Correspondence between time-evolution dynamics of a tumor and an attractively interacting Bose-Einstein Condensate with feeding and dissipation.

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I. SUMMARY

The morphology and time-evolution dynamics of tumors are expected to depend heavily on the detailed balance of the overall physics of the cell assembly (e.g., the kinetic pressure, the cell-cell interaction, and the external trapping by the tissue) and the biological processes of mitosis, necrosis, etc. Here, for the first time, we include such a detailed balance in a theoretical model for tumor by exploiting an ab initio mathematical framework of the atomic Bose-Einstein Condensate (BEC) with feeding and dissipation. We show that the Gross-Pitaevskii equation, which describes the many-body atomic BEC characteristics, indeed explains the detailed features of a prevascular tumor culture data with a characteristic length scaling. The agreement suggests the prevascular carcinoma may be a natural analog to BEC and predicts an intercellular wave connecting the cells.

II. INTRODUCTION

Studies on tumors reveal that they are finite-sized and inhomogeneous assembly of cancer cells which appear in a bound spheroid form for prevascular carcinomas [1–3]. We emphasize that, whether in vivo or in vitro they certainly do experience an external trapping potential exerted by the surrounding medium (suspension or tissue). So, at any instant of time, the tumor morphology might be an outcome of a balance of the overall physics of the cell assembly: the kinetic pressure, the intercellular interaction, and the external trapping potential. Consequently, the tumor evolution is expected to be guided by the balance of these physical forces together with the biological processes: 1) cell proliferation or mitosis, 2) impediment to mitosis (pre-vascular case) in the region of higher cell density, 3) and consequent appearance of quiescent cells and cell death due to nutrient level lower than that needed to proliferate or
sustain life, etc.

Theoretical studies, however, mainly employ first-order differential equations to simulate the number or volume growth by shooting various mitosis and necrosis rates and immunological reactions [4,5], spatio-temporal equations (differential and integro-differential) [6–8] to take into account the diffusion of nutrients, and cellular automation (lattice simulation) models [9–11] to mimic the growth pattern considering empirical cell-cell interactions. None of the previous attempts emphasizes this balance of the physical potentials and the biological reactions and it remains a challenge to embed them together in a non-empirical framework.

Looking at the recently discovered [12–14] new form of matter, the Bose-Einstein Condensate (BEC), and their time-evolution dynamics for an attractive atom-atom interaction [15–17], we understand that the underlying physical factors (kinetic pressure, atom-atom interaction, external trapping) of the trapped atomic assembly are quite similar to those expected to be present in the tumors. Also, atomic BEC states are finite-sized and inhomogeneous, like the tumors. The feeding to the condensate and dissipation from it can mimic the role of mitosis and necrosis. Consequently, we conjecture that the Gross-Pitaevskii equation which successfully describes the BEC matter configuration and their time-evolution, could, in some form, be employed to the tumor of cells.

Indeed, we show here that a scaled form of the Gross-Pitaevskii equation, can explain all the intricate features of the in-vitro tumor culture data [3].

III. THE GROSS-PITAEVSKI (GP) EQUATION

The nonlinear GP equation is regarded as a classical field approximation to the many-body Heisenberg equation [18,19]. Also, it can be derived from a field Lagrangian [20] with self-interaction terms. In a non-conservative form it is represented as [15,16]:

\[ i\hbar \frac{\partial}{\partial t} \Phi(r, t) = \left[ -\frac{\hbar^2}{2m} \nabla^2 + \frac{4\pi \hbar^2 a}{m} |\Phi|^2 + V_{\text{trap}} + V_{\text{nc}} \right] \Phi(r, t) \]  

(3.1)

where \( \Phi \) is a classical field approximation to the Heisenberg field operator \( \hat{\Psi} \) and the atom-atom interaction is considered in a mean-field approximation [18]

\[ V(r' - r) = \frac{4\pi \hbar^2 a}{m} \delta(r' - r) \]  

(3.2)

