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A spatiotemporal model of drug resistance in bacteria with mutations

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"This paper is dedicated to the sixtieth birthday of Professor Julian Lopez-Gomez"

Abstract. *A spatio-temporal dynamics model is presented to study the effects of mutations on the persistence and extinction of bacteria under the antibiotic inhibition. We construct a mixed type Lyapunov functional to prove the global stability of extinction state and coexistence state for the case of forward mutation and forward-backward mutation respectively.*

Keywords: strong maximum principle, Lyapunov functional, invariance principle, drug-resistance,mutations, competitive exclusion, uniform persistence.
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1. Introduction

Antibiotic drug resistance is a global health problems [11]. Today, clinically important bacteria are characterized by their drug resistance to single or multiple drug. Historically penicillin- resistant Staphylococcus aureus are discovered soon after the introduction of penicillin in the 1940s in clinical environments [2] and still up to now the antibiotic drug resistance is still a subject of intense research [6, 7, 8, 9, 15, 16]. Most of the experiments on drug resistance in the laboratory setup are conducted in a well-mixed environment [6, 8]. For mathematical modeling on the subject of drug-resistance of bacteria, the authors [4, 5] constructed a system of ordinary differential equations with impulse conditions to study the selection of drug resistance mutants in a device called "Morbidostat"[4, 5]. In [3] Kishony et al. presented a device for the evolution of bacteria that allows migration and adaption in a large, spatially structured environment. The microbial evolution and growth arena(MEGA)-plate consists of a rectangle acrylic dish 120x60cm, in which successive regions of black-colored agar containing different concentrations of antibiotics are overlaid by soft agar allowing bacterial motility. Motile bacteria inoculated at on location on the plate and spread by chemotaxis to other regions. Only increasing resistant mutants can spread into sections containing higher levels of antibiotic. Interested

readers can consult the paper for biological details. Based on their experiments, we shall study the spatiotemporal dynamics of bacteria under antibiotics inhibition by constructing a system of reaction-diffusion equations. The rest of this paper is organized as follows. In Section 2 we describe the mathematical models with forward mutations and forward-backward mutations. In Section 3 we state our main results. Technical proofs are collected in Section 4. We analyze the global stability of the extinction state for the case of forward mutations and the coexistence state for the case of forward-backward mutations respectively. A Lyapunov functional of mixed type is constructed and invariance principle [1] is applied to the establishment of the global stability of the extinction and coexistence state.

2. Description of our models

In the simplest scenario, we formulate the transition from a wild type population $u(x,t)(v_0 := u)$ to N mutant strains $v_i(x,t), i = 1,2,\ldots,N$ where $x \in \Omega$, Ω is a bounded domain in R^n. Let $P(x)$ be a given distribution of drug inhibitor in Ω and $U = U(x,t) = u(x,t) + \sum_{i=1}^{n} v_i(x,t)$ be the total population in Ω. For the forward mutation model mutant v_i mutates to mutant v_{i+1} with a forward mutation rate q_i. For the forward - backward mutation model, mutant v_i mutates to mutant v_{i+1} with a forward mutation rate q_i, while mutant v_{i+1} mutates to mutant v_i with a backward mutation rate $\tilde{q}_i$. The spatiotemporal dynamics with forward mutation and forward - backward mutation under the influence of the drug inhibition $P(x)$ are given by the following models (1) and (2) respectively.

$$\begin{cases} \frac{\partial u}{\partial t} = d_0\Delta u + r_0 u(1-\frac{U}{K})f_0(P(x)) - q_0 u \\ \frac{\partial v_i}{\partial t} = d_i\Delta v_i + r_i v_i(1-\frac{U}{K})f_i(P(x)) + q_{i-1}v_{i-1} - q_i v_i, \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad i = 1,2,\ldots,N-1, \\ \frac{\partial v_N}{\partial t} = d_N\Delta v_N + r_N v_N(1-\frac{U}{K})f_N(P(x)) + q_{N-1}v_{N-1} \end{cases} \tag{1}$$

and

$$\begin{cases} \frac{\partial u}{\partial t} = d_0\Delta u + r_0 u(1-\frac{U}{K})f_0(P(x)) - q_0 u + \tilde{q}_0 v_1 \\ \frac{\partial v_i}{\partial t} = d_i\Delta v_i + r_i v_i(1-\frac{U}{K})f_i(P(x)) + q_{i-1}v_{i-1} - (\tilde{q}_{i-1}+q_i)v_i + \tilde{q}_i v_{i+1}, \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad i = 1,2,\ldots,N-1, \\ \frac{\partial v_N}{\partial t} = d_N\Delta v_N + r_N v_N(1-\frac{U}{K})f_N(P(x)) + q_{N-1}v_{N-1} - \tilde{q}_{N-1}v_N \end{cases} \tag{2}$$

