Free boundary problems for mechanical models of tumor growth

Juan Luis Vázquez
Universidad Autónoma de Madrid

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Outline

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Models for tumor growth

The talk explains results of a Project with

Benoît Perthame, Univ. Paris VI,

and Fernando Quirós, Univ. Autónoma de Madrid.

to understand the mathematics of some models that have been proposed for tumor growth

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Main paper:

Arch. Ration. Mech. Anal. 212 (2014), no. 1, 93-127.

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- A first class of models, initiated in the 70's by Greenspan, Greenspan, H. P. *Models for the growth of a solid tumor by diffusion*. Stud. Appl. Math. 51 (1972), no. 4, 317–340,consideres that cancerous cells multiplication is limited by nutrients (glucosis, oxygen) brought by blood vessels.

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- Models of this class rely on two kinds of descriptions; either they describe the dynamics of cell population density or they consider the 'geometric' motion of the tumor through a free boundary problem (Friedman, Cui, ...)

- Mechanical models:
  - Competition for space
  - Pressure limited growth
- Kinds of descriptions:
  - Cell scale $\Rightarrow$ cell population density
  - Solid tumor $\Rightarrow$ free boundary problem

AIM: To explain how asymptotic analysis can link the two main approaches, cell density models and free boundary models, in the context of fluid mechanics.

Outline

Purely mechanical model (cell scale)

We start from the simplest cell population density model, proposed in Byrne, H. M.; Drasdo, D. (2009) *Individual-based and continuum models of growing cell populations: a comparison*. J. Math. Biol. 58 in which the cell population density ϱ evolves under pressure forces and cell multiplication

$$\begin{cases} \partial\varrho - \operatorname{div}(\varrho\nabla p) = \varrho\Phi(p), \quad x \in \mathbb{R}^N, \ t > 0 \\ \varrho(\cdot, 0) = \varrho^0 \geq 0 \end{cases}$$

- ϱ: cell population density
- p: pressure.
- $\overrightarrow{v} = -\nabla p$

Constitutive Relations

- Pressure-limited growth): $\Phi'(p) < 0, \qquad \Phi(p_M) = 0$
  - where $p_M > 0$: is the homeostatic pressure (lower pressure that prevents cell multiplication by contact inhibition).
- Pressure-density relation: $p = P(\varrho), \qquad P'(\varrho) \geq 0$
  - $p = P_m(\varrho) := \frac{m}{m-1}\left(\frac{\varrho}{\varrho_c}\right)^{m-1}, \qquad m \gg 1$
  - ϱ_c: maximum packing density of cells ($m \to \infty$), $\qquad \varrho_c = 1$

We arrive at the evolution problem

$$\begin{cases} \partial_t \varrho_m - \Delta \varrho_m^m = \varrho_m \Phi(p_m), \quad x \in \mathbb{R}^N,\ t > 0 \\ \varrho_m(\cdot, 0) = \varrho_m^0 \geq 0 \end{cases}$$

that we want to study in the limit of large m (the Hele-Shaw limit).

- The pressure-density relation becomes singular:

$$p = P_m(\rho) = \frac{m}{m-1}(\rho/\rho_c)^{m-1}.$$

Put $\rho_c = 1$

- Pressure equation

$$\partial_t p_m - |\nabla p_m|^2 = (m-1) p_m \Delta p_m + (m-1) p_m \Phi(p_m)$$

Hele-Shaw graph

- $P_\infty(\varrho) = \begin{cases} 0, & 0 \le \varrho < 1, \\ [0,\infty), & \varrho = 1. \end{cases}$
  - $\varrho_m p_m = \left(\frac{m-1}{m}\right)^{1/(m-1)} p_m^{m/(m-1)} \quad \Rightarrow \quad (1-\varrho_\infty)p_\infty = 0$
- Diffusivity: $D(\varrho) = m\varrho^{m-1}$
  - Huge if $\varrho > 1$ and m large!
- $\|\varrho^0\|_\infty > 1 \Rightarrow$ expected convergence towards a solution of the same problem with a projected initial data

Precedents $m \to \infty$ (without growth term)

• Two kinds of limit situations.

