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Dynamics of a kinetic model describing protein transfers in a cell population

PIERRE MAGAL^(a) AND GAËL RAOUL^(b)

^(a)*University of Bordeaux, IMB, UMR CNRS 5251, 33076 Bordeaux, France.*

^(b)*CMAP, Ecole Polytechnique, CNRS, Université Paris-Saclay, Route de Saclay, 91128 Palaiseau cedex, France.*

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Abstract

We consider a cell population structured by a positive real number $x \in \mathbb{R}_+$, which represents the number of P-glycoproteins carried by the cell. Those proteins combine two interesting properties: they are involved in the resistance of cancer cells to chemotherapy drugs, and the cells proceed to frequent transfers of those proteins. In this article, we introduce a kinetic model to describe the dynamics of the cell population. We then consider an asymptotic limit of this equation: if transfers are frequent, the population can be described through a system of two coupled ordinary differential equations. Finally, we show that the solutions of the kinetic model converge to a unique steady-state in large times. The main idea of this manuscript is to combine Wasserstein distance estimates on the kinetic operator to more classical estimates on the macroscopic quantities.

Keywords: structured population, transfer operator, asymptotic analysis, macroscopic limit, Wasserstein estimates, mathematical ecology.

MSC 2000 subject classification: 35B40, 92D15, 92D25, 92D40.

1 Introduction

In this study, we are interested a population of cells structured by a trait $x \in \mathbb{R}_+$, which measures the quantity of P-glycoprotein (P-gp) carried by the cell. The P-gp are membrane proteins that play an important role in tumors. Cells transfer their P-gp to one another [23, 30, 31], and experiments show that those transfers have a significant effect on the number of P-gp that the cells carry. These features motivate the modelling of both the birth-death and transfer processes. The mathematical estimates and metrics adapted to the birth-death operator and to the transfer operator are of a different nature, and the challenge of this study is to combine those two types of approaches. Note that the transfer phenomenon that we model and analyse in this manuscript are related to other biological, physical and economical phenomena, and we believe that the new mathematical methods that we introduce here will also be useful in other contexts.

In [22], a model was proposed to model the transfer of P-gp in a cell population. The authors study the dynamics of the population, under the following assumption on the nature of transfers: if two cells carrying originally $x_1, x_2 \in \mathbb{R}_+$ P-gp interact, they end up with respectively $x'_1 = x_1 + f(x_2 - x_1)$ and $x'_2 = x_2 - f(x_2 - x_1)$ P-gp, where $f \in (0, 1)$ is a parameter of the model. After the derivation of this transfer operator, the authors show the existence of solutions for the model (where only transfers are present), and prove that all solutions converge to a Dirac mass (in other words, all the individuals ultimately carry the same number of P-gp). The transfer operator that we consider in this study is an extension of their work, when we assume that the cells do not exchange any information: the number of P-gp a cell sends to its transfer partner only depends on the number of P-gp it originally carries. This assumption has a direct impact on the dynamics of the population: a population where all cells carry the same number of P-gp would be quickly destabilized (in an exchange between two cells containing an equal number of P-gp, it is likely that one cell will send more of its P-gp than the other). This new transfer kernel assumption makes the analysis of the dynamics of the solution more delicate: the methods developed in [22] cannot be extended to our problem.

To analyse the dynamics of the population, we will take advantage of an entropy functional introduced by Tanaka in 1978 for the Boltzmann equation [34]. This functional describes a contracting effect of the equation’s flow, and allows the author to describe the long-time dynamics of solutions. In [10], this idea was extended to inelastic Boltzmann equations. We show (see Section 3.1 and Section 6.2) that estimates similar to the estimates developed in [34, 10] can be obtained for the transfer operator appearing in (7). In the case of the W_2 –Wasserstein distance, the operator decreases strictly the distance between solutions, while for the W_1 –Wasserstein distance, the operator cannot increase the distance between solutions (but it is not a strict contraction). The methods employed in our study are indeed related to another set of distances between probability measures, based on the Fourier transform. Those methods were introduced in [8, 9], and we refer to [14] for a review of the relations of those metrics to Wasserstein distances. Those Fourier-based arguments have proven useful to study the properties of the Boltzmann equation in the Maxwellian case, and they could probably also be used to study the dynamics of (7). The Fourier-based distance was used to study a range of models from econometrics [6] and opinion formation theory. In [3], an large class of transfer operators similar to the one we describe here was introduced. Using probability methods and Fourier-based distances, the authors were able to prove that those operators (and in particular the transfer operator we consider in the present study) imply a contraction.

This article is structured as follows: in Section 2, we build the model (see (7)) from biological considerations. We detail in particular the derivation of the transfer operator. Then, in Section 2.3, we state the two main results of this study: an asymptotic limit of the kinetic model when the frequency of transfers is high, and the long time convergence of the solutions of the kinetic model to a unique equilibrium. In section 3, we prove the first result of our study, namely Theorem 2.2. The proof is based on the contraction property of the transfer operator for the W_2 –Wasserstein distance. Section 4 is devoted to the second important result of this study, that is Theorem 2.3. The proof of this second result is based on the W_1 –Wasserstein distance. Finally, in the Appendix (see Section 6), we recall the definition of Wasserstein distances and some properties of those metric that we will use throughout this study. We also show how the the W_2 –Wasserstein distance contraction implied by the transfer operator can be used to study the long-time dynamics of the population when the other terms in the model have a simple structure.

2 Model and main results

We assume that all the cells are genetically identical: the trait x , corresponding to the quantity of P-gp on the membrane of the cell, is not transmitted from a mother cell to the daughter cells (no heritability of the trait). We can then assume that the traits of new born cells are drawn from a given distribution independent from the trait of the parent (we discuss possible generalizations of this model in the discussion, see Section 5). We assume that the trait of an individual has an effect on its reproduction rate. This is indeed the case when some chemotherapy drugs are present in the environment of the cells: the P-gp pump cytotoxic drugs out of the cells [32]. The P-gp thus play an important role in the emergence of chemotherapy resistance in tumor cell populations, and in certain conditions the cancer carrying a large number of P-gp can duplicate despite the presence of cytotoxic drugs.

2.1 Derivation of the transfer operator

To model transfers of P-gp, we assume that when two cells (the cell 1 and the cell 2) interact, no information is exchanged: the cell 1 does not know how many P-gp the cell 2 carries. The number of P-gp the cell 1 sends to the cell 2 thus only depends on its own number of P-gp. If we denote by x_i (resp x'_i) the number of P-gp the cell i contains before (resp. after) the transfer, and X_i the number of P-gp the cell i sends to the other cell, we have the relation:

$$x'_1 = x_1 - X_1 + X_2. \tag{1} \quad \{\mathbf{xX}\}$$

We have assumed that the number of pumps the cell 1 sends to the cell 2 only depends on x_1 , so that the law of X_1 only depends on x_1 . To simplify notations, we describe the law of X_1 by a density of probability $x \mapsto \mathcal{B}(x, x_1)$ that only depends on x_1 . Note that we allow the law of X_1 to be a measure with singular parts, even though we denote $\mathcal{B}(x, x_1)$ as if it were a function throughout this manuscript.

To be consistent biologically, a cell cannot give a negative number of pumps, or more pumps than it originally had, that is

$$\forall x_1 \in \mathbb{R}_+, \quad \text{supp } \mathcal{B}(\cdot, x_1) \subset [0, x_1]. \quad (2) \quad \{\text{condbio1}\}$$

Thanks to (1), we can relate the law of x'_1 , that we denote by $K(\cdot, x_1, x_2)$, to the laws of X_1 and X_2 :

$$\int_0^x K(y, x_1, x_2) dy = \mathbb{P}(x'_1 \leq x | x_1, x_2) = \int_0^{x_1} \left(\int_0^{x-x_1+w} \mathcal{B}(z, x_2) dz \right) \mathcal{B}(w, x_1) dw,$$

that is, thanks to a derivation in x

$$K(x, x_1, x_2) = \int_0^{x_1} \mathcal{B}(x - x_1 + w, x_2) \mathcal{B}(w, x_1) dw.$$

We can check that $\text{supp } K(\cdot, x_1, x_2) \subset [0, x_1 + x_2]$, and

$$\begin{aligned} \int_0^{x_1+x_2} K(x, x_1, x_2) dx &= \int_0^{x_1} \mathcal{B}(w, x_1) \int_0^{x_1+x_2} \mathcal{B}(x - x_1 + w, x_2) dx dw \\ &= \int_0^{x_1} \mathcal{B}(w, x_1) \int_{x_1-w}^{(x_1-w)+x_2} \mathcal{B}(x - x_1 + w, x_2) dx dw = 1. \end{aligned}$$

We further assume that the law of the number of P-gp the cell 1 (resp. 2) sends to the cell 2 (resp. 1) is proportional to the number of P-gp it originally contained, that is, for $y \in [0, x]$,

$$\mathcal{B}(y, x) = \frac{1}{x} B\left(\frac{y}{x}\right), \quad B \in \mathcal{P}([0, 1]) \cap C^0([0, 1]). \quad (3) \quad \{\text{Ass-B}\}$$

Note that in this study, we assume that $B \in \mathcal{P}([0, 1]) \cap C^0([0, 1])$ is a probability density, and we may extend it into $B \in \mathcal{P}([0, 1])$ with $B(x) = 0$ for $x > 1$. K is then given by

$$K(x, x_1, x_2) = \frac{1}{x_1 x_2} \int_0^{x_1} B\left(\frac{w}{x_1}\right) B\left(\frac{x - x_1 + w}{x_2}\right) dw. \quad (4) \quad \{\text{def:K1}\}$$

Since $B \in \mathcal{P}([0, 1]) \cap C^0([0, 1])$, this formula defines $K(x_1, x_2)$ as a continuous probability distribution as soon as $x_1 > 0$ and $x_2 > 0$. In this manuscript, we will consider solutions of the model that do not have mass in the singleton $\{0\}$, to avoid the technical difficulty of defining K for $x_1 = 0$ and/or $x_2 = 0$ (it should then be defined as a measure even if B is a continuous function). We refer to [24] for an analysis of the transfer operator in full generality. For $x_1, x_2 > 0$, a convenient way to write the operator K is as follows:

$$K(x, x_1, x_2) = \frac{1}{x_1 x_2} \int_0^{x_2} \int_0^{x_1} \delta_{x=x_1-y_1+y_2} B\left(\frac{y_1}{x_1}\right) B\left(\frac{y_2}{x_2}\right) dy_1 dy_2. \quad (5) \quad \{\text{def:K2}\}$$

2.2 Derivation of the model

As mentioned previously, we consider a population of cells that is well-mixed and where all the cells are genetically identical. Cells can however differ by the number x of P-gp they carry (the phenotype x is *plastic*). The population is thus structured by the trait $x \in \mathbb{R}_+$, and we denote by $n = n(t, x)$ the density of the population at time $t \geq 0$ along the trait $x \in \mathbb{R}_+$.