\( m \) is the mass of an atom; \( a \) is the s-wave scattering length also known as the hard-sphere radius [19] of the interaction potential; and \( \hbar \) is the Planck’s constant \( (\hbar = \hbar/2\pi) \). The normalization of the order parameter \( \Phi \) provides the number of atoms \( N(t) \) at any time \( t \): \( N(t) = \int |\Phi(r, t)|^2 d^3r \). \( \nabla^2 \) is the Laplacian operator; \( V_{\text{trap}} \) is the external trap potential.
which can be of any form: harmonic, cylindrical, square well, etc. $V_{nc}$ is a non-conservative term in the Hamiltonian which has been introduced by Kagan et al [15] as

$$V_{nc} = i \frac{\gamma}{2} \hbar \omega - 2i \xi \left( \frac{4\pi \hbar e}{m \omega} \right)^2 \hbar \omega |\Phi|^4$$

(3.3)

for a harmonic trap: $V_{\text{trap}} = \frac{1}{2} m \omega^2 r^2$, where $\omega$ is the frequency of the trap. The first term of (3.3) corresponds to growth in the condensate by feeding from thermal cloud, and the second term corresponds to loss of atoms due to atomic dimer formation from three-body interactions. $\gamma$ and $\xi$ are parameters.

Defining an oscillator length $a_{ho} = \sqrt{\hbar / (2m \omega)}$ (normally it is defined as $a_{ho} = \sqrt{\hbar / (m \omega)}$), and a dimensionless length, time and order parameter as $x = r / a_{ho}$, $\tau = \omega t$, $\phi(x, \tau) = \sqrt{8\pi |a|} \Phi r$, one represents eqn.3.1 in the following dimensionless form:

$$i \frac{d\phi}{d\tau} = \left[ - \frac{d^2}{dx^2} + \frac{1}{4} x^2 - \frac{1}{4} x^2 - 2i \xi \frac{|\phi|^4}{x^4} + i \frac{\gamma}{2} \right] \phi$$

(3.4)

In terms of $\phi$, the number of atoms and the mean-square radius are given by:

$$N(\tau) = \frac{4\pi}{8\pi |a|} a_{ho} \times \int |\phi(x, \tau)|^2 dx = \frac{1}{2|a|} a_{ho} \times n(\tau)$$

(3.5)

$$\langle R^2(\tau) \rangle = a_{ho}^2 \times \frac{\int x^2 |\phi(x, \tau)|^2 dx}{\int |\phi(x, \tau)|^2 dx} = a_{ho}^2 \langle x^2(\tau) \rangle.$$ (3.6)

where $n(\tau) = \int |\phi(x, \tau)|^2 dx$. The time-independent conservative form of eqn.3.4 is given by [21]:

$$\left[ - \frac{d^2}{dx^2} + \frac{1}{4} x^2 - \frac{|\varphi|^2}{x^2} \right] \varphi = \beta \varphi$$

(3.7)

where $\phi$ in eqn.3.4 is taken as $\phi(x, \tau) \equiv \exp(-i \beta \tau) \varphi(x)$; with $\beta = \mu / \hbar \omega$; $\mu$ representing the chemical potential or average single-particle energy. This equation (3.7) has various stable, metastable, or unstable solutions [20] corresponding to various values of $\beta$. Each solution corresponds to a particular value of $N|a| / a_{ho}$ (see eqn.3.5). The time-evolution of the condensate is studied by feeding the solution of this equation as an input to eqn.3.4.

A. Compatibility of the GP equation

The GP eqn.3.1, which is obtained by replacing the field operator $\hat{\Psi}$ by a classical order parameter $\Phi$ in the many-body Heisenberg equation [22], constraints the theory to remain valid till the condensate population is very high so that the annihilation and the creation operators can be considered as $c$-numbers. In atomic BEC this condition is achieved in the limit of $T \to 0$ when most of the particles are expected to occupy the lowest energy state making its population very high. A tumor, which we call a 'cell-condensate', is represented by a density of about $\sim 10^6 - 10^8$ cells per cc. and the size varies from fraction of a few mm to a few cm at a temperature of $37 - 39^\circ F$. 