The initial conditions and boundary conditions for both of (1) and (2) are given below in (3) and (4) respectively. The initial conditions are

$$\begin{cases} u(x,0) = u_0(x) \le K, & x \in \Omega \\ v_i(x,0) = v_{i0}(x) \equiv 0, & i = 1,2,\ldots,N,\ x \in \Omega \end{cases} \tag{3}$$

and the boundary conditions are

$$\begin{cases} \frac{\partial u}{\partial n}(x,t) = 0, & x \in \partial\Omega,\ t > 0 \\ \frac{\partial v_i}{\partial n}(x,t) = 0, & i = 1, 2, \ldots, N,\ x \in \partial\Omega,\ t > 0, \end{cases} \tag{4}$$

where $\frac{\partial}{\partial n}$ denotes the differentiation along the outward normal n to $\partial\Omega$. In (1) and (2), we assume that the wild type population $v_0 := u$ and the mutant population $v_i, i = 1, 2, \ldots, N$ share the same carrying capacity K and have intrinsic growth rate $r_i, i = 0, 1, \ldots, N$. In (1) and (2), $d_i > 0$ is the diffusion coefficient for species v_i; the mutation rate q_i and $\tilde{q_i}$ are assumed to be small. The effect of the drug inhibition is described by $f_0(p)$ and $f_i(p)$ which satisfies $f_i(0) = 1, i = 0, 1, \ldots, N$ and $f_i'(p) < 0, p > 0$.
$f_i'(p) < 0$ means a larger drug concentration leads to stronger inhibition of the bacteria species i. Because the mutants have stronger resistance to the inhibition than wild type, we have the following assumption:

$$(H1) \qquad f_0(p) < f_1(p) < \cdots < f_N(p).$$

The example of $f_i(p)$ take the form of Hill function of order L, which are:

$$f_i(p) = \frac{1}{1 + (\frac{p}{K_i})^L},\ i = 0, 1, 2, \ldots, N.$$

Thus, (H1) becomes $K_0 < K_1 < \cdots < K_N$.

It is generally accepted that the bacterial drug resistance comes at the cost of lower reproductive fitness. The classical trade off is that in the absence of drug inhibition the wild type has the competitive advantage (hypothesis (H2) below), whereas when the drug in present, the advantage shifts to the resistant types (hypothesis (H1)). Thus in addition to hypothesis (H1), we assume that the intrinsic growth rates $r_i, i = 0, \ldots, N$ satisfy :

$$(H2) \qquad r_0 > r_1 > \cdots > r_N.$$

Furthermore it is reasonable to assume that the wild type and mutants have the same diffusion coefficient, i.e.,

$$(H3) \qquad d_0 = d_1 = \cdots = d_N =: d.$$

Now we present the main result of this paper.

THEOREM 2.1. *Suppose that the assumptions* (H1), (H2), (H3) *hold and the initial function* $u(x, 0)$ *is nontrivial. Then*

(i) *the solutions* $u(x,t)$ *and* $v_i(x,t)$ *of* (1), (3), (4) *satisfy* $\lim_{t\to\infty} u(x,t) = 0$, $\lim_{t\to\infty} v_i(x,t) = 0, i = 1, \cdots, N-1$ *and* $\lim_{t\to\infty} v_N(x,t) = K$; *and*