We assume that the P-gp are only produced at birth, in a quantity that is drawn from a given distribution $n_b \in \mathcal{P}([0, 1])$. We assume that there is no heritability of this trait (the Heritability Index is 0), this distribution is then independent from the trait of the parent. We assume however that the birth rate of a cell depends on its trait x : as described in the introduction, the P-gp are membrane proteins that pump chemotactic drugs out of the cell. If some drugs are present in the cell culture, the fitness of an individual depends on the number of pumps it carries. We assume that the fitness of an individual is given by $r + \alpha(x)$, where $\alpha \in W^{1,\infty}(\mathbb{R}_+)$. The rate of births of individuals with trait $x \in \mathbb{R}_+$ in the population is then

$$\left(\int_0^\infty (r + \alpha(y)) n(t, y) dy \right) n_b(x) = \left(r + \int_0^\infty \alpha(y) \frac{n(t, y)}{N(t)} dy \right) N(t) n_b(x),$$

where

$$N(t) := \int_0^\infty n(t, z) dz. \quad (6) \quad \{\text{def:N}\}$$

We assume that the death rate $\beta N(t)$ of individual cells does not depend on their trait $x \in \mathbb{R}_+$ and is proportional to the total population size $N(t)$. This assumption leads to the classical logistic regulation model, with the following rate of deaths of individuals with trait $x \in \mathbb{R}_+$:

$$-\beta N(t)n(t, x).$$

During its lifetime, each cell will proceed to transfers at a rate $\gamma > 0$ independent of the size of the population (we assume that finding transfer partners is not a limiting factor). Moreover, we assume that the traits have no influence on the selection of the transfer partner, which is chosen uniformly among the population. Considering the transfer operator described in Section 2.1, the effect of the transfers can then be represented as follows:

$$\gamma \left(\frac{1}{N(t)} \int_0^\infty \int_0^\infty K(\cdot, x_1, x_2) n(t, x_1) n(t, x_2) dx_1 dx_2 - n(t, \cdot) \right).$$

Bringing all those terms together, we obtain the following model:

$$\begin{aligned} \partial_t n(t, x) = & \left(r + \int_0^\infty \alpha(y) \frac{n(t, y)}{N(t)} dy \right) N(t) n_b(x) - \beta N(t) n(t, x) \\ & + \gamma \left(\frac{1}{N(t)} \int_0^\infty \int_0^\infty K(x, x_1, x_2) n(t, x_1) n(t, x_2) dx_1 dx_2 - n(t, x) \right), \end{aligned} \quad (7) \quad \{\text{eq:model-rep}\}$$

where $r, \beta, \gamma > 0$, $\alpha \in W^{1,\infty}(\mathbb{R}_+)$, K is defined by (5), and the population size $N(t)$ is given by (6).

In this study, we have chosen to focus our attention on the dynamics of solutions, rather than their existence and uniqueness. We will therefore assume that B is continuous, and state the results for any solution that is C^1 in time and L^1 in x . The last term of (7) is then well defined and these are solution if they satisfy (7) holds as an pointwise equality between continuous functions. We believe the results we develop here can be extended to more general cases, where B is a probability measure.

If $\text{supp } B \subset [\delta, 1]$ for some $\delta > 0$ and if n_b is smooth, it should be possible to show the existence and uniqueness of solutions of (7) following the proof of Lemma 3.1 from [6]. The general case where B is a probability measure is considered in upcoming [24], as we will discuss in Section 5.

2.3 Main results

We will analyse the dynamics of solutions of (7) under the following assumption:

Assumption 1: Let $\beta > 0$ and $M > 0$. We consider:

- $B \in \mathcal{P}([0, 1]) \cap C^0([0, 1])$ and K as in (5).
- $\alpha \in W^{1,\infty}(\mathbb{R}_+)$ and $n_b \in \mathcal{P}_2(\mathbb{R}_+) \cap C^0(\mathbb{R}_+)$ with $\int_0^\infty x n_b(x) dx < M$.
- For $Z > 0$, we assume that there is a unique $\bar{u}_Z \in \mathcal{P}_2(\mathbb{R}_+) \cap L^1(\mathbb{R}_+)$ satisfying

$$\bar{u}_Z(x) = \int_0^\infty \int_0^\infty K(x, x_1, x_2) \bar{u}_Z(x_1) \bar{u}_Z(x_2) dx_1 dx_2, \quad x \in \mathbb{R}_+, \quad (8) \quad \{\text{eq:micro-equ}\}$$

such that $\int_0^\infty x \bar{u}_Z(x) dx = Z$.

We develop in the proposition below an argument indicating the existence and uniqueness of the distribution \bar{u}_Z for any $B \in \mathcal{P}([0, 1]) \cap C^0([0, 1])$. To do so, however, we apply the transfer operator T (see (17)) to measures. It is not obvious to extend the definition of T to measures and it is beyond the scope of this manuscript: it is an interesting argument, but it is technical and more remote from biological considerations, which is why we chose to do so in a different manuscript, see [24]. We provide below a heuristic result, that should become rigorous with a proper definition of the transfer operator acting on measures.

Proposition 2.1 (Heuristic proof only). *Let T defined by (17), with $B \in \mathcal{P}([0, 1]) \cap C^0([0, 1])$, and $Z \in \mathbb{R}_+$. There exists a unique probability measure $\bar{u}_Z \in \mathcal{P}_2(\mathbb{R}_+) \cap L^1(\mathbb{R}_+)$ such that*

$$T(\bar{u}_Z) = \bar{u}_Z \quad \text{and} \quad \int_0^\infty x \bar{u}_Z(x) dx = Z.$$

Moreover there exists $C > 0$ such that for any $Z_1, Z_2 \geq 0$,

$$W_2(\bar{u}_{Z_1}, \bar{u}_{Z_2}) \leq C|Z_1 - Z_2|, \quad (9) \quad \{\text{eq:different}\}$$

and $W_2(\bar{u}_{Z_1}, \delta_0) \leq C|Z_1|$.

An explicit expression for \bar{u}_Z is known for \bar{u}_Z in a few particular cases only, see [4]. We will see that despite the non-explicit nature of the steady-states of the transfer operator T , a rigorous macroscopic asymptotic limit of the model (7) can be built. Note also that a numerical approach could be used to compute approximations of the profiles \bar{u}_Z .

In the theorem below, we provide an asymptotic limit of the model (7): we show that when $\gamma > 0$ is large, the macroscopic quantities $N(t)$ (defined by (6)) and

$$Z(t, x) = \int_0^\infty \frac{n(t, x)}{N(t)} dx, \quad (10) \quad \{\text{def:Z}\}$$

are close to solutions of the following ordinary differential equation:

$$\begin{cases} \bar{N}'(t) = (r + \int_0^\infty \alpha(x) \bar{u}_{\bar{Z}(t)}(x) dx - \beta \bar{N}(t)) \bar{N}(t), \\ \bar{Z}'(t) = (r + \int_0^\infty \alpha(x) \bar{u}_{\bar{Z}(t)}(x) dx) (\int_0^\infty x n_b(x) dx - \bar{Z}(t)), \end{cases} \quad (11) \quad \{\text{eq:EDO}\}$$

where \bar{u}_Z is the unique solution of (8) such that $\int_0^\infty x \bar{u}_Z(x) dx = Z$. The theorem below also shows that the distribution of $x \mapsto n(t, x)$ is well approximated by $n(t, x) \sim \bar{N}(t) \bar{u}_{\bar{Z}(t)}$ when $\gamma > 0$ is large.

Theorem 2.2. *Let $\beta, M, B, K, \alpha, n_b$ and \bar{u}_Z (for $Z \geq 0$) satisfying Assumption 1. We assume that the initial population $n^0 \in C^0(\mathbb{R}_+)$ satisfies $\int x^2 n^0(x) dx < M$, and define $t \mapsto (\bar{N}(t), \bar{Z}(t)) \in (\mathbb{R}_+)^2$ as the solution of (11), with*

$$(\bar{N}(0), \bar{Z}(0)) = \left(\int_0^\infty n^0(x) dx, \int_0^\infty \frac{x n^0(x)}{\int_0^\infty n^0(x) dx} dx \right).$$

There are $C > 0$ and $\zeta > 0$ such that if $\gamma > 0$ is large enough and if $n = n(t, x) \in C^1(\mathbb{R}_+, L^1(\mathbb{R}_+))$ is a solution of (7) with initial value n^0 , then,

$$\forall t \geq 0, \quad W_2 \left(\frac{n(t, \cdot)}{N(t)}, \bar{u}_{\bar{Z}(t)} \right) \leq \frac{C}{\sqrt{\gamma}} + C e^{-\zeta \gamma t}, \quad |N(t) - \bar{N}(t)| + |Z(t) - \bar{Z}(t)| \leq \frac{C}{\gamma^\zeta}, \quad (12) \quad \{\text{eq:distance-}\}$$

where $N(t) = \int_0^\infty n(t, x) dx$, $Z(t, x) = \int_0^\infty \frac{n(t, x)}{N(t)} dx$, and $\bar{u}_{\bar{Z}(t)}$ is defined by (8).

The proof of this theorem is given in Section 3.3. Theorem 2.2 shows that the dynamics of solutions of (7) can be described by the system of two coupled ordinary differential equations (11), provided $\gamma > 0$ is large. One consequence is that the two first moments of the population, that is $N(t)$ and $Z(t)$, are sufficient to describe its distribution when $\gamma > 0$ is large, which is an interesting property of the population. Indeed, we observe in (11) that the growth rate of the population only depends on the population size and the mean number of PgP, while the dynamics of the mean number of PgP, that is $Z(t)$ can be approximated by a closed relaxation differential equation.

In Theorem 2.2, we show that the population, for $\gamma > 0$ and $t > 0$ large, is close to $\bar{u}_{\int_0^\infty n_b(x) dx}$. However, it does not show the convergence of the population to a steady-state when $t \rightarrow \infty$, when $\gamma > 0$ is large but fixed. Obtain such a convergence would complete the analysis of the dynamics of the model. A strong asymptotic theory for such models could unlock of models related to (7) (see [18]) and allow us to use these as building blocks for complex biological models. We have not succeeded to DEVELOP the approach introduced in Theorem 2.2, based on a meso-macro decomposition and on the W_2 distance, to prove the long time convergence of solutions. We show below that it is possible to use a different idea, based on the Wasserstein distance W_1 , to prove this convergence. We believe however that this W_1 approach is less flexible. It however shows how Wasserstein approaches can be used to obtain long time convergence of solutions in non-linear biological models:

Theorem 2.3. Let $\beta, M, B, K, \alpha, n_b$ and u_Z (for $Z \geq 0$) satisfying Assumption 1. Let $\gamma > 0$ and

$$\kappa := r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)} > 0,$$

If $n = n(t, x) \in C^1(\mathbb{R}_+, L^1(\mathbb{R}_+))$ is a solution of (7) such that $\int x n(0, x) dx < M$, then it converges to a limit $\bar{N}\bar{n}$, with $\bar{N} > 0$ and $\bar{n} \in \mathcal{P}_2(\mathbb{R}_+)$, as $t \rightarrow \infty$ for the weak-* topology of measures over \mathbb{R}_+ . More precisely, there exists a constant $C > 0$ such that

$$\forall t \geq 0, \quad W_1 \left(\frac{n(t, \cdot)}{N(t)}, \bar{n} \right) \leq C e^{-\kappa t}, \quad |N(t) - \bar{N}| \leq C e^{-\min(\kappa, \frac{\beta \bar{N}}{4})t},$$

where $N(t) = \int_0^\infty n(t, x) dx$.

Remark 2.4. Note that the limit $\bar{N}\bar{n}$ of the solution n is actually a steady-solution of (7), but since it could be measure-valued, we do not define it as such here. The argument (52) in the proof of this Theorem actually shows that this limit is unique and independent from the solution n and its initial condition.

This theorem is proven in Section 4. This proof relies on the convergence of the renormalized function $t \mapsto \frac{n(t, \cdot)}{\int_0^\infty n(t, x) dx}$ for the Wasserstein distance W_1 . This convergence can then be used to prove the convergence of $N(t)$. The method employed in the proof is more specific to (7) than Theorem 2.2: it relies on the fact that the distribution of $n_b(\cdot)$ is not affected by the solution, and on the fact that the transfer operator is a contraction (although not a strict contraction, as it is with W_2) for the transfer operator.

2.4 Equations satisfied by moments of n

For $t \geq 0$, we define $N(t)$, by (6), $Z(t)$ by (10) and $Z(t), \tilde{n}(t, x)$ by

$$\tilde{n}(t, x) := \frac{n(t, x)}{N(t)}. \tag{13} \quad \{\text{def:tilden}\}$$

We can integrate the equation (7) to get the following equation on N :

$$\frac{d}{dt} N(t) = \left(r + \int_0^\infty \alpha(x) \tilde{n}(t, x) dx - \beta N(t) \right) N(t). \tag{14} \quad \{\text{eq:N2}\}$$

We derive next an equation on \tilde{n} :

$$\begin{aligned} \partial_t \tilde{n}(t, x) &= \frac{1}{N(t)} \partial_t n(t, x) - \frac{n(t, x)}{N(t)^2} N'(t) \\ &= \left(r + \int_0^\infty \alpha(y) \tilde{n}(t, y) dy \right) (n_b(x) - \tilde{n}(t, x)) \\ &\quad + \gamma \left[\int_0^\infty \int_0^\infty K(x, x_1, x_2) \tilde{n}(t, x_1) \tilde{n}(t, x_2) dx_1 dx_2 - \tilde{n}(t, x) \right]. \end{aligned} \tag{15} \quad \{\text{eq:model-tild}\}$$

We notice next that $Z(t) = \int_0^\infty x \tilde{n}(t, x) dx$ and (15) then implies

$$\frac{d}{dt} Z(t) = \int_0^\infty x \partial_t \tilde{n}(t, x) dx = \left(r + \int_0^\infty \alpha(x) \tilde{n}(t, x) dx \right) (Z_b - Z(t)), \tag{16}$$

where $Z_b := \int_0^\infty x n_b(x) dx$.

