\delta} \left[n^{(1)}\left(t, x + \frac{v}{N}\right) - n^{(1)}(t, x) \right] g(v) dv, & \forall t \geq 0, x \geq 0, \\ n_{\partial}^{(1)}(t) = b \int_0^{\delta} n^{(1)}\left(t, \frac{v}{N}\right) (1 - G(v)) dv, & \forall t \geq 0, \\ n^{(1)}(0, x) = n_0(x), & \forall x \geq 0. \end{cases} \quad (3.4)$$

We aim to derive a system corresponding to the limit version of (3.4) as $N \rightarrow +\infty$. In fact, this system can be intuitively obtained. To do so, one has to observe that by the definition of the derivative and the equality $\int_0^{\delta} (1 - G(v)) dv = \int_0^{\delta} vg(v) dv = m_1$ (integration by part), we have the two following results, for all $t \geq 0$,

$$\begin{aligned} N \int_0^{\delta} \left[n^{(1)}\left(t, x + \frac{v}{N}\right) - n^{(1)}(t, x) \right] g(v) dv &\underset{N \rightarrow +\infty}{\approx} \int_0^{\delta} \left[v \partial_x n^{(1)}(t, x) \right] g(v) dv = m_1 \partial_x n^{(1)}(t, x), \\ \int_0^{\delta} n^{(1)}\left(t, \frac{v}{N}\right) (1 - G(v)) dv &\underset{N \rightarrow +\infty}{\approx} m_1 n^{(1)}(t, 0). \end{aligned}$$

Then, by plugging the above in (3.4), we can conjecture that the following system of partial differential equations approximates (3.4)

$$\begin{cases} \partial_t u^{(1)}(t, x) = bm_1 \partial_x u^{(1)}(t, x), & \forall t \geq 0, x \geq 0, \\ u_{\partial}^{(1)}(t) = bm_1 u^{(1)}(t, 0), & \forall t \geq 0, \\ u^{(1)}(0, x) = n_0(x), & \forall x \geq 0. \end{cases} \quad (3.5)$$

Remark 3.1. *By using the characteristics of the transport equation in the first line of (3.5), we also have the following alternative representation for $u^{(1)}$ and $u_{\partial}^{(1)}$, for all $t \geq 0, x \geq 0$,*

$$u^{(1)}(t, x) = n_0(bm_1 t + x), \quad \text{and} \quad u_{\partial}^{(1)}(t) = bm_1 n_0(bm_1 t). \quad (3.6)$$

Another more qualitative way to obtain this conjecture is to observe that (3.4) corresponds to telomere shortening dynamics with an accelerated birth rate bN and a significantly reduced maximum shortening value $\frac{\delta}{N}$. Then, when $N \rightarrow +\infty$, we have instantaneous divisions with an infinitesimal shortening at each division. The latter can be seen as a continuous erosion of the trait over time, represented by a transport term. This corresponds to what is modelled by the first line of (3.5). In addition, in this model, cells with telomere length $y \in [0, \frac{\delta}{N}]$ go to the cemetery with probability $1 - G(y)$ when they divide (see the second line of (2.3)). Then, by letting N tend to infinity, we obtain that cells enter in senescence with probability 1 when their telomere length is 0. This corresponds to what is modelled by the second line of (3.5).

In fact, our conjecture can be rigorously proven. Specifically, the following result provides bounds on the pointwise error between (3.4) and (3.5), stating that this error tends to 0 when $N \rightarrow +\infty$. This proposition is proved in Section 3.5.

Proposition 3.2 (Pointwise approximation errors, one telomere). *We recall the constant λ_N defined in (2.11). The following statements hold.*

(a) *Assume $(H_1) - (H_2)$. Then, there exists $c'_0 > 0$ such that for all $t \geq 0, x \geq 0$, we have*

$$\left| n^{(1)}(t, x) - u^{(1)}(t, x) \right| \leq \frac{c'_0 b t}{N} \exp(-bm_1 \lambda_N t) \exp(-\lambda x),$$

where c'_0 depends only on g and C_λ .

(b) *Assume $(H_1) - (H_2)$. Then, there exists $c'_1 > 0$ such that for all $t \geq 0$, we have*

$$\left| n_{\partial}^{(1)}(t) - u_{\partial}^{(1)}(t) \right| \leq \frac{c'_1 b (bm_1 t + 1)}{N} \exp(-bm_1 \lambda_N t),$$

where c'_1 depends only on g, C_λ and C'_λ .

As for Theorem 2.6, a result in norm can also be obtained to obtain bounds on the global approximation errors. Again, this corollary is proved by using Proposition 3.2 and the fact that for all $p \geq 0$, we have $\int_0^{+\infty} x^p e^{-\beta x} dx = \frac{\Gamma(p+1)}{\beta^{p+1}}$.

Corollary 3.3 (Approximation errors in Lebesgue spaces, one telomere). *We recall the constant λ_N defined in (2.11). The following statements hold.*

(a) *Assume $(H_1) - (H_2)$. Then, for all $p > 0$ we have*

$$\left\| n^{(1)} - u^{(1)} \right\|_{L^p(\mathbb{R}_+ \times \mathbb{R}_+)} \leq \frac{c'_0 b}{N} \left(\frac{(\Gamma(p+1))^{\frac{1}{p}}}{(bm_1 \lambda_N p)^{1+\frac{1}{p}} (\lambda p)^{\frac{1}{p}}} \right),$$

where c'_0 is the same constant as in Proposition 3.2-(a).

(b) Assume $(H_1) - (H_2)$. Then, for all $p > 0$ we have

$$\left\| n_{\partial}^{(1)} - u_{\partial}^{(1)} \right\|_{L^p(\mathbb{R}_+)} \leq \frac{c'_1 b}{N} \left(\frac{(bm_1 \Gamma(p+1))^{\frac{1}{p}}}{(bm_1 \lambda_N p)^{1+\frac{1}{p}}} + \frac{1}{(bm_1 \lambda_N p)^{\frac{1}{p}}} \right),$$

where c'_1 is the same constant as in Proposition 3.2-(b).

The main interest of Proposition 3.2 is that it allows us to get an upper bound on the error done by the estimator $\widehat{n}_0^{(1)}$. In particular, one can easily obtain from this proposition the following statement, which directly implies that Theorem 2.6-(a) holds with $c_1 = \frac{c'_1}{m_1}$.

Corollary 3.4 (Pointwise estimation error, one telomere). *We recall the constant λ_N defined in (2.11). Assume that $(H_1) - (H_2)$ hold. Then, for all $x \geq 0$, we have*

$$\left| \widehat{n}_0^{(1)}(x) - n_0(x) \right| \leq \frac{c'_1 (x+1)}{m_1 N} \exp(-\lambda_N x),$$

where c'_1 is the same constant as in Proposition 3.2-(b).

Proof. Let $x \geq 0$. First observe that by the right-hand side of (3.6), the following equality holds: $n_0(x) = \frac{1}{bm_1} u_{\partial}^{(1)}\left(\frac{x}{bm_1}\right)$. Therefore, in view of the definition of $\widehat{n}_0^{(1)}(x)$ given in (2.12) and then (2.13), we have that

$$\left| \widehat{n}_0^{(1)}(x) - n_0(x) \right| = \frac{1}{bm_1} \left| n_{\partial}^{(1)}\left(\frac{x}{bm_1}\right) - u_{\partial}^{(1)}\left(\frac{x}{bm_1}\right) \right|.$$

From the above, the corollary is proved by simply applying Proposition 3.2-(b). \square

By this corollary, if we manage to justify that Proposition 3.2 is true, then Theorem 2.6-(a) will be proved. Explaining why this proposition holds is thus what we do in the next subsections. In particular, we now present the main arguments and the auxiliary statements used to obtain it.

3.2 Plan of the proof of Proposition 3.2

To prove Proposition 3.2, we need to start by obtaining its first statement, as the second one uses the first statement in its proof. We thus first present the plan of the proof of Proposition 3.2-(a), and then give the plan of Proposition 3.2-(b).

The proof of the first statement of Proposition 3.2 consists in controlling the absolute value of $\bar{u}^{(1)} := n^{(1)} - u^{(1)}$. To do so, we first obtain an integro-differential equation verified by $\bar{u}^{(1)}$. This would allow us to apply results related to this equation to bound $|\bar{u}^{(1)}|$. By taking the difference between the first lines of (3.4) and (3.5), then decomposing $n^{(1)}$ with the equality $n^{(1)} = \bar{u}^{(1)} + u^{(1)}$, and finally using that $bm_1 = bN \int_0^{\delta} \frac{v}{N} g(v) dv$, we have for all $t \geq 0$, $x \geq 0$,

$$\begin{aligned} \partial_t \bar{u}^{(1)}(t, x) &= bN \int_0^{\delta} \left[n^{(1)}\left(t, x + \frac{v}{N}\right) - n^{(1)}(t, x) \right] g(v) dv - bm_1 \partial_x u^{(1)}(t, x) \\ &= bN \int_0^{\delta} \left[\bar{u}^{(1)}\left(t, x + \frac{v}{N}\right) - \bar{u}^{(1)}(t, x) \right] g(v) dv \\ &\quad + bN \int_0^{\delta} \left[u^{(1)}\left(t, x + \frac{v}{N}\right) - u^{(1)}(t, x) - \frac{v}{N} \partial_x u^{(1)}(t, x) \right] g(v) dv. \end{aligned} \tag{3.7}$$

Therefore, if we are able to bound a solution of the above equation, then Proposition 3.2-(a) will be proved. The following lemma, proved in Section 3.3, allows us to do this. This lemma is stated for equations in a multidimensional trait space instead of only \mathbb{R}_+ , as we use it later in Section 4.4 for the approximation of the model with several telomeres.

Lemma 3.5 (Key lemma for approximating lengths densities). *Let $d \in \mathbb{N}^*$, ξ a probability measure on \mathbb{R}^d with finite first and second moments, and $F : \mathbb{R}_+ \times \mathbb{R}_+^d \rightarrow \mathbb{R}$. We also consider u_ξ the solution of the following integro-differential equation, for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$,*

$$\begin{aligned} \partial_t u_\xi(t, x) &= bN \int_{v \in \mathbb{R}_+^d} \left[u_\xi \left(t, x + \frac{v}{N} \right) - u_\xi(t, x) \right] \xi(dv) \\ &+ bN \int_{v \in \mathbb{R}_+^d} \left[F \left(t, x + \frac{v}{N} \right) - F(t, x) - \sum_{i=1}^d \frac{v_i}{N} \partial_{x_i} F(t, x) \right] \xi(dv), \end{aligned} \quad (3.8)$$

with initial condition $u_\xi(0, \cdot) \equiv 0$. Assume that there exist $\alpha, \beta > 0$ and $C > 0$ verifying for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$

$$\sup_{(\ell, \ell') \in \llbracket 1, d \rrbracket^2} (|\partial_{x_\ell x_{\ell'}} F(t, x)|) \leq C \exp \left(-\alpha t - \beta \sum_{i=1}^d x_i \right), \quad (3.9)$$

$$bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) \leq \alpha. \quad (3.10)$$

Then, denoting the constant $\sigma_\xi = \sum_{1 \leq \ell, \ell' \leq d} \int_{v \in \mathbb{R}_+^d} v_\ell v_{\ell'} \xi(dv)$, we have for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$

$$|u_\xi(t, x)| \leq \frac{btC\sigma_\xi}{2N} \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t \right] \exp \left(-\beta \sum_{i=1}^d x_i \right). \quad (3.11)$$

One can easily see that (3.7) is an equation of the form given in (3.8), with $d = 1$, $u_\xi = \bar{u}^{(1)}$, $\xi = g$ and $F = u^{(1)}$. The proof of the first statement of Proposition 3.2 is thus to check the other assumptions of Lemma 3.5, namely (3.9) and (3.10), and then to apply it. We do this in Section 3.5.

To prove Proposition 3.2-(b), we need this time to control $|\bar{u}_\partial^{(1)}| := |n_\partial^{(1)} - u_\partial^{(1)}|$. Again, we do this by obtaining the equation verified by $\bar{u}_\partial^{(1)}$, and then applying a general lemma allowing to control this equation. By taking the difference between the second lines of (3.4) and (3.5), then decomposing $n^{(1)}$ with the equality $n^{(1)} = \bar{u}^{(1)} + u^{(1)}$, and finally using that $\int_0^\delta (1 - G(v))dv = \int_0^\delta vg(v)dv = m_1$ (integration by part), we have for all $t \geq 0$

$$\begin{aligned} \bar{u}_\partial^{(1)}(t) &= b \int_0^\delta n^{(1)} \left(t, \frac{v}{N} \right) (1 - G(v))dv - bm_1 u^{(1)}(t, 0) \\ &= b \int_0^\delta \bar{u}^{(1)} \left(t, \frac{v}{N} \right) (1 - G(v))dv + b \int_0^\delta \left[u^{(1)} \left(t, \frac{v}{N} \right) - u^{(1)}(t, 0) \right] (1 - G(v))dv. \end{aligned} \quad (3.12)$$

We thus need to control an equation with the same form as (3.12), and the second statement of Proposition 3.2 will be obtained. This control is done by using the following lemma, that is proved in Section 3.4. Again, we give a general lemma for functions in a multidimensional trait because we reuse it for the model with several telomeres, see Section 4.5.

Lemma 3.6 (Key lemma for approximating cemeteries). *Assume that the assumptions of Lemma 3.5 hold. We consider a set of functions $(h_i)_{i \in \llbracket 1, d \rrbracket}$ from $\mathbb{R}_+ \times \mathbb{R}_+^d$ to \mathbb{R} and $C' > 0$ such that for all $t \geq 0$, $x \in \mathbb{R}_+^d$ and $i \in \llbracket 1, d \rrbracket$, it holds*

$$|h_i(t, x)| \leq \frac{C'x_i}{N} \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t - \beta \sum_{j=1, j \neq i}^d x_j \right]. \quad (3.13)$$

We denote the function $v_\xi : \mathbb{R}_+ \rightarrow \mathbb{R}$, defined for all $t \geq 0$ as

$$v_\xi(t) := bN \int_{y \in \mathbb{R}_+^d} u_\xi(t, y) \xi(\{v \in \mathbb{R}_+^d \mid Ny - v \notin \mathbb{R}_+^d\}) dy + b \sum_{i=1}^d \int_{y \in \mathbb{R}_+^d} h_i(t, y) (1 - G(y_i)) 1_{\{y_i \leq \delta\}} dy. \quad (3.14)$$

Then, recalling the constant σ_ξ introduced in Lemma 3.5, we have for all $t \geq 0$

$$|v_\xi(t)| \leq \left(\frac{bC\sigma_\xi\alpha}{2\beta^d N} + \frac{bC'm_2d}{2\beta^{d-1}N} \right) \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t \right]. \quad (3.15)$$

This is less evident to see it, but Eq. (3.12) and a change of variable imply that $\bar{u}_\partial^{(1)}$ is of the form presented in (3.14) for $\xi = g$. More details about this are given in Section 3.5, as well as the proof of Proposition 3.2-(b) from Lemma 3.6.

We now prove the auxiliary statements given in this section, and then obtain Proposition 3.2 from them.

3.3 Proof of Lemma 3.5

We begin with preliminaries. To simplify notations, we denote $H_N : \mathbb{R}_+ \times \mathbb{R}_+^d \rightarrow \mathbb{R}$, the function defined for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$ as

$$\begin{aligned} H_N(t, x) &:= bN \int_{v \in \mathbb{R}_+^d} \left[F \left(t, x + \frac{v}{N} \right) - F(t, x) - \sum_{i=1}^d \frac{v_i}{N} \partial_{x_i} F(t, x) \right] \xi(dv) \\ &= \frac{b}{N} \sum_{1 \leq \ell, \ell' \leq d} \int_{v \in \mathbb{R}_+^d} \left[\int_0^1 (1-w) \left(\partial_{x_\ell x_{\ell'}} F \left(t, x + w \frac{v}{N} \right) v_\ell v_{\ell'} \right) dw \right] \xi(dv). \end{aligned} \quad (3.16)$$

The above last equality comes from expanding $F \left(t, x + \frac{v}{N} \right) - F(t, x) - \sum_{i=1}^d \frac{v_i}{N} \partial_{x_i} F(t, x)$ using the Taylor's expansion with remainder in integral form. We also introduce the linear operator $\Phi : L^1(\mathbb{R}^d) \rightarrow C(\mathbb{R}_+, L^1(\mathbb{R}^d))$, defined such that for all $f_0 \in L^1(\mathbb{R}^d)$, $m = \Phi(f_0)$ is the solution in $C(\mathbb{R}_+, L^1(\mathbb{R}^d))$ of the following integro-differential equation

$$\begin{cases} \partial_t m(t, x) = bN \int_{\mathbb{R}_+^d} m \left(t, x + \frac{v}{N} \right) \xi(dv) - bNm(t, x), & \forall t \geq 0, x \in \mathbb{R}_+^d, \\ m(0, x) = f_0(x), & \forall x \in \mathbb{R}_+^d. \end{cases} \quad (3.17)$$

This operator is well-posed by Proposition A.1.

The proof of Lemma 3.5 is done in two steps. First, in Step 1, we prove that for all $(t, s, x) \in \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+^d$ such that $t \geq s$, it holds

$$|\Phi(H_N(s, \cdot))(t - s, x)| \leq \frac{bC\sigma_\xi}{2N} \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t \right] \exp \left(-\beta \sum_{i=1}^d x_i \right). \quad (3.18)$$

Then, in Step 2, we prove that for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$, we have

$$u_\xi(t, x) = \int_0^t \Phi(H_N(s, \cdot))(t - s, x) ds. \quad (3.19)$$

In view of the fact that for all $s \geq 0$, $H_N(s, \cdot)$ is the source term in (3.8) at time s , Eq. (3.19) means that we have rewritten u_ξ as the sum of the evolutions of the source terms over time. This equation and Eq. (3.18) imply that the lemma is proved, as we only have to plug (3.18) in (3.19) and then integrate to obtain (3.11).

Step 1: Assume first that for all $(s, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$ it holds

$$|H_N(s, x)| \leq \frac{bC\sigma_\xi}{2N} \exp(-\alpha s) f_\beta(x), \quad (3.20)$$

where $f_\beta(x) := \exp(-\beta \sum_{i=1}^d x_i)$. By Corollary A.2 and the definition of Φ , a maximum principle holds for the operator Φ . The latter is characterised by the fact that for all $(h, \varphi) \in (L^1(\mathbb{R}_+^d))^2$ verifying $|h| \leq \varphi$, we have $|\Phi(h)| \leq \Phi(\varphi)$. To bound from above the left-hand side of (3.18), we first apply this principle for $h = H_N(s, \cdot)$ and $\varphi = \frac{bC\sigma_\xi}{2N} \exp(-\alpha s) f_\beta$. Then, we use that it holds $\Phi(\varphi) = \frac{bC\sigma_\xi}{2N} \exp(-\alpha s) \Phi(f_\beta)$ (same h as before), as Φ is a linear operator. Finally, we apply Proposition A.3 to compute $\Phi(f_\beta)$. We obtain that for all $(t, s, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$ such that $s \leq t$

$$|\Phi(H_N(s, \cdot))(t - s, x)| \leq \frac{bC\sigma_\xi}{2N} \exp(-\alpha s) \exp\left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N}\right)\right) (t - s)\right] \exp\left[-\beta \sum_{i=1}^d x_i\right]. \quad (3.21)$$

Then, by using (3.10) to bound from above the first exponential, we get that (3.18) is true assuming that (3.20) holds.

It thus remains to prove (3.20), and Step 1 will be done. To do so, we first plug (3.9) in the second line of (3.16). Then, we bound from above $\exp(-\alpha s - \sum_{i=1}^d \beta(x_i + w \frac{v_i}{N}))$ by $\exp(-\alpha s) f_\beta(x)$, and use the equality $\int_0^1 (1 - w) dw = \frac{1}{2}$. It comes the following, which proves (3.20) and concludes the proof of the first step, for all $(s, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$,

$$\begin{aligned} |H_N(s, x)| &\leq \frac{bC}{N} \sum_{1 \leq \ell, \ell' \leq d} \int_{v \in \mathbb{R}_+^d} \left[\int_0^1 (1 - w) \exp\left(-\alpha s - \sum_{i=1}^d \beta\left(x_i + w \frac{v_i}{N}\right)\right) v_\ell v_{\ell'} dw \right] \xi(dv) \\ &\leq \frac{bC}{2N} \left[\sum_{1 \leq \ell, \ell' \leq d} \int_{v \in \mathbb{R}_+^d} v_\ell v_{\ell'} \xi(dv) \right] \exp(-\alpha s) f_\beta(x) = \frac{bC\sigma_\xi}{2N} \exp(-\alpha s) f_\beta(x). \end{aligned}$$

Step 2: To obtain (3.19), we prove that the function \tilde{u}_ξ , defined for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$ as

$$\tilde{u}_\xi(t, x) = \int_0^t \Phi(H_N(s, \cdot))(t - s, x) ds \quad (3.22)$$

is a solution of (3.8), the equation verified by u_ξ . Then, as by Proposition A.1 this equation has a unique solution in $C(\mathbb{R}_+, L^1(\mathbb{R}_+^d))$ with initial condition identically zero, we will have that $u_\xi = \tilde{u}_\xi$, so that (3.19) is true.

To do the above, we first compute $\partial_t \tilde{u}_\xi(t, x)$, by using that for all $f \in W^{1,1}(\mathbb{R}_+, L^1(\mathbb{R}_+))$ such that $s \mapsto f(s, s) \in L^1(\mathbb{R}_+)$, it holds $\frac{d}{dt} \left(\int_0^t f(t, s) ds \right) = \int_0^t \partial_1 f(t, s) ds + f(t, t)$. In our case, the fact that for all $y \geq 0$, the function $(t, s) \mapsto \Phi(H_N(s, \cdot))(t - s, y)$ belongs to this set is a consequence of (3.21), (3.10), and the first line of (3.17). Thereafter, we simplify the terms $\partial_t \Phi(H_N(s, \cdot))(t - s, x)$ and $\Phi(H_N(s, \cdot))(0, x)$ that appear after the previous computation, in view of the fact that $\Phi(H_N(s, \cdot))$ is a solution of (3.17) with initial condition $f_0 = H_N(s, \cdot)$. Finally, we switch the integrals, and use (3.22) to replace the integrals in ds with the function \tilde{u}_ξ .

We obtain that for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$

$$\begin{aligned} \partial_t \tilde{u}_\xi(t, x) &= \int_0^t \partial_t \Phi(H_N(s, \cdot))(t - s, x) ds + \Phi(H_N(t, \cdot))(0, x) \\ &= bN \int_0^t \left[\int_{\mathbb{R}_+^d} \Phi(H_N(s, \cdot)) \left(t - s, x + \frac{v}{N}\right) \xi(dv) - \Phi(H_N(s, \cdot))(t - s, x) \right] ds + H_N(t, x) \\ &= bN \int_{\mathbb{R}_+^d} \tilde{u}_\xi \left(t, x + \frac{v}{N}\right) \xi(dv) - bN \tilde{u}_\xi(t, x) + H_N(t, x). \end{aligned}$$

The above equation is in fact the same as (3.8) in view of the definition of H_N , see (3.16). Then, we have that $u_\xi = \tilde{u}_\xi$, which concludes the proof of the second step, and thus of the lemma. \square

3.4 Proof of Lemma 3.6

To simplify notations, we denote for all $y \in \mathbb{R}_+^d$ the set $A_{Ny} := \{v \in \mathbb{R}_+^d \mid Ny - v \notin \mathbb{R}_+^d\}$. We consider $v_{\xi,1}$ and $v_{\xi,2}$ the functions defined for all $t \geq 0$ as

$$v_{\xi,1}(t) = bN \int_{y \in \mathbb{R}_+^d} u_\xi(t, y) \xi(A_{Ny}) dy, \quad \text{and} \quad v_{\xi,2}(t) = b \sum_{i=1}^d \int_{y \in \mathbb{R}_+^d} h_i(t, y) (1 - G(y_i)) 1_{\{y_i \leq \delta\}} dy.$$

By (3.14), we have that $v_\xi = v_{\xi,1} + v_{\xi,2}$. Then, to prove this lemma, we bound $v_{\xi,1}$ and $v_{\xi,2}$, and conclude by summing their bounds, in view of the triangular inequality.

Let $t \geq 0$. We begin by bounding $v_{\xi,2}(t)$. First, for all $i \in \llbracket 1, d \rrbracket$, we apply (3.13) to bound from above the function h_i in the integral. Then, we compute the integrals with respect to the measures $(dy_j)_{j \in \llbracket 1, d \rrbracket, j \neq i}$, by using that

$$\prod_{j \in \llbracket 1, d \rrbracket, j \neq i} \left(\int_{y_j \in \mathbb{R}_+} \exp(-\beta y_j) dy_j \right) = \left(\int_{s \in \mathbb{R}_+} \exp(-\beta s) ds \right)^{d-1} = \frac{1}{\beta^{d-1}}.$$

Finally, we use the equality $\int_{y_i \in [0, \delta]} y_i (1 - G(y_i)) dy_i = \int_{y_i \in [0, \delta]} \frac{(y_i)^2}{2} g(y_i) dy_i = \frac{m_2}{2}$ (integration by part) to compute the integral that remains. It comes

$$\begin{aligned} |v_{\xi,2}(t)| &\leq b \sum_{i=1}^d \frac{C'}{N} \frac{1}{\beta^{d-1}} \frac{m_2}{2} \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t \right] \\ &= \frac{bC'm_2d}{2\beta^{d-1}N} \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t \right]. \end{aligned} \tag{3.23}$$

Now, we focus on bounding $v_{\xi,1}(t)$. To do so, we first apply (3.11) to bound from above the term $u_\xi(t, y)$ in $|v_{\xi,1}(t)|$. Thereafter, we use the fact that for all $y \in \mathbb{R}^d$ it holds $\xi(A_{Ny}) = 1 - \xi((A_{Ny})^c)$ to develop the bound obtained in two different integrals. Finally, we compute the value of the first integral, which is $\int_{y \in \mathbb{R}_+^d} \exp(-\beta \sum_{i=1}^d y_i) dy = \frac{1}{\beta^d}$. We get the following intermediate inequality

$$\begin{aligned} |v_{\xi,1}(t)| &\leq \frac{b^2 t C \sigma_\xi}{2} \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t \right] \int_{y \in \mathbb{R}_+^d} \exp \left(-\beta \sum_{i=1}^d y_i \right) \xi(A_{Ny}) dy \\ &= \frac{b^2 t C \sigma_\xi}{2} \exp \left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right) \right) t \right] \left[\frac{1}{\beta^d} - \int_{y \in \mathbb{R}_+^d} \exp \left(-\beta \sum_{i=1}^d y_i \right) \xi((A_{Ny})^c) dy \right]. \end{aligned} \tag{3.24}$$

To continue our computations, we need to find a better expression for the last term of (3.24). We notice that an alternative writing for A_{Ny} is $A_{Ny} = \{v \in \mathbb{R}_+^d \mid \exists i \in \llbracket 1, d \rrbracket \text{ s.t. } Ny_i < v_i\}$, for all $y \geq 0$. By this writing, it holds $\xi((A_{Ny})^c) = \int_{v \in \mathbb{R}_+^d} 1_{\{\forall i \in \llbracket 1, d \rrbracket: y_i \geq \frac{v_i}{N}\}} \xi(dv)$, for all $y \geq 0$. Using this equality, then Fubini's theorem to switch the integrals, and finally the fact that $\int_{y_i \in [\frac{v_i}{N}, +\infty)} \exp(-\beta y_i) dy_i = \frac{\exp(-\frac{\beta v_i}{N})}{\beta}$ for all $i \in \llbracket 1, d \rrbracket$, we have

$$\begin{aligned} \int_{y \in \mathbb{R}_+^d} \exp\left[-\beta \sum_{i=1}^d y_i\right] \xi((A_{Ny})^c) dy &= \int_{v \in \mathbb{R}_+^d} \left[\int_{y \in \mathbb{R}_+^d} 1_{\{\forall i \in \llbracket 1, d \rrbracket: y_i \geq \frac{v_i}{N}\}} \exp\left(-\beta \sum_{i=1}^d y_i\right) dy \right] \xi(dv) \\ &= \frac{1}{\beta^d} \mathcal{L}(\xi) \left(\frac{\beta}{N} \right). \end{aligned}$$

The above expression is what we need to continue the computations interrupted at (3.24). First, we plug the above equation in (3.24), and put the terms $\frac{1}{\beta^d}$ in factors. Then, we use (3.10) to bound the term $1 - \mathcal{L}(\xi) \left(\frac{\beta}{N} \right)$ that appears from the previous step by $\frac{\alpha}{bN}$. We obtain

$$\begin{aligned} |v_{\xi,1}(t)| &\leq \frac{b^2 t C \sigma_\xi}{2\beta^d} \exp\left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N}\right)\right) t\right] \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N}\right)\right) \\ &\leq \frac{bt C \sigma_\xi \alpha}{2\beta^d N} \exp\left[-bN \left(1 - \mathcal{L}(\xi) \left(\frac{\beta}{N}\right)\right) t\right]. \end{aligned} \quad (3.25)$$

The lemma is thus proved by summing (3.23) and (3.25). \square

3.5 Proof of Proposition 3.2

We prove this proposition statement by statement. We first deal with Proposition 3.2-(a). We need to verify the assumptions of Lemma 3.5 for $u_\xi = \bar{u}^{(1)}$ to obtain it. First, recall that Eq. (3.7), the equation verified by $\bar{u}^{(1)}$, corresponds to (3.8) with $F = u^{(1)}$ and $\xi = g$. Then, notice that by the left-hand side of (3.6) and (H₂), we have for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$

$$\left| \partial_{xx} u^{(1)}(t, x) \right| = |n_0''(bm_1 t + x)| \leq C_\lambda \exp(-\lambda b m_1 t - \lambda x),$$

which corresponds to Eq. (3.9) with $\alpha = \lambda b m_1$, $\beta = \lambda$ and $C = C_\lambda$. Finally, by the inequality $1 - e^{-x} \leq x$ for all $x \in \mathbb{R}$, one can easily obtain that

$$bN \left(1 - \mathcal{L}(g) \left(\frac{\lambda}{N}\right)\right) = bN \int_0^{+\infty} (1 - e^{-\frac{\lambda}{N} u}) g(u) du \leq \lambda b \int_0^{+\infty} u g(u) du = \lambda b m_1. \quad (3.26)$$

The above is exactly Eq. (3.10) with the same α and β as before. Combining these three results, we have that all the assumptions of Lemma 3.5 are verified. We therefore use this lemma to bound $u_\xi = \bar{u}^{(1)}$, in view of the fact that $\sigma_\xi = \int_0^\delta u^2 g(u) du = m_2$. We obtain that for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$

$$\left| \bar{u}^{(1)}(t, x) \right| \leq \frac{bt C_\lambda m_2}{2N} \exp\left[-bN \left(\mathcal{L}(g) \left(\frac{\beta}{N}\right) - 1\right) t\right] \exp(-\lambda x).$$

As it holds $bN \left(1 - \mathcal{L}(g) \left(\frac{\lambda}{N}\right)\right) = b m_1 \lambda_N$ by Eq. (2.11), the above inequality yields that Proposition 3.2-(a) is true with $c'_0 = C_\lambda \frac{m_2}{2}$.

