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THE CONTINUUM REACTION-DIFFUSION LIMIT OF A STOCHASTIC CELLULAR GROWTH MODEL

ABSTRACT. — A competition-diffusion system, where populations of healthy and malignant cells compete and move on a neutral matrix, is analyzed. A coupled system of degenerate nonlinear parabolic equations is derived through a scaling procedure from the microscopic, Markovian dynamics. The healthy cells move much slower than the malignant ones, such that no diffusion for their density survives in the limit. The malignant cells may locally accumulate, while for the healthy ones an exclusion rule is considered. The asymptotic behavior of the system can be partially described through the analysis of the stationary wave which connects different equilibria.

KEY WORDS: Tumor growth model; Hydrodynamic limits; Degenerate Reaction-Diffusion system.

1. INTRODUCTION

The aim of this paper is to treat a model of tumor growth, or more precisely a model of competition between populations of malignant and normal cells, concentrating on one particular distinguishing feature of certain malignant cell type. We start from an individual-cell based model, in our case a stochastic process on a lattice. On that scale lateral contact inhibition can be convincingly modelled by the exclusion property, *i.e.* prohibiting multiple occupancy of a site. We just take this exclusion property, and lower motility, to distinguish the normal from the malignant cell type, neglecting all other aspects to show the effect of this particular property.

Especially we set birth and death rates equal for both cell types. The death rate is depending on the occupation number of a site, modelling the role of local density. We suppose that on an underlying matrix, modelled by the two-dimensional lattice $\mathbb{Z}^2$, two random fields, U and V, are defined: $U(x)$ is the number of malignant cells in the site $x \in \mathbb{Z}^2$, with a-priori any nonnegative value, while $V(x)$ is the number of healthy cells in the site x, with values in the set $\{0, 1\}$. The evolution, represented by a Markov process, will be given by a stirring mechanism, which we suppose acting much faster on the field U than on V, and a birth-death mechanism which will be described as follows. The specific death rate for the U-cells (*i.e.* the malignant ones) in x depends on the local overall crowding, while their specific birth rate is a positive constant independent of the crowding. We suppose that the V-cells (*i.e.* the healthy ones) die according to the same rule, while their births are conditioned by the «exclusion» rule; the birth never takes place in x if this site is occupied, moreover it is proportional to the number of V-cell in the first (4, in the plane) neighbours. The stirring part of the generator, the one related to the U-cells, has to be enhanced in such a way that in the continuum limit, there comes out for the continuum density u describing the ma-

lignant tissue, a diffusion term with a positive diffusive constant: this is achieved by an amplification of the stirring term as big as the square of the ratio between the macroscopic and the microscopic space. The part of the stirring term which is related to the V-field will be speeded up sufficiently fast (same as the macro-micro ratio) to provide enough mixing, yet not so much to get a diffusion term in the limit equation for the related density v. These different terms will be written down in Section 2.

In the same section we'll consider the hydrodynamic limit of this stochastic model, along the lines of [10, 8, 14]. The resulting system will be a reaction-diffusion one for the resulting densities u and v, with the absence of diffusion of the density v as its particular feature.

It is important that the nonlinearities have to be calculated with the help of local distributions, Poisson and Bernoulli respectively, *i.e.* by a local (not global), mean field approach, [4].

The analysis of the reaction-diffusion system leads to the following result: first analysing the spatially uniform states, *i.e.* the ODE system, one sees that there is always a stable state with only malignant cells, but in a certain regime for the death rates a stable state with only normal cell surviving appears. Secondly, for the spatially nonuniform behavior, by analysing the Lyapunov functional for the system, one gets a regime where the stable state of normal cells has an advantage versus the stable state of malignant cells. The analysis on the next time scale, *i.e.* of the travelling fronts is in progress. We know that there may be a discontinuous (because of the vanishing motility of normal cells), standing wave solution of the PDE system, and we may guess that in the limit the motion of the front between normal and malignant cells would be driven by the positive part of the mean curvature. But this mathematical question is still open. An interesting conclusion of the results obtained so far is that, at least in this model, a change in the death rate, let's call it an aggressive treatment, which doesn't differentiate by itself between normal and malignant cells, can improve the long term survival chance of the normal cells, «making the tumor shrink». And this effect depends on the evaluation of the local invariant measure of the process, the microstructure created by it, it would disappear in a large-scale (*i.e.* global) mean field model.