3 A macroscopic limit for the model (7)

The estimates we derive on the transfer operator (Section 4.1) and on the pure transfer model (Section 4.2) have been considered for related models in e.g. [6] and [3], using different methods: Fourier transform techniques or probabilistic tools. We have chosen to derive all the necessary estimates required to prove Theorem 2.2 using Wasserstein distance methods.

3.1 The W_2 -distance contraction implied by the transfer operator

Let $T : \mathcal{P}_2(\mathbb{R}_+) \rightarrow \mathcal{P}_2(\mathbb{R}_+)$ the transfer operator: for $u \in \mathcal{P}_2(\mathbb{R}_+)$,

$$T(u)(x) = \int_0^\infty \int_0^\infty K(x, x_1, x_2) u(x_1) u(x_2) dx_1 dx_2, \quad (17) \quad \{\text{def:exchange}\}$$

where K is defined by (5). To understand the effect of T , we will use the following technical lemma:

Lemma 3.1. *Let $x_1, x_2, x'_1, x'_2 \in \mathbb{R}_+^*$, and K as in (5). We define $\lambda_1, \lambda_2 \in [0, 1]$ as*

$$\lambda_1 := \int_0^1 xB(x) dx, \quad \lambda_2 := \int_0^1 x^2B(x) dx. \quad (18) \quad \{\text{def:lambdai}\}$$

We have

$$\begin{aligned} W_2^2\left(K(\cdot, x_1, x_2), K(\cdot, x'_1, x'_2)\right) &\leq (1 + \lambda_2 - 2\lambda_1)(x_1 - x'_1)^2 + \lambda_2(x_2 - x'_2)^2 \\ &\quad + 2(1 - \lambda_1)\lambda_1(x_1 - x'_1)(x_2 - x'_2). \end{aligned} \quad (19) \quad \{\text{eq:KW2}\}$$

Proof of Lemma 3.1. To estimate the Wasserstein distance $W_2^2\left(K(\cdot, x_1, x_2), K(\cdot, x'_1, x'_2)\right)$, we will use the Kantorovich dual formula. We consider $(\varphi, \psi) \in \Phi_2$ (see (57)), and estimate

$$\begin{aligned} I &= \int_0^\infty \varphi(x) K(x, x_1, x_2) dx + \int_0^\infty \psi(X) K(X, x'_1, x'_2) dX \\ &= \int_0^\infty \varphi(x) \int_0^{x_2} \int_0^{x_1} \delta_{x=x_1-y_1+y_2} \frac{1}{x_1x_2} B\left(\frac{y_1}{x_1}\right) B\left(\frac{y_2}{x_2}\right) dy_1 dy_2 dx \\ &\quad + \int_0^\infty \psi(X) \int_0^{x_2} \int_0^{x_1} \delta_{X=x'_1-y'_1+y'_2} \frac{1}{x'_1x'_2} B\left(\frac{y'_1}{x'_1}\right) B\left(\frac{y'_2}{x'_2}\right) dy'_1 dy'_2 dX \\ &= \int_0^{x_2} \int_0^{x_1} \varphi(x_1 - y_1 + y_2) \frac{1}{x_1x_2} B\left(\frac{y_1}{x_1}\right) B\left(\frac{y_2}{x_2}\right) dy_1 dy_2 \\ &\quad + \int_0^{x'_2} \int_0^{x'_1} \psi(x'_1 - y'_1 + y'_2) \frac{1}{x'_1x'_2} B\left(\frac{y'_1}{x'_1}\right) B\left(\frac{y'_2}{x'_2}\right) dy'_1 dy'_2, \end{aligned}$$

and then, thanks to the changes of variable $\tilde{y}_i = \frac{y_i}{x_i}$ and $\tilde{y}'_i = \frac{y'_i}{x'_i}$ for $i = 1, 2$, we get

$$\begin{aligned} I &= \int_0^1 \int_0^1 \varphi(x_1 - x_1y_1 + x_2y_2) B(y_1) B(y_2) dy_1 dy_2 \\ &\quad + \int_0^1 \int_0^1 \psi(x'_1 - x'_1y'_1 + x'_2y'_2) B(y'_1) B(y'_2) dy'_1 dy'_2 \\ &= \int_0^1 \int_0^1 (\varphi(x_1 - x_1y_1 + x_2y_2) + \psi(x'_1 - x'_1y_1 + x'_2y_2)) B(y_1) B(y_2) dy_1 dy_2. \end{aligned} \quad (20)$$

Since $(\varphi, \psi) \in \Phi_2$ (see (57)), we have

$$\begin{aligned} I &\leq \int_0^1 \int_0^1 |(x_1 - x_1y_1 + x_2y_2) - (x'_1 - x'_1y_1 + x'_2y_2)|^2 B(y_1) B(y_2) dy_1 dy_2 \\ &= \int_0^1 \int_0^1 |(x_1 - x'_1)(1 - y_1) + (x_2 - x'_2)y_2|^2 B(y_1) B(y_2) dy_1 dy_2 \\ &= \int_0^1 \int_0^1 \left((x_1 - x'_1)^2(1 - y_1)^2 + (x_2 - x'_2)^2y_2^2 + 2(x_1 - x'_1)(x_2 - x'_2)(1 - y_1)y_2 \right) \\ &\quad B(y_1) B(y_2) dy_1 dy_2 \\ &= (x_1 - x'_1)^2 \int_0^1 (1 - y_1)^2 B(y_1) dy_1 + (x_2 - x'_2)^2 \int_0^1 y_2^2 B(y_2) dy_2 \\ &\quad + 2(x_1 - x'_1)(x_2 - x'_2) \left(\int_0^1 (1 - y_1) B(y_1) dy_1 \right) \left(\int_0^1 y_2 B(y_2) dy_2 \right), \end{aligned}$$

and then, with the notations (18),

$$I \leq (x_1 - x'_1)^2(1 + \lambda_2 - 2\lambda_1) + (x_2 - x'_2)^2\lambda_2 + 2(x_1 - x'_1)(x_2 - x'_2)(1 - \lambda_1)\lambda_1.$$

Since this is true for any $(\varphi, \psi) \in \Phi_2$ (see (57)), we can use this estimate and (56) to show that

$$\begin{aligned} W_2^2\left(K(\cdot, x_1, x_2), K(\cdot, x'_1, x'_2)\right) &= \max_{(\varphi, \psi) \in \Phi_2} I \\ &\leq (1 + \lambda_2 - 2\lambda_1)(x_1 - x'_1)^2 + \lambda_2(x_2 - x'_2)^2 + 2(1 - \lambda_1)\lambda_1(x_1 - x'_1)(x_2 - x'_2). \end{aligned}$$

□

We can now prove the following result, which provides an explicit estimate of the W_2 -Wasserstein distance contraction implied by the transfer operator T :

Proposition 3.2. *Let T defined by (17), with $B \in \mathcal{P}([0, 1]) \cap C^0([0, 1])$. Then, for any $u_1, u_2 \in \mathcal{P}_2(\mathbb{R}_+)$ we have*

$$W_2(T(u_1), T(u_2)) \leq \frac{3}{2}W_2(u_1, u_2). \quad (21) \quad \{\text{eq:estW2gene}\}$$

Moreover, if

$$\int_0^\infty xu_1(x) dx = \int_0^\infty xu_2(x) dx, \quad (22) \quad \{\text{eq:1ermoment}\}$$

we have

$$W_2(T(u_1), T(u_2)) \leq \left(1 + 2 \int_0^1 x(x-1)B(x) dx\right)^{\frac{1}{2}} W_2(u_1, u_2), \quad (23) \quad \{\text{eq:estK1}\}$$

Moreover,

$$\left(1 + 2 \int_0^1 x(x-1)B(x) dx\right)^{\frac{1}{2}} < 1.$$

Proof of Proposition 3.2. We want to estimate the W_2 distance between $T(u_1)$ and $T(u_2)$ thanks to (56). We consider $(\varphi, \psi) \in \Phi_2$, and estimate

$$\begin{aligned} I &:= \int_0^\infty \varphi(x)T(u_1)(x) dx + \int_0^\infty \psi(X)T(u_2)(X) dX \\ &= \int_0^\infty \varphi(x) \int_0^\infty \int_0^\infty K(x, x_1, x_2)u_1(x_1)u_1(x_2) dx_1 dx_2 dx \\ &\quad + \int_0^\infty \psi(X) \int_0^\infty \int_0^\infty K(X, x'_1, x'_2)u_2(x'_1)u_2(x'_2) dx'_1 dx'_2 dX \\ &= \int_0^\infty \int_0^\infty \left(\int_0^\infty \varphi(x)K(x, x_1, x_2) dx\right) u_1(x_1)u_1(x_2) dx_1 dx_2 \\ &\quad + \int_0^\infty \int_0^\infty \left(\int_0^\infty \psi(X)K(X, x'_1, x'_2) dX\right) u_2(x'_1)u_2(x'_2) dx'_1 dx'_2 \end{aligned}$$

Since $u_1, u_2 \in \mathcal{P}_2(\mathbb{R}_+)$, we have $\int_0^\infty u_1(x)dx = \int_0^\infty u_2(x)dx = 1$ and then

$$\begin{aligned} I &= \int_0^\infty \int_0^\infty \int_0^\infty \int_0^\infty \left(\int_0^\infty \varphi(x)K(x, x_1, x_2) dx + \int_0^\infty \psi(X)K(X, x'_1, x'_2) dX\right) \\ &\quad u_1(x_1)u_1(x_2)u_2(x'_1)u_2(x'_2) dx_1 dx_2 dx'_1 dx'_2 \end{aligned}$$

Let now $\pi \in \Pi(u_1, u_2)$ (see (55)). The above equality can be rewritten as follow

$$\begin{aligned} I &= \int_{\mathbb{R}_+^2} \int_{\mathbb{R}_+^2} \left(\int_0^\infty \varphi(x)K(x, x_1, x_2) dx + \int_0^\infty \psi(X)K(X, x'_1, x'_2) dX\right) d\pi(x_1, x'_1) d\pi(x_2, x'_2) \\ &\leq \int_{\mathbb{R}_+^2} \int_{\mathbb{R}_+^2} W_2^2(K(\cdot, x_1, x_2), K(\cdot, x'_1, x'_2)) d\pi(x_1, x'_1) d\pi(x_2, x'_2), \end{aligned} \quad (24) \quad \{\text{est:L}\}$$

where we have used the fact that $(\varphi, \psi) \in \Phi_2$ as in formula (56). We now use the result of Lemma 3.1 (and the notations λ_1, λ_2 introduced in that lemma) to obtain

$$\begin{aligned}
I &\leq \int_{\mathbb{R}_+^2} \int_{\mathbb{R}_+^2} ((1 + \lambda_2 - 2\lambda_1)(x_1 - x'_1)^2 + \lambda_2(x_2 - x'_2)^2 + 2(1 - \lambda_1)\lambda_1(x_1 - x'_1)(x_2 - x'_2)) \\
&\quad d\pi(x_1, x'_1) d\pi(x_2, x'_2) \\
&\leq (1 + \lambda_2 - 2\lambda_1) \int_{\mathbb{R}_+^2} \left(\int_{\mathbb{R}_+^2} (x_1 - x'_1)^2 d\pi(x_1, x'_1) \right) d\pi(x_2, x'_2) \\
&\quad + \lambda_2 \int_{\mathbb{R}_+^2} \left(\int_{\mathbb{R}_+^2} (x_2 - x'_2)^2 d\pi(x_2, x'_2) \right) d\pi(x_1, x'_1) \\
&\quad + 2(1 - \lambda_1)\lambda_1 \left(\int_{\mathbb{R}_+^2} (x_1 - x'_1) d\pi(x_1, x'_1) \right) \left(\int_{\mathbb{R}_+^2} (x_2 - x'_2) d\pi(x_2, x'_2) \right). \tag{25} \quad \{\text{eq:different}\}
\end{aligned}$$

If the equality (22) holds,

$$\int_{\mathbb{R}_+^2} (x - x') d\pi(x, x') = \int_0^\infty xu_1(x) dx - \int_0^\infty xu_2(x) dx = 0, \tag{26} \quad \{\text{eq:different}\}$$

and then, since this estimate holds for any $(\varphi, \psi) \in \Phi_2$ and the right hand side is independent from (φ, ψ) , we can use the Kantorovich dual formula (56) to obtain

$$W_2^2(T(u_1), T(u_2)) \leq (1 + 2\lambda_2 - 2\lambda_1) \int_{\mathbb{R}_+^2} (x_1 - x'_1)^2 d\pi(x_1, x'_1).$$

Since this inequality holds for any $\pi \in \Pi(u_1, u_2)$ (with the notation Π introduced in (55)), we can take the minimum over such π , and get

$$\begin{aligned}
W_2^2(T(u_1), T(u_2)) &\leq (1 + 2\lambda_2 - 2\lambda_1) W_2^2(u_1, u_2) \\
&= \left(1 + 2 \int_0^1 x(x-1)B(x) dx \right) W_2^2(u_1, u_2).
\end{aligned}$$

Moreover, $\left(1 + 2 \int_0^1 x(x-1)B(x) dx \right)^{\frac{1}{2}} < 1$, since B is a continuous function and a probability distribution, and thus $1 + 2 \int_0^1 x(x-1)B(x) dx < 1 + 2 \int_0^1 \frac{1}{4}B(x) dx = 1$.