(ii) *The solutions* $u(x,t)$ *and* $v_i(x,t)$ *of* (2), (3), (4) *satisfy*

$$\lim_{t\to\infty} u(x,t) = u^* := v_0^* > 0, \ \lim_{t\to\infty} v_i(x,t) = v_i^* > 0, i = 1, \cdots, N$$

where

$$v_N^* = \frac{K}{\frac{\tilde{q}_0\tilde{q}_1\cdots\tilde{q}_{N-1}}{q_0q_1\cdots q_{N-1}} + \frac{\tilde{q}_1\cdots\tilde{q}_{N-1}}{q_1\cdots q_{N-1}} + \cdots + \frac{\tilde{q}_{N-1}}{q_{N-1}} + 1},$$

$$v_{N-1}^* = \frac{\tilde{q}_{N-1}}{q_{N-1}}v_N^*, \quad v_{N-2}^* = \frac{\tilde{q}_{N-2}\tilde{q}_{N-1}}{q_{N-2}q_{N-1}}v_N^*, \quad \cdots$$

$$\cdots, v_1^* = \frac{\tilde{q}_1\cdots\tilde{q}_{N-1}}{q_1\cdots q_{N-1}}v_N^*, \quad u^* := v_0^* = \frac{\tilde{q}_0\tilde{q}_1\cdots\tilde{q}_{N-1}}{q_0q_1\cdots q_{N-1}}v_N^*.$$

REMARK 2.2: The result is independent of the drug distribution $P(x)$.

3. Proof of the main result

Let R_+^{N+1} denote the nonnegative orthant of R^{N+1} and $C(\bar{\Omega}, R_+^{N+1})$ the nonnegative value continuous functions space. Set

$$\Lambda := \Big\{ v \in R_+^{N+1} : U := \sum_{i=0}^{N} v_i \le K \Big\}$$

$$\text{and } X_\Lambda := \Big\{ \phi \in C(\bar{\Omega}, R_+^{N+1}) : \phi(x) \in \Lambda, x \in \bar{\Omega} \Big\}.$$

For $\phi := (\phi_0, \phi_1, \cdots, \phi_N) \in C(\bar{\Omega}, R_+^{N+1})$, we denote $\Phi_t(\phi)$ the solution of (1) or (2) with Neumann boundary condition (4) passing through ϕ. Then we first prove that both $C(\bar{\Omega}, R_+^{N+1})$ and X_Λ are positively invariant.

PROPOSITION 3.1. *Suppose that the assumptions* (H1), (H2) *and* (H3) *hold. Then both* $C(\bar{\Omega}, R_+^{N+1})$ *and* X_Λ *are positively invariant for the solution semiflow* $\Phi_t(\phi)$ *of both models of* (1) *and* (2) *with Neumann boundary condition* (4). *Furthermore,* $v_i(x,t) > 0$ *for all* $x \in \bar{\Omega}, t > 0$ *and* $i = 0, 1, \cdots, N$ *if* $\phi \in X_\Lambda$ *with* $\phi_0 \not\equiv 0$.

Proof. Let $w(x,t) := (u(x,t), v_1(x,t), \cdots, v_N(x,t))$ and denote the reaction term of (1) or (2) by $F(x,w)$. Then $F : \bar{\Omega} \times R_+^{N+1}$ satisfies

$$F_i(x,w) \ge 0 \text{ whenever } x \in \bar{\Omega} \text{ and } w \in R_+^{N+1}, w_i = 0$$

for $i = 0, 1, \cdots, N$. Applying Corollary 3.2 in [13, p.129], we obtain that $v_i(x,t) \ge 0$ for $t > 0, x \in \Omega$ and $i = 0, 1, \cdots, N$, that is, $C(\bar{\Omega}, R_+^{N+1})$ is

positively invariant for the solution semiflow $\Phi_t(\phi)$ of both models of (1) and (2) with Neumann boundary condition (4).

Let $U(x,t) := \sum_{i=0}^{N} v_i(x,t) \geq 0$ and

$$K(x,t) := K^{-1} \sum_{i=0}^{N} r_i f_i(P(x)) v_i(x,t) \geq 0\,.$$

Assume that $U(x,0) = \sum_{i=0}^{N} \phi_i(x) \leq K$ for $x \in \Omega$. Then $U(x,t)$ satisfies

$$\begin{cases} \frac{\partial U}{\partial t} = d\Delta U + K(x,t)(K-U),\ x \in \Omega \\ \frac{\partial U}{\partial n} = 0,\ x \in \partial\Omega,\ t > 0 \\ U(x,0) \leq K,\ x \in \Omega. \end{cases} \tag{5}$$