2. The microscopic model and its scaling limit

In this section, we set up our microscopic model of competition-diffusion, defining various terms which correspond to the behaviour described above. The evolution will correspond to an interacting particle system, namely a Markov process $(U_t, V_t)_{t \geq 0}$ on $S_N = \{(U(x), V(x)), x \in \mathbb{T}_N^2, U(x) \in \mathbb{N}, V(x) \in \{0, 1\}\}$, where, as usual $\mathbb{T}_N^2$ is the (discrete) torus in $\mathbb{Z}^2$, its sites having coordinates x_1, x_2 ranging from 0 to $N-1$ (dimension 2 is just for simplification). We shall identify these sites x with the points of the $1/N$-grid in the unit torus $\mathbb{T}^2 \in \mathbb{R}^2$: *i.e.* for $r = (r_1, r_2) \in \mathbb{T}^2$, $r_1 = x_1/N$, $r_2 = x_2/N$.

The Markov evolution on S_N will be described by a semi-group P_t^N whose infinitesimal generator L_N will contain various terms. The general construction and properties of interacting particle systems are given in [12, 10]. The generator has two parts with two terms for each population of cells (*i.e.* the U- and the V-random fields), and, for any function f on S_N, is expressed as follows:

$$(L_N f)(U, V) = (N^2 L_0^U f + N L_0^V D f + L_R^U f + L_R^V f)(U, V). \tag{2.1}$$

The evolution induced by L_0^U and L_0^V is called a *stirring* in the particle system terminology (see [12]), L_R^U, (L_R^V) are the corresponding birth-death operators. Let $y \sim x$ mean that y is first neighbor of x (*i.e.* $|y - x| = 1$), $\gamma : \mathbb{N} \to \mathbb{R}^+$ is the death rate per cell, $\beta > 0$ is the birth rates for both type of cells.

$$L_0^U f(U, V) = 1/4 \sum_{x, y \sim x} U(x)[f(U^{x, y}, V) - f(U, V)] \tag{2.2}$$

$$L_0^V f(U, V) = \sum_{x, y \sim x} V(x)(1 - V(y))[f(U, V^{x, y}) - f(U, V)] \tag{2.3}$$

$$\begin{aligned} L_R^U f(U, V) = \sum_x \beta U(x)[f(U^{x, +}, V) - f(U, V)] + \\ + \sum_x \gamma(U(x) + V(x)) U(x)[f(U^{x, -}, V) - f(U, V)] \end{aligned} \tag{2.4}$$

$$\begin{aligned} L_R^V f(U, V) = \sum_x \beta(1 - V(x)) \mathbf{1}_{U(x) = 0)} 1/4 \left(\sum_{y \sim x} V(y) \right) [f(U, V^{x, +}) - f(U, V)] + \\ + \sum_x \gamma(U(x) + V(x)) V(x)[f(U, V^{x, -}) - f(U, V)]. \end{aligned} \tag{2.5}$$

The stirring operator L_0^U acts on the U-population, and is accelerated by a factor N^2 in order to lead to finite diffusion after rescaling, and consists of a one-cell jump between neighboring sites; $U^{x, y}(z) = U(z) - \delta_x(z) + \delta_y(z)$, *i.e.* is the configuration which differs from U for a jump of a particle from x to y (similarly for the V-field): to get a non-zero jump rate, the site x has at least one particle on it, and for the V-field the exclusion rule forces the site y to be without any V-particle (a more radical request would be that of being empty at all). The other stirring operator L_0^V is accelerated by a factor N in order to get the right mixing (local equilibrium), yet the continuum limit is zero. In both cases we assume that the rate of the jump of one U-(V-)cell from a given site is proportional to the number of U-(V-)cells in that site. We further derive the *continuum limit* for this model. In order to extract a macroscopic behavior from a microscopic description, we rescale space by N, and take the limit $N \to \infty$. In this way, any fixed macroscopic region in $\mathbb{T}^2$ will contain a very large number of microscopic sites, infinite in the limit. We define the death rate function D, asking the necessary convergence in $\mathbb{R}$ of the power series, as follows

