FLUID LIMIT FOR A GENETIC MUTATION MODEL

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Abstract. We trace the time evolution of the number U_t of non-deleterious mutations, present in a gene modeled by a word of length L and DNA fragments by characters labeled $0, 1, \ldots, N$. For simplification, deleterious mutations are codified as equal to 0. The discrete case studied in [9] is a modified version of the Pólya urn, where the two types are exactly the zeros and non-zeros. A random continuous time binary mutation model, where the probability of creating a deleterious mutation is $1/N$, while the probability of recovery $\gamma(L^{-1}U_{Lt})$, γ continuous, is studied under a Eulerian scaling $u_t^L = L^{-1}U_{Lt}$, $L \to \infty$. The fluid limit u_t, emerging due to the *high-frequency* scale of mutations, is the solution of a deterministic generalized logistic equation. The power law $\gamma(u) = cu^a$ captures important features in both genetical and epidemiological interpretations, with c being the intensity of the intervention, a the strength/virulence of the disease, and $1/N$ the decay rate/infectiousness. Among other applications, we obtain a quantitative study of ΔT, the maximal interval between tests. Several stochastic optimization problems, including a generalization of the Shepp urn [13] are proposed.

1. Introduction

In this paper we investigate a mathematical model of a mutations occurring in a gene within a cell. Genes undergo mutations randomly, with the possibility of reaching special configurations; some are beneficial and mark a step in the evolutionary process, but some are deleterious - as would be the case in cancer formation and inherited genetic disorders such as phenylketonuria, cystic fibrosis, and color-blindness, just to mention a few. The idea of random mutations explaining cancer cell dynamics is subject to a vast literature, e.g. [7] and the references therein, but even more so, appears verified by recent experimental breakthroughs [16] and [11]. Quoting the authors, these show that "this 'bad luck' component explains a far greater number of cancer types than do hereditary and environmental factors". Here "luck" means randomness as opposed to causation. It remains open to biologists to make such determinations. Mathematically, we are much closer in scope to the genetic model from [17], [9], and more recently [5].

More specifically, we propose a model where the incidence of a certain character (deleterious, denoted by zero) is proportional to the pathology of the cell. When the the number of non-deleterious U_t drops below a certain threshold α, the disease becomes detectable; when reaching another threshold $u_1 < \alpha$, it becomes irreversible, and, in between, we obtain a time window for possible intervention (treatment). This is represented by the probability of recovery γ, a function of the current state of the cell. The system, while simple in biological sense, allows putting in evidence a clear interplay between parameters: the probability of deleterious mutation $1/N$, $N \geq 1$; the virulence of the disease through an exponent $a > 0$; and the treatment, through a constant $c \in [0, 1]$, all present in γ. In addition, an interpretation of the recommended *time interval for testing* ΔT is provided.

In discrete time, the model can be seen as an urn model with the two types $(U_t, L - U_t)$. The first type (which determines the second) moves down by one unit with probability $1 - U_t/L$ and up by $\gamma(U_t/L)$. We note that for $\gamma(x) = x$ the dynamcs is an urn model with a power law probability of mutation. Its connection to optimal stopping is outlined in the modified Shepp's urn [13] proposed in Section 5.

Scaling is essential, observing a random behavior on the microscopic scale $1/L$, when $L < \infty$ is fixed, seen as a moderate frequency of the motion. In the macroscopic scale $L \to \infty$, the profile becomes deterministic (Theorem 1), as the mutations have high frequency.

The paper is organized as follows. Section 2 will describe the exact mathematical model, including the fluid limit contained in Theorem 1, which is the main result. Its proof is in Section 3. Section 4 is the most important from the point of view of the applications. We distinguish Subsection 4.4, defining the *time window of intervention* and the discussion from Subsection 4.7 where we give a comprehensive interpretation of the model in the most relevant case of two nonzero equilibria ($a > 1$). A special place is occupied by Section

5, making the connection to stochastic optimization and formulating two optimal stopping problems. Finally, Sections 6 and 7 prove the detailed stability results for $a > 1$, respectively $0 \leq a < 1$ in the power law model $\gamma(u) = cu^a$.

2. The scaling model

In this paper, we build upon a genetic model introduced in [17] aimed at estimating the so called *time for evolution* as a function of the length of the gene (word). The case was to prove that random mutations can lock in a certain configuration in logarithmic time, i.e. an achievable scale.

The model is extended in [9] by allowing a small probability of mutation after reaching the preferred evolutionary state. In the present work, *the evolutionary biology aspect is not pursued*, instead we shall apply the same mathematical construction to analyze cell pathology and possible recovery, as well as the parallel epidemiological model.

Consider the set of alleles of length L with N possible types, which are determined by sequences of nucleotides, here interpreted as characters. Mathematically, this set can be described as the set of words of length L formed with letters from an alphabet of size N, both positive integers. We'll represent the alphabet as $\mathbb{Z}_N = \{0, 1, ..., N-1\}$, as $N \geq 1$ and the set of words of length $L \geq 1$ using the alphabet by $S = \mathbb{Z}_N^L$. This will be the state space of a pure jump continuous time Markov process $(Z_t)_{t\geq 0}$.

For convenience, we chose $0 \in \mathbb{Z}_N$ (zero) as the singular value of interest. The evolution depends on the number of letters equal to this special value.

Let $Z_t^j \in \mathbb{Z}_N$ denote the components, $1 \leq j \leq L$ of the configuration at time $t \geq 0$ of the vector-valued $Z_t = (Z_t^1, ..., Z_t^L)$. In the model, the standard construction of pure jump processes is done via exponential holding times (i.e. Poissonization) and a transition matrix (2.1)-(2.3) prescribing how the process evolves at jump times τ.

Assume that $0 \leq g(Z) \leq 1$ is a measurable function depending on the configuration $Z \in S$. In the model, it will represent the *rate of recovery*, i.e. the probability to escape the state 0 (deleterious). A Poisson clock of intensity $\lambda = 1$ triggers a jump from one configuration of $Z \in S$ to another, performed as follows. We pick randomly one component Z^j, $1 \leq j \leq L$, of the vector Z, with probability $1/L$, and then:

If $Z_{\tau-}^j \neq 0$, Z^j changes uniformly to *any value, including* 0,

$$Z_\tau^j = k \quad \text{with probability} \quad \frac{1}{N}\,, \qquad \text{for all} \quad k \in \mathbb{Z}_N\,, \tag{2.1}$$

while if $Z^j_{\tau-} = 0$, then

$$Z^j_\tau = k \quad \text{with probability} \quad \frac{g(Z_{\tau-})}{N-1}\,, \qquad \text{when} \quad k \neq 0\,, \tag{2.2}$$

$$Z^j_\tau = k \quad \text{with probability} \quad 1 - g(Z_{\tau-})\,, \qquad \text{when} \quad k = 0\,. \tag{2.3}$$

We notice that if $g(\cdot)$ is a constant, the components are independent. In [17], the state equal to the zero vector $\mathbf{0} = (0, ..., 0) \in S$ models a preferred configuration of the random evolutionary model, the only one where fixation is possible, and the expected time to reach it is calculated with an exact asymptotic formula as $L \to \infty$.