Now, we deal with Proposition 3.2-(b). This time, we check the assumptions of Lemma 3.6 for the function $v_\xi = \bar{u}^{(1)}$. We denote h_1 the function defined for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$ as

$$h_1(t, x) = u^{(1)}\left(t, \frac{x}{N}\right) - u^{(1)}(t, 0). \quad (3.27)$$

In the first term of the last line of (3.12), we do the change of variable $y = \frac{v}{N}$, and replace $\bar{u}^{(1)}$ with u_ξ (we use the same u_ξ as in the first statement). In the second term, we plug Eq. (3.27). We obtain that for all $t \geq 0$

$$\bar{u}_\partial^{(1)}(t) = bN \int_0^{\frac{\delta}{N}} u_\xi(t, y) (1 - G(Ny)) dy + b \int_0^\delta h_1(t, v) (1 - G(v)) dv,$$

so that (3.14) holds. It remains to prove (3.13). To do so, in view of (3.27), we first write h_1 as an integral of $\partial_x u^{(1)}$. Then, we use the left side of (3.6) to write $u^{(1)}$ in terms of n_0 . Thereafter, we use (H₂) to bound from above the integral. Finally, we use (3.26) to bound from above the exponential. We obtain that for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$,

$$\begin{aligned} |h_1(t, x)| &= \left| \int_0^{\frac{x}{N}} \partial_x u^{(1)}(t, v) dv \right| = \left| \int_0^{\frac{x}{N}} n'_0(bm_1 t + v) dv \right| \leq \frac{C'_\lambda x}{N} \exp(-\lambda b m_1 t) \\ &\leq \frac{C'_\lambda x}{N} \exp \left[-bN \left(1 - \mathcal{L}(g) \left(\frac{\lambda}{N} \right) \right) t \right]. \end{aligned}$$

This is exactly (3.13) with $C' = C'_\lambda$. Since all the assumptions of Lemma 3.6 are verified, we apply this lemma to bound $v_\xi = \bar{u}_\partial^{(1)}$ (the constants C , σ_ξ , α and β in (3.15) are the same as for the first statement). We then use that it holds $bN \left(1 - \mathcal{L}(g) \left(\frac{\lambda}{N} \right) \right) = b m_1 \lambda_N$ to simplify the term $bN \left(1 - \mathcal{L}(g) \left(\frac{\lambda}{N} \right) \right)$ in the bound, see (2.11). We obtain that Proposition 3.2-(b) is true. \square

4 The model with several telomeres

Having solved the single-telomere case, let us now turn to the case with $2k$ telomeres. As for the single-telomere model, approximating (2.8) with a transport equation is the main argument. The difference with the previous section is that here, obtaining Theorem 2.6-(b) from this approximation is not straightforward because we have to control the term at the denominator in $\hat{n}_0^{(2k)}$, see (2.12). The model approximation, similarly, requires to prove an additional statement to Lemmas 3.5 and 3.6. This section is devoted to handling these technicalities.

First, in Section 4.1, we rewrite (2.8), and explain how a model approximation can be conjectured from this rewriting. Then, in Section 4.2, we present the main arguments and the auxiliary statements required to approximate our model and to obtain Theorem 2.6-(b). Thereafter, in Section 4.3, we prove these auxiliary statements. Finally, we prove the telomere length densities approximation in Section 4.4, the cemetery approximation in Section 4.5, and Theorem 2.6-(b) in Section 4.6. In all this section, we assume that (H₁) holds.

4.1 Rewriting of the integro-differential equation and model approximation

As for the single-telomere model, the approximation of the model with several telomeres is obtained by letting the scaling parameter N introduced in (H₁) tend to infinity. We thus need to rewrite (2.8) to make N appears. As the measure $\tilde{\mu}$ is composed of both Dirac and Lebesgue measures, see (2.6)-(2.7), rewriting the model and stating its model approximation requires more work than in Section 3.1. We thus split this subsection into two parts: first, we rewrite our model. Then, we intuit and state a model approximation based on this rewriting.

Rewriting of the model. Let us begin by rewriting the first line of (2.8). In Section 3.1, one argument in the rewriting of the first line of (2.3) was to do change of variables, allowing us to replace the term $\int_{u \in [0, \delta]} n^{(1)}(t, x+v) \tilde{g}(v) dv$ with $\int_{v \in [0, \delta]} n^{(1)}(t, x + \frac{v}{N}) g(v) dv$. Here, we proceed similarly, and aim at substituting the term $\int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x+v) \tilde{\mu}(dv)$ in the first line of (2.8)

for the term $\int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}\left(t, x + \frac{v}{N}\right) \mu(dv)$. We denote for all $i \in \llbracket 1, 2k \rrbracket$ the i -th vector of the canonical basis $e_i \in \mathbb{R}_+^{2k}$. By using both equalities in (2.10) to develop μ , and then integrating in the Dirac measures, we have that for all $t \geq 0$, $x \in \mathbb{R}_+^{2k}$,

$$\begin{aligned} \int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}\left(t, x + \frac{v}{N}\right) \mu(dv) &= \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}\left(t, x + \frac{v}{N}\right) \left[\prod_{i \in I} g(v_i) dv_i \right] \left[\prod_{i \notin I} \delta_0(dv_i) \right] \\ &= \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \int_{(v_i, i \in I) \in \mathbb{R}_+^k} n^{(2k)}\left(t, x + \sum_{i \in I} \frac{v_i}{N} e_i\right) \left[\prod_{i \in I} g(v_i) dv_i \right]. \end{aligned} \quad (4.1)$$

We therefore need to prove that $\int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x+v) \tilde{\mu}(dv)$ is equal to the right-hand side of (4.1), and the substitution presented above will be possible. To do so, in the equation below, we first develop the measure $\tilde{\mu}$ by using (2.7) and (2.6). Then, for all $I \in \mathcal{I}_k$, $i \in I$, we replace $\tilde{g}(v_i)$ with $Ng(Nv_i)$ in view of (H₁), and we integrate in the Dirac measures. Finally, we do the change of variable $v'_i = Nv_i$ for all $I \in \mathcal{I}_k$, $i \in I$. We obtain that for all $t \geq 0$, $x \in \mathbb{R}_+^{2k}$,

$$\begin{aligned} \int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x+v) \tilde{\mu}(dv) &= \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x+v) \left[\prod_{i \in I} \tilde{g}(v_i) dv_i \right] \left[\prod_{i \notin I} \delta_0(dv_i) \right] \\ &= \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \int_{(v_i, i \in I) \in \mathbb{R}_+^k} n^{(2k)}\left(t, x + \sum_{i \in I} v_i e_i\right) \left[\prod_{i \in I} Ng(Nv_i) dv_i \right] \\ &= \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \int_{(v'_i, i \in I) \in \mathbb{R}_+^k} n^{(2k)}\left(t, x + \sum_{i \in I} \frac{v'_i}{N} e_i\right) \left[\prod_{i \in I} g(v'_i) dv'_i \right]. \end{aligned}$$

Therefore, it holds $\int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x+v) \tilde{\mu}(dv) = \int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}\left(t, x + \frac{v}{N}\right) \mu(dv)$ by (4.1). We now use this equality to rewrite the first line of (2.8). First, in view of the last equality, we substitute $\int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}(t, x+v) \tilde{\mu}(dv)$ for $\int_{v \in \mathbb{R}_+^{2k}} n^{(2k)}\left(t, x + \frac{v}{N}\right) \mu(dv)$. Then, again on the first line of (4.1), we replace \tilde{b} with bN in view of (H₁). Finally, we put the term $n^{(2k)}(t, x)$ into the integral, by using that μ is a probability measure. The following rewriting comes, for all $t \geq 0$, $x \in \mathbb{R}_+^{2k}$,

$$\partial_t n^{(2k)}(t, x) = bN \int_{\mathbb{R}_+^{2k}} \left[n^{(2k)}\left(t, x + \frac{v}{N}\right) - n^{(2k)}(t, x) \right] d\mu(v). \quad (4.2)$$

Now, we aim at rewriting the second line of (2.8). In Section 3.1, the rewriting of the second line of (2.3) was obtained by proving an equality involving \tilde{G} and G , given in (3.2). Here, we need to obtain the equivalent equality, involving $\tilde{\mu}$ and μ , which is the following, for all $y \geq 0$,

$$\tilde{\mu}\left(\left\{v \in \mathbb{R}_+^{2k} \mid y - v \in \mathbb{R}_+^{2k}\right\}\right) = \mu\left(\left\{v \in \mathbb{R}_+^{2k} \mid Ny - v \in \mathbb{R}_+^{2k}\right\}\right). \quad (4.3)$$

To obtain it, we compute both sides of (4.3), and prove that they are equal to the same expression. We begin by computing the left-hand side. In the equation below, we develop $\tilde{\mu}$ by using Eq. (2.7), Eq. (2.6), and the fact that $y - v \in \mathbb{R}_+^{2k} \iff \forall i \in \llbracket 1, 2k \rrbracket : y_i \geq v_i$. Then, we use the equality $1_{\{\forall i \in \llbracket 1, 2k \rrbracket : y_i \geq v_i\}} = \prod_{i \in \llbracket 1, 2k \rrbracket} 1_{\{y_i \geq v_i\}}$, and integrate. We obtain the following expression, for all $y \in \mathbb{R}_+^{2k}$,

$$\begin{aligned} \tilde{\mu}\left(\left\{v \in \mathbb{R}_+^{2k} \mid y - v \in \mathbb{R}_+^{2k}\right\}\right) &= \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \int_{v \in \mathbb{R}_+^{2k}} 1_{\{\forall i \in \llbracket 1, 2k \rrbracket : y_i \geq v_i\}} \left[\prod_{i \in I} \tilde{g}(v_i) dv_i \right] \left[\prod_{i \notin I} \delta_0(dv_i) \right] \\ &= \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \left(\prod_{i \in I} \tilde{G}(y_i) \right). \end{aligned} \quad (4.4)$$

Now, we focus on the right-hand side of (4.3). In fact, by (2.10), (2.6), and (2.7), μ have the same expression as $\tilde{\mu}$, with g instead of \tilde{g} . Therefore, by doing the same steps presented above, replacing \tilde{g} with g , we have that (4.4) holds with (G, μ) instead of $(\tilde{G}, \tilde{\mu})$. Using now this equality, and then (3.2), yields that for all $y \in \mathbb{R}_+^{2k}$

$$\mu \left(\left\{ v \in \mathbb{R}_+^{2k} \mid Ny - v \in \mathbb{R}_+^{2k} \right\} \right) = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \left(\prod_{i \in I} G(Ny_i) \right) = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \left(\prod_{i \in I} \tilde{G}(y_i) \right). \quad (4.5)$$

One can easily see that both left-hand sides of (4.4) and (4.5) are equal to the same expression. Then, Eq. (4.3) is true. In particular, as μ and $\tilde{\mu}$ are probability measures, we have by taking the complement of both sets in (4.3)

$$\tilde{\mu} \left(\left\{ v \in \mathbb{R}_+^{2k} \mid y - v \notin \mathbb{R}_+^{2k} \right\} \right) = \mu \left(\left\{ v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k} \right\} \right). \quad (4.6)$$

We now use (4.6) to rewrite the second line of (2.8). First, we plug it in the second line of (2.8). Then, we replace \tilde{b} with bN , in view of (H₁). We obtain the following rewriting, for all $t \geq 0$,

$$n_{\partial}^{(2k)}(t) = bN \int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) \mu \left(\left\{ v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k} \right\} \right) dy. \quad (4.7)$$

We conclude by presenting the full rewriting of the model. By combining (4.2) and (4.7), we have the following new version of (2.8)

$$\begin{cases} \partial_t n^{(2k)}(t, x) = bN \int_{\mathbb{R}_+^{2k}} \left[n^{(2k)}\left(t, x + \frac{v}{N}\right) - n^{(2k)}(t, x) \right] d\mu(v), & \forall t \geq 0, x \in \mathbb{R}_+^{2k}, \\ n_{\partial}^{(2k)}(t) = bN \int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) \mu \left(\left\{ v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k} \right\} \right) dy, & \forall t \geq 0, \\ n^{(2k)}(0, x) = \prod_{i=1}^{2k} n_0(x_i), & \forall x \in \mathbb{R}_+^{2k}. \end{cases} \quad (4.8)$$

The above is the system of integro-differential equations that we study in the rest of the section.

Model approximation. Now, we derive from (4.8) a model approximation. As for the model with one telomere, we start by giving the intuition allowing us to obtain the approximant of (4.8). Then, we present the theoretical results which justify this approximation.

Let us first intuit how the first line of (4.8) can be approximated. In view of the Taylor's expansion, we have the following for the first line of (4.8)

$$bN \int_{\mathbb{R}_+^{2k}} \left[n^{(2k)}\left(t, x + \frac{v}{N}\right) - n^{(2k)}(t, x) \right] d\mu(v) \underset{N \rightarrow +\infty}{\approx} b \sum_{i=1}^{2k} \int_{\mathbb{R}_+^{2k}} v_i d\mu(v) \partial_{x_i} n^{(2k)}(t, x).$$

Then, in view of the above, we conjecture that the first line of (4.8) can be approximated by a transport equation with drift $b \int_{\mathbb{R}_+^{2k}} v_i d\mu(v)$ in the i -th coordinate, for all $i \in \llbracket 1, 2k \rrbracket$. In fact, the drift can be explicitly computed thanks to the following statement.

Lemma 4.1 (First moment of μ). *Assume that (H₁) holds. Then, for all $i \in \llbracket 1, 2k \rrbracket$, we have*

$$\int_{\mathbb{R}_+^{2k}} v_i d\mu(v) = \frac{m_1}{2}.$$

Proof. Let $i \in \llbracket 1, 2k \rrbracket$. To obtain the above expression, we first develop μ by using the right-hand side of (2.10). Then, we integrate both measures, in view of the fact that for all $I \in \mathcal{I}_k$, it holds by the left-hand side of (2.10)

$$\int_{\mathbb{R}_+^{2k}} v_i \mu^{(I)}(dv) = \left[\int_{v_i \in \mathbb{R}_+} v_i g(v_i) dv_i \right] \mathbf{1}_{\{i \in I\}} + \left[\int_{v_i \in \mathbb{R}_+} v_i \delta_0(dv_i) \right] \mathbf{1}_{\{i \notin I\}} = m_1 \mathbf{1}_{\{i \in I\}}.$$

We obtain

$$\int_{\mathbb{R}_+^{2k}} v_i d\mu(v) = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} m_1 \mathbb{1}_{\{i \in I\}} = \frac{m_1 \#(\{I \in \mathcal{I}_k \mid i \in I\})}{2^k}.$$

Then, we conclude the proof of the lemma by using Lemma A.7 to compute the ratio. \square

Hence, denoting the vector $\mathbb{1}_{2k} := (1, \dots, 1) \in \mathbb{R}^{2k}$ and recalling that $n_0 \in W^{2,1}(\mathbb{R}_+) \cap L_{\text{loc}}^\infty(\mathbb{R}_+)$ (see Section 2.1), our conjecture becomes that (4.8) can be approximated by the function $u^{(2k)} \in C(\mathbb{R}_+, W^{2,1}(\mathbb{R}_+^{2k}) \cap L_{\text{loc}}^\infty(\mathbb{R}_+^{2k}))$, solution of the following equation

$$\partial_t u^{(2k)}(t, x) = \frac{bm_1}{2} \nabla \cdot (u^{(2k)} \mathbb{1}_{2k})(t, x). \quad (4.9)$$

Now, we intuit how the second line of (4.8) can be approximated. In comparison with what is done in Section 3.1, it is necessary to decompose $n_\partial^{(2k)}$ into two terms to obtain our conjecture. Notice that by the first equality in (4.5), the fact that $G(x) = 1$ for all $x \geq \delta$, and Lemma A.7, we have

$$\forall y \in \left(\frac{\delta}{N}, +\infty\right)^{2k} : \mu\left(\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\}\right) = 1 - \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \left(\prod_{i \in I} G(Ny_i)\right) = 0. \quad (4.10)$$

Then, in view of (4.10) and the fact that for all $y \in \mathbb{R}_+^{2k}$,

$$\mathbb{1}_{\{\#\{i \in [1, 2k] \mid y_i \leq \frac{\delta}{N}\} = 0\}} + \mathbb{1}_{\{\#\{i \in [1, 2k] \mid y_i \leq \frac{\delta}{N}\} = 1\}} + \mathbb{1}_{\{\#\{i \in [1, 2k] \mid y_i \leq \frac{\delta}{N}\} \geq 2\}} = 1, \quad (4.11)$$

our decomposition of $n_\partial^{(2k)}$ is the following, for all $t \geq 0$,

$$\begin{aligned} n_\partial^{(2k)}(t) &= bN \int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) \mu\left(\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\}\right) \mathbb{1}_{\{\#\{i \in [1, 2k] \mid y_i \leq \frac{\delta}{N}\} = 1\}} dy \\ &\quad + bN \int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) \mu\left(\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\}\right) \mathbb{1}_{\{\#\{i \in [1, 2k] \mid y_i \leq \frac{\delta}{N}\} \geq 2\}} dy \\ &=: n_{\partial,1}^{(2k)}(t) + n_{\partial,2}^{(2k)}(t). \end{aligned} \quad (4.12)$$

Qualitatively, $n_{\partial,1}^{(2k)}$ corresponds to the cemetery of cells with only one *short telomere* (length smaller than $\frac{\delta}{N}$), while $n_{\partial,2}^{(2k)}$ is the cemetery of cells with several *short telomeres*. In fact, each of these two cemeteries has a different behaviour when $N \rightarrow +\infty$. The behaviour of $n_{\partial,2}^{(2k)}$ is easy to conjecture. As the domain of integration of the integral in its definition correspond to points with at least two coordinates smaller than $\frac{\delta}{N}$, we have, roughly speaking, that this integral vanishes at least at a rate $\frac{1}{N^2}$ when $N \rightarrow +\infty$. Then, by multiplying it by bN , we obtain that for all $t \geq 0$

$$n_{\partial,2}^{(2k)}(t) = bN \times O\left(\frac{1}{N^2}\right)_{N \rightarrow +\infty} \approx 0. \quad (4.13)$$

To conjecture the behaviour of $n_{\partial,1}^{(2k)}$ when $N \rightarrow +\infty$, we need to obtain a better expression for it. To do so, in its definition given in the first line of (4.12), we first decompose the indicator, by using that for all $y \in \mathbb{R}_+^{2k}$, we have

$$\mathbb{1}_{\{\#\{i \in [1, 2k] \mid y_i \leq \frac{\delta}{N}\} = 1\}} = \sum_{i=1}^{2k} \mathbb{1}_{\{y_i \leq \frac{\delta}{N}, \forall j \in [1, 2k] \setminus \{i\}: y_j > \frac{\delta}{N}\}}.$$

Then, we use the following equality to replace the term $\mu(\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\})$ in the first line of (4.12). This equality is obtained by applying the first equality in (4.5), the fact that $G(x) = 1$ when $x \geq \delta$, and Lemma A.7. For all $i \in \llbracket 1, 2k \rrbracket$ and $y \in \mathbb{R}_+^{2k}$ verifying $y_i \leq \frac{\delta}{N}$ and $y_j > \frac{\delta}{N}$ when $j \neq i$, it holds

$$\begin{aligned} \mu(\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\}) &= 1 - \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \left(\prod_{j \in I} G(Ny_j) \right) \\ &= 1 - \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} (G(Ny_i) \mathbf{1}_{\{i \in I\}} + \mathbf{1}_{\{i \notin I\}}) \\ &= 1 - \frac{1}{2} G(Ny_i) - \frac{1}{2} = \frac{1}{2} (1 - G(Ny_i)). \end{aligned}$$

Finally, for each index $i \in \llbracket 1, 2k \rrbracket$ of the sum, we do the change of variables $y'_i = Ny_i$, and $y'_j = y_j$ for all $j \in \llbracket 1, 2k \rrbracket \setminus \{i\}$. We obtain that for all $t \geq 0$

$$\begin{aligned} n_{\partial,1}^{(2k)}(t) &= \frac{bN}{2} \sum_{i=1}^{2k} \int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) (1 - G(Ny_i)) \mathbf{1}_{\{y_i \leq \frac{\delta}{N}, \forall j \in \llbracket 1, 2k \rrbracket \setminus \{i\}: y_j > \frac{\delta}{N}\}} dy \\ &= \frac{b}{2} \sum_{i=1}^{2k} \int_{y' \in \mathbb{R}_+^{2k}} n^{(2k)}\left(t, \sum_{j=1, j \neq i}^{2k} y'_j e_j + \frac{y'_i}{N} e_i\right) (1 - G(y'_i)) \mathbf{1}_{\{y'_i \leq \delta, \forall j \in \llbracket 1, 2k \rrbracket \setminus \{i\}: y'_j > \frac{\delta}{N}\}} dy'. \end{aligned} \quad (4.14)$$

Then, we are now able to conjecture the behaviour of $n_{\partial,1}^{(2k)}$ when $N \rightarrow +\infty$. Indeed, by letting N tend to infinity, and by using that $\int_{s \in [0, \delta]} (1 - G(s)) ds = m_1$, we have for all $t \geq 0$

$$n_{\partial,1}^{(2k)}(t) \underset{N \rightarrow +\infty}{\approx} \frac{bm_1}{2} \sum_{i=1}^{2k} \int_{y' \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) \delta_0(dy_i) \left(\prod_{j=1, j \neq i}^{2k} dy_j \right).$$

Combining the above with (4.13) and (4.9) finally yields that the following system seems a good approximant of (4.8)

$$\begin{cases} \partial_t u^{(2k)}(t, x) = \frac{bm_1}{2} \nabla \cdot (u^{(2k)} \mathbb{1}_{2k})(t, x), & \forall t \geq 0, x \in \mathbb{R}_+^{2k}, \\ u_{\partial}^{(2k)}(t) = \frac{bm_1}{2} \sum_{i=1}^{2k} \int_{y \in \mathbb{R}_+^{2k}} u^{(2k)}(t, y) \delta_0(dy_i) \left(\prod_{j=1, j \neq i}^{2k} dy_j \right), & \forall t \geq 0, \\ u^{(2k)}(0, x) = \prod_{i=1}^{2k} n_0(x_i), & \forall x \in \mathbb{R}_+^{2k}. \end{cases} \quad (4.15)$$

Remark 4.2. By using the characteristics of the transport equation in the first line of (4.15), we have the following alternative representation for $u^{(2k)}$, for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$,

$$u^{(2k)}(t, x) = \prod_{i=1}^{2k} n_0\left(\frac{bm_1}{2}t + x_i\right). \quad (4.16)$$

We also have the following alternative representation for $u_{\partial}^{(2k)}$ by plugging (4.16) in the second line of (4.15), and then doing the change of variables $y' = y + \frac{bm_1 t}{2} \mathbb{1}_{2k}$, for all $t \geq 0$,

$$u_{\partial}^{(2k)}(t) = \frac{bm_1}{2} \sum_{i=1}^{2k} n_0\left(\frac{bm_1 t}{2}\right) \prod_{\substack{j=1 \\ j \neq i}}^{2k} \left[\int_{\frac{bm_1 t}{2}}^{+\infty} n_0(y'_j) dy'_j \right] = kbm_1 n_0\left(\frac{bm_1 t}{2}\right) \left[\int_{\frac{bm_1 t}{2}}^{+\infty} n_0(s) ds \right]^{2k-1}. \quad (4.17)$$

Remark 4.3. *The conservation of the number of individuals, presented in Remark 2.5, still holds for the approximated model when (H₂) – (H₃) are verified. To obtain it, first integrate (4.17), in view of the fact that for all $f \in W^{1,1}(\mathbb{R}_+) \cap W^{1,2k}(\mathbb{R}_+) \cap L^{2k-1}(\mathbb{R}_+)$ it holds $(f^{2k})' = 2kf'f^{2k-1}$. Then, do the change of variable $s' = s - \frac{bm_1}{2}t$. Finally, apply (4.16). It comes for all $t \geq 0$*

$$\int_t^{+\infty} u_{\partial}^{(2k)}(s) ds = \left[\int_{\frac{bm_1 t}{2}}^{+\infty} n_0(s) ds \right]^{2k} = \left[\int_0^{+\infty} n_0\left(\frac{bm_1}{2}t + s'\right) ds' \right]^{2k} = \int_{x \in \mathbb{R}_+^{2k}} u(t, x) dx. \quad (4.18)$$

All we have intuited above can in fact be justified rigorously. Specifically, the statement below provides that the error between $(n^{(2k)}, n_{\partial}^{(2k)})$ and $(u^{(2k)}, u_{\partial}^{(2k)})$ tends to 0 when $N \rightarrow +\infty$. Its proof is separated into two parts, one part for each statement, which are done in Sections 4.4 and 4.5.

Proposition 4.4 (Pointwise approximation errors, several telomeres). *We recall the constant λ'_N defined in (2.11). The following statements hold.*

(a) *Assume (H₁) – (H₃). Then, there exists $d'_0 > 0$ such that for all $t \geq 0$, $x \in \mathbb{R}_+^{2k}$, we have*

$$\left| n^{(2k)}(t, x) - u^{(2k)}(t, x) \right| \leq d'_0 (\lambda D_{\lambda})^{2k} \frac{k^2 b t}{2N} \exp(-k b m_1 \lambda'_N t) \exp\left(-\lambda \sum_{i=1}^{2k} x_i\right), \quad (4.19)$$

where d'_0 depends only on $g, \lambda, C_{\lambda}, C'_{\lambda}$ and D_{λ} .

(b) *Assume (H₁) – (H₃). Then, there exists $d'_1 > 0$ such that for all $t \geq 0$, we have*

$$\left| n_{\partial}^{(2k)}(t) - u_{\partial}^{(2k)}(t) \right| \leq \frac{b d'_1}{N} (D_{\lambda})^{2k} \left(k^3 \frac{b m_1}{2} t + k^2 + k \right) \exp(-k b m_1 \lambda'_N t), \quad (4.20)$$

where d'_1 depends only on $g, \delta, \lambda, C_{\lambda}, C'_{\lambda}$ and D_{λ} .

Again, using that for all $p > 0, \beta > 0$, it holds $\int_0^{+\infty} x^p e^{-\beta x} dx = \frac{\Gamma(p+1)}{\beta^{p+1}}$, we derive from this proposition the following corollary, which provides bounds on the approximation errors in all the Lebesgue spaces.

Corollary 4.5 (Approximation errors in Lebesgue spaces, several telomeres). *We recall the constant λ'_N defined in (2.11). The following statements hold.*

(a) *Assume (H₁) – (H₃). Then, for all $p > 0$ we have*

$$\left\| n^{(2k)} - u^{(2k)} \right\|_{L^p(\mathbb{R}_+ \times \mathbb{R}_+^{2k})} \leq d'_0 (\lambda D_{\lambda})^{2k} \frac{k^2 b}{2N} \left(\frac{(\Gamma(p+1))^{\frac{1}{p}}}{(k b m_1 \lambda'_N p)^{1+\frac{1}{p}} (\lambda p)^{\frac{2k}{p}}} \right),$$

where d'_0 is the same constant as in Proposition 4.4-(a).

(b) *Assume (H₁) – (H₃). Then, for all $p > 0$ we have*

$$\left\| n_{\partial}^{(2k)} - u_{\partial}^{(2k)} \right\|_{L^p(\mathbb{R}_+)} \leq \frac{b d'_1}{N} (D_{\lambda})^{2k} \left(k^3 \frac{b m_1}{2} \frac{(\Gamma(p+1))^{\frac{1}{p}}}{(k b m_1 \lambda'_N p)^{1+\frac{1}{p}}} + \frac{k^2 + k}{(k b m_1 \lambda'_N p)^{\frac{1}{p}}} \right),$$

where d'_1 is the same constant as in Proposition 4.4-(b).

We now present the main arguments and the auxiliary statements required to prove Proposition 4.4 and Theorem 2.6-(b).

4.2 Plan of the proofs of Proposition 4.4 and Theorem 2.6-(b)

Theorem 2.6-(b) uses Proposition 4.4-(b) in its proof, and Proposition 4.4-(b) also employs arguments presented in the proof of Proposition 4.4-(a). We therefore first present the plan of the proof of Proposition 4.4-(a), then the one to prove Proposition 4.4-(b), and finally the plan to obtain Theorem 2.6-(b).

To get Proposition 4.4-(a), we need to control the absolute value of $\bar{u}^{(2k)} := n^{(2k)} - u^{(2k)}$. By taking the difference between the first lines of (4.8) and (4.15), then using the equality $n^{(2k)} = \bar{u}^{(2k)} + u^{(2k)}$, and finally using Lemma 4.1 to put the term $\frac{bm_1}{2} \nabla \cdot (u^{(2k)} \mathbb{1}_{2k})(t, x)$ into the integral, we have that for all $t \geq 0$, $x \in \mathbb{R}_+^{2k}$,

$$\begin{aligned} \partial_t \bar{u}^{(2k)}(t, x) &= bN \int_0^\delta \left[n^{(2k)} \left(t, x + \frac{v}{N} \right) - n^{(2k)}(t, x) \right] \mu(dv) - \frac{bm_1}{2} \nabla \cdot (u^{(2k)} \mathbb{1}_{2k})(t, x) \\ &= bN \int_0^\delta \left[\bar{u}^{(2k)} \left(t, x + \frac{v}{N} \right) - \bar{u}^{(2k)}(t, x) \right] \mu(dv) \\ &\quad + bN \int_0^\delta \left[u^{(2k)} \left(t, x + \frac{v}{N} \right) - u^{(2k)}(t, x) - \sum_{i=1}^{2k} \frac{v_i}{N} \partial_{x_i} u^{(2k)}(t, x) \right] \mu(dv). \end{aligned} \quad (4.21)$$

Then, $\bar{u}^{(2k)}$ is a solution of an equation of the form presented in (3.8), with $d = 2k$, $u_\xi = \bar{u}^{(2k)}$, $\xi = \mu$ and $F = u^{(2k)}$. From this result, a natural plan to prove Proposition 4.4 is to proceed as in the proof of Proposition 3.2-(a), and check the assumptions of Lemma 3.5 to obtain Proposition 4.4-(a). Here, we do not do this directly because we must first obtain the value of the constant σ_ξ , defined in Lemma 3.5, for $\xi = \mu$. The reason is that the value of this constant provides information on how the approximation error varies when k increases. The following statement gives us the exact value of σ_μ . It is proved in Section 4.3.1.

