



Asymptotic analysis of a selection model with space



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ARTICLE INFO

Article history:

Received 18 July 2014

Available online 7 July 2015

MSC:

35B25

45M05

92C50

92D15

Keywords:

Asymptotic concentration

Adaptive evolution

Tumor growth

Resistance to therapy

ABSTRACT

Selection of a phenotypical trait can be described in mathematical terms by ‘stage structured’ equations which are usually written under the form of integral equations so as to express competition for resource between individuals whatever is their trait. The solutions exhibit a concentration effect (selection of the fittest); when a small parameter is introduced they converge to a Dirac mass.

An additional space variable can be considered in order to take into account local environmental conditions. Here we assume this environment is a single nutrient which diffuses in the domain. In this framework, we prove that the solution converges to a Dirac mass in the physiological trait which depends on time and on the location in space with Lipschitz continuity. The major mathematical difficulties come from the lack of compactness in time, space and trait variables. Usual Bounded Variation estimates in time are not available and we recover strong convergence in space–time, from uniqueness in the limiting constrained Hamilton–Jacobi equation after Hopf–Cole change of unknown. For this reason, we are forced to work in a concavity framework for the trait variable, where enough compactness allows us to derive this constrained Hamilton–Jacobi equation.

Our analysis is motivated by a model of tumor growth introduced in [15] in order to explain emergence of resistance to therapy.

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RÉSUMÉ

La sélection des traits phénotypiques peut être décrite en termes mathématiques par des équations structurées par type qui sont souvent écrites sous forme d'équations intégralo-différentielles afin d'exprimer la compétition pour ressource des individus de différents traits. Les solutions représentent un effet de concentration (sélection du meilleur trait); lorsqu'un petit paramètre est introduit, elles convergent vers une masse de Dirac.

Une variable d'espace peut être ajoutée aux modèles afin de prendre en compte les conditions locales de l'environnement. Ici on suppose que l'environnement a un seul nutriment qui se diffuse dans le domaine. Dans ce cadre, on démontre que la solution converge vers une masse de Dirac en un trait physiologique qui dépend

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du temps et de la localisation en espace, avec une dépendance Lipschitz continue. La difficulté mathématique principale vient du manque de compacité en variables de temps, espace et trait. Des estimations BV habituelles en temps ne sont pas disponibles ici et on démontre la convergence forte en temps et en espace, par l'unicité de la solution de l'équation de Hamilton–Jacobi avec contrainte que l'on obtient à la limite à l'aide d'une transformation de Hopf–Cole. Pour cette raison, on est amené à faire des hypothèses de concavité par rapport à la variable de trait, afin de disposer d'assez de propriétés de compacité pour pouvoir dériver cette équation de Hamilton–Jacobi avec contrainte.

Cette analyse est motivée par un modèle de croissance tumorale introduit dans [15] pour expliquer l'émergence de la résistance aux thérapies.

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1. Setting the problem

In this paper, we are interested in the study of the evolutionary dynamics of populations structured by phenotypical traits and space. While our motivation comes from the study of tumor growth, we investigate the selection of the fittest individuals and the heterogeneity of the population. A population structured by a phenotypical trait can be modeled using integro-differential Lotka–Volterra equations. The solutions of such equations, when we consider small mutation steps and in long time, converge to Dirac masses (see [21,16]); this property corresponds to the selection of the fittest traits. In this paper, we study such behavior considering a spatial structure for the population.

A simple way to describe the selection of the fittest individuals, when environmental conditions depend on space, was proposed in [15] as a model for emergence of resistance to drug in cancer therapy. This model assumes the evolution of cells and is written as a coupled system of integro-differential equations structured by trait v and by a space variable y

$$\begin{cases} \varepsilon \partial_t n_\varepsilon(y, v, t) = [r(v)c_\varepsilon(t, y) - d(v)(1 + \varrho_\varepsilon(y, t))] n_\varepsilon(y, v, t), & y \in \mathbb{R}, 0 < v < 1, t \geq 0, \\ -\Delta_y c_\varepsilon(y, t) + [\varrho_\varepsilon(y, t) + \lambda] c_\varepsilon(y, t) = \lambda c_B, & \varrho_\varepsilon(y, t) = \int n_\varepsilon(y, v, t) dv. \end{cases} \quad (1)$$

The first equation describes the dynamics of a cell population density n_ε . The second equation describes a nutrient c_ε (and a drug can be included in the same way) diffused within the tumor from a constant input concentration c_B with rate λ . The term $r(v)$ denotes the proliferation rate of cells expressing trait v due to the consumption of resource. The function $d(v)$ models the death rate of cells with trait v due to the competition with other cells at the same position. The small parameter ε is introduced to consider the long time behavior of the cell population. Note that we do not consider mutations in this model, supposing that all traits are already present in the population, possibly at very small quantities.

Our goal is to show that, when ε vanishes, there is selection of a space and time dependent fittest trait $V(y, t)$ in the cell population as numerically shown in [15].

Motivated by its mathematical properties, in order to prove more complete results, and to show better the technical difficulties posed by the time variable, we also study a related model where the integral equation for n_ε is coupled to a parabolic equation for the nutrient,

$$\varepsilon \partial_t n_\varepsilon(y, v, t) = [r(v)c_\varepsilon(t, y) - d(v)(1 + \varrho_\varepsilon(y, t))] n_\varepsilon(y, v, t), \quad y \in \mathbb{R}, 0 < v < 1, t \geq 0, \quad (2)$$

$$\frac{\partial}{\partial t} c_\varepsilon - \Delta_y c_\varepsilon(y, t) + [\varrho_\varepsilon(y, t) + \lambda] c_\varepsilon(y, t) = \lambda c_B, \quad (3)$$

$$\varrho_\varepsilon(y, t) = \int n_\varepsilon(y, v, t) dv. \quad (4)$$

Recent technologic advances reveal evidence of heterogeneity within cancer tumors (see for instance [14]). Taking into account this intratumor heterogeneity is crucial in the study of the tumor growth and the emergence of drug resistance (see [7,23,14]), and leads to important challenges in finding effective

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