If the equality (22) does not hold, we can estimate the two last terms of (9) with a Cauchy-Schwarz inequality to show

$$I \leq ((1 + \lambda_2 - 2\lambda_1) + \lambda_2 + 2(1 - \lambda_1)\lambda_1) \int_{\mathbb{R}_+^2} (x_1 - x'_1)^2 d\pi(x_1, x'_1) \leq W_2^2(u_1, u_2),$$

where we have used $(1 + \lambda_2 - 2\lambda_1) + \lambda_2 = 1 + 2 \int_0^1 x(x-1)B(x) dx \leq 1$ and $2(1 - \lambda_1)\lambda_1 \leq 1/2$. This estimate proves (21) when we consider the maximum of I over $(\varphi, \psi) \in \Phi_2$. \square

3.2 Fixed points of the transfer operator: Heuristic proof of Proposition 2.1

In this section, we will apply the transfer operator T to probability measures. We have not extended the operator T to measures and our arguments in this section are thus not rigorous. We refer to [24] for an extension of T that would make the present argument rigorous.

Note that $\{u \in \mathcal{P}_2(\mathbb{R}_+); \int_0^\infty xu(x) dx = Z\}$ is a closed subset of $\mathcal{P}_2(\mathbb{R}_+)$ for W_2 and thus

$$\left(\left\{ u \in \mathcal{P}_2(\mathbb{R}_+); \int_0^\infty xu(x) dx = Z \right\}, W_2 \right) \tag{27} \quad \{\text{eq:setT}\}$$

is a complete metric space (see e.g. [36]). For any $u \in \mathcal{P}_2(\mathbb{R}_+)$, $\int_0^\infty T(u) dx = 1$ and $T(u) \geq 0$, that is $T(u)$ is a probability measure. Moreover,

$$\begin{aligned} \int_0^\infty x^2 T(u)(x) dx &= \int_0^\infty \int_0^\infty \left(\int_0^\infty x^2 K(x, x_1, x_2) dx \right) u(x_1) u(x_2) dx_1 dx_2 \\ &= \int_0^\infty \int_0^\infty \left(\int_0^{x_2} \int_0^{x_1} (x_1 - y_1 + y_2)^2 B\left(\frac{y_1}{x_1}\right) B\left(\frac{y_2}{x_2}\right) \frac{dy_1}{x_1} \frac{dy_2}{x_2} \right) u(x_1) u(x_2) dx_1 dx_2 \\ &= \int_0^\infty \int_0^\infty (x_1^2(1 + \lambda_2 - 2\lambda_1) + x_2^2\lambda_2 + 2x_1x_2(\lambda_1 - \lambda_1^2)) u(x_1) u(x_2) dx_1 dx_2 \\ &= \left(\int_0^\infty x^2 u(x) dx \right) (1 + 2\lambda_2 - 2\lambda_1) + 2Z^2(\lambda_1 - \lambda_1^2) < \infty. \end{aligned}$$

We can thus define T as an operator mapping $\mathcal{P}_2(\mathbb{R}_+)$ into itself. Moreover,

$$\begin{aligned} \int_0^\infty x T(u)(x) dx &= \int_0^\infty \int_0^\infty \left(\int_0^\infty x K(x, x_1, x_2) dx \right) u(x_1) u(x_2) dx_1 dx_2 \\ &= \int_0^\infty \int_0^\infty \left(\int_0^{x_2} \int_0^{x_1} (x_1 - y_1 + y_2) B\left(\frac{y_1}{x_1}\right) B\left(\frac{y_2}{x_2}\right) \frac{dy_1}{x_1} \frac{dy_2}{x_2} \right) u(x_1) u(x_2) dx_1 dx_2 \\ &= \int_0^\infty \int_0^\infty (x_1 - x_1\lambda_1 + x_2\lambda_1) u(x_1) u(x_2) dx_1 dx_2 = \int_0^\infty xu(x) dx = Z, \end{aligned}$$

for any $u \in \{u \in \mathcal{P}_2(\mathbb{R}_+); \int_0^\infty xu(x) dx = Z\}$. The application T therefore maps the set defined by (27) into itself. Finally, thanks to Proposition 3.2, the application is a strict contraction on this set for the distance W_2 . We can apply the Banach fixed point Theorem to show the existence of a unique measure $\bar{u} \in \{u \in \mathcal{P}_2(\mathbb{R}_+); \int_0^\infty xu(x) dx = Z\}$ such that $\bar{u} = T(\bar{u})$.

To prove (9), we can reproduce the proof of Proposition 3.2 until (25) with $u_1 := \bar{u}_{Z_1}$ and $u_2 := \bar{u}_{Z_2}$. Here, (26) becomes

$$\int_{\mathbb{R}^2} (x - x') d\pi(x, x') = \int_0^\infty xu_1(x) dx - \int_0^\infty xu_2(x) dx = Z_1 - Z_2,$$

and then, since this estimate holds for any $(\varphi, \psi) \in \Phi_2$, thanks to the Kantorovich dual formula (56),

$$W_2^2(T(\bar{u}_{Z_1}), T(\bar{u}_{Z_2})) \leq (1 + 2\lambda_2 - 2\lambda_1) \int_{\mathbb{R}^2} (x_1 - x'_1)^2 d\pi(x_1, x'_1) + 2(1 - \lambda_1)\lambda_1|Z_1 - Z_2|^2.$$

Since this inequality holds for any $\pi \in \Pi(\bar{u}_{Z_1}, \bar{u}_{Z_2})$ (with the notation of (55)), we can take the minimum over such π , and get

$$W_2^2(T(\bar{u}_{Z_1}), T(\bar{u}_{Z_2})) \leq (1 + 2\lambda_2 - 2\lambda_1)W_2^2(\bar{u}_{Z_1}, \bar{u}_{Z_2}) + 2(1 - \lambda_1)\lambda_1|Z_1 - Z_2|^2.$$

Since $T(u_1) = u_1 = \bar{u}_{Z_1}$ and $T(u_2) = u_2 = \bar{u}_{Z_2}$, this estimate implies

$$W_2^2(\bar{u}_{Z_1}, \bar{u}_{Z_2}) \leq \frac{(1 - \lambda_1)\lambda_1}{\lambda_1 - \lambda_2} |Z_1 - Z_2|^2,$$

and notice that $B \in C^0([0, 1])$ implies $\lambda_1 - \lambda_2 \neq 0$, and thus $\frac{(1 - \lambda_1)\lambda_1}{\lambda_1 - \lambda_2} < \infty$. Finally, we notice that $T(\delta_0) = \delta_0$, and then $W_2(\bar{u}_{Z_1}, \delta_0) \leq C|Z|$.

3.3 Macroscopic limit: Proof of Theorem 2.2

Step 1: Preliminaries

We recall the definition (6) of $N(t)$, (10) of $Z(t)$ and (13) of $\tilde{n}(t, x)$, as well as the equations (14), (16) and (15) they satisfy. Thanks to (14),

$$\forall t \geq 0, \quad 0 < \min\left(N(0), \frac{r}{\beta}\right) \leq N(t) \leq \max\left(N(0), \frac{r + \|\alpha\|_{L^\infty(\mathbb{R}_+)}}{\beta}\right), \quad \|N'(t)\|_{L^\infty(\mathbb{R}_+)} \leq C, \quad (28) \quad \{\text{eq:Nlifty}\}$$

where the constant $C > 0$ is independent of $\gamma > 0$. Moreover, (15) and a Duhamel formula can be used to show

$$\begin{aligned} \tilde{n}(t, x) &= \tilde{n}(0, x) e^{-(\gamma+r)t - \int_0^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \\ &+ \int_0^t e^{-(\gamma+r)(t-s) - \int_s^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \left[\left(r + \int_0^\infty \alpha(y) \tilde{n}(s, y) dy \right) n_b(x) + \gamma T(\tilde{n}(s, \cdot)) \right] ds, \end{aligned} \quad (29) \quad \{\text{eq:tildenduh}\}$$

where we have use the notation T introduced in (17). Since $\alpha \geq 0$ and thanks to (16), we have

$$\forall t \geq 0, \quad 0 < \min(Z(0), Z_b) \leq Z(t) \leq \max \left(\int_0^\infty x \frac{n(0, x)}{N(0)} dx, Z_b \right), \quad \|Z'(t)\|_{L^\infty(\mathbb{R}_+)} \leq C, \quad (30) \quad \{\text{eq:ZLinfy}\}$$

where the constant $C > 0$ is independent of $\gamma > 0$.

Step 2: Estimates on $W_2(\tilde{n}(t, \cdot), \bar{u}_{Z(t)})$

Since $\bar{u}_{Z(t)}$ is a fixed point of T (see Proposition 2.1), it satisfies

$$0 = - \left(\gamma + r + \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma \right) \bar{u}_{Z(t)} + \left(r + \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma \right) \bar{u}_{Z(t)} + \gamma T(\bar{u}_{Z(t)}),$$

for $t \geq 0$ and $\sigma \in [0, t]$. Then, for any $t \geq 0$, $\bar{u}_{Z(t)}$ satisfies a relation similar to (29):

$$\begin{aligned} \bar{u}_{Z(t)}(x) &= \bar{u}_{Z(t)}(x) e^{-(\gamma+r)t - \int_0^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \\ &+ \int_0^t e^{-(\gamma+r)(t-s) - \int_s^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \left[\left(r + \int_0^\infty \alpha(y) \tilde{n}(s, y) dy d\sigma \right) \bar{u}_{Z(t)} + \gamma T(\bar{u}_{Z(t)})(x) \right] ds. \end{aligned}$$

We consider $(\varphi, \psi) \in \Phi_2$, and estimate

$$I := \int_0^\infty \varphi(x) \tilde{n}(t, x) dx + \int_0^\infty \psi(X) \bar{u}_{Z(t)}(X) dX.$$

$$\begin{aligned} I &= e^{-(\gamma+r)t - \int_0^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \left(\int_0^\infty \varphi(x) \tilde{n}(0, x) dx + \int_0^\infty \psi(X) \bar{u}_{Z(t)}(X) dX \right) \\ &+ \int_0^t e^{-(\gamma+r)(t-s) - \int_s^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \left(r + \int_0^\infty \alpha(y) \tilde{n}(s, y) dy \right) \\ &\quad \left(\int_0^\infty \varphi(x) n_b(x) dx + \int_0^\infty \psi(X) \bar{u}_{Z(t)}(X) dX \right) ds \\ &+ \gamma \int_0^t e^{-(\gamma+r)(t-s) - \int_s^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \left(\int_0^\infty \psi(X) T(\tilde{n}(s, \cdot)) + \int_0^\infty \varphi(x) T(\bar{u}_{Z(t)})(X) dX \right) ds. \end{aligned}$$