Lemma 4.6 (Sum of second moments of μ). *Assume that (H₁) holds. Then, we have*

$$\sigma_\mu := \sum_{1 \leq \ell, \ell' \leq 2k} \int_{v \in \mathbb{R}_+^{2k}} v_\ell v_{\ell'} \mu(dv) = (m_1)^2 k^2 + (m_2 - (m_1)^2) k.$$

Now that we know the value of σ_μ , as stated above, the plan to prove this statement is to check the assumptions of Lemma 3.5. We do this in Section 4.4.

To prove Proposition 4.4-(b), we control $|\bar{u}_\partial^{(2k)}| := |n_\partial^{(2k)} - u_\partial^{(2k)}|$. To do this, a decomposition of $\bar{u}_\partial^{(2k)}$ is required, inspired by the one given in (4.12). Let us introduce for all $t \geq 0$

$$\begin{aligned} u_{\partial,0}^{(2k)}(t) &:= bN \int_{y \in \mathbb{R}_+^{2k}} u^{(2k)}(t, y) \mu \left(\left\{ v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k} \right\} \right) dy, \\ u_{\partial,1}^{(2k)}(t) &:= \frac{b}{2} \sum_{i=1}^{2k} \int_{y' \in \mathbb{R}_+^{2k}} u^{(2k)} \left(t, \sum_{j=1, j \neq i}^{2k} y'_j e_j + \frac{y'_i}{N} \right) (1 - G(y'_i)) \mathbb{1}_{\{y'_i \leq \delta\}} dy', \\ u_{\partial,2}^{(2k)}(t) &:= u_{\partial,0}^{(2k)}(t) - u_{\partial,1}^{(2k)}(t). \end{aligned} \quad (4.22)$$

Then, in view of the fact that $u_{\partial,0}^{(2k)} = u_{\partial,1}^{(2k)} + u_{\partial,2}^{(2k)}$, we have the following decomposition, for all $t \geq 0$,

$$\bar{u}_\partial^{(2k)}(t) = \left(n_\partial^{(2k)}(t) - u_{\partial,0}^{(2k)}(t) + u_{\partial,1}^{(2k)}(t) - u_{\partial,2}^{(2k)}(t) \right) + u_{\partial,2}^{(2k)}(t). \quad (4.23)$$

This decomposition allows us to control $|\bar{u}_\partial^{(2k)}|$, by bounding each of the terms that compose it. The term $n_\partial^{(2k)} - u_{\partial,0}^{(2k)} + u_{\partial,1}^{(2k)} - u_{\partial,2}^{(2k)}$, on the one hand, can be bounded by using Lemma 3.6, already proved in Section 3.4. The term $u_{\partial,2}^{(2k)}$, on the other hand, can be bounded with the following lemma, proved in Section 4.3.2.

Lemma 4.7 (Control of the probability of having several short telomeres). *Assume that (H₁) and (H₃) hold. Then, there exists $\tilde{d} > 0$ such that for all $t \geq 0$ we have*

$$\left| u_{\partial,2}^{(2k)}(t) \right| \leq \frac{b\tilde{d}}{N} (D_\lambda)^{2k} k^2 \exp(-k\lambda b m_1 t), \quad (4.24)$$

where \tilde{d} depends only on δ , λ and g .

As a result, we have a control over $|\bar{u}_\partial^{(2k)}|$ by summing the bounds we have on the two terms presented above, in view of (4.23) and the triangular inequality. We detail how we apply these lemmas and sum the bounds to prove Proposition 4.4-(b) in Section 4.5.

The proof of Theorem 2.6-(b), finally, is based on the fact that the following statement holds. This statement is proved below, as it is relatively short.

Lemma 4.8 (Link between n_0 and u_∂). *Assume that (H₁) – (H₃) hold. Then, for all $x \geq 0$, we have*

$$n_0(x) = \frac{1}{k b m_1} \frac{u_\partial^{(2k)}\left(\frac{2x}{b m_1}\right)}{\left(\int_{\frac{2x}{b m_1}}^{\infty} u_\partial^{(2k)}(s) ds\right)^{1-\frac{1}{2k}}}. \quad (4.25)$$

Proof. Let $x \geq 0$. By setting $t = \frac{2x}{b m_1}$, and raising both sides of the first equality in (4.18) to the power of $\frac{1}{2k}$, we have

$$\left(\int_{\frac{2x}{b m_1}}^{+\infty} u_\partial^{(2k)}(s) ds\right)^{\frac{1}{2k}} = \int_x^{+\infty} n_0(s) ds.$$

Then, by taking the derivative of the above, the lemma is proved. \square

Specifically, if we replace $\hat{n}_0^{(2k)}$ with its definition (see (2.12)), thereafter use (2.13) to replace $\tilde{b} \tilde{m}_1$ with $b m_1$, and finally write n_0 with the right-hand side of (4.25), then we obtain that for all $x \geq 0$

$$\left| \hat{n}_0^{(2k)}(x) - n_0(x) \right| = \frac{1}{k b m_1} \left| \frac{n_\partial^{(2k)}\left(\frac{2x}{b m_1}\right)}{\left(\int_{\frac{2x}{b m_1}}^{\infty} n_\partial^{(2k)}(s) ds\right)^{1-\frac{1}{2k}}} - \frac{u_\partial^{(2k)}\left(\frac{2x}{b m_1}\right)}{\left(\int_{\frac{2x}{b m_1}}^{\infty} u_\partial^{(2k)}(s) ds\right)^{1-\frac{1}{2k}}} \right|. \quad (4.26)$$

We thus need to control this difference, and Theorem 2.6-(b) will be proved. Proposition 4.4 provides us statements to control the error between $n_\partial^{(2k)}$ and $u_\partial^{(2k)}$, or their integrals. However, there is still a difficulty related to the fact that the denominator of the two terms tends to 0 when $x \rightarrow +\infty$. We need to control the speed this denominator goes to 0, to ensure that the pointwise error does not explode when $x \rightarrow +\infty$. The latter is done by proving the two following lemmas, in Sections 4.3.3 and 4.3.4 respectively.

Lemma 4.9 (Power series expansion of the cemetery tail). *Assume that (H₁) and (H₃) hold. Let us consider the function $\tilde{n}_0 \in W^{2,1}(\mathbb{R}_+^{2k}) \cap L_{loc}^\infty(\mathbb{R}_+^{2k})$, defined such that for all $x \in \mathbb{R}_+^{2k}$*

$$\tilde{n}_0(x) := \prod_{i=1}^{2k} n_0(x_i). \quad (4.27)$$

Then, for all $t \geq 0$, we have

$$\int_t^{+\infty} n_\partial^{(2k)}(s) ds = e^{-b N t} \left[1 + \sum_{\ell \geq 1} \frac{(b N t)^\ell}{\ell!} \int_{(x,v) \in \mathbb{R}_+^{2k} \times (\mathbb{R}_+^{2k})^\ell} \tilde{n}_0\left(x + \sum_{j=1}^{\ell} \frac{v_j}{N}\right) dx \mu(dv_1) \dots \mu(dv_\ell) \right]. \quad (4.28)$$

Lemma 4.10 (Lower bound for cemetery tails). *Assume that (H₁) – (H₄) hold. Then, for all $t \geq 0$ we have*

$$\min \left(\int_t^{+\infty} n_{\partial}^{(2k)}(s) ds, \int_t^{+\infty} u_{\partial}^{(2k)}(s) ds \right) \geq (D_{\omega})^{2k} \exp(-k b m_1 \omega t).$$

In fact, the statement that allows us to do this control is Lemma 4.10. Lemma 4.9 corresponds to an intermediate step to obtain Lemma 4.10. Thus, the proof of Theorem 2.6-(b) consists in controlling the right-hand side term of (4.26), by using Proposition 4.4 and Lemma 4.10. We do this in Section 4.6.

We now prove all the statements given in this section, and then obtain Proposition 4.4 and Theorem 2.6-(b) from them.

4.3 Proof of the auxiliary statements

This section is devoted to the proof of the auxiliary statements presented in Section 4.2. These statements are proved one by one, in the same order in which they were stated.

4.3.1 Proof of Lemma 4.6

We consider for all $(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2$ the integral $I_{\ell, \ell'} := \int_{y \in \mathbb{R}_+^{2k}} y_{\ell} y_{\ell'} \mu(dy)$. One can easily see that $\sigma_{\mu} = \sum_{1 \leq \ell, \ell' \leq 2k} I_{\ell, \ell'}$. Thus, our aim is to compute the values of the integrals $(I_{\ell, \ell'})_{(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2}$, and then conclude by summing their values. To do this, we fix $(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2$ and do a distinction between cases.

Assume first that $\ell = \ell'$. In view of Eq. (2.10), we have that for all $I \in \mathcal{I}_k$

$$\int_{y \in \mathbb{R}_+^{2k}} y_{\ell} y_{\ell'} \mu^{(I)}(dy) = \begin{cases} \int_{y' \in [0, \delta]} (y')^2 g(y') dy' = m_2, & \text{if } \ell = \ell' \in I, \\ 0, & \text{otherwise.} \end{cases}$$

Then, by using Eq. (2.10) and Lemma A.7, we obtain that

$$I_{\ell, \ell} = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k, \ell = \ell' \in I} m_2 = \frac{m_2}{2}. \quad (4.29)$$

Assume now that $\ell \neq \ell'$. In this case, in view of the left-hand side of (2.10), we have that for all $I \in \mathcal{I}_k$

$$\int_{y \in \mathbb{R}_+^{2k}} y_{\ell} y_{\ell'} \mu^{(I)}(dy) = \begin{cases} \left(\int_{y' \in [0, \delta]} y' g(y') dy' \right)^2 = (m_1)^2, & \text{if } \ell \in I \text{ and } \ell' \in I, \\ 0, & \text{otherwise.} \end{cases} \quad (4.30)$$

In addition, by the definition of \mathcal{I}_k (see (2.5)), we have that when $\ell = \ell' \bmod k$

$$\{I \in \mathcal{I}_k \mid \{\ell, \ell'\} \subset I\} = \emptyset.$$

Then, by combining these results, we obtain that when $\ell \neq \ell'$ and $\ell = \ell' \bmod k$

$$I_{\ell, \ell'} = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k, \ell \in I, \ell' \in I} (m_1)^2 = 0. \quad (4.31)$$

We also obtain by combining Eq. (4.30) with Lemma A.8 that when $\ell \neq \ell' \bmod k$

$$I_{\ell, \ell'} = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k, \ell \in I, \ell' \in I} (m_1)^2 = \begin{cases} 0, & \text{if } k = 1, \\ \frac{(m_1)^2}{4}, & \text{if } k \geq 2. \end{cases} \quad (4.32)$$

We now conclude. First, we combine (4.29), (4.31) and (4.32). Then, we use the fact that as the set

$$\{(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2 \mid \ell = \ell' \bmod k\} = \left(\bigcup_{i=1}^{2k} \{(i, i)\} \right) \cup \left(\bigcup_{i=1}^k \{(i, i+k)\} \right) \left(\bigcup_{i=k+1}^{2k} \{(i, i-k)\} \right)$$

has a cardinality of $4k$, it holds

$$\#(\{(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2 \mid \ell \neq \ell' \bmod k\}) = (2k)^2 - 4k = 4k^2 - 4k.$$

We obtain at the end the following (note that $(4k^2 - 4k)1_{\{k \geq 2\}} = 4k^2 - 4k$, as $k \in \mathbb{N}^*$), which ends the proof

$$\begin{aligned} \sigma_\mu &= \sum_{1 \leq \ell = \ell' \leq 2k} I_{\ell, \ell} + \sum_{\substack{1 \leq \ell \neq \ell' \leq 2k \\ \text{s.t. } \ell = \ell' \bmod k}} I_{\ell, \ell'} + \sum_{\substack{1 \leq \ell \neq \ell' \leq 2k \\ \text{s.t. } \ell \neq \ell' \bmod k}} I_{\ell, \ell'} \\ &= 2k \frac{m_2}{2} + 0 + (4k^2 - 4k) \frac{(m_1)^2}{4} 1_{\{k \geq 2\}} = (m_1)^2 k^2 + (m_2 - (m_1)^2) k. \end{aligned}$$

□

4.3.2 Proof of Lemma 4.7

We first need to obtain a better expression for $u_{\partial, 2} = u_{\partial, 0} - u_{\partial, 1}$, where $u_{\partial, 0}$ and $u_{\partial, 1}$ are defined in (4.22). To do so, we develop the function $u_{\partial, 0}$ in its definition. One can notice that for all $t \geq 0$, it holds in view of (4.10) and (4.11)

$$\begin{aligned} u_{\partial, 0}(t) &= bN \int_{y \in \mathbb{R}_+^{2k}} u^{(2k)}(t, y) \mu\left(\left\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\right\}\right) 1_{\{\#\{i \in \llbracket 1, 2k \rrbracket \mid y_i \leq \frac{\delta}{N}\} = 1\}} dy \\ &\quad + bN \int_{y \in \mathbb{R}_+^{2k}} u^{(2k)}(t, y) \mu\left(\left\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\right\}\right) 1_{\{\#\{i \in \llbracket 1, 2k \rrbracket \mid y_i \leq \frac{\delta}{N}\} \geq 2\}} dy. \end{aligned}$$

The function on the first line of the above has the same definition as $n_{\partial, 1}^{(2k)}$, see (4.12), with $u^{(2k)}$ instead of $n^{(2k)}$. Then, following exactly the same steps as those to obtain (4.14), replacing $n^{(2k)}$ with $u^{(2k)}$, yields that for all $t \geq 0$

$$\begin{aligned} u_{\partial, 0}(t) &= \frac{b}{2} \sum_{i=1}^{2k} \int_{y' \in \mathbb{R}_+^{2k}} u^{(2k)}\left(t, \sum_{j=1, j \neq i}^{2k} y'_j e_j + \frac{y'_i}{N} e_i\right) (1 - G(y'_i)) 1_{\{y'_i \leq \delta, \forall j \in \llbracket 1, 2k \rrbracket \setminus \{i\}: y'_j > \frac{\delta}{N}\}} dy' \\ &\quad + bN \int_{y \in \mathbb{R}_+^{2k}} u^{(2k)}(t, y) \mu\left(\left\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\right\}\right) 1_{\{\#\{i \in \llbracket 1, 2k \rrbracket \mid y_i \leq \frac{\delta}{N}\} \geq 2\}} dy. \end{aligned} \tag{4.33}$$

Now, we use the above equation to develop $u_{\partial, 2}$. Specifically, we subtract $u_{\partial, 1}$ from both sides of (4.33), in view of (4.22) and the following equality

$$1_{\{y'_i \leq \delta, \forall j \in \llbracket 1, 2k \rrbracket \setminus \{i\}: y'_j > \frac{\delta}{N}\}} - 1_{\{y'_i \leq \delta\}} = -1_{\{y'_i \leq \delta, \exists j \in \llbracket 1, 2k \rrbracket \setminus \{i\}: y'_j \leq \frac{\delta}{N}\}}.$$

We obtain that for all $t \geq 0$

$$\begin{aligned} u_{\partial, 2}(t) &= -\frac{b}{2} \sum_{i=1}^{2k} \int_{y' \in \mathbb{R}_+^{2k}} u^{(2k)}\left(t, \sum_{\ell=1, \ell \neq i}^{2k} y'_\ell e_\ell + \frac{y'_i}{N} e_i\right) (1 - G(y'_i)) 1_{\{y'_i \leq \delta, \exists j \in \llbracket 1, 2k \rrbracket \setminus \{i\}: y'_j \leq \frac{\delta}{N}\}} dy' \\ &\quad + bN \int_{y \in \mathbb{R}_+^{2k}} u^{(2k)}(t, y) \mu\left(\left\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\right\}\right) 1_{\{\#\{i \in \llbracket 1, 2k \rrbracket \mid y_i \leq \frac{\delta}{N}\} \geq 2\}} dy \\ &=: -u_{\partial, 3}(t) + u_{\partial, 4}(t). \end{aligned}$$

As $-u_{\partial,3}$ and $u_{\partial,4}$ have an opposite sign, the above implies that $|u_{\partial,2}(t)| \leq \max(u_{\partial,3}(t), u_{\partial,4}(t))$ for all $t \geq 0$. We thus now obtain an upper bound for both $u_{\partial,3}$ and $u_{\partial,4}$ in order to prove (4.24).

To bound $u_{\partial,3}$, we first bound $1_{\{y'_i \leq \delta, \exists j \in [1, 2k] \setminus \{i\} : y'_j \leq \frac{\delta}{N}\}}$ by $\sum_{j \in [1, 2k] \setminus \{i\}} 1_{\{y'_i \leq \delta, y'_j \leq \frac{\delta}{N}\}}$. Then, we use (4.16) to write $u^{(2k)}$ in terms of n_0 , and apply (H₃) to bound from above n_0 . Finally, we integrate in dy' , by using that $\int_0^\delta (1 - G(y'_i)) dy'_i = m_1$, that $\int_0^{\frac{\delta}{N}} \exp(-\lambda y'_j) dy'_j \leq \frac{\delta}{N}$, and that $\int_0^{+\infty} \exp(-\lambda y'_\ell) dy'_\ell = \frac{1}{\lambda}$ for all $\ell \in [1, 2k] \setminus \{i, j\}$. We obtain that for all $t \geq 0$

$$\begin{aligned} |u_{\partial,3}(t)| &\leq \frac{b}{2} \sum_{i=1}^{2k} \sum_{\substack{j=1 \\ j \neq i}}^{2k} \int_{y' \in \mathbb{R}_+^{2k}} n_0 \left(\frac{bm_1}{2} t + \frac{y'_i}{N} \right) \left[\prod_{\substack{\ell=1 \\ \ell \neq i}}^{2k} n_0 \left(\frac{bm_1}{2} t + y_\ell \right) \right] (1 - G(y'_i)) 1_{\{y'_i \leq \delta, y_j \leq \frac{\delta}{N}\}} dy' \\ &\leq \frac{bm_1 \delta}{2N} \sum_{i=1}^{2k} \sum_{\substack{j=1 \\ j \neq i}}^{2k} \frac{\lambda^{2k} (D_\lambda)^{2k}}{\lambda^{2k-2}} \exp(-k\lambda bm_1 t) = 2k(2k-1) \frac{bm_1 \delta}{2N} \lambda^2 (D_\lambda)^{2k} \exp(-k\lambda bm_1 t). \end{aligned} \quad (4.34)$$

To bound $u_{\partial,4}$, we first bound the term $\mu(\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\})$ in $u_{\partial,4}$ by 1, as μ is a probability measure. Then, we bound the term $1_{\{\#\{i \in [1, 2k] \mid y_i \leq \frac{\delta}{N}\} \geq 2\}}$ by the sum $\sum_{(i,j) \in [1, 2k]^2, i \neq j} 1_{\{y_i \leq \frac{\delta}{N}, y_j \leq \frac{\delta}{N}\}}$. Finally, as done before, we successively use Eq. (4.16) to write $u^{(2k)}$ in terms of n_0 , apply (H₃) to bound from above n_0 , and integrate by using the same inequalities/equalities. We obtain that for all $t \geq 0$

$$\begin{aligned} |u_{\partial,4}(t)| &\leq bN \sum_{i=1}^{2k} \sum_{\substack{j=1 \\ j \neq i}}^{2k} \int_{y \in \mathbb{R}_+^{2k}} u^{(2k)}(t, y) 1_{\{y_i \leq \frac{\delta}{N}, y_j \leq \frac{\delta}{N}\}} dy \\ &\leq 2k(2k-1) \frac{b\delta^2}{N} \lambda^2 (D_\lambda)^{2k} \exp(-k\lambda bm_1 t). \end{aligned} \quad (4.35)$$

From (4.34), (4.35) and the fact that $|u_{\partial,2}| \leq \max(u_{\partial,3}, u_{\partial,4})$, the lemma is proved. \square

4.3.3 Proof of Lemma 4.9

We consider two functions $F : \mathbb{R}_+ \times \mathbb{R}_+^{2k} \rightarrow \mathbb{R}$ and $\bar{F} : \mathbb{R}_+ \times \mathbb{R}_+^{2k} \rightarrow \mathbb{R}$, defined for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$ as

$$F(t, x) := \tilde{n}_0(x) + \sum_{\ell \geq 1} \frac{(bN)^\ell t^\ell}{\ell!} \int_{v_1 \in \mathbb{R}_+^{2k}} \cdots \int_{v_\ell \in \mathbb{R}_+^{2k}} \tilde{n}_0 \left(x + \sum_{j=1}^{\ell} \frac{v_j}{N} \right) \mu(dv_\ell) \cdots \mu(dv_1), \quad (4.36)$$

$$\bar{F}(t, x) := e^{-bNt} F(t, x).$$

We begin by proving that $n^{(2k)} = \bar{F}$. By deriving F , and then taking $m = \ell - 1$, one has that for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$

$$\begin{aligned} \partial_t F(t, x) &= \sum_{\ell \geq 1} \frac{(bN)^\ell t^{\ell-1}}{(\ell-1)!} \int_{v_1 \in \mathbb{R}_+^{2k}} \cdots \int_{v_\ell \in \mathbb{R}_+^{2k}} \tilde{n}_0 \left(x + \sum_{j=1}^{\ell} \frac{v_j}{N} \right) \mu(dv_\ell) \cdots \mu(dv_1) \\ &= bN \sum_{m \geq 0} \frac{(bNt)^m}{m!} \int_{v_1 \in \mathbb{R}_+^{2k}} \cdots \int_{v_{m+1} \in \mathbb{R}_+^{2k}} \tilde{n}_0 \left(x + \sum_{j=1}^{m+1} \frac{v_j}{N} \right) \mu(dv_{m+1}) \cdots \mu(dv_1) \\ &= bN \int_{v_1 \in \mathbb{R}_+^{2k}} F \left(t, x + \frac{v_1}{N} \right) \mu(dv_1). \end{aligned}$$

Then, combining the above with the fact that $\partial_t \bar{F}(t, x) = e^{-bNt} \partial_t F(t, x) - bN e^{-bNt} F(t, x)$ by the second line of (4.36), yields that \bar{F} is solution of the following integro-differential equation

$$\begin{cases} \partial_t \bar{F}(t, x) = bN \int_{v_1 \in \mathbb{R}_+^{2k}} \bar{F}(t, x + \frac{v_1}{N}) \mu(dv_1) - bN \bar{F}(t, x), & \forall t \geq 0, x \in \mathbb{R}_+^{2k}, \\ \bar{F}(0, x) = \tilde{n}_0(x), & \forall x \in \mathbb{R}_+^{2k}. \end{cases}$$

The above equation corresponds to the same integro-differential equation as the one verified by $n^{(2k)}$ (see Eq. (4.8)). In addition, this integro-differential equation has a unique solution in $C(\mathbb{R}_+, L^1(\mathbb{R}_+^{2k}))$ by Proposition A.1. Then, by combining these two results, we obtain that $n^{(2k)} = \bar{F}$.

Now, we prove Eq. (4.28). By applying the right-hand side of (2.9), and then combining the fact that $n^{(2k)} = \bar{F}$ with the second line of (4.36), we have that for all $t \geq 0$

$$\int_t^{+\infty} n_{\partial}^{(2k)}(s) ds = e^{-bNt} \int_{x \in \mathbb{R}_+^{2k}} F(t, x) dx.$$

Therefore, by plugging the first line of (4.36) in the above equation, and then using that $\int_{x \in \mathbb{R}_+^{2k}} \tilde{n}_0(x) dx = 1$ to compute the term that is not in the sum, we obtain that (4.28) is true, which concludes the proof. \square

4.3.4 Proof of Lemma 4.10

To prove this lemma, we proceed in two steps. In Step 1, we prove that for all $t \geq 0$, we have

$$\int_t^{+\infty} n_{\partial}^{(2k)}(s) ds \geq (D_{\omega})^{2k} \exp(-k b m_1 \omega t), \quad (4.37)$$

and in Step 2, we prove that for all $t \geq 0$, it holds

$$\int_t^{+\infty} u_{\partial}^{(2k)}(s) ds \geq (D_{\omega})^{2k} \exp(-k b m_1 \omega t). \quad (4.38)$$

Step 1: To simplify notations, we also use in this step the function \tilde{n}_0 , defined in (4.27), to represent the product of the functions n_0 . Our aim here is to bound from below the right-hand side term of (4.28). To do so, we begin by bounding the coefficients in the sum. By applying (H₄) to bound from below \tilde{n}_0 , and then using that f_{ω} is non-decreasing to bound $f_{\omega}(x_i + \sum_{j=1}^{\ell} \frac{(v_j)_i}{N})$ by $f_{\omega}(x_i)$, we have that for all $\ell \in \mathbb{N}^*$, $x \in \mathbb{R}_+^{2k}$ and $(v_1, \dots, v_{\ell}) \in (\mathbb{R}_+^{2k})^{\ell}$

$$\begin{aligned} \tilde{n}_0 \left(x + \sum_{j=1}^{\ell} \frac{v_j}{N} \right) &\geq (D_{\omega})^{2k} \frac{\prod_{i=1}^{2k} (f_{\omega}(x_i + \sum_{j=1}^{\ell} \frac{(v_j)_i}{N}) \exp[-\omega(x_i + \sum_{j=1}^{\ell} \frac{(v_j)_i}{N})])}{(\int_0^{+\infty} f_{\omega}(y) \exp(-\omega y) dy)^{2k}} \\ &\geq (D_{\omega})^{2k} \frac{\prod_{i=1}^{2k} (f_{\omega}(x_i) \exp[-\omega x_i])}{(\int_0^{+\infty} f_{\omega}(y) \exp(-\omega y) dy)^{2k}} \exp \left(-\omega \sum_{i=1}^{2k} \sum_{j=1}^{\ell} \frac{(v_j)_i}{N} \right). \end{aligned}$$

Then, by integrating both sides in dx and $(\mu(dv_i))_{i \in \llbracket 1, \ell \rrbracket}$, and simplifying the last term with a Laplace transform, we obtain that for all $\ell \in \mathbb{N}^*$

$$\begin{aligned} &\int_{x \in \mathbb{R}_+^{2k}} \int_{v_1 \in \mathbb{R}_+^{2k}} \dots \int_{v_{\ell} \in \mathbb{R}_+^{2k}} \tilde{n}_0 \left(x + \sum_{j=1}^{\ell} \frac{v_j}{N} \right) \mu(dv_{\ell}) \dots \mu(dv_1) dx \\ &\geq (D_{\omega})^{2k} \left[\prod_{j=1}^{\ell} \int_{v_j \in \mathbb{R}_+^{2k}} \exp \left(-\omega \sum_{i=1}^{2k} \frac{(v_j)_i}{N} \right) \mu(dv_j) \right] = (D_{\omega})^{2k} \left(\mathcal{L}(\mu) \left(\frac{\omega}{N} \right) \right)^{\ell}. \end{aligned} \quad (4.39)$$

We now plug (4.39) in the right-hand side of (4.28). Then, we use that $1 \geq (D_\omega)^{2k}$ (as $D_\omega < 1$) to bound from below the term that is not in the sum. We obtain that for all $t \geq 0$

$$\begin{aligned} \int_t^{+\infty} n_\partial^{(2k)}(s) ds &\geq e^{-bNt} (D_\omega)^{2k} \left[1 + \sum_{\ell \geq 1} \frac{(bN)^\ell t^\ell}{\ell!} \left(\mathcal{L}(\mu) \left(\frac{\omega}{N} \right) \right)^\ell \right] \\ &= (D_\omega)^{2k} \exp \left[bN \left(\mathcal{L}(\mu) \left(\frac{\omega}{N} \right) - 1 \right) t \right]. \end{aligned}$$

It thus only remains to prove that $bN \left(\mathcal{L}(\mu) \left(\frac{\omega}{N} \right) - 1 \right) \geq -kbm_1\omega$ and Eq. (4.37) will be proved. In fact, the latter is easy to obtain because in view of the inequality $e^{-x} - 1 \geq -x$ for all $x \in \mathbb{R}$ and Lemma 4.1, we have

$$\mathcal{L}(\mu) \left(\frac{\omega}{N} \right) - 1 = \int_{\mathbb{R}_+^{2k}} \left[\exp \left(-\frac{\omega}{N} \sum_{i=1}^{2k} u_i \right) - 1 \right] \mu(du) \geq -\frac{\omega}{N} \sum_{i=1}^{2k} \int_{\mathbb{R}_+^{2k}} u_i \mu(dx) = -\frac{km_1\omega}{N}.$$

Step 2: First, notice that by applying (H₄) to bound from below n_0 , then doing the change of variable $s' = s - \frac{bm_1 t}{2}$, and finally using that f_ω is non-decreasing to bound from below $f_\omega \left(s' + \frac{bm_1 t}{2} \right)$ by $f_\omega(s')$, we have for all $t \geq 0$

$$\begin{aligned} \int_{\frac{bm_1 t}{2}}^{+\infty} n_0(s) ds &\geq \frac{D_\omega \int_{\frac{bm_1 t}{2}}^{+\infty} f_\omega(s) \exp(-\omega s) ds}{\int_0^{+\infty} f_\omega(z) \exp(-\omega z) dz} \\ &= \frac{D_\omega \int_0^{+\infty} f_\omega \left(s' + \frac{bm_1 t}{2} \right) \exp \left(-\omega s' - \frac{bm_1 \omega t}{2} \right) ds'}{\int_0^{+\infty} f_\omega(z) \exp(-\omega z) dz} \geq D_\omega \exp \left(-\frac{bm_1 \omega t}{2} \right). \end{aligned}$$

Then, by combining the above equation with the first equality in (4.18), we obtain that (4.38) is true, which ends the proof of the lemma. \square

4.4 Proof of Proposition 4.4-(a)

To recall, in view of (4.21), our aim is to check the assumptions of Lemma 3.5 for $u_\xi = \bar{u}^{(2k)}$, $\xi = \mu$ and $F = u^{(2k)}$, and then to apply it to obtain the statement. First, notice that by (4.16), we have for all $(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2$, $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$,

$$\partial_{x_\ell x_{\ell'}} u^{(2k)}(t, x) = \begin{cases} n'_0 \left(\frac{bm_1 t}{2} + x_\ell \right) n'_0 \left(\frac{bm_1 t}{2} + x_{\ell'} \right) \prod_{i=1, i \notin \{\ell, \ell'\}}^{2k} n_0 \left(\frac{bm_1 t}{2} + x_i \right), & \text{if } \ell \neq \ell', \\ n''_0 \left(\frac{bm_1 t}{2} + x_\ell \right) \prod_{i=1, i \neq \ell}^{2k} n_0 \left(\frac{bm_1 t}{2} + x_i \right), & \text{if } \ell = \ell'. \end{cases}$$

