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The Interplay between Stress and Growth
in Solid Tumors

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Abstract

A number of biological phenomena are interlaced with classical mechanics. In this review we discuss the role of mechanics in tumor growth, namely the avascular phase of solid tumors. While a growing mass produces a traction of the surrounding tissues, a feedback mechanism controls the proliferation of the malignant cells depending on the tensional state. The formalism of continuum mechanics, possibly accompanied by numerical simulations, is able to shed light on biological controversial subjects. The converse is also true: non-standard mechanical problems suggest new challenging theoretical questions.

Keywords: Continuum Mechanics, Biology, Tumors, Growth, Mechanotrasduction

Introduction

Mechanobiology is an area of increasing interest in continuum mechanics. The impressive improvements of experimental techniques offer to scientists a huge number of data, at several spatial scales. The accuracy of experimental measures and the novelty of the observed phenomena make the mathematical modelling of living matter a very attractive field. Biochemistry currently plays a major role, but there is quite a consensus that mechanics, and in particular continuum mechanics, is the correct tool for an insight of several

open questions, as, for instance, mechanotrasduction (19).

In this paper we review the state of the art of the research in a biological problem where the mathematical formalization is an effective tool to understand the inner mechanisms of a living system: solid tumor growth. The choice of the subject and the way to treat it is manifestly driven by our own scientific activity and personal taste. Namely, the mathematical modelling is not purely addressed to *reproduce*, possibly numerically, something observed in nature, but there are more ambitious aims.

- It may happen that the biological literature is controversial on the mechanism driving a specific phenomenon; different plausible explanations for the same complex biological behavior can be conjectured and they look equally satisfactory at a qualitative level. In these cases, a knock–out strategy is usually adopted to devise among the candidates at experimental level: the role of a possible mechanism is checked observing the system when it is inhibited (for instance by suppression of a gene). This classical procedure can be effectively accompanied by the formalization of the phenomenology into equations that obey the laws of physics: their numerical solution represents a promising tool to discriminate quantitatively among possible mechanisms and tumors are a good example in this respect.

- The mathematical model of some tumors are known and rather assessed, at least in simple geometries or with deterministically known parameters. Then numerics becomes the essential tool to face complex geometries or to include the stochastic nature of the parameters. This application of mechanobiology becomes particularly important in medical applications, where predictions of the development of human diseases always faces uncertain and patient–specific data.

In this review we do not enter the details of the biological behavior and mathematical modelling: the intent is instead to stress the original perspective that mathematics and mechanics can provide in a biological framework and stimulate the interest of the reader to deepen this exciting subject.

1. Solid tumor growth

After Folkman & Hochbergand (10), the typical experimental setting to determine the uncontrolled duplication rate of tumor cells *in vitro* is a cluster

of cells, freely floating in a culture medium, called *multicell spheroid*. A tumor spheroid is therefore an ensemble of cells freely proliferating in an environment with large availability of nutrient. The specific characteristics of the system is that cells have lost the ability to self–regulate their own number through a normal apoptosis mechanism. In absence of external cues the shape of the cell cluster is basically spherical, as gravity exerts no influence.

In the standard free–growth case, a plot of the diameter of the tumor vs. time typically exhibits an early stage of exponential growth, followed by a linear one. The transition from one regime to the other is mainly regulated by the availability of nutrient, that occurs by diffusion. In fact, when the size of the tumor $\bar{r}(t)$ is smaller than the typical diffusion length, the nutrient is everywhere available in the spheroid and the growth is volumetric:

$$\frac{d\bar{r}^3}{dt} \simeq \bar{r}^3, \tag{1}$$

so that $\bar{r}(t) \simeq e^t$. Conversely, when the diameter of the spheroid is much larger than the penetration length of the nutrient one obtains surface growth, that is

$$\frac{d\bar{r}^3}{dt} \simeq \bar{r}^2, \tag{2}$$

and $\bar{r}(t) \simeq t$. See (6) and the references therein for a review of the literature on growth of spatially uniform models of avascular tumors.

The availability of nutrients is definitely the major factor affecting tumor growth, but other external agents can affect it. The mechanical influence of external loading on tumor growth has been investigated by Helmlinger *et al.* (12). They design an experimental setup in order to control the traction applied at the boundary of clusters of cells grown *in vitro*, and check the influence of such a tensional state on the growth rate of the multicell spheroid. In a standard apparatus multicell spheroids freely grow, floating in the culture medium; conversely, these authors plug the tumor cells in a gel, produced at given (known) stiffness by suitably tuning the solid phase concentration. As the spheroid grows, it displaces the surrounding gel, which then exerts a traction at the surface of the tumor spheroid. An *a priori* mechanical characterization of the gel allows to calculate the pressure exerted by the gel on the spheroid depending on its radius.

