Asymptotic analysis of a selection model with space

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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.

Key words Asymptotic concentration; Adaptive evolution; Tumor growth; Resistance to therapy;

Mathematics Subject Classification 35B25; 45M05; 92C50; 92D15

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.

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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

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

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,

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

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

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

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 treatment strategies. The above model introduces a simple way to include spatial and phenotypical structure of the cell population together with the diffusion of the nutrient in the domain. Our study indicates that intratumor heterogeneity can emerge as an evolutionary process and provides a description of the space-dependent dominant traits.

The dynamics of phenotypically structured populations under the effect of mutations and competition between the traits has been studied widely during the last decade using stochastic methods and integro-differential equations (see for instance [13, 9, 12, 8, 22, 17] and the references therein). In particular an approach based on a WKB type ansatz, leading to a constrained Hamilton-Jacobi equations (CHJE in short), provides an analysis of the asymptotic behavior of the populations structured by phenotypical traits (see [21, 3, 16] and the references therein). It can be shown using this method that, considering small mutation steps and after a change of variable in time to study the long time behavior, the population concentrates on a dominant trait that evolves in time. In other words, the

population density tends to a Dirac mass in the phenotypical trait. The location and the mass of this Dirac mass evolve in time.

Several refinements are necessary to consider problems which are more relevant biologically. In particular, one can include the interaction of the population with nutrients (see [18, 10] for some results in this direction). The introduction of the resource leads to the study of integro-differential coupled systems. Moreover, most of the cited works neglect the spatial structure of the environment and consider a well-mixed population. However, as mentioned above the environmental heterogeneity is an important element to be considered, for instance in the study of the tumor growth and emergence of drug resistance. The study of models of populations structured jointly by space and trait has gained much attention recently and leads to several important difficulties to be overcome. These difficulties are mainly due to the integral term in one of the variables in the equations. Most of the recent attempts to tackle these problems concentrate mostly on the spatial propagation of the population and less on the phenotypical selection (see [19, 1, 6, 4, 24], and also [11, 2] for the stochastic derivation of such models and the study of steady states). In this paper, using the WKB approach mentioned above, we study models which take into account the spatial and phenotypical structure of the population and lead to the selection of a space and time dependent phenotypical trait. Note that in our model the spatial heterogeneity is induced by a nutrient which diffuses in the domain. The major new mathematical difficulties come from the lack of compactness in time, space and trait variables. A route to handle the nonlinearity, and thus to obtain strong compactness, has been a priori Bounded Variation estimates in time for the quantity denoted below by $\varrho_\varepsilon(y, t)$ where y is the space variable. In the present context, these are not available due to the space variable. Therefore we use another framework, using concavity assumptions, which allows us to recover strong convergence in space-time, from uniqueness in the limiting CHJE for the trait variable, after the WKB change of unknown. This is the reason why we are forced to introduce concavity assumptions for the trait variable; it provides enough compactness (in time-trait) to derive the CHJE, however this procedure uses y-dependent subsequences and this is the other major difficulty. It can be handled using uniqueness for the CHJE, [21], enforcing specific assumptions for the growth-death term (see however the comment in section 6).

For these reasons, we assume some conditions on the model parameters and on the initial data

$$\varrho_m \leq \varrho_\varepsilon^0(y) \leq \varrho_M, \qquad \varrho_m := c_B \frac{\lambda}{\lambda + \varrho_M} \min_{0 < v < 1} \frac{r(v)}{d(v)} - 1 > 0, \quad \varrho_M := c_B \max_{0 < v < 1} \frac{r(v)}{d(v)} - 1, \quad (5)$$

$$c_m < c^0(y) < c_B, \quad c_m := c_B \frac{\lambda}{\lambda + \varrho_M}, \qquad c^0 \in W^{1,\infty}(\mathbb{R}). \tag{6}$$

Note that the non-extinction condition, $\varrho_m > 0$, is equivalent to write

$$\lambda c_B \min_{0 < v < 1} \frac{r(v)}{d(v)} \geq \lambda + c_B \max_{0 < v < 1} \frac{r(v)}{d(v)},$$

a condition which is satisfied for parameters λ and c_B sufficiently large.