Then, by applying (H₂) and (H₃) to the above, we obtain that for all $(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2$ and $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$

$$\left| \partial_{x_\ell x_{\ell'}} u^{(2k)}(t, x) \right| \leq \begin{cases} (C'_\lambda)^2 (\lambda D_\lambda)^{2k-2} \exp \left(-kbm_1 \lambda t - \lambda \sum_{i=1}^{2k} x_i \right), & \text{if } \ell \neq \ell', \\ C_\lambda (\lambda D_\lambda)^{2k-1} \exp \left(-kbm_1 \lambda t - \lambda \sum_{i=1}^{2k} x_i \right), & \text{if } \ell = \ell'. \end{cases}$$

This implies that (3.9) holds with $C = \max \left((C'_\lambda)^2, C_\lambda \lambda D_\lambda \right) (\lambda D_\lambda)^{2k-2}$, $\alpha = kbm_1 \lambda$, and $\beta = \lambda$. In addition, in view of the inequality $1 - e^{-x} \leq x$ for all $x \in \mathbb{R}$ and Lemma 4.1, we have that

$$bN \left[1 - \mathcal{L}(\mu) \left(\frac{\lambda}{N} \right) \right] = bN \int_{\mathbb{R}_+^{2k}} \left[1 - \exp \left(-\frac{\lambda}{N} \sum_{i=1}^{2k} u_i \right) \right] \mu(du) \leq b\lambda \sum_{i=1}^{2k} \int_{\mathbb{R}_+^{2k}} u_i \mu(dx) = kbm_1 \lambda, \quad (4.40)$$

so that (3.10) holds with the same α and β as before. From these two results, all the assumptions of Lemma 3.5 are verified. We thus apply this lemma, and it comes for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$

$$\left| \bar{u}^{(2k)}(t, x) \right| \leq \max \left((C'_\lambda)^2, C_\lambda \lambda D_\lambda \right) (\lambda D_\lambda)^{2k-2} \frac{bt\sigma_\mu}{2N} \exp \left[-bN \left(1 - \mathcal{L}(\mu) \left(\frac{\lambda}{N} \right) \right) t - \lambda \sum_{i=1}^{2k} x_i \right]. \quad (4.41)$$

We now slightly manipulate the right-hand side of (4.41) to obtain the same bound as the one stated in (4.19). As $\sigma_\mu \underset{k \rightarrow +\infty}{\sim} k^2$ by Lemma 4.6, we have that there exists $d'_0 > 0$, independent of k , such that

$$\max \left((C'_\lambda)^2, C_\lambda \lambda D_\lambda \right) \sigma_\mu \leq d'_0 (\lambda D_\lambda)^2 k^2. \quad (4.42)$$

In addition, by first using the right-hand side of (2.10) to develop $\mathcal{L}(\mu)$, then the left-hand side of (2.10) to obtain that $\mathcal{L}(\mu^{(I)}) = (\mathcal{L}(g))^k$ for all $I \in \mathcal{I}_k$, and finally the first equality in Lemma A.7 to simplify the sum and the fraction, we have that for all $p > 0$

$$\mathcal{L}(\mu)(p) = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} \mathcal{L}(\mu^{(I)})(p) = \frac{1}{2^k} \sum_{I \in \mathcal{I}_k} (\mathcal{L}(g))^k(p) = (\mathcal{L}(g))^k(p). \quad (4.43)$$

The above yields, in view of (2.11), that

$$bN \left(1 - \mathcal{L}(\mu) \left(\frac{\lambda}{N} \right) \right) = bN \left(1 - (\mathcal{L}(g))^k \left(\frac{\lambda}{N} \right) \right) = kbm_1 \lambda'_N. \quad (4.44)$$

Then, by plugging this equality and Eq. (4.42) in (4.41), we obtain the same bound as in (4.19), so that Proposition 4.4-(a) is true. \square

4.5 Proof of Proposition 4.4-(b)

In view of (4.23), we consider the function $v_\mu := n_{\partial}^{(2k)} - u_{\partial,0}^{(2k)} + u_{\partial,1}^{(2k)} - u_{\partial}^{(2k)}$. Assume that there exists a set of functions $(h_i)_{i \in \llbracket 1, 2k \rrbracket}$ from $\mathbb{R}_+ \times \mathbb{R}_+^{2k}$ to \mathbb{R} verifying (3.13) with $C' = \frac{1}{2} C'_\lambda (\lambda D_\lambda)^{2k-1}$ and $\beta = \lambda$, such that for all $t \geq 0$

$$u_{\partial,1}^{(2k)}(t) - u_{\partial}^{(2k)}(t) = b \sum_{i=1}^{2k} \int_{y \in \mathbb{R}_+^{2k}} h_i(t, y) (1 - G(y_i)) 1_{\{y_i \leq \delta\}} dy. \quad (4.45)$$

By developing $n_{\partial}^{(2k)}$ and $u_{\partial,0}^{(2k)}$ with their definitions, given in (4.8) and (4.22) respectively, we have that for all $t \geq 0$

$$n_{\partial}^{(2k)}(t) - u_{\partial,0}^{(2k)}(t) = bN \int_{y \in \mathbb{R}_+^{2k}} \left[n^{(2k)}(t, y) - u^{(2k)}(t, y) \right] \mu \left(\left\{ w \in \mathbb{R}_+^{2k} \mid Ny - w \notin \mathbb{R}_+^{2k} \right\} \right) dy. \quad (4.46)$$

Then, by plugging (4.45) and (4.46) in the definition of v_μ , we have that v_μ verifies (3.14) with $u_\xi = n^{(2k)} - u^{(2k)}$ and $\xi = \mu$. As u_ξ verifies the assumptions of Lemma 3.5 by the proof of Proposition 4.4-(a), see Section 4.4, this means that all the assumptions of Lemma 3.6 are verified for $v_\xi = v_\mu$. Then, by applying this lemma, and using (4.42) and (4.44) to simplify the bound (as done in Section 4.4), we obtain that for all $t \geq 0$

$$\begin{aligned} |v_\mu(t)| &\leq \left[d'_0 \lambda (D_\lambda)^{2k} \frac{k^3 b^2 m_1 t}{2N} + \frac{b C'_\lambda (D_\lambda)^{2k-1} m_2 k}{2N} \right] \exp(-k b m_1 \lambda'_N t) \\ &= \frac{b}{N} (D_\lambda)^{2k} \left(d'_0 \lambda \frac{k^3 b m_1 t}{2} + \frac{C'_\lambda m_2 k}{2 D_\lambda} \right) \exp(-k b m_1 \lambda'_N t). \end{aligned}$$

Recalling Eq. (4.23), combining the above with (4.24) through a triangular inequality, and then using that $-k b m_1 \lambda \leq -k b m_1 \lambda'_N$ (as a consequence of (4.40) and (4.44)), yields that (4.20) is true. Then, Proposition 4.4-(b) is proved, assuming that the set of functions $(h_i)_{i \in \llbracket 1, 2k \rrbracket}$ presented at the beginning of the proof exists.

It thus remains to prove that such a sequence exists. We consider for all $i \in \llbracket 1, 2k \rrbracket$, $(t, y) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$,

$$h_i(t, y) := \frac{1}{2} \left[u^{(2k)} \left(t, \sum_{j=1, j \neq i}^{2k} y_j e_j + \frac{y_i}{N} \right) - u^{(2k)} \left(t, \sum_{j=1, j \neq i}^{2k} y_j e_j \right) \right]. \quad (4.47)$$

By taking the difference between the second lines of Eq. (4.22) and Eq. (4.15), and using that $m_1 = \int_{y_i \in [0, \delta]} (1 - G(y_i)) dy_i$ for each index $i \in \llbracket 1, 2k \rrbracket$ of the sum in the second line of (4.15), we have that (4.45) holds with the set of functions defined in (4.47). In addition, by using (4.16), then writing n_0 as an integral of n'_0 , and finally applying (H₂) and (H₃), we have that for all $i \in \llbracket 1, 2k \rrbracket$, $(t, y) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$,

$$\begin{aligned} h_i(t, y) &= \frac{1}{2} \left[n_0 \left(\frac{b m_1}{2} t + \frac{y_i}{N} \right) - n_0 \left(\frac{b m_1}{2} t \right) \right] \left[\prod_{j=1, j \neq i}^{2k} n_0 \left(\frac{b m_1}{2} t + y_j \right) \right] \\ &= \frac{1}{2} \left[\int_0^{\frac{y_i}{N}} n'_0 \left(\frac{b m_1}{2} t + u \right) du \right] \left[\prod_{j=1, j \neq i}^{2k} n_0 \left(\frac{b m_1}{2} t + y_j \right) \right] \\ &\leq \frac{1}{2} C'_\lambda (\lambda D_\lambda)^{2k-1} \frac{y_i}{N} \exp \left[-k b m_1 \lambda t - \lambda \sum_{j=1, j \neq i}^{2k} y_j \right]. \end{aligned}$$

This implies, by using (4.40) to bound the coefficient $-k b m_1 \lambda$ in the exponential, that $(h_i)_{i \in \llbracket 1, 2k \rrbracket}$ verifies (3.13) with $C' = \frac{1}{2} C'_\lambda (\lambda D_\lambda)^{2k-1}$ and $\beta = \lambda$. Then, from these points, we have that the set of functions we need exists, which concludes the proof of Proposition 4.4-(b). \square

4.6 Proof of Theorem 2.6-(b)

Let $x \geq 0$. To simplify notations, we denote

$$\widehat{N}_0(x) := \int_{\frac{2x}{b m_1}}^{+\infty} n_\partial^{(2k)}(s) ds, \quad \text{and} \quad \widehat{U}_0(x) := \int_{\frac{2x}{b m_1}}^{+\infty} u_\partial^{(2k)}(s) ds.$$

In view of (4.26) and the triangular inequality, the following holds

$$\begin{aligned} \left| \widehat{n}_0^{(2k)}(x) - n_0(x) \right| &\leq \frac{\left| n_\partial^{(2k)} \left(\frac{2x}{b m_1} \right) - u_\partial^{(2k)} \left(\frac{2x}{b m_1} \right) \right|}{k b m_1 \widehat{N}_0(x)^{1-\frac{1}{2k}}} + \frac{u_\partial^{(2k)} \left(\frac{2x}{b m_1} \right)}{k b m_1} \left| \frac{1}{\widehat{N}_0(x)^{1-\frac{1}{2k}}} - \frac{1}{\widehat{U}_0(x)^{1-\frac{1}{2k}}} \right| \\ &=: \Delta_1(x) + \Delta_2(x). \end{aligned} \quad (4.48)$$

Thus, our aim is to obtain an upper bound for both $\Delta_1(x)$ and $\Delta_2(x)$. Theorem 2.6 then comes by summing these bounds.

By applying Proposition 4.4-(b) to bound the numerator, and Lemma 4.10 to bound the denominator, we have the following

$$\begin{aligned} \Delta_1(x) &\leq \frac{\frac{b d'_1}{N} (D_\lambda)^{2k} (k^3 x + k^2 + k) \exp(-2k \lambda'_N x)}{k b m_1 \left[(D_\omega)^{2k} \exp(-2k \omega x) \right]^{1-\frac{1}{2k}}} \\ &= \frac{d'_1 D_\omega}{N m_1} \left(\frac{D_\lambda}{D_\omega} \right)^{2k} (k^2 x + k + 1) \exp(-\lambda'_N x + (2k - 1)(\omega - \lambda'_N) x). \end{aligned} \quad (4.49)$$

We thus now focus on finding an upper bound for $\Delta_2(x)$, which requires more computations. For this purpose, we begin by obtaining an intermediate inequality. In the equation below, first apply the equality $\left|\frac{1}{c} - \frac{1}{d}\right| = \frac{|c-d|}{cd}$ for $c = \widehat{N}_0(x)^{1-\frac{1}{2k}}$ and $d = \widehat{U}_0(x)^{1-\frac{1}{2k}}$ to develop $\Delta_2(x)$. Then, use that it holds $\frac{1}{k b m_1} u_{\partial}^{(2k)}\left(\frac{2x}{b m_1}\right) = n_0(x) \widehat{U}_0(x)^{1-\frac{1}{2k}}$ by Lemma 4.8 to simplify the term $\widehat{U}_0(x)^{1-\frac{1}{2k}}$ at the denominator. Finally, apply (H₃) to bound from above the term $n_0(x)$ coming from the previous computation, and use Lemma 4.10 to bound the term $\widehat{N}_0(x)^{1-\frac{1}{2k}}$ at the denominator. It comes the following inequality

$$\begin{aligned} \Delta_2(x) &= \frac{u_{\partial}^{(2k)}\left(\frac{2x}{b m_1}\right)}{k b m_1} \frac{\left|\widehat{N}_0(x)^{1-\frac{1}{2k}} - \widehat{U}_0(x)^{1-\frac{1}{2k}}\right|}{\widehat{N}_0(x)^{1-\frac{1}{2k}} \widehat{U}_0(x)^{1-\frac{1}{2k}}} = n_0(x) \frac{\left|\widehat{N}_0(x)^{1-\frac{1}{2k}} - \widehat{U}_0(x)^{1-\frac{1}{2k}}\right|}{\widehat{N}_0(x)^{1-\frac{1}{2k}}} \\ &\leq \lambda D_{\lambda} \exp(-\lambda x) \frac{\left|\widehat{N}_0(x)^{1-\frac{1}{2k}} - \widehat{U}_0(x)^{1-\frac{1}{2k}}\right|}{(D_{\omega})^{2k-1} \exp[-(2k-1)\omega x]}. \end{aligned} \quad (4.50)$$

To continue our computations, we need to bound the numerator of (4.50). To do so, we first develop it by using the inequality $|c^{\ell} - d^{\ell}| \leq \ell \frac{|c-d|}{\min(c,d)^{1-\ell}}$ for $c = \widehat{N}_0(x)$, $d = \widehat{U}_0(x)$ and $\ell = 1 - \frac{1}{2k}$. This inequality comes from the Taylor's inequality applied to the function $y \mapsto y^{\ell}$, and is true when $\ell \in (0, 1)$. Thereafter, we apply Lemma 4.10 to bound the term $\frac{1}{\min(c,d)^{1-\ell}}$ coming from the previous step. Finally, to bound the term $|c - d|$ coming from the first step, we use the following equality, which comes from (2.9)-(4.18), Proposition 4.4-(a), and the fact that $\int_{y \in \mathbb{R}_+^{2k}} \exp\left(-\lambda \sum_{i=1}^{2k} y_i\right) dy = \frac{1}{\lambda^{2k}}$,

$$\begin{aligned} \left|(\widehat{N}_0 - \widehat{U}_0)(x)\right| &= \left| \int_{y \in \mathbb{R}_+^{2k}} \left(n^{(2k)} - u^{(2k)}\right) \left(\frac{2x}{b m_1}, y\right) dy \right| \\ &\leq d'_0 (\lambda D_{\lambda})^{2k} \frac{k^2 b \frac{2x}{b m_1}}{2N} \exp\left[-k b m_1 \lambda'_N \frac{2x}{b m_1}\right] \frac{1}{\lambda^{2k}} = d'_0 (D_{\lambda})^{2k} \frac{k^2 x}{N m_1} \exp[-2k \lambda'_N x]. \end{aligned}$$

We obtain

$$\left|\widehat{N}_0(x)^{1-\frac{1}{2k}} - \widehat{U}_0(x)^{1-\frac{1}{2k}}\right| \leq \left(1 - \frac{1}{2k}\right) \frac{d'_0 (D_{\lambda})^{2k} \frac{k^2 x}{N m_1} \exp[-2k \lambda'_N x]}{D_{\omega} \exp(-\omega x)}. \quad (4.51)$$

Then, by plugging (4.51) in (4.50) and bounding the term $1 - \frac{1}{2k}$ by 1, we get the following upper bound for $\Delta_2(x)$

$$\begin{aligned} \Delta_2(x) &\leq \lambda D_{\lambda} \exp(-\lambda x) \frac{d'_0 (D_{\lambda})^{2k} \frac{k^2 x}{N m_1} \exp(-2k \lambda'_N x)}{(D_{\omega})^{2k} \exp[-2k \omega x]} \\ &= \frac{d'_0 \lambda D_{\lambda}}{N m_1} \left(\frac{D_{\lambda}}{D_{\omega}}\right)^{2k} k^2 x \exp(-\lambda x + 2k(\omega - \lambda'_N)x). \end{aligned} \quad (4.52)$$

We now conclude. Recall that $\omega \geq \lambda$. By combining (4.40) with (4.44), we have that $\lambda \geq \lambda'_N$, and so that $\omega \geq \lambda'_N$. These inequalities yield

$$\max\left(-\lambda'_N x + (2k-1)(\omega - \lambda'_N)x, -\lambda x + 2k(\omega - \lambda'_N)x\right) \leq -\lambda'_N x + 2k(\omega - \lambda'_N)x. \quad (4.53)$$

Thus, by plugging (4.49) and (4.52) in (4.48), and then using (4.53) to bound the coefficients in the exponentials, we obtain Theorem 2.6-(b). \square

5 Estimation on simulations and data

Now that we have studied the quality of our estimators from a theoretical point of view, we verify if they work in practice. Specifically, we choose a certain number of parameters for our models, and compare the curves of $\widehat{n}_0^{(1)}$ and $\widehat{n}_0^{(2k)}$ with n_0 . We show that we have encouraging results for the single-telomere model, and when k is small for the model with several telomeres. We also highlight estimation issues that appear when the initial distribution of telomere lengths has a small variability, and when k is large.

First, in Section 5.1, we present estimation results in the single-telomere model. Then, in Section 5.2, we present estimation results in the model with several telomeres. Thereafter, in Section 5.3, we study how our inference method can be adapted in a more realistic framework where we observe noisy values of $n_\partial^{(1)}$ and $n_\partial^{(2k)}$, focusing in particular on the noise related to sampling. Finally, we test our inference method on experimental data in Section 5.4.

5.1 Estimation results in the single-telomere model

Estimation results in the single-telomere model depend on the variability of the initial distribution. More precisely, if n_0 corresponds to a distribution with a sufficiently large coefficient of variation, then the estimation works very well. Conversely, if the coefficient of variation is small, then the estimation has poor results. To present each of these cases precisely, this subsection is divided into two parts. First, in Section 5.1.1, we present two examples in which the estimation results are very satisfactory. Then, in Section 5.1.2, we illustrate how the quality of the estimation decreases as the variability of the initial distribution decreases, by comparing estimations of initial distributions with different coefficients of variation.

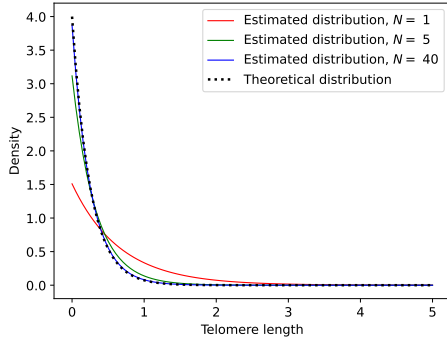
5.1.1 Two examples with a good estimation

Let us start by presenting the framework we use here. We introduce for all $(\ell, \beta) \in \mathbb{N}^* \times \mathbb{R}_+^*$ the following functions, for all $x \geq 0$,

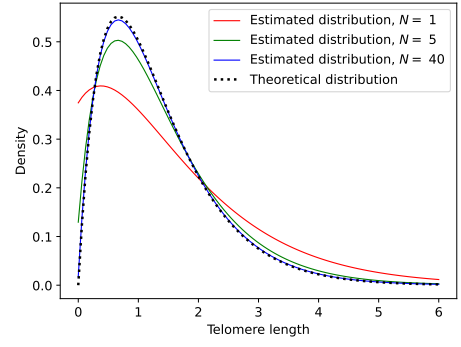
$$h_{\ell, \beta}(x) := \frac{\beta^\ell}{\Gamma(\ell)} x^{\ell-1} \exp(-\beta x), \quad \text{and} \quad H_{\ell, \beta}(x) := \int_0^x \frac{\beta^\ell}{\Gamma(\ell)} y^{\ell-1} \exp(-\beta y) dy. \quad (5.1)$$

These functions correspond respectively to the probability density and the cumulative density function of an Erlang distribution with parameter (ℓ, β) . In the estimations presented here, we choose n_0 belonging to the set $\{h_{\ell, \beta} \mid (\ell, \beta) \in \mathbb{N}^* \times \mathbb{R}_+^*\}$. The first reason of this choice is that in this case, $n^{(1)}$ is explicit by Propositions A.9 and A.10. We thus do not have to approximate this function to compute $n_\partial^{(1)}$ (see the second line of (2.3)), and then the estimator $\widehat{n}_0^{(1)}$ (see (2.12)), which would have reduced the quality of our estimations. The second reason is that our main result assumptions are easily verified for these functions (direct from the fact that they correspond to the product of a polynomial and an exponential). We therefore work in a setting in which Theorem 2.6 holds.

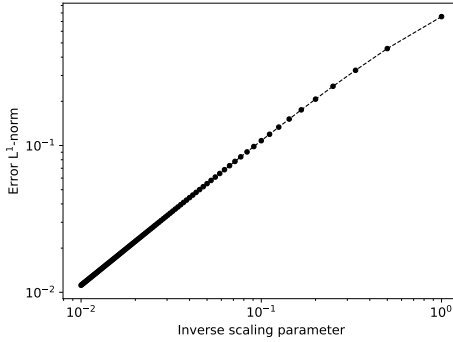
We now illustrate that our inference method works for initial distributions with a sufficiently large coefficient of variation. We assume that (H_1) is verified for $b = 1$, $g = 1_{[0,1]}$, and N not yet fixed. Our aim is to check numerically that the curve of $\widehat{n}_0^{(1)}$ is close to the one of n_0 . To do so, we first plot in Figures 1a and 1b the curve of $\widehat{n}_0^{(1)}$ as a function of telomere lengths when $n_0 \in \{h_{1,4}, h_{2,1}\}$, and for $N \in \{1, 5, 40\}$. In each of these figures, the curve of n_0 is also plotted in black for comparison. We then plot in Figures 1c and 1d the error in L^1 -norm between $\widehat{n}_0^{(1)}$ and n_0 , for the same model parameters, and as a function of $\frac{1}{N}$. We observe that when N is large, the estimation performs very well. Indeed, in Figures 1a and 1b, the blue curves, which



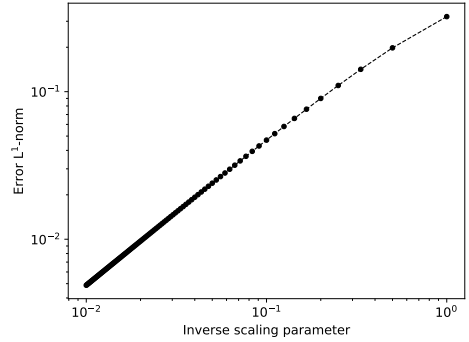
(a) Estimation results when $n_0 = h_{1,4}$ and $N \in \{1, 5, 40\}$. The errors in L^1 -norm are respectively 0.755, 0.207 and 0.0278.



(b) Estimation results when $n_0 = h_{2,1.5}$ and $N \in \{1, 5, 40\}$. The errors in L^1 -norm are respectively 0.323, 0.0900 and 0.0121.



(c) Error in L^1 -norm between $n_0 = h_{1,4}$ and $\hat{n}_0^{(1)}$ versus $1/N$ for $N \in \llbracket 1, 100 \rrbracket$, at the log-log scale.



(d) Error in L^1 -norm between $n_0 = h_{2,1.5}$ and $\hat{n}_0^{(1)}$ versus $1/N$ for $N \in \llbracket 1, 100 \rrbracket$, at the log-log scale.

Figure 1: Estimation results in the single-telomere model for different values of N , when $b = 1$, $g = 1_{[0,1]}$ and $n_0 \in \{h_{1,4}, h_{2,1.5}\}$.

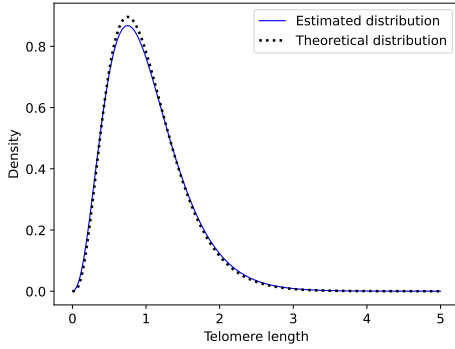
correspond to the estimations for $N = 40$, are almost superposed with the dotted curves. We also observe, in Figures 1c and 1d, that as predicted by our theorem, the L^1 -norm error increases linearly as $\frac{1}{N}$ increases, and that this error goes to 0 when $N \rightarrow +\infty$. The estimation results are thus very satisfactory. This is even more true since N does not need to be huge to obtain good results.

Remark 5.1. We have chosen $N = 40$ for the maximum scaling parameter here because this is the most realistic value for budding yeast, see the discussion about (H_1) p. 13. This species is one of our case studies because it is often used by biologists for experiments, see for example [41, 55, 56].

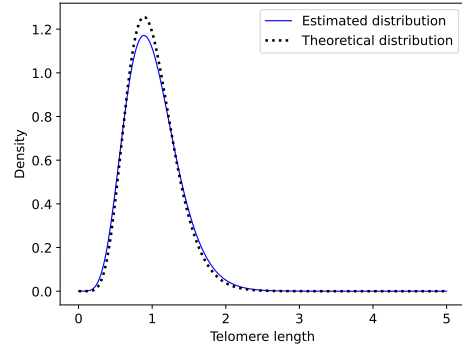
5.1.2 Problems of estimation when n_0 has a small variability

As mentioned in the previous section, it is required to have an initial distribution with a sufficiently large coefficient of variation to ensure a good estimation. We present here the problems that occur when this is not the case and the reasons behind it. Again, we work with Erlang initial distributions. We assume that (H_1) is verified with $b = 1$, $g = 1_{[0,1]}$, and $N = 40$. To show how the variability of n_0 influences the estimations results, we proceed to estimations

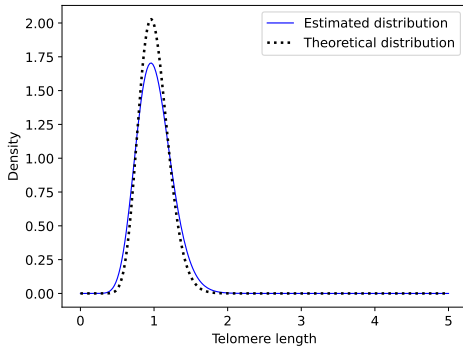
of initial distributions with the same mean, but different coefficients of variation (cv). To do so, in view of Eq. (5.1) and Proposition A.11, we first introduce for all $cv > 0$ the function $\mathcal{H}_{cv} = h_{1/cv^2, 1/cv^2}$, which is the density of an Erlang distribution with mean $m = 1$ and coefficient of variation cv . Then, we plot in Figure 2 the curve of $\hat{n}_0^{(1)}$ (blue curves), that we compare with the curve of n_0 (dotted curves), for $n_0 \in \{\mathcal{H}_{1/2}, \mathcal{H}_{1/3}, \mathcal{H}_{1/5}, \mathcal{H}_{1/7}\}$. We observe that the smaller the coefficient of variation is, the worse the estimation becomes. In particular, the spread of the initial laws is not well-captured, although the position of the mode is correctly estimated.



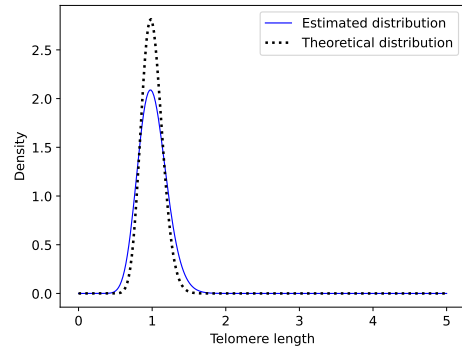
(a) Estimation result when $n_0 = \mathcal{H}_{1/2}$. The error in L^1 -norm is 0.0310.



(b) Estimation result when $n_0 = \mathcal{H}_{1/3}$. The error in L^1 -norm is 0.0675.



(c) Estimation result when $n_0 = \mathcal{H}_{1/5}$. The error in L^1 -norm is 0.168.



(d) Estimation result when $n_0 = \mathcal{H}_{1/7}$. The error in L^1 -norm is 0.287.

Figure 2: Estimation results in the model with one telomere when $b = 1$, $g = 1_{[0,1]}$, $N = 40$, and $n_0 \in \{\mathcal{H}_{1/2}, \mathcal{H}_{1/3}, \mathcal{H}_{1/5}, \mathcal{H}_{1/7}\}$.

There are two reasons for this, one qualitative, and one quantitative. The qualitative reason is that when the initial distribution has a small coefficient of variation, the randomness of shortening values and cell division times plays a greater role than the heterogeneity of the initial distribution. The variability of senescence times is therefore mainly influenced by these two sources of diffusion, and less by the one of n_0 . This leads to a poor estimation, as the information on n_0 obtained from senescence times is blurred by the information on g and b . The quantitative reason is that the second derivative of the initial distribution is large when its coefficient of variation is small. Thus, as the error between $\hat{n}_0^{(1)}$ and n_0 is mainly given by the second derivative of n_0 (see Sections 3.3 and 3.5), the estimation constants increase. We illustrate this in Figure 3, in which we show the second derivatives of the probability

distribution functions $\mathcal{H}_{1/2}$, $\mathcal{H}_{1/3}$, $\mathcal{H}_{1/5}$, and $\mathcal{H}_{1/7}$. We observe that their values increase when the coefficient of variation of their associated Erlang distribution decreases.

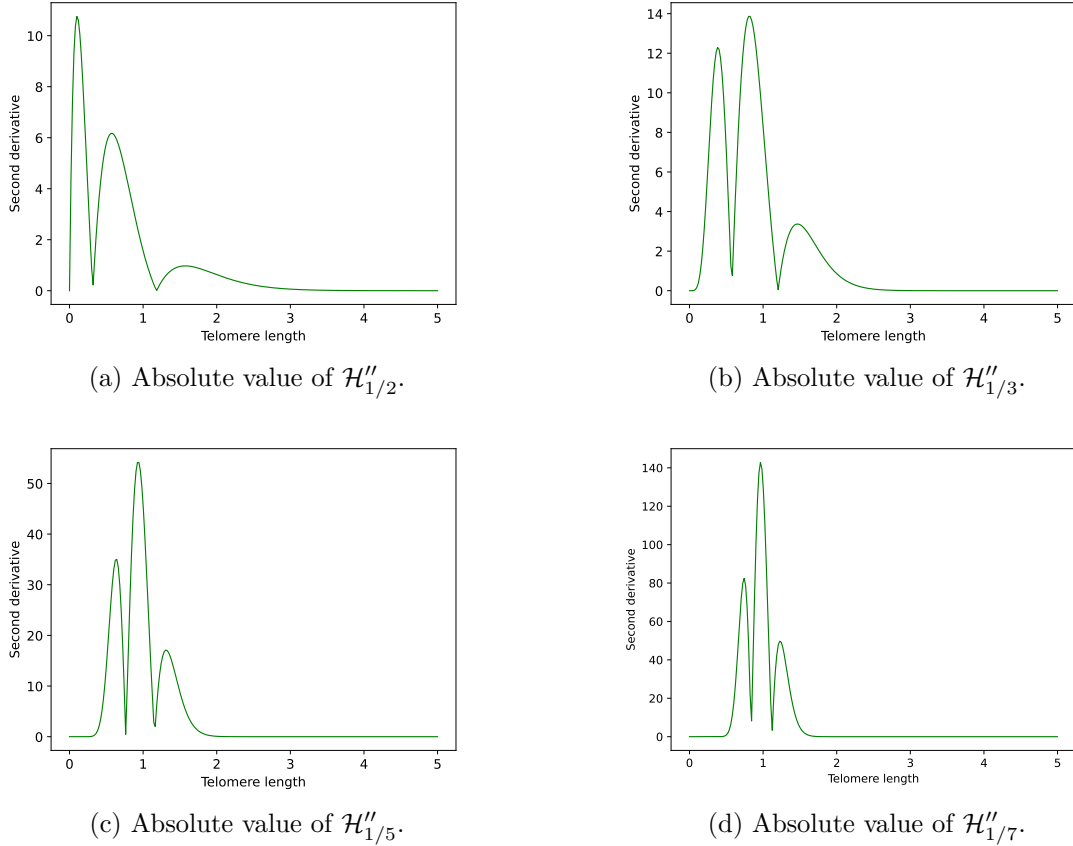


Figure 3: Absolute values of the second derivatives of the functions in the set $\{\mathcal{H}_{1/2}, \mathcal{H}_{1/3}, \mathcal{H}_{1/5}, \mathcal{H}_{1/7}\}$.