2. Tumor as a fail of homeostatic control

An evocative definition of a tumor is "a system that has lost its self–regulating ability towards homeostasis". In other words, tumor cells do not correctly detect or elaborate the external signals that regulate its proliferation and apoptosis, and duplicate without a control. Among many others cues, a regulator of the homeostatic state of an organ is its tensional state. In some biological systems this mechanism is well known and a striking example are epithelial cells in arteries: they are able to discriminate among a blood pressure increase (normal stress) and flow rate modification (shear stress). The "arterial system" remodels according to the detected mechanical stimula, thus increasing the width of the wall or the thickness of the lumen, respectively (20). This very smart behavior can be mechanically encoded assuming that cells duplicate and die in order to produce an environment with optimal ("homeostatic") stress.

A mathematical model that accounts for such a pictorial description is the following. Assume a multiplicative decomposition of the tensor gradient of deformation (15)

$$\mathbf{F} = \mathbf{F}_e \mathbf{G} \tag{3}$$

where $\mathbf{G}$ and $\mathbf{F}_e$ account for growth and elastic energy storage, respectively. A simple thermodynamically admissible growth law for the system (3) is then (5)

$$\dot{\mathbf{G}} = -(\mathbf{E} - \mathbf{E}_0)\mathbf{G}, \tag{4}$$

where $\mathbf{E}$ is the Eshelby tensor, a frame–invariant measure of the stress defined as

$$\mathbf{E} := \psi \mathbf{I} - \mathbf{F}_e^T \psi'. \tag{5}$$

where $\psi(\mathbf{F}_e)$ is the strain energy and the prime indicates its Fréchet derivative (8; 9).

In the present context, the evolution equation (4) can be interpreted as follows: when the stress state of the system is not in the homeostatic equilibrium $\mathbf{E}_0$, it remodels (growing or resorbing matter) until the target tensional state is recovered. In this respect, all the genetic information that detail the shape and function of organs are encoded in the target stress $\mathbf{E}_0$. A suggestive mechanical interpretation of a tumor therefore naturally arises: a tumor is an open system such that the information contained in $\mathbf{E}_0$ is damaged, or the feedback self–regulation does not work, so that the stress–modulated control does not work properly.

3. Are solid tumors fluids?

The main result of the experiments carried out by the group of Rakesh Jain (12) is that the stress field reduces the final size of the spheroids, inhibiting proliferation and stimulating apoptosis. It is therefore clear that a precise determination of the constitutive laws that characterize the mechanical behavior of a tumour spheroid is a pre-requisite in order to assess a reliable stress–growth relationship.

Early attempts in this respect assume that a cell conglomerate behaves like a viscoelastic fluid, able to bear a static load because of its surface tension (11). At equilibrium, measurements of the curvature radius of a loaded sample provide the surface tension of the "fluid". According to the Laplace formula, the pressure jump across a curved interface between two fluids is inversely proportional to the radius of curvature. If the spheroid is upper loaded with the force F acting on a contact surface S, by continuity of the stress, the inner pressure is F/S and therefore

$$\frac{F}{S} = \sigma \left(\frac{1}{R_1} + \frac{1}{R_2} \right) \tag{6}$$

where σ is the surface tension and R_1, R_2 are the curvature radii of the free surface. According to the experiments, the surface tension of a cell aggregate ranges between 10^{-3} and $22 \ 10^{-3}$ Newton/meter (as a reference value, the surface tension of the water is about $72 \ 10^{-3}$ Newton/meter). Relaxation times range between 1 and 50 seconds.

The opposite approach is to describe a solid tumour as a viscoelastic solid. In this case, at equilibrium the external load should be balanced by the stress in the body, depending on the strain of its material points. Assuming an homogeneous deformation and using the same data provided by the experiments above, one can estimate the Young modulus E according to the following rule:

$$\frac{F}{S} = E \frac{h - h_0}{h_0} \tag{7}$$

where h, h_0 are the height of the loaded and unloaded sample, respectively. In this case one finds $E \simeq 4$ kPascal, a typical soft–range value for living cells (14).

