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► **To cite this version:**

Romain Bourget, Loïc Chaumont, Natalia Sapoukhina. On emergence times in competition processes. 2011. hal-00595912v3

HAL Id: hal-00595912

<https://hal.science/hal-00595912v3>

Preprint submitted on 8 Jul 2011 (v3), last revised 23 Oct 2013 (v5)

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On emergence times in competition processes

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Received: date / Accepted: date

Abstract The estimation of the time by which mutants adapted to control measures emerge is a new challenge in modern epidemiology. Here, we use competition processes, the extension of birth-death processes in higher dimensions, to study the time S by which a particular type emerges in a controlled population through a spontaneous birth or mutation. We give some bounds for the tail of the probability distribution of S . Then using properties of quasi-stationary distributions, we give conditions for the existence of an initial law under which S is exponentially distributed. Finally, we provide some examples of our model use for the estimation of the emergence time of pathogen mutants overcoming host resistance in a host-pathogen system.

Keywords Competition processes · emergence time · exponential decay · quasi-stationary distribution · host-pathogen system.

Mathematics Subject Classification (2000) 92D25 · 60J28

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1 Introduction

The population adaptation to control measures, such as emergence of a pathogen pathotype infecting a resistant host, or of a pathogen evading chemical treatment, or a cancer cell escaping from chemotherapy, etc. [5, 7, 8, 17], leads to a swift reduction of the number of effective disease control strategies. Thus, the estimation of the time by which adapted mutants emerge, like the estimation of the durability of a new crop resistance or the success probability of a new treatment, is a crucial problem in modern epidemiology. Indeed, studying the emergence time could help us to clarify key-factors and processes allowing us to prolong the durability of control strategies.

Stochastic modelling is a well suited approach for describing such a random process in adaptive dynamics like mutations. Paradoxally, branching processes suited well for studying population extinction [2, 12] are not widespread for studying the emergence of new populations. There are only a few works where authors consider emergence but only under specific progeny distribution laws [8, 16, 17]. Emergence problem has also been considered in multitype Moran models [4] and within the framework of the adaptation theory [13]. Unfortunately, Moran type models are inefficient for the estimation of the emergence time, since the population size grows with the appearance of a new adapted subpopulation. In adaptation theory, emergence is described by the estimation of the fixation time of an allele. The fixation time represents the time before one allele have invade whole population, so it can not be applied to the time when pathogen has defeated a control strategy. Thus, there is a lack of the general theoretical framework for the estimation of the emergence time in branching processes.

In comparison with the aforesaid approaches, multitype birth and death processes models, called *competition processes*, are more adapted to the general study of the emergence problems, since they allow adjusting birth, death and mutation rates to studied biological system. A competition process $(X, \{\mathbb{P}_i : i \in \mathbb{N}_0^d\})$ is a continuous time homogeneous Markov chain with state space \mathbb{N}_0^d , for $d \geq 1$, whose transition matrix only allows jumps to certain nearest neighbors. Competition processes were introduced by Reuter [15] as the natural extensions of birth and death processes and are often involved in epidemic models [3, 5, 8, 10]. Here, we use competition processes in order to study adaptive population dynamics. Let us first give a proper definition.

We call $\{p_t(i, j) : t \geq 0, i, j \in \mathbb{N}_0^d\}$ the transition probability functions of the Markov chain $X = \{(X_t^{(1)}, \dots, X_t^{(d)}), t \geq 0\}$, and we denote by $Q = \{q(i, j) : i, j \in \mathbb{N}_0^d\}$ the associated Q -matrix, i.e. $q(i, j) = p'_0(i, j)$. Let $i =$

(i_1, \dots, i_d) , then this matrix is defined as follows:

$$\begin{aligned}
q(i, j) &= \lambda_k(i), \quad j = (i_1, \dots, i_{k-1}, i_k + 1, i_{k+1}, \dots, i_d) \\
&= \mu_k(i), \quad j = (i_1, \dots, i_{k-1}, i_k - 1, i_{k+1}, \dots, i_d) \\
&= \gamma_{kl}(i), \quad j = (i_1, \dots, i_{k-1}, i_k - 1, i_{k+1}, \dots, i_{l-1}, i_l + 1, i_{l+1}, \dots, i_d) \\
&= \gamma_{lk}(i), \quad j = (i_1, \dots, i_{k-1}, i_k + 1, i_{k+1}, \dots, i_{l-1}, i_l - 1, i_{l+1}, \dots, i_d) \\
&= - \sum_{x \neq i} q(i, x), \quad j = i \\
&= 0, \quad \text{for other } j.
\end{aligned}$$

The value $q(i, j)$ is the transition rate at which the process jumps from the state i to the state j . For $k, l \in \{1, \dots, d\}$, λ_k , μ_k and γ_{kl} , are nonnegative functions. The values $\lambda_k(i)$ and $\mu_k(i)$ represent the rates at which an individual of type k is born or dies, respectively, when the population is of size $i \in \mathbb{N}_0^d$. The values γ_{kl} represent the rates at which an individual of type k mutates into an individual of type l . We assume that for all k and l , $\mu_k(i) = \gamma_{kl}(i) = 0$ if $i_k = 0$. We emphasize that Q is conservative, i.e. $q(i, i) = - \sum_{j \neq i} q(i, j)$, for all $i \in \mathbb{N}_0^d$, so that the Q -matrix is related to the transition functions through the backward and forward Kolmogorov equations. We also make the classical regularity assumption under which the Q -matrix determines the law of X , see for instance [6]. So X stays in state i for an exponential time with parameter $\sum_{x \neq i} q(i, x)$ and then jumps to state j with probability $q(i, j) \left(\sum_{x \neq i} q(i, x) \right)^{-1}$.

In this paper, we are interested in the computation of the law of the first time S_r when an individual of type $r = 1, \dots, d$ first emerges from the population (Fig. 1), i.e.

$$S_r = \inf\{t \geq 0 : X_t^{(r)} = 1\},$$

which can biologically represent the first appearance of a particular mutant in the population. Let us also point out that in some cases, type r may become extinct after the time S_r , so that this time may not correspond to the first time at which type r will settle definitively in the population. In such situations, it is still possible to use the same method to study the time $\inf\{t \geq 0 : X_t^{(r)} = n\}$, when n is a level by which type r is definitively settled, with an arbitrary large probability.

This paper is organized as follows. In Section 2, we first give an estimation of the distribution function of the emergence time when the process starts from any initial law supported by the set $\{i \in \mathbb{N}_0^d : i_r = 0\}$. Then we show that when the initial law is a quasi-stationary distribution, the emergence time is exponentially distributed with a parameter which is made explicit in terms of the transition rates. In Section 3, we discuss some conditions for the existence of quasi-stationary distributions. In Section 4, as an application of these results, we give a biological example of the time for pathogen type overcome host resistance. Section 5 summarizes our findings and gives some implications of our general model in evolutionary epidemiology. Then Section 6 is an annex which is devoted to the proof of a technical lemma.

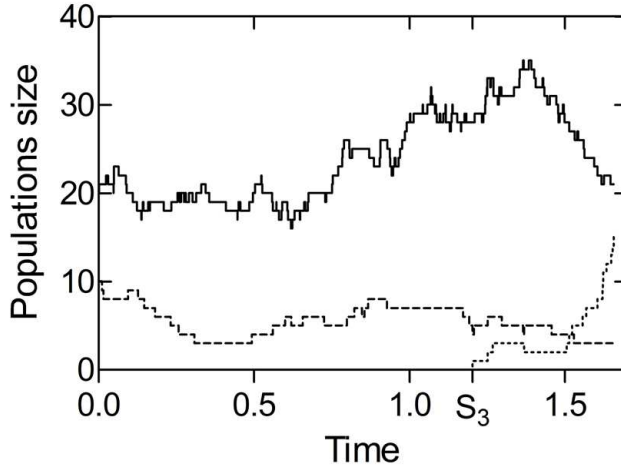


Fig. 1 Emergence time of a three dimensional competition process. This sample path shows the variations of the three populations over the time. Solid line, big dashed line and small dashed line correspond to first, second and third type, respectively. Then S_3 is the emergence time of the third type.

2 Emergence of a particular type.

In this section, we consider a competition process $(X, \{\mathbb{P}_i : i \in \mathbb{N}_0^d\})$ as it is defined in the introduction. Although our model is based on competition processes, some results of this section may be generalized to general continuous time Markov chains. For the sake of simplicity, we suppose that the type whose emergence time is of interest is d . So in the sequel, we denote S_d by S , i.e. with $X = (X^{(1)}, \dots, X^{(d)})$, we set

$$S = \inf\{t \geq 0 : X_t^{(d)} = 1\}.$$

2.1 Some bounds for the tail distribution.

This subsection aims at describing the time S in terms of the characteristics of the competition process X , in order to determine the exponential decay of its distribution function, under general conditions.