We can now use the Kantorovich formula (56) to get:

$$\begin{aligned} I &\leq e^{-(\gamma+r)t - \int_0^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} W_2^2(\tilde{n}(0, \cdot), \bar{u}_{Z(t)}) \\ &+ \int_0^t e^{-(\gamma+r)(t-s) - \int_s^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} \left(r + \int_0^\infty \alpha(y) \tilde{n}(s, y) dy \right) W_2^2(n_b, \bar{u}_{Z(t)}) ds \\ &+ \gamma \int_0^t e^{-(\gamma+r)(t-s) - \int_s^t \int_0^\infty \alpha(y) \tilde{n}(\sigma, y) dy d\sigma} W_2^2(T(\tilde{n}(s, \cdot)), T(\bar{u}_{Z(t)})) ds. \end{aligned} \quad (31)$$

We notice that

$W_2(\tilde{n}(0, \cdot), \bar{u}_{Z(t)}) \leq W_2(\tilde{n}(0, \cdot), \delta_0) + W_2(\delta_0, \bar{u}_{Z(t)}) \leq C$, $W_2(n_b, \bar{u}_{Z(t)}) \leq W_2(n_b, \delta_0) + W_2(\delta_0, \bar{u}_{Z(t)}) \leq C$, since $W_2(\delta_0, f) = \int_{\mathbb{R}_+} x^2 f(x) dx$ and $\tilde{n}(0, \cdot)$, n_b and $\bar{u}_{Z(t)}$ have uniformly bounded second moments (see (9) and the uniform bound (30) on $Z(t)$). Furthermore,

$$\begin{aligned} W_2(T(\tilde{n}(s, \cdot)), T(\bar{u}_{Z(t)})) &\leq W_2(T(\tilde{n}(s, \cdot)), T(\bar{u}_{Z(s)})) + W_2(T(\bar{u}_{Z(s)}), T(\bar{u}_{Z(t)})) \\ &\leq (1 + 2\lambda_2 - 2\lambda_1) W_2(\tilde{n}(s, \cdot), \bar{u}_{Z(s)}) + \frac{3}{2} W_2(\bar{u}_{Z(s)}, \bar{u}_{Z(t)}), \end{aligned}$$

thanks to Proposition 3.2. (30) provides a uniform bound on $Z'(s)$, which combined to Proposition 2.1 implies

$$W_2(T(\tilde{n}(s, \cdot)), T(\bar{u}_{Z(t)})) \leq (1 + 2\lambda_2 - 2\lambda_1)^{1/2} W_2(\tilde{n}(s, \cdot), \bar{u}_{Z(s)}) + C|s - t|.$$

These inequalities can be used to estimate (31) further:

$$\begin{aligned} I &\leq C e^{-\gamma t} + C \int_0^t e^{-(\gamma+r)(t-s)} d\sigma \\ &\quad + \gamma \int_0^t e^{-(\gamma+r)(t-s)} \left((1 + 2\lambda_2 - 2\lambda_1)^{1/2} W_2(\tilde{n}(s, \cdot), \bar{u}_{Z(s)}) + C|t - s| \right)^2 ds \\ &\leq C e^{-\gamma t} + C \int_0^t e^{-(\gamma+r)(t-s)} d\sigma \\ &\quad + \gamma \int_0^t e^{-(\gamma+r)(t-s)} (1 + \lambda_2 - \lambda_1) W_2^2(\tilde{n}(s, \cdot), \bar{u}_{Z(s)}) + C|t - s|^2 ds, \end{aligned}$$

where we have used a Young inequality, that is $(a + b)^2 \leq (1 + 2\varepsilon)a^2 + (1 + 2/2\varepsilon)b^2$ and notice that $0 < \frac{(1+2\lambda_2-2\lambda_1)+1}{2} = (1 + \lambda_2 - \lambda_1) < 1$. Thanks to a change of variable, $\gamma \int_0^t e^{-(\gamma+r)(t-s)} |t - s|^2 ds \leq \frac{1}{\gamma^2} \int_0^\infty e^{-(\gamma s)} (\gamma s)^2 d(\gamma s) \leq \frac{C}{\gamma^2}$, and then, for $t \geq 0$,

$$I \leq C e^{-\gamma t} + \frac{C}{\gamma} + \gamma(1 + \lambda_2 - \lambda_1) \int_0^t e^{-\gamma(t-s)} W_2^2(\tilde{n}(s, \cdot), \bar{u}_{Z(s)}) ds + \frac{C}{\gamma^2}.$$

Thanks to the Wasserstein duality formula (56),

$$W_2^2(\tilde{n}(t, \cdot), \bar{u}_{Z(t)}) = \sup_{(\varphi, \psi) \in \Phi_2} \int_0^\infty \varphi(x) \tilde{n}(t, x) dx + \int_0^\infty \psi(X) \bar{u}_{Z(t)}(X) dX = \sup_{(\varphi, \psi) \in \Phi_2} I,$$

and then

$$W_2^2(\tilde{n}(t, \cdot), \bar{u}_{Z(t)}) \leq C e^{-\gamma t} + \frac{C}{\gamma} + (1 + \lambda_2 - \lambda_1) \int_0^t e^{-\gamma(t-s)} W_2^2(\tilde{n}(s, \cdot), \bar{u}_{Z(s)}) ds,$$

and we apply a Gronwall inequality (see [38], Theorem 1) to show, for $t \geq 0$,

$$\begin{aligned} W_2^2(\tilde{n}(t, \cdot), \bar{u}_{Z(t)}) &\leq C e^{-\gamma t} + \frac{C}{\gamma} + \gamma(1 + \lambda_2 - \lambda_1) \int_0^t \left(C e^{-\gamma s} + \frac{C}{\gamma} \right) e^{-\gamma(t-s)} e^{\gamma(1+\lambda_2-\lambda_1)(t-s)} ds \\ &\leq \frac{C}{\gamma} + C e^{-\gamma(\lambda_1-\lambda_2)t} + \frac{C}{\gamma(\lambda_1-\lambda_2)}. \end{aligned} \tag{32} \quad \{\text{est:tilden-b}\}$$

Step 3: Estimate on $|Z(t) - \bar{Z}(t)|$

The equations satisfied by $Z(t)$ and $\bar{Z}(t)$ (see (16), (11)) imply

$$\begin{aligned} \left| \frac{d}{dt} \ln \left(\frac{Z(t) - Z_b}{\bar{Z}(t) - Z_b} \right) \right| &= \left| \int_0^\infty \alpha(x) (\bar{u}_{\bar{Z}(t)}(x) - \tilde{n}(t, x)) dx \right| \leq \|\alpha'\|_{L^\infty(\mathbb{R}_+)} W_1(\tilde{n}(t, \cdot), \bar{u}_{\bar{Z}(t)}) \\ &\leq \|\alpha'\|_{L^\infty(\mathbb{R}_+)} [W_1(\tilde{n}(t, \cdot), \bar{u}_{Z(t)}) + W_1(\bar{u}_{Z(t)}, \bar{u}_{\bar{Z}(t)})] \leq \frac{C}{\sqrt{\gamma}} + C e^{-\gamma(\lambda_1-\lambda_2)t} + C |Z(t) - \bar{Z}(t)|, \end{aligned}$$

thanks to (32) and Proposition 2.1. Since $Z'(t)$ and $\bar{Z}'(t)$ are bounded (see (30)) and $Z(0) = \bar{Z}(0)$, we have $|Z(t) - \bar{Z}(t)| \leq Ct$ and then,

$$\left| \ln \left(\frac{Z(t) - Z_b}{\bar{Z}(t) - Z_b} \right) \right| \leq \frac{C}{\sqrt{\gamma}} t + \frac{C}{\gamma} + C \int_0^t |Z(s) - \bar{Z}(s)| ds \leq \frac{C}{\sqrt{\gamma}} t + \frac{C}{\sqrt{\gamma}} + Ct^2,$$

and thus

$$(\bar{Z}(t) - Z_b) e^{-\left(\frac{C}{\sqrt{\gamma}}t + \frac{C}{\sqrt{\gamma}} + Ct^2\right)} \leq Z(t) - Z_b \leq (\bar{Z}(t) - Z_b) e^{\left(\frac{C}{\sqrt{\gamma}}t + \frac{C}{\sqrt{\gamma}} + Ct^2\right)}.$$

As a consequence,

$$|Z(t) - \bar{Z}(t)| \leq C \left(e^{C\sqrt{\gamma}t + \frac{C}{\sqrt{\gamma}} + Ct^2} - 1 \right) \leq \frac{C}{\sqrt{\gamma}}t + \frac{C}{\sqrt{\gamma}} + Ct^2,$$

provided $t \in [0, 1]$, and in particular,

$$\forall t \in [0, \gamma^{-1/4}], \quad |Z(t) - \bar{Z}(t)| \leq \frac{C}{\sqrt{\gamma}}. \quad (33) \quad \{\text{eq:shorttime}\}$$

For $t \geq \gamma^{-1/4}$, we estimate

$$\begin{aligned} Z(t) - \bar{Z}(t) &= (Z(t) - Z_b) - (\bar{Z}(t) - Z_b) \\ &= (Z(0) - Z_b)e^{-\int_0^t (r + \int \alpha(x)\tilde{n}(s,x) dx) ds} - (Z(0) - Z_b)e^{-\int_0^t (r + \int \alpha(x)\bar{u}_{\bar{Z}(s)}(x) dx) ds} \\ &= (Z(0) - Z_b) \left(e^{-\int_0^t (\int_0^\infty \alpha(x)(\tilde{n}(s,x) - \bar{u}_{\bar{Z}(s)}(x)) dx) ds} - 1 \right) e^{-\int_0^t (r + \int_0^\infty \alpha(x)\bar{u}_{\bar{Z}(s)}(x) dx) ds}. \end{aligned}$$

We notice that

$$W_1(\tilde{n}(s, \cdot), \bar{u}_{\bar{Z}(s)}) \leq W_2(\tilde{n}(s, \cdot), \bar{u}_{\bar{Z}(s)}) \leq W_2(\tilde{n}(s, \cdot), \bar{u}_{Z(s)}) + W_2(\bar{u}_{Z(s)}, \bar{u}_{\bar{Z}(s)}),$$

and thus, thanks to (32) and Proposition 2.1, for $t \geq C' \frac{\ln \gamma}{\gamma}$ (and provided we select $C' > 0$ large enough),

$$W_1(\tilde{n}(s, \cdot), \bar{u}_{\bar{Z}(s)}) \leq \frac{C}{\sqrt{\gamma}} + C|Z(s) - \bar{Z}(s)|. \quad (34) \quad \{\text{est:intalpha}\}$$

We can use this estimate and the Kantorovich-Rubinstein formula (see (58)) to show

$$\begin{aligned} &\int_0^t \left| \int_0^\infty \alpha(x) (\tilde{n}(s, x) - \bar{u}_{\bar{Z}(s)}(x)) dx \right| ds \\ &\leq \int_0^{C' \ln \gamma / \gamma} \left| \int_0^\infty \alpha(x) (\tilde{n}(s, x) - \bar{u}_{\bar{Z}(s)}(x)) dx \right| ds + \int_{C' \ln \gamma / \gamma}^t \left| \int_0^\infty \alpha(x) (\tilde{n}(s, x) - \bar{u}_{\bar{Z}(s)}(x)) dx \right| ds \\ &\leq \int_0^{C' \ln \gamma / \gamma} 2\|\alpha\|_{L^\infty(\mathbb{R}_+)} ds + \|\alpha'\|_{L^\infty(\mathbb{R}_+)} \int_{C' \ln \gamma / \gamma}^t W_1(\tilde{n}(s, \cdot), \bar{u}_{\bar{Z}(s)}) ds \\ &\leq C \frac{\ln \gamma}{\gamma} + \frac{C}{\sqrt{\gamma}}t + C \int_0^t |Z(s) - \bar{Z}(s)| ds \leq \frac{C}{\sqrt{\gamma}}(1+t) + C \int_0^t |Z(s) - \bar{Z}(s)| ds. \end{aligned}$$