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The MF A is valid when the condensate is "sufficiently dilute" so that $\rho |a|^3 << 1$ ($\rho$ is the density; $a$ is the $s-$wave scattering length). For cells in a temperature of $37 - 39^\circ F$, it is not expected that the cell-cell interaction be fully represented by the $s$-wave scattering length alone. Also, the latter is not known for the cells. However, to deal with the huge number of complex cancer cells inside the tumor, the mean field approximation appears to the most suitable choice at the moment, if the condition $\rho |a|^3 << 1$ does not appear nonconducive, where $|a|$ is properly simulated to represent the cell-cell interaction. We approximately fix it by considering that the hard-sphere potential range is of the same order of the effective cell radius and take $|a| \approx \bar{r}$ as the interactions are of short range. Then from the measured [3] total number of cells $N(t)$ for the V-79 spheroids and its average volume $V(t)$ at an instant $t$, we see that $\rho |a|^3 \sim 10^{-2}$ except at the very beginning (day-10) where it is still less than 1, but marginally.

B. Scaling of the GP equation

The essential two parameters of the dimension of length, which prevail in a BEC matter, are 1) $\lambda$—the thermal wavelength ($= \hbar/\sqrt{2\pi mkT}$; $k =$Boltzmann constant and $T =$condensate temperature) and 2) $v^{1/3}$—the average interparticle separation. For an ideal case, $\lambda$ satisfies the relation [19]:

$$\frac{\lambda^3}{v} = g_{3/2}(1) + \frac{\lambda^3}{V} \frac{z}{1-z} \geq g_{3/2}(1).$$

(3.8)

where $z$ is the fugacity of the atoms, $V$ is the volume of the container, and $g_{3/2}(1) = 2.612$. In a tumor, the parameter corresponding to the interatomic separation $v^{1/3}$ in a BEC matter is the intercellular separation $\bar{v}^{1/3}$. Any correspondence of a tumor of cells to a BEC of atoms should then be reflected through a length scaling of the form $(\bar{v}/v)^{1/3}$. From eqs.3.5 and 3.6, we see that the number of atoms and the condensate volume are defined by the dimensionless order parameter $\phi(x, \tau)$, a characteristic length $a_{ho}$, and the $s-$wave scattering length $a$. So, we embed the length scaling to the characteristic oscillator length $a_{ho}$ of the GP equation and set

$$a_{ho} = (\bar{v}/v)^{1/3} a_{ho} = (\bar{d}/d)a_{ho}.$$  

(3.9)

where $d (\bar{d})$ is the effective size of an atom (cell) in a particular BEC (tumor) configuration. Consequently, we define the number of cells and the size of the tumors by replacing $a_{ho}$ with $\bar{a}_{ho}$ in eqs.3.5 and 3.6.

$$N(\tau) = \frac{1}{2|a|} \bar{a}_{ho} \times n(\tau) \approx \left(\frac{a_{ho}}{d}\right) \times n(\tau)$$

(3.10)

$$R(\tau) = \bar{a}_{ho} \sqrt{\langle x^2(\tau) \rangle} = \left(\frac{a_{ho}}{d}\right) \times \bar{d} \times \sqrt{\langle x^2(\tau) \rangle}$$

(3.11)

The value of $\bar{d}$ is obtained from the measured data of ref. [3] while the value of $a_{ho}/d$ is fixed by selecting an appropriate solution of the GP equation for the short-range, attractively interacting, and externally trapped $^7$Li.
condensate [15–17].

Before presenting the results, we comment on the effect of the length scaling on $\lambda$, the thermal wave. Applying the scaling we see that the intercellular separation in a tumor could satisfy a relation of the form:

$$\bar{\lambda}^3 \geq \bar{v}g_{3/2}(1)$$ (3.12)

Although we do not investigate the physical existence of such an wave length in living bodies, we mention here that any existence of such an wave, connecting the cells would be very useful to directly account for the observed ultraweak and coherent biological light emanating from tissues [23] and support the school of opinion that it comes from an organized energy field which communicates within the whole organism: an intercellular communication [24].

IV. RESULTS AND DISCUSSIONS

To demonstrate the basic features of the theory we intend to reproduce the tumor culture data on the viable cell count and volume on the V-79 Chinese Hamster lung cells as measured by Folkman and Hochberg (FH) [3].

To simulate the experimental condition of the tumor spheroids suspended (trapped) in soft agar, we consider a agar trap defined by $V_{ext} = V_x \bar{h}\omega$, with the boundary condition $V_x = \infty$ at the container walls. (For a trap independent of $\omega$, the latter is a simple parameter with the dimension of time-inverse.) We then solve eqn.3.7 for a bound ground state solution for a few cells (about five) and next evolute the tumor state in time using eqn.3.4. FH has tried to maintained a constant feeding by replacing the agar at regular intervals of 2-3 days. Similarly, we consider a constant feeding in the Hamiltonian given by $\frac{i}{2}\gamma \bar{h}\omega$, replicating a fixed mitosis rate. ($\gamma$ is a parameter representing the strength of the feeding.) In practice, although feeding remains constant for a prevascular tumor, the mitosis rate is slowed down with increasing size and density of the tumor. It is now known that the 1) diffusion of nutrient become less in the central region; 2) consequently, some cells therein enter a quiescent phase where they remain alive but non-proliferating; and 3) some of the quiescent cells die due to nutrient diffusion lower than that needed for survival. All the above mentioned negative aspects of the growth are expected to depend on the density and the kinetic profile of the cell assembly. We find that a non-linear density dependence proportional to $\rho^2(x, t) (\equiv |\Phi(x, t)|^4)$ in the Hamiltonian, explains the intricate features of the viable cell count data of FH [3] for the V-79 cells.

In figure-1a we present the number of cells $N(t)$ versus the time $t = \tau/\omega$. First, to fix the time scale ($t = \tau/\omega$) we observe that $\omega$ corresponds to a value $\omega \sim 1$ per day and thus we set $\omega = 1/(24 \times 60 \times 60)sec^{-1}$. From figure-1a we find that 1) initially the number increases with a steep exponential fashion; 2) it attains a local peak at around day-26 (solid line); 3) here it suffers a partial collapse; 4) after completing the collapse, it again starts a strong exponential
growth at around day-35 but for a short duration and gradually it gets stabilized with a viable count around \( N \sim 10^5 \).

From figure-1b (reproduced from figure 3b of ref. [3]) we see that all the characteristic features described above are present in the measured data of FH including the (approximate) positions of the peak and collapse.

Among the crucial features in the measured data (figure 1b), **we highlight the partial collapse after day 24 and the short but strong regrowth without an angiogenesis near day-30.** This is a typical characteristic of an atomic BEC with atom-atom short-range nonlinear attractive interaction and three-body recombination losses [15–17]. Studying the density profile (see figure 2), we find that with growing number, the central density increases the most. The tumor appears to form a multilayer system as can be seen from figure 2c. The increasing central zone density reaches a maximum around day 24 when it triggers a contraction or partial collapse of the system, exactly similar to that reported for the many-body atomic condensate [15]. In the process of contraction there could be a substantial loss of cells in that region as can be seen from the density profile at day-28 in figure 2d. This loss in turn would diminish the attractive pseudopotential resulting a fresh rapid expansion of the system which is evident both in figure 1a and and figure 1b around day-30 (for a similar event in an atomic BEC see around \( \tau \sim 5.0 \) in figure-1 of ref. [15]). The inviable and dead cells in the central region are referred as a necrotic core [3,9]. The fluctuation in number in the steady (dormant) state is a repetition of the expansion and the contraction process mentioned above.

In the following we discuss the volume evolution of the V-79 spheroids which represents some apparent anomaly with their number evolution.

Comparing the measured data on the viable and total cell counts in figure 1b and the spheroid volume (circles with error bar in figure 3), we note that 1) while both the cell numbers approximately stabilize since day 50-55, the diameter of the tumor at that time is about one-third of its stabilized value of 3.6 ± 0.5mm (figure 3). 2) From day-55 onwards, the size triples against a constant (approx.) number. From the V-79 data, we evaluate the effective cell size and find that it varies from \( \bar{d} \approx 65\mu m \) near day 10, to \( \bar{d} \approx 10\mu m \) near day 42, to finally get stable with a value of \( \bar{d} \approx 40\mu m \) at around day 200. The abrupt decrease in the effective cell size from 65\( \mu m \) to 10\( \mu m \) might be due to the fact that in the initial phase of aggressive mitosis (day 0-24), the cells might be undergoing mitosis before they could double their individual size. The volume gain in the latter phase (day 50-160) against a approximately fixed number of cells may be attributed to a gain in the effective and individual cell size as we cannot expect any other mechanism of volume expansion from a lower attractive pseudo potential as the number is fixed.

To check this assertion, we approximately formulate the variation in the average cell size as:

\[
\bar{d}(t) = d_m^-(t) + d_g^+(t)
\]

(4.1)

where \( d_m^- (= d_0 e^{-\epsilon_1 t}) \), is a rapidly diminishing variable of size representing aggressive mitosis and \( d_g^+ (= d_f (1 - \epsilon_2 t)) \),
\( e^{-c_2t^c_3} \)), is a rather slowly increasing variable of size. Where \( d_0 = 65\mu\text{m} \), \( d_f = 40\mu\text{m} \) and we choose the value of the parameters \( c_1, c_2, c_3 \) such that we obtain a minimum average size \( \sim 10\mu\text{m} \) and a stabilization size of \( 40\mu\text{m} \) (after day 160).

The variation of \( \bar{d} \) will have no effect in eqn.3.10 as it is expected to cancel from a similar variation in \( |a| \) as can be seen from our consideration \( |a| \approx \bar{r} (= \bar{d}/2) \). However, it will affect the volume as we see from eqn.3.11. In our calculation \( \phi \) represents the ‘wave function’ for the proliferating (viable) cells and so \( \sqrt{\langle x^2(\tau) \rangle} \) in eqn.3.11, will provide the average spread of the proliferating cells which occupy the outermost boundaries (the necrotic mass is concentrated in the center). Consequently, eqn.3.11 is expected to give the size of the tumor provided the effective cell size \( \bar{d} \) is appropriate. Theoretical results are shown in the solid curve in figure 3 and the experimental data of ref [3] are shown as circles with the error bars. The time-variation in the tumor size agree quite well with the measured data vindicating the possibility of the above explanation to the volume gain against a fixed number count. The crucial aspect is the agreement in the number count of proliferating (viable) cells and the stabilized tumor size.

Present investigation reveals a correspondence between a many-body atomic system in a condensed state to a multicellular tumor spheroid. Invoking a dimensionless form of the GP equation, and considering the tumors as bound and trapped assembly of cancer cells with nonlinear intercellular interactions, we explain the long-standing time-evolution data [3] on spherical carcinoma with all their essential features. This raises the possibility of viewing a prevascular carcinoma as a natural analog to BEC. The response of the avascular tumors to the GP equation and to the nonlinear physics of BEC matters mark a significant new development of the cell-proliferation dynamics and is expected to usher a new era in the future studies of tumor evolution. The involved scaling of the BEC matter lead to a matter wave with wavelength of the order of intercellular separation. The physical presence of such an wave will provide a foundation to the biophoton hypothesis and establish an intercellular communication, conjectured previously [24].

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Figure captions:

Figure 1a: Number evolution for the proliferating (viable) V-79 cells in a spherical carcinoma in agar.

Figure 1b: Figure reproduced from Folkman and Hochberg [3] by scanning. V-79 data: Solid curve- viable cell count; dashed curve- total cell count.

Figure 2: Density \(|\phi(x, \tau)/x|^2\) distribution of the V-79 spherical carcinoma in their early stages. a) initial tumor with five cells at \(\tau = 0\), b) \(\tau = 10\), c) \(\tau = 24\), and d) \(\tau = 28\).

Figure 3: Volume evolution of V-79 spherical carcinoma. Circles with error bars are the measured data reproduced from figure 3b of ref. [3]; Solid curve - present results.
This figure "figure1b.gif" is available in "gif" format from:

http://arXiv.org/ps/cond-mat/0306539v1