It is easy to see that the constant function K is a solution of the equation in (5). Let $V(x,t) := U(x,t) - K$. Then V satisfies

$$\begin{cases} \frac{\partial V}{\partial t} = d\Delta V - K(x,t)V,\ x \in \Omega, t > 0 \\ \frac{\partial V}{\partial n} = 0,\ x \in \partial\Omega,\ t > 0 \\ V(x,0) \leq 0,\ x \in \Omega. \end{cases} \tag{6}$$

We claim that $V(x,t) \leq 0,\ x \in \bar{\Omega},\ t \geq 0$. Suppose not. Then there exist $\bar{x} \in \bar{\Omega},\ \bar{t} > 0$ such that $V(\bar{x},\bar{t}) > 0$. Denote M^* the maximal value of the function $V(x,t)$ on $\bar{\Omega} \times [0,\bar{t}]$ and let $M^* = V(x^*,t^*)$ with $x^* \in \bar{\Omega},\ t^* \leq \bar{t}$. Then $M^* > 0$. If $x^* \in \Omega$, then it follows from Theorem 2.5 and Remark 2.1 [13, p.126-127] or Theorem 15, Chapter 3 [12], that $V(x,t) \equiv M^*$ for all $x \in \bar{\Omega}$ and $t \leq t^*$. In particular, $M^* = V(x,0) \leq 0$, a contradiction. This proves $x^* \in \partial\Omega$. Applying Theorem 2.5 and Remark 2.1 [13, p.126-127] again, we obtain that $\frac{\partial V}{\partial n}(x^*,t^*) < 0$, this contradicts the Neumann boundary condition of (6).

Similarly, we may prove that $u(x,t) > 0$ for all $x \in \bar{\Omega}, t > 0$ if $\phi \in X_\Lambda$ with $\phi_0 \not\equiv 0$. In the following, we only consider the system (1), the proof of the system (2) is similar.

From (1) and the positive invariance of X_Λ, we get that

$$d\Delta v_1 - \frac{\partial v_1}{\partial t} - q_1 v_1 = -r_1 v_1 \left(1 - \frac{U}{K}\right) f_1(P(x)) \leq 0.$$

We assert that $v_1(x,t) > 0$ for all $x \in \bar{\Omega}, t > 0$. Otherwise, there exist $\bar{x} \in \bar{\Omega},\ \bar{t} > 0$ such that $v_1(\bar{x},\bar{t}) = 0$. Theorem 2.5 and Remark 2.1 [13, p.126-127] and the Neumann boundary condition imply that $\bar{x} \in \Omega$, and hence $v_1(x,t) \equiv 0$ for all $x \in \bar{\Omega}, t \leq \bar{t}$. From the second equation of (1) it follows that $u(x,t) = 0$ for all $x \in \bar{\Omega}, t \leq \bar{t}$, a contradiction. Inductively, we can prove that $v_i(x,t) > 0$ for all $x \in \bar{\Omega}, t > 0$ for $i = 2, \cdots, N$. This completes the proof. □

PROPOSITION 3.2. (i) *The steady state* $E_N = (0, 0, \cdots, K)$ *is locally asymptotically stable for the system* (1), (3), (4) (*Forward mutation model*).

(ii) *The steady state* $E^* = (u^*, v_1^*, \cdots, v_N^*)$ *is locally asymptotically stable for the system* (2), (3), (4) (*Forward-backward mutation model*).

Proof. (i) Let $w_i = v_i,\ i = 0, 1, \cdots, N-1,\ w_N = v_N - K$. Then for (1) we have

$$\begin{cases} \frac{\partial w_0}{\partial t} = d\Delta w_0 + r_0 w_0 \left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_0(P(x)) - q_0 w_0,\ x \in \Omega \\ \frac{\partial w_i}{\partial t} = d\Delta w_i + r_i w_i \left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_i(P(x)) + q_{i-1} w_{i-1} - q_i w_i, \\ \qquad\qquad i = 1, \cdots, N-1,\ x \in \Omega, \\ \frac{\partial w_N}{\partial t} = d\Delta w_N + r_N (w_N + K) \left(-\frac{\sum_{k=0}^N w_k}{K}) f_N(P(x)\right) + q_{N-1} w_{N-1}, \\ \qquad\qquad x \in \Omega, \\ \frac{\partial w_i}{\partial n}(x,t) = 0,\ x \in \partial\Omega,\ t > 0,\ i = 0, 1, 2, \cdots, N \end{cases} \tag{7}$$