For n_ε, we assume initially a 'Gaussian type' concentration

$$\begin{cases} n_\varepsilon^0 \rightharpoonup \varrho^0(y)\delta(v - V^0(y)), & \text{with the condition } r(V^0(y))c^0(y) - d(V^0(y))(1 + \varrho^0(y)) = 0, \\[2mm] n_\varepsilon^0 = e^{u_\varepsilon^0(y,v)/\varepsilon}, \quad u_\varepsilon^0(y,v) \xrightarrow[\varepsilon\to 0]{} u^0(y,v) \text{ locally uniformly,} \\[2mm] |\frac{\partial}{\partial v}u_\varepsilon^0| + |\frac{\partial^3}{\partial v^3}u_\varepsilon^0| \le K^0, \quad \frac{\partial^2}{\partial v^2}u_\varepsilon^0 \le -a < 0 \quad \text{and with } u^0 \text{ Lipschitz-continuous with respect to } y. \end{cases}$$
$$(7)$$

In particular these conditions imply that

$$\max_{0\le v\le 1} u_\varepsilon^0(y,v) = u_\varepsilon^0(y, V_\varepsilon^0(y)) \xrightarrow[\varepsilon\to 0]{} 0 = \max_{0\le v\le 1} u^0(y,v) = u^0(y, V^0(y))$$

with $V_\varepsilon^0(y)) \xrightarrow[\varepsilon\to 0]{} V^0(y)$ locally uniformly.

Finally, we assume that c and d are smooth and that for some constant K^0

$$\begin{cases} |r'| + |d'| + |r''| + |d''| + |r'''| + |d'''| \le K^0, \\[2mm] r'' < 0, \qquad d'' > 0. \end{cases}$$
$$(8)$$

Theorem 1.1 (Parabolic case) *With assumptions* (5)–(8), *there is* $V(y,t) \in W^{1,\infty}(\mathbb{R}\times\mathbb{R}^+)$, $\varrho(y,t) \in C(\mathbb{R} \times \mathbb{R}^+)$ *and* $c(y,t) \in C(\mathbb{R} \times \mathbb{R}^+)$, *such that solutions of* (2)–(4) *satisfy, as* $\varepsilon \to 0$,

$$\varrho_\varepsilon(y,t) \to \varrho(y,t), \quad \text{almost everywhere,} \tag{9}$$
$$c_\varepsilon(y,t) \to c(y,t), \quad \text{locally uniformly,} \tag{10}$$
$$n_\varepsilon(y,v,t) \rightharpoonup \varrho(y,t)\delta(v - V(y,t)), \quad \text{weakly in measures.} \tag{11}$$

Moreover, we have

$$\frac{\partial}{\partial t}c(y,t) - \Delta_y c(y,t) + [\,\varrho(y,t) + \lambda\,]\,c(y,t) = \lambda c_B, \qquad y \in \mathbb{R},\ t \ge 0, \tag{12}$$

and

$$r\big(V(y,t)\big)c(y,t) - d\big(V(y,t)\big)\big(1 + \varrho(y,t)\big) = 0. \tag{13}$$

Finally, $\varrho(y,t)$ *and* $c(y,t)$ *are Hölder continuous in* t *and Lipschitz continuous in* y.

Note that our results and proofs also hold for the multi-dimensional case $y \in \mathbb{R}^N$. However, for the sake of simple representation, we show the result for $y \in \mathbb{R}$.

The convergence of c_ε can be derived from parabolic regularity, while more elaborate arguments are needed to obtain the limit of n_ε. To obtain a priori bounds on n_ε we first use a Hopf-Cole transformation to deal with bounded values. Next, we prove regularity estimates on variables v and t. However, we don't have a priori estimates on variable y due to the nonlocal term $\varrho_\varepsilon(t,y)$. To handle this difficulty we first pass to the weak limit, fixing the variable y, and next we recover pointwise and strong convergence from the uniqueness and the structure of the limit.