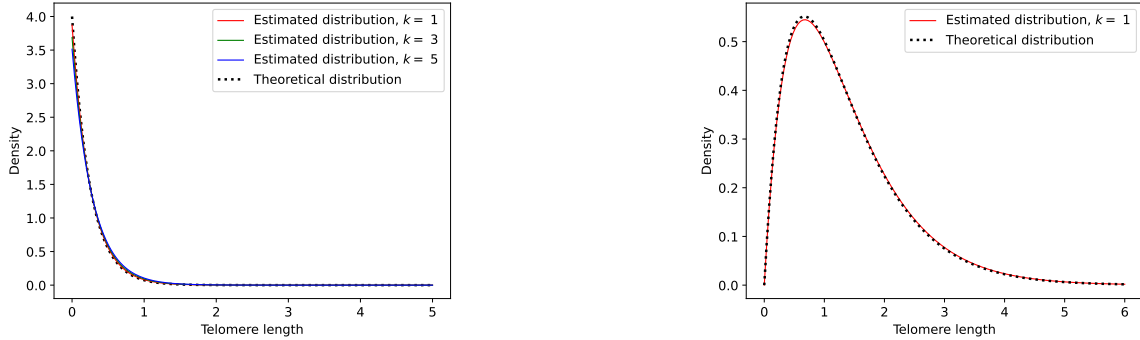
5.2 Estimation results in the model with several telomeres

We now study how the inference method works on the model with several telomeres. As for the single-telomere model, the quality of the estimation depends on the parameters of the model. More specifically, the results here are highly dependent on the number of telomeres in the species studied. To show this dependence, we separate this section into two parts. First, we present in Section 5.2.1 the estimation results when k is small. Then, in Section 5.2.2, we show the estimation results when k is large.

5.2.1 Estimation with a small number of telomeres

The estimations presented here are made in the same way as those presented in Section 5.1. Indeed, we first assume that (H_1) is verified with $b = 1$, $g = 1_{[0,1]}$, and $N = 40$. Then, we plot in Figure 4a the curve of the estimator $\hat{n}_0^{(2k)}$ when $k \in \{1, 3, 5\}$ and $n_0 = h_{1,4}$, and in Figure 4b the curve of the estimator $\hat{n}_0^{(2k)}$ when $k = 1$ and $n_0 = h_{2,1.5}$. In the first case, the estimator is computed thanks to (A.18). In the second case, it is computed by first using (A.20) to compute $n^{(2k)}$, and then numerical methods to compute $\hat{n}_0^{(2k)}$ from $n^{(2k)}$ (see (2.12) and (2.8)). We observe that in both cases, the estimated initial distributions almost overlap

with the theoretical initial distributions. The estimation is thus very satisfactory, as for the single-telomere model.



(a) Estimation results when $n_0 = h_{1,4}$ and $k \in \{1, 3, 5\}$. The errors in L^1 -norm are respectively 0.0266, 0.0657 and 0.104.

(b) Estimation results when $n_0 = h_{2,1.5}$ and $k = 1$. The error in L^1 -norm is 0.0133.

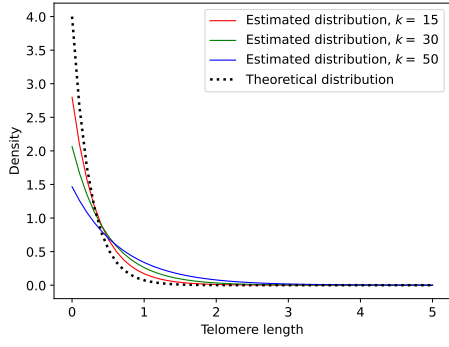
Figure 4: Estimation results in the model with several telomeres when $b = 1$, $g = 1_{[0,1]}$, $N = 40$, $n_0 = \{h_{1,4}, h_{2,1.5}\}$, and for different values of k .

One can notice that when $n_0 = h_{2,1.5}$, we only have studied the case in which $k = 1$ i.e. in which there are 2 telomeres. The reason is that our way to compute $\hat{n}_0^{(2k)}$ cannot be readapted when $k \geq 2$. As obtaining them is not the primary objective of this study, we have limited ourselves to the case where $n_0 \in \{h_{1,\beta} \mid \beta \in \mathbb{R}_+^*\}$ for such values of k . This is equivalent to assuming that n_0 is the density of an exponential distribution.

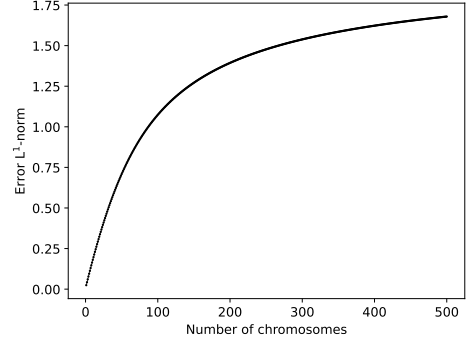
5.2.2 Estimation with a large number of telomeres

We now focus on the case in which k is large. This case is important to consider because biologists mostly study species with a large number of telomeres. For example, we can mention budding yeast cells which have 32 telomeres (16 chromosomes), or human cells which have 92 telomeres (46 chromosomes). We assume that (H_1) is verified with $b = 1$, $g = 1_{[0,1]}$, and N not yet fixed. We also restrict ourselves to the case where $n_0 = h_{1,4}$, for the same reasons as those presented at the end of Section 5.2.1. We plot in Figures 5a and 5b respectively the curve of the estimator $\hat{n}_0^{(2k)}$ when $N = 40$ and $k \in \{15, 30, 50\}$, and the L^1 -norm between n_0 and $\hat{n}_0^{(2k)}$ when $N = 40$ for all $k \in \llbracket 1, 500 \rrbracket$. We observe in Figure 5a that more k is large, more the estimated curve is far from the curve of n_0 (dotted curve). In addition, the estimated curves appear more diffuse than the initial curve, similarly to what was observed in the estimations presented in Figure 2. We also see in Figure 5b that the estimation error in L^1 -norm has high values when k is large. From these observations, we conclude that the estimation is poor. We provide below a quantitative and qualitative reason for this.

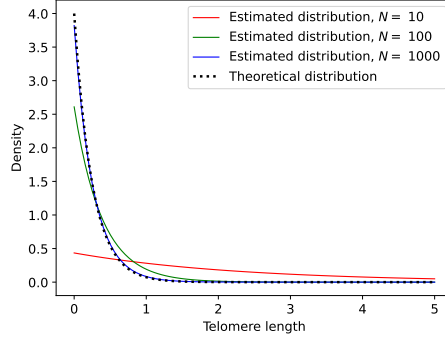
The quantitative reason is that the model approximation used to construct our estimator is no longer valid when k is large. Indeed, the bounds obtained in Proposition 4.4 and Theorem 2.6 increase with the value of k . It follows that using $\hat{n}_0^{(2k)}$ to estimate n_0 does not really make sense, because we now have no control over its estimation error. The qualitative reason is that the senescence times distribution becomes more and more determined by the distribution of cell division times when $k \rightarrow +\infty$, while the influence of the initial distribution diminishes. This is shown in Figure 6 for the model studied in the previous paragraph, where we plot in red the error in L^1 -norm between $n_\partial^{(2k)}$ and the density of an exponential distribution of



(a) Estimation results when $n_0 = h_{1,4}$, $N = 40$ and $k \in \{15, 30, 50\}$. The errors in L^1 -norm are respectively 0.329, 0.589, and 0.848.



(b) Error in L^1 -norm between $n_0 = h_{1,4}$ and $\hat{n}_0^{(2k)}$ when $N = 40$, for $k \in \llbracket 1, 500 \rrbracket$.



(c) Estimation results when $n_0 = h_{1,4}$, $k = 46$ and $N \in \{10, 100, 1000\}$. The errors in L^1 -norm are respectively 1.341, 0.348 and 0.0386.

Figure 5: Estimation results in the model with several telomeres when $b = 1$, $g = 1_{[0,1]}$, $n_0 = h_{1,4}$, and for large values of k .

parameter bN , namely $h_{1,bN}$, for $k \in \llbracket 1, 125 \rrbracket$. We observe that this error progressively decreases to 0 when $k \rightarrow +\infty$, so that $n_{\partial}^{(2k)}$ is more and more influenced by the cell cycle distribution. The estimation is thus less accurate as the information on n_0 is blurred by the influence of the division times distribution, and that this influence is not taken into account in the construction of our estimator. The increasing dependence of the senescence times distribution on the division times distribution is related to the fact that the probability of having at least one short telomere at the beginning of the dynamics grows with the number of telomeres. As a result, the initial minimum length tends to concentrate near zero, and fewer shortenings are required to obtain a telomere with length below zero (which is the criterion for senescence). This yields that the initial condition and the randomness of the shortening values lose their impact on the senescence times distribution when k is large, and that only the randomness of the division times remains to influence the latter.

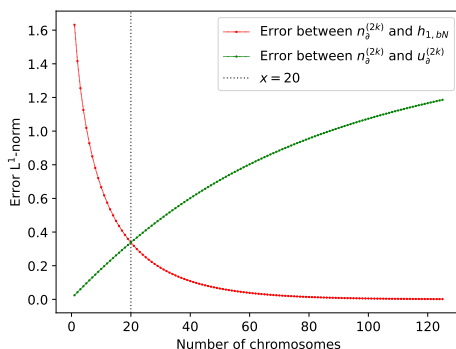


Figure 6: Comparison of the error in L^1 -norm between $n_{\partial}^{(2k)}$ and $h_{1,bN}$, and between $n_{\partial}^{(2k)}$ and $u_{\partial}^{(2k)}$, as a function of $k \in \llbracket 1, 125 \rrbracket$, when the model parameters are $b = 1$, $g = 1_{[0,1]}$, $N = 40$ and $n_0 = h_{1,4}$. We observe that $u_{\partial}^{(2k)}$ is a better approximation of $n_{\partial}^{(2k)}$ than $h_{1,bN}$ when $k \geq 20$, because we have that $\left\| n_{\partial}^{(2k)} - u_{\partial}^{(2k)} \right\|_{L^1(\mathbb{R}_+)} \geq \left\| n_{\partial}^{(2k)} - h_{1,bN} \right\|_{L^1(\mathbb{R}_+)}$ in this case.

The only way to solve these issues is to have a larger value of the scaling parameter N . This is illustrated in Figure 5c in which we have plot the curve of $\hat{n}_0^{(2k)}$ when $k = 46$ and $N \in \{10, 100, 1000\}$. We observe that when $N = 1000$, the estimation is very good, whereas for the other scaling parameters, the estimation is poor. The problem is that the value of N we need for a good estimation is not realistic. Indeed, the case where we have $k = 46$ chromosomes corresponds to the human case. In this case, the ratio between the average shortening value and the average telomere length is of the order of $\frac{1}{100}$, see the discussion about (H_1) p. 13. Hence, the realistic value for the scaling parameter is $N = 100$, for which the estimation is poor in Figure 5c, and not $N = 1000$.

5.3 Estimation with random variables

In practice, we never have the full density $n_{\partial}^{(1)}$ or $n_{\partial}^{(2k)}$. Instead, we observe a collection of senescence times $(T_i)_{1 \leq i \leq m}$, where $m \in \mathbb{N}^*$, that are noisy measurements of random variables identically distributed according to $n_{\partial}^{(1)}$ or $n_{\partial}^{(2k)}$. We thus need to investigate if our inference method is adaptable in this setting, and to check if the estimation still works after adaptation. This section is devoted to these points, when only the noise linked to sampling is considered, and not to measurement error. We first focus in Section 5.3.1 on adapting our method when we only observe senescence times distributed according to $n_{\partial}^{(1)}$, and verifying the quality of the estimation on simulations. We then do the same when senescence times are distributed according to $n_{\partial}^{(2k)}$ in two different parts, as the construction of the estimator requires more work in this case. More precisely, we present the estimator we use in Section 5.3.2, and check its quality on simulations in Section 5.3.3. We show in this last case that issues related to the curse of the dimensionality arise. From now on, we assume that (H_1) is verified with $b = 1$, $g = 1_{[0,1]}$, and $N = 40$.

5.3.1 Estimator and estimation with random variables distributed according to $n_{\partial}^{(1)}$

Let us consider $n_s \in \mathbb{N}^*$, and $(T_{1,i})_{1 \leq i \leq n_s}$ a sequence of random variables independent and identically distributed according to $n_{\partial}^{(1)}$. Our first objective in this section is to construct an

estimator of n_0 based on these random variables. In fact, this can be easily done. What we only have to do is to first construct an estimator of $n_{\partial}^{(1)}$ that depends only on the variables $(T_{1,i})_{1 \leq i \leq n_s}$, and then to adapt the expression of $\hat{n}_0^{(1)}$ given in (2.12) to this estimator. We will thus have an estimator of n_0 that corresponds to a Monte-Carlo estimation of $\hat{n}_0^{(1)}$. Let us detail these two steps.

To obtain an estimator of $n_{\partial}^{(1)}$ using the times $(T_{1,i})_{1 \leq i \leq n_s}$, we do a log-transform kernel density estimation [8, 33]. Denoting for all $x \geq 0$ the Gaussian kernel $\rho(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}}$, and $\alpha > 0$ as a smoothing parameter, the log-transform kernel density estimator is defined for all $t \geq 0$ as

$$\bar{n}_{\partial}^{(1,\alpha)}(t) := \frac{1}{n_s} \sum_{i=1}^{n_s} \frac{1}{t\alpha} \rho\left(\frac{1}{\alpha} \log\left(\frac{t}{T_{1,i}}\right)\right). \quad (5.2)$$

This is a classical method of estimation to estimate a density on \mathbb{R}_+ , when we have a finite number of variables distributed according to this density. The main idea behind this estimator is to smooth the Dirac measures in the empirical estimator of the density, defined as $\frac{1}{n_s} \sum_{i=1}^{n_s} \delta_{T_{1,i}}$. This smoothing is due to that for all $f \in \mathcal{C}_c^\infty(\mathbb{R}_+^*)$ and $X \in \mathbb{R}_+^*$, by the change of variable $t' = \log\left(\frac{t}{X}\right)$ and the fact that $\frac{1}{\alpha} \rho\left(\frac{\cdot}{\alpha}\right) \xrightarrow{\alpha \rightarrow 0} \delta_0$ (as it is a classical mollifier), we have

$$\lim_{\alpha \rightarrow 0} \int_{t \in \mathbb{R}_+^*} \frac{1}{t\alpha} \rho\left(\frac{1}{\alpha} \log\left(\frac{t}{X}\right)\right) f(t) dt = \lim_{\alpha \rightarrow 0} \int_{t' \in \mathbb{R}} \frac{1}{\alpha} \rho\left(\frac{t'}{\alpha}\right) f(X \exp(t')) dt' = \delta_X(f). \quad (5.3)$$

Thus, by the above and the fact that $\rho \in \mathcal{C}^\infty(\mathbb{R})$, the terms that are summed in (5.2) are smoothed approximations of the measures $(\delta_{T_{1,i}})_{i \in [1, n_s]}$. In particular, when α is small, $\bar{n}_{\partial}^{(1,\alpha)}$ is close to the empirical estimator of the density but the smoothing is weak. When α is large, it is the opposite. We do not use a classical kernel density estimation [37, 44] because this method works to estimate densities with support on \mathbb{R} , and is much less satisfactory on \mathbb{R}_+ . An explanation of the different issues that may arise due to this difference of support is given in Section D.

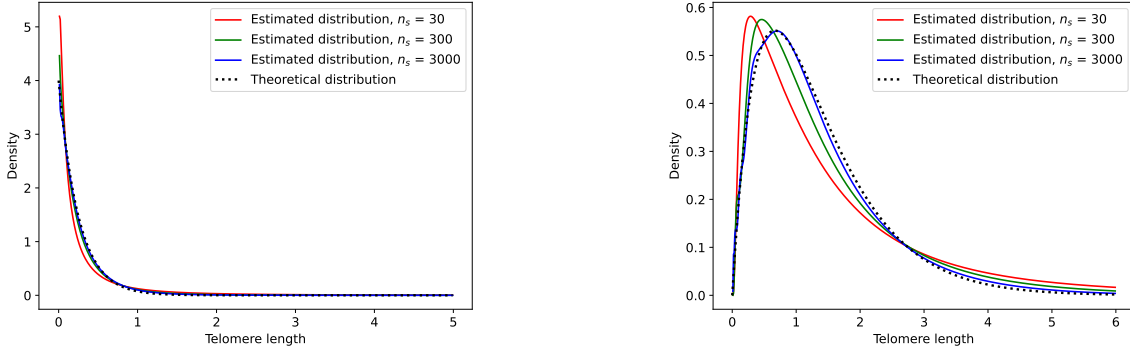
Adapting now the definition of \hat{n}_0 , see (2.12), by replacing $n_{\partial}^{(1)}$ with $\bar{n}_{\partial}^{(1,\alpha)}$, we obtain the following estimator for n_0 that depends on the smoothing parameter $\alpha > 0$, for all $x \geq 0$,

$$\bar{n}_0^{(1,\alpha)}(x) := \frac{1}{\bar{b}\bar{m}_1} \bar{n}_{\partial}^{(1,\alpha)}\left(\frac{x}{\bar{b}\bar{m}_1}\right) = \frac{1}{n_s} \sum_{i=1}^{n_s} \frac{1}{x\alpha} \rho\left(\frac{1}{\alpha} \log\left(\frac{x}{\bar{b}\bar{m}_1 T_{1,i}}\right)\right). \quad (5.4)$$

This estimator is what we use to estimate n_0 from the sequence $(T_{1,i})_{1 \leq i \leq n_s}$. Theoretical results concerning its quality are given in Section E, by transferring those already established for $\hat{n}_0^{(1)}$. In particular, we show in this section that for all $p \in (0, 1)$, there exists a smoothing parameter α_p for which we have a qualitative bound on $\left\| \text{Id} \left[\bar{n}_0^{(1,\alpha_p)} - n_0 \right] \right\|_{L^1(\mathbb{R}_+)}$ with probability $1 - p$, see Corollary E.4. In the estimations done in this section, we use for smoothing parameter an approximation of α_p for $p = 0.1$, denoted $\hat{\alpha}_{0.1}$. This approximation is obtained by computing the constant $C_{\hat{n},d}$ in its definition, see (E.8) and (E.4), by using the formulae given in Eq. (E.13) and Eq. (E.14). The problem of choosing the parameter with this method is that we use *a priori* information about the initial distribution (the fact that it is an Erlang distribution), which cannot always be done on experimental data. Developing a method for choosing a good smoothing parameter without *a priori* information is very challenging. We thus postpone this study to another work.

We now verify numerically that our estimator has good estimation results. To do so, we proceed to estimations on simulations. We first choose $n_s \in \{30, 300, 3000\}$, and simulate a

sequence of random variables $(T_{1,i})_{1 \leq i \leq n_s}$ distributed according to $n_\partial^{(1)}$, when $n_0 \in \{h_{1,4}, h_{2,1.5}\}$. We refer to Section C for the detail of how we simulate them. Then, in Figure 7, we compare the curve of $\bar{n}_0^{(1,\alpha)}$ with the curve of n_0 , for $\alpha = \hat{\alpha}_{0,1}$ defined in the above paragraph. We observe that when $n_s = 3000$, the curve of $\bar{n}_0^{(1,\hat{\alpha}_{0,1})}$ follows perfectly the one of n_0 , so is very satisfactory. We also observe that when $n_s = 300$, the quality of the estimation decreases, but remains correct. When $n_s = 30$, however, the estimation is not very accurate, but not so bad given that we have very few simulations in this case (the shape of n_0 is still well-estimated). We therefore have from these observations that the estimation stays reliable when we use $\bar{n}_0^{(1,\hat{\alpha}_{0,1})}$ to estimate instead of $\hat{n}_0^{(1)}$. We also have that the quality of the estimation increases with the number of data, as expected.



(a) Comparison between $\hat{n}_0^{(1,\hat{\alpha}_{0,1})}$ and $n_0 = h_{1,4}$, for $n_s \in \{30, 300, 3000\}$. The errors in L^1 -norm are respectively 0.306, 0.108 and 0.0501.

(b) Comparison between $\hat{n}_0^{(1,\hat{\alpha}_{0,1})}$ and $n_0 = h_{2,1.5}$, for $n_s \in \{30, 300, 3000\}$. The errors in L^1 -norm are respectively 0.283, 0.144 and 0.0457.

Figure 7: Estimation results for the estimator $\bar{n}_0^{(1,\hat{\alpha}_{0,1})}$ defined in (5.4), for the parameters $b = 1$, $g = 1_{[0,1]}$, $N = 40$, $n_0 \in \{h_{1,4}, h_{2,1.5}\}$, and different values of n_s .

5.3.2 Estimator with random variables distributed according to $n_\partial^{(2k)}$

We now focus on the case in which we observe a sequence of random variables $(T_{2k,i})_{1 \leq i \leq n_s}$ identically distributed according to $n_\partial^{(2k)}$, where $n_s \in \mathbb{N}^*$. In particular, in this section, we construct the estimator of n_0 we use in this context. We assume that the random variables we observe have been ordered in increasing order, so that $T_{2k,i} \leq T_{2k,i+1}$ for all $i \in \llbracket 1, n_s - 1 \rrbracket$. Thus, the random variables $(T_{2k,i})_{1 \leq i \leq n_s}$ are independent only up to a permutation. We consider the survival function associated with n_∂ , defined for all $t \geq 0$ as $N_\partial(t) := \int_t^{+\infty} n_\partial^{(2k)}(s) ds$. We also introduce its empirical estimator, which is the complement of the empirical distribution function (see [49, p. 2])

$$\forall t \geq 0 : \widehat{N}_\partial(t) := \frac{1}{n_s} \sum_{i=1}^{n_s} 1_{\{T_{2k,i} > t\}} = 1 - \frac{1}{n_s} \sum_{i=1}^{n_s} 1_{\{T_{2k,i} \leq t\}}. \quad (5.5)$$

The strategy for constructing our estimator of n_0 here is slightly different from that followed in the previous section. It is based on the fact that $\hat{n}_0^{(2k)}$ is the weak derivative of the function $x \mapsto - \left[N_\partial \left(\frac{2x}{b\bar{m}_1} \right) \right]^{\frac{1}{2k}}$, see (2.12). From this last property and the fact that N_∂ can be estimated by \widehat{N}_∂ , a natural estimator for n_0 would be to use the weak derivative of

$M(x) := - \left[\widehat{N}_\partial \left(\frac{2x}{b\tilde{m}_1} \right) \right]^{\frac{1}{2k}}$. The problem is that the latter cannot be represented by a function, as we can see in the following statement.

Proposition 5.2 (Derivative of M). *Let us denote $T_{2k,0} = 0$ and $T_{2k,n_s+1} = +\infty$. Then, it holds*

$$M' = \sum_{j=0}^{n_s} \left(1 - \frac{j}{n_s} \right)^{\frac{1}{2k}} \left[\delta_{\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,j+1}} - \delta_{\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,j}} \right].$$

Proof. Notice that as the times $(T_{2k,i})_{0 \leq i \leq n_s+1}$ are ordered in increasing order, we have for all $t \geq 0$

$$\sum_{i=1}^{n_s} 1_{\{T_{2k,i} \leq t\}} = \sum_{i=1}^{n_s} \sum_{j=i}^{n_s} 1_{\{T_{2k,j} \leq t < T_{2k,j+1}\}} = \sum_{j=1}^{n_s} \sum_{i=1}^j 1_{\{T_{2k,j} \leq t < T_{2k,j+1}\}} = \sum_{j=0}^{n_s} j \cdot 1_{\{T_{2k,j} \leq t < T_{2k,j+1}\}}. \quad (5.6)$$

Therefore, by combining the above with (5.5), and using that the intervals in the indicators in (5.6) are disjoint, we obtain for all $f \in \mathcal{C}_c^\infty(\mathbb{R}_+^*)$

$$\begin{aligned} \int_{\mathbb{R}_+^*} M(x) f'(x) dx &= - \sum_{j=0}^{n_s} \left(1 - \frac{j}{n_s} \right)^{\frac{1}{2k}} \int_{\mathbb{R}_+^*} 1_{\{T_{2k,j} \leq \frac{2x}{b\tilde{m}_1} < T_{2k,j+1}\}} f'(x) dx \\ &= - \sum_{j=0}^{n_s} \left(1 - \frac{j}{n_s} \right)^{\frac{1}{2k}} \left[f \left(\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,j+1} \right) - f \left(\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,j} \right) \right]. \end{aligned}$$

This ends the proof of the proposition. \square

To solve the issue presented above, we use a smoothed version of M' to estimate n_0 . This version is obtained by using that in view of (5.3), we can approximate $\delta_{\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,j}}$ for all $j \in \llbracket 0, n_s + 1 \rrbracket$ by the measure $\frac{1}{\alpha x} \rho \left(\frac{1}{\alpha} \log \left(\frac{2x}{b\tilde{m}_1 T_{2k,j}} \right) \right) dx$, where $\alpha > 0$ is a smoothing parameter. This gives us the following estimator, depending on the parameter α , for all $x \geq 0$,

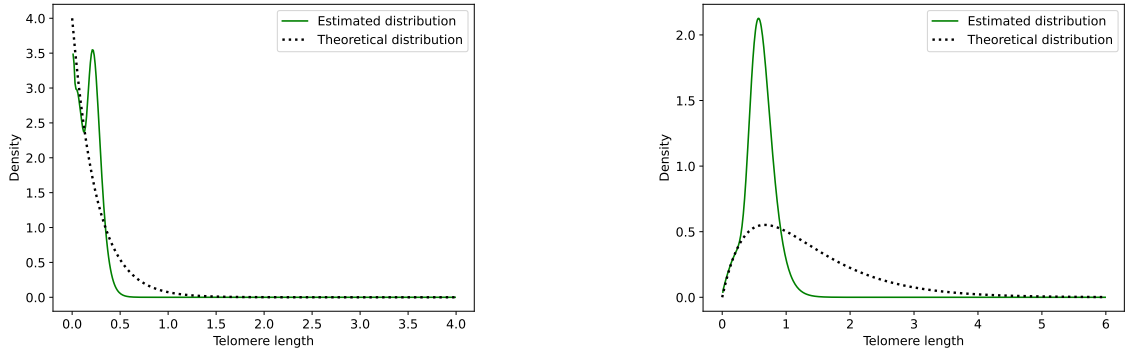
$$\bar{n}_0^{(2k,\alpha)}(x) := \sum_{j=0}^{n_s} \left(1 - \frac{j}{n_s} \right)^{\frac{1}{2k}} \frac{1}{\alpha x} \left[\rho \left(\frac{1}{\alpha} \log \left(\frac{2x}{\tilde{b}\tilde{m}_1 T_{2k,j+1}} \right) \right) - \rho \left(\frac{1}{\alpha} \log \left(\frac{2x}{\tilde{b}\tilde{m}_1 T_{2k,j}} \right) \right) \right]. \quad (5.7)$$

The above is what we use to estimate n_0 from the random variables $(T_{2k,i})_{1 \leq i \leq n_s}$. At first sight, other estimators than this one seems more natural to use. In view of the definition of $\widehat{n}_0^{(2k)}$ given in (2.12), we can for example mention estimators corresponding to the ratio between an estimator of the numerator of $\widehat{n}_0^{(2k)}$ and an estimator of the denominator of $\widehat{n}_0^{(2k)}$. We prefer here to use the estimator presented in (5.7) for two reasons. The first one is that the way we have obtained a theoretical result on the quality of the estimators $(\bar{n}_0^{(1,\alpha)})_{\alpha > 0}$ can be adapted to the estimators $(\bar{n}_0^{(2k,\alpha)})_{\alpha > 0}$, see Section E, and not for the estimators previously mentioned. The second one is that this allows us to not have an estimator with a denominator tending to 0 when $x \rightarrow +\infty$, which can generate instability.

5.3.3 Estimation with random variables distributed according to $n_\partial^{(2k)}$

We now check how the estimator constructed in the previous section works on simulated data. We consider two examples: first, the case where the model with several telomeres, defined in (2.8), has for parameters $(n_0, k) = (h_{1,4}, 5)$. Second, the case where this model has for

parameters $(n_0, k) = (h_{2,1.5}, 16)$. For each of these examples, we fix $n_s = 3000$ and simulate a sequence of random variables $(T_{2k,i})_{1 \leq i \leq n_s}$ independent and identically distributed according to $n_\partial^{(2k)}$. Then, we compute an estimation of n_0 from these times by using $\widehat{n}_0^{(2k,\alpha)}$ for $\alpha = 0.275$. The smoothing parameter has been chosen more or less arbitrarily, and does not need to be optimal, as it does not really change the quality of the estimation here. We plot in Figure 8 the estimated initial distribution in each case (green curves), and compare them with their theoretical values (dotted curves). What we observe is surprising. The left tails of the initial distributions are first correctly estimated. However, at a certain telomere length, a peak appears on each estimated curve and the estimated density is 0 immediately afterwards. We therefore have a very poor estimation.



(a) Comparison between $\widehat{n}_0^{(2k,\alpha)}$ and $n_0 = h_{1,4}$, for $k = 5$. The error in L^1 -norm is 0.452.

(b) Comparison between $\widehat{n}_0^{(2k,\alpha)}$ and $n_0 = h_{1,4}$, for $k = 16$. The error in L^1 -norm is 1.061.