Definition 1 We set for all $i \in \mathbb{N}_0^d$,

$$\eta(i) = \lambda_d(i) + \sum_{l=1}^d \gamma_{ld}(i).$$

The values $\eta(i)$ will be called the *emergence rates* (of type d). In particular, when X is in a state i , an individual of type d will appear with probability $\eta(i) \left(\sum_{j \neq i} q(i, j) \right)^{-1}$.

We define the restricted process \hat{X} as the $(d-1)$ -dimensional competition process with rates $\hat{q}(x, y) = q(x', y')$, if $x \neq y$, where $x = (x_1, \dots, x_{d-1})$, $y = (y_1, \dots, y_{d-1})$ and $x' = (x_1, \dots, x_{d-1}, 0)$, $y' = (y_1, \dots, y_{d-1}, 0)$ and $\hat{q}(x, x) = -\sum_{y \in \mathbb{N}_0^{d-1}, x \neq y} \hat{q}(x, y)$. We denote by $\{\hat{\mathbb{P}}_x : x \in \mathbb{N}_0^{d-1}\}$ the family of probability distributions of the process \hat{X} . Then we may check that $(\hat{X}, \{\hat{\mathbb{P}}_x : x \in \mathbb{N}_0^{d-1}\})$ is a competition process on \mathbb{N}_0^{d-1} whose Q -matrix is $\hat{Q} = \{\hat{q}(x, y) : x, y \in \mathbb{N}_0^{d-1}\}$.

In all the remainder of this paper, we assume that the Q -matrices Q and \hat{Q} are regular, i.e. they determine the laws of X and \hat{X} respectively, in a unique way. We refer to Section 2 of [6] where some sufficient conditions for regularity of Q -matrices of competition processes are obtained. We begin this subsection with the following lemma which presents a decomposition of the process X up to time S .

Lemma 1 *Let $\{\varepsilon(x) : x \in \mathbb{N}_0^{d-1}\}$ be a family of random variables which is independent of the process \hat{X} . We suppose that each random variable $\varepsilon(x)$ is exponentially distributed with parameter $\eta(x')$, where $x' = (x_1, \dots, x_{d-1}, 0)$. Let $(T_n)_{n \geq 1}$ be the sequence of jump times of \hat{X} , set $T_0 = 0$, define $I_n = T_n - T_{n-1}$, $n \geq 1$ and*

$$\hat{S} = \sum_{n=0}^{\infty} (T_n + \varepsilon(\hat{X}_{T_n})) \mathbb{I}_{\Omega_n}, \quad (2.1)$$

where $\Omega_n = \{\varepsilon(\hat{X}_{T_0}) > I_1, \dots, \varepsilon(\hat{X}_{T_{n-1}}) > I_n, \varepsilon(\hat{X}_{T_n}) \leq I_{n+1}\}$, for $n \geq 1$ and $\Omega_0 = \{\varepsilon(\hat{X}_0) \leq I_1\}$. Then for all $x \in \mathbb{N}_0^{d-1}$, we have the identity in law

$$[(X_u^{(1)}, \dots, X_u^{(d-1)}), u < S], \mathbb{P}_{(x,0)} = [(\hat{X}_u, u < \hat{S}), \hat{\mathbb{P}}_x].$$

Proof This result is a direct consequence of the general structure of continuous time Markov chains. Indeed, it suffices to observe that when the process X is in a state $i \in \mathbb{N}_0^{d-1} \times \{0\}$, the waiting time for type d to emerge is independent from the past and exponentially distributed, with parameter $\eta(i) = \lambda_r(i) + \sum_{l=1}^d \gamma_{lr}(i)$. Hence it is clear that before time S , the process X behaves like a competition process in \mathbb{N}_0^{d-1} , i.e. \hat{X} killed at a time \hat{S} , whose decomposition is given by equation (2.1).

As an application of this lemma, the following result provides exponential bounds for the distribution function of the emergence time. From now on we set

$$E = \mathbb{N}_0^{d-1} \times \{0\}.$$

Theorem 1 Define the rates $\alpha_0 = \inf_{i \in E} \eta(i)$ and $\alpha_1 = \sup_{i \in E} \eta(i)$. Then the tail distribution of the emergence time S satisfies the inequalities:

$$e^{-\alpha_1 t} \leq \mathbb{P}_i(t < S) \leq e^{-\alpha_0 t}, \quad (2.2)$$

for all $t \geq 0$ and for all $i \in E$. In particular, if there exists $\alpha > 0$ such that $\eta(i) = \alpha$, for all $i \in E$, then the emergence time S has an exponential law with parameter α under \mathbb{P}_μ , for all initial distribution μ with support in E .

Proof It follows from Lemma 1 that for all $x \in \mathbb{N}_0^{d-1}$ and $t \geq 0$,

$$\begin{aligned} & \mathbb{P}_{(x,0)}(t < S) \quad (2.3) \\ &= \hat{\mathbb{P}}_x(t < \hat{S}) \\ &= \sum_{n=0}^{\infty} \sum_{x_0, \dots, x_n \in \mathbb{N}_0^{d-1}} \hat{\mathbb{P}}_x(t < T_n + \varepsilon(\hat{X}_{T_n}), \Omega_n \mid \hat{X}_{T_0} = x_0, \dots, \hat{X}_{T_n} = x_n) \times \\ & \quad \hat{\mathbb{P}}_x(\hat{X}_{T_0} = x_0, \dots, \hat{X}_{T_n} = x_n), \quad (2.4) \end{aligned}$$

where $x_0 = x$. Then, from the Markov property and the assumption on the random variables $\{\varepsilon(x) : x \in \mathbb{N}_0^{d-1}\}$ in Lemma 1, under $\hat{\mathbb{P}}_x$, conditionally on $\{\hat{X}_{T_0} = x_0, \dots, \hat{X}_{T_n} = x_n\}$, the random variables $I_1, \dots, I_{n+1}, \varepsilon(x_0), \dots, \varepsilon(x_n)$ are independent. So with $I = (I_1, \dots, I_{n+1})$ and $y = (y_1, \dots, y_{n+1})$, one has

$$\begin{aligned} & \hat{\mathbb{P}}_x(t < T_n + \varepsilon(\hat{X}_{T_n}), \Omega_n \mid \hat{X}_{T_0} = x_0, \dots, \hat{X}_{T_n} = x_n) \quad (2.5) \\ &= \int_{\mathbb{R}_+^{n+1}} \hat{\mathbb{P}}_x(I \in dy) \hat{\mathbb{P}}_x(\varepsilon(x_0) > y_1, \dots, \varepsilon(x_{n-1}) > y_n, t - t_n < \varepsilon(x_n) < y_{n+1}), \end{aligned}$$

where $t_n = y_1 + \dots + y_n$. For all $k \geq 0$, set $x'_k = (x_k, 0)$. The integrand in the above integral may be written as

$$\begin{aligned} & \hat{\mathbb{P}}_x(\varepsilon(x_0) > y_1, \varepsilon(x_1) > y_2, \dots, \varepsilon(x_{n-1}) > y_n, t - t_n < \varepsilon(x_n) < y_{n+1}) \quad (2.6) \\ &= e^{-\eta(x'_0)y_1 - \eta(x'_1)y_2 - \dots - \eta(x'_{n-1})y_n} (e^{-\eta(x'_n)[(t-t_n) \vee 0]} - e^{-\eta(x'_n)y_{n+1}}) \mathbb{1}_{\{t < t_{n+1}\}}, \end{aligned}$$

where for $n = 0$, the term $e^{-\eta(x'_0)y_1 - \eta(x'_1)y_2 - \dots - \eta(x'_{n-1})y_n}$ is understood to be 1. Hence by applying successively (2.6), (2.5) and (2.4), it follows

$$\begin{aligned} & \mathbb{P}_{(x,0)}(t < S) \\ &= \hat{\mathbb{E}}_x \left(\sum_{n=0}^{\infty} e^{-\eta(X'_0)I_1 - \dots - \eta(X'_{n-1})I_n} \left[e^{-\eta(X'_n)[(t-T_n) \vee 0]} - e^{-\eta(X'_n)I_{n+1}} \right] \mathbb{1}_{\{t < T_{n+1}\}} \right), \end{aligned}$$

where for each n , $X'_n = (\tilde{X}_n, 0)$ and $\{\tilde{X}_n : n \geq 0\}$ is a sequence of random variables which has the same law as $\{\hat{X}_n : \geq 0\}$ under $\hat{\mathbb{P}}_x$ and which is independent of the sequence $\{T_n : n \geq 0\}$. Let k be the (random) index such that