We postpone the statement and proof of a similar result in elliptic case, that is system (1) to the end of the paper (Section 5). We begin by giving general a priori bounds which hold both for the elliptic and parabolic case, in Section 2. With these at hand, we prove Theorem 1.1 in the next section. For the sake of completeness, we recall some Hölder continuity results for parabolic equations in Section 4. Some conclusions and perspectives are drawn in Section 6.

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2   Preliminary estimates

Several bounds can be obtained from elementary manipulations of the equations (1) or equations (2)–(4). Here we make the assumptions (5)–(7) in the parabolic case and assume (5) and (7) in the elliptic case. These bounds are

Lemma 2.1 *The following estimates hold true:*

(i) $0 \leq c_\varepsilon(y,t) \leq c_B$,

(ii) $\varrho_\varepsilon(y,t) \leq c_B \max\limits_{0<v<1} \dfrac{r(v)}{d(v)} - 1 = \varrho_M$,

(iii) $c_\varepsilon(y,t) \geq c_B \dfrac{\lambda}{\lambda + \varrho_M} = c_m$,

(iv) $\varrho_\varepsilon(y,t) \geq c_m \min\limits_{0<v<1} \dfrac{r(v)}{d(v)} - 1 = \varrho_m > 0$.

Proof. We only give the proofs for the parabolic case (2)–(4). The estimates can be proved for the elliptic case (1) following similar arguments.

We first notice, from (2) and (7), that $n_\varepsilon > 0$, in $\mathbb{R} \times \mathbb{R} \times \mathbb{R}^+$. In particular, $\varrho_\varepsilon > 0$ in $\mathbb{R} \times \mathbb{R}^+$. Similarly, from (3), (6) and the comparison principle we obtain that $c_\varepsilon > 0$ in $\mathbb{R} \times \mathbb{R}^+$.

(i) From (3), (6), $\varrho_\varepsilon > 0$ and the comparison principle, we immediately deduce that $c_\varepsilon \leq c_B$ in $\mathbb{R} \times \mathbb{R}^+$.

(ii) We integrate (2) with respect to v and use (i) to obtain

$$\varepsilon \partial_t \varrho_\varepsilon(y,t) \leq \left(c_B \max_{0<v<1} \frac{r(v)}{d(v)} - (1 + \varrho_\varepsilon(y,t)) \right) \int d(v) n_\varepsilon(v,t) dv.$$

Using the above inequality together with the definitions (5), we obtain (ii).

(iii) The third inequality follows directly from (ii), (6) and the comparison principle for (3).

(iv) We integrate (2) with respect to v, use (iii) and obtain

$$\varepsilon \partial_t \varrho_\varepsilon \geq \left(c_m \min_{0<v<1} \frac{r(v)}{d(v)} - (1 + \varrho_\varepsilon) \right) \int d(v) n_\varepsilon(v,t) dv.$$

Using the above inequality together with the definitions (5), we obtain (iv).

3   The limiting problem

First step. Strong limit for $c_\varepsilon(y,t)$ and weak limit for $\varrho_\varepsilon(y,t)$. From the uniform bound on $\varrho_\varepsilon(y,t)$, we define $\langle \varrho(y,t) \rangle$ as the weak limit

$$\varrho_\varepsilon(y,t) \rightharpoonup \langle \varrho(y,t) \rangle \quad \text{in} \ \ L^\infty\big(\mathbb{R} \times (0,\infty)\big)\text{-w-} *\,. \tag{14}$$

Then, we may pass to the limit in the equation (3) for c_ε, and for that, we use that

$$c_\varepsilon(y,t) \xrightarrow[\varepsilon \to 0]{} c(y,t) \quad \text{locally uniformly in } \mathbb{R} \times [0,\infty], \tag{15}$$

(see Section 4 for a proof) and we find the equation for the limiting nutrient concentration

$$\frac{\partial}{\partial t}c - \Delta_y c(y,t) + [\langle \varrho(y,t)\rangle + \lambda]\, c(y,t) = \lambda c_B, \qquad y \in \mathbb{R}. \tag{16}$$

Its solution is $C^{1,\alpha}$ in y, with $\alpha \in (0,1)$, by parabolic regularity (see also Section 4).