Figure 8: Estimation results for the estimator $\widehat{n}_0^{(2k,\alpha)}$ defined in (5.7), with $(T_{2k,i})_{1 \leq i \leq n_s}$ generated with Algorithm 1, for the parameters $b = 1$, $g = 1_{[0,1]}$, $N = 40$, $n_s = 3000$, $(n_0, k) \in \{(h_{1,4}, 5), (h_{2,1.5}, 16)\}$, and $\alpha = 0.275$.

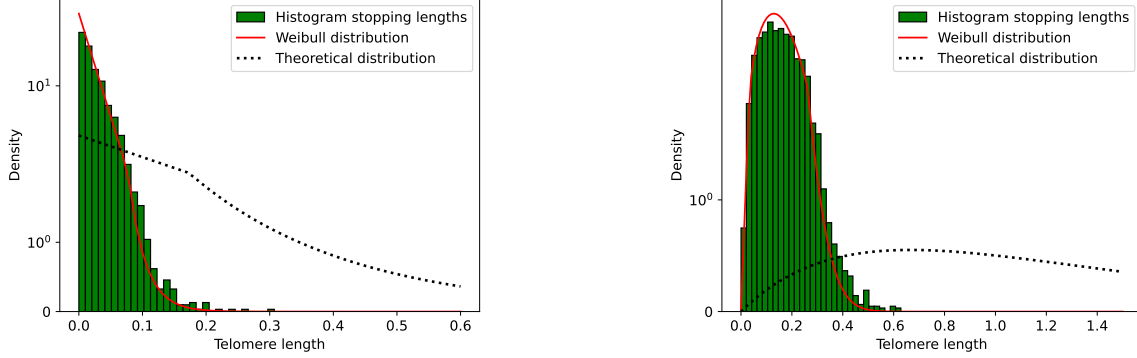
To understand why we observe this, we investigate the n_s simulations of the probabilistic model used to generate our sequence of senescence times $(T_{2k,i})_{1 \leq i \leq n_s}$ (see Section C). For each of these simulations, we collect the initial length of the telomere signalling senescence. Then, we plot in Figure 9 the histogram of these lengths (green bars), and superpose the curve of n_0 on this histogram (black curve). In Figure 9a, which corresponds to the case where $(n_0, k) = (h_{1,4}, 5)$, we observe that even if n_0 has a large density after the length 0.35, no telomere with an initial length greater than 0.35 has signalled senescence. In Figure 9b, which corresponds to the case where $(n_0, k) = (h_{1,4}, 5)$, we have a similar observation. No telomere with an initial length greater than 0.65 has signalled senescence, whereas the density of n_0 is still large at this length. The random variables $(T_{2k,i})_{1 \leq i \leq n_s}$ therefore do not contain a significant part of the information about n_0 in these two cases. This lack of information explains the poor estimation in Figure 8. It also explains why we observe peaks: a smoothed Dirac measure appears in each estimation due to the abrupt loss of information.

The only way to manage this issue is to do the estimation with a larger number of data points. The reason is that it allows us to have better coverage of the telomere length that signals senescence at time $t = 0$, resulting in less loss of information. The problem is that the number of data points required to obtain a sufficiently large coverage of n_0 is far too high. To get an idea of this number, let us compute the number of data points we need to have information about n_0 after the length 1.5 when $(n_0, k) = (h_{2,1.5}, 16)$ (n_0 has still large values at this length, see Figure 8b). We do the approximation that it is always the telomere that was the shortest

at $t = 0$ that signals senescence to simplify computations (justified by Theorem 2.6, but strong assumption in practice, see [7]). Under this approximation, for every $i \in \llbracket 1, n_s \rrbracket$, the probability that the senescence time $T_{2k,i}$ has been signalled by a telomere that had a length greater than 1.5 at $t = 0$ is

$$\left(\int_{1.5}^{+\infty} n_0(s) ds \right)^{2 \times 16} = \left(\int_{1.5}^{+\infty} h_{2,1.5}(s) ds \right)^{32} \simeq 1.291 \times 10^{-15}.$$

We thus need around 10^{15} data points to have a reasonable probability that $(T_{2k,i})_{1 \leq i \leq n_s}$ contains information about n_0 after 1.5, which is very large.



(a) Histogram when $(n_0, k) = (h_{1,4}, 5)$, and comparison with a Weibull distribution with parameters $(1, (H_{1,4})^{-1}(\frac{1}{10}))$.

(b) Histogram when $(n_0, k) = (h_{2,1.5}, 16)$, and comparison with a Weibull distribution with parameters $(2, (H_{2,1.5})^{-1}(\frac{1}{32}))$.

Figure 9: Histograms of the initial lengths of telomeres signalling senescence for the simulations done to generate $(T_{2k,i})_{1 \leq i \leq n_s}$, where $n_s = 3000$, at the symlog scale [52]. Comparison with the curve of n_0 (black curves) and with the density of a Weibull distribution (red curves). The symlog scale uses a logarithmic scale for large values and a linear scale for small ones. It allows us to make appear very small bars, while preserving the shape of the histogram close to that of the linear scale.

This problem of lack of data is in fact very common when working in high dimension, and is often referred to as *curse of the dimensionality*. In this context, we can go further, and linked this problem with the extreme value theory [18, 26]. This link is shown in the following statement.

Proposition 5.3 (Minimum initial length when $k \rightarrow +\infty$). *Let $(\ell, \beta) \in \mathbb{N}^* \times \mathbb{R}_+^*$ and $(X_i)_{1 \leq i \leq 2k}$ some random variables independent and identically distributed according to $h_{\ell, \beta}$. Then, for all $x \geq 0$, we have*

$$\mathbb{P}[\min(X_1, \dots, X_{2k}) \leq x] \underset{k \rightarrow +\infty}{\sim} 1 - \exp\left(-\left(\frac{x}{(H_{\ell, \beta})^{-1}(\frac{1}{2k})}\right)^\ell\right), \quad (5.8)$$

where $(H_{\ell, \beta})^{-1}$ is the reciprocal of the function $H_{\ell, \beta}$ defined in (5.1).

Remark 5.4. *The cumulative distribution function at the right-hand side of (5.8) corresponds to the cumulative distribution of a Weibull distribution with parameters $(\ell, (H_{\ell, \beta})^{-1}(\frac{1}{2k}))$.*

Proof. First, notice that as X_1 has for cumulative distribution function $H_{\ell, \beta}$, by the L'Hospital's rule and (5.1), we have for all $s \geq 0$

$$\lim_{h \rightarrow 0^+} \frac{\mathbb{P}[-X_1 > -hs]}{\mathbb{P}[-X_1 > -h]} = \lim_{h \rightarrow 0^+} \frac{H_{\ell, \beta}(hs)}{H_{\ell, \beta}(h)} = \lim_{h \rightarrow 0^+} \frac{s \times h_{\ell, \beta}(hs)}{h_{\ell, \beta}(h)} = s^\ell. \quad (5.9)$$

Therefore, by using (5.9) to verify the assumptions of the Fisher-Tippett-Gnedenko's theorem [26, Corollary 1.6.3, Type III], we obtain that for all $y \geq 0$

$$\lim_{k \rightarrow +\infty} \mathbb{P} \left[\frac{\max(-X_1, \dots, -X_{2k})}{(H_{\ell, \beta})^{-1} \left(\frac{1}{2k} \right)} \leq -y \right] = \exp(-y^\ell).$$

We thus have that the proposition is proved, by using the above and the fact that for all $x \geq 0$ it holds $\mathbb{P}[\min(X_1, \dots, X_{2k}) \leq x] = 1 - \mathbb{P}[\max(-X_1, \dots, -X_{2k}) \leq -x]$. \square

From this result and the third line of (2.8), we have that if n_0 is the density of an Erlang distribution and k is large, then the distribution of the shortest telomere at $t = 0$ depends only on the left tail of n_0 . As this telomere is the one signalling senescence in most cases [7], this explains why we only have a good estimation of the left tail in Figure 8a. This explanation is all the more valid since each of the histograms of stopping lengths presented in Figure 9 has a shape similar to that of the density of a Weibull distribution with the parameters given in Remark 5.4.

From these observations, we conclude that even if our inference method is theoretically adaptable when we observe random variables instead of $n_{\partial}^{(2k)}$, it is in fact not usable in practice. In most cases, due to the lack of data, only information about the left tail can be inferred, and not about the whole curve. This suggests that the senescence times distribution is in fact mainly influenced by the left tail of n_0 , and much less by the overall distribution.

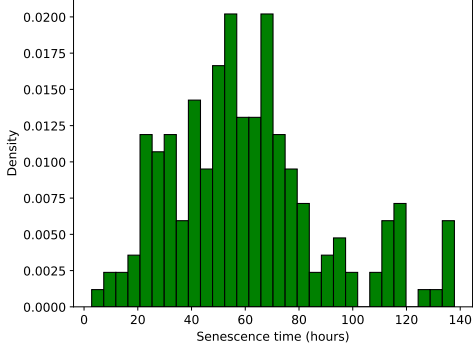
Remark 5.5. *The study done in this section has been completed in Section E.2. Specifically, we have shown in Corollary E.4 that the bound on the error of our estimator increases exponentially with respect to k .*

5.4 Estimation on experimental data

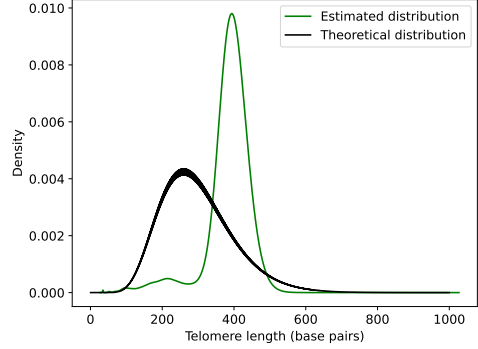
To conclude this study, we test our inference method on experimental data. The data we use comes from microfluidic experiments done by biologists, namely Maria Teresa Teixeira and Zhou Xu, on budding yeast cells. It is a dataset that contains, for 187 lineages, the generation of senescence onset and times between each division before the senescence onset (in hours). By summing these division times, we also have the senescence times of each lineage, for which we plot the histogram in Figure 10a. Our aim is to use these times to obtain an estimation of n_0 . Then, we will compare this estimation with a previous estimation of the initial length distribution, obtained in [55] on the basis of an elongation-shortening model, see also [5, 35].

The budding yeast is a species with 16 chromosomes, for which we have estimated its division rate as 0.719 hours^{-1} in Section B.1, on data from the same experiments as those presented here. In addition, the shortening distribution of this species is often taken as a uniform distribution from 5 to 10 base pairs, see [17], and the threshold for senescence has been recently be estimated as $L_{\min} = 27$ base pairs in [41]. We thus proceed to the estimation by using the estimator $\bar{n}_0^{(2k, \alpha)}$ with the parameters $k = 16$, $\tilde{b} = 0.719$, $\tilde{m}_1 = 7.5$, and the smoothing parameter $\alpha = 0.1$. We apply this estimator to the senescence times presented in the previous paragraph, and plot in Figure 10b the density we have inferred shifted by L_{\min} (green curve). We also plot the estimation of the initial distribution coming from [55] on the same figure (black curve). As for the estimations presented in Section 5.3.3, we observe in Figure 10b that we first have an estimation of the left tail, then a peak, and finally an estimate of 0 everywhere. Let us comment on the estimated left tail, that is the only reliable estimation, see Section 5.3.3.

We observe in Figure 10b that our estimated tail does not grow as quickly as the tail of the distribution obtained in [55]. What is the most surprising is that even at lengths close to the



(a) Histogram of senescence times coming from experiments.



(b) Estimation results on experimental data using $\bar{n}_0^{(32,\alpha)}$ with $\alpha = 0.1$. Comparison with the distribution obtained in [55]. The error in L^1 -norm between the two distributions is 0.999.

Figure 10: Inference on experimental data: dataset and estimation results.

mode of the black curve (around 200 – 240 base pairs), the tail of the estimated distribution has not grown yet. We thus have an estimation that differs from the one of [55]. The reason for this difference is surely linked to the fact that the model described by (2.8) is too simple. For example, using an exponential distribution for division times is not realistic, and we do not know yet if the assumption discussed in Remark 2.4 is problematic or not. Solving this inverse problem in more complex models, and then observing what this gives on data, will allow us to identify which are the strongest assumptions. This work therefore opens up new modelling perspectives.

Remark 5.6. Let us denote $T_{obs} > 0$ the time at which the biologists have stopped their experiments. Then, in view of (2.12), the condition required to completely estimate n_0 with $\bar{n}_0^{(2k,\alpha)}$, where $\alpha > 0$, is $T_{obs} \geq \frac{2\text{supp}(n_0)}{b\bar{m}_1}$. Such a condition is called *observability inequality*.

6 Discussion

Our work began with a theoretical study, during which we study the connection between the senescence times distribution and the initial length density. We showed that there is a strong link between the two, provided that the ratio between the average telomere length and the average shortening value, denoted N , is large. In the single-telomere model, we found that the senescence time distribution $n_\partial^{(1)}$ is approximatively a scaled version of n_0 . This implies that these two distributions have the same shape, so are deeply connected. For the model with several telomeres, there is a similar link between these two distributions. However, its expression is more complicated (see (2.12)) and implies that n_0 and n_∂ do not have the same shape.

We then have done a numerical study to understand how our method works in practice. Even if this study is encouraging in many cases, it has revealed several limitations for our method. The first limitation is in the estimation of initial distributions with a small coefficient of variation, see Section 5.1.2. In this case, the senescence times distribution is more sensitive to other sources of randomness than the initial distribution (shortening values, cell cycle duration). This results in a poor estimation, as our estimators do not take into account well these other sources. The second limitation is related to the curse of dimensionality. Most of the species that motivate our study (yeast, humans) have a large number of telomeres. We illustrated in

Section 5.3 that this poses problems in practice because the number of data points required for a good approximation becomes too large. A second issue, related to the fact that we work in high dimension, is that the approximation error of our model is too large when k is large (see Theorem 2.6). Our theorem therefore fails to provide guarantees on the quality of our estimators.

This work opens up new perspectives for telomere shortening models, including applications beyond those presented in this study. We have provided a rigorous justification that these models can be approximated by a transport equation, and have used this approximation to solve our inverse problem. However, this justification has limitations, since for the species that motivate our study, N is not very large (for example, $N = 40$ for the yeast). The first perspective, is thus to improve our approximation by adding a diffusion term to our transport equation, representing the fluctuations related to the model approximation. Indeed, if we manage to show that telomere shortening models can be approximated by transport-diffusion equations with an error of order $\frac{1}{N^2}$ instead of $\frac{1}{N}$, then it will be possible to construct estimators with estimation errors of order $\frac{1}{N^2}$ and solve the problems presented in (5.1.2). For example, we would have an error of approximation of $\frac{1}{40^2} = 6.25 \times 10^{-4}$ for the budding yeast, instead of $\frac{1}{40} = 2.5 \times 10^{-2}$, which is far better. This work is currently in progress.

The second perspective is to find a model approximation when $k \rightarrow +\infty$. As mentioned above, problems arise when k is large, that may be related to extreme value theory or to the fact that the approximation error depends on k (see Theorem 2.6). It is therefore necessary to understand how the dynamics evolve when k is large. The main approach to achieve this is to use the extreme value theory to our advantage, by constructing a typical particle representing the telomere with the smallest length among the $2k$ telomeres in a cell. In view of the Fisher–Tippett–Gnedenko’s theorem [26, Theorem 1.6.2], it will thus be possible to obtain a parametric law for the evolution of the minimum telomere lengths over time, and thus to simplify the study of the phenomenon.

The third perspective, more directly linked to the inverse problem, is to improve our bounds on the approximation and estimation errors for the model with several telomeres. As explained in Section 2.2, the constants $(D_\lambda)^{2k}$ and $\left(\frac{D_\lambda}{D_\omega}\right)^{2k}$ in respectively Proposition 4.4 and Theorem 2.6-(b) are not optimal. There are related to the loss of information on n_0 that occurs when we apply (H_3) or (H_4) to bound n_0 , and this loss increases exponentially with the dimension. We would like to obtain bounds on the estimation and approximation errors in which these two constants do not appear. This will allow us to prove that the approximation and estimation errors grow at most polynomially when the number of chromosomes increases.

The other perspectives are not related to model approximation or error bounds, and correspond to questions that remain open. First, we would like to know whether our inference method can be adapted for non-exponential division times (i.e. age-dependent models). Second, we would like to know if the inverse problem is identifiable or not. Finally, we would like to obtain a more rigorous justification for the fact that $n^{(2k)}(0, x) = n_0(x_i)$, for all $x \in \mathbb{R}_+^{2k}$. These three perspectives are the subject of future work, and will allow us to consolidate the biological relevance and the rigour behind this study.

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A Auxiliary statements

We present here auxiliary statements which are quite standard to obtain, and used frequently during all the paper. The first statements we provide, in Section [A.1](#) are classical results for the integro-differential equations we use in this work. The statements we then present, in Section [A.2](#), deal with the cardinalities of subsets of \mathcal{I}_k . The final statements we give, in

Section A.3, correspond to the results about Erlang distributions that we use in our numerical study, see Section 5.

A.1 Auxiliary statements related to our integro-differential equations

We begin by presenting the statement that justifies the well-posedness of the integro-differential equations used in this work. This statement also provides a criterion for ensuring the non-negativity of solutions, and guarantees their uniqueness. Its proof is inspired by the ideas presented in [38, Chap. 3].

Proposition A.1 (Well-posedness of the equations). *Let $d \in \mathbb{N}^*$, $\tilde{\xi}$ a finite measure on \mathbb{R}_+^d , $F \in C(\mathbb{R}_+, L^1(\mathbb{R}_+^d))$, and $w_0 \in L^1(\mathbb{R}_+^d)$. Then, there exists a unique solution in $C(\mathbb{R}_+; L^1(\mathbb{R}_+^d))$ to the following integro-differential equation*

$$\begin{cases} \partial_t w(t, x) = \int_{\mathbb{R}_+^d} [w(t, x + v) - w(t, x)] \tilde{\xi}(dv) + F(t, x), & \forall (t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d, \\ w(0, x) = w_0(x), & \forall x \in \mathbb{R}_+^d. \end{cases} \quad (\text{A.1})$$

In addition, if F and w_0 are non-negative, then w is non-negative.

Proof. We denote $\tilde{\xi}(1) := \int_{v \in \mathbb{R}_+^d} 1 \tilde{\xi}(dv)$ and consider an arbitrary $T \in \left(0, \frac{1}{\tilde{\xi}(1)}\right)$. We also consider the set

$$E = C\left([0, T]; L^1(\mathbb{R}_+^d)\right),$$

that we endow with the norm $\|\cdot\|_E$, defined for all $f \in E$ as $\|f\|_E = \sup_{t \in [0, T]} \left(\|f(t, \cdot)\|_{L^1(\mathbb{R}_+^d)}\right)$. As such, $(E, \|\cdot\|_E)$ is a Banach space. We finally consider an operator $L : E \rightarrow E$ defined such that for all $m \in E$, $\tilde{w} = L(m)$ is a solution to the following equation

$$\begin{cases} \partial_t \tilde{w}(t, x) = \int_{\mathbb{R}_+^d} m(t, x + v) \tilde{\xi}(dv) + F(t, x), & \forall (t, x) \in [0, T] \times \mathbb{R}_+^d, \\ \tilde{w}(0, x) = w_0(x), & \forall x \in \mathbb{R}_+^d. \end{cases} \quad (\text{A.2})$$

Our aim is to apply the Banach fixed point theorem to this operator, in order to obtain that there exists a unique solution in $C([0, T], L^1(\mathbb{R}_+^d))$ to the following integro-differential equation

$$\begin{cases} \partial_t \tilde{w}(t, x) = \int_0^\delta \tilde{w}(t, x + v) \tilde{\xi}(dv) + F(t, x), & \forall (t, x) \in [0, T] \times \mathbb{R}_+^d, \\ \tilde{w}(0, x) = w_0(x), & \forall x \in \mathbb{R}_+^d. \end{cases} \quad (\text{A.3})$$

Then, one can easily get from the above that there exists a unique solution to (A.1) in $C(\mathbb{R}_+, L^1(\mathbb{R}_+^d))$, by first iterating this procedure on the intervals $[T, 2T]$, $[2T, 3T]$, \dots , and then considering the function $w(t, x) = e^{-\tilde{\xi}(1)t} \tilde{w}(t, x)$, for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$.

As the derivative of \tilde{w} in (A.2) does not depend on \tilde{w} itself, we have for all $(t, x) \in [0, T] \times \mathbb{R}_+^d$ and $m \in E$ that

$$L(m)(t, x) = w_0(x) + \int_0^t \int_0^\delta m(s, x + v) \tilde{\xi}(dv) ds + \int_0^t F(s, x) ds. \quad (\text{A.4})$$

Then, one can easily obtain from the above, that for all $(m_1, m_2) \in E^2$, $(t, x) \in [0, T] \times \mathbb{R}_+^d$, it holds

$$|L(m_1)(t, x) - L(m_2)(t, x)| = \left| \int_0^t \int_{\mathbb{R}_+^d} (m_1 - m_2)(s, x + v) \tilde{\xi}(dv) ds \right|.$$

Integrating in dx the above equation, yields that for all $t \in [0, T]$

$$\begin{aligned} \|L(m_1)(t, \cdot) - L(m_2)(t, \cdot)\|_{L^1(\mathbb{R}_+^d)} &\leq \int_0^t \int_{\mathbb{R}_+^d} \|(m_1 - m_2)(s, \cdot)\|_{L^1(\mathbb{R}_+^d)} \tilde{\xi}(dv) ds \\ &\leq \tilde{\xi}(1)T \sup_{s \in [0, T]} \left(\|(m_1 - m_2)(s, \cdot)\|_{L^1(\mathbb{R}_+^d)} \right). \end{aligned}$$

Therefore, as $T < \frac{1}{\tilde{\xi}(1)}$, the above implies that the operator L is a strict contraction. We thus now apply the Banach fixed point theorem to L , and obtain, in view of the explanation below (A.3), that there exists a unique solution to (A.1) in $C(\mathbb{R}_+, L^1(\mathbb{R}_+^d))$.

It remains to prove that a solution of (A.1) is non-negative when both w_0 and F are non-negative. We denote L_0 the operator that is defined exactly as L , except that the initial condition is $\tilde{w}(0, \cdot) \equiv 0$ and that $F \equiv 0$. When $w_0 \geq 0$ and $F \geq 0$, we have, in view of the expression of a solution to (A.2) given in (A.4), that for all $m \in E$ it holds $L(m) \geq L_0(m)$. Then, as the zero function is the fixed point of L_0 , we get from this inequality that $\tilde{w} \geq 0$ (see the Picard iterative process). This yields that w is non-negative because $w(t, x) = e^{-\tilde{\xi}(1)t} \tilde{w}(t, x)$ for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$. Then, from this last result, we obtain that the proposition is proved. \square

We now present the second statement of this section, which corresponds to a maximum principle for solutions of (A.1) when the source term F is identically equal to 0. This statement is essential in this work, because it is one of the main arguments for approximating our models, see Section 3.3. It corresponds in fact to a corollary of Proposition A.1.

Corollary A.2 (Maximum principle). *We work under the setting of Theorem 2.6, with $F = 0$ and w_0 non-negative. We consider $v_0 \in L^1(\mathbb{R}_+^d)$ verifying $|v_0| \leq w_0$, and $(v, w) \in (C(\mathbb{R}_+; L^1(\mathbb{R}_+^d)))^2$ two solutions of (A.1) with respective initial condition v_0 and w_0 . Then, for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$, we have*

$$|v(t, x)| \leq w(t, x).$$

Proof. Let $\Phi : L^1(\mathbb{R}_+^d) \rightarrow C(\mathbb{R}_+; L^1(\mathbb{R}_+^d))$ the operator such that for all $f_0 \in L^1(\mathbb{R}_+^d)$, $\tilde{w} = \Phi(f_0)$ is the solution of (A.1) with initial condition f_0 . This operator is linear when $F = 0$. Indeed, in view of the fact that by the first line of (A.1), we have for all $(f_0, f_1) \in (L^1(\mathbb{R}_+^d))^2$ that

$$\partial_t [\Phi(f_0) + \Phi(f_1)](t, x) = \int_{\mathbb{R}_+^d} [(\Phi(f_0) + \Phi(f_1))(t, x + v) - (\Phi(f_0) + \Phi(f_1))(t, x)] \tilde{\xi}(dv),$$

which implies that $\Phi(f_0) + \Phi(f_1)$ is a solution of (A.1) with initial condition $f_0 + f_1$.

As $w_0 \geq v_0$ and $w_0 \geq -v_0$, we have by the last statement of Proposition A.1 that $\Phi(w_0 - v_0) = \Phi(w_0) - \Phi(v_0) \geq 0$ and $\Phi(w_0 + v_0) = \Phi(w_0) + \Phi(v_0) \geq 0$. Then, in view of the fact that $w = \Phi(w_0)$ and $v = \Phi(v_0)$, these inequalities give that $w \geq v$ and $w \geq -v$, so that $|v| \leq w$ is true. \square

The third statement we present in this section allows us to compute explicitly a solution of (A.1) when the initial distribution has an exponential form. It is particularly useful when it is combined with the maximum principle presented above. Specifically, combining these two statements allows us to obtain exponential bounds for solutions of equations of the form given in (A.1), see for example Section 3.3.

Proposition A.3 (Explicit solution to (A.1)). *We work under the setting of Theorem 2.6, with $F = 0$. Let us assume that there exist $C > 0$, $\beta > 0$, such that for all $x \in \mathbb{R}_+^d$ we have $w_0(x) = C^d \exp\left(-\beta \sum_{i=1}^d x_i\right)$. Then, for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$, it holds*

$$w(t, x) = C^d \exp \left[-\left(\tilde{\xi}(1) - \mathcal{L}(\tilde{\xi})(\beta) \right) t - \beta \sum_{i=1}^d x_i \right],$$

where $\tilde{\xi}(1) := \int_{v \in \mathbb{R}_+^d} 1 \tilde{\xi}(dv)$.

Remark A.4. *This proposition implies that exponential functions are quasi-stationary distributions of Eq. (A.1), see [32, Def. 3].*

Proof. We consider the function \tilde{w} , defined for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$ as

$$\tilde{w}(t, x) = C^d \exp \left[-\left(\tilde{\xi}(1) - \mathcal{L}(\tilde{\xi})(\beta) \right) t - \beta \sum_{i=1}^d x_i \right]. \quad (\text{A.5})$$

Our aim is to prove that \tilde{w} is a solution of (A.1). Then, as this equation as a unique solution in $C(\mathbb{R}_+; L^1(\mathbb{R}_+^d))$ by Proposition A.1, we will have that our proposition is true.

On the one hand, by computing the partial derivative in the first variable of \tilde{w} , we have that for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^d$

$$\partial_t \tilde{w}(t, x) = \left[\mathcal{L}(\tilde{\xi})(\beta) - \tilde{\xi}(1) \right] \tilde{w}(t, x). \quad (\text{A.6})$$

On the other hand, by using the following equality for all $(t, x, v) \in \mathbb{R}_+ \times \mathbb{R}_+^d \times \mathbb{R}_+^d$ (directly obtained from (A.5))

$$\tilde{w}(t, x + v) = \exp \left(-\beta \sum_{i=1}^d v_i \right) \tilde{w}(t, x),$$

we have that

$$\begin{aligned} \int_{\mathbb{R}_+^d} [\tilde{w}(t, x + v) - \tilde{w}(t, x)] \tilde{\xi}(dv) &= \left[\int_{\mathbb{R}_+^d} \exp \left(-\beta \sum_{i=1}^d v_i \right) \tilde{\xi}(dv) - \tilde{\xi}(1) \right] \tilde{w}(t, x) \\ &= \left[\mathcal{L}(\tilde{\xi})(\beta) - \tilde{\xi}(1) \right] \tilde{w}(t, x). \end{aligned} \quad (\text{A.7})$$

Then, by combining (A.6) with (A.7), we obtain that $\partial_t \tilde{w}(t, x) = \int_{\mathbb{R}_+^d} [\tilde{w}(t, x + v) - \tilde{w}(t, x)] \tilde{\xi}(dv)$. This implies that \tilde{w} is a solution of (A.1) in $C(\mathbb{R}_+, L^1(\mathbb{R}_+^d))$, in view of the fact that $\tilde{w}(0, \cdot) = w_0$. Then, we conclude that the proposition is proved. \square

The fourth statement we present here is directly related to Eq. (2.3) and Eq. (2.8). It allows us to justify that $n_{\partial}^{(1)}$ and $n_{\partial}^{(2k)}$ correspond to probability density functions. It is a consequence of the two previous statements.

Proposition A.5. *For all $d \in \{1, 2k\}$, we have*

$$\int_0^{\infty} n_{\partial}^{(d)}(s) ds = 1. \quad (\text{A.8})$$

Proof. We only give the proof when $d = 1$, as the proof when $d = 2k$ follows exactly the same steps. To obtain (A.8) when $d = 1$, we only have to prove that for all $\varepsilon > 0$

$$1 \geq \int_0^{+\infty} n_{\partial}^{(1)}(s) ds \geq 1 - \varepsilon. \quad (\text{A.9})$$

To do this, in view of the fact that $\int_0^{+\infty} n_0(x)dx = 1$, we first introduce for all $\varepsilon > 0$ a constant $L_\varepsilon > 0$, verifying $\int_0^{L_\varepsilon} n_0(x)dx \geq 1 - \varepsilon$. Then, we define $n_{0,\varepsilon} := n_0 1_{[0,L_\varepsilon]}$, and the function $n_\varepsilon^{(1)} \in C(\mathbb{R}_+, L^1(\mathbb{R}_+))$ verifying the first line of (2.3) with initial condition $n_{0,\varepsilon}$. Finally, we consider for all $t \geq 0$: $n_{\partial,\varepsilon}^{(1)}(t) := \tilde{b} \int_0^{\tilde{\delta}} n_\varepsilon^{(1)}(t, v) (1 - \tilde{G}(v)) dv$, which corresponds to the cemetery associated to the function $n_\varepsilon^{(1)}$. Our aim is to use these constants and functions to obtain (A.9). To do so, we proceed in two steps. First, in Step 1, we prove that for all $\varepsilon > 0$

$$\int_0^\infty n_{\partial,\varepsilon}^{(1)}(s)ds \geq 1 - \varepsilon. \quad (\text{A.10})$$

Then, in Step 2, we conclude.

