Weierstrass Institute for
Applied Analysis and Stochastics

On some diffuse interface models of tumour growth

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- Well–posedness and long-time behavior of a tumor growth model proposed in [A. Hawkins-Daarud, K.G. van der Zee, J.T. Oden, Int. J. Numer. Methods Biomed. Eng., 2011] – **with S. Frigeri and M. Grasselli:**

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- Asymptotics and error estimates of its viscous version derived in [D. Hilhorst, J. Kampmann, T.N. Nguyen, K.G. van der Zee, M3AS, 2015] – **with P. Colli, G. Gilardi, J. Sprekels:**

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CGRS2 Asymptotic analyses and error estimates for a Cahn–Hilliard type phase field system modelling tumor growth, to appear in DCDS-S

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It is a two-phase model, considering tumorous and non-tumorous phases only. The tissue velocity field is taken equal to 0. The proliferating cell fraction is assumed to be a given function of the tumor cell phase

NEW Plan of the talk

$\Longrightarrow$ More recently we could **include the** evolution of the **velocity** and treat a **multispecies** tumor growth model proposed by [**CWSL**: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014]

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- Comment on possible open problems

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Diffuse interface model

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Diffuse interface model

The resulting PDE system couples four different types of equations:

- a Cahn-Hilliard type equation for the tumor cells (which include proliferating and dead cells) with transport and reaction terms – depending on the nutrient concentration (e.g., oxygen) – which governs various types of cell concentrations
- a Darcy law for the tissue velocity field, whose divergence may be different from 0 and depend on the other variables, where, besides the pressure gradient, appears also the so-called Korteweg force due to the cell concentration
- a transport equation for the proliferating (viable) tumor cells
- a quasi-static advection reaction diffusion equation for the nutrient concentration, which is coupled to the Cahn-Hilliard equations

- $\phi_i, i = 1, 2, 3$: the volume fractions of the cells:
  - $\phi_1 = P$: **proliferating tumor cell fraction**
  - $\phi_2 = \phi_D$: dead tumor cell fraction
  - $\phi_3 = \phi_H$: host cell fraction

  The variables above are naturally constrained by the relation $\sum_{i=1}^{3} \phi_i = \phi_H + \Phi = 1$
- Π: the cell-to-cell **pressure**
- $\mathbf{u}$:=$\mathbf{u}_i, i = 1, 2, 3$: **the tissue velocity field**. We assume that the cells are tightly packed and they march together
- n: **the nutrient concentration**
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Moreover, we denote by

- $\mathbf{J}_i$: the fluxes that account for mechanical interactions among the species
- $S_i, i = 1, 2, 3$: the terms accounting for inter-component mass exchange as well as gains due to proliferation of cells and loss due to cell death

The volume fractions obey the mass conservation (advection-reaction-diffusion) equations:

$$\partial_t \phi_i + \mathrm{div}_x(\mathbf{u}\phi_i) = -\mathrm{div}_x \mathbf{J}_i + \Phi S_i$$

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The total energy adhesion has the form

$$E = \int_\Omega \left(\mathcal{F}(\Phi) + \frac{1}{2}|\nabla_x \Phi|^2 \right) \, \mathrm{d}x$$

where $\mathcal{F}$ is a logarithmic type mixing potential

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We define the fluxes $\mathbf{J}_\Phi$ and $\mathbf{J}_H$ as follows:

$$\mathbf{J}_\Phi = \mathbf{J}_1 + \mathbf{J}_2 := -\nabla_x \left(\frac{\delta E}{\delta \Phi} \right) = -\nabla_x \left(\mathcal{F}'(\Phi) - \Delta\Phi \right) := -\nabla_x \mu$$

$$\mathbf{J}_H = \mathbf{J}_3 := -\nabla_x \left(\frac{\delta E}{\delta \phi_H} \right) = \nabla_x \left(\frac{\delta E}{\delta \Phi} \right)$$

where we have used in the last equality the fact that $\phi_H = 1 - \Phi$ and where μ is the chemical potential of the system

For the source of mass in the host tissue we have the following relations:

- $S_T = S_D + S_P := S_2 + S_1$
- $\Phi S_H := \Phi S_3 := \phi_H S_T = (1 - \Phi) S_T$

Assuming the mobility of the system to be constant, then the tumor volume fraction Φ and the host tissue volume fraction ϕ_H obey the following mass conservation equations

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) = -\mathrm{div}_x \mathbf{J}_\Phi + \Phi(S_2 + S_1)$$

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Using now the fact that $S_T = S_1 + S_2$ and recalling that $\phi_H + \Phi = 1$, we can forget of the equation for ϕ_H and we recover the equation for Φ in the form

$$\boxed{\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = \Phi S_T, \ \mu = \mathcal{F}'(\Phi) - \Delta\Phi}$$

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Suppose the net source of tumor cells S_T to be given by

$$S_T = S_T(n, P, \Phi) = \lambda_M n P - \lambda_L(\Phi - P)$$

where $\lambda_M \geq 0$ is the mitotic rate and $\lambda_L \geq 0$ is the lysing rate of dead cells

The volume fraction of dead tumor cells ϕ_D would satisfy an equation similar to the one of Φ. However, we prefer to couple the equation for Φ with the one for $P = \Phi - \phi_D$ which then reads

$$\boxed{\partial_t P + \mathrm{div}_x(\mathbf{u}P) = \Phi(S_T - S_D)}$$

where the source of dead cells is taken as

$$S_D = S_D(n, P, \Phi) = (\lambda_A + \lambda_N H(n_N - n))\, P - \lambda_L(\Phi - P)$$

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Here

- $\lambda_A P$ describes the death of cells due to apoptosis with rate $\lambda_A \geq 0$ and the term $\lambda_N H(n_N - n)P$ models the death of cells due to necrosis with rate $\lambda_N \geq 0$
- for mathematical reasons, we choose H to be a regular and nonnegative function of n
- the term n_N represents the necrotic limit, at which the tumor tissue dies due to lack of nutrients

The tumor velocity field $\mathbf{u}$ (given by the mass-averaged velocity of all the components) is assumed to fulfill Darcy's law:

$$\boxed{\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi}$$

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Summing up the mass balance equations, we end up with the following constraint for the velocity field:

$$\boxed{\mathrm{div}_x \mathbf{u} = S_T = \lambda_M n P - \lambda_L (\Phi - P)}$$

Since the time scale for nutrient diffusion is much faster than the rate of cell proliferation, the nutrient is assumed to evolve quasi-statically:

$$\boxed{-\Delta n + \nu_U n P = T_c(n, \Phi)}$$

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Here

- ν_U represents the nutrient uptake rate by the viable tumor cells
- ν_1, ν_2 denote the nutrient transfer rates for preexisting vascularization in the tumor and host domains
- n_c is the nutrient level of capillaries
- the function $Q(\Phi)$ is assumed to be regular and to satisfy $\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi) \geq 0$

- We chose the boundary conditions proposed in [**CWSL**: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014] for Φ, μ, Π and n (with ν denoting the outer normal unit vector to $\partial\Omega$):

$$\mu = \Pi = 0, \quad n = 1, \quad \nabla_x \Phi \cdot \nu = 0$$

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$$P\mathbf{u} \cdot \nu \geq 0$$

which are natural in connection with the transport equation for P

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  In particular, the proliferation function at the boundary has to be nonnegative on the set where the velocity $\mathbf{u}$ satisfies $\mathbf{u} \cdot \nu > 0$. By maximum principle, then $P \geq 0$ in Ω, which is an information we need for proving well-posedness of the system

In summary, let $\Omega \subset \mathbb{R}^3$ be a bounded domain and $T > 0$ the final time of the process. For simplicity, choose $\lambda_M = \nu_U = 1$, $\lambda_A = \lambda_1$, $\lambda_N = \lambda_2$, $\lambda_L = \lambda_3$.

In summary, let $\Omega \subset \mathbb{R}^3$ be a bounded domain and $T > 0$ the final time of the process. For simplicity, choose $\lambda_M = \nu_U = 1$, $\lambda_A = \lambda_1$, $\lambda_N = \lambda_2$, $\lambda_L = \lambda_3$.
Then, in $\Omega \times (0,T)$, we have the following system of equations:

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = \Phi S_T, \;\; \mu = -\Delta\Phi + \mathcal{F}'(\Phi)$$

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \mathrm{div}_x \mathbf{u} = S_T$$

$$\partial_t P + \mathrm{div}_x(\mathbf{u}P) = \Phi(S_T - S_D)$$

$$-\Delta n + nP = T_c(n, \Phi)$$

where

$$S_T(n,P,\Phi) = nP - \lambda_3(\Phi - P)$$

$$S_D(n,P,\Phi) = (\lambda_1 + \lambda_2 H(n_N - n))\, P - \lambda_3(\Phi - P)$$

$$T_c(n,\Phi) = [\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)]\,(n_c - n)$$

coupled with the boundary conditions on $\partial\Omega \times (0,T)$: $\mu = \Pi = 0$, $n = 1$, $\nabla_x \Phi \cdot \nu = 0$, $P\mathbf{u} \cdot \nu \geq 0$ and with the initial conditions $\Phi(0) = \Phi_0$, $P(0) = P_0$ in Ω

We suppose that the potential $\mathcal{F}$ supports the natural bounds

$$0 \leq \Phi(t,x) \leq 1$$

To this end, we take $\mathcal{F} = \mathcal{C} + \mathcal{B}$, where $\mathcal{B} \in C^2(\mathbb{R})$ and

$\mathcal{C} : \mathbb{R} \mapsto [0,\infty]$ convex, lower-semi continuous, $\mathcal{C}(\Phi) = \infty$ for $\Phi < 0$ or $\Phi > 1$

Moreover, we ask that

$$\mathcal{C} \in C^1(0,1), \quad \lim_{\Phi \to 0^+} \mathcal{C}'(\Phi) = \lim_{\Phi \to 1^-} \mathcal{C}'(\Phi) = \infty$$

A typical example of such $\mathcal{C}$ is the *logarithmic potential*

$$\mathcal{C}(\Phi) = \begin{cases} \Phi \log(\Phi) + (1-\Phi)\log(1-\Phi) \text{ for } \Phi \in [0,1], \\ \\ \infty \text{ otherwise} \end{cases}$$

Regarding the functions the constants in the definitions of S_T and S_D, we assume $Q, H \in C^1(\mathbb{R})$ and

$$\lambda_i \geq 0 \text{ for } i = 1, 2, 3, \quad H \geq 0$$

$$[\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)] \geq 0, \quad 0 < n_c < 1$$

Finally, we suppose Ω be a bounded domain with smooth boundary in $\mathbb{R}^3$ and impose the following conditions on the initial data:

$$\Phi_0 \in H^1(\Omega), \quad 0 \leq \Phi_0 \leq 1, \quad \mathcal{C}(\Phi_0) \in L^1(\Omega)$$

$$P_0 \in L^2(\Omega), \quad 0 \leq P_0 \leq 1 \quad \text{a.e. in } \Omega$$

R1. Note that, as $P \geq 0$, the boundary condition $P\mathbf{u} \cdot \nu \geq 0$ should be interpreted as $P = 0$ whenever $\mathbf{u} \cdot \nu < 0$, meaning on the part of the inflow part of the boundary. Moreover, in the weak formulation, that condition will be incorporated into the equation for P turning it into a variational inequality

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R2. Condition

$$\mathcal{C} \in C^1(0,1), \lim_{\Phi \to 0^+} \mathcal{C}'(\Phi) = \lim_{\Phi \to 1^-} \mathcal{C}'(\Phi) = \infty$$

has mainly a technical character and is assumed just for the purpose of constructing a not too complicated approximation scheme. At the price of some additional technical work it could be avoided. One may, for instance, consider the case where $\mathcal{C}(\Phi) = I_{[0,1]}(\Phi)$ (the *indicator function* of $[0,1]$), which does not satisfy this condition

$(\Phi, \mathbf{u}, P, n)$ is a weak solution to the problem in $(0,T) \times \Omega$ if

(i) these functions belong to the regularity class:

$$\Phi \in C^0([0,T]; H^1(\Omega)) \cap L^2(0,T; W^{2,6}(\Omega))$$

$$\mathcal{C}(\Phi) \in L^\infty(0,T; L^1(\Omega)), \text{ hence, in particular, } 0 \le \Phi \le 1 \text{ a.a. in } (0,T) \times \Omega$$

$$\mathbf{u} \in L^2((0,T) \times \Omega; \mathbb{R}^3), \ \mathrm{div}\,\mathbf{u} \in L^\infty((0,T) \times \Omega)$$

$$\Pi \in L^2(0,T; W_0^{1,2}(\Omega)), \quad \mu \in L^2(0,T; W_0^{1,2}(\Omega))$$

$$P \in L^\infty((0,T) \times \Omega), \ 0 \le P \le 1 \text{ a.a. in } (0,T) \times \Omega$$

$$n \in L^2(0,T; W^{2,2}(\Omega)), \ 0 \le n \le 1 \text{ a.a. in } (0,T) \times \Omega$$

(ii) the following integral relations hold:

$$\int_0^T \int_\Omega [\Phi \partial_t \varphi + \Phi \mathbf{u} \cdot \nabla_x \varphi + \mu \Delta \varphi + \Phi S_T \varphi] \ \mathrm{d}x \ \mathrm{d}t = -\int_\Omega \Phi_0 \varphi(0,\cdot) \ \mathrm{d}x$$

for any $\varphi \in C_c^\infty([0,T) \times \Omega)$, where

$$\mu = -\Delta\Phi + \mathcal{F}'(\Phi), \ \mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi$$

$$\mathrm{div}_x \mathbf{u} = S_T \text{ a.a. in } (0,T) \times \Omega; \quad \nabla_x \Phi \cdot \nu|_{\partial\Omega} = 0$$

$$\int_0^T \int_\Omega [P \partial_t \varphi + P \mathbf{u} \cdot \nabla_x \varphi + \Phi(S_T - S_D)\varphi] \ \mathrm{d}x \ \mathrm{d}t \ge -\int_\Omega P_0 \varphi(0,\cdot) \ \mathrm{d}x$$

for any $\varphi \in C_c^\infty([0,T) \times \overline{\Omega})$, $\varphi|_{\partial\Omega} \ge 0$

$$-\Delta n + nP = T_c(n, \Phi) \text{ a.a. in } (0,T) \times \Omega; \ n|_{\partial\Omega} = 1$$

Now, we are able to state the main result of **[M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, Analysis of a diffuse interface model of multispecies tumor growth, preprint arXiv:1507.07683 (2015)]**

Theorem

Let $T > 0$ be given. Under the previous assumptions the variational formulation of our initial-boundary value problem admits **at least one solution** *on the time interval* $[0, T]$

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Hence we consider the system for Φ and $\mathbf{u}$, decoupled from the rest, of the form

$$\partial_t \Phi + \operatorname{div}_x(\mathbf{u}\Phi) - \operatorname{div}_x(\nabla_x \mu) = 0, \ \mu = -\varepsilon^2 \Delta\Phi + \mathcal{F}'(\Phi)$$

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \operatorname{div}_x \mathbf{u} = 0$$

with the boundary conditions

$$\mathbf{u} \cdot \mathbf{n}|_{\partial\Omega} = 0, \ \nabla_x \Phi \cdot \mathbf{n}|_{\partial\Omega} = 0, \ \mu|_{\partial\Omega} = 0$$

Notice that, in particular, we are considering here a no-flux condition for Π in place of the Dirichlet condition

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Notice that, in particular, we are considering here a no-flux condition for Π in place of the Dirichlet condition

Main goal: pass to the limit as $\varepsilon \to 0$

We derive the energy balance

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \left[\frac{\varepsilon^2}{2}|\nabla_x\Phi|^2 + \mathcal{F}(\Phi)\right]\,\mathrm{d}x + \int_\Omega |\nabla_x\mu|^2 + |\mathbf{u}|^2\,\mathrm{d}x = 0$$

Next, we have

$$\int_\Omega \left[\varepsilon^2|\Delta\Phi|^2 + \mathcal{F}''(\Phi)|\nabla_x\Phi|^2\right]\,\mathrm{d}x = \int_\Omega \nabla_x\mu\cdot\nabla_x\Phi\,\mathrm{d}x$$

Then, assuming strict convexity of $\mathcal{F}$, namely

$$\mathcal{F}'' \geq \lambda > 0$$

the following estimates can be deduced

$$\int_0^T \|\varepsilon\Delta\Phi\|^2_{L^2(\Omega)}\,\mathrm{d}t \leq c, \quad \int_0^T \|\nabla_x\Phi\|^2_{L^2(\Omega;\mathbb{R}^3)}\,\mathrm{d}t \leq c$$

Hence, we may assume there is a subsequence such that

$$\mathbf{u}_\varepsilon \to \mathbf{u} \quad \text{weakly in } L^2((0,T)\times\Omega;\mathbb{R}^3)$$

Obviously, we have $\mathrm{div}_x\mathbf{u} = 0$, $\mathbf{u}\cdot\mathbf{n}|_{\partial\Omega} = 0$ We can now write

$$\mathbf{u}_\varepsilon = -\nabla_x\left(\Pi_\varepsilon - \mathcal{F}(\Phi_\varepsilon)\right) - \varepsilon^2\Delta\Phi_\varepsilon\nabla_x\Phi_\varepsilon$$

whence, seeing that

$$\varepsilon^2\Delta\Phi_\varepsilon\nabla_x\Phi_\varepsilon \to 0 \text{ in } L^1((0,T)\times\Omega)$$

we conclude that $\mathbf{curl}_x\mathbf{u} = 0$, which, combined with $\mathrm{div}_x\mathbf{u} = 0$, $\mathbf{u}\cdot\mathbf{n}|_{\partial\Omega} = 0$, yields

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Therefore, taking $\varepsilon \to 0$, our system converges to

$$\partial_t\Phi - \Delta\mu = 0, \qquad \mu = \mathcal{F}'(\Phi)$$

and satisfies the energy law

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \mathcal{F}(\Phi)\ \mathrm{d}x + \int_\Omega |\nabla_x\mu|^2\ \mathrm{d}x = 0$$

Theorem

Let the assumptions listed before hold, let $\mathcal{F}$ satisfy the strict convexity assumption, and let $(\Phi_\varepsilon, \mu_\varepsilon, \mathbf{u}_\varepsilon)$ denote a family of weak solutions to the system

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = 0, \; \mu = -\varepsilon^2 \Delta \Phi + \mathcal{F}'(\Phi)$$

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \mathrm{div}_x \mathbf{u} = 0$$

with the b.c. $\mathbf{u} \cdot \mathbf{n}|_{\partial\Omega} = 0$, $\nabla_x \Phi \cdot \mathbf{n}|_{\partial\Omega} = 0$, $\mu|_{\partial\Omega} = 0$ and the Cauchy conditions. Then, as $\varepsilon \to 0$, the functions $(\Phi_\varepsilon, \mu_\varepsilon, \mathbf{u}_\varepsilon)$ suitably tend to a triple $(\Phi, \mu, 0)$ satisfying

$$\partial_t \Phi - \Delta \mu = 0, \qquad \mu = \mathcal{F}'(\Phi)$$

together with the energy law

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_\Omega \mathcal{F}(\Phi) \, \mathrm{d}x + \int_\Omega |\nabla_x \mu|^2 \, \mathrm{d}x = 0$$

and the initial and boundary conditions

- **Numerical simulations** of diffuse-interface models for tumor growth have been carried out in several papers (cf., e.g., [V. Cristini, J. Lowengrub, Cambridge Univ. Press, 2010] and more recently [H. Garcke, K.F. Lam, E. Sitka, V. Styles, arXiv:1508.00437, 2015]). However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning

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- To the best of our knowledge, the first related papers are concerned with a simplified model, the so-called **Cahn-Hilliard-Hele-Shaw system** ([J. Lowengrub, E. Titi, K. Zhao, European J. Appl. Math., 2013], [X. Wang, H. Wu, Asymptot. Anal., 2012], [X. Wang, Z. Zhang, Ann. Inst. H. Poincaré Anal. Nonlinéaire, 2013]) in which the nutrient n, the source of tumor S_T and the fraction S_D of the dead cells are neglected or [J. Jang, H. Wu, S. Zheng, J. Differential Equations, 2015] where S_T is not 0 but it's not depending on the other variables but just on time and space

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- Moreover, very recent contributions **FGR** and **CGRS1, CGRS2** are devoted to the analysis of a newly proposed simpler model in [A. Hawkins-Daarud, K.G. van der Zee, J.T. Oden, Int. J. Numer. Methods Biomed. Eng., 2012] and [D. Hilhorst, J. Kampmann, T.N. Nguyen, K.G. van der Zee, M3AS, 2015]. In this model, velocities are set to zero and the state variables are reduced to the tumor cell fraction and the nutrient-rich extracellular water fraction

- It would be interesting to investigate whether similar estimates could be derived for the singular flux

$$\mathbf{u} = -\nabla_x \Pi + \frac{1}{\varepsilon} \mu \nabla_x \Phi$$

  However, the above argument does **not** seem to be easily **adaptable** to cover such a situation. For instance, we cannot prove uniform integrability of the product

$$\varepsilon \Delta \Phi \nabla_x \phi$$

  in that case
- **Uniqueness** of solutions at fixed ε is still open
- ...