► Keeping data for $\rho_0(x)$ fixed leads to a Stationary limit after an initial collapse of the region $\{\rho_0(x) > 1\}$.Then the pressure goes to zero for all $t > 0$ (after a violent transition at $t = 0+$) :

- [Elliot-Herrero-King-Ockendon, 1986]
- [Caffarelli, Friedman], [Sacks],
- [Benilan-Igbida], [Igbida]...
- For fractional Laplacian version of the model [Vazquez, 2013]

► Keeping the size of $p(x,t)$ nontrivial (e.g., by a source at the boundary) leads to nontrivial limit evolution for pressures and free boundaries, in the Hele-Shaw class of models:

Hele-Shaw Limit $m \to \infty$ (without growth term)

► Keeping the size of $p(x,t)$ nontrivial (e.g., by a source at the boundary) leads to nontrivial limit evolution for pressures and free boundaries, in the Hele-Shaw class of models:

$$\Delta p = 0 \qquad in \quad \Omega(t)$$

$$|\nabla p| = 0 \qquad in \quad \partial\Omega(t)$$

Huge literature, specially in 2D.
Variational formulation : Elliott and Janovski (1981)

for the PME to HS limit

- [Aronson-Gil-Vázquez, 1998]
- [Gil-Quirós, 2001], [Gil-Quirós, 2003]

- [Jakobsen-Karlsen, 2002],
- [Kim, 2003], ...

Setting for the Problem

- $Q = \mathbb{R} \times (0,\infty), \qquad Q_T = \mathbb{R}^N \times (0,T),\, T > 0$

Conditions on the data:

- $\|\varrho_m^0 - \varrho^0\|_{L^1(\mathbb{R}^N)} \underset{m\to\infty}{\longrightarrow} 0, \qquad \varrho^0 \in L^1_+(\mathbb{R}^N)$
- $P_m(\varrho_m^0) \le p_M \qquad (\Rightarrow \quad 0 \le \varrho^0 \le 1,$ no initial layers)
- $\|\partial_{x_i}\varrho_m^0\|_{L^1(\mathbb{R}^N)} \le C, \quad i = 1,\ldots,N$

Pictures

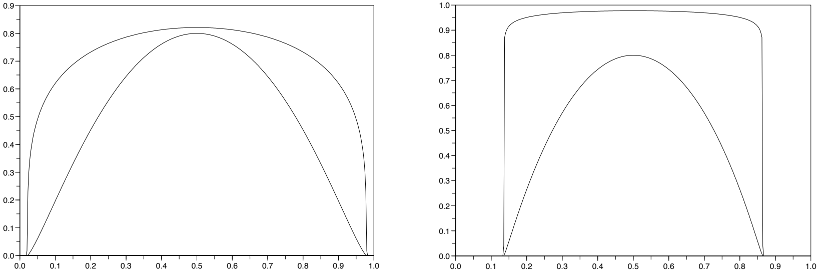

Figure: *Effect of m large.* A solution to the mechanical model in one dimension with $\Phi(p) = 5(1-p)$. Left: $m = 5$. Right: $m = 40$. The upper line is ϱ; the bottom line is p (scale enlarged for visibility). Notice that the density scales are not the same in the two figures. The initial data is taken with compact support and the solution is displayed for a time large enough (see Figure below for an intermediate regime).

Pictures 2

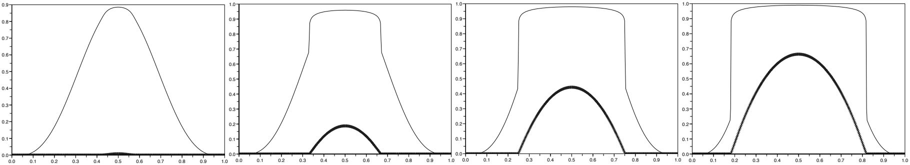

Figure: *Cell density and pressure carry different informations.* Here $m = 40$ and the initial data ϱ is less than 1. The solution is displayed at four different times. It shows how the smooth part of ϱ strictly less than 1 is growing with $p = 0$ (figure on the left). When ϱ reaches the value 1, the pressure becomes positive, increases and creates a moving front that delimitates the growing domain where $\varrho \approx 1$. Thin line is ϱ and thick line is p as functions of x.