Second step. The WKB change of unknown. Rather than working on ϱ_ε directly, we define as usual the function

$$u_\varepsilon = \varepsilon \ln(n_\varepsilon), \tag{17}$$

which satisfies

$$\partial_t u_\varepsilon(y,v,t) = r(v)c_\varepsilon(t,y) - d(v)(1 + \varrho_\varepsilon(y,t)), \qquad y \in \mathbb{R},\ 0 < v < 1. \tag{18}$$

It is standard to derive the bounds

$$\begin{cases} |\frac{\partial}{\partial t}u_\varepsilon(v,y,t)| \le K(t), \quad |\frac{\partial}{\partial v}u_\varepsilon(v,y,t)| + |\frac{\partial^3}{\partial v^3}u_\varepsilon(v,y,t)| + |\frac{\partial^3}{\partial tvv}u_\varepsilon(v,y,t)| \le K(t), \\[2mm] \frac{\partial^2}{\partial v^2}u_\varepsilon(y,v,t) \le -a, \quad u_\varepsilon(y,v,t) \le o(1). \end{cases} \tag{19}$$

Indeed, these estimates can be obtained by differentiating (18) and using (7), (8) and Lemma 2.1.

For our arguments below, we fix y and pass to the limit. Extracting several subsequences which a priori depend on y,

$$\varrho_\varepsilon(y,t) \rightharpoonup \varrho(y,t),\ L^\infty(0,\infty)\text{-w-}* \qquad \varrho_m \le \varrho(y,t) \le \varrho_M,$$

$$u_\varepsilon(y,v,t) \longrightarrow u(y,v,t),\ \text{uniformly in } v,\ t \in [0,T], \quad \forall t > 0.$$

Notice that this value $\varrho(y,t)$ may differ from $\langle \varrho(y,t)\rangle$. Passing to the limit, y by y, we find, that

$$\begin{cases} u(y,v,t) = u^0(y,v) + r(v)\int_0^t c(s,y)ds - d(v)t + d(v)\int_0^t \varrho(y,s)ds, \qquad t \ge 0, \quad 0 < v < 1, \\[2mm] \max_{0 \le v \le 1} u(y,v,t) = 0 = u(y,V(y,t),t), \\[2mm] u(y,v,t=0) = u^0(y,v). \end{cases} \tag{20}$$

Note that the first equality in the second line above derives from the upper and lower bound for ϱ_ε and the Hopf-Cole transformation (17). Moreover, by concavity of u in y, the maximum point $V(y,t)$ is unique.

Third step. $\langle \varrho(y,t)\rangle = \varrho(y,t)$ *and pointwise convergence of* u_ε *in* y. Because of the particular structure on the right hand side, we know there is a unique solution $(u(y,t),\int_0^t \varrho(y,s)ds)$ of (20) for each y (see also [21] for general argument): note indeed that since $d(v)$ is positive, for all $y \in \mathbb{R}$ there is a unique quantity $\int_0^t \varrho(y,s)ds$ such that $\max_{0 \le v \le 1} u(y,v,t) = 0$, with u given by the first line of (20). This guarantees the uniqueness of $(u(y,t),\int_0^t \varrho(y,s)ds)$. Therefore the full families $\int_0^t \varrho_\varepsilon(y,s)ds$ and $u_\varepsilon(y,t)$ converge pointwise and not only subsequences, for each y and t. In particular, u_ε converges strongly in $\mathbb{R} \times \mathbb{R}^+$ and not only y by y. Moreover, by Lipschitz continuous dependence upon the parameter y in the initial condition u^0 and the coefficient c in the first line of (20), both $u(y,v,t)$ and $\int_0^t \varrho(y,s)ds$ also have Lipschitz continuous dependence on y.

Consequently $\int_0^t \varrho(y,s)ds = \int_0^t \langle\varrho(y,s)\rangle ds$ and thus $\langle\varrho(y,t)\rangle = \varrho(y,t)$. However this does not imply strong convergence of $\varrho_\varepsilon(y,t)$ in the time variable.