$T_k \leq t < T_{k+1}$, then we easily check that the term which is in the expectation of the right hand side of the above equality is

$$\begin{aligned} & \sum_{n=0}^{\infty} e^{-\eta(X'_0)I_1 - \dots - \eta(X'_{n-1})I_n} \left[e^{-\eta(X'_n)[(t-T_n) \vee 0]} - e^{-\eta(X'_n)I_{n+1}} \right] \mathbb{1}_{\{t < T_{n+1}\}} \\ &= e^{-\eta(X'_0)I_1 - \dots - \eta(X'_{k-1})I_k} \left[e^{-\eta(X'_k)(t-T_k)} - e^{-\eta(X'_k)I_{k+1}} \right] \\ & \quad + \sum_{n=k+1}^{\infty} e^{-\eta(X'_0)I_1 - \dots - \eta(X'_{n-1})I_n} \left[1 - e^{-\eta(X'_n)I_{n+1}} \right] \\ &= e^{-\eta(X'_0)I_1 - \dots - \eta(X'_{k-1})I_k} e^{-\eta(X'_k)(t-T_k)}. \end{aligned}$$

But from the assumption, we have $\eta(X'_n) \geq \alpha_0$, a.s., for each $n \geq 0$, so that it follows $e^{-\eta(X'_0)I_1 - \dots - \eta(X'_{k-1})I_k} e^{-\eta(X'_k)(t-T_k)} \leq e^{-\alpha_0(I_1 + \dots + I_k)} e^{-\alpha_0(t-T_k)} = e^{-\alpha_0 t}$, a.s. which gives the second inequality in (2.2).

The other inequality is proved in the same way, by obtaining an upper bound for $\hat{\mathbb{P}}_x(T_n + \varepsilon(\hat{X}_{T_n}) \leq t, \Omega_n \mid \hat{X}_{T_1} = x_1, \dots, \hat{X}_{T_n} = x_n)$. As above, this term can be desintegrated as

$$\begin{aligned} & \hat{\mathbb{P}}_x(T_n + \varepsilon(\hat{X}_{T_n}) \leq t, \Omega_n \mid \hat{X}_{T_1} = x_1, \dots, \hat{X}_{T_n} = x_n) \\ &= \int_{\mathbb{R}_+^n} P(I \in dy) P(\varepsilon(x_0) > y_1, \varepsilon(x_1) > y_2, \dots, \varepsilon(x_{n-1}) > y_n, \\ & \quad \varepsilon(x_n) < y_{n+1} \wedge (t - t_n)), \end{aligned}$$

and for the integrand, we have

$$\begin{aligned} & P(\varepsilon(x_0) > y_1, \varepsilon(x_1) > y_2, \dots, \varepsilon(x_{n-1}) > y_n, \varepsilon(x_n) < y_{n+1} \wedge (t - t_n)) \\ &= e^{-\eta(x'_0)y_1 - \eta(x'_1)y_2 - \dots - \eta(x'_{n-1})y_n} (1 - e^{-\eta(x'_n)[y_{n+1} \wedge (t-t_n)]}) \mathbb{1}_{\{t_n \leq t\}}, \end{aligned}$$

so that

$$\begin{aligned} & \mathbb{P}_{(x,0)}(t < S) \\ &= \hat{\mathbb{E}}_x \left(\sum_{n=0}^{\infty} e^{-\eta(X'_0)I_1 - \eta(X'_1)I_2 - \dots - \eta(X'_{n-1})I_n} (1 - e^{-\eta(X'_n)[I_{n+1} \wedge (t-T_n)]}) \mathbb{1}_{\{T_n \leq t\}} \right). \end{aligned}$$

If k is such that $T_k \leq t < T_{k+1}$, then

$$\begin{aligned} & \sum_{n=0}^{\infty} e^{-\eta(X'_0)I_1 - \eta(X'_1)I_2 - \dots - \eta(X'_{n-1})I_n} (1 - e^{-\eta(X'_n)[I_{n+1} \wedge (t-T_n)]}) \mathbb{1}_{\{T_n \leq t\}} \\ &= \sum_{n=0}^{k-1} e^{-\eta(X'_0)I_1 - \eta(X'_1)I_2 - \dots - \eta(X'_{n-1})I_n} (1 - e^{-\eta(X'_n)I_{n+1}}) + \\ & \quad e^{-\eta(X'_0)I_1 - \eta(X'_1)I_2 - \dots - \eta(X'_{k-1})I_k} (1 - e^{-\eta(X'_k)(t-T_k)}) \\ &= 1 - e^{\eta(X'_k)t}. \end{aligned}$$

But since $\eta(X'_k) \leq \alpha_1$, a.s., we have $1 - e^{\eta(X'_k)t} \leq 1 - e^{-\alpha_1 t}$, a.s., which proves the first inequality in (2.2).

We emphasize that for Proposition 1 to be relevant in the applications it is necessary that $\alpha_0 > 0$ and/or $\alpha_1 < \infty$. In practice, the emergence rates are often bounded away from 0 and ∞ . At least, most of the time, it is reasonable to make this assumption, see the application of Section 4.

2.2 Using quasi-stationary distributions

As already seen in the previous subsection, in order to study the emergence time S , it is necessary to have a good description of the whole process X up to this time. To be more specific, we introduce the killed process at time S , as follows:

$$X_t^S = \begin{cases} X_t, & \text{if } t < S, \\ \Delta, & \text{if } t \geq S, \end{cases} \quad (2.7)$$

where Δ is a cemetery point. Then X^S is a continuous time Markov chain which is valued in $E \cup \{\Delta\}$, whose Q -matrix $Q^S = (q^S(i, j))$ is given by

$$q^S(i, j) = \begin{cases} q(i, j), & i, j \in E \\ q(i, \Delta) = \eta(i), & i \in E \\ q(\Delta, j) = 0, & j \in E \cup \{\Delta\}. \end{cases} \quad (2.8)$$

Again, we assume that the matrix Q^S is regular, so that there exists a unique associated transition probability that we will denote by P^S . We define the vector δ by $\delta(i) = 0$, if $i \in E$ and $\delta(\Delta) = 1$.

Theorem 2 *A probability distribution μ on E satisfies*

$$\mathbb{P}_\mu(X_t = i \mid S > t) = \mu(i), \quad (2.9)$$

for all $t \geq 0$ and $i \in E$, if and only if it solves the equation

$$\mu Q^S = -\alpha \mu + \alpha \delta, \quad (2.10)$$

for some $\alpha \in [0, \infty)$. Moreover under \mathbb{P}_μ , the time S is exponentially distributed with parameter

$$\alpha = \sum_{i \in E} \eta(i) \mu(i). \quad (2.11)$$

Proof Let us first show that under condition (2.9), the time S is exponentially distributed. Let $s, t \geq 0$, then from the definition of S and the Markov property applied at time s , we have

$$\begin{aligned} \mathbb{P}_\mu(S > s + t) &= \mathbb{P}_\mu(\mathbb{1}_{\{t < S\}} \mathbb{P}_{X_t}(s < S)) \\ &= \mathbb{P}_\mu(t < S) \mathbb{P}_\mu(s < S), \end{aligned}$$

where the last equality follows from (2.9). This proves our assertion.

Then suppose that condition (2.9) holds and let α be the parameter of the law of time S . Since $\eta(i) < \infty$, for all $i \in E$, we have $\mathbb{P}_i(S = 0) = 0$, for all

$i \in E$, so that $\mathbb{P}_\mu(S = 0) = 0$, therefore $\alpha < \infty$. We extend the law μ on $E \cup \Delta$ by setting $\mu(\Delta) = 0$. Then for all $i \in E \cup \Delta$, one has

$$\mathbb{P}_\mu(X_t^S = i) = \mathbb{P}_\mu(X_t = i, t < S) + \mathbb{1}_{i=\Delta} \mathbb{P}_\mu(t \geq S).$$

Since $\mathbb{P}_\mu(X_t = i, t < S) = e^{-\alpha t} \mu(i)$, the transition function $P^S(t)$ of X^S satisfies

$$\mu P^S(t) = e^{-\alpha t} \mu + (1 - e^{-\alpha t}) \delta. \quad (2.12)$$

Differentiating with respect to t and applying Kolmogorov's backward equation gives

$$\begin{aligned} \mu \frac{d}{dt} P^S(t) &= -\alpha e^{-\alpha t} \mu + \alpha e^{-\alpha t} \delta \\ &= \mu Q^S P^S(t). \end{aligned} \quad (2.13)$$

Note that this differentiation is justified since each state in E is connected to a finite number of neighbors through (P_t) (and hence (P_t^S)), so that the term $\mu P^S(t)$ is the sum of a finite number of functions. Then from (2.12) and since $\delta P^S(t) = \delta$, we see that a solution of equation (2.13) is given by

$$\mu Q^S = -\alpha \mu + \alpha \delta.$$

We finally deduce that $\mu Q^S(\Delta) = \sum_{i \in E \cup \Delta} \mu(i) q^S(i, \Delta) = \sum_{i \in E} \mu(i) \eta(i) = \alpha$.