Let's denote by $U = U(Z)$ the number of non-zero components of $Z \in S$. In addition, it will be assumed throughout the paper that the rate of recovery has the special form

$$g(Z) = \gamma(\frac{U}{L})\,, \quad Z \in S\,, \tag{2.4}$$

where $\gamma : [0, 1] \to [0, 1]$ is continuous.

With this definition U_t, $t \geq 0$, corresponding to Z_t, is also Markov process on the space $\{0, 1, ..., L\}$. In general, a function $Z \to U(Z)$ on the state space does not determine a new Markov process, here possible only due to the special form of $g(Z)$. The presence of the factor L in (2.4) indicates dependence on the empirical measure (relative frequency) U_t/L of the non-zero states.

To obtain a quantity behaving well as $L \to \infty$, in addition to dividing U by L, time will be sped up by the same factor $t \to Lt$, in what is known as the Eulerian scaling, to obtain

$$u^L_t := \frac{U_{Lt}}{L} = \frac{1}{L}\sum_{j=1}^{L} \mathbf{1}_{\mathbb{Z}_N \setminus \{0\}}(Z^j_{Lt})\,, \qquad t \geq 0\,. \tag{2.5}$$

Theorem 1 is our first result. It proves that u^L_t converges, as $L \to \infty$, to a deterministic trajectory defined by the solution of an ODE. It is the continuous time analogue of Theorem 3 in [9]. In that paper, the scaled process is a deterministic discrete time dynamical system.

In Proposition 1 we shall show that, based on the construction of (Z_t), now with a Poisson clock of intensity $\lambda = L > 0$ (as opposed to $\lambda = 1$), the derived process (u^L_t) has the infinitesimal generator

$$\mathcal{A}^L f(u) = L\left[\frac{u}{N}\left(f(u - \frac{1}{L}) - f(u)\right) + \gamma(u)(1-u)\left(f(u + \frac{1}{L}) - f(u)\right)\right]\,, \tag{2.6}$$

defined on functions $f \in C([0, 1])$.

When $\gamma(0) = 0$, which may occur when $U_t = 0$, the process will never leave the state 0. Let $\xi = \inf\{t > 0 \,|\, u^L_t = 0\}$ be the time of extinction. This will not play a significant role in this paper. First, on a technical level, extinction only happens when the intensity

u/L vanishes, which does not require boundary conditions on f. Second, in applications (Corollary 1) like the power law for γ, the solution exists for all times after scaling.

Eq. (2.5) points to a *mean-field* dependence, leading to a Law of Large Numbers at the level of the random trajectories. Such a scaling limit is known as a *fluid limit*. The empirical measure of the zero states, here simply U_t/L, converges in probability to the deterministic solution of an ode (2.7).

With $\gamma(u)$ defined in (2.4), $H \in C([0,1])$ will denote the vector field and its associated initial value problem for $\bar{u} \in [0,1]$

$$H(u) := -\frac{u}{N} + \gamma(u)(1-u)\,, \qquad \frac{du}{dt} = H(u)\,, \qquad u(0) = \bar{u}\,. \tag{2.7}$$

The solution is denoted (u_t). The subscript notation for time $t \geq 0$ is motivated by consistency with the notation of the stochastic process u_t^L and should not be confused with the derivative.

Theorem 1. *Assume that $\gamma = \gamma(u)$, $0 \leq u \leq 1$ from (2.4) is continuous, $u_0^L = U_0/L$ converges in probability to the deterministic state $\bar{u} \in [0,1]$ and (2.7) has a unique solution. Then, the laws of the of processes (u_t^L), indexed by $L \geq 1$, form a tight family in the Skorohod space and any limit point is a delta function concentrated on the deterministic solution (u_t) of (2.7). It follows that (u_t^L) converges in probability to (u_t).*

Remark. Theorem 1 is proven in Section 3. In fact, we prove a slightly stronger result. The convergence takes place in probability, uniformly on finite time intervals.

Corollary 1. *When $\gamma(u) = cu^a$ with $c, a \geq 0$ and $\bar{u} \in (0,1]$, the conditions of Theorem 1 are met. In particular, equation (2.7) has a unique solution (u_t) with maximal existence interval $[0,\infty)$ satisfying $u_t \in (0,1)$, $t > 0$.*

Remark. When $c > 0$, $a \in (0,1)$, $\bar{u} = 0$ the stationary solution is not unique, in general.

Proof. In all cases, $\gamma \in C^1((0,\infty))$, thus $H \in C^1((0,\infty))$. For $\bar{u} \in (0,1] \subseteq (0,\infty)$, the initial value problem has a unique solution (u_t) with continuous derivative on the maximal interval $[0,t')$ starting from any $\bar{u} \in (0,1]$. We have to prove that $t' = +\infty$ and the solutions remain in $(0,1)$ at all positive times. First, we show the existence of the upper and lower bounds.

Since $\gamma(u) \in [0,1]$, the inequality $-\frac{u}{N} \leq H(u) \leq 1 - (1 + \frac{1}{N})u$ holds. First it shows that the derivative of $(u_t - \frac{N}{1+N})e^{(1+\frac{1}{N})t}$ is negative. Its value at $t = 0$ is an upper bound. Second, for a lower bound, we check the derivative of $u_t e^{\frac{t}{N}}$. Putting them together, the solution satisfies

$$0 < \bar{u}e^{-\frac{t}{N}} \leq u_t \leq \frac{N}{N+1}(1 - e^{-(1+\frac{1}{N})t}) + \bar{u}e^{-(1+\frac{1}{N})t} < \max\{\frac{N}{1+N}, \bar{u}\} = u_+ \leq 1\,, \quad t > 0$$

proving that u_t remains in $(0,1)$ at all times $t \in (0,t')$ and in $(0,1]$ at $t \in [0,t')$. To show that $t' = +\infty$, it is sufficient that the solution remains in a compact subset of the open set $D \subseteq \mathbb{R}$, provided that $H \in C^1(D)$ ([12], Corollary 2, Section 2.4).

If either $c = 0$ or $c > 0$ and $a \in \{0\} \cup [1, \infty)$, then $D = \mathbb{R}$ and the bound $u_t \in (0, u_+] \subseteq [0, u_+]$ shows that $t' = +\infty$.

The remaining case is $c > 0$ and $a \in (0,1)$. Here $D = (0, \infty)$ and $u_0 = 0$ is an equilibrium point. Writing $H(u) = cu(-\frac{1}{Nc} + u^{a-1}(1-u))$, we notice that the function in parenthesis is strictly decreasing with value $+\infty$ as $u \to 0$ and $-\frac{1}{Nc} < 0$ at $u = 1$. Then, there exists exactly one more equilibrium point $u_2 \in (0,1)$ (the notation is consistent with that in Proposition 6, where the case is treated in more detail). Moreover, u_2 is stable. In particular $H(u) > 0$ for $u \in (0, u_2)$. A solution starting at $\bar{u} \in (0, u_2)$ is increasing and stays in the interval $[\bar{u}, u_2]$. A solution starting at $\bar{u} \geq u_2$ stays in $[u_2, u_+]$, since u_2 is an interior point of $D = (0, \infty)$. In both cases, we derive that $t' = +\infty$. □

3. Proof of Theorem 1

We start with the derivation of the formula for the generator (2.6).