Fourth step. The mapping $t \mapsto V(y,t)$ is Lipschitz continuous in t, y by y. To prove this, let V_ε be the unique maximum point of u_ε and hence $\partial_v u_\varepsilon(y, V_\varepsilon(y,t),t) = 0$. We differentiate this equality with respect to t and find

$$\partial_{vt}u_\varepsilon(y, V_\varepsilon(y,t),t) + \partial_{vv}u_\varepsilon(y, V_\varepsilon(y,t),t)\frac{d}{dt}V_\varepsilon(y,t) = 0.$$

It follows that

$$-\partial_{vv}u_\varepsilon(y, V_\varepsilon(y,t),t)\frac{d}{dt}V_\varepsilon(y,t) = r'(v)c_\varepsilon(t,y) - d'(v)(1 + \varrho_\varepsilon(y,t)).$$

As a consequence, $t \mapsto V_\varepsilon(y,t)$ is Lipschitz continuous for all y. Therefore, by the Arzelà-Ascoli Theorem, as $\varepsilon \to 0$, $V_\varepsilon(y,t)$ converges locally uniformly along subsequences. However, note that the limit $V(y,t)$ is uniquely determined as the unique maximum of $u(y,v,t)$. It follows that the full sequence $(V_\varepsilon(y,t))_\varepsilon$ indeed converges to $V(y,t)$, as $\varepsilon \to 0$. Finally, since, for all y, $V_\varepsilon(y,t)$ is uniformly Lipschitz continuous, $V(y,t)$ is also Lipschitz continuous in t.

From the estimates on $\partial_{vvv}u$ and $\partial_{tvv}u$, we may pass to the strong limit in the term $-\partial_{vv}u_\varepsilon\big(y, V_\varepsilon(y,t),t\big)$ and obtain

$$\dot{V}(y,t) = \big(-\partial_{vv}u\big(y, V(y,t),t\big)\big)^{-1} \big(r'(V(y,t))c(t,y) - d'(V(y,t))(1 + \varrho(y,t))\big), \tag{21}$$

Using the arguments in [21] we can also show, using (20), that at the Lebesgue points in t of $\varrho(y,t)$ we have

$$r\big(V(y,t)\big)c(t,y) - d\big(V(y,t)\big)(1 + \varrho(y,t)) = 0. \tag{22}$$

Since $\varrho \in L^\infty$, we deduce that the above equality holds true for almost every t. This implies that ϱ is also Hölder continuous in t.

Fifth step. The mapping $y \mapsto V(y,t)$ is Lipschitz continuous in y. We can use the value of $1 + \varrho(y,t)$ given by formula (22), and write the equation (21) for V under the form

$$\dot{V}(y,t) = \big(-\partial_{vv}u\big(y, V(y,t),t\big)\big)^{-1} \left(r'(V(y,t)) - \frac{d'(V(y,t))r(V(y,t))}{d(V(y,t))}\right)c(t,y).$$

This is an ordinary differential equation which inherits the regularity of the initial data and coefficients, $c(y,t)$ and $u(y,t)$. Therefore its solution $V(y,t)$ is Lipschitz continuous in y. Consequently, $\varrho(y,t)$ is also Lipschitz continuous thanks to (22).

Sixth step. Strong convergence of ϱ_ε. With the steps above, the conclusion on the weak convergence of $n_\varepsilon(y,v,t)$ to $n(y,v,t) := \varrho(y,t)\delta\big(v - V(y,t)\big)$ is a direct consequence of the analysis of the convergence of u_ε.