Step 1: Let $\varepsilon > 0$. By proceeding as in Remark 2.1, we have for all $t \geq 0$

$$\frac{d}{dt} \left[\int_0^{+\infty} n_\varepsilon^{(1)}(t, x)dx + \int_0^t n_{\partial,\varepsilon}^{(1)}(s)ds \right] = 0.$$

Then, as $n_\varepsilon^{(1)}(0, \cdot) = n_{0,\varepsilon} = n_0 1_{[0,L_\varepsilon]}$ and $\int_0^{L_\varepsilon} n_0(x)dx \geq 1 - \varepsilon$, we obtain

$$\lim_{t \rightarrow +\infty} \int_0^{+\infty} n_\varepsilon^{(1)}(t, x)dx + \int_0^\infty n_{\partial,\varepsilon}^{(1)}(s)ds = \int_0^{+\infty} n_\varepsilon^{(1)}(0, x)dx + \int_0^0 n_{\partial,\varepsilon}^{(1)}(s)ds \geq 1 - \varepsilon. \quad (\text{A.11})$$

In addition, as $n_0 \in L_{\text{loc}}^\infty(\mathbb{R}_+)$, we have for all $x \geq 0$

$$|n_{0,\varepsilon}(x)| \leq \sup_{y \in [0, L_\varepsilon]} (n_0(y)) 1_{[0, L_\varepsilon]}(x) \leq \sup_{y \in [0, L_\varepsilon]} (n_0(y)) \exp(L_\varepsilon) \exp(-x).$$

Then, by combining Corollary A.2 with Proposition A.3, we obtain that for all $t \geq 0, x \geq 0$

$$\left| n_\varepsilon^{(1)}(t, x) \right| \leq \sup_{y \in [0, L_\varepsilon]} (n_0(y)) \exp(L_\varepsilon) \exp(-\tilde{b} [1 - \mathcal{L}(\tilde{g})(1)] t - x).$$

The above inequality implies that $\lim_{t \rightarrow +\infty} \int_{\mathbb{R}_+} n_\varepsilon^{(1)}(t, x)dx = 0$. Then, by combining it with (A.11), we obtain (A.10), which concludes the first step.

Step 2: Let $\varepsilon > 0$. As $n_0 \geq n_{0,\varepsilon}$, we have by Corollary A.2 that $n^{(1)} \geq n_\varepsilon^{(1)}$, so that $n_{\partial}^{(1)} \geq n_{\partial,\varepsilon}^{(1)}$. Then, by combining this last result with (A.10), we obtain

$$\int_0^{+\infty} n_{\partial}^{(1)}(s)ds \geq \int_0^{+\infty} n_{\partial,\varepsilon}^{(1)}(s)ds \geq 1 - \varepsilon. \quad (\text{A.12})$$

On the other side, in view of (2.4), we have that

$$\lim_{t \rightarrow +\infty} \int_0^{+\infty} n^{(1)}(t, x)dx + \int_0^{+\infty} n_{\partial}^{(1)}(s)ds = \int_0^{+\infty} n(0, x)dx + \int_0^0 n_{\partial}^{(1)}(s)ds = 1, \quad (\text{A.13})$$

so that $\int_0^{+\infty} n_{\partial}^{(1)}(s)ds \leq 1$. Then, by combining this last inequality with (A.12), we obtain (A.9), which ends the proof. \square

By plugging (A.8) in (A.13), we finally have the following corollary for Proposition A.5. This corresponds to the last statement of this section.

Corollary A.6. *For all $d \in \{1, 2k\}$, it holds*

$$\lim_{t \rightarrow +\infty} \int_{\mathbb{R}_+^d} n^{(d)}(t, x)dx = 0.$$

A.2 Auxiliary statements related to \mathcal{I}_k

We now provide statements related to \mathcal{I}_k . In particular, the statements presented here give results on the number of elements in subsets of \mathcal{I}_k . The first statement we present is the following, and comes directly from [35, Lemma 4.9]. It provides information about the number of sets in \mathcal{I}_k , and about the number of sets that contain/not contain a chosen index.

Lemma A.7 (Cardinality of subsets of \mathcal{I}_k , 0 or 1 index removed). *It holds*

$$\#(\mathcal{I}_k) = 2^k, \quad \text{and} \quad \forall i \in \llbracket 1, 2k \rrbracket : \frac{\#(\{I \in \mathcal{I}_k \mid i \in I\})}{2^k} = \frac{\#(\{I \in \mathcal{I}_k \mid i \notin I\})}{2^k} = \frac{1}{2}.$$

The second lemma we present is not given in [35, Lemma 4.9]. It provides the number of sets in \mathcal{I}_k that do not contain a chosen pair. It is a statement useful in the proof of Lemma 4.6, see Section 4.3.1. We prove this lemma below in the case where $k \in \{1, 2\}$. We also briefly sketch its proof but do not detail it when $k \geq 3$, as it only consists in slightly readapting the proof of [35, Lemma 4.9].

Lemma A.8 (Cardinality of subsets of \mathcal{I}_k , 2 indexes removed). *For all $(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2$ such that $\ell \neq \ell' \bmod k$, we have*

$$\#(\{I \in \mathcal{I}_k \mid \ell \in I, \ell' \in I\}) = \begin{cases} 0, & \text{if } k = 1, \\ 2^{k-2}, & \text{if } k \geq 2. \end{cases} \quad (\text{A.14})$$

Proof. First assume that $k = 1$. Then, by (2.5), we have $\mathcal{I}_1 = \{\{1\}, \{2\}\}$. This implies that $\#(\{I \in \mathcal{I}_1 \mid \ell \in I, \ell' \in I\}) = 0$ for all $(\ell, \ell') \in \llbracket 1, 2 \rrbracket^2$ such that $\ell \neq \ell' \bmod 1$. Therefore, (A.14) is true when $k = 1$.

Now, assume that $k = 2$. In view of the expression of \mathcal{I}_2 given in Example 2.3, we have that $\{I \in \mathcal{I}_2 \mid \ell \in I, \ell' \in I\} = \{\{\ell, \ell'\}\}$ for all $(\ell, \ell') \in \llbracket 1, 4 \rrbracket^2$ such that $\ell \neq \ell' \bmod 2$. Then, the cardinality of the sets we are interested in is 1, and we have that (A.14) holds in this case.

Finally, assume that $k \geq 3$. Let us consider $(\ell, \ell') \in \llbracket 1, 2k \rrbracket^2$ such that $\ell \neq \ell' \bmod k$. Following [35, Section 4.4.3], one can prove that the function $f : \{0, 1\}^{k-2} \rightarrow \{I \in \mathcal{I}_k \mid \ell \in I, \ell' \in I\}$ defined for all $x \in \{0, 1\}^{k-2}$ as

$$f(x) = \{kx_j + j \mid j \in \llbracket 1, k \rrbracket, j \neq \ell \bmod k, j \neq \ell' \bmod k\} \cup \{\ell, \ell'\}$$

is bijective. Hence, as $\#(\{0, 1\}^{k-2}) = 2^{k-2}$, we obtain that (A.14) is true when $k \geq 3$. This concludes the proof of the lemma. \square

A.3 Auxiliary statements related to Erlang distributions

We conclude by presenting the statements related to Erlang distributions that we need for Section 5. These statements allow us to either have the explicit formula of the solutions to (2.3)-(2.8) when n_0 is an Erlang distribution, or to compute the moments of these distributions. Throughout this section, for all $\beta > 0$, we denote the following constants:

$$\beta_{N,1} = \frac{N}{m_1} \left[1 - \mathcal{L}(g) \left(\frac{\beta}{N} \right) \right], \quad \beta_{N,2k} = \frac{N}{km_1} \left[1 - \left(\mathcal{L}(g) \left(\frac{\beta}{N} \right) \right)^k \right].$$

These constants are similar to the ones introduced in (2.11), and correspond to approximation of β when N is large.

The first statement we present is useful in the specific case where n_0 is an exponential distribution (which is an Erlang distribution with parameter $\ell = 1$). It gives the explicit formulae of the densities $n^{(d)}$ and $n_{\partial}^{(d)}$ for all $d \in \{1, 2k\}$, as well as the one of the estimator $\widehat{n}_0^{(d)}$. It extends in some sense the result of Proposition A.3.

Proposition A.9 (Explicit solutions for exponential initial distributions). *Assume that there exists $\beta > 0$ such that $n_0 = h_{1,\beta}$, defined in (5.1). Then, the following statements hold.*

(a) For all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$, we have

$$n^{(1)}(t, x) = \beta \exp[-bm_1\beta_{N,1}t - \beta x], \quad \text{and} \quad n_{\partial}^{(1)}(t) = bm_1\beta_{N,1} \exp[-bm_1\beta_{N,1}t]. \quad (\text{A.15})$$

(b) For all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^{2k}$, we have

$$n^{(2k)}(t, x) = \beta^{2k} \exp\left[-kbm_1\beta_{N,2k}t - \beta \sum_{i=1}^{2k} x_i\right], \quad (\text{A.16})$$

$$n_{\partial}^{(2k)}(t) = kbm_1\beta_{N,2k} \exp[-kbm_1\beta_{N,2k}t]. \quad (\text{A.17})$$

(c) For all $d \in \{1, 2k\}$, $x \geq 0$, we have

$$\widehat{n}_0^{(d)}(x) = \beta_{N,d} \exp[-\beta_{N,d}x]. \quad (\text{A.18})$$

Proof. We begin by proving (a) and (b). The proofs of (a) and (b) follow exactly the same steps, so we only give the proof of (b) that is slightly more difficult. Precisely, we focus on the proof of (A.17), since, in view of (4.8), Eq. (A.16) is a direct consequence of Proposition A.3 and (4.43). Notice that by writing $\mu(\{v \in \mathbb{R}_+^{2k} \mid Ny - v \notin \mathbb{R}_+^{2k}\})$ in the second line of (4.8) with an integral, then using that $1_{\{Ny - v \notin \mathbb{R}_+^{2k}\}} = 1 - 1_{\{\forall i \in [1, 2k]: Ny_i \geq v_i\}}$, and finally switching the integrals, we have for all $t \geq 0$

$$\begin{aligned} n_{\partial}^{(2k)}(t) &= bN \int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) \left[\int_{v \in \mathbb{R}_+^{2k}} 1_{\{Ny - v \notin \mathbb{R}_+^{2k}\}} \mu(dv) \right] dy \\ &= bN \int_{v \in \mathbb{R}_+^{2k}} \left[\int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) (1 - 1_{\{\forall i \in [1, 2k]: Ny_i \geq v_i\}}) dy \right] \mu(dv). \end{aligned}$$

Then, as it holds $\int_{y \in \mathbb{R}_+^{2k}} n^{(2k)}(t, y) (1 - 1_{\{\forall i \in [1, 2k]: Ny_i \geq v_i\}}) dy = e^{-kbm_1\beta_{N,2k}t} (1 - e^{-\beta \sum_{i=1}^{2k} \frac{v_i}{N}})$ by (A.16), we obtain that (A.17) is true.

It remains to prove (c). To do so, we only have to plug the right-hand side of (A.15) and Eq. (A.17) in (2.12), and then apply (2.13) to simplify bm_1 and $\tilde{b}\tilde{m}_1$. This gives Eq. (A.18). \square

The second proposition we present is devoted to the more general case in which n_0 is an Erlang distribution, but not necessarily an exponential distribution. In this case, $n^{(1)}$ is explicit, and $n^{(2k)}$ is explicit when $k = 1$. One can then find an explicit representation involving an integral for $n_{\partial}^{(1)}$ and $n_{\partial}^{(2k)}$ by using (2.3)-(2.8), and then for $\widehat{n}_0^{(1)}$ and $\widehat{n}_0^{(2k)}$ by using (2.12). When $k > 1$, we have not been able to obtain an explicit formula for $n^{(2k)}$. The main reason is that when $k > 1$, at each cell division, several coordinates are updated, see (2.7). This creates dependency between the coordinates, which is more difficult to handle.

Proposition A.10 (Explicit solutions for Erlang initial distributions). *Assume that there exist $\ell \in \mathbb{N}^*$ and $\beta > 0$ such that $n_0 = h_{\ell,\beta}$, defined in (5.1). We consider for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$ the function $\psi_{x,t} \in L^1(\mathbb{R}_+^*)$, defined for all $\alpha > 0$ as $\psi_{x,t}(\alpha) := -bN [1 - \mathcal{L}(g)(\frac{\alpha}{N})] t - \alpha x$. Then, for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$, we have*

$$n^{(1)}(t, x) = (-1)^{\ell-1} \frac{\beta^{\ell}}{\Gamma(\ell)} B_{\ell-1} \left[\frac{d}{d\alpha} \psi_{x,t}(\beta), \dots, \frac{d^{\ell-1}}{d\alpha^{\ell-1}} \psi_{x,t}(\beta) \right] \exp(-bm_1\beta_{N,1}t - \beta x), \quad (\text{A.19})$$

where $B_{\ell-1}$ is a complete Bell polynomial of order $\ell - 1$, see [9, Eq. 3.c, p. 134]. In addition, if we work with $k = 1$, then for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^2$ we have

$$n^{(2k)}(t, x) = n^{(1)}\left(\frac{t}{2}, x_1\right) n^{(1)}\left(\frac{t}{2}, x_2\right). \quad (\text{A.20})$$

Proof. Let us first prove Eq. (A.19). We denote for all $(\alpha, t, x) \in \mathbb{R}_+^* \times \mathbb{R}_+ \times \mathbb{R}_+$

$$f(\alpha, t, x) := \exp\left[-bN\left[1 - \mathcal{L}(g)\left(\frac{\alpha}{N}\right)\right]t - \alpha x\right] = \exp[\psi_{x,t}(\alpha)].$$

We know by the proof of Proposition A.3 that f verifies for all $(\alpha, t, x) \in \mathbb{R}_+^* \times \mathbb{R}_+ \times \mathbb{R}_+$

$$\partial_t f(\alpha, t, x) = bN \int_0^\delta [f(\alpha, t, x+u) - f(\alpha, t, x)] g(u) du. \quad (\text{A.21})$$

We also know by the Faà di Bruno's formula [9, Theorem C, p. 137] and the definition of a complete Bell polynomial [9, Eq. 3.c, p. 134], that it holds for all $(\alpha, t, x) \in \mathbb{R}_+^* \times \mathbb{R}_+ \times \mathbb{R}_+$

$$\frac{d^{\ell-1}}{d\alpha^{\ell-1}} f(\alpha, t, x) = B_{\ell-1}\left[\frac{d}{d\alpha}\psi_{x,t}(\alpha), \dots, \frac{d^{\ell-1}}{d\alpha^{\ell-1}}\psi_{x,t}(\alpha)\right] \exp\left[-bN\left[1 - \mathcal{L}(g)\left(\frac{\alpha}{N}\right)\right]t - \alpha x\right]. \quad (\text{A.22})$$

Then, by using Eq. (A.21) and Eq. (A.22), we have that the function $\varphi_1 \in L^1(\mathbb{R}_+^2)$ defined for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+$ as $\varphi_1(t, x) := (-1)^{\ell-1} \frac{\beta^\ell}{\Gamma(\ell)} \frac{d^{\ell-1}}{d\alpha^{\ell-1}} f(\beta, t, x)$ verifies

$$\partial_t \varphi_1(t, x) = bN \int_0^\delta \left[\varphi_1\left(t, x + \frac{v}{N}\right) - \varphi_1(t, x)\right] g(v) dv, \quad (\text{A.23})$$

and

$$\varphi_1(t, x) = (-1)^{\ell-1} \frac{\beta^\ell}{\Gamma(\ell)} B_{\ell-1}\left[\frac{d}{d\alpha}\psi_{x,t}(\beta), \dots, \frac{d^{\ell-1}}{d\alpha^{\ell-1}}\psi_{x,t}(\beta)\right] \exp(-bm_1\beta_{N,1}t - \beta x). \quad (\text{A.24})$$

Eq. (A.23) is in fact the same as the one satisfied by $n^{(1)}$, see (3.4). In addition, we have that $\varphi_1(0, \cdot) = n^{(1)}(0, \cdot) = h_{\ell, \beta}$, in view of (A.24) and the fact that $B_{\ell-1}(y, 0, \dots, 0) = y^{\ell-1}$ for all $y \in \mathbb{R}$ (see [9, Eq. 3.n', p. 136] and [9, Eq. 3.c, p. 136]). As the first line of (3.4) has a unique solution in $C(\mathbb{R}_+, L^1(\mathbb{R}_+))$ by Proposition A.1, we obtain that $\varphi_1 = n^{(1)}$, so that (A.19) is true.

Let us now prove Eq. (A.20). We denote $\varphi_2 \in C(\mathbb{R}, L^1(\mathbb{R}_+^2))$ the function defined for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^2$ as $\varphi_2(t, x) = n^{(1)}\left(\frac{t}{2}, x_1\right) n^{(1)}\left(\frac{t}{2}, x_2\right)$. Our aim is to find the equation verified by this function. To do so, we first derivate it in its first variable. Then, we compute $\partial_t n^{(1)}(t, x_1)$ and $\partial_t n^{(1)}(t, x_2)$ thanks to the first line of (3.4). Finally, we use (2.10), the fact that $\mathcal{I}_1 = \{\{1\}, \{2\}\}$ by (2.5), and the definition of φ_2 to simplify the equality. We obtain that for all $(t, x) \in \mathbb{R}_+ \times \mathbb{R}_+^2$

$$\begin{aligned} \partial_t \varphi_2(t, x) &= \frac{1}{2} bN \left[\int_0^\delta n^{(1)}\left(\frac{t}{2}, x_1 + \frac{v}{N}\right) g(v) dv - n^{(1)}\left(\frac{t}{2}, x_1\right) \right] \times n^{(1)}\left(\frac{t}{2}, x_2\right) \\ &\quad + \frac{1}{2} n^{(1)}\left(\frac{t}{2}, x_1\right) \times bN \left[\int_0^\delta n^{(1)}\left(\frac{t}{2}, x_2 + \frac{v}{N}\right) g(v) dv - n^{(1)}\left(\frac{t}{2}, x_2\right) \right] \\ &= bN \int_{u \in \mathbb{R}_+^2} \varphi_2(t, x+u) \mu(du) - bN \varphi_2(t, x). \end{aligned}$$

Thus, φ_2 satisfies the same integro-differential equation as $n^{(2k)}$, see (4.8). One can easily see that it also has the same initial condition. Then, from these two points and the fact that the first line of (4.8) has a unique solution in $C(\mathbb{R}, L^1(\mathbb{R}_+^2))$ (see Proposition A.1), we obtain that $\varphi_2 = n^{(2k)}$, which ends the proof. \square

The final proposition we present provides the value of the mean, the variance, and the coefficient of variation of an Erlang distribution. It is useful for the study presented in Section 5.1.2, see in particular Figure 2. This result is, in fact, very classical, so we do not prove it. We however refer to [23, p. 138] for a proof of the expression of the mean and the variance (the expression of the coefficient of variation can be easily obtained from the two other ones).

Proposition A.11 (Moments of Erlang distributions). *Let us fix $\ell \in \mathbb{N}^*$ and $\beta > 0$. We consider*

$$m = \int_0^{+\infty} x h_{\ell, \beta}(x) dx \quad \text{and} \quad \sigma^2 = \int_0^{+\infty} x^2 h_{\ell, \beta}(x) dx - m^2,$$

which correspond respectively to the mean and the variance of a random variable distributed according to $h_{\ell, \beta}$. We also consider $cv = \frac{\sigma}{m}$ the coefficient of variation of this distribution. Then, we have

$$m = \frac{\ell}{\beta}, \quad \sigma^2 = \frac{\ell}{\beta^2}, \quad \text{and} \quad cv = \frac{1}{\sqrt{\ell}}. \quad (\text{A.25})$$

B Additional information about the models

In this section, we present additional information about the models introduced in Section 2. In particular, we complement the discussion of certain points presented in Section 2.3. First, in Section B.1, we complete our discussion about extending our model with an age-dependent rate, by showing that division times on our experimental dataset do not seem to follow an exponential distribution. Then, in Section B.2, we complete our discussion about having a model with a continuous state space, by illustrating with an example that for telomeres with a large number of nucleotides, discrete lengths distributions have a continuous equivalent.

B.1 Distribution of division times

To simplify the computations, we have assumed that cell division times follow an exponential distribution. However, this is not realistic and data coming from experiments illustrate this. In Figure 11 we show the measurements of 1430 division times of *Saccharomyces cerevisiae* made by biologists. The division times were measured to the nearest decaminute, which reduces the granularity of the dataset. This explains why we have a discrete distribution of division times rather than a continuous one. We observe that the distribution of division times does not seem to have the allure of an exponential distribution. Indeed, the histogram we have corresponds to the histogram of a shifted modal distribution, whereas the exponential distribution has neither of these two properties. We thus conclude, from this observation, that we need to extend our inference method to make it work for models with age-dependent division rates.

B.2 Comparison between discrete and continuous distributions

In this subsection, we illustrate the fact that when we study species with a large number of nucleotides, the approximation that we are in a continuous state space is relevant. To do so, we give two examples: one example where we have a lot of nucleotides, and one example where we have a small number of nucleotides.

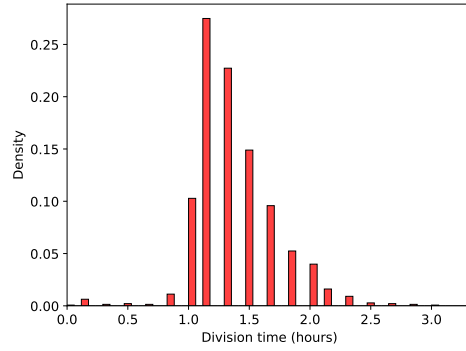
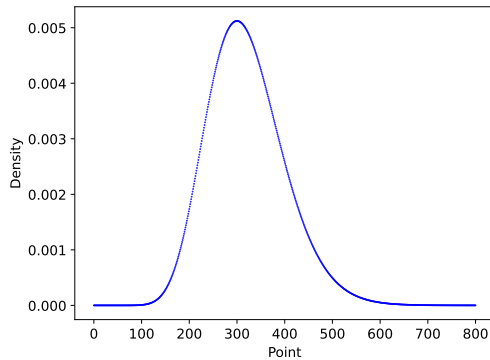


Figure 11: Histogram of division times coming from experiments. *The average division time is 1.39 hours. This yields that we can estimate the division rate as $1/1.39 = 0.719 \text{ hours}^{-1}$.*

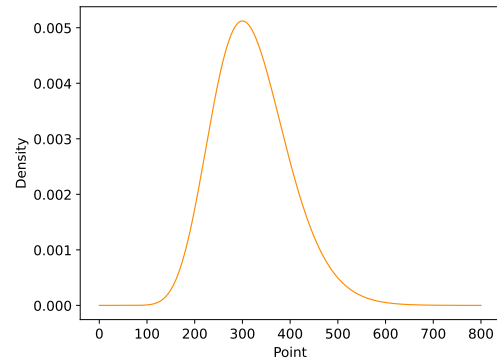
Example 1: The approximation is relevant. When the number of nucleotides is of the order of 100 base pairs, which is the case of the budding yeast, the approximation is relevant. To illustrate this, denoting $a = 16$ and $\theta = 20$, we plot

- In Figure 12a, the curve of $p_1(i) = \frac{1}{\sum_{\ell=0}^{800} \frac{\ell^{a-1} \exp(-\theta \ell)}{\Gamma(a)\theta^a}} \frac{i^{a-1} \exp(-i/\theta)}{\Gamma(a)\theta^a}$ as a function of i , for $i \in \llbracket 0, 800 \rrbracket$.
- In Figure 12b, the curve of $p_2(x) = \frac{x^{a-1} \exp(-\theta x)}{\Gamma(a)\theta^a}$ as a function of x , for $x \in [0, 800]$ (p_2 is the density of a Gamma distribution).

One can easily see that p_1 is a discrete distribution, and that p_2 is its continuous equivalent. We see that even if Figure 12a corresponds to the discrete case, as the gaps between points are very small, the curve looks like its continuous equivalent.



(a) $p_1(i)$ versus i , for $i \in \llbracket 0, 800 \rrbracket$.



(b) $p_2(x)$ versus x , for $x \in [0, 800]$.

Figure 12: Comparison between the distribution of p_1 (blue) and its continuous equivalent p_2 (orange).

Example 2: The approximation is not relevant. When the number of nucleotides is too small, the approximation is not relevant. To illustrate this, denoting $\mu = 10$ and $\beta = 5$, we plot

- In Figure 13a, the curve of $p_3(i) = \frac{\frac{1}{\beta} \exp\left(-\frac{i-\mu}{\beta} - \exp\left(-\frac{i-\mu}{\beta}\right)\right)}{\frac{1}{\beta} \sum_{\ell=0}^{25} \exp\left(-\frac{\ell-\mu}{\beta} - \exp\left(-\frac{\ell-\mu}{\beta}\right)\right)}$ as a function of i , for $i \in \llbracket 0, 800 \rrbracket$.
- In Figure 13b, the curve of $p_4(x) = \frac{1}{\beta} \exp\left(-\frac{x-\mu}{\beta} - \exp\left(-\frac{x-\mu}{\beta}\right)\right)$ as a function of x , for $x \in [0, 800]$ (p_4 is the density of a Gumbel distribution).

As for the previous case, p_4 is the continuous equivalent of p_3 . We easily see in Figure 13a that the gaps between points are too large for the curve of p_3 . Hence, the approximation is not relevant at all.

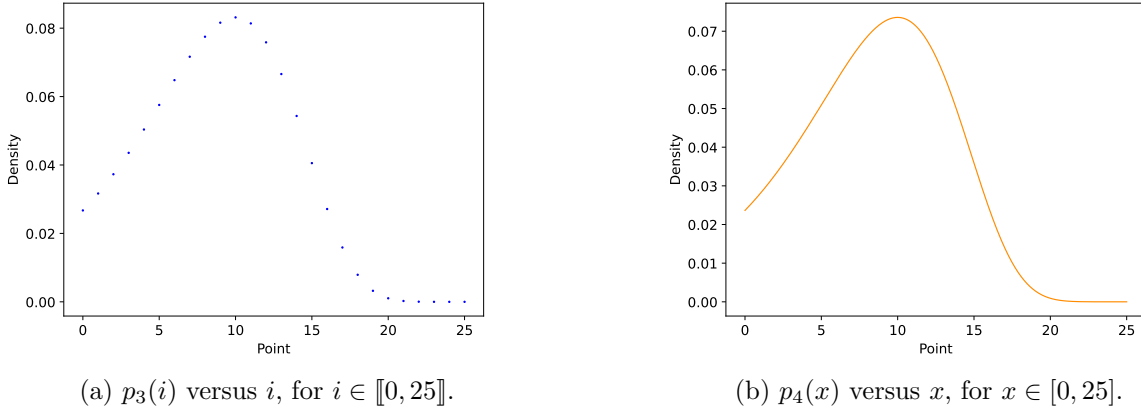


Figure 13: Comparison between the distribution of p_3 (blue), and its continuous equivalent p_4 (orange).

C Simulation of random variables with distribution $n_{\partial}^{(1)}$ or $n_{\partial}^{(2k)}$

This appendix is devoted to the presentation of the simulations of the random variables $(T_{d,i})_{1 \leq i \leq n_s}$, where $d \in \{1, 2k\}$ and $n_s \in \mathbb{N}^*$, used for the estimations done in Section 5.3. To simulate these variables, we need a probabilistic model with underlying integro-differential equation (2.3) or (2.8), depending on the dimension. This model is easy to obtain here in view of the dynamics described by these equations, see Section 2. To present it, let us introduce for all $d \in \{1, 2k\}$ a vector $X_0 = (X_0^{(1)}, \dots, X_0^{(d)})$, and a sequence of independent and identically distributed random variables $(Y_i^{(d)})_{i \in \mathbb{N}^*}$. We assume that $X_0^{(1)}$ is distributed according to n_0 , that $Y_1^{(1)}$ is distributed according to \tilde{g} , and that $Y_1^{(2k)}$ is distributed according to $\tilde{\mu}$. Let us also introduce a Poisson process $(N_t)_{t \geq 0}$ with parameter \tilde{b} . Then, by the dynamics of our model, for all $d \in \{1, 2k\}$ and $t \geq 0$, the random variable

$$X_t^{(d)} = X_0^{(d)} - \sum_{i=1}^{N_t} Y_i^{(d)}$$

models telomere lengths of one cell at time t , and is distributed according to $n^{(d)}(t, \cdot)$. As the senescence occurs when a cell has a telomere with a length below 0, we also have that

$$T^{(d)} = \inf \left\{ t \geq 0 \mid X_t^{(d)} \notin \mathbb{R}_+^d \right\}$$

models the time a lineage goes to senescence, so is distributed according to $n_{\partial}^{(d)}$.

By the above, to simulate random variables $(T_{d,i})_{1 \leq i \leq n_s}$ independent and identically distributed according to $n_{\partial}^{(d)}$, where $d \in \{1, 2k\}$ and $n_s \in \mathbb{N}^*$, we need to simulate the stochastic process $(X_t^{(d)})_{t \geq 0}$. Thereafter, we return the first time at which one of its coordinates goes below 0. Algorithm 1 shows the procedure to do this. In this algorithm, $\mathcal{E}(\tilde{b})$ denotes an exponential distribution with parameter \tilde{b} , $\text{Ber}(\frac{1}{2})$ represents a Bernoulli distribution with parameter $\frac{1}{2}$, and for any probability density function $f \in L^1(\mathbb{R}_+)$, $\text{draw}(f)$ is a random variable distributed according to f .

Algorithm 1 Simulation of a telomere shortening model

```

1: senescences  $\leftarrow$  array(size =  $n_s$ )
2: for  $s = 1, \dots, n_s$  do
3:   lengths  $\leftarrow$  array(size =  $d$ )
4:   for  $i = 1, \dots, d$  do
5:     lengths[ $i$ ] = draw( $n_0$ )
6:   end for
7:   time  $\leftarrow$  0
8:   while min(lengths)  $\geq$  0 do
9:     time = time +  $\mathcal{E}(\tilde{b})$ 
10:    if  $d = 1$  then
11:      lengths[1] = lengths[1] - draw( $\tilde{g}$ )
12:    else
13:       $n_{\text{chrom}} = d/2$ 
14:      for  $i = 1, \dots, n_{\text{chrom}}$  do
15:         $p \leftarrow \text{Ber}(\frac{1}{2})$ 
16:        lengths[ $i + p \cdot n_{\text{chrom}}$ ] = lengths[ $i + p \cdot n_{\text{chrom}}$ ] - draw( $\tilde{g}$ )
17:      end for
18:    end if
19:  end while
20:  senescences[ $s$ ] = time
21: end for
22: return senescences

```

By adapting this algorithm, it is also possible to have the lengths at $t = 0$ of the telomere signalling senescence. To do so, we only have to keep the value of the initial lengths, and then to return the initial length at the index $i_0 \in \llbracket 1, d \rrbracket$ where we have lengths[i_0] < 0. The latter is what we do to plot the histograms presented in Figure 9.