Proposition 1. *The process (u_t^L), $t \geq 0$ from (2.5) is a pure jump Markov process and has generator equal to $\mathcal{A}^L$ from eq. (2.6).*

Proof. The process described by (2.1)-(2.3) is a pure jump process with generator

$$\widetilde{\mathcal{A}}^L F(Z) = \frac{1}{L} \sum_{j=1}^{L} \Bigg[\Big(\frac{1}{N} \sum_{k=0}^{N} (F(Z^{j \to k}) - F(Z)) \Big) \mathbf{1}_{\mathbb{Z}_N \setminus \{0\}}(Z^j) \tag{3.1}$$

$$+ \Big(\frac{g(Z)}{N-1} \sum_{k=1}^{N-1} (F(Z^{j \to k}) - F(Z)) + (1 - g(Z))(F(Z^{j \to 0}) - F(Z)) \Big) \mathbf{1}_{\{0\}}(Z^j) \Bigg] , \tag{3.2}$$

where $F \in C_c(\mathbb{R})$, $Z \in \mathbb{Z}_N^L$ is a configuration of the process, i.e. an element in the state space. For $j \in \{1, \ldots, L\}$ and $k \in \{0, 1, \ldots, N-1\}$, we denote Z^j the j-th component of Z and $Z^{j \to k}$ is the configuration obtained from Z by replacing the component j with the number k. Denote $u^L = U/L$ - see (2.5). More precisely $u^L(Z) = \frac{1}{L} \sum_{j=1}^{N} \mathbf{1}_{\mathbb{Z}_N \setminus \{0\}}(Z^j)$ is a deterministic function of the configuration Z.

The process u_t^L is obtained by

(i) speeding up time by a factor of L creating the process $t \to Z_{Lt}$ and

(ii) mapping $Z \to u^L(Z)$.

Assume now $g(Z) = \gamma(u^L)$. Pick $F(Z) := f \circ u^L(Z)$ for $f \in C([0,1])$. Then, the action of $L\widetilde{\mathcal{A}}^L$ (notice the pre-factor L from the change of speed) on $f(u^L)$ will be of two kinds.

If component j is chosen (with probability $1/L$) and $Z^j \neq 0$, as shown in (3.1), then u^L can only decrease to $u^L - 1/L$, which will happen when it it changes to the value $k = 0$,

with probability $1/N$. This will be repeated for all j with $Z^j \neq 0$, which adds up to exactly $U = Lu^L$. This gives the first term of $\mathcal{A}^L$ from (2.6).

If component j is chosen (with probability $1/L$) and $Z^j = 0$, as shown in (3.2), then u^L can only increase to $u^L + 1/L$ in the first, respectively remain the same in the second term of (3.2). So the increase happens with probability $(N-1) \times \frac{\gamma(u^L)}{N-1} = \gamma(u^L)$ for all j when $Z^j = 0$, i.e. $L - U = L(1 - u^L)$ times. This gives the second term of $\mathcal{A}^L$ from (2.6).

In addition, this calculation proves that (u_t^L), $t \geq 0$ is a pure jump, finite state space Markov process. □

The following general definitions are necessary to state and prove the fluid limit of Theorem 1. A *Polish space* is a separable, complete metric space; here it will be a normed linear space $(X, ||\cdot||)$, specifically $\mathbb{R}$ with the Euclidean norm.

Pure jump processes, and a large class of Feller processes can be canonically constructed on the Skorohod space $\mathbf{D}([0,\infty), X)$ of right-continuous with left-limit paths (rcll, also known as càdlàg). Tightness is the notion of pre-compactness of probability laws defined by Prokhorov's theorem, meanwhile *C-tightness* refers to the fact that the family of processes indexed by $N > 0$ is not only tight as a family on the Skorohod space with the usual J_1 Skorohod topology, but in addition, any limit point is supported on the subset of continuous paths. For more details we refer the reader to [14], Ch. VI, p. 324.

Definition 1. *A sequence of processes* $(Y_\cdot^L)_{L>0}$ *on a Polish space* $(\mathbb{X}, ||\cdot||)$ *with right-continuous with left limits paths (in the Skorohod space) is* C-tight *(i.e. the probability laws are a tight family), if for any* $T \geq 0$

$$(i) \qquad \lim_{M\to\infty} \limsup_{L\to\infty} P\Big(||Y_T^L|| > M\Big) = 0 \quad \textit{and} \tag{3.3}$$

$$(ii) \quad \forall\, \epsilon > 0 \qquad \lim_{\delta\to 0} \limsup_{L\to\infty} P\Big(\sup_{t,t'\in[0,T],|t'-t|<\delta} ||Y_{t'}^L - Y_t^L|| > \epsilon\Big) = 0\,. \tag{3.4}$$

Definition 2. *A sequence of processes* $(Y_\cdot^L)_{N>0}$ *on a Polish space* $(\mathbb{X}, ||\cdot||)$ converges in probability *to* $(Y_\cdot)$*, uniformly in finite time, if for any* $T > 0$*, the process* $t \to (Y_t^L)_{t\geq 0}$ *satisfies*

$$\forall \epsilon > 0 \qquad \lim_{L\to\infty} P\Big(\sup_{t\in[0,T]} ||Y_t^L - Y_t|| > \epsilon\Big) = 0\,. \tag{3.5}$$

Proposition 2. *The processes* $(u_t^L)_{t\geq 0}$*, indexed by* $L \in \mathbb{N}$*, have a* C-tight *family of probability laws.*

Proof. Since $u_t^L \in [0,1]$ by construction, we adopt test functions $f \in C^2([0,1])$ and consider their extensions to the space $C_c^2(\mathbb{R})$. First, we write the action of the generator (2.6) of the

underlying pure jump process (u_t^L) . We obtain the martingale

$$M_t^{L,f} = f(u_t^L) - f(u_0^L) - \int_0^t \mathcal{A}^L f(u_s^L)\, ds$$

with quadratic variation

$$\langle M^{L,f}\rangle_t = \int_0^t \mathcal{A}^L f^2(u_s^L) - 2f(u_s^L)\mathcal{A}^L f(u_s^L)\, ds\,. \tag{3.6}$$

More precisely

$$\langle M^{L,f}\rangle_t = \int_0^t L\Big[\frac{u_s^L}{N}(f(u_s^L - \frac{1}{L}) - f(u_s^L))^2 + \gamma(u_s^L)(1-u_s^L)(f(u_s^L + \frac{1}{L}) - f(u_s^L))^2\Big]\, ds\,.$$

After writing the Taylor formula with remainder of order two, there exist two constants $c(f), c_1(f)$ depending only on f such that

$$\mathcal{A}^L f(u) = H(u)f'(u) + c(f,u,L)\,, \qquad |c(f,u,L)| \le c(f)L^{-1}\,, \tag{3.7}$$

and

$$\langle M^{L,f}\rangle_t \le c_1(f)L^{-1}\,. \tag{3.8}$$

For the last bound, the quadratic variation comprises only jumps of size $1/L$; these are squared and sum up to a total of $O(1/L)$, uniformly in time and $u \in [0,1]$, since the bounds are depending only on the derivatives of f.