To conclude, we prove the strong convergence of ϱ_ε following an argument in [16], equation (9.23). We divide equation (2) by $d(v)$ and integrate. We obtain

$$\varepsilon\frac{\partial}{\partial t}\int_0^1 \frac{n_\varepsilon(y,v,t)}{d(v)}dv = c_\varepsilon(t,y)\int_0^1 \frac{r(v)n_\varepsilon(y,v,t)}{d(v)}dv - \varrho_\varepsilon(y,t)(1 + \varrho_\varepsilon(y,t)).$$

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We pass to the limit and obtain, since c_ε converges strongly and n_ε and ρ_ε converge weakly,

$$\varrho(y,t)^2 \leq c(t,y) \int_0^1 \frac{r(v)n(y,v,t)}{d(v)} dv - \varrho(y,t).$$

We can then identify the right hand side as below

$$c(t,y) \int_0^1 \frac{r(v)n(y,v,t)}{d(v)} dv - \varrho(y,t) = \varrho(y,t)c(t,y)\frac{r\big(V(y,t)\big)}{d\big(V(y,t)\big)} - \varrho(y,t),$$

which implies that

$$\varrho(y,t)^2 \leq \varrho(y,t)c(t,y)\frac{r\big(V(y,t)\big)}{d\big(V(y,t)\big)} - \varrho(y,t).$$

Comparing with (22), we conclude that this inequality is, in fact, an equality and thus the strong convergence of ρ_ε.

The proof of Theorem 1.1 is complete.

4   Uniform estimates on c_ε (parabolic case)

In the analysis of the limit of u_ε and ϱ_ε, we have used standard local uniform continuity for $c(y,t)$. We recall the proof for the sake of completeness and show that, locally, $c_\varepsilon(y,t)$ is uniformly 1/4-Hölder continuous in t and is 1/2-Hölder continuous in y. Better regularity can be obtained using regularizing effects of parabolic equations with the available Lipschitz regularity of $\rho(\cdot,t)$; however, we have chosen to keep a simple complete proof and find a weaker result which is enough for our purpose.

First step. Localization method. We first indicate how to work in L^2 after localizing the problem.

Consider a smooth cut-off function $\chi(y)$ with compact support, such that

$$\begin{cases} \chi(y) = 1, & \text{for } |y| \leq M \\ 0 < \chi(y) < 1, & \text{for } M < |y| < 2M \\ \chi(y) = 0, & \text{for } |y| \geq 2M, \end{cases}$$

with M a positive constant. From equation (3) for c_ε (which is uniformly bounded in $L^\infty(\mathbb{R}^+ \times \mathbb{R})$), we find

$$\frac{\partial}{\partial t}[\chi c_\varepsilon] - \Delta_y[\chi c_\varepsilon(t,y)] + 2\nabla\chi.\nabla c_\varepsilon + c_\varepsilon\Delta\chi = \chi F_\varepsilon, \qquad y \in \mathbb{R},\ t \geq 0, \tag{23}$$

with $F_\varepsilon = c_B - c_\varepsilon(\lambda + \varrho_\varepsilon(y,t))$ which is also uniformly bounded in L^∞.

Therefore, multiplying by χc_ε and integrating in y, we find after integrations by part

$$\frac{1}{2}\frac{d}{dt}\int_\mathbb{R}[\chi c_\varepsilon]^2 dy + \int_\mathbb{R}|\nabla(\chi c_\varepsilon)|^2 dy \leq \int_\mathbb{R} c_\varepsilon^2\,|\nabla\chi|^2 dy + \int_\mathbb{R} c_\varepsilon F_\varepsilon \chi^2 dy \leq C.$$

From this estimate, we also control uniformly $\int_0^T \int_B |\nabla c_\varepsilon|^2 dy ds$ on each ball B and for each $T \in \mathbb{R}^+$.

Next, we multiply equation (23) by $2\Delta_y[\chi c_\varepsilon(y,t)]$ and integrate and obtain

$$\frac{d}{dt}\int_\mathbb{R}|\nabla(\chi c_\varepsilon)|^2 + 2\int_\mathbb{R}|\Delta_y(\chi c_\varepsilon(y,t))|^2 \leq \int_\mathbb{R}|\Delta_y(\chi c_\varepsilon(y,t))|^2 + R_\varepsilon$$

where $R_\varepsilon = \int_\mathbb{R}|\chi F_\varepsilon - c_\varepsilon\Delta\chi - 2\nabla\chi.\nabla c_\varepsilon|^2 dy$ is uniformly controlled in L^1_{loc} thanks to the previous estimates on $\int_0^T \int_B |\nabla c_\varepsilon|^2 dy ds$.