D Illustration of the issues with the classical kernel density estimation

As said in Section 5.3, we prefer to do a log-transform kernel density estimation rather than a classical kernel density estimation. Formally, this means that we prefer to use the estimators

presented in (5.4) and (5.7), rather than the following estimators, for all $x \geq 0$,

$$\begin{aligned} \underline{n}_0^{(1,\alpha)}(x) &:= \frac{1}{n_s} \sum_{i=1}^{n_s} \frac{1}{\tilde{b}\tilde{m}_1\alpha} \rho\left(\frac{\frac{x}{\tilde{b}\tilde{m}_1} - T_{1,i}}{\alpha}\right), \\ \underline{n}_0^{(2k,\alpha)}(x) &:= \sum_{j=0}^{n_s} \left(1 - \frac{j}{n_s}\right)^{\frac{1}{2k}} \frac{1}{\alpha} \left[\rho\left(\frac{x - \frac{\tilde{b}\tilde{m}_1 T_{2k,j+1}}{2}}{\alpha}\right) - \rho\left(\frac{x - \frac{\tilde{b}\tilde{m}_1 T_{2k,j}}{2}}{\alpha}\right) \right]. \end{aligned} \quad (\text{D.1})$$

The main reason is that to have a good estimation of n_0 at a point $x \in \mathbb{R}_+$, we need to have enough realisations of $(T_{1,i})_{1 \leq i \leq n_s}$ smaller and larger than $\frac{x}{\tilde{b}\tilde{m}_1}$ for the single-telomere model. Similarly, we need to have enough realisations of $(T_{2k,i})_{1 \leq i \leq n_s}$ smaller and larger than $\frac{2x}{\tilde{b}\tilde{m}_1}$ for the model in \mathbb{R}_+^{2k} . However, as \mathbb{R}_+ has a hard boundary at 0, we cannot ensure to have a sufficient number of realisations of the variables $(T_{d,i})_{d \in \{1,2k\}, 1 \leq i \leq n_s}$ smaller than these values when x is too close to 0. This leads that we have problems of estimation when we estimate $n_0(x)$, with x small. The latter is illustrated in Figure 14, where we do the same estimation as the one presented in Figure 7a, with $\underline{n}_\partial^{(1,\hat{\alpha}_{0.1})}$ instead of $\bar{n}_\partial^{(1,\hat{\alpha}_{0.1})}$, where $\hat{\alpha}_{0.1}$ is defined in the third paragraph of Section 5.3.1.

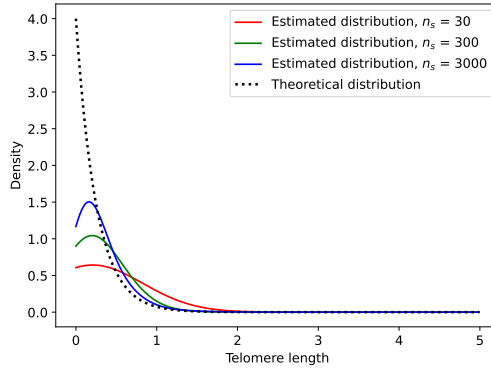


Figure 14: Estimation results in the same setting as in Figure 7a, by doing a kernel density estimation instead of a log-transform kernel density estimation. *When x is close to 0, the estimated initial distribution is far from the theoretical initial distribution, whatever the value of n_s .*

The other problem of using one of the estimators presented in (D.1) is that the integral on \mathbb{R}_+ of each of these estimators is not equal to 1. This yields that our estimation of n_0 does not correspond to a probability density function on when one of these estimators is used, whereas n_0 is normally such a function.

E Impact of the noise

In this section, we provide bounds on the errors of the estimators we use in Section 5.3, namely $\bar{n}_0^{(1,\alpha)}$ and $\bar{n}_0^{(2k,\alpha)}$, defined in (5.4) and (5.7) respectively. These bounds result from those obtained for $\hat{n}_0^{(1)}$ and $\hat{n}_0^{(2k)}$, presented in Theorem 2.6. What changes is that we need to manage how the fact that we do not observe directly $n_\partial^{(1)}$ and $n_\partial^{(2k)}$ affects the quality of the estimation. We also need to handle how the smoothing influences this quality.

In Section E.1, we introduce the notations and auxiliary results we need to prove our the-

oretical result. In Section E.2, we present the bounds on the error between $\bar{n}_0^{(d,\alpha)}$ and n_0 we have obtained, for all $d \in \{1, 2k\}$ and $\alpha > 0$.

E.1 Notations and auxiliary statements

We begin by introducing the notations we use in this section. We first consider the following set

$$W^{-1,\infty}(\mathbb{R}) = \left\{ f \in \mathcal{D}'(\mathbb{R}) \mid f = h + \varphi' \text{ where } (h, \varphi) \in (L^\infty(\mathbb{R}))^2 \right\}.$$

This set contains distributions that are not necessarily representable by a function. For example, as for all $x \in \mathbb{R}$ and $x_0 \in \mathbb{R}$ it holds $\frac{d}{dx}(1_{x \leq x_0}) = \delta_{x_0}(\{x\})$, and as the shifted Heaviside functions are in $L^\infty(\mathbb{R})$, we have $\delta_{x_0} \in W^{-1,\infty}(\mathbb{R})$. We then introduce for all $p > 0$ the norm $\|\cdot\|_{-1,\infty,p}$ on $W^{-1,\infty}(\mathbb{R})$, defined for all $f \in W^{-1,\infty}(\mathbb{R})$ as

$$\|f\|_{-1,\infty,p} = \inf_{(h,\varphi) \in (L^\infty(\mathbb{R}))^2, \text{ s.t. } f=h+\varphi'} \left(p \|h\|_{L^\infty(\mathbb{R})} + \|\varphi\|_{L^\infty(\mathbb{R})} \right). \quad (\text{E.1})$$

As such, the space $(W^{-1,\infty}(\mathbb{R}), \|\cdot\|_{-1,\infty,p})$ is a Banach space. These norms allow us to control the distance between irregular distributions by regular ones. For example, we can control the distance between two Dirac measures by two shifted Heaviside functions with them. The parameter p of the norms allows us to choose the weight we give to the regular part of the functions in $W^{-1,\infty}(\mathbb{R})$. We finally define the following function, for all $y \in \mathbb{R}$

$$n_{\log}^{(d)}(y) = \exp(y) \hat{n}_0^{(d)}(\exp(y)), \quad (\text{E.2})$$

and the following measures

$$\begin{aligned} \bar{n}_{\log}^{(1)}(dx) &= \frac{1}{n_s} \sum_{i=1}^{n_s} \delta_{\log(\tilde{b}\tilde{m}_1 T_{1,i})}(dx), \\ \bar{n}_{\log}^{(2k)}(dx) &= \sum_{j=0}^{n_s} \left(1 - \frac{j}{n_s}\right)^{\frac{1}{2k}} \left[\delta_{\log(\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,j+1})} - \delta_{\log(\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,j})} \right], \end{aligned} \quad (\text{E.3})$$

where $(T_{1,i})_{1 \leq i \leq n_s}$ and $(T_{2k,i})_{0 \leq i \leq n_s+1}$ are the sequence of random variables introduced in Sections 5.3.1 and 5.3.2. Since Dirac measures belong to $W^{-1,\infty}(\mathbb{R})$, we have that $\bar{n}_{\log}^{(d)} \in W^{-1,\infty}(\mathbb{R})$ for all $d \in \{1, 2k\}$. The function $n_{\log}^{(d)}$, defined in (E.2), is the distribution of the random variable $\log(Z^{(d)})$, where $Z^{(d)}$ is distributed according to $\hat{n}_0^{(d)}$. The measure $\bar{n}_{\log}^{(1)}$, in the first line of (E.3), is the empirical estimator of $n_{\log}^{(1)}$. The measure $\bar{n}_{\log}^{(2k)}$, in the next line, is an estimator of $n_{\log}^{(2k)}$. The latter has been constructed by computing the weak derivative of the empirical cumulative distribution function to the power $\frac{1}{2k}$. We refer to the proof of Proposition 5.2 for a similar example in which we have done this.

One of our objectives is to obtain information about how the smoothing by the Gaussian kernel $\rho(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}}$, where $x \in \mathbb{R}$, influences the quality of our estimators $(\bar{n}_0^{(d,\alpha)})_{d \in \{1, 2k\}, \alpha > 0}$. To this end, we need results describing how the norm of a distribution in the space $W^{-1,\infty}(\mathbb{R})$ behaves after smoothing. The following lemma provides these results. It corresponds to the key lemma of this section.

Lemma E.1 (Inequalities related to ρ). *Let us fix $\alpha > 0$, and let us consider $\rho_\alpha(x) = \frac{1}{\alpha} \rho\left(\frac{x}{\alpha}\right)$ for all $x \in \mathbb{R}$. Then, the following statements hold*

(a) For all $f \in W^{1,\infty}(\mathbb{R})$, we have

$$\|\rho_\alpha * f - f\|_{L^\infty(\mathbb{R})} \leq \sqrt{\frac{2}{\pi}} \alpha \|f'\|_{L^\infty(\mathbb{R})}.$$

(b) For all $f \in L^\infty(\mathbb{R})$, $n \in \mathbb{N}$, we have

$$\left\| \rho_\alpha * \frac{d^n}{dx^n} f \right\|_{L^\infty(\mathbb{R})} \leq \alpha^{-n} \left\| \frac{d^n}{dx^n} \rho \right\|_{L^1(\mathbb{R})} \|f\|_{L^\infty(\mathbb{R})}.$$

(c) For all $f \in W^{-1,\infty}(\mathbb{R})$, we have

$$\|\rho_\alpha * f\|_{L^\infty(\mathbb{R})} \leq \sqrt{\frac{2}{\pi}} \alpha^{-1} \|f\|_{-1,\infty,\alpha\sqrt{\frac{\pi}{2}}}.$$

Proof. We first prove (a). We observe by the change of variable $t' = \frac{t}{\alpha}$ and a Taylor's expansion, that for all $x \in \mathbb{R}$, it holds

$$(\rho_\alpha * f)(x) - f(x) = \int_{\mathbb{R}} \rho(t') (f(x - \alpha t') - f(x)) dt' = -\alpha \int_{\mathbb{R}} \int_0^1 t' \rho(t') f'(x - \alpha t' u) du dt'.$$

Therefore, by taking the supremum of the above, and then using that $\int_{\mathbb{R}} |t| \rho(t) dt = \sqrt{\frac{2}{\pi}}$, we obtain that (a) is true.

We now prove (b). Let us fix $n \in \mathbb{N}$. First, by using the equality $h' * \varphi = \varphi * h'$ for all $(h, \varphi) \in L^\infty(\mathbb{R}) \times W^{1,1}(\mathbb{R})$, and then doing the change of variable $t' = \frac{t}{\alpha}$, we have for all $x \geq 0$

$$\left| \left(\rho_\alpha * \frac{d^n}{dx^n} f \right) (x) \right| = \frac{1}{\alpha^{n+1}} \left| \int_{\mathbb{R}} \frac{d^n}{dx^n} \rho \left(\frac{t}{\alpha} \right) f(x - t) dt \right| = \frac{1}{\alpha^n} \left| \int_{\mathbb{R}} \frac{d^n}{dx^n} \rho(t') f(x - \alpha t') dt' \right|.$$

Then, taking the supremum in the above equation yields that (b) is true.

We finally prove (c). Let $f \in W^{-1,\infty}(\mathbb{R}_+)$, and $(h, \varphi) \in (L^\infty(\mathbb{R}))^2$ such that $f = h + \varphi'$. By first using that $\|\rho_\alpha * f\|_{L^\infty(\mathbb{R})} \leq \|\rho_\alpha * h\|_{L^\infty(\mathbb{R})} + \|\rho_\alpha * \varphi'\|_{L^\infty(\mathbb{R})}$, and then applying (b) to bound each of these terms, we have

$$\|\rho_\alpha * f\|_{L^\infty(\mathbb{R})} \leq \|\rho\|_{L^1(\mathbb{R})} \|h\|_{L^\infty(\mathbb{R})} + \alpha^{-1} \|\rho'\|_{L^1(\mathbb{R})} \|\varphi\|_{L^\infty(\mathbb{R})}.$$

Therefore, in view of (E.1), by taking the infimum of functions $(h, \varphi) \in (L^\infty(\mathbb{R}))^2$ verifying $f = h + \varphi'$ and then using the equalities $\|\rho\|_{L^1(\mathbb{R})} = 1$ and $\|\rho'\|_{L^1(\mathbb{R})} = \sqrt{\frac{2}{\pi}}$, we obtain that (c) is true. \square

E.2 Error in practice and optimal smoothing parameter

We now use the statements of Lemma E.1 to obtain bounds on the errors done by the estimators $(\bar{n}_0^{(d,\alpha)})_{d \in \{1, 2k\}, \alpha > 0}$. The first statement that we present is the following. It provides for all $d \in \{1, 2k\}$ a bound on the supremum error between $\bar{n}_0^{(d,\alpha)}$ and n_0 , when the error between $\bar{n}_{\log}^{(d)}$ and $n_{\log}^{(d)}$ is known.

Proposition E.2 (Error bounds for simulated data). *Let us consider $d \in \{1, 2k\}$, $\varepsilon > 0$ and $\alpha > 0$. Assume that (H₁) – (H₄) hold, that $\beta'_N = (2k + 1)\lambda'_N - 2k\omega > 0$, and finally that $\left\| \bar{n}_{\log}^{(d)} - n_{\log}^{(d)} \right\|_{-1, \infty, \alpha \sqrt{\frac{\pi}{2}}} \leq \varepsilon$. We denote the constant*

$$C_{\hat{n}, d} := \left\| \text{Id}^2 \left(\hat{n}_0^{(d)} \right)' + \text{Id} \hat{n}_0^{(d)} \right\|_{L^\infty(\mathbb{R}_+)}. \quad (\text{E.4})$$

Then, there exists a sequence $(L_{d,n})_{n \in \mathbb{N}}$ of positive numbers such that $\limsup_{n \rightarrow +\infty} L_{d,n} < +\infty$ and

$$\left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - n_0 \right] \right\|_{L^\infty(\mathbb{R}_+)} \leq \sqrt{\frac{2}{\pi}} \alpha^{-1} \varepsilon + \sqrt{\frac{2}{\pi}} \alpha C_{\hat{n}, d} + \frac{L_{d,N}}{N}.$$

Remark E.3. *The minimum of the function $\alpha \in \mathbb{R}_+^* \mapsto \sqrt{\frac{2}{\pi}} \alpha^{-1} \varepsilon + \sqrt{\frac{2}{\pi}} \alpha C_{\hat{n}, d}$ can be computed by analysing the sign of its derivative, and is in $\alpha^* = \left(\frac{\varepsilon}{C_{\hat{n}, d}} \right)^{\frac{1}{2}}$. Then, the smoothing parameter providing the best bound on the error is $\left(\frac{\varepsilon}{C_{\hat{n}, d}} \right)^{\frac{1}{2}}$.*

Proof. First, decomposing $\left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - n_0 \right] \right\|_{L^\infty(\mathbb{R}_+)}$ into two terms thanks to the triangular inequality, and then using Theorem 2.6 to bound the second term, yields that there exists a sequence $(L_{d,n})_{n \in \mathbb{N}}$ of positive real numbers such that $\limsup_{n \rightarrow +\infty} L_{d,n} < +\infty$ and

$$\left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - n_0 \right] \right\|_{L^\infty(\mathbb{R}_+)} \leq \left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - \hat{n}_0^{(d)} \right] \right\|_{L^\infty(\mathbb{R}_+)} + \frac{L_{d,N}}{N}. \quad (\text{E.5})$$

We thus only have to bound the term $\left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - \hat{n}_0^{(d)} \right] \right\|_{L^\infty(\mathbb{R}_+)}$, and the proposition will be proved. To do so, notice that in view of the change of variable $y = \log(x)$, the definition of $\bar{n}_0^{(1, \alpha)}$ given in (5.4), and the ones of $n_{\log}^{(d)}$ and $\bar{n}_{\log}^{(d)}$ given in (E.2)-(E.3), we have when $d = 1$ (we recall that $\rho_\alpha = \frac{1}{\alpha} \rho \left(\frac{\cdot}{\alpha} \right)$)

$$\begin{aligned} \left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - \hat{n}_0^{(d)} \right] \right\|_{L^\infty(\mathbb{R}_+)} &= \sup_{x \in \mathbb{R}_+} \left[x \left| \bar{n}_0^{(d, \alpha)}(x) - \hat{n}_0^{(d)}(x) \right| \right] \\ &= \sup_{y \in \mathbb{R}} \left[\exp(y) \left| \bar{n}_0^{(d, \alpha)}(\exp(y)) - \hat{n}_0^{(d)}(\exp(y)) \right| \right] \\ &= \sup_{y \in \mathbb{R}} \left[\left| \frac{1}{n_s} \sum_{i=1}^{n_s} \frac{1}{\alpha} \rho \left(\frac{y - \log(\tilde{b} \tilde{m}_1 T_{1,i})}{\alpha} \right) - n_{\log}^{(d)}(y) \right| \right] \\ &= \left\| \rho_\alpha * \bar{n}_{\log}^{(d)} - n_{\log}^{(d)} \right\|_{L^\infty(\mathbb{R})}. \end{aligned} \quad (\text{E.6})$$

Notice also that when $d = 2k$, in view of the definition of $\bar{n}_0^{(2k, \alpha)}$ given in (5.7), we have with similar computations (we do not detail them as they are more laborious)

$$\left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - \hat{n}_0^{(d)} \right] \right\|_{L^\infty(\mathbb{R}_+)} = \left\| \rho_\alpha * \bar{n}_{\log}^{(d)} - n_{\log}^{(d)} \right\|_{L^\infty(\mathbb{R})}. \quad (\text{E.7})$$

Then, decomposing the right-hand sides of (E.6) and (E.7) into two terms thanks to the triangular inequality, and using Lemma E.1-(c) and Lemma E.1-(a), yields that whatever the value of d

$$\begin{aligned} \left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - \hat{n}_0^{(d)} \right] \right\|_{L^\infty(\mathbb{R}_+)} &\leq \left\| \rho_\alpha * \left(\bar{n}_{\log}^{(d)} - n_{\log}^{(d)} \right) \right\|_{L^\infty(\mathbb{R})} + \left\| \rho_\alpha * n_{\log}^{(d)} - n_{\log}^{(d)} \right\|_{L^\infty(\mathbb{R})} \\ &\leq \sqrt{\frac{2}{\pi}} \alpha^{-1} \left\| \bar{n}_{\log}^{(d)} - n_{\log}^{(d)} \right\|_{-1, \infty, \alpha \sqrt{\frac{\pi}{2}}} + \sqrt{\frac{2}{\pi}} \alpha \left\| \left(n_{\log}^{(d)} \right)' \right\|_{L^\infty(\mathbb{R})}. \end{aligned}$$

We thus only have to use the fact that $\left\| \bar{n}_{\log}^{(d)} - n_{\log}^{(d)} \right\|_{-1, \infty, \alpha \sqrt{\frac{\pi}{2}}} \leq \varepsilon$, and that in view of (E.2) and the change of variable $x = \log(y)$ it holds

$$\begin{aligned} \left\| (n_{\log}^{(d)})' \right\|_{L^\infty(\mathbb{R})} &= \sup_{y \in \mathbb{R}} \left| \exp(2y) (\widehat{n}_0^{(d)})'(\exp(y)) + \exp(y) \widehat{n}_0^{(d)}(\exp(y)) \right| \\ &= \sup_{x \in \mathbb{R}_+} \left| x^2 (\widehat{n}_0^{(d)})'(x) + x \widehat{n}_0^{(d)}(x) \right|, \end{aligned}$$

and we get our upper bound for $\left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - \widehat{n}_0^{(d)} \right] \right\|_{L^\infty(\mathbb{R}_+)}$. By plugging this bound in Eq. (E.5), we obtain that the proposition is proved. \square

What is interesting with Proposition E.2 is that we need to weight the L^∞ -norm by the identity to obtain a qualitative bound on the error. This weighting implies that the guarantees we have on the estimation of $n_0(x)$, where $x \geq 0$, decrease when x is small. This is due to the fact the logarithm explodes near 0, which generates instability. Thus, even after applying a logarithmic transformation to our data, estimating n_0 at the boundary of \mathbb{R}_+ remains difficult.

The second statement we present is a consequence of the first one. It provides for any $d \in \{1, 2k\}$ a bound on the estimation error when the error between $\bar{n}_{\log}^{(d)}$ and $n_{\log}^{(d)}$ is known, with a certain degree of confidence. It also gives us information on how the smoothing parameter must be chosen to have a good estimation.

Corollary E.4 (Confidence intervals). *Assume that the assumptions of Proposition E.2 hold, except that $\left\| \bar{n}_{\log}^{(d)} - n_{\log}^{(d)} \right\|_{-1, \infty, \alpha \sqrt{\frac{\pi}{2}}} \leq \varepsilon$. We fix $p \in [0, 1]$, and the smoothing parameter*

$$\alpha_p := \frac{1}{(C_{\widehat{n}, d})^{\frac{1}{2}}} \left(\frac{\log\left(\frac{2}{p}\right)}{2n_s} \right)^{\frac{1}{4d}}. \quad (\text{E.8})$$

Then, with probability at least $1 - p$, it holds

$$\left\| \text{Id} \left[\bar{n}_0^{(d, \alpha)} - n_0 \right] \right\|_{L^\infty(\mathbb{R}_+)} \leq 2\sqrt{\frac{2}{\pi}} (C_{\widehat{n}, d})^{\frac{1}{2}} \left(\frac{\log\left(\frac{2}{p}\right)}{2n_s} \right)^{\frac{1}{4d}} + \frac{L_{d, N}}{N}, \quad (\text{E.9})$$

where $L_{d, N}$ is the same constant as in Proposition E.2.

Proof. We only give the proof in the case where $d = 2k$. The proof in the case where $d = 1$ is easier, and follows the same steps. Our objective here is to apply Proposition E.2. To do so, we begin by computing the probability that $\left\| \bar{n}_{\log}^{(2k)} - n_{\log}^{(2k)} \right\|_{-1, \infty, \alpha_p \sqrt{\frac{\pi}{2}}} \leq \varepsilon_p$, where $\varepsilon_p = \left(\frac{\log\left(\frac{2}{p}\right)}{2n_s} \right)^{\frac{1}{4k}}$. We denote for all $y \in \mathbb{R}$

$$R(y) := \left[1 - \frac{1}{n_s} \sum_{i=1}^{n_s} \mathbf{1}_{\left\{ \log\left(\frac{\tilde{b}\tilde{m}_1}{2} T_{2k, i}\right) \leq y \right\}} \right]^{\frac{1}{2k}} - \int_y^{+\infty} n_{\log}^{(2k)}(s) ds, \quad (\text{E.10})$$

and for all $t \geq 0$: $N_\partial(t) = \int_t^\infty n_\partial^{(2k)}(s) ds$. In view of (E.2), the change of variable $s' = \exp(s)$, and the fact that $\widehat{n}_0^{(2k)}$ is the derivative of $x \mapsto -(N_\partial)^{\frac{1}{2k}} \left(\frac{2x}{\tilde{b}\tilde{m}_1} \right)$ (see (2.12)), we have for all $y \in \mathbb{R}$

$$\int_y^{+\infty} n_{\log}^{(2k)}(s) ds = \int_{\exp(y)}^{+\infty} \widehat{n}_0^{(2k)}(s') ds' = N_\partial \left(\frac{2e^y}{\tilde{b}\tilde{m}_1} \right)^{\frac{1}{2k}}. \quad (\text{E.11})$$

Our aim is to use the above equality to bound the probability that $\sup_{y \in \mathbb{R}} |R(y)| > \varepsilon_p$. To do so, we first use that $\left| a^{\frac{1}{2k}} - c^{\frac{1}{2k}} \right| \leq |a - c|^{\frac{1}{2k}}$ for all $a, c \geq 0$ to bound from above $|R|$. This inequality is a consequence of the reverse triangular inequality that holds for the quasi-distance $D(a, c) := |a - c|^{\frac{1}{2k}}$, where $(a, c) \in \mathbb{R}^2$. Then, we apply (E.11) to simplify the expression in the measure. Finally, we use the Dvoretzky–Kiefer–Wolfowitz–Massart inequality [15, 31, 42], in view of the fact that $x \mapsto 1 - N_\partial \left(\frac{2e^x}{\tilde{b}\tilde{m}_1} \right)$ is the cumulative distribution function of the random variables $\left(\log \left(\frac{\tilde{b}\tilde{m}_1}{2} T_{2k,i} \right) \right)_{1 \leq i \leq n_s}$ (as $1 - N_\partial$ is the one of $(T_{2k,i})_{1 \leq i \leq n_s}$). We obtain

$$\begin{aligned} \mathbb{P} \left[\sup_{y \in \mathbb{R}} |R(y)| > \varepsilon_p \right] &\leq \mathbb{P} \left[\sup_{y \in \mathbb{R}} \left| 1 - \frac{1}{n_s} \sum_{i=1}^{n_s} 1_{\{\log(\frac{\tilde{b}\tilde{m}_1}{2} T_{d,i}) \leq y\}} - \left[\int_y^{+\infty} n_{\log}^{(2k)}(s) ds \right]^{2k} \right|^{\frac{1}{2k}} > \varepsilon_p \right] \\ &= \mathbb{P} \left[\sup_{y \in \mathbb{R}} \left| \left[1 - N_\partial \left(\frac{2e^y}{\tilde{b}\tilde{m}_1} \right) \right] - \frac{1}{n_s} \sum_{i=1}^{n_s} 1_{\{\log(\frac{\tilde{b}\tilde{m}_1}{2} T_{d,i}) \leq y\}} \right| > (\varepsilon_p)^{2k} \right] \\ &\leq 2e^{-2n_s(\varepsilon_p)^{4k}}. \end{aligned} \tag{E.12}$$

In addition, in view of (E.10), (E.3), and the reasoning that allowed us to obtain Proposition 5.2, we have that $R' = n_{\log}^{(2k)} - \bar{n}_{\log}^{(2k)}$. This yields, in view of the fact that $R \in L^\infty(\mathbb{R})$ and the infimum in (E.1), that it holds

$$\left\| n_{\log}^{(2k)} - \bar{n}_{\log}^{(2k)} \right\|_{-1, \infty, \alpha_p \sqrt{\frac{\pi}{2}}} \leq \alpha_p \sqrt{\frac{\pi}{2}} \times 0 + \|R\|_{L^\infty(\mathbb{R})} = \|R\|_{L^\infty(\mathbb{R})}.$$

Then, by combining this inequality with (E.12), we obtain that

$$\mathbb{P} \left[\left\| n_{\log}^{(2k)} - \bar{n}_{\log}^{(2k)} \right\|_{-1, \infty, \alpha_p \sqrt{\frac{\pi}{2}}} \leq \varepsilon_p \right] \geq \mathbb{P} \left[\sup_{y \in \mathbb{R}} |R(y)| \leq \varepsilon_p \right] \geq 1 - 2e^{-2n_s(\varepsilon_p)^{4k}} = 1 - p.$$

We thus only have to combine the above with Proposition E.2 for $\varepsilon = \varepsilon_p$ and $\alpha = \alpha_p$ to conclude that (E.9) is true with probability at least $1 - p$. \square

Remark E.5. For all $p \in [0, 1]$, we have taken $\alpha_p = \left(\frac{\varepsilon_p}{C_{\hat{n},d}} \right)^{\frac{1}{2}}$ in our proof. This means by Remark E.3 that the smoothing parameter presented in Eq. (E.8) is optimal.

From Corollary 2.7, we have that when $n_s \rightarrow +\infty$ and $N \rightarrow +\infty$, the error between our estimators and n_0 tends to 0 with probability 1. We also see that the rate at which we have this convergence is $\frac{1}{(n_s)^{\frac{1}{4}}}$ when $d = 1$, and $\frac{1}{(n_s)^{\frac{1}{8k}}}$ when $d = 2k$. Then, the number of simulations needed to have a good bound grows exponentially with the value of k . This is in accordance with what we have presented in Section 5.3.3. We emphasise that when $\hat{n}_0^{(d)} \in W^{m, \infty}(\mathbb{R})$, where $m \in \mathbb{N}^*$, it is possible to obtain a better rate of convergence by proceeding as in [3]. We do not obtain it here, as this would imply laborious computations that are not relevant here.

We now conclude this appendix with the following two remarks. They deal with the estimation of $C_{\hat{n},d}$, for all $d \in \{1, 2k\}$, when we want to use a smoothing parameter of the form given in (E.8) in practice.

Remark E.6. Recall (5.1) and assume that $n_0 = h_{1,\beta}$, where $\beta > 0$. Then, we have by (E.4), Proposition A.9-(c), and the change of variable $y = \beta_{N,d} x$, that for all $d \in \{2, k\}$

$$C_{\hat{n},d} = \sup_{x \geq 0} \left[\left(-(\beta_{N,d} x)^2 + \beta_{N,d} x \right) \exp(-\beta_{N,d} x) \right] = \sup_{y \geq 0} \left[\left(-y^2 + y \right) \exp(-y) \right]. \tag{E.13}$$

Remark E.7. Recall (5.1) and assume that $n_0 = h_{\ell, \beta}$, where $\ell \in \mathbb{N}^*$ and $\beta > 0$. Denote for all $f \in L^1(\mathbb{R}_+)$ the quantity $\psi(f) = \frac{\left(\int_0^{+\infty} xf(x)dx\right)^2}{\int_0^{+\infty} x^2 f(x)dx - \left(\int_0^{+\infty} xf(x)dx\right)^2}$. Then, when $d = 1$, we can estimate α_p for a chosen $p \in (0, 1)$ by using the following conjecture

$$C_{\hat{n}, 1} \approx \frac{1}{\Gamma(\hat{\ell})} \sup_{y \geq 0} \left[\left| \hat{\ell} y^{\hat{\ell}} - y^{\hat{\ell}+1} \right| e^{-y} \right], \quad (\text{E.14})$$

where $\hat{\ell} := \psi(n_{\partial}^{(1)})$. The above comes from the fact that in view of (E.4), Theorem 2.6-(a), and the change of variable $y = \beta x$, we can conjecture that

$$C_{\hat{n}, 1} \approx \left\| Id^2(n_0)' + Idn_0 \right\|_{L^\infty(\mathbb{R}_+)} = \sup_{x \geq 0} \left[\left| \frac{\ell(\beta x)^\ell}{\Gamma(\ell)} - \frac{(\beta x)^{\ell+1}}{\Gamma(\ell)} \right| e^{-\beta x} \right] = \sup_{y \geq 0} \left[\left| \frac{\ell y^\ell}{\Gamma(\ell)} - \frac{y^{\ell+1}}{\Gamma(\ell)} \right| e^{-y} \right].$$

Then, as by the right-hand side of (A.25), the right-hand side of (3.6) (combined with a change of variable) and Proposition 3.2-(b) it holds $\ell = \psi(n_0) = \psi(u_{\partial}^{(1)}) \approx \psi(n_{\partial}^{(1)}) = \hat{\ell}$, we obtain (E.14). Obtaining a rigorous justification for this may be part of future work.