We now can show that for any test function f defined at the beginning of this proof, $Y_t^L = f(u_t^L)$ is *C-tight*. Condition (i) in (3.3)is trivial because $u_t^L \in [0,1]$ and f has compact support without further restrictions necessary. Condition (ii) in (3.4) is implied by the fact that $|\mathcal{A}^L f(u_s^L)|$ is bounded by $1 + c(f)/L$.

To obtain (3.4) for the martingale $M_t^{L,f}$, we apply the Doob's L^2-norm maximal inequality, taking without loss of generality $0 \le t \le t' \le T$. First, note that $M_0^{L,f} = 0$. Then

$$P\Big(\sup_{t,t'\in[0,T],|t'-t|<\delta} |M_{t'}^{L,f} - M_t^{L,f}| > \epsilon\Big) \le 2P\Big(\sup_{t\in[0,T]} |M_t^{L,f}| > \frac{\epsilon}{2}\Big) \le$$

$$\frac{8}{\epsilon^2}E\Big[(\sup_{t\in[0,T]} M_t^{L,f})^2\Big] \le \frac{32}{\epsilon^2}E\Big[(M_T^{L,f})^2\Big] = \frac{32}{\epsilon^2}E\Big[\langle M^{L,f}\rangle_T\Big] \le \frac{32c_1(f)}{\epsilon^2 L}\,. \tag{3.9}$$

The last inequality is a direct estimate from the quadratic variation (3.8). As $L \to \infty$, the estimate (3.4) is satisfied independently of δ. We have shown that the martingale is tight, and the integral term $\int_0^t \mathcal{A}^L f(u_s^L)ds$ are *C-tight*, hence $f(u_t^L)$ is *C-tight*. Choosing $f(u) = u$ on a neighborhood of $[0,1]$, we obtain that $(u_t^L)_{t\in[0,T]}$, indexed by L, is *C-tight*. □

Denote $(\eta(t))_{t\ge 0}$, written simply as $\eta.$, a path in the Skorohod space $\mathbf{D}([0,\infty);\mathbb{R})$. Let $\chi \in C_c^\infty(\mathbb{R}$ be a smooth version of the indicator function of the interval $[0,1]$. Pick $T > 0$

arbitrary but momentarily fixed. We define the functional $\Psi : \mathbf{D}([0,T];\mathbb{R}) \to \mathbb{R}$

$$\Psi(\eta(\cdot)) := \sup_{t\in[0,T]} \left| f(\eta(t)) - f(\bar{u}) - \int_0^t H(\eta_s) f'(\eta_s)\, \chi(\eta(s))\, ds \right|. \tag{3.10}$$

To explain the presence of the factor $\chi(\eta(s))$ we note that $\eta(s)$ may assume arbitrary large values, while we are interested in a a bounded functional Ψ. On the other hand, the actual process $(u_s^L)_{s\geq 0}$ is naturally bounded by one, and the factor $\chi(u_s^L)$ will be simply equal to one once we apply the functional to the process, as seen below.

Proposition 2 proved that the probability laws of the processes $(u_t^L)_{t\geq 0}$, indexed by L and defined on the common space $\mathbf{D}([0,\infty);\mathbb{R})$, form a $C-tight$ family. The family will have at least one limit law, a probability measure on $\mathbf{D}([0,\infty);\mathbb{R})$. Let $(u_t)_{t\geq 0}$ be a process having the limit law. Then $\lim_{k\to\infty}(u_t^{L_k})_{t\geq 0} \Rightarrow (u_t)_{t\geq 0}$ (in distribution) over a sequence $(L_k)_{k\geq 1}$. To simplify notation we shall omit the subscript k.

We shall prove that such limit law is unique, implying the sequence $(u_t^L)_{t\geq 0}$ converges in distribution. Moreover, the limit law will be a delta measure concentrated on the trajectory given by the solution $(u_t)_{t\geq 0}$ of (2.7), proving that the convergence is, in fact, in probability, concluding the proof of Theorem 1.

First, the limit law is concentrated on $C([0,T];\mathbb{R})$ (C-tightness), i.e. the limit point $t \to u_t$ is a.s. continuous. We claim that Ψ is a bounded, continuous functional on the Skorohod space $\mathbf{D}([0,T];\mathbb{R})$. Boundedness is immediate form the definition of the functions f, χ and H. The supremum $\sup_{t\in[0,T]} |\eta(t)|$ is a continuous functional on the full interval $[0,T]$ of $\mathbf{D}([0,T];\mathbb{R})$. It is then sufficient to prove that the functional over which we take the supremum in the formula of Ψ is a continuous functional itself. The functional has a first term, equal to $f(\eta(\cdot))$, which is continuous in $\eta(\cdot) \in \mathbf{D}([0,T];\mathbb{R})$ because as long as the limit point is (uniformly) continuous on $[0,T]$, convergence in the Skorohod topology implies uniform convergence, and a second term, equal to a time integral, evidently continuous.

Next, Portmanteau's Theorem implies that, over the subsequence converging in distribution to $u_\cdot$ (we keep the same notation $L \to \infty$),

$$\lim_{L\to\infty} E\Big[\Psi(u_\cdot^L)\Big] = E\Big[\Psi(u_\cdot)\Big].$$

We want to show that the limit on the left hand side is actually equal to zero. For this we refer again to the martingale (3.6) and see that

$$\Psi(u_\cdot^L) \leq \sup_{t\in[0,T]} \Big| \int_0^t \Big[H(u_s^L) f'(u_s^L) \chi(u_s^L) - \mathcal{A}^L(u_s^L) \Big]\, ds \Big| + \sup_{t\in[0,T]} \Big| M_t^{L,f} \Big|.$$

The first term contains $\chi(u_s^L) \equiv 1$ because $0 \leq u_s^L \leq 1$ by construction. The difference under the integral is bounded above by $c(f)/L$ from (3.7), making the first term on the

right hand side of the inequality bounded by $c(f)T/L$. Letting $L \to \infty$, the first term vanishes.

The second term uses the martingale estimate (3.9) and vanishes as $L \to \infty$.

We showed that $E[\Psi(u_\cdot)] = 0$ under the limit law. We still have a factor $\chi(u_s)$ under the time integral. Let $\phi \in C_c^\infty(\mathbb{R})$. Then $(\eta(t))_{t\in[0,T]} \to \phi(\sup_{t\in[0,T]} \eta_t)$ is also a bounded C-functional. It follows by Portmanteau's Theorem and optimizing over ϕ to approximate $\mathbf{1}_{(1,\infty)}(u)$ that $P(\sup_{t\in[0,T]} u_t > 1) = 0$. Similarly we obtain $P(\inf_{t\in[0,T]} u_t < 0) = 0$, and finally that $P(u_t \in [0,1]\,,\, t \in [0,T]) = 1$. This allows us to omit χ in the formula of Ψ under the limit law.