Conversely, let us assume that μ is a distribution on E which satisfies equation (2.10), for some value $\alpha \in [0, \infty)$. Let us denote by P^S its associated transition function. (Note that P^S is unique according to our assumption of regularity.) Then from Kolmogorov's backward equation and (2.10), the transition function μP^S satisfies the equation

$$\frac{d}{dt} \mu P^S(t) = -\alpha \mu P(t) + \alpha \delta.$$

This equation admits $\mu P^S(t) = e^{-\alpha t} \mu + (1 - e^{-\alpha t}) \delta$ as a unique solution. But the later equality is equivalent to (2.9).

A probability distribution μ which satisfies (2.9) is called a *quasi-stationary* distribution. We refer to [11] and Chap. 3 of [9] where some connections between quasi-stationary distributions and the Q -matrix are presented for general continuous time Markov chains. In population dynamics, these distributions are very much involved, and most of the time they are used to study extinction of populations, see for instance [2], [10], [12] and [19].

Remark 1 *There are situations when the emergence time may not correspond to the first time at which the subpopulation of type d will fix in the population. More specifically, this time may occur only when the subpopulation size reaches a certain level. For example, in epidemiology, it is interesting to know the time at which the pathogen population reaches a certain level (in order to start treatments for instance). In this case one is rather interested in the waiting time $S^{(n)}$:*

$$S^{(n)} = \inf\{t \geq 0 : X_t^{(d)} = n\}.$$

Previous results may easily be adapted to $S^{(n)}$ by considering:

$$E_n = \mathbb{N}_0^{d-1} \times \{0, 1, \dots, n-1\}.$$

Then we define the killed process $X^{S^{(n)}}$ as in (2.7). The later is a $E_n \cup \{\Delta\}$ -valued continuous time Markov chain whose Q -matrix $Q^{S^{(n)}} = (q^{S^{(n)}}(i, j))$ may be expressed as in (2.8), with

$$\eta(i) = \begin{cases} \lambda_d(i) + \sum_{l=1}^d \gamma_{ld}(i), & \text{if } i_d = n, \\ 0, & \text{otherwise.} \end{cases}$$

Then the same conclusion as in Theorem 2 holds, that is a probability distribution μ on E_n satisfies

$$\mathbb{P}_\mu(X_t = i \mid S^{(n)} > t) = \mu(i),$$

for all $t > 0$ and $i \in E_n$, if and only if it solves the equation

$$\mu Q^S = -\alpha \mu + \alpha \delta,$$

for some $\alpha \geq 0$, and under \mathbb{P}_μ , the time $S^{(n)}$ is exponentially distributed with parameter

$$\alpha = \sum_{i \in E} \eta(i) \mu(i).$$

3 On the existence of quasi-stationary distributions

In the following subsection, we provide some sufficient conditions for the existence of quasi-stationary distributions. Then in the next subsection, we will apply these results to a particular case of 2-dimensional competition process.

3.1 General results

We keep the assumptions of Section 2, that is $(X, \{\mathbb{P}_i : i \in \mathbb{N}_0^d\})$ is a competition process such that the conservative Q -matrices Q and Q^S are regular. We denote by \Rightarrow the weak convergence of probability measures.

Theorem 3 *If there exist probability measures π and μ on E , such that*

$$\mathbb{P}_\pi(X_t \in dx \mid S > t) \Rightarrow \mu(dx), \quad \text{as } t \rightarrow +\infty,$$

then μ satisfies condition (2.9).

Proof From the hypothesis, for all bounded function $f : \mathbb{N}_0^d \rightarrow \mathbb{R}$,

$$\lim_{t \rightarrow \infty} \mathbb{P}_\pi(f(X_t) | S > t) = \int f(x) \mu(dx).$$

Let $u > 0$ and $A \subseteq E$, then applying this identity to the function $f(x) = \mathbb{P}_x(X_u \in A, S > u)$ and the Markov property gives

$$\begin{aligned} \int f(x) \mu(dx) &= \lim_{t \rightarrow \infty} \mathbb{E}_\pi(\mathbb{P}_{X_t}(X_u \in A, S > u) | S > t) \\ &= \lim_{t \rightarrow \infty} \mathbb{P}_\pi(X_{t+u} \in A, S > t+u) \frac{1}{\mathbb{P}(S > t)} \\ &= \lim_{t \rightarrow \infty} \mathbb{P}_\pi(X_{t+u} \in A | S > t+u) \frac{\mathbb{P}_\pi(S > t+u)}{\mathbb{P}_\pi(S > t)}. \end{aligned} \quad (3.14)$$

Let $A = E$ in this identity. We obtain that for each $u > 0$,

$$\lim_{t \rightarrow \infty} \frac{\mathbb{P}_\pi(S > t+u)}{\mathbb{P}_\pi(S > t)} = \mathbb{P}_\mu(S > u).$$

Since $\mathbb{P}_\mu(S = 0) = 0$, the above identity shows that S is exponentially distributed under \mathbb{P}_μ , with parameter $\alpha = -\log \mathbb{P}_\mu(S > 1) > 0$, i.e., for all $u \geq 0$, $\mathbb{P}_\mu(S > u) = e^{-\alpha u}$. Plugging this equality into (3.14), gives

$$\begin{aligned} e^{\alpha u} \mathbb{P}_\mu(X_u \in A, u < S) &= \lim_{t \rightarrow \infty} \mathbb{P}_\pi(X_{t+u} \in A | S > t+u) \\ &= \mu(A), \end{aligned}$$

which is identity (2.9).

Theorem 1 provides a sufficient condition for the existence of a quasi-stationary distribution. However, in practice, for this result to be exploitable, we need some information on the law of X_u conditionally to $\{S > u\}$.

Now we focus on conditions regarding the Q -matrix which are a bit more technical than Theorem 1 but that can be verified provided this matrix is sufficiently explicit. An application will be given in subsection 3.2. We first state a general result on the existence of negative eigenvalues.

Proposition 1 *Let $M = (m_{ij})$ be any matrix on E and denote by I the matrix of the identity on E . If there exists a real $c \in (0, \infty)$ such that,*

(a) *for all $i, j \in E$ and $k \in \mathbb{N}_0$,*

$$m_{ij}^{(k)} < \infty, \quad (3.15)$$

(b) *the matrix $(M + cI)$ is nonnegative and irreducible,*

(c) *there exists $i, j \in E$ such that*

$$0 < \lim_{n \rightarrow +\infty} \left(\sum_{k=0}^n C_n^k m_{ij}^{(k)} c^{n-k} \right)^{1/n} \leq c, \quad (3.16)$$

then M admits a negative left eigenvalue with an associated positive eigenvector (i.e. there are $\alpha \geq 0$ and μ such that $0 < \mu(i) < \infty$, for all $i \in E$ and $\mu M = -\alpha\mu$).

Proof This result is a consequence of Theorem 3.3 in [1]. Let us first check that $M + cI$ satisfies the three conditions of this theorem. We denote by $(c_{ij})_{i,j \in E}$ the entries of this matrix. First we derive from (a) that for all $i, j \in E$ and $n \in \mathbb{N}_0$,

$$c_{ij}^{(n)} = \sum_{k=0}^n C_n^k m_{ij}^{(k)} c^{n-k} < \infty,$$

so that condition i) of Theorem 3.3. in [1] is satisfied. Then since from assumption (b), the matrix $M + cI$ is irreducible, by definition for all $i, j \in E$ there exists $n \geq 1$ such that $c_{ij}^{(n)} > 0$, which is condition ii) of Theorem 3.3. in [1]. From Theorem A in [20], the limits $\lim_{n \rightarrow +\infty} (c_{ij}^{(n)})^{1/n} = \lim_{n \rightarrow +\infty} \left(\sum_{k=0}^n C_n^k m_{ij}^{(k)} c^{n-k} \right)^{1/n}$ exist and do not depend on $i, j \in E$. Let us denote by λ^* their common value. From Theorem A in [20], λ^* is the maximum eigenvalue of $M + cI$. Moreover, from (c) we have

$$0 < \lambda^* \leq c.$$

This implies, condition iii) of Theorem 3.3 in [1]. We deduce from this theorem that there exists a vector μ such that for all i , $0 < \mu(i) < +\infty$ and

$$\mu(M + cI) = \mu M + c\mu I = \mu M + c\mu = \lambda^* \mu.$$

Since $\lambda^* \leq c$, we have

$$\mu M = \lambda^* \mu - c\mu = -\alpha\mu,$$

with $\alpha = c - \lambda^* \geq 0$, and the conclusion of the proposition follows.