And the linearized system of (7) around E_N is

$$\begin{cases} \frac{\partial w_0}{\partial t} = d\Delta w_0 - q_0 w_0,\ x \in \Omega \\ \frac{\partial w_i}{\partial t} = d\Delta w_i + q_{i-1} w_{i-1} - q_i w_i,\ i = 1, \cdots, N-1,\ x \in \Omega. \\ \frac{\partial w_N}{\partial t} = d\Delta w_N - r_N \sum_{k=0}^N w_k f_N(P(x)) + q_{N-1} w_{N-1},\ x \in \Omega \\ \frac{\partial w_i}{\partial n}(x,t) = 0,\ x \in \partial\Omega,\ t > 0,\ i = 0, 1, 2, \cdots, N \end{cases} \tag{8}$$

Let $w_i(x,t) = e^{\lambda t}\varphi_i(x),\ i = 0, 1, 2, , \cdots, N$. Then it follows that

$$\begin{cases} \lambda\varphi_0 = d\Delta\varphi_0 - q_0\varphi_0,\ x \in \Omega \\ \lambda\varphi_i = d\Delta\varphi_i + q_{i-1}\varphi_{i-1} - q_i\varphi_i,\ x \in \Omega. \\ \lambda\varphi_N = d\Delta\varphi_N - r_N \sum_{k=0}^N \varphi_k f_N(P(x)) + q_{N-1}\varphi_{N-1},\ x \in \Omega \\ \frac{\partial\varphi_i}{\partial n}(x) = 0,\ x \in \partial\Omega \end{cases} \tag{9}$$

Then the principal eigenvalue is

$$\begin{aligned} \lambda &= \inf_{\substack{\varphi_0 \in H^1(\Omega) \\ \varphi_0 \neq 0}} \frac{d\int_\Omega \varphi_0 \Delta\varphi_0\, dx - q_0 \int_\Omega \varphi_0^2(x)\, dx}{\int_\Omega \varphi_0^2(x)\, dx} \\ &= \inf_{\substack{\varphi_0 \in H^1(\Omega) \\ \varphi_0 \neq 0}} \frac{-d\int_\Omega |\nabla\varphi_0(x)|^2\, dx - q_0 \int_\Omega \varphi_0^2(x)\, dx}{\int_\Omega \varphi_0^2(x)\, dx} < 0. \end{aligned}$$

Hence, E_N is locally asymptotically stable for the system (1), (2), (3).

(ii) Let $E^* = (v_0^*, v_1^*, \cdots, v_N^*)$, $w_i = v_i - v_i^*$, $i = 0, 1, 2, \cdots, N$. Then from (2) we have

$$\begin{cases} \frac{\partial w_0}{\partial t} = d\Delta w_0 + r_0(w_0 + v_0^*)\left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_0(P(x)) \\ \qquad\qquad -q_0 w_0 + \tilde{q_0} w_1, \ x \in \Omega \\ \frac{\partial w_i}{\partial t} = d\Delta w_i + r_i(w_i + v_i^*)\left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_i(P(x)) + q_{i-1} w_{i-1} \\ \qquad\qquad -(\tilde{q}_{i-1} + q_i) w_i + \tilde{q}_i w_{i+1}, \ i = 1, \cdots, N-1, \ x \in \Omega \\ \frac{\partial w_N}{\partial t} = d\Delta w_N + r_N(w_N + v_N^*)\left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_N(P(x)) \\ \qquad\qquad +q_{N-1} w_{N-1} - \tilde{q}_{N-1} w_N, \ x \in \Omega \\ \frac{\partial w_i}{\partial n}(x,t) = 0, \ x \in \partial\Omega, \ t > 0, \ i = 0, 1, 2, \cdots, N \end{cases} \tag{10}$$