Then, with probability one, the (possibly random) continuous process $u_\cdot$ satisfies

$$\sup_{t\in[0,T]} \left| f(u(t)) - f(\bar{u}) - \int_0^t H(u_s) f'(u_s)\, ds \right| = 0\,.$$

This identity is valid for any $f \in C_c^2(\mathbb{R})$; in particular, since $0 \le u \le 1$, we can take $f(u) = u$ on a neighborhood of $[0,1]$. This shows that any possible continuous limit solves

$$u_t - \bar{u} - \int_0^t H(u_s)\, ds = 0\,,$$

which is exactly (2.7) in integral form. The function H is continuous, so is $u_\cdot$, thus the integrand is continuous, implying that u_t is differentiable in classical sense. We proved that any limit point solves the ode (2.7). Moreover, $u' = H(u)$, $u_0 = \bar{u}$ has a unique solution by hypothesis. We proved that any limit law is supported on only one possible trajectory, *equal to the unique solution to the initial value problem (2.7).* Finally, the convergence takes place in distribution, to a delta function concentrated on the unique solution of the ode. Convergence in distribution to a delta measure is equivalent to convergence in probability. Because all along the convergence was uniform in time over $[0,T]$, T fixed but arbitrary, we concluded the proof of Definition 2, and hence of the theorem.

4. Applications

Both the random process U_t (macroscopic scale) and its deterministic scaling u_t (microscopic scale) from eq. (2.7) can be regarded as population dynamics models. Two main setups are proposed: (i) *the cancer development model* and (ii) *the epidemic model.* In (i), the number U_t, calculated out of the total population L, is understood as the set of alleles in non-deleterious states; in (ii) it is the non-infected population. After scaling, asymptotically as $L \to \infty$, the trajectory u_t is the averaged value, consistent with a law of large numbers for empirical measures, calculated out of a normalized population of size one.

Equation (2.7) is valid for a general continuous function $\gamma(u)$. Since it is an autonomous equation, we are interested in stability about the equilibria u, given by the solutions of

$H(u) = 0$. In both micro - and macroscopic models, we are still interested in the relation between the solution and the sensitive state 0 (zero). For this reason, we shall adopt models when $\gamma(0) = 0$, so that $u = 0$ is an equilibrium point. In general, since the initial value $\bar{u}$ is non-negative and the equation is autonomous, the solution u_t remains non-negative.

In a reasonable model, the zero state should be absorbing, as the intrinsic condition is that recovery depends with positive correlation on the non-deleterious/infected population u_t. To satisfy that assumption, the mathematical model proposed, for both cancer and epidemic examples, will be a power law for the *probability of recovery*

$$\gamma(u) = cu^a\,, \quad \text{for} \quad 0 \le c \le 1\,, \quad a \ge 0\,. \tag{4.1}$$

The framework is as follows. In the natural state, the population follows (2.7) with $c = 0$ (i.e: $\gamma \equiv 0$). This is the pre-intervention level. It is assumed hereby that an exponential rate of aging/contamination (cancer and epidemic, respectively) drives the healthy population down, towards eventual extinction, *in the absence of treatment*, here represented by $\gamma(u)$. An empirical level $u = \alpha \in (0, 1)$ designates the *detection threshold*. It is only as soon as u drops below α that tests or symptoms make the disease detectable. At this point, an intervention takes place, with a specific *probability of recovery* $\gamma(u)$ (4.1) depending on the "healthy" proportion of the population u; the strength of the treatment c; and the intensity or virulence of the disease a.

A couple of observations are in order to motivate the definition of γ. First, notice that this function is increasing in u meaning that, for bigger u our probability of recovery is greater, consistent with u being the healthy proportion of the population. Also, if we fix $u \in (0, 1)$ and consider $a \to \infty$, then the function $\gamma(u) = cu^a \to 0$, thus the probability of recovery reduces as the intensity of the disease increases.

Equation (2.7) depends on the *logistic* factor $\gamma(u)$. Since $g(Z)$ from eq. (2.4) belongs to $[0, 1]$ macroscopically (before letting $L \to \infty$), it is the case that $\gamma(u) = cu^a \in [0, 1]$ as well. Thus, to avoid technical complications, we adopt $c \in [0, 1]$ while $u \in [0, 1]$. As explained in the previous paragraph, for $a \ge 0$, the power function is increasing in u but decreasing in a, again consistent with the model interpretation.

The particular cases $a = 0$ and $a = 1$ are studied in [9] in a discrete time setting. The continuous time case is briefly discussed in Subsections 4.5 ($a = 0$) and 7.1, Proposition 5 ($a = 1$).

4.1. **The intrinsic parameters.** These are parameters intrinsic imbedded in the recovery probability function $\gamma(u)$, i.e. a, C and N; they are defined as opposed to the *extrinsic* parameters described below. In the cancer growth model setup, $1/N$ is the probability of a deleterious mutation, a feature of aging, and intrinsic to the cell; c is the effectiveness of the intervention (treatment); a is the cancer type, or aggressiveness. In the epidemic

model, $1/N$ is the contagiousness of the disease (e.g. probability to contract the virus); c is the strength of a treatment of vaccine, and a is the virulence of the disease.

4.2. **The extrinsic parameters.** As opposed to the parameters defining the disease, these parameters are set independently. We postulate two values $\alpha, \beta \in [0,1]$, where $u = \alpha$ is the *detectability* level and $u = \beta$ is the *quality of life*, a satisfactory health threshold, especially in the cancer setting. In the epidemic model it is the containment level, at which the population is considered out of an epidemic state. It is natural to consider $\alpha < \beta$. The case $\alpha \geq \beta$ is practically trivial and prophylactic care would prevail, as it allows apriori early detection.

4.3. **The equilibrium values.** All cases in the power law model have at least one stable equilibrium in the interval $[0,1)$. If $c = 0$, then $u_0 = 0$ is the only equilibrium value (Subsection 4.4). If $c > 0$, then

(i) If $a = 0$, there exists only one equilibrium value u_2 (Newton's equation, Subsection 4.5);

(ii) If $a > 1$, the number of equilibrium points of the system (2.7) will depend on the parameter a, varying from only one equilibria for large a (fig. 1) to three (fig. 3), below a critical point where there are exactly two (fig. 2). In this case the point $u_0 = 0$ is always a stable equilibrium, in the sense that $H(u) < 0$ for u near zero. In the case of the presence of just another non zero-equilibrium point u_1, this will be half-stable. Finally, the case of three points $0 = u_0 < u_1 < u_2 < 1$, will exhibit u_1 as unstable and u_2 as stable - see Section 6.

(iii) If $0 < a \leq 1$, there exist two equilibrium values $0 = u_0 = u_1 < u_2 < 1$, where u_0 is unstable and u_2 is stable - see Section 7.

4.4. **Natural State of the System $c = 0$.** A natural state of the system is when there is no intervention, i.e. $c = 0$. In this case, the only dynamics is due to aging $u(t) = u(0)e^{-\frac{1}{N}t}$ determined by the exponential rate of decay $1/N$, with unique stable equilibrium at $u_0 = 0$ (see section 1.1 in [8]).

Let u_1 be the unstable equilibrium, where $u_1 > 0$ for $a > 1$ and $u_1 = u_0 = 0$ when $a \in (0,1]$. The simple but important *intervention window* ΔT between reaching α and u_1 is defined by

$$\Delta T = T_{u_1} - T_\alpha = -N \ln(\frac{u_1}{\alpha}), \tag{4.2}$$

noticing that $\Delta T = +\infty$ when $u_1 = 0$. This is important because it prescribes the *time between tests or checkups*, obviously meaningful only when $a > 1$, which corresponds to a more aggressive disease.