A Q -matrix Q on \mathbb{N}_0^d being given, we consider the matrix $\bar{Q} = (\bar{q}_{ij})$ on E which is defined by

$$\bar{q}_{ij} = q_{ij}, \quad i, j \in E. \quad (3.17)$$

Note that if Q^S satisfies equation (2.10) for some nonnegative vector μ (i.e. such that $\mu(i) \geq 0$, for all $i \in E$ and $\sum_{i \in E} \mu(i) > 0$) and $\alpha \in [0, \infty)$, then $-\alpha$ is a left eigenvalue of \bar{Q} and μ is an associated eigenvector, i.e.

$$\mu \bar{Q} = -\alpha\mu. \quad (3.18)$$

Conversely, if μ is a nonnegative vector such that $0 < \sum_{i \in E} \mu(i) < \infty$, then equation (3.18), for μ and $\alpha \in [0, \infty)$ implies equation (2.10) and hence (2.11), for the vector $(\sum_{i \in E} \mu(i))^{-1} \mu$ and the value α .

Therefore if the matrix \bar{Q} satisfies the conditions of Proposition 1 with an eigenvector μ such that $0 < \sum_{i \in E} \mu(i) < \infty$, then we may conclude to the existence of a quasi-stationary distribution. Note that the condition $\sum_{i \in E} \mu(i) < \infty$ is satisfied whenever the state space E is finite and that in this case, Proposition 1 amounts to Perron-Frobenius Theorem.

3.2 Application to a 2-dimensional competition process

In this subsection we apply Proposition 1 and the consecutive discussion to the particular case of a 2-dimensional competition process with constant birth and death rates $q > 0$ and bounded emergence rates, i.e. $\alpha_1 = \sup_{i \in E} \eta_i < \infty$. The state space is then $E = \mathbb{N}_0 \times \{0\}$ which will be identified to the set of nonnegative integers, i.e. $E = \mathbb{N}_0$.

The matrix \bar{Q} introduced in (3.17) which is associated to the Q-matrix of this competition process is then given by

$$\bar{Q} = \begin{pmatrix} -2q - \eta_1 & 2q & 0 & \dots \\ q & -2q - \eta_2 & q & 0 & \dots \\ 0 & q & -2q - \eta_3 & q & 0 & \dots \\ \vdots & \ddots & \ddots & \ddots & \ddots & \ddots \end{pmatrix}.$$

In the remainder of this subsection, we will check that the matrix \bar{Q} satisfies conditions (a), (b) and (c) of Proposition 1. First note that condition (a) is necessarily satisfied since the matrix \bar{Q} has a finite number of nonzero coefficients on each line and column.

Then in order to show that conditions (b) and (c) are satisfied, we state a couple of preliminary results bearing on the matrix $D = (d_{ij})_{i,j \in E}$ with coefficients

$$d_{ij} = \begin{cases} 1, & \text{if } i + 1 = j \text{ or } i - 1 = j, \\ 0, & \text{otherwise.} \end{cases}$$

We first notice the following relations which follow directly from the definition of D : for all $i \in \mathbb{N}_0$, $j > 0$ and $n > 1$,

$$d_{ij}^{(n)} = d_{i(j-1)}^{(n-1)} + d_{i(j+1)}^{(n-1)} \quad \text{and} \quad d_{i0}^{(n)} = d_{i1}^{(n-1)}, \quad (3.19)$$

where $d_{ij}^{(n)}$ denote the coefficients of the matrix D^n . The proof of the following lemma is postponed to the annex, in Section 6.

Lemma 2 *The coefficients of the matrix D^n satisfy the following relations.*

1. For all $i, j \in E$ and $n > 0$,

$$d_{ij}^{(n)} = 0 \quad \text{if} \quad \begin{cases} j > 2 + i + n, \\ \text{or } i > 2 + j + n, \\ \text{or } i = j \pmod{2}, \text{ when } n \text{ is odd,} \\ \text{or } i + 1 = j \pmod{2}, \text{ when } n \text{ is even,} \end{cases} \quad \text{and} \\ d_{ij}^{(n)} > 0, \text{ otherwise.} \quad (3.20)$$

2. For all $n > 0$, $d_{0n}^{(n)} = 1$ and for all $k > 0$ and $n \geq 2k$, the coefficient $d_{0(n-2k)}^{(n)}$ may be expressed through the following sum:

$$d_{0(n-2k)}^{(n)} = \sum_{i_0=0}^{n-2k} \sum_{i_1=0}^{n-2k+1-i_0} \sum_{i_2=0}^{n-2k+2-i_0-i_1} \cdots \sum_{i_{k-2}=0}^{n-k-2-i_0-i_1-\cdots-i_{k-3}} \sum_{i_{k-1}=0}^{n-k-1-i_0-i_1-\cdots-i_{k-2}} 1. \quad (3.21)$$

3. For all $k > 0$ and $n \geq 2k$,

$$d_{0(n-2k)}^{(n)} = \frac{(2n+4-2k)(n+1-2k)}{2k(n+3-2k)} d_{0(n+2-2k)}^{(n)}. \quad (3.22)$$

Now let us define the matrix, $B = (b_{ij})_{i,j \in E}$, with coefficients:

$$b_{ij} = \begin{cases} 1, & \text{if } i+1 = j \text{ or } i-1 = j, \text{ and } (i,j) \neq (0,1), \\ 2, & \text{if } (i,j) = (0,1), \\ 0, & \text{otherwise.} \end{cases}$$

Let c be a real such that $c - 2q > \alpha_1$, then we have the decomposition:

$$\overline{Q} + cI = qB + \begin{pmatrix} u_1 & 0 & \cdots & & \\ 0 & \ddots & \ddots & & \\ \vdots & \ddots & u_i & & \\ & & & \ddots & \end{pmatrix}, \quad (3.23)$$

where $u_i = c - 2q - \eta_i > 0$. From our assumption, it follows that $u \stackrel{(\text{def})}{=} \inf_{i \in E} u_i > 0$ and from (3.23), we derive that $(\overline{Q} + cI)_{ij}^{(n)} \geq (qB + uI)_{ij}^{(n)} = \sum_{k=0}^n C_n^k b_{ij}^{(k)} u^{n-k}$, for all i, j and n . Note that the coefficients of the matrix B are very close to those of D , indeed we have $b_{ij} = d_{ij}$, for all $(i, j) \neq (0, 1)$ and $b_{01} = 2d_{01}$. Then we easily see similar arguments to those of the proof of part 1. of Lemma 2, can be applied to B in order to show that for all $i, j \in E$, there exists k such that $b_{ij}^{(k)} > 0$. This property, together with the previous inequality proves that $\overline{Q} + cI$ is irreducible, so that \overline{Q} satisfies part (b) of Proposition 1.

Now we shall focus on the particular value $d_{00}^{(2n)}$. The following result presents some interest in its own since it provides a new characterization of Catalan numbers.

Proposition 2 For all $n \in \mathbb{N}$, the first element of the matrix D^{2n} , (i.e. $d_{00}^{(2n)}$) is equal to the n^{th} Catalan number,

$$C_n \stackrel{(\text{def})}{=} \frac{1}{n+1} C_{2n}^n. \quad (3.24)$$

Proof The proof bears on the characterization of the n^{th} Catalan number which is given in Corollary 6.2.3 of [18]. This result asserts that C_n is the number of monotonic paths along the edges of a grid with $n \times n$ square cells, which do not pass above the diagonal.

Recall from (3.21) that we have, for all $n > 0$,

$$d_{00}^{(2n)} = \sum_{i_0=0}^0 \sum_{i_1=0}^{1-i_0} \sum_{i_2=0}^{2-i_0-i_1} \cdots \sum_{i_{n-2}=0}^{n-2-i_0-i_1-\cdots-i_{n-3}} \sum_{i_{n-1}=0}^{n-i_0-i_1-\cdots-i_{n-2}} 1. \quad (3.25)$$

Then there is $\sum_{i_0=0}^0 1 = C_1 = 1$ way to perform the first step. There are $\sum_{i_0=0}^0 \sum_{i_1=0}^{1-i_0} 1 = C_2 = 2$ ways to perform the second step (hence there are 2 ways to perform the two first steps). There are $\sum_{i_0=0}^0 \sum_{i_1=0}^{1-i_0} \sum_{i_2=0}^{2-i_0-i_1} 1 = C_3 = 5$ ways to perform the three first steps, and so on... Hence the representation (3.25) agrees with the characterization which is given in Corollary 6.2.3 of [18] and the result follows.