THEOREM

- $\varrho_m \xrightarrow{L^1(Q_T)} \varrho_\infty \in C\big([0,\infty); L^1(\mathbb{R}^N)\big) \cap BV(Q_T)$
- $p_m \xrightarrow{L^1(Q_T)} p_\infty \in BV(Q_T)$
- $0 \le \varrho_\infty \le 1, \qquad 0 \le p_\infty \le p_M$
- $\partial_t \varrho_\infty = \Delta p_\infty + \varrho_\infty \Phi(p_\infty)$ in $\mathcal{D}'(Q)$, $\qquad \varrho_\infty(0) = \varrho^0$ in $L^1(\mathbb{R}^N)$
- $p_\infty \in P_\infty(\varrho_\infty)$

Pressure equation / complementarity formula

- From the pressure equation
$\partial_t p_m = (m-1)p_m \Delta p_m + |\nabla p_m|^2 + (m-1)p_m \Phi(p_m)$
and $m \to \infty$ we get

- Complementarity formula: $\quad p_\infty\big(\Delta p_\infty + \Phi(p_\infty)\big) = 0$

THEOREM : $\displaystyle\int_{\mathbb{R}^N} \big(-|\nabla p_\infty|^2 + p_\infty \Phi(p_\infty)\big) = 0$ a.e. $t > 0$

- Equivalent to strong convergence of ∇p_m in $L^2(Q_T)$
- Main difficulty: lack of time regularity (regularization *à la Steklov*)

Free Boundary Problem

- $\Omega(t) := \{x;\ p_\infty(x,t) > 0\} = \{x;\ \varrho_\infty(x,t) = 1\}$
- $-\Delta p_\infty(t) = \Phi(p_\infty(t))$ in $\Omega(t)$, $\qquad p_\infty(t) \in H_0^1\big(\Omega(t)\big)$
- $\partial_t p_\infty = |\nabla p_\infty|^2$ at $\partial\Omega(t) \quad \Rightarrow \quad V = |\nabla p_\infty|$ at $\partial\Omega(t)$

Hele-Shaw type problem

- Expected to be true if $p_m(0) = p^0$ is prescribed $\quad (\varrho_m^0 \to \mathbb{1}_{\{p^0>0\}})$

Precancer zones

- $0 < \varrho < 1$ (only possible if $0 < \varrho^0 < 1$)
- $V = \dfrac{|\nabla p_\infty|}{1 - \overline{\varrho}}$ (open problem, challenging)
- Precancer zones: $\partial_t \varrho_\infty = \varrho_\infty \Phi(0)$
  - Exponential growth
  - Density equation required to describe the limit

First estimates

- L^∞ estimates:
  - Standard comparison arguments
  - $0 \le \varrho_m \le \left(\frac{m-1}{m} p_M\right)^{1/(m-1)} \underset{m\to\infty}{\longrightarrow} 1, \qquad 0 \le p_m = P_m(\varrho_m) \le p_M$
- L^1 estimates:
  - $\int_{\mathbb{R}^N} \{\varrho_m(t) - \hat{\varrho}_m(t)\}_+ \le \mathrm{e}^{\Phi(0)t} \int_{\mathbb{R}^N} \{\varrho_m(0) - \hat{\varrho}_m(0)\}_+$
  - $\|\varrho_m(t)\|_{L^1(\mathbb{R}^N)} \le \mathrm{e}^{\Phi(0)t} \|\varrho_m^0\|_{L^1(\mathbb{R}^N)} \le C\mathrm{e}^{\Phi(0)t}$
  - $\|p_m(t)\|_{L^1(\mathbb{R}^N)} \le C\mathrm{e}^{\Phi(0)t} \qquad \left(p_m = \frac{m}{m-1} \varrho_m \left(\frac{m-1}{m} p_m\right)^{\frac{m-2}{m-1}}\right)$

Semiconvexity

$$r_\Phi = \min_{p\in[0,p_M]} \big(\Phi(p) - p\Phi'(p)\big) > 0$$

$$\underbrace{\Delta p_m(t) + \Phi(p_m(t))}_{w} \geq -r_\Phi \mathrm{e}^{-(m-1)r_\Phi t}/(1-\mathrm{e}^{-(m-1)r_\Phi t})$$