Remark. The equilibrium value u_1 is a function of Nc and a, and thus ΔT is a function depending on the dynamical system (2.7) and not just on the trivial exponential decay. This time for detection successfully describes the interplay between the equilibrium point u_1 and the threshold α. Notice that if $u_1 > \alpha$ the time of intervention is negative, which means that the detection was late.

We now start analyzing the power law model (4.1) case by case.

4.5. **Case $c > 0$, $a = 0$.** This borderline case, when $a = 0$ and $c > 0$, the solution is the so called Newton's equation (usually of temperature) approaching its unique stable nonzero equilibrium $u_2 = (1 + \frac{1}{Nc})^{-1}$ exponentially fast. In our interpretation, this permits an intervention since $u_2 > 0$; yet, it is successful only if $u_2 \geq \beta$ as $c \uparrow 1$.

4.6. **Case $c > 0$, $a > 0$.** This is by far the most important case and is treated in detail in Sections 6 ($a > 1$), respectively 7 ($0 < a \leq 1$). We recall that the equilibrium points of the system (2.7) are given by the zeroes of the function in (2.7). With the power law,

$$H(u) = cuf(u)\,, \qquad f(u) := u^{a-1}(1-u) - \frac{1}{Nc}\,, \quad u \in [0,1]\,. \tag{4.3}$$

Let u be an equilibrium point of the dynamical system (2.7), then $H(u) = 0$ which implies that either $u = 0$ or, for the non-zero equilibrium points of (2.7), are the solutions $u > 0$ of $f(u) = 0$. It will be shown that there are at most two $0 < u_1 \leq u_2 < 1$ such solutions.

The analysis of the stability of the equilibrium points of (2.7) will require to determine the sign of H' (see, in Section 2.4, p 24 in [15]) or, because we are in dimension one, equivalently, just the sign of H. We write H and its derivative H' in terms of f, and focus essentially on the analysis of the function f. Any result that we obtain for the function f will easily imply the corresponding consequence for the functions H, H' via the formulas

$$H(u) = cuf(u)\,, \quad H'(u) = c\left(f(u) + uf'(u)\right)\,. \tag{4.4}$$

Without loss of generality, we assume $c > 0$ and $a > 0$, since the analysis regards the system after intervention ($c > 0$) and $a = 0$ is trivial because the recovery probability $\gamma(u)$ does not depend on u. Then $0 = u_0 \leq u_1 < u_2 < 1$.

4.7. **Discussion and interpretation of the results.** The most complex case is studied in Section 6, when $a > 1$ and there are exactly two nonzero stable points. This is characterized exactly in Proposition 3 eq. (6.1) in case (2), visualized in Figure 2. The following discussion can be applied to the other cases, with the corresponding simplifications.

It is the relation between the stable points (equilibria) and α, β that decides the outcome of the treatment c, applied to the disease, identified by the parameter a. From the outset, we see that $\alpha < u_1 < \beta$, detection will occur too late. When $u_2 < \beta$, one can never

regain a satisfactory health level, even after detection. Thus the ideal configuration (6.4) is $u_1 < \alpha < \beta < u_2$, as seen below.

• **Successful treatment.** When $u_1 < \alpha < \beta < u_2$, if detection occurs at a state $u \in (u_1, \alpha)$, then recovery is achieved as the solution evolves towards u_2. Detection occurs if testing is done at intervals not greater than $\Delta T = T_\alpha - T_{u_1} = N \ln(\frac{u_1}{\alpha})$.

• **Successful detection, insufficient treatment.** Here $u_1 < \alpha < u_2 < \beta$. Detection is successful but the treatment achieves a state u_2 that may be pathological/endemic.

• **Ineffective detection, unsuccessful prophylactic treatment.** If $\alpha < u_1 < \beta < u_2$. Detection would be too late, but prophylactic treatment would prevent the disease/epidemic.

• **Non intervention case, follow up.** If $u_1 < u_2 < \alpha < \beta$, detection is early and a follow up is required. No treatment should be necessary.

• **Ineffective detection and treatment.** If $\alpha < u_1 < u_2 < \beta$, detection is too late and treatment would be ineffective. The most pessimistic scenario.

• **Ineffective detection, successful early treatment.** If $\alpha < \beta < u_1 < u_2$, detection is too late and only early treatment would be effective.

While a modulates the aggressiveness of the disease, making γ smaller, c would push it up. For a given a, u_2 is increasing, and u_1 decreasing, in c. In the first application model introduced before, the action of increasing c is equivalent to improve the treatment. Since $\gamma(u)$ is a probability, $0 \le c \le 1$, thus we could improve treatment up to $c = 1$. It is of interest to see the optimal values of u_1, u_2 we can achieve, as shown, for example in case $a > 1$, in Proposition 4.

5. Stochastic optimization approach

It is known from [1, 6] that the window of detection ΔT defined in Subsection 4.4 is one of the most important quantities from a clinical point of view. In the previous discussion, we looked at the deterministic setting when $L \to \infty$ and the limit u_t is monotone between equilibrium points of the phase diagram of (2.7).

We now propose a different approach, where the process (u_t^L) is investigated in the microscopic (moderate frequency) setting, when $L < \infty$, u_t^L is random and moves up and down, albeit in biased fashion. In this section we suppress the superscript L since it is irrelevant, and remind the reader that u_t is random.

The goal is to put in context ΔT. Consider a non-decreasing utility function $Q(u)$, $0 \le u \le 1$, a stopping time τ and the value function, defined for the initial nonrandom value $\bar{u}$

$$V(\bar{u}) = \sup_\tau E_{\bar{u}}\Big[\int_\tau^\infty Q(u_t)dt\Big].$$

Natural choices of $Q(u)$, which we interpret as a *quality of life index*, should satisfy $Q(u) \leq 0$ for $0 < \beta$, $Q(u) \geq 0$ for $\beta \leq u \leq 1$, e.g. $Q(u) = \mathbf{1}_{[\beta,1]}(u)$ as we assume in (4.2) in the simplest case. Another candidate is $Q(u) = \ln \frac{u}{\beta}$. This example emphasizes that $\lim_{u\to 0^+} Q(u) = -\infty$. The problem is of practical interest when $\alpha < \bar{u} < \beta$. In this interval, we cannot detect the disease but the quality of life index is negative. We are interested if $V(\bar{u}) > 0$ is possible. Evaluating $\tau = \tau(\bar{u})$ suggests the relation

$$\Delta T \sim \lim_{\bar{u}\downarrow\alpha} E_{\bar{u}}[\tau]$$

if the window of detection corresponds to the worst-case scenario that would still allow a positive outcome. A similar model may be formulated when the utility function is the cost of the treatment, incorporating the cost of testing to counterbalance the benefits of too early testing; otherwise it may appear beneficial to test with the highest frequency, provided there is no cost involved.