Then, provided $\gamma > 0$ is large enough and $t \geq \gamma^{-1/4}$

$$\begin{aligned} |Z(t) - \bar{Z}(t)| &\leq |Z(0) - Z_b| \left(e^{\frac{C}{\sqrt{\gamma}}(1+t) + \bar{C} \int_0^t |Z(s) - \bar{Z}(s)| ds} - 1 \right) e^{-\int_0^t (r + \int_0^\infty \alpha(x)\bar{u}_{\bar{Z}(s)}(x) dx) ds} \\ &\leq C \left(e^{\frac{C}{\sqrt{\gamma}}(1+t) + \bar{C} \int_0^t |Z(s) - \bar{Z}(s)| ds} - 1 \right). \end{aligned} \quad (35) \quad \{\text{eq:intermtim}\}$$

We have the following estimate as well, still for $t \geq \gamma^{-1/4}$ and $\gamma > 0$ large enough,

$$|Z(t) - \bar{Z}(t)| \leq C e^{\frac{C}{\sqrt{\gamma}}(1+t) + \bar{C} \int_0^t |Z(s) - \bar{Z}(s)| ds - rt} \leq C e^{\bar{C} \int_0^t |Z(s) - \bar{Z}(s)| ds - \frac{r}{2}t}, \quad (36) \quad \{\text{eq:longertim}\}$$

Note that we have specified the constant $\bar{C} > 0$ in the expressions above ((35) and (36)), to define

$$\bar{t} := \min \left\{ t \geq 0; \int_0^t |Z(s) - \bar{Z}(s)| ds \geq \frac{4\bar{C}}{\ln(\gamma)}t \right\},$$

and notice that (33) implies $\bar{t} > C\gamma^{-1/4}$ (we recall that $\gamma > 0$ is large). For $t \in [\gamma^{-1/4}, \min(\ln(\gamma)/(4\bar{C}), \bar{t})]$, thanks to (35),

$$|Z(t) - \bar{Z}(t)| \leq \frac{C}{\sqrt{\gamma}}(1+t) + \bar{C} \int_0^t |Z(s) - \bar{Z}(s)| ds \leq \frac{C \ln \gamma}{\sqrt{\gamma}} + \bar{C} \int_0^t |Z(s) - \bar{Z}(s)| ds.$$

This inequality implies, thanks to a Grönwall inequality,

$$|Z(t) - \bar{Z}(t)| \leq \frac{C \ln \gamma}{\sqrt{\gamma}} e^{\bar{C}t} \leq \frac{C}{\gamma^{1/4}}, \quad (37) \quad \{\text{est:ZZmoyen}\}$$

provided $\gamma > 0$ is large enough and $t \in [\gamma^{-1/4}, \min(\ln(\gamma)/(4\bar{C}), \bar{t})]$. This estimate implies in particular that $\bar{t} > \ln(\gamma)/(4\bar{C})$, provided $\gamma > 0$ is large enough. If $\bar{t} > \ln(\gamma)/(4\bar{C})$, we notice that, thanks to (36),

$$\forall t \in [\ln(\gamma)/(4\bar{C}), \bar{t}], \quad |Z(t) - \bar{Z}(t)| \leq C e^{-\frac{r}{4}t} \leq C \gamma^{-\frac{r}{16\bar{C}}}, \quad (38) \quad \{\text{est:ZZlong}\}$$

and in particular $\bar{t} = \infty$ provided $\gamma > 0$ is small enough. Brought together (33), (37) and (38) imply

$$\forall t \geq 0, \quad |Z(t) - \bar{Z}(t)| \leq C e^{-\frac{r}{4}t} \leq C \gamma^{-\frac{r}{16\bar{C}}}. \quad (39) \quad \{\text{est:ZZtotal}\}$$

Step 4: Estimates on $|N(t) - \bar{N}(t)|$

We define $\tilde{N} := \frac{1}{\beta} (r + \int_0^\infty \alpha(x) \bar{u}_{Z_b}(x) dx) > 0$. For $t \geq 0$,

$$\begin{aligned} \frac{d}{dt} (\bar{N}(t) - \tilde{N}) &= \left(r + \int_0^\infty \alpha(x) \bar{u}_{\bar{Z}(t)}(x) dx - \beta \bar{N}(t) \right) \bar{N}(t) \\ &= \left[\left(r + \int_0^\infty \alpha(x) \bar{u}_{\bar{Z}(t)}(x) dx - \beta \bar{N}(t) \right) - \left(r + \int_0^\infty \alpha(x) \bar{u}_{Z_b}(x) dx - \beta \tilde{N} \right) \right] \bar{N}(t) \quad (40) \quad \{\text{eq:NmN}\} \\ &= \left(\mathcal{O}(e^{-rt}) - \beta (\bar{N}(t) - \tilde{N}) \right) \bar{N}(t), \quad (41) \quad \{\text{eq:NmN2}\} \end{aligned}$$

where we have used $|\bar{Z}(t) - Z_b| \leq C e^{-rt}$, thanks to the equation satisfied by $\bar{Z}(t)$ (see (11)) and Proposition 2.1 to estimate

$$\left| \int_0^\infty \alpha(x) (\bar{u}_{\bar{Z}(t)}(x) - \bar{u}_{Z_b}(x)) dx \right| \leq C W_1(\bar{u}_{\bar{Z}(t)}, \bar{u}_{Z_b}) \leq C W_2(\bar{u}_{\bar{Z}(t)}, \bar{u}_{Z_b}) \leq C |\bar{Z}(t) - Z_b| \leq C e^{-rt}.$$

Since $N(t)$ is bounded from below (see (28)), estimate (41) proves the exponential convergence of $\bar{N}(t)$ to $\tilde{N} > 0$:

$$\begin{aligned} \frac{d}{dt} \left(e^{\min(r, \beta N(0))t} |\bar{N}(t) - \tilde{N}| \right) &= \text{sgn}(\bar{N}(t) - \tilde{N}) \left[\left(\mathcal{O}(e^{-rt}) - \beta (\bar{N}(t) - \tilde{N}) \right) \bar{N}(t) e^{\min(r, \beta N(0))t} \right. \\ &\quad \left. + \min(r, \beta N(0)) e^{\min(r, \beta N(0))t} (\bar{N}(t) - \tilde{N}) \right] \\ &\leq C + (\min(r, \beta N(0)) - \beta \bar{N}(t)) e^{\min(r, \beta N(0))t} |\bar{N}(t) - \tilde{N}|, \end{aligned}$$

and $(\min(r, \beta N(0)) - \beta \bar{N}(t)) < 0$ (see (28)) implies

$$\forall t \geq 0, \quad |\bar{N}(t) - \tilde{N}| \leq C e^{-\min(r, \beta N(0))t}. \quad (42) \quad \{\text{eq:cvbarZ}\}$$

Thanks to (14) and a calculation analogous to (40),

$$(N - \tilde{N})'(t) = \left(\int_0^\infty \alpha(x) (\tilde{n}(t, x) - \bar{u}_{Z_b}(x)) dx - \beta (N(t) - \tilde{N}) \right) N(t). \quad (43) \quad \{\text{eq:NNtilde}\}$$

Note that the definition of \tilde{N} and (11) imply $|\bar{Z}(t) - Z_b| \leq C e^{-rt}$. This estimate, (32), (39), and Proposition 2.1 imply

$$\begin{aligned} \left| \int_0^\infty \alpha(x) (\tilde{n}(t, x) - \bar{u}_{Z_b}(x)) dx \right| &\leq \|\alpha'\|_{L^\infty(\mathbb{R}_+)} (W_2(\tilde{n}(t, \cdot), \bar{u}_{Z_b}) + W_2(\bar{u}_{Z_b}, \bar{u}_{\bar{Z}(t)}) + W_2(\bar{u}_{\bar{Z}(t)}, \bar{u}_{Z_b})) \\ &\leq C \left(\frac{1}{\sqrt{\gamma}} + e^{-\gamma \frac{\lambda_1 - \lambda_2}{2} t} + \gamma^{-\frac{r}{16\bar{C}}} + e^{-rt} \right), \end{aligned}$$

provided $\gamma > 0$ is large enough. Then, for any $\nu \in (0, \min(1/2, r/(16\bar{C}))]$, $|\int_0^\infty \alpha(x) (\tilde{n}(t, x) - \bar{u}_{Z_b}(x)) dx| \leq C\gamma^{-\nu}$ as soon as $t \geq \frac{\nu}{r} \ln \gamma$. If we multiply (43) by $\text{sgn}(N - \tilde{N})(t)$ and use this last estimate, we obtain that for $t \geq \frac{\nu}{r} \ln \gamma$ and $\gamma > 0$ large enough,

$$\frac{d}{dt} |N - \tilde{N}|(t) \leq \left(C\gamma^{-\nu} - \beta |N(t) - \tilde{N}| \right) N(t) \leq C\gamma^{-\nu} - \frac{\beta}{C} |N(t) - \tilde{N}|.$$

Since additionally $|N - \tilde{N}|$ is bounded uniformly in γ (see Step 1), we have, for $t \geq \left(1 + \frac{C}{\beta}\right) \nu \ln \gamma$ and $\gamma > 0$ large enough,

$$|N(t) - \tilde{N}| \leq C\gamma^{-\nu}.$$

This estimate and (42) show that if $\eta > 0$ is small enough,

$$\forall t \geq \left(1 + \frac{C}{\beta}\right) \nu \ln \gamma, \quad |N(t) - \bar{N}(t)| \leq C\gamma^{-\nu}. \quad (44) \quad \{\text{eq:estN-large}\}$$

To estimate $(N(t) - \bar{N}(t))$ for $t \in [0, (1 + C/\beta)\nu \ln \gamma]$, we notice that thanks to (14), for $t \geq 0$,

$$\begin{aligned} (N - \bar{N})'(t) &= \left(r + \int_0^\infty \alpha(x) \tilde{n}(t, x) dx - \beta (N(t) + \bar{N}(t)) \right) (N(t) - \bar{N}(t)) \\ &\quad + \bar{N}(t) \int_0^\infty \alpha(x) (\tilde{n}(t, x) - \bar{u}_{\bar{Z}(t)}(x)) dx, \end{aligned}$$

and thus, thanks to a Duhamel formula,

$$\begin{aligned} (N - \bar{N})(t) &= \int_0^t \left(\bar{N}(s) \int_0^\infty \alpha(x) (\tilde{n}(s, x) - \bar{u}_{\bar{Z}(s)}(x)) dx \right) \\ &\quad \exp \left[\int_s^t \left(r + \int_0^\infty \alpha(x) \tilde{n}(\sigma, x) dx - \beta(\bar{N}(\sigma) + N(\sigma)) \right) d\sigma \right] ds, \end{aligned}$$

Thanks to (34), (39) and the boundedness of N , for $t \geq 0$,

$$|N(t) - \bar{N}(t)| \leq C \int_0^t \left(\frac{1}{\sqrt{\gamma}} + \gamma^{-\frac{r}{16\bar{C}}} \right) e^{(r + \|\alpha\|_{L^\infty(\mathbb{R}_+)}) (t-s)} ds \leq C\gamma^{-\min(\frac{r}{16\bar{C}}, \frac{1}{2})} e^{(r + \|\alpha\|_{L^\infty(\mathbb{R}_+)}) t}.$$

This estimate implies $|N(t) - \bar{N}(t)| \leq C\gamma^{(1+C/\beta)(r + \|\alpha\|_{L^\infty(\mathbb{R}_+)})\nu - \min(\frac{r}{16\bar{C}}, \frac{1}{2})}$ for $t \leq (1 + C/\beta)\nu \ln \gamma$. If we choose $\nu > 0$ small enough, this estimate and (44) imply:

$$\forall t \geq 0, \quad |N(t) - \bar{N}(t)| \leq C\gamma^{-\nu'}, \quad (45) \quad \{\text{est:N}\}$$

for some $\nu' > 0$. Together, (39), (45) and (32) conclude the proof of Theorem 2.2.