- $$\begin{aligned} \partial_t w \geq (m-1)p_m\Delta w \quad &+ \quad 2m\nabla p_m\cdot\nabla w + (m-1)w^2 \\ &- \quad (m-1)\big(\Phi(p_m) - p_m\Phi'(p_m)\big)w \end{aligned}$$
- $W(t) = -r_\Phi \mathrm{e}^{-(m-1)r_\Phi t}/(1-\mathrm{e}^{-(m-1)r_\Phi t})$ subsolution

Monotonicity

- Pressure equation: $\partial_t p_m = (m-1)p_m w + |\nabla p_m|^2$

- $\partial_t p_m(t) \geq -(m-1)p_m(t) r_\Phi \dfrac{e^{-(m-1)r_\Phi t}}{1-e^{-(m-1)r_\Phi t}}$

- $\partial_t \varrho_m(t) \geq -\varrho_m(t) r_\Phi \dfrac{e^{-(m-1)r_\Phi t}}{1-e^{-(m-1)r_\Phi t}}$

Corollary: $\partial_t \varrho_\infty \geq 0, \qquad \partial_t p_\infty \geq 0$

- $\|\partial_t \varrho_m(t)\|_{L^1(\mathbb{R}^N)} \leq C \quad t \in \left[\dfrac{1}{m-1}, T\right], \qquad \int_{\frac{1}{m-1}}^{T} \int_{\mathbb{R}^N} |\partial_t p_m| \leq C(T)$

BV estimates / convergence

- $\|\partial_{x_i}\varrho_m(t)\|_{L^1(\mathbb{R}^N)} \le K e^{\Phi(0)t}, \qquad \|\partial_{x_i}p_m\|_{L^1(Q_T)} \le C(T)$

  - Equation for $\partial_{x_i}\varrho_m$
  - Multiply by $\mathrm{sign}(\partial_{x_i}\varrho_m) = \mathrm{sign}(\partial_{x_i}p_m)$
  - Kato's inequality + strict sign of Φ'

- Strong convergence in $L^1(Q_T)$:

  - Estimates in $W^{1,1}_{\mathrm{loc}}(Q) \quad \Rightarrow \quad$ strong convergence in $L^1_{\mathrm{loc}}(Q)$
  - Control of the mass in an initial strip (L^1 estimates)
  - Control of the tails (equation + L^1 and L^∞ estimates)

L^1 continuity of the density / initial trace

$0 < \zeta(x) < 1$ test function, $0 < t_1 < t_2 \le T$

- $\varrho_\infty \in C\big([0,\infty); L^1(\mathbb{R}^N)\big)$

  - $$\int_{\mathbb{R}^N} |\varrho_\infty(t_2) - \varrho_\infty(t_1)|\zeta = \int_{\mathbb{R}^N} (\varrho_\infty(t_2) - \varrho_\infty(t_1))\,\zeta$$
    $$= \int_{t_1}^{t_2}\int_{\mathbb{R}^N} (p_\infty\Delta\zeta + \varrho_\infty\Phi(p_\infty)\zeta) \le C(T)(t_2 - t_1)\,(\|\Delta\zeta\|_\infty + 1)$$
  - $\zeta \to 1$

- $\varrho_\infty(0) = \varrho^0$ in $L^1(\mathbb{R}^N)$

  - $\int_{\mathbb{R}^N} \varrho_m(t)\zeta - \int_{\mathbb{R}^N} \varrho_m^0\zeta = \int_0^t \int_{\mathbb{R}^N} (p_m\Delta\zeta + \varrho_m\Phi(p_m))\,\zeta$

  - $m \to \infty$, $t \to 0$, $\zeta \to 1$

- $p_\infty(t) : (0,\infty) \mapsto L^p(\mathbb{R}^N)$ discontinuous (in general) for any $p \ge 1$

Finite speed of propagation

- $\partial_t p \le (m-1)p\Delta p + |\nabla p|^2 + (m-1)p\Phi(0)$

- $P(x,t) = \left(C - \frac{|x|^2}{4(\tau+t)}\right)_+, \quad \tau = N/(4\Phi(0))$:

  - Viscosity solutions of $P_t = |\nabla P|^2$ (Hamilton-Jacobi equation)

  - $\partial_t P - (m-1)P\Delta P - |\nabla P|^2 - (m-1)P\Phi(0) \ge 0, \quad t \in [0, \frac{N}{4\Phi(0)}]$

Uniqueness

- **Difficulty**: p is not a Lipschitz, single-valued function of ϱ

- **Trick**: (ϱ_1, p_1), (ϱ_2, p_2) solutions

  - Ω containing the supports of ϱ_1, ϱ_2 for all $t \in [0, T]$, $\Omega_T = \Omega \times (0, T)$

  - $\iint_{\Omega_T} (\varrho_1 - \varrho_2 + p_1 - p_2)\,[A\partial_t\psi + B\Delta\psi + A\Phi(p_1)\psi - CB\psi] = 0 \qquad (*)$

  - For some fixed $\nu > 0$:

$$0 \le A = \frac{\varrho_1 - \varrho_2}{(\varrho_1 - \varrho_2) + (p_1 - p_2)} \le 1,$$

$$0 \le B = \frac{p_1 - p_2}{(\varrho_1 - \varrho_2) + (p_1 - p_2)} \le 1,$$

$$0 \le C = -\varrho_2 \frac{\Phi(p_1) - \Phi(p_2)}{p_1 - p_2} \le \nu.$$

Hilbert's duality method

- For any smooth G, solve

$$\begin{cases} A\partial_t\psi + B\Delta\psi + A\Phi(p_1)\psi - CB\psi = AG \quad \text{in } \Omega_T, \\ \psi = 0 \quad \text{in } \partial\Omega \times (0,T), \quad \psi(\cdot, T) = 0 \quad \text{in } \Omega, \end{cases}$$

  - Non smooth coefficients, A, B not estrictly positive $\Rightarrow$ Approximation

- Use ψ as test function $\quad \Rightarrow \quad \iint_{\Omega_T} (\varrho_1 - \varrho_2)G = 0 \quad \Rightarrow \quad \varrho_1 = \varrho_2$

- Uniqueness for ϱ + equation (*) $\Rightarrow p_1 = p_2$

  - $\iint_{\Omega_T} \big((p_1 - p_2)\Delta\psi + \varrho_1(\Phi(p_1) - \Phi(p_2))\psi\big) = 0$

  - $\psi = p_1 - p_2 \qquad + \qquad$ monotonicity of Φ

Outline

Mechanical model with nutrients

$$\begin{cases} \partial_t \varrho - \operatorname{div}(\varrho \nabla p) = \varrho\, \Phi(p, c) \\ \partial_t c - \Delta c = -\varrho\, \Psi(p, c) \\ c(x, t) \to c_B > 0 \qquad \text{as } \ |x| \to \infty \end{cases}$$

- c: density of nutrients

- $$\partial_p \Phi < 0, \qquad \partial_c \Phi \geq 0, \qquad \Phi(p_M, c_B) = 0$$
  $$\partial_p \Psi \leq 0, \qquad \partial_c \Psi \geq 0, \qquad \Psi(p, 0) = 0$$
  - It may happen that $\Phi(p, c) < 0$ for c small

Model with nutrients. Initial data

- Additional assumptions: c^0 such that

  - $c_B - c^0 \in L^1_+(\mathbb{R}^N)$
  - $0 \le c_m^0 < c_B$
  - $\|c_m^0 - c^0\|_{L^1(\mathbb{R}^N)} \underset{m\to\infty}{\longrightarrow} 0$
  - $\|(c_m^0)_{x_i}\|_{L^1(\mathbb{R}^N)} \le C, \quad i = 1, \dots, N$
  - $\|\mathrm{div}(\varrho_m^0 \nabla p_m^0) + \varrho_m^0\, \Phi(p_m^0, c_m^0)\|_{L^1(\mathbb{R}^N)} \le C$
  - $\|\Delta c_m^0 - \varrho_m^0\, \Psi(p_m^0, c_m^0)\|_{L^1(\mathbb{R}^N)} \le C$

Model with nutrients. Main results

- Strong convergence in $L^1(Q_T)$ towards BV functions solving

$$\begin{cases} \partial_t \varrho_\infty = \Delta p_\infty + \varrho_\infty \Phi(p_\infty, c_\infty), & \varrho_\infty(0) = \varrho^0, \\ \partial_t c_\infty = \Delta c_\infty - \varrho_\infty \Psi(p_\infty, c_\infty) & c_\infty(0) = c^0, \end{cases} \quad \text{in } \mathcal{D}'$$

$$p_\infty \in P_\infty(\varrho_\infty)$$

- Finite speed of propagation for ϱ_∞, p_∞ (not true for c_∞)

- Uniqueness

Outline

Tumor spheroids

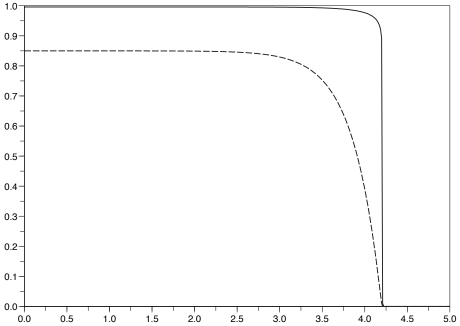

Figure: *Traveling wave.* A traveling wave solution to the mechanical model in one dimension with $m = 40$. The upper continuous line is ϱ; the bottom dashed line is p. Here $p_M = .85$.

A typical application of the Hele-Shaw equations is to describe tumor spheroids (Bru, Byrne-chaplain, Byrne-drasdo, Cui-escher, Friedman, Friedman-hu, Lowengrub-survey). When nutrients are ignored, the tumor is assumed to fill a ball centered at 0,

$$\Omega(t) := \{p_\infty(t) > 0\} = \{\varrho_\infty(t) = 1\} = B_{R(t)}(0).$$

The radius $R(t)$ of this ball is computed according to the geometric motion rules; that is, we consider the unique (and thus radially symmetric) solution to

$$-\Delta p_\infty(t) = \Phi(p_\infty(t)) \quad \text{in } B_{R(t)}(0), \qquad p_\infty(R(t), t) = 0, \tag{1}$$

and evolve the radius according to

$$R'(t) = V = |\nabla p_\infty(R(t), t)|. \tag{2}$$

Then, we consider ϱ_∞ defined as

$$\varrho_\infty(t) = \mathbb{1}_{B_{R(t)}(0)}. \tag{3}$$

Result. TW. KPP like behaviour

This is indeed a correct solution to our model.

Theorem

Let $R(0)=R^0$ *be given. Problem* (1)–(3) *defines a unique dynamic* $R(t)$, $\varrho_\infty(t)$, $p_\infty(t)$, *which turns out to be the unique solution to the Hele-Shaw limit problem with initial data* $\varrho_\infty^0 = \mathbb{1}_{B_{R^0}(0)}$. *For long times it approaches a 'traveling wave' solution with a limiting speed independent of the dimension,*

$$R'(t) \underset{t\to\infty}{\longrightarrow} \sqrt{2Q(p_M)}, \qquad Q(p)=\int_0^p \Phi(q)dq. \tag{4}$$

The limit profile can also be calculated and is one-dimensional.

For several more elaborate one dimensional models, it is also possible to compute the traveling waves which define the asymptotic shape for large times.

Outline

As a regularized variant of the previous model Perthame, Quirós, Tang and Vauchelet (*preprint 2013, to appear in Interfaces and Free Boundaries*) consider the mechanical model with a regularization term due to the active motion of the cell

$$\partial_t \rho_m - \nabla \cdot (\rho_m \nabla p_m) - \nu \Delta \rho_m = \rho_m G(p_m)$$

with small $\nu > 0$. Again, there is a porous medium relation $p_m = P_m(\rho_m)$.

► The regularity of ρ_∞ is better because there always exists a residual diffusion $\nu \Delta \rho_\infty$, but the alternative represented by the previous complementarity formula disappears and the formula becomes

$$p_\infty \Delta p_\infty = p_\infty G(p_\infty) - \nu \frac{\nabla p_\infty \cdot \nabla \rho_\infty}{\rho_\infty}$$

that is not so standard. There is a system of 3 equations characterizing the limit (uniqueness).

Some related references

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Thank you all for your attention

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Best wishes, Nina Nikolaevna!