We finally point to a connection to Shepp's urn [13], where L. Shepp proved the Chow-Robbins conjecture (see also [2, 3, 4] later on). Let's assume the urn under consideration has U_t lucky marbles and $L - U_t$ unlucky marbles. Drawing the former increases K_t by one unit, a quantity we shall call the individual's *health capital* (see, for example, [10]), while drawing the latter decreases it by one unit. Somewhat speculatively, K_t should be an index related, but not equal, to the life expectancy, incorporating quality of life as a weighing factor. It is reasonable to adopt the value K_0 at $t = 0$ satisfying $0 \leq K_0 \leq L$ and a policy of *risk aversion*, i.e. $K_t \geq 0$ at all times $t \geq 0$. If zero is reached, we stop. Let τ_0 be the hitting time of zero. The natural optional stopping problem, generalizing both [13] and [4], which we shall call the *Modified Shepp Urn with Risk Aversion*, is to maximize the health capital looking forward in time, when starting at $U = \bar{U}$, obtaining the value function

$$V(K_0, \bar{U}) = \sup_{\tau\wedge\tau_0} E_{K_0,\bar{U}}\left[K_\tau\right].$$

The modification comes from the fact that the number of marbles is constant, whereas in the original Shepp's urn it is done without replacement. In this case, τ in the optimal stopping aims at maximizing the health capital rather *before intervention*.

6. The case $a > 1$

Proposition 3. *If $\gamma(u) = cu^a$ and $a > 1$, then the point $u_0 = 0$ is always a stable equilibrium point in the sense that $H(u) < 0$ in a positive neighborhood of u_0. For any $a > 1$ the function $f(u)$ (4.3) has a maximum value at $u_m = 1 - \frac{1}{a}$*

$$q = \frac{1}{a}\left(1 - \frac{1}{a}\right)^{a-1} - \frac{1}{Nc}. \tag{6.1}$$

Then, the number of equilibrium points in $[0,1]$ *of the dynamical system (2.7) is determined by the sign of the number* q*;*

(1) *if* $q<0$*, the only equilibrium point is* $u_0=0$*.*
(2) *if* $q>0$*, there are 3 equilibrium points* $0=u_0<u_1<u_2<1$*. The points* u_0 *(seen for* $u\geq 0$*) and* u_2 *are stable, and* u_1 *is unstable and* $u_1<u_m<u_2$*.*
(3) *if* $q=0$*, there are two equilibrium points, namely* $u_0=0$ *and* $u_1=u_2=u_m$*;* u_0 *is stable, and* u_m *is half-stable.*

Proof. Part 1. Number of equilibrium points. The function f defined in (4.3) satisfies $f(0)=f(1)=-\frac{1}{Nc}<0$, thus it has an extreme value in the interval $(0,1)$. The derivative of the function f is given by

$$f'(u)=au^{a-2}\left(\frac{a-1}{a}-u\right), \tag{6.2}$$

hence it has a unique zero at the point $u_m=\frac{a-1}{a}$ on the interval $(0,1)$. This point is a global maximum over the interval $[0,1]$. Hence the function f, over the same interval, is less or equal to the value q given by

$$q=f\left(\frac{a-1}{a}\right)=\frac{1}{a}\left(1-\frac{1}{a}\right)^{a-1}-\frac{1}{Nc}\,. \tag{6.3}$$

The function f is continuous and it is strictly monotone restricted to the intervals $[0,u_m]$ and $[u_m,1]$; then f is injective on each of these intervals. If $q<0$, the equation $f=0$ has no solutions. If $q=0$, a unique solution is obtained at u_m, and if $q>0$, then there are two solutions that we denote by $0<u_1<u_2<1$ (see Section 2).

Part 2. Stability. For the point $u_0=0$ we have that $H'(0)=-\frac{1}{N}<0$, and thus it is always a stable point.

In the case $q>0$, let's denote these points by $u_0=0$, u_1, and u_2, with $u_1<u_2$ as before. We notice that $u_1\in(0,u_m)$ and that $u_2\in(u_m,1)$. Hence, we have from 4.4 that, $H'(u_1)=cu_1f'(u_1)>0$, and hence u_1 is an unstable point. Similarly, we have that $H'(u_2)=cu_2f'(u_2)<0$ which means that u_2 is a stable point.

In case $q=0$, we have that $f(u_m)=f'(u_m)=0$. Since f attains global maximum at u_m we have that: $H(u)=cuf(u)<cuf(u_m)=0$, $\forall u\in[0,1]$. Hence, the point u_m is half-stable.

□

Proposition 4. *(i) The function* $q=q(a)$ *is decreasing for* $a\geq 1$ *with maximum value at* $a=1$ *equal to* $q(1)=1-\frac{1}{cN}$*, equal to the limiting value of* u_1 *when* $a\downarrow 1$ *and minimum value* $q(\infty)=-\frac{1}{cN}<0$*.*

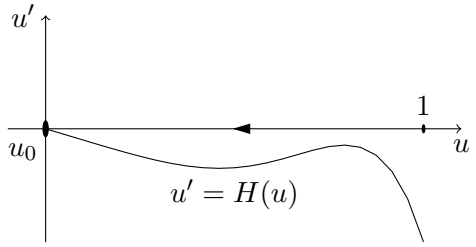

FIGURE 1. Phase Portrait case $q < 0$, obtained by selecting $a = 5$, $N = 10$, $c = 1$. The unique equilibrium point u_0 is stable.

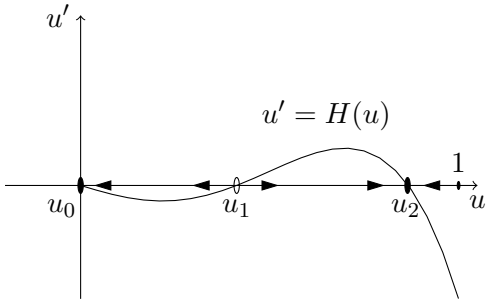

FIGURE 2. Phase Portrait case $q > 0$, obtained by selecting $a = 3$, $N = 10$, $c = 1$. The equilibrium points u_0, u_2 are stable, and u_1 is unstable.

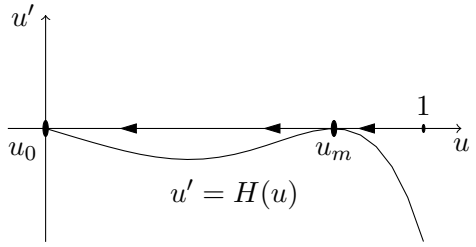

FIGURE 3. Phase Portrait case q = 0, obtained by selecting $a = 4.2$, $N = 10$, $c = 1$. The equilibrium point u_0 is stable, and $u_m = u_1 = u_2$ is half-stable.

(ii) If $q(1) \leq 0$, then $H(u) \leq 0$ and the only equilibrium point is $u_0 = 0$; no recovery is possible (fig. 1).

(iii) In case $q(1) > 0$, there exists a critical value $a_* = a_*(cN)$ equal to the solution of $q(a) = 0$, satisfying $1 < a_* < cN$. For $a \in (1, a_*)$ the system is in case (2) of Proposition 3 (fig. 2), reaching case (3) for $a = a_*$ (fig. 3). For $a > a_*$ we are in case (1).