As a consequence, integrating the above equation in t we obtain, for all $0 \leq t \leq T$,

$$\int_\mathbb{R}\big|\nabla[\chi c_\varepsilon(y,t)]\big|^2 dy \leq C_0(T). \tag{24}$$

Next, we consider a second cutoff function $\widetilde{\chi} : \mathbb{R} \to \mathbb{R}^+$ which is compactly supported in $B_M(0)$, where $B_r(a)$ denotes a ball of radius r with center a. We then multiply (3) by $\widetilde{\chi}^2 \frac{\partial}{\partial t} c_\varepsilon$ and integrate in y to obtain

$$\int_\mathbb{R}|\frac{\partial}{\partial t}[\widetilde{\chi}c_\varepsilon]|^2 dy + \frac{1}{2}\frac{d}{dt}\int_\mathbb{R}|\nabla[\widetilde{\chi}c_\varepsilon]|^2 dy + 2\int_\mathbb{R}\nabla\widetilde{\chi}.\nabla c_\varepsilon\frac{\partial}{\partial t}[\widetilde{\chi}c_\varepsilon]dy + \int_\mathbb{R}c_\varepsilon\Delta\widetilde{\chi}\frac{\partial}{\partial t}[\widetilde{\chi}c_\varepsilon]dy = \int_\mathbb{R}\widetilde{\chi}F_\varepsilon\frac{\partial}{\partial t}[\widetilde{\chi}c_\varepsilon]dy.$$

We then integrate in t and from (24) and the fact that $|\nabla\widetilde{\chi}| \leq \widetilde{C} = \widetilde{C}\chi$ in $B_M(0)$, for some constant $\widetilde{C}$, we deduce that

$$\int_\mathbb{R}\big|\nabla[\widetilde{\chi}c_\varepsilon(y,t)]\big|^2 dy \leq C_1(T), \qquad \int_0^T \int_\mathbb{R}|\frac{\partial}{\partial t}[\widetilde{\chi}c_\varepsilon]|^2 dy dt \leq C_2(T). \tag{25}$$

Second step. Hölder regularity. We set $g(y,t) = \widetilde{\chi}(y)c_\varepsilon(y,t)$ and prove the following uniform estimate

Lemma 4.1 *A function $g : \mathbb{R} \times \mathbb{R}^+ \to \mathbb{R}$ with compact support which satisfies (25) is $1/4$-Hölder continuous in t and is $1/2$-Hölder continuous in y.*

Proof. The space regularity is obvious since from the first bound (uniform in time) and the Cauchy Schwarz inequality

$$|g(y_2,t) - g(y_1,t)| \leq \int_{(y_1,y_2)}|\nabla g(y,t)|dy \leq |y_2 - y_1|^{1/2}C_1(T)^{1/2}.$$

Then, we estimate the time increments as follows (with $h = |t_2 - t_1|$)

$$|g(y,t_2) - g(y,t_1)| \leq \int_{(t_1,t_2)}|\frac{\partial}{\partial t}g(y,t)|dt \leq h^{1/2}\left(\int_0^T |\frac{\partial}{\partial t}g(y,t)|^2 dt\right)^{1/2}$$

and thus, being given y_0 and $k > 0$,

$$\int_{|y-y_0|\leq k}|g(y,t_2) - g(y,t_1)|dy \leq h^{1/2}\int_{|y-y_0|\leq k}\left(\int_0^T |\frac{\partial}{\partial t}g(y,t)|^2 dt\right)^{1/2}dy \leq C_3(T)h^{1/2}k^{1/2}.$$

Finally, we write for all $y \in \mathbb{R}$,

$$|g(y_0, t_2) - g(y_0, t_1)| \leq |g(y, t_1) - g(y_0, t_1)| + |g(y_0, t_2) - g(y, t_2)| + |g(y, t_2) - g(y, t_1)|$$

and we integrate in y for $|y - y_0| \leq k$ (with k to be chosen later). We find

$$2k|g(y_0, t_2) - g(y_0, t_1)| \leq \frac{8}{3} C_1(T)^{\frac{1}{2}} k \; k^{1/2} + C_3(T) h^{1/2} k^{1/2}.$$

We take $k = h^{1/2}$ and find the result.