The linearized system of (10) around E^* is

$$\begin{cases} \frac{\partial w_0}{\partial t} = d\Delta w_0 + r_0 v_0^*\left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_0(P(x)) - q_0 w_0 + \tilde{q_0} w_1, \ x \in \Omega \\ \frac{\partial w_i}{\partial t} = d\Delta w_i + r_i v_i^*\left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_i(P(x)) + q_{i-1} w_{i-1} \\ \qquad\qquad -(\tilde{q}_{i-1} + q_i) w_i + \tilde{q}_i w_{i+1}, \ i = 1, \cdots, N-1, \ x \in \Omega \\ \frac{\partial w_N}{\partial t} = d\Delta w_N + r_N v_N^*\left(-\frac{\sum_{k=0}^N w_k}{K}\right) f_N(P(x)) + q_{N-1} w_{N-1} \\ \qquad\qquad -\tilde{q}_{N-1} w_N, \ x \in \Omega \\ \frac{\partial w_i}{\partial n}(x,t) = 0, \ x \in \partial\Omega, \ t > 0, \ i = 0, 1, 2, \cdots, N \end{cases} \tag{11}$$

Let $w_i(x,t) = e^{\lambda t}\varphi_i(x)$, $i = 0, 1, 2, , \cdots, N$. Then it follows that

$$\begin{cases} \lambda\varphi_0 = d\Delta\varphi_0 + \frac{r_0}{K} v_0^*\left(-\sum_{k=0}^N \varphi_k\right) f_0(P(x)) - q_0\varphi_0 + \tilde{q_0}\varphi_1, \ x \in \Omega \\ \lambda\varphi_i = d\Delta\varphi_i + \frac{r_i}{K} v_i^*\left(-\sum_{k=0}^N \varphi_k\right) f_i(P(x)) + q_{i-1}\varphi_{i-1} \\ \qquad\qquad -(\tilde{q}_{i-1} + q_i)\varphi_i + \tilde{q}_i\varphi_{i+1}, \ x \in \Omega \\ \lambda\varphi_N = d\Delta\varphi_N + \frac{r_N}{K} v_N^*\left(-\sum_{k=0}^N \varphi_k\right) f_N(P(x)) + q_{N-1}\varphi_{N-1} \\ \qquad\qquad -\tilde{q}_{N-1}\varphi_N, \ x \in \Omega \\ \frac{\partial\varphi_i}{\partial n}(x) = 0, \ x \in \partial\Omega, \ i = 0, 1, 2, \cdots, N \end{cases} \tag{12}$$

Adding the equations in (12) yields

$$\lambda \sum_{k=0}^N \varphi_k = d\Delta\left(\sum_{k=0}^N \varphi_k\right) + \left(-\sum_{k=0}^N \varphi_k\right)\left(\sum_{i=0}^N \frac{r_i}{K} v_i^* f_i(P(x))\right).$$

Let $\Phi(x) = \sum_{k=0}^{N} \varphi_k(x)$. From above we have

$$\lambda\Phi(x) = d\Delta\Phi(x) + (-\Phi(x)) \left(\sum_{i=0}^{N} \frac{r_i}{K} v_i^* f_i(P(x)) \right),$$

and

$$\lambda = \inf_{\substack{\Phi \in H^1(\Omega) \\ \Phi \neq 0}} \frac{-d \int_\Omega |\nabla\Phi|^2 \, dx - \int_\Omega (\Phi^2(x)) \left(\sum_{i=0}^{N} \frac{r_i}{K} v_i^* f_i(P(x)) \right) dx}{\int_\Omega \Phi^2(x) \, dx} < 0.$$

Hence, $E^* = (v_0^*, \cdots, v_N^*)$ is locally asymptotically stable for the system (2), (3), (4). □

Proof of Theorem 2.1. Let $w(x,t) = (u(x,t), v_1(x,t), \cdots, v_N(x,t))$. Introduce Lyapunov functional

$$V(w(\cdot,t)) = \int_\Omega \left(U(x,t) - K - K \ln \frac{U(x,t)}{K} \right) dx,$$