(iv) Additionally, for fixed $N > 1$ and $a \in (1, a_*(N))$, there exists a value c_0 such that $a \in (1, a_*(cN))$ when $c \in (c_0, 1]$ and letting the treatment *intensity $c \uparrow 1$, the values of $u_i(c)$, $i = 1, 2$, seen as functions of c satisfy $u_1 \downarrow u_1(1)$ and $u_2 \uparrow u_2(1)$. The* successful treatment window *exists at $c = 1$, most efficient treatment, if the double inequality*

$$0 \le u_1(1) \le \alpha < \beta \le u_2(1) < 1 \tag{6.4}$$

is satisfied.

Remark. The restriction that $c \le 1$ is intrinsic to the power law model $\gamma(u) = cu^a$, $a \ge 0$, since $\gamma(\frac{U}{L})$ must be a probability, before scaling. In principle, it appears meaningful to have monotonicity in c (increasing) for γ, and other models may be considered, including $\gamma(u) = cu^a \wedge 1$ or a consistent mollification.

Proof. The function $a \to q(a)$ will be decreasing if and only if the function $a \to p(a) = \frac{1}{a}\left(1 - \frac{1}{a}\right)^{(a-1)}$ is decreasing since q is a translation of p. An elementary calculation shows that the derivative of p is negative when $a > 1$. In detail,

$$\ln(p(a)) = -\ln(a) + (a-1)\left(\ln(a-1) - \ln(a)\right), \quad \frac{d}{da}\ln(p(a)) = \ln\left(1 - \frac{1}{a}\right) < 0\,.$$

With this in mind, it is imemdiate that (i), (ii) and (iii) hold. The inequality $a_* < cN$ is necessary because in the formula of $q(a)$ the factor $(1 - \frac{1}{a})^{a-1} < 1$. To prove (iv), note that now $N > 0$ and $a \in (1, a_*(N))$ are fixed. From the analysis of the function $a \to p(a)$, we see that $c \to a_*(cN)$ is increasing, as follows. The larger c is, $1/cN$ is smaller and so, knowing that $a \to p(a)$ is decreasing, $p(a_*) = \frac{1}{cN}$ implies $a_*(cN)$ is larger. Now, we see that for $a \in (1, a_*(N))$, there exists a value c_0 such that $a \in (1, a_*(cN))$ when $c \in (c_0, 1]$. To conclude (iv), we have to prove the dependence of $u_i = u_i(c)$, $i = 1, 2$ using the implicit function theorem in $f(u) = 0$, or equivalently, $u^{a-1}(1-u) = \frac{1}{cN}$. Put $B(u) = (a-1)\ln u + \ln(1-u) = -\ln N - \ln c$. Since

$$(\frac{\partial B}{\partial u})(\frac{\partial u}{\partial c}) = -\frac{1}{c} < 0$$

we only have to show that

$$\frac{\partial B(u_1)}{\partial u} > 0 \quad \text{and} \quad \frac{\partial B(u_2)}{\partial u} < 0 \tag{6.5}$$

to prove the monotonicity of $u_i(c)$ in the variable c, $i = 1, 2$. But $u \to B(u)$ is strictly concave, hence $u \to B'(u)$ is decreasing. It has values $B'(0+) = +\infty$ and $B(1-) = -\infty$. We know that $B(u_1) = B(u_2)$ so the only zero of $B'(u)$ is in between u_1 and u_2. This proves (6.5). The claim (6.4) reflects the discussion in Subsection 4.7, first bullet sign, *Successful treatment*. For given $0 < \alpha < \beta < 1$ we need to verify that there exists $c \in [0, 1]$ such that

$u_1(c) < \alpha < \beta < u_2(c)$. We just proved that the smallest $u_1(c)$ and the largest $u_2(c)$ are achieved at $c = 1$. □

7. Case $a \in (0, 1]$

7.1. **The case $a = 1$.** We start analyzing the case $a = 1$. The following proposition is the continuous version discussed in [9]. We note that now $q(1) = 1 - \frac{1}{Nc}$.

Proposition 5. *Under the conditions of Theorem 1, if $a = 1$, equivalently $\gamma = cu$, then $u(t)$ solves the standard logistic equation*

$$\frac{du}{dt} = cu(u_2 - u)\,, \qquad u(0) = \bar{u}\,. \tag{7.1}$$

with carrying capacity $u_2 = q(1)$. For $q(1) \leq 0$ the solution converges to zero, and for $q(1) > 0$, the solution converges to the unique nonzero stable stationary state u_2. There is no unstable equilibrium u_1.

Proof. The classical solution of the logistic equation (see Section 1.2 in [8])

$$u(t) = u_2 \left(1 + (\frac{u_2}{\bar{u}} - 1)e^{-cu_2 t}\right)^{-1}\,, \qquad \bar{u} \neq 0 \tag{7.2}$$

and $u(t) \equiv 0$ when $\bar{u} = 0$, proves the results, considering that the initial value $\bar{u} \in [0, 1]$ by construction. □

7.2. **The case $a \in (0, 1)$.**

Proposition 6. *If $\gamma(u) = cu^a$, $0 < a < 1$, then there are exactly two equilibrium points $u_0 = 0$, and u_2 in $(0, 1)$ of the dynamical system 2.7. The point u_0 is unstable, and u_2 is stable (fig. 4).*

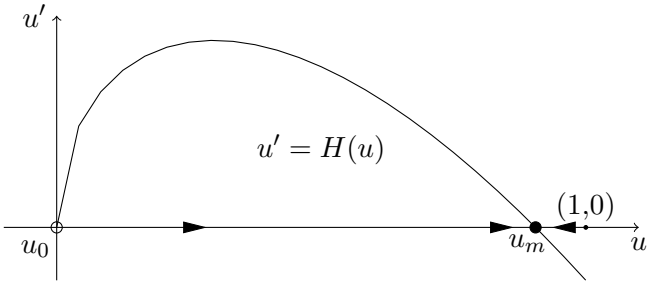

Figure 4. Phase Portrait obtained by selecting $a = \frac{1}{2}$, $N = 10$, $c = 1$. The equilibrium point u_0 is unstable, and $u_m = u_2$ is stable. Note that u_m is defined in Proposition 3, part (3).

Proof. Part 1. Number of equilibrium points. As before $u_0 = 0$ is an equilibrium point.

Let $u > 0$, we have that $\lim_{u\to 0^+} f(u) = +\infty$ and $f(1) = -\frac{1}{Nc}$. The continuity of f on $(0, 1]$ guarantees that $f = 0$ has a solution on the same interval. Thus, we will have at least one more equilibrium point on $(0, 1)$.

To determine the precise number of solutions we recall that $f'(u) = au^{a-2}\left(\frac{a-1}{a} - u\right)$. Since $a < 1$, then $f'(u) < 0$, thus f' is strictly decreasing and therefore f injective. Hence, we obtain only one equilibrium point u_2 in $(0, 1)$ (see Section 1).

Part 2. Stability. For the point $u_0 = 0$ we notice that, since $\lim_{u\to 0^+} f(u) = +\infty$, then for points greater but close enough to zero the expression $H(u) = cuf(u)$ is positive. We conclude then that $u_0 = 0$ is unstable in this case.

For the analysis of the point u_2 we begin by noticing that since $f' < 0$, then in particular $f'(u_2) < 0$. Thus, $H'(u_2) = cu_2f'(u_2) < 0$, so u_2 is a stable point. □

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