$$D(u) = \sum_{k=0}^{\infty} \gamma(k + 1) \frac{u^k}{k!} \exp(-u).$$

It represents the expected value of a nonnegative-integer-valued random variable dis-

tributed with a Poisson law of density u; and it will be useful to write it as $D(u) = \delta(u) \exp(-u)$, *i.e.* taking out the absolutely monotone factor $\delta(\cdot)$. Technically, we prove that the empirical measures for the cell repartitions,

$$\alpha_U^N(t,.) = \frac{1}{N^2} \sum_{x \in \mathbb{Z}_N^2} U(x) \delta_{x/N}(.), \qquad \alpha_V^N(t,.) = \frac{1}{N^2} \sum_{x \in \mathbb{Z}_N^2} V(x) \delta_{x/N}(.) \tag{2.6}$$

converge weakly for $t \in [0, T]$ (when $N \to \infty$) to the densities $u(\cdot, t)$, and $v(\cdot, t)$, solutions of the following non-linear reaction-diffusion system,

$$\partial_t u = \Delta u + u(\beta - D(u) - D'(u) v) \tag{2.7}$$

$$\partial_t v = v(\beta(1 - v) \exp(-u) - D(u)) \tag{2.8}$$

with some given initial smooth density profile $u_0(.)$, $v_0(.)$.

These equations are formally deduced by considering the evolution of the local functions $U(x)$, $V(x)$, for a given x, and performing the limit $N \to \infty$, identifying $r \in \mathbb{T}^2$ with x/N, $x \in \mathbb{Z}_N^2$. More precisely, let μ_t^N be the evolved state coming from μ^N, which has to be suitably close to a local equilibrium state given by the initial densities (see later for details). The main point is then the following: for any couple of test functions G_U, G_V, defined on $\mathbb{T}^2$, and any $\delta > 0$, let

$$\mathcal{A}_{N,\delta} = \left\{ (U, V) : \left| \frac{1}{N^2} \sum_x U(x) G_U(x/N) - \int G_U(r) u(r, t) \, dr \right| > \delta \right. \tag{2.9}$$

$$\left. \text{and} \quad \left| \frac{1}{N^2} \sum_x V(x) G_V(x/N) - \int G_V(r) v(r, t) \, dr \right| > \delta \right\}.$$

Then prove that

$$\limsup_{N \to \infty} \sup_{t \in [0, T]} \mu_t^N \{ \mathcal{A}_{N,\delta} \} = 0. \tag{2.10}$$

We use the so-called *relative entropy method*, explained for instance in [10]. The hypothesis on the initial states μ^N is given in term of a relative entropy inequality, but first we need some definitions: Let $\nu_{w(\cdot)}^N$ is the local equilibrium (Poisson) distribution of the U-field modulated by the profile $w(\cdot)$, $w(r) \geq 0$:

$$\nu_{w(\cdot)}^N \{ U(x) = k \} = \exp\{ -w(x/N) \} \frac{w(x/N)^k}{k!}, \qquad x \in \mathbb{Z}_N^2, \quad k = 0, 1, 2, \ldots$$

and $p_{z(\cdot)}^N$ is the local equilibrium (Bernoulli) distribution of the V-field modulated by the profile $z(\cdot)$, $0 \leq z(r) \leq 1$:

$$p_{z(\cdot)}^N \{ V(x) = \varepsilon \} = \varepsilon z(x/N) + (1 - \varepsilon)(1 - z(x/N)), \quad x \in \mathbb{Z}_N^2, \quad \varepsilon = 0, 1.$$

Then the needed property of the μ^N's is the following:

$$\limsup_{N \to \infty} N^{-2} \mathcal{H}(\mu^N \mid \nu_{u_0(\cdot)}^N \times p_{v_0(\cdot)}^N) = 0. \tag{2.11}$$

Remark that we do not need that the initial state is of local equilibrium, but just that the density of its relative entropy w.r.t. the initial local equilibrium one, goes to zero as

$N \to \infty$. It comes out that this behavior persists in time, that is

$$\limsup_{N \to \infty} \sup_{t \in [0, T]} N^{-2} \mathcal{H}(\mu_t^N \,|\, \nu^N_{u(\cdot, t)} \times p^N_{v(\cdot, t)}) = 0. \tag{2.12}$$