4 Convergence to a unique steady-state: Proof of Theorem 2.3

Step 1: Rough estimate on the first moment of $\tilde{n}(t, \cdot)$

We recall the notation \tilde{n} introduced in (13), and the equation (16) satisfied by $Z(t) = \int_0^\infty x \tilde{n}(t, x) dx$, which implies

$$\left| Z(t) - \int_0^\infty x n_b(x) dx \right| \leq \left| Z(0) - \int_0^\infty x n_b(x) dx \right| \leq \max \left(\int_0^\infty x \tilde{n}(0, x) dx, \int_0^\infty x n_b(x) dx \right) \leq M,$$

for $t \geq 0$, and in particular

$$W_1(n_b, \tilde{n}(t, \cdot)) \leq W_1(n_b, \delta_0) + W_1(\delta_0, \tilde{n}(t, \cdot)) \leq 3M. \quad (46) \quad \{\text{est:barx}\}$$

Step 2: The contraction argument

Let n_1, n_2 two solutions of (7), associated to two initial functions n_1^0, n_2^0 . We denote \tilde{n}_1, \tilde{n}_2 the two corresponding renormalized measures, and

$$\omega(t) := r + \frac{1}{2} \left(\int_0^\infty \alpha(y) \tilde{n}_1(t, y) dy + \int_0^\infty \alpha(y) \tilde{n}_2(t, y) dy \right). \quad (47) \quad \{\text{def:omega}\}$$

Thanks to (15), \tilde{n}_i , for $i = 1, 2$ can be written

$$\begin{aligned} \tilde{n}_i(t, x) &= \tilde{n}_i^0(x) e^{-\int_0^t \omega(s) + \gamma ds} + \int_0^t e^{-\int_s^t \omega(s) + \gamma ds} \left[\left(r + \int_0^\infty \alpha(y) \tilde{n}_i(s, y) dy \right) n_b(x) \right. \\ &\quad \left. + \left(\int_0^\infty \alpha(y) \frac{\tilde{n}_{i^c}(s, y) - \tilde{n}_i(s, y)}{2} dy \right) \tilde{n}_i(s, x) + \gamma \int_0^\infty \int_0^\infty K(x, x_1, x_2) \tilde{n}_i(s, x_1) \tilde{n}_i(s, x_2) dx_1 dx_2 \right] ds, \end{aligned}$$

where $i^c = 1$ if $i = 2$, and $i^c = 2$ if $i = 1$. We consider $\psi \in W^{1, \infty}(\mathbb{R}_+)$ such that $\|\psi'\|_{L^\infty(\mathbb{R}_+)}$ (see the Kantorovich-Rubinstein formula (58)), and estimate:

$$\begin{aligned} I &= \int_0^\infty \psi(x) (\tilde{n}_1(t, x) - \tilde{n}_2(t, x)) dx \\ &= e^{-\int_0^t \omega(s) + \gamma ds} \left[\int_0^\infty \psi(x) (\tilde{n}_1^0(x) - \tilde{n}_2^0(x)) dx \right] \\ &\quad + \int_0^t e^{-\int_s^t \omega(s) + \gamma ds} \left[\int_0^\infty \psi(x) \left\{ \left(\left(r + \int_0^\infty \alpha(y) \tilde{n}_1(s, y) dy \right) n_b(x) \right. \right. \right. \\ &\quad \left. \left. + \left(\int_0^\infty \alpha(y) \frac{\tilde{n}_2(s, y) - \tilde{n}_1(s, y)}{2} dy \right) \tilde{n}_1(s, x) \right) \right. \\ &\quad \left. - \left(\left(r + \int_0^\infty \alpha(y) \tilde{n}_2(s, y) dy \right) n_b(x) \right. \right. \\ &\quad \left. \left. + \left(\int_0^\infty \alpha(y) \frac{\tilde{n}_1(s, y) - \tilde{n}_2(s, y)}{2} dy \right) \tilde{n}_2(s, x) \right) \right\} dx \right] ds \\ &\quad + \gamma \int_0^t e^{-\int_s^t \omega(s) + \gamma ds} \left[\int_0^\infty \psi(x) \left\{ \left(\int_0^\infty \int_0^\infty K(x, x_1, x_2) \tilde{n}_1(s, x_1) \tilde{n}_1(s, x_2) dx_1 dx_2 \right) \right. \right. \\ &\quad \left. \left. - \left(\int_0^\infty \int_0^\infty K(x, x_1, x_2) \tilde{n}_2(s, x_1) \tilde{n}_2(s, x_2) dx_1 dx_2 \right) \right\} dx \right] ds \end{aligned} \quad (48) \quad \{\text{eq:estIrep}\}$$

The first term can be estimated thanks to the dual formulation of the Wasserstein distance (see (56)), and to estimate the second term we introduce

$$\theta(t) := \int_0^\infty \alpha(y) \frac{\tilde{n}_1(t, y) - \tilde{n}_2(t, y)}{2} dy,$$

and consider (we recall the definition (47) of ω)

$$\begin{aligned} J &:= \int_0^\infty \psi(x) \left\{ \left(\left(r + \int_0^\infty \alpha(y) \tilde{n}_1(s, y) dy \right) n_b(x) + \left(\int_0^\infty \alpha(y) \frac{\tilde{n}_2(s, y) - \tilde{n}_1(s, y)}{2} dy \right) \tilde{n}_1(s, x) \right) \right. \\ &\quad \left. - \left(\left(r + \int_0^\infty \alpha(y) \tilde{n}_2(s, y) dy \right) n_b(x) + \left(\int_0^\infty \alpha(y) \frac{\tilde{n}_1(s, y) - \tilde{n}_2(s, y)}{2} dy \right) \tilde{n}_2(s, x) \right) \right\} dx \\ &= \omega(s) \int_0^\infty \psi(x) (n_b(x) - n_b(x)) dx + \theta(s) \int_0^\infty \psi(x) (n_b(x) - \tilde{n}_2(x)) dx \\ &\quad - \theta(s) \int_0^\infty \psi(x) (\tilde{n}_1(s, x) - n_b(x)) dx \end{aligned}$$

the first term on the right hand side cancels, and thanks to the dual formula (58), we get

$$J \leq |\theta(s)| \left(W_1(n_b, \tilde{n}_1(s, \cdot)) + W_1(n_b, \tilde{n}_2(s, \cdot)) \right).$$

Using the dual formula (58) again, we can show $|\theta(s)| \leq \frac{\|\alpha'\|_{L^\infty(\mathbb{R}_+)}}{2} W_1(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot))$, which, combined to (46), implies

$$J \leq 3M\|\alpha'\|_{L^\infty(\mathbb{R}_+)} W_1(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot)). \quad (49) \quad \{\text{est:J}\}$$

Finally, to estimate the last term of (48), we notice that for any $\pi_s \in \Pi(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot))$ (see (55)),

$$\begin{aligned} L &= \int_0^\infty \psi(x) \left\{ \left(\int_0^\infty \int_0^\infty K(x, x_1, x_2) \tilde{n}_1(s, x_1) \tilde{n}_1(s, x_2) dx_1 dx_2 \right) \right. \\ &\quad \left. - \left(\int_0^\infty \int_0^\infty K(x, x_1, x_2) \tilde{n}_2(s, x_1) \tilde{n}_2(s, x_2) dx_1 dx_2 \right) \right\} dx \\ &\leq \int_{\mathbb{R}_+^2} \int_{\mathbb{R}_+^2} \left(\int_0^\infty \psi(x) (K(x, x_1, x_2) - K(x, x'_1, x'_2)) dx \right) d\pi_s(x_1, x'_1) d\pi_s(x_2, x'_2) \\ &\leq \int_{\mathbb{R}_+^2} \int_{\mathbb{R}_+^2} W_1(K(\cdot, x_1, x_2), K(\cdot, x'_1, x'_2)) d\pi_s(x_1, x'_1) d\pi_s(x_2, x'_2). \end{aligned}$$

We can now use the second estimate of Lemma 6.1 to get

$$\begin{aligned} L &\leq \int_0^\infty \int_0^\infty [(1 - \lambda_1)|x_1 - x'_1| + \lambda_1|x_2 - x'_2|] d\pi_s(x_1, x'_1) d\pi_s(x_2, x'_2) \\ &= \int_0^\infty |x_1 - x'_1| d\pi_s(x_1, x'_1), \end{aligned}$$

and since this estimate holds for any $\pi_s \in \Pi(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot))$, we get (see (55)):

$$L \leq W_1(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot)). \quad (50) \quad \{\text{est:L2}\}$$

Finally, (48) becomes

$$\begin{aligned} I &\leq e^{-\int_0^t \omega(s) + \gamma ds} W_1(\tilde{n}_1^0, \tilde{n}_2^0) + 6M\|\alpha'\|_{L^\infty(\mathbb{R}_+)} \int_0^t e^{-\int_s^t \omega(\sigma) + \gamma d\sigma} W_1(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot)) ds \\ &\quad + \gamma \int_0^t e^{-\int_s^t \omega(\sigma) + \gamma d\sigma} W_1(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot)) ds. \end{aligned}$$

Since this estimate is independent of $\psi \in W^{1,\infty}(\mathbb{R}_+)$ with $\|\psi'\|_{L^\infty(\mathbb{R}_+)} \leq 1$, we can apply (58) to get

$$\begin{aligned} W_1(\tilde{n}_1(t, \cdot), \tilde{n}_2(t, \cdot)) &\leq e^{-\int_0^t \omega(s) + \gamma ds} W_1(\tilde{n}_1^0, \tilde{n}_2^0) \\ &\quad + \int_0^t e^{-\int_s^t \omega(\sigma) + \gamma d\sigma} (3M\|\alpha'\|_{L^\infty(\mathbb{R}_+)} + \gamma) W_1(\tilde{n}_1(s, \cdot), \tilde{n}_2(s, \cdot)) ds. \end{aligned}$$

Then $y(t) := e^{\int_0^t \omega(s) + \gamma ds} W_1(\tilde{n}_1(t, \cdot), \tilde{n}_2(t, \cdot))$ satisfies:

$$y(t) \leq W_1(\tilde{n}_1^0, \tilde{n}_2^0) + \int_0^t (3M\|\alpha'\|_{L^\infty(\mathbb{R}_+)} + \gamma) y(s) ds,$$

and then, thanks to a Grönwall inequality,

$$y(t) \leq W_1(\tilde{n}_1^0, \tilde{n}_2^0) e^{(3M\|\alpha'\|_{L^\infty(\mathbb{R}_+)} + \gamma)t},$$

that is

$$W_1(\tilde{n}_1(t, \cdot), \tilde{n}_2(t, \cdot)) \leq W_1(\tilde{n}_1^0, \tilde{n}_2^0) e^{3M\|\alpha'\|_{L^\infty(\mathbb{R}_+)} t - \int_0^t \omega(s) ds}.$$

Since $\omega \geq r + \min_{x \in \mathbb{R}_+} \alpha(x)$, we have

$$W_1(\tilde{n}_1(t, \cdot), \tilde{n}_2(t, \cdot)) \leq W_1(\tilde{n}_1^0, \tilde{n}_2^0) e^{-(r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M\|\alpha'\|_{L^\infty(\mathbb{R}_+)})t}. \quad (51) \quad \{\text{est:n1n2}\}$$

Step 3: Convergence of \tilde{n}

For any $0 \leq \sigma \leq \tau$, we use the estimate (51) with $\tilde{n}_1(t, x) = \tilde{n}(t, x)$, $\tilde{n}_2(t, x) = \tilde{n}((\tau - \sigma) + t, x)$, to get

$$\begin{aligned} W_1(\tilde{n}_1(\sigma, \cdot), \tilde{n}_2(\tau, \cdot)) &\leq W_1(\tilde{n}(0, \cdot), \tilde{n}(\tau - \sigma, \cdot)) e^{-(r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)}) \sigma} \\ &\leq (W_1(\tilde{n}(0, \cdot), \delta_0) + W_1(\delta_0, \tilde{n}(\tau - \sigma, \cdot))) e^{-(r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)}) \sigma} \\ &\leq 6M e^{-(r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)}) \sigma}, \end{aligned} \quad (52) \quad \{\text{est:Cauchy1}\}$$

It follows that for any sequence $t_n \rightarrow \infty$, $(\tilde{n}(t_n, \cdot))_n$ is a Cauchy sequence in the complete metric space $(\mathcal{P}_1(\mathbb{R}_+), W_1)$, and the sequence then converges to a limit. Thanks to (52), this limit $\bar{n} \in \mathcal{P}_1(\mathbb{R}_+)$ is actually independent of the sequence (t_n) . Note that \bar{n} is actually a steady-state of (15). Since we have not defined the transfer operator on measure spaces, we will not develop this aspect in this manuscript.