5 Elliptic coupling

In case of elliptic coupling, that is of the system given by equations (1), an additional difficulty occurs because the regularizing effect in time for c_ε and c cannot occur. Therefore, $c_\varepsilon(y, t)$ and $\varrho_\varepsilon(y, t)$ have the same regularity in t, that is we only handle L^∞ bounds and, consequently, weak limits. For that reason our result is weaker

Theorem 5.1 (Elliptic case) *With assumptions* (5), (6)–(8), *there is* $\varrho(y, t) \in L^\infty\big(\mathbb{R} \times (0, \infty)\big)$, $V(y, t) \in W^{1,\infty}\big(\mathbb{R} \times [0, \infty)\big)$ *and* $c(y, t) \in L^\infty\big(\mathbb{R} \times (0, \infty)\big)$, *such that solutions of* (1) *satisfy, as* $\varepsilon \to 0$,

$$\varrho_\varepsilon \rightharpoonup \varrho(y, t), \qquad c_\varepsilon \rightharpoonup c(y, t), \quad L^\infty\big(\mathbb{R} \times (0, \infty)\big)\text{-}w\text{-}*, \tag{26}$$

$$n_\varepsilon(y, v, t) \rightharpoonup \varrho(y, t)\delta\big(v - V(y, t)\big), \quad \text{weakly in measures.} \tag{27}$$

Moreover, we have, almost everywhere in t,

$$-\Delta_y c(y, t) + \langle \varrho \, c \rangle(y, t) + \lambda \, c(y, t) = \lambda c_B, \qquad y \in \mathbb{R}, \; t \geq 0, \tag{28}$$

and

$$r\big(V(y, t)\big)c(y, t) - d\big(V(y, t)\big)\big(1 + \varrho(y, t)\big) = 0. \tag{29}$$

Proof. We just indicate the modifications to the proof of Theorem 1.1.

With the uniform estimates of Lemma 2.1, we can follow the limiting procedure of Section 3. The limit in (15) is just a weak limit because of the time variable, but a.e. in t, $c(y, t)$ belongs to $W^{2,\infty}(\mathbb{R})$ and the equation (16) is replaced by equation (28). Then, the analysis of the limit $u(y, t)$ can be performed as in Section 3 and both equations (21) and (22) hold a.e. in t. The y-regularity can be derived for ϱ, but not t-Lipschitz regularity, because of the lack of time regularity in c. However V itself wins one degree of regularity and is indeed Lipschitz continuous. The Sixth step (strong convergence of ϱ_ε) also fails.

6 Conclusion and perspectives

The asymptotic problem we have handled is one of the simplest where both a trait variable v and a space variable y are used. The main difficulty is that the behaviors in these variables are very different because the solution concentrates as a Dirac mass in v and stays bounded in y. We do not know of methods adapted to prove compactness in this kind of situations. Indeed, a simple tool would be to prove a priori estimates in Sobolev spaces in the variables t and y for integrals in v as

$\rho(y,t)$ here; because of the concentration in the variable v we cannot expect such regularity except for the Hopf-Cole transform which however gives indirect information. Here we have been able to use uniqueness for the limit in order to recover compactness avoiding strong a priori estimates. This method is limited to the particular situation at hand. We cannot expect it to work in several other situations, for example more general (nonlinear) growth rates under the form $R(y, c, \varrho)$ or dispersion depending on the trait (as in [5, 4]).

After this paper was under referee, a new and general uniqueness result has been proved in the concavity framework [20], which certainly allows to generalize our assumptions. Also, another result for space-trait models in the full space was achieved in [24], which provides a priori bounds for the traveling wave problem with dispersion as the trait.

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