The local equilibrium profiles are given by the solution $u(\cdot, t)$, $v(\cdot, t)$ of the R-D system, with that initial data $u_0(\cdot)$, $v_0(\cdot)$. Recall now the entropy inequality, which, for two probability measures ϱ and σ and the associated relative entropy $\mathcal{H}(\varrho \,|\, \sigma)$, has the following general form (for any positive α and any observable Φ):

$$\alpha \langle \Phi \rangle_\varrho \leqslant \log \langle \exp(\alpha \Phi) \rangle_\sigma + \mathcal{H}(\varrho \,|\, \sigma)$$

(as usual, $\langle \Phi \rangle_\varrho \equiv \int \Phi d\varrho$, *i.e.* the expectation of Φ w.r.t. ϱ). We recall that this inequality may provide the definition of relative entropy $\mathcal{H}(\varrho \,|\, \sigma)$ as follows

$$\mathcal{H}(\varrho \,|\, \sigma) = \sup_{\Phi} (\langle \Phi \rangle_\varrho - \log \langle \exp(\Phi) \rangle_\sigma).$$

This will be applied, for the evolved states μ_t^N and $\nu^N_{u(\cdot, t)} \times p^N_{v(\cdot, t)}$, to the observable $\mathbf{1}_{\mathcal{A}_{N, \delta}}$, getting the inequality

$$\mu_t^N \{\mathcal{A}_{N, \delta}\} \leqslant \frac{\log 2 + \mathcal{H}(\mu_t^N \,|\, n^N_{u(\cdot, t)} \times p^N_{v(\cdot, t)})}{\log [1 + (\nu^N_{u(\cdot, t)} \times p^N_{v(\cdot, t)})[\mathcal{A}_{N, \delta}]^{-1}]}. \tag{2.13}$$

Dividing the numerator by N^2 we get zero in the limit, by the entropy result (2.12), while the denominator, via a large deviation result [10], stays away from zero. The proofs are cumbersome and essentially not different from the ones in [14], the main variance being in the «defective» scaling of the V-stirring operator. This will be written elsewhere.

3. Macroscopic behavior: the space homogeneous case

In this section, we start to analyse the behavior of the system of equations which have been shown to control the macroscopic evolution of the stochastic model. We present here some properties of the space-independent system.

Let u be the density of malignant cells, which has just to be nonnegative, and v the (nonnegative) density of healthy ones which is bounded from above by 1.

Let

$$g_1(u, v) \equiv (\beta - D(u) - D'(u)v) \qquad \text{and} \qquad g_2(u, v) \equiv (\beta(1 - v) \exp(-u) - D(u))$$

then

$$\dot{u} = u g_1(u, v) \qquad \text{and} \qquad \dot{v} = v g_2(u, v).$$

We recall that

$$D(u) = \delta(u) \exp(-u) = \sum_{k=0}^{\infty} \gamma(k+1) \frac{u^k}{k!} \exp(-u)$$

and we suppose now some structural hypotheses on the parameters. Let $D(0) = \gamma(1) < \beta$: this insures a stationary solution $(u, v) = (0, \bar{v})$, with

$$0 < \beta(1 - \bar{v}) = D(0) = \gamma(1).$$

On the other hand we suppose that for $v = 0$, a stationary solution $(\bar{u}, 0)$ exists; $\bar{u}$ has

to satisfy $\beta = D(\bar{u})$. We'll assume first an increasing behavior for γ, this will be reflected in an analogous behavior for $D(\cdot)$; moreover it will be assumed a (discrete) superharmonic behavior of the $\{\gamma(\cdot)\}$, *i.e.* $\Delta_{discr}\gamma(k+2) \equiv \gamma(k+3) - 2\gamma(k+2) + \gamma(k+1) \leqslant 0$. Let us first see the first derivative:

$$D'(u) = \exp(-u)(\delta'(u) - \delta(u)) = \exp(-u) \sum_{k=0}^{\infty} (\gamma(k+2) - \gamma(k+1)) \frac{u^k}{k!}.$$

Observe that the property $\gamma \nearrow$ reflects in $D \nearrow$, so that we first ask that $\beta > D(0) = \gamma(1)$. Moreover we ask that $\gamma(2) - \gamma(1) > \beta$. Concavity of D readily follows, as this elementary computation shows;

$$D''(u) = \exp(-u)(\delta''(u) - 2\delta'(u) - \delta(u)) =$$

$$= \exp(-u) \sum_{k=0}^{\infty} (\gamma(k+3) - 2\gamma(k+2) + \gamma(k+1)) \frac{u^k}{k!}.$$