With $\sigma = t$ and $\tau \rightarrow \infty$, we obtain

$$W_1(\tilde{n}(t, \cdot), \bar{n}) \leq 6M e^{-(r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)}) t}. \quad (53) \quad \{\text{est:cv-tilde}\}$$

Step 4: Convergence of N and n

Thanks to the definition of \tilde{n} , we simply need to show that $N(t) = \int_0^\infty n(t, x) dx$ converges to the following limit:

$$\bar{N} := \frac{1}{\beta} \left(r + \int_0^\infty \alpha(x) d\bar{n}(x) \right).$$

We recall that $N(t)$ satisfies (14), where

$$\begin{aligned} \left| \int_0^\infty \alpha(x) d(\tilde{n}(t, \cdot) - \bar{n})(x) \right| &\leq \|\alpha'\|_{L^\infty(\mathbb{R}_+)} W_1(\tilde{n}(t, \cdot), \bar{n}) \\ &\leq 6M \|\alpha'\|_{L^\infty(\mathbb{R}_+)} e^{-(r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)}) t}, \end{aligned}$$

thanks to (53). There exists then $T > 0$ such that for any $t \geq T$, $|\int_0^\infty \alpha(x) d(\tilde{n}(t, \cdot) - \bar{n})(x)| \leq \frac{\beta \bar{N}}{2}$, and for $t \geq T$,

$$N'(t) = \left(\int_0^\infty \alpha(x) d(\tilde{n}(t, \cdot) - \bar{n})(x) - \beta(N(t) - \bar{N}) \right) N(t) \geq \beta \left(\frac{\bar{N}}{2} - N(t) \right) N(t),$$

and then $N(t) \geq \frac{\bar{N}}{4}$ for t large enough, that is for $t \geq T'$. Then, thanks to the equality above, for $t \geq T'$,

$$\begin{aligned} |N(t) - \bar{N}| &\leq |N(T') - \bar{N}| e^{-\beta \int_{T'}^t N(s) ds} + \int_{T'}^t \left| \int_0^\infty \alpha(x) d(\tilde{n}(s, \cdot) - \bar{n})(x) \right| e^{-\beta \int_s^t N(\sigma) d\sigma} ds \\ &\leq \max \left(\frac{3\bar{N}}{4}, M \right) e^{-\frac{\beta \bar{N}}{4}(t - T')} + 6M \|\alpha'\|_{L^\infty(\mathbb{R}_+)} \int_{T'}^t e^{-(r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)}) s} e^{-\frac{\beta \bar{N}}{4}(t - s)} ds \\ &\leq C e^{-\min \left(\frac{\beta \bar{N}}{8}, (r + \min_{x \in \mathbb{R}_+} \alpha(x) - 3M \|\alpha'\|_{L^\infty(\mathbb{R}_+)}) \right) t}. \end{aligned} \quad (54)$$

Finally, we check that the convergence of \tilde{n} and N implies the convergence of n for the weak-* topology of measures. Let $\varphi \in C^0(\mathbb{R}_+)$ and any $\varepsilon > 0$. Thanks to the density of $C^1(\mathbb{R}_+)$ in $C^0(\mathbb{R}_+)$, there exists $\tilde{\varphi} \in C^1(\mathbb{R}_+)$ such that $\|\tilde{\varphi}'\|_{L^\infty(\mathbb{R}_+)} < \infty$, and $\|\varphi - \tilde{\varphi}\|_{L^\infty(\mathbb{R}_+)} \leq \varepsilon$. Then,

$$\begin{aligned} \left| \int_0^\infty \varphi(x) (n(t, x) - \bar{N} \bar{n}(x)) dx \right| &\leq \|\varphi - \tilde{\varphi}\|_{L^\infty(\mathbb{R}_+)} (\|n(t, \cdot)\|_{L^1} + \bar{N} \|\bar{n}\|_{L^1}) \\ &\quad + \left| \int_0^\infty \tilde{\varphi}(x) (N(t, x) \bar{n}(t, x) - \bar{N} \bar{n}(x)) dx \right| \\ &\leq C \varepsilon + |N(t) - \bar{N}| \|\tilde{\varphi}\|_{L^\infty(\mathbb{R}_+)} + \bar{N} \|\tilde{\varphi}'\|_{L^\infty(\mathbb{R}_+)} W_1(\tilde{n}(t, \cdot), \bar{n}) \\ &\leq (C + 1) \varepsilon, \end{aligned}$$

provided t is large enough, thanks to (53) and (54). This estimate with (53) and (54) concludes the proof of Theorem 2.3.

5 Discussion

The model considered in this manuscript describes the effect of PgP transfers on the ecological dynamics of a population of tumour cells, inspired by the experiments carried out in [30]. In [22], a simple transfer operator has been proposed, where cells exchange a fixed fraction of their proteins PgP. We have introduced a generalisation of that model, where the exchanged quantities can be given by a probability variable. For a full theory of these operators, we refer to upcoming [24], and to [21] for another generalisation of that model. An interesting property of these generalisation is that while the transfer model in [30] led the population to a monomorphic population with all cells carrying the same number of PgP, we observe for general transfer kernels the convergence to a non-singular distribution (see [24]).

Apart from the transfer model that we introduce, the model we consider includes death and birth events, that depend on the number of PgP carried by the cell. This is coherent with the protection effect provided by the PgP against cytostatic drugs used in chemotherapy treatments. These ecological terms in the models could however take numerous forms, and it would also be very relevant biologically to include interactions with other types of cells: PgP are produced in larger quantities in Chemotherapy-resistant cells than in sensitive cancer cells, and the experiments in [30, 31] used a combination of these two types of cells. Another fascinating effect is the exchange of proteins between cells through different means: we have considered here transfers through nanotubes (see [30]), but PgP can also be relieved in the environment within microparticles [19]. These microparticles are then captured by any other cell. We have chosen to focus our analysis on a simple model, but we believe the Wasserstein W_2 -based theory developed in the proof of Theorem 2.2 could be used for many generalisation of the model considered here. The approach developed for Theorem 2.3 is probably more limited.

The transfer operator that is at the heart of this study is related to non-linear operators that appear in different contexts. In [15, 5], a population of bacteria carrying plasmids was considered. An operator related to our transfer operator describes how plasmids move between cells. More broadly, the transfer operator can be seen as a model for plastic effect on population phenotypes, and an interesting aspect of the approach developed here is its proximity with recent developments in the analysis of structured population models for sexual populations, see e.g. [27, 13, 33, 2, 11, 12], cooperation models (see e.g. [25, 29, 1]), as well as some models for animal flocking [18, 17]. Having coherent framework for these models could be an asset to consider more complex models combining several effects.

The model we consider incorporates the effect of births and deaths of individuals, which happen at a rate that depends on the trait x (number of PgP carried by the cell). It may seem difficult to use the methods introduced by Tanaka (contraction of non-linear operators based on the Wasserstein distance W_2 , see [34]) in this context: the solutions are no longer probability measures, and the birth-death operator is of a different nature than the transfer operator. Our strategy is to combine the Wasserstein estimates on the transfer operator to Ordinary Differential Equation estimates on the macroscopic moments $N(t)$ and $Z(t)$. In the special case where $\alpha(x) = ax + b$, it is possible to derive closed equations on $N(t)$ and $Z(t)$, and the two types of estimates (Wasserstein estimates for the transfer operator and ODE estimates for $N(t)$ and $Z(t)$) can be done independently. In the general case, those two types of estimates have to be carefully combined, as we propose in the proof of Theorem 2.2. Notice that the output of that Theorem is very simple: we describe the dynamics of a complex model through a simple differential system. This is an asset to build predictions in biological systems that are robust and that could provide a pathway for experimental testing.

6 Appendix

6.1 Wasserstein distances

Our analysis is based on Wasserstein distances, and more precisely, the W_p -Wasserstein distances for $p = 1$ and $p = 2$. We refer to [36, 14] for a detailed description of those distances, but review below the definition and a few properties of these metrics that we will use in this manuscript. The distance W_p is defined on the set $\mathcal{P}_p(\mathbb{R}_+)$ of measures supported on \mathbb{R}_+ with a finite p -moment:

$$\mathcal{P}_p(\mathbb{R}_+) := \left\{ \mu \geq 0 \text{ a probability measure over } \mathbb{R}_+, \text{ such that } \int_0^\infty x^p d\mu(x) < \infty \right\}.$$

for two such probability measures $\mu, \nu \in \mathcal{P}_p(\mathbb{R})$, we define

$$W_p(\mu, \nu) := \left(\sup_{\pi \in \Pi(\mu, \nu)} \int_0^\infty \int_0^\infty |x - y|^p d\pi(x, y) \right)^{\frac{1}{p}}, \quad (55) \quad \{\text{def:Wasserst}\}$$

where $\Pi(\mu, \nu)$ is the set on measures on \mathbb{R}_+^2 with marginals μ and ν , that is such that for any measurable set $\omega \subset \mathbb{R}_+$,

$$\mu(\omega) = \pi(\omega \times \mathbb{R}_+), \quad \nu(\omega) = \pi(\mathbb{R}_+ \times \omega).$$

For $\mu, \nu \in \mathcal{P}_p(\mathbb{R})$, the Kantorovich formula states that

$$W_p(\mu, \nu)^p = \sup_{(\varphi, \psi) \in \Phi_p} \left(\int_0^\infty \varphi(x) d\mu(x) + \int_0^\infty \psi(X) d\nu(X) \right), \quad (56) \quad \{\text{def:Wasserst}\}$$

where the supremum is taken over all functions

$$(\varphi, \psi) \in \Phi_p := \{(\varphi, \psi) \in C_b(\mathbb{R}); \varphi(x) + \psi(X) \leq |x - X|^p\}. \quad (57) \quad \{\text{def:Phi}\}$$

Finally, for $p = 1$, the supremum in (56) can be taken over functions $(\psi, -\psi)$, which leads to the Kantorovich-Rubinstein formula:

$$W_1(\mu, \nu) = \sup_{\|\psi'\|_{L^\infty(\mathbb{R}_+)} \leq 1} \left(\int_0^\infty \psi(x) d\mu(x) - \int_0^\infty \psi(x) d\nu(x) \right). \quad (58) \quad \{\text{def:Wasserst}\}$$

6.2 Technical lemma on the transfer operator for the W_1 -distance

Lemma 6.1. *Let $x_1, x_2, x'_1, x'_2 \in \mathbb{R}_+^*$, K as in (5), and $\lambda_1 \in [0, 1]$ as in (18). Then,*

$$W_1\left(K(\cdot, x_1, x_2), K(\cdot, x'_1, x'_2)\right) \leq (1 - \lambda_1)|x_1 - x'_1| + \lambda_1|x_2 - x'_2|. \quad (59) \quad \{\text{eq:KW1}\}$$

Proof of Lemma 6.1. The proof of the first part of Lemma 3.1 can be reproduced for $(\varphi, \psi) \in \Phi_1$ until (20). Similarly, we can use the fact that $(\varphi, \psi) \in \Phi_1$ (see (57)) to get

$$\begin{aligned} I &\leq \int_0^1 |(x_1 - x_1 y_1 + x_2 y_2) - (x'_1 - x'_1 y_1 + x'_2 y_2)| B(y_1) B(y_2) dy_1 dy_2 \\ &\leq |x_1 - x'_1| \int_0^1 (1 - y_1) B(y_1) dy_1 + |x_2 - x'_2| \int_0^1 y_2 B(y_2) dy_2 \end{aligned}$$

and then, with the notations (18),

$$I \leq |x_1 - x'_1|(1 - \lambda_1) + |x_2 - x'_2|\lambda_1.$$

Since this is true for any $(\varphi, \psi) \in \Phi_1$ (see (57)), we can use this estimate and (56) to show that

$$\begin{aligned} W_1\left(K(\cdot, x_1, x_2), K(\cdot, x'_1, x'_2)\right) &= \max_{(\varphi, \psi) \in \Phi_1} I \\ &\leq |x_1 - x'_1|(1 - \lambda_1) + |x_2 - x'_2|\lambda_1. \end{aligned}$$

□

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Declarations

Conflict of interest The authors declare that they have no Conflict of interest. No data have been used in this manuscript.

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