From Proposition 2 and (3.20), we may state, for all $n > 0$,

$$d_{00}^{(n)} = \begin{cases} 0, & \text{if } n \text{ is odd,} \\ C_{\frac{n}{2}}, & \text{if } n \text{ is even.} \end{cases} \quad (3.26)$$

Lemma 3 *The coefficients (b_{ij}) satisfy the following properties:*

1. For all $n > 0$ and for all $k < n/2$,

$$b_{0(n-2k)}^{(n)} = \frac{2n+2-2k}{n+1-2k} d_{0(n-2k)}^{(n)} \quad \text{and} \quad b_{00}^{(n)} = \frac{n+2}{2} d_{00}^{(n)}.$$

2. For all $n > 0$, $b_{00}^{(2n)} < 2^{2n}$.

Proof Let us prove part 1. by induction. The relation is obviously true for $n = 1$. Suppose that for all $k < n/2$, $b_{0(n-2k)}^{(n)} = \frac{2n+2-2k}{n+1-2k} d_{0(n-2k)}^{(n)}$ and $b_{00}^{(n)} =$

$\frac{n+2}{2}d_{00}^{(n)}$. Then for all $k < n/2$,

$$\begin{aligned}
b_{0(n+1-2k)}^{(n+1)} &= b_{0(n-2k)}^{(n)} + b_{0(n+2-2k)}^{(n)} \\
&= \frac{2n+2-2k}{n+1-2k}d_{0(n-2k)}^{(n)} + \frac{2n+4-2k}{n+3-2k}d_{0(n+2-2k)}^{(n)} \\
&= \frac{2n+4-2k}{n+2-2k}d_{0(n-2k)}^{(n)} + \frac{2k}{(n+1-2k)(n+2-2k)}d_{0(n-2k)}^{(n)} \\
&\quad + \frac{2n+4-2k}{n+2-2k}d_{0(n+2-2k)}^{(n)} - \frac{2n+4-2k}{(n+2-2k)(n+3-2k)}d_{0(n+2-2k)}^{(n)} \\
&= \frac{2n+4-2k}{n+2-2k}(d_{0(n-2k)}^{(n)} + d_{0(n+2-2k)}^{(n)}) \\
&\quad + \frac{2k}{(n+1-2k)(n+2-2k)}\frac{(2n+4-2k)(n+1-2k)}{2k(n+3-2k)}d_{0(n+2-2k)}^{(n)} \\
&\quad - \frac{2n+4-2k}{(n+2-2k)(n+3-2k)}d_{0(n+2-2k)}^{(n)}, \quad \text{from (3.22)} \\
&= \frac{2n+4-2k}{n+2-2k}d_{0(n+1-2k)}^{(n+1)}, \quad \text{from (3.19)}.
\end{aligned}$$

If n is even, then $k < (n+1)/2 \Leftrightarrow k \leq n/2$ and if n is odd, then $k < (n+1)/2 \Leftrightarrow k \leq (n-1)/2$. The case $k < n/2$ has already been considered above. So the only remaining case is $k = n/2$, for which we can write

$$\begin{aligned}
b_{01}^{(n+1)} &= 2b_{00}^{(n)} + b_{02}^{(n)} \\
&= \frac{2(n+2)}{2}d_{00}^{(n)} + \frac{n}{3}d_{02}^{(n)} \\
&= \frac{n+4}{2}(d_{00}^{(n)} + d_{02}^{(n)}) + \frac{n}{2}d_{00}^{(n)} + \left(\frac{n}{3} - \frac{n+4}{2}\right)d_{02}^{(n)} \\
&= \frac{n+4}{2}d_{01}^{(n)} + \left(\frac{n(n+4)}{6} + \frac{n}{3} - \frac{n+4}{2}\right)d_{02}^{(n)}, \quad \text{from (3.22)} \\
&= \frac{n+4}{2}d_{01}^{(n)}.
\end{aligned}$$

Moreover,

$$\begin{aligned}
b_{00}^{(n+1)} &= b_{01}^{(n)} \\
&= \frac{n+3}{2}d_{01}^{(n)} \\
&= \frac{n+1+2}{2}d_{00}^{(n+1)}.
\end{aligned}$$

So by induction, for all n and $k < n/2$, $b_{0(n-2k)}^{(n)} = \frac{2n+2-2k}{n+1-2k}d_{0(n-2k)}^{(n)}$ and $b_{00}^{(n)} = \frac{n+2}{2}d_{00}^{(n)}$. This ends the proof of part 1.

Again, we prove part 2. by induction. We have $b_{00}^{(2)} = 2 < 2^2$. Suppose that $b_{00}^{(2(n-1))} < 2^{2(n-1)}$ then, from Proposition 2 and part 1. of Lemma 3,

$$\begin{aligned} b_{00}^{(2n)} &= \frac{(n+2)}{2} \frac{(2n)!}{n!(n+1)!} \\ &= b_{00}^{(2(n-1))} \frac{n+2}{n+1} \frac{(2n-1)2n}{n(n+1)} \\ &= 4b_{00}^{(2(n-1))} \frac{n^3 + (3/2)n^2 - n}{n^3 + 2n^2 + n} \\ &< 4 * 2^{2n-2} = 2^{2n}, \end{aligned}$$

which ends the proof of part 2.

Define the matrix

$$(e_{ij})_{i,j \in E} = qB + (c - 2q)I.$$

On the one hand, from (3.23), for all $i, j \in E$, $(\bar{Q} + cI)_{ij} \leq e_{ij}$, hence

$$\sum_{k=0}^n C_n^k \bar{q}_{00}^{(k)} c^{n-k} \leq e_{00}^{(n)}.$$

Moreover, from (3.26) and Lemma 3, $b_{00}^{(k)} < 2^k$, for all $k > 0$, so that

$$\begin{aligned} e_{00}^{(n)} &= \sum_{k=0}^n C_n^k q^k b_{00}^{(k)} (c - 2q)^{n-k} \\ &< \sum_{k=0}^n C_n^k q^k 2^k (c - 2q)^{n-k} \\ &= c^n. \end{aligned}$$

On the other hand, from (3.23), for all $i, j \in E$, $(\bar{Q} + cI)_{ij} > qb_{ij}$ and from

Lemma 3 and Proposition 2, $\lim_{n \rightarrow +\infty} (b_{00}^{(2n)})^{\frac{1}{2n}} > 0$, hence $0 < \lim_{n \rightarrow +\infty} \left(\sum_{k=0}^n C_n^k \bar{q}_{00}^{(k)} c^{n-k} \right)^{1/n}$.

Therefore, we have proved that there exists $c > 0$, such that

$$0 < \lim_{n \rightarrow +\infty} \left(\sum_{k=0}^n C_n^k \bar{q}_{00}^{(k)} c^{n-k} \right)^{1/n} \leq c,$$

and we conclude that the matrix Q satisfies part (c) of Proposition 1. Then, applying this result, we derive that there is $\alpha \geq 0$ and a positive eigenvector μ such that

$$\mu \bar{Q} = -\alpha \mu.$$

Finally, note that the coordinates of the eigenvector μ are given explicitly in terms of the coefficients of the matrix $\bar{Q} + cI$, in the proof of Theorem 3.3 of [1]. However, this expression does not allow us to conclude that $\sum_{i \in E} \mu(i) < \infty$.

4 Breakdown of host resistance

Consider the emergence of pathogen mutants overcoming host resistance in a host-pathogen system. For example, in a host-pathogen system where resident live on susceptible host, we introduce resistant host. We want to estimate how long it take to pathogens to defeat the resistance. We then assume that, in the model, there are two types of habitat for pathogen individuals: susceptible and resistant host subpopulations. Denote ξ as the proportion of the resistant host subpopulation (so the proportion of susceptible host subpopulation is $1 - \xi$). We distinguish mutant and resident individuals in the pathogen population. A resident individual can only live on the susceptible hosts while mutants can live on both susceptible and resistant host subpopulations. We denote by $X^{(1)}$ the number of residents individuals on susceptible host, by $X^{(2)}$ the number of mutants on susceptible host and by $X^{(3)}$ the number of mutants on resistant host. Every pathogen individual can give birth to another individual of the same type or die. Suppose that resident individuals can mutate ($X^{(1)} \rightarrow X^{(2)}$) and mutants can migrate between the two habitats ($X^{(2)} \rightleftharpoons X^{(3)}$). So we have a three dimensional competition process, $X_t = (X_t^{(1)}, X_t^{(2)}, X_t^{(3)})$ with for example non linear transition rates (based on Lotka-Volterra equations). When X reaches the state $i = (i_1, i_2, i_3) \in \mathbb{N}_0^3$, transition rates are:

$$\begin{cases} \lambda_1(i_1) &= r(1 - \nu)i_1 \\ \lambda_2(i_1, i_2) &= \beta r i_2 + r \nu i_1 \\ \lambda_3(i_3) &= \beta r i_3 \\ \mu_1(i_1, i_2) &= \left(\frac{r(1-\nu)}{(1-\xi)K} (i_1 - 1 + \beta i_2) + \xi D \right) i_1 \\ \mu_2(i_1, i_2) &= \left(\frac{\beta r}{(1-\xi)K} (i_2 - 1 + \frac{1}{\beta} i_1) \right) i_2 \\ \mu_3(i_3) &= \left(\frac{\beta r}{\xi K} (i_3 - 1) \right) i_3 \\ \gamma_{23}(i_2) &= \begin{cases} \xi D i_2 & \text{if } i_2 < \gamma K \\ \xi D \gamma K & \text{else} \end{cases} \\ \gamma_{32}(i_3) &= (1 - \xi) D i_3 \end{cases} \quad (4.27)$$

where r is a growth rate, ν is a mutation rate, β is a mutation cost, K is the total pathogen carrying capacity, D is a migration rate and γ is a constant such that γK is the maximum size that we are sure i_2 will not exceed ($\gamma \geq \xi$). The rate γ_{23} is assumed to be finite, since the size of a biological population is finite even if the population is large. Moreover, since a mutation always occurs together with a reproduction, the rate γ_{12} is 0 and has been identified to the spontaneous birth rate of type 2. So, we are interested in the emergence of the third type – a virulent mutant able to invade and present on the resistant host subpopulation:

$$S = \inf\{t \geq 0 : X_t^{(3)} = 1\}.$$

Let us assume that π is a probability distribution on \mathbb{N}_0^3 such that for all $t > 0$ and $i \in \mathbb{N}_0^2 \times \{0\}$,

$$\mathbb{P}_\pi(X_t = (i_1, i_2, 0) | S > t) = \pi(i_1, i_2, 0).$$

Then π solves the equation

$$\pi Q^S = -\alpha\pi + \alpha\delta, \quad (4.28)$$

for some $\alpha \geq 0$. Applying Theorem 2, this shows that the time S is exponentially distributed with parameter

$$\alpha = \sum_{(i_1, i_2, 0)} \eta(i_1, i_2, 0)\pi(i_1, i_2, 0) = \sum_{i_2=1}^{\infty} (\gamma_{23}(i_2) \sum_{i_1=0}^{\infty} \pi(i_1, i_2, 0)). \quad (4.29)$$

In order to solve the system (4.28), we used numerical methods of the Gauss-Jordan Elimination and Raphson-Newton, see [14]. If a new resistant host is introduced into the pathogen habitat and the initial pathogen population structure follows the law π at this time, it will take, on average, a time equal to $1/\alpha$ before the resistance will be broken. The distribution of the emergence time can be estimated by simulations of the competition process (4.27) using the Gillespie algorithm (Fig. 2).

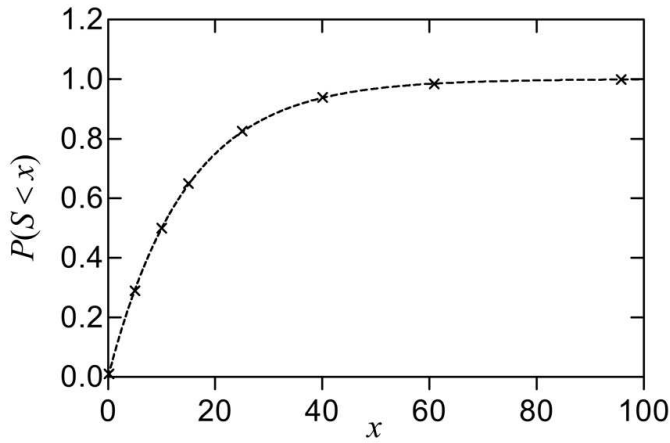


Fig. 2 Probability distribution function of the emergence time S . Dotted line represents the distribution function of the exponential law with parameter α given in (4.29). Crosses represent the distribution function of S obtained by simulations of the competition process (4.27). The values of the parameters are $K = 10$, $\mu = 0.05$, $r = 1$, $D = 1$, $\beta = 1$, $\xi = 0.5$ and $\gamma = 30$.

From (4.29) one can derive key-processes and parameter values prolonging the durability of host resistance. The approach can be generalized to n types

of resistances. In this case, we may check that the number of different types of pathogen is then $N \stackrel{\text{(def)}}{=} \sum_{i=0}^n C_n^i 2^{n-i}$, which corresponds to the dimension of the competition process. Indeed, there are C_n^i areas with i resistances in the environment, and there are 2^{n-i} types of mutant living on each of these areas. This N -dimensional competition process can include recombinations between pathogen types and it can be used to study the effects of the host population structure on the pathogen adaptive dynamics.

5 Conclusion

We have developed a stochastic model based on birth and death processes with mutations to describe a population adaptation to an unsuitable environment. Using properties of quasi-stationary distributions, we have obtained the analytical estimation of the emergence time of an adapted mutant. We have showed conditions under which the probability distribution of the emergence time follows an exponential law. We have also provided an example of our model use dealing with the problem of the durability of plant genetic resistance.

Our approach is strikingly different from that of other models describing adaptive dynamics. Most of these modelling approaches focus on the appearance of new types of individuals that are able to escape extinction. They do not consider the possibility to have different environments with differences in individuals response [8,16,17]. Here, we have shown that the time for a pathogen to adapt to a unsuitable environment follows an exponential law, whose parameter depends on the initial law, in any structured environment. So we can consider our model as a generalization of existing models focusing on the emergence problem to a multi-environmental situation. Moreover, the other approaches are concerned with the fixation time of an allele [13]. However this time is different from the emergence time, since it corresponds to the moment when an allele have completely invaded the population. Here, we are interested in the time of the emergence of an allele overcoming a control strategy. We provide conditions for key-processes determining dynamics of a biological system under which quasi-stationary law μ exists. For instance, if two populations have constant birth and death rates, our model exhibits the evolution of the pathogen infectivity. Since the model can be resolved numerically, it can be applied in situations when a quasi stationary law is implicit or when biological processes impose a particular initial law.

Our model is a first attempt to derive a general law of the emergence time in competition processes. We have shown that competition processes are a powerful tool allowing us to gain insight into processes steering the emergence rate of the adapted mutants. The flexibility of competition processes allows us to estimate the durability of disease control strategies based on a diversification whether by mixing different host populations, or by using several treatments with different mechanisms of action. In particular, our model can be used to estimate the effect of the crop diversification on the durability of

the deployed genetic resistances and to select the most suitable strategies to control pathogen dynamics.

6 Annexe: Proof of lemma 2.

Let us prove part 1. by induction. For $n = 1$ the result is obviously true. Then let us suppose that it is true for some $n \geq 1$.

– For all $i \geq 0$ and $j > 0$:

if $j > 2 + i + n + 1$, then $j - 1 > 2 + i + n$ and $j + 1 > 2 + i + n$,
 if $i > 2 + j + n + 1$, then $i > 2 + (j - 1) + n$ and $i > 2 + (j + 1) + n$,
 if $i = j \pmod{2}$ and $n+1$ odd, then $i+1 = (j-1) \pmod{2} = (j+1) \pmod{2}$
 and n is even,
 if $i + 1 = j \pmod{2}$ and $n + 1$ even, then $i = (j - 1) \pmod{2} = (j + 1) \pmod{2}$ and n is odd.

Therefore in all these cases, $d_{ij}^{(n+1)} = d_{i(j-1)}^{(n)} + d_{i(j+1)}^{(n)} = 0$.

– For all $i \geq 0$ and for $j = 0$: we have $0 < 2 + i + n + 1$, so the first condition never holds. Therefore,

if $i > 2 + n + 1$, then $i > 2 + 1 + n$,
 if $i = 0 \pmod{2}$ and $n + 1$ is odd, then $i + 1 = (0 + 1) \pmod{2}$ and n is even,
 if $i + 1 = 0 \pmod{2}$ and $n + 1$ is even, then $i = (0 + 1) \pmod{2}$ and n is odd.

So in all these cases, $d_{i0}^{(n+1)} = d_{i(0+1)}^{(n)} = 0$.

– If the triple $(i, j, n + 1)$ is not in one of the previous cases, then neither are the triples $(i, j - 1, n)$ and $(i, j + 1, n)$. Hence $d_{ij}^{(n+1)} = d_{i(j-1)}^{(n)} + d_{i(j+1)}^{(n)} > 0$.

So we conclude that part 1. is true for all $n > 0$.