Let us now pass to the discussion of the dynamical system given by the ODE system in the plane (u, v). The nullclines $\{g_1(u, v) = 0\}$ and $\{g_2(u, v) = 0\}$ are graphs of two decreasing functions:

$$v = \Gamma_1(u) = (\beta - D(u))/D'(u))$$

and

$$v = \Gamma_2(u) = (\beta - \exp(u) D(u))/\beta).$$

As a consequences of the hypotheses on γ we have that they cross once, and the resulting stationary point is unstable (of saddle type), see fig. 1. Heteroclinic orbits connect these points, in particular one from the origin to this «coexistence» point, and two from this to the stable ones on the axes. Concluding this section, we note that simple conditions on the birth-death rates imply qualitative changes in the structure of the system. The relations $\gamma(2) - \gamma(1) > \beta > \gamma(1)$ and the concavity requirement provide

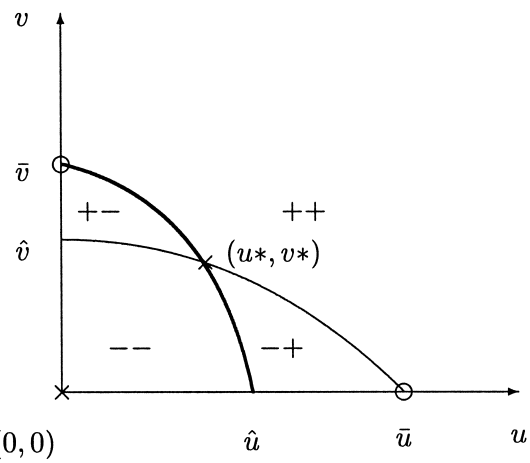

Fig. 1. – Graphs of the decreasing functions: $v = \Gamma_1(u)$ (thin) and $v = \Gamma_2(u)$ (thick). $(0, 0)$ and $(u*, v*)$ are the unstable stationary points $(\times)$, while $(0, \bar{v})$ and $(\bar{u}, 0)$ are the stable ones $(\circ)$. The signs of the components of ∇G are shown too.

a simple and significant picture of the system; in particular the «large» value of $\gamma(2)$ implies the existence of a stable «healthy» state.

4. Macroscopic behavior: the space-dependent case

We pass to study some features of the PDE system (2.7), (2.8) which from now on we assume to hold in the full space. Consider first the following functional $\mathcal{F}[u, v]$:

$$\mathcal{F}[u, v](t) = \int \frac{1}{2} |\nabla u|^2(x, y, t)\, dxdy + \int G(u(x, y, t), v(x, y, t))\, dxdy$$

where the integrations are over the full space, and the «density» G has to be computed. By imposing that the time-derivative of $\mathcal{F}$ is nonpositive, getting in this way a Lyapunov functional, we have the explicit form of $\nabla G(u, v)$:

$$G_u(u, v) = -ug_1(u, v); \quad G_v(u, v) = -\int_{\Gamma_2^{-1}(v)}^{u} s\partial_v g_1(s, v)\, ds.$$

See fig. 1 for an overall picture of the situation. Notice that the components of ∇G become zero on the respective nullclines; so G_u is zero on the (thin) nullcline $\{(u, v): v = \Gamma_1(u)\}$ and G_v is zero on the (thick) nullcline $\{(u, v): v = \Gamma_2(u)\}$.

As it is well known, besides the homogeneous equilibria, the next «simple» solutions to study are the stationary space-dependent ones, or more generally, the travelling waves, which may connect different equilibria and propagate steadily, with a fixed shape. The starting point for this analysis is the reduction to the one-dimensional case; in this way the solution u and v will depend on (x, t), and we look for those solutions which have limits $(u_{\pm\infty}, v_{\pm\infty})$ at $x = \pm\infty$ given by the values of the different equilibria ($(u_{-\infty}, v_{-\infty}) = (0, \bar{v})$ and $(u_{+\infty}, v_{+\infty}) = (\bar{u}, 0)$, say).

These solutions provide «connection» between those equilibria and describe the way the system evolves (or stays still, if the wave is stationary), keeping this behavior at $\pm\infty$. In the case where the wave moves, keeping its shape fixed, the sign of its velocity reveals which equilibrium will invade the whole space, in the long run. This qualitative information may sometimes be extracted without much effort if the system is one-dimensional; but the exact computation of the speed and the actual shape of the moving interface are usually difficult to compute, and generally they are just estimated or numerically evaluated. The system for the travelling waves, where the parameter c represents the unknown velocity, is the following (the independent variable is now $z = x - ct$ while $u(x, t) = \mathcal{U}(x - ct)$, $v(x, t) = \mathcal{V}(x - ct)$)

$$-c\mathcal{U}'(z) = \mathcal{U}''(z) + \mathcal{U}g_1(\mathcal{U}, \mathcal{V}) \tag{4.1}$$

$$-c\mathcal{V}'(z) = \mathcal{V}g_2(\mathcal{U}, \mathcal{V}) \tag{4.2}$$

$$(\mathcal{U}(-\infty), \mathcal{V}(-\infty)) = (0, \bar{v}), \quad (\mathcal{U}(\infty), \mathcal{V}(\infty)) = (\bar{u}, 0). \tag{4.3}$$

The analysis of the travelling waves will be made elsewhere, but we may point out here that linearized analysis around the stationary points $(\bar{u}, 0, 0)$ and $(0, \bar{v}, 0)$ for the

associated 3d ODE system (the third variable being $\mathcal{W} \equiv \mathcal{U}'$), shows that there is no solution with positive c. This depends on the position of the stable/unstable manifold of these points. But if $G(\overline{u}, 0) > G(0, \overline{v})$ there is always – actually a continuum of – discontinuous stationary connections (*i.e.* with $c = 0$ speed), between these points: in the Appendix we'll see it explicitly, in a special case.

5. Appendix

Let's see here a specific example to show an explicit discontinuous stationary wave. Let us consider the special (limit) case of a linear nonhomogenous death rate, *i.e.* $\gamma(k+1) = Ak + B$. In this case it is easy to see that the death function has the same form, *i.e.* $D(u) = Au + B$. The qualitative properties hold as before, so that

$$A = \gamma(2) - \gamma(1) > \beta > \gamma(1) = B.$$

Taking some numerical values as follows: $A = 3$, $B = 0.1$, $\beta = 1$, we want to study the possible one-dimensional stationary connections between the stable states, (*i.e.*, between $(0, \overline{v} = 0.9)$ and $(\overline{u} = 0.3, 0)$).

If we consider the eqs. (4.1) - (4.2), with $c = 0$, we may try to substitute in the first equation for u, the value of v coming from the nullcline $g_2(u, v) = 0$, for $0 \leqslant u \leqslant \widehat{u} = 0.224691$, and $v = 0$ for $\widehat{u} \leqslant u \leqslant \overline{u}$.

$$v = \Gamma_2(u) = 1 - e^u(3u + 0.1), \quad \text{for } 0 \leqslant \widehat{u} = 0.224691; \; v = 0, \quad \text{for } 0.224691 \leqslant u \leqslant 0.3.$$

Consider now a general equation with a «potential» F

$$u'' + f(u) = 0, \quad f = F'.$$

The condition on the existence of a stationary connection between two equilibrium states $u_\pm$ at $\pm\infty$ is the well known one: $F(u_+) = F(u_-)$. In our case the function f is given by

$$f(u) = \begin{cases} ug_1(u, \Gamma_2(u)) = u(0.9 - 3(u + 1 - e^u(3u + 0.1)), & \text{for } 0 \leqslant u \leqslant \widehat{u} = 0.224691 \\ ug_1(u, 0) = u(0.9 - 3u), & \text{for } 0.224691 \leqslant u \leqslant 0.3. \end{cases}$$

It is easy to compute the potential function, for which $0 = F(0) > F(0.3)$, implying nonexistence of the stationary wave.

But we may change the value where v has to be put zero, in particular there exists a value $u_j \sim 0.12$ such that defining f as before, but just changing the point $\widehat{u}$ to u_j, we get that the corresponding potential has the same values at $\pm\infty$.

In this way a stationary connection, with a jump in v (corresponding to that well defined value of $u = u_j$), is shown to exist.

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