where $U(x,t) = u(x,t) + v_1(x,t) + \cdots + v_N(x,t)$. Then

$$\begin{aligned}
\dot{V}(w(\cdot,t)) &= \frac{d}{dt} V(w(\cdot,t)) = \int_\Omega \frac{\partial U}{\partial t} \cdot \frac{U(x,t) - K}{U(x,t)} \, dx \\
&= \int_\Omega \sum_{i=0}^{N} (v_i)_t(x,t) \cdot \frac{U(x,t) - K}{U(x,t)} \, dx \\
&= \int_\Omega \left\{ d\Delta U + \sum_{i=0}^{N} r_i f_i(P(x)) v_i \left(1 - \frac{U}{K} \right) \right\} \frac{U - K}{U} \, dx \\
&= \int_\Omega \left(d\Delta U \left(1 - \frac{K}{U} \right) - \frac{(U-K)^2}{KU} \sum_{i=0}^{N} r_i f_i(P(x)) v_i \right) dx \\
&= d \left[\int_{\partial\Omega} \frac{\partial U}{\partial v} \left(1 - \frac{K}{U} \right) dS - \int_\Omega |\nabla U|^2 \frac{K}{U^2} dx \right] \\
&\qquad - \int_\Omega \frac{(U-K)^2}{KU} \sum_{i=0}^{N} r_i f_i(P(x)) v_i dx \\
&= -d \int_\Omega |\nabla U|^2 \frac{K}{U^2} \, dx - \int_\Omega r_N f_0(P(x)) \frac{(U-K)^2}{K} \, dx \leq 0.
\end{aligned}$$

For the systems (1) and (2), by invariance principle [1] the $\omega-$limit set lies on the simplex $S = \{(u, v_1, \cdots, v_N) : U = u + v_1 + \cdots + v_N = K\} \subset X_\Lambda$.

(i) Forward mutation.
For system (1), (3), (4), the dynamics on S satisfies

$$\begin{cases} u_t = d\Delta u - q_0 u \\ (v_i)_t = d\Delta v_i + q_{i-1}v_{i-1} - q_i v_i,\ i = 1, 2, \cdots, N-1. \\ (v_N)_t = d\Delta v_N + q_{N-1}v_{N-1} \end{cases} \tag{13}$$

Introduce Lyapunov functional on the simplex S,

$$V(w(\cdot,t)) = \int_\Omega \left(u + v_1 + \cdots + v_{N-1} + v_N - K - K\ln\frac{v_N}{K}\right) dx.$$

Then

$$\begin{aligned} \dot{V}(w(\cdot,t)) &= \frac{d}{dt}V(w(\cdot,t)) \\ &= -\int_\Omega \left(|\nabla v_N|^2 \frac{dK}{v_N^2} + q_{N-1}K\right) dx < 0. \end{aligned}$$

It follows that $E_N = (0, 0, \cdots, K)$ is globally asymptotically stable in S. Since the $\omega-$limit set of the solution of (1), (3), (4) lies in the maximal invariant set M in S, from Proposition 3.2(i), E_N is locally asymptotically stable for the system (1), (3), (4), thus E_N is globally asymptotically stable for the system (1), (3), (4). Hence we complete the proof of Theorem 2.1(i).

(ii) Forward - backward mutation.

For the system (2), (3), (4), the dynamics on the simplex S satisfies

$$\begin{cases} u_t = d\Delta u - q_0 u + \tilde{q}_0 v_1 \\ (v_i)_t = d\Delta v_i + q_{i-1}v_{i-1} - (\tilde{q}_{i-1} + q_i)v_i + \tilde{q}_i v_{i+1}, \\ \qquad\qquad\qquad\qquad\qquad i = 1, 2, \cdots, N-1 \\ (v_N)_t = d\Delta v_N + q_{N-1}v_{N-1} - \tilde{q}_{N-1}v_N \end{cases} \tag{14}$$

It is easy to see the linear system(14) is monotone and irreducible and it possesses the invariant function (see [10]) $U = \sum_{i=0}^N v_i$ which determines a family of $d-$hypersurfaces [14]: $U \equiv c, c \in R$. Applying Theorem 6.3 of [10], we know that every solution of (14) is convergent to a steady state in $L := \{\mu E^* : \mu \in R\}$. Precisely, every solution on the invariant $d-$hypersurface : $U \equiv c$ converges to the unique steady state $\frac{c}{K}E^*$ lying on this $d-$hypersurface. In particular, on the simplex $S : U \equiv K$, all solutions on the simplex $S : U \equiv K$

tend to the steady state E^*. This means that E^* is the unique compact invariant set on the S.

Since the $\omega-$limit set of the solution of (2), (3), (4) lies in the maximal invariant M in S, from Proposition 3.2 (ii), E^* is locally asymptotically stable for the system (2), (3), (4), thus E^* is globally asymptotically stable for the system (2), (3), (4). Hence we complete the proof of Theorem 2.1(ii). □

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