We would like to emphasize that a thorough understanding of the rheological nature of cell aggregates (in tumors as well in embryos) is not a

purely academic matter. In fact, the experimental evidence of the dependence of growth rate on the stress state of the cells naturally calls for a stress–modulated growth law that must stand on a firm constitutive basis. If one accepts that equation (4) holds in some form, a correct measure of the stress in the tumor must be known, otherwise no reasonable prediction can be done. A correct constitutive equation for the Eshelby stress as a function of deformation is mandatory.

As an example of such a strict relationship, one can take anisotropic growth: stress driven growth along preferential directions, can be produced by a tensorial stress field only. A purely spherical stress, as pressure, cannot account for preferential directions at equilibrium. In other words, in systems where directional growth is observed, very likely the living matter is not a simple fluid characterized by a pure scalar pressure field in its tensional state.

A second argument supporting the importance of reliable constitutive equations is the possibility to account for residual stresses, generated by the inhomogeneous duplication of the cells. Only solids can be subjected to residual stress, due to the evolution of their relaxed configuration produced by incompatible growth (4). However, energy can be elastically stored in growth only by a solid, possibly a viscoelastic solid. As a rule of thumb, (viscoelastic)solids reach equilibrium under a constant shear stress, while (viscoelastic)fluids do not. According to this elementary classification, one should then refer to "Maxwell fluid" and "Voigt–Kelvin solid" (13).

Residual stresses are relevant in many living systems. Some biological tissues, although conventionally classified as "soft tissues", are actually stiffer than a cell agglomerate. In this respect, we do not define a conglomerate of cells as a "tissue", since it lacks of the warp and weft structure of elastin and collagen fibers that provide the structure of the material. For instance, arteries have a Young modulus of a few hundreds of kPascal and are characterized by relaxation times that range between 1-1000 seconds. They can therefore be classified as hyperelastic material for phenomena occurring at time scales of days or more. In their development arteries grow inhomogeneously, thus producing a residual stress that is inhomogeneous, anisotropic and of the same order of magnitude as the blood pressure. Does the same arguments apply to multicellular aggregates, that are much softer? In other words, do cells under load store strain energy proportionally to their mutual displacement, before that stress relaxation occurs?

Recent experiments show that the proliferation and apoptosis in a mechanically loaded spheroid can be inhomogeneous, thus supporting indirectly the

thesis that an inhomogeneous stress modulates the macroscopic growth. In a paper that is somehow the prosecution of previous work of the Jain's group, Cheng et al. again grow aggregates of tumor cells in an agarose gel (7). The difference here is that they do not tune the stiffness of the gel, but they apply a mechanical load on it and compare the evolution of the stressed system with a free one.

Their main result is that mechanical stress affects proliferation and apoptosis inside the spheroid in a non–homogeneous way, a correlation existing between strong apoptosis and high stress. These findings support the idea that a cell aggregate is not mechanically a fluid that, at equilibrium, is characterized by the same pressure everywhere [1]: only a material that exhibits, at some extent at least, a solid behavior can produce a non–homogeneous stress. In the next section we delineate a plasticity type theory that tries to recombine the ability of cells to bind and unbind with a very small supply of energy, while preserving solid–type properties at small stress.

4. A plasticity theory based on cellular arguments

One way to overcome the oversimplification inherent to the hyperlasticity assumption, while preserving the possibility to account for a stress depending on the deformation, is to refine the theory including the plastic nature of the rearrangement between cells (3). Stress relaxation can be introduced at a macroscopic level on the basis of cellular arguments. It is known that cells adhere each other via cadherin junctions. In standard experiments to test the adhesive strength of a cell, a microsphere is fixed to the tip of an atomic force microscopy cantilever. The microsphere is posed in contact with the cell and then the cantilever is slowly pulled away, at constant speed. Typical experimental plots of force vs. displacement are shown in Fig. 1; the characteristic strength of a bond can be measured as a function of the displacement.

If a cluster of cells is subject to a sufficiently high tension, locally some bonds break and new ones form. The mechanism of cell attachment-detachment becomes relevant during growth under an external load, when duplicating cells displace their neighbours (if the needed energy is available). At a macroscopic level, this argument suggests the introduction of a formalism analogous

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[1]For a fluid at equilibrium, when gravity is negligible, the Navier–Stokes equations reduce to $\nabla p = 0$
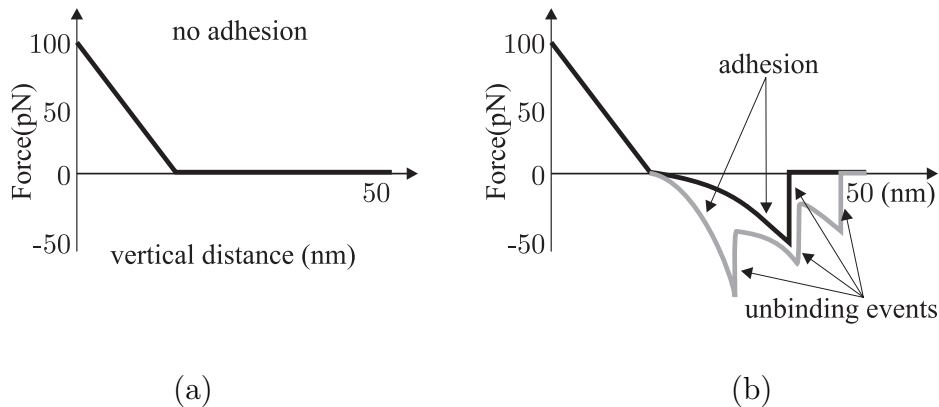
Figure 1: Sketch of a typical plot of force vs. displacement produced by an adhesive bead attached to the surface of a cell. The initial behavior is elastic non–linear, but for larger displacements (and larger strains of the cell membrane) bonds start breaking with single or multiple unbinding events, until complete detachment. In this plot positive force indicates compression.

to the one developed for plastic deformations in continuum mechanics. The mechanical energy spent to break the cell-to-cell bonds and allow their re-arrangement in a different micro-configuration, is not stored. Moreover, a cell aggregate preserves its elastic properties at sufficiently small loads after an internal rearrangement. This suggest the existence of a yield stress that separates the elastic and plastic regimes.

To include elasto-visco-plastic effects in the mechanics of cell aggregates, the starting point is the following experimental evidence, valid for cell aggregates under compression

1. for a moderate amount of stress, the cell aggregate deforms elastically;
2. above a yield value the cell aggregate undergoes internal re-organization which is modelled at a macroscopic level as a visco-plastic deformation.

The formalization of these intuitive arguments from a cellular to a continuum level can be approached in terms of the plasticity theory: an example of visco-elastoplastic model of tumor growth is illustrated in (3). Here below are resumed the main results of such a work in a slightly simplified way.

A useful paradigm for elastoplastic deformations is, again, the multiplicative decomposition of the deformation gradient $\mathbf{F}$. When loading a solid material at large strains, it can happen that energy is provided externally

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in terms of work of external forces, without apparent displacement. This macroscopic behavior has a microscopic explanation: energy is not stored as strain energy, but is spent in form of internal rearrangement of the material that does not produce apparent macroscopic deformation. The basic idea is to represent such a physical behavior by the introduction of a virtual, intermediate configuration between the reference (relaxed) configuration and the current one. In such an intermediate, possibly evolving configuration, the body is stress free but, because of possible plastic rearrangements, it might not coincide with the original relaxed configuration. The relaxed state can differ from the originally relaxed one because, during the deformation, cells in the configuration can undergo internal re-organization, which implies re-arranging of the adhesion links among the cells. We identify the deformation that takes from the current (loaded) state to the relaxed one without cell re-organization $\mathbf{F}_e^{-1}$. The deformation gradient is then split as [2]

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_p. \tag{8}$$

The definition of the following tensors will turn useful in the next:

$$\mathbf{B}_e = \mathbf{F}_e \mathbf{F}_e^T, \qquad \mathbf{L}_p = \dot{\mathbf{F}}_p \mathbf{F}_p^{-1}. \tag{9}$$

We denote by τ the yield stress, the minimum tension that induces shearing. It is to be compared with a frame invariant measure of the stress $f(\mathbf{T})$. According to our assumptions, an elastic-type constitutive equation is valid at the moderate-stress regime

$$\mathbf{T}_p = \mathbf{T}_p(\mathbf{B}_e), \qquad \text{if} \quad f(\mathbf{T}) \leq \tau. \tag{10}$$

where the stress in the current configuration $\mathbf{T}$ is obtained from $\mathbf{T}_p$ by a pull-forward: $\mathbf{T} = \mathbf{T}_p^T \mathbf{F}_p / \det(\mathbf{F}_p)$. The tangential component of the stress vector relative to the surface identified by the normal $\mathbf{n}$ is

$$\mathbf{t}(\mathbf{n}) = \mathbf{T}\mathbf{n} - (\mathbf{n} \cdot \mathbf{T}\mathbf{n})\mathbf{n}. \tag{11}$$

A suitable measure of the stress is

$$f(\mathbf{T}) = \max_{|\mathbf{n}|=1} |\mathbf{t}(\mathbf{n})|, \tag{12}$$

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