Now, we prove part 2. again by using mathematical induction. For $n = 1$, we have $d_{01}^{(1)} = 1$. Suppose that, $d_{0(n-1)}^{(n-1)} = 1$, then $d_{0n}^{(n)} = d_{0(n-1)}^{(n-1)} + d_{0(n+1)}^{(n-1)} = 1 + 0 = 1$, from part 1. We conclude that the first assertions of part 2. are true.

We can check equation (3.21) for $n = 2$, by a simple calculation. Suppose that (3.21) holds for all $k \geq 1$ and $2k \leq n$, then for $2k \leq n$,

– if $k > 1$, then

$$\begin{aligned}
& d_{0(n+1-2k)}^{(n+1)} \\
&= d_{0(n-2k)}^{(n)} + d_{0(n-2(k-1))}^{(n)} \\
&= \sum_{i_0=0}^{n-2k} \sum_{i_1=0}^{n-2k+1-i_0} \cdots \sum_{i_{k-2}=0}^{n-k-2-i_0-i_1-\cdots-i_{k-3}} \sum_{i_{k-1}=0}^{n-k-1-i_0-i_1-\cdots-i_{k-2}} 1 \\
&\quad + \sum_{i_0=0}^{n-2(k-1)} \sum_{i_1=0}^{n-2(k-1)+1-i_0} \cdots \sum_{i_{k-3}=0}^{n-(k-1)-2-i_0-i_1-\cdots-i_{k-4}} \sum_{i_{k-2}=0}^{n-(k-1)-1-i_0-i_1-\cdots-i_{k-3}} 1 \\
&= \sum_{i_0=1}^{n+1-2k} \sum_{i_1=0}^{n+1-2k+1-i_0} \cdots \sum_{i_{k-2}=0}^{n+1-k-2-i_0-i_1-\cdots-i_{k-3}} \sum_{i_{k-1}=0}^{n+1-k-1-i_0-i_1-\cdots-i_{k-2}} 1 \\
&\quad + \sum_{i_0=0}^{n+1-2k+1} \sum_{i_1=0}^{n+1-2k+2-i_0} \cdots \sum_{i_{k-3}=0}^{n+1-k-2-i_0-i_1-\cdots-i_{k-4}} \sum_{i_{k-2}=0}^{n+1-k-1-i_0-i_1-\cdots-i_{k-3}} 1 \\
&= \sum_{i_0=0}^{n+1-2k} \sum_{i_1=0}^{n+1-2k+1-i_0} \cdots \sum_{i_{k-2}=0}^{n+1-k-2-i_0-i_1-\cdots-i_{k-3}} \sum_{i_{k-1}=0}^{n+1-k-1-i_0-i_1-\cdots-i_{k-2}} 1.
\end{aligned}$$

– if $k = 1$, then

$$d_{0(n+1-2)}^{(n+1)} = d_{0(n-2)}^{(n)} + d_{0n}^{(n)} = \sum_{i_0=0}^{n-2} 1 + 1 = \sum_{i_0=1}^{n+1-2} 1.$$

Let us extend this equality to the case where $2k \leq n + 1$. If n is even, then $2k \leq n + 1 \Leftrightarrow 2k \leq n$. If n is odd, then for $2k = n + 1$,

$$\begin{aligned}
& d_{0(n+1-2k)}^{(n+1)} = d_{00}^{(n+1)} = d_{01}^{(n)} \\
&= \sum_{i_0=0}^1 \sum_{i_1=0}^{2-i_0} \sum_{i_2=0}^{3-i_0-i_1} \cdots \\
&\quad \sum_{i_{(n-1)/2-2}=0}^{n-(n-1)/2-2-i_0-i_1-\cdots-i_{(n-1)/2-3}} \sum_{i_{(n-1)/2-1}=0}^{n-(n-1)/2-1-i_0-i_1-\cdots-i_{(n-1)/2-2}} 1 \\
&= \sum_{i_0=0}^0 \sum_{i_1=0}^{1-i_0} \sum_{i_2=0}^{2-i_0-i_1} \cdots \\
&\quad \sum_{i_{(n-1)/2-2+1}=0}^{n-(n-1)/2-2-i_0-i_1-\cdots-i_{(n-1)/2+1-3}} \sum_{i_{(n-1)/2-1+1}=0}^{n-(n-1)/2-1-i_0-i_1-\cdots-i_{(n-1)/2-2+1}} 1 \\
&= \sum_{i_0=0}^0 \sum_{i_1=0}^{1-i_0} \sum_{i_2=0}^{2-i_0-i_1} \cdots \\
&\quad \sum_{i_{(n+1)/2-2}=0}^{n+1-(n+1)/2-2-i_0-i_1-\cdots-i_{(n+1)/2-3}} \sum_{i_{(n+1)/2-1}=0}^{n+1-(n+1)/2-1-i_0-i_1-\cdots-i_{(n+1)/2-2}} 1.
\end{aligned}$$

So by induction (3.21) is true for all $k > 0$ and $2k \leq n$.

Again, we prove part 3. using mathematical induction. For $n = 2$, we have $d_{00}^{(2)} = \frac{(4+4-2)(2+1-2)}{2(2+3-2)} d_{02}^{(2)} = \frac{6}{6} d_{02}^{(2)} = 1$. Suppose that for all $k > 0$ and $2k \leq n$,

$$d_{0(n-2k)}^{(n)} = \frac{(2n+4-2k)(n+1-2k)}{2k(n+3-2k)} d_{0(n+2-2k)}^{(n)}.$$

Then

$$\begin{aligned} & d_{0(n+1-2k)}^{(n+1)} \\ &= d_{0(n-2k)}^{(n)} + d_{0(n+2-2k)}^{(n)} = \left(\frac{(2n+4-2k)(n+1-2k)}{2k(n+3-2k)} + 1 \right) d_{0(n+2-2k)}^{(n)} \\ &= \frac{2n^3 + 14n^2 + 28n + 16 + 8k^2 - 24k^2 - 32kn - 8kn^2 + 8k^2n}{2k(n+3-2k)(n+4-2k)} d_{0(n+2-2k)}^{(n)} \end{aligned}$$

and

$$\begin{aligned} & \frac{(2n+6-2k)(n+2-2k)}{2k(n+4-2k)} d_{0(n+3-2k)}^{(n+1)} \\ &= \frac{2n+6-2k(n+2-2k)}{2k(n+4-2k)} (d_{0(n+2-2k)}^{(n)} + d_{0(n+4-2k)}^{(n)}) \\ &= \frac{(2n+6-2k)(n+2-2k)}{2k(n+4-2k)} (d_{0(n-2(k-1))}^{(n)} + d_{0(n+2-2(k-1))}^{(n)}) \\ &= \frac{(2n+6-2k)(n+2-2k)}{2k(n+4-2k)} \left(\frac{(2k-2)(n+5-2k)}{(2n+6-2k)(n+3-2k)} + 1 \right) d_{0(n-2(k-1))}^{(n)} \\ &= \frac{2n^3 + 14n^2 + 28n + 16 + 8k^2 - 24k^2 - 32kn - 8kn^2 + 8k^2n}{2k(n+3-2k)(n+4-2k)} d_{0(n+2-2k)}^{(n)}. \end{aligned}$$

Then we extend this equality to the case where $2k \leq n+1$. If n even, then $2k \leq n+1 \Leftrightarrow 2k \leq n$. If n odd, then for $2k = n+1$,

$$d_{0(n+1-2k)}^{(n+1)} = d_{00}^{(n+1)} = d_{01}^{(n)} = \frac{n+5}{2(n-1)} d_{03}^{(n)}$$

and

$$\begin{aligned} & \frac{(2(n+1)+4-2k)(n+1+1-2k)}{2k(n+1+3-2k)} d_{0(n+1+2-2k)}^{(n+1)} \\ &= \frac{n+5}{3(n+1)} d_{02}^{(n+1)} = \frac{n+5}{3(n+1)} (d_{01}^{(n)} + d_{03}^{(n)}) \\ &= \frac{n+5}{3(n+1)} \left(\frac{n+5}{2(n-1)} + 1 \right) d_{03}^{(n)} \\ &= \frac{n+5}{2(n-1)} d_{03}^{(n)}. \end{aligned}$$

Hence for all $k > 0$ and $2k \leq n + 1$,

$$d_{0(n+1-2k)}^{(n+1)} = \frac{(2(n+1) + 4 - 2k)(n+1 + 1 - 2k)}{2k(n+1 + 3 - 2k)} d_{0(n+1+2-2k)}^{(n+1)}.$$

By induction the relation is true for all $n \geq 2$.

Acknowledgements We would like to thank Michaël Bulois who has drawn our attention to the identity between Catalan numbers and the coefficients of the matrix D^{2n} , in Proposition 2. This work was supported by MODEMAVE research project from the Région Pays de la Loire and by Department of "Santé des Plantes et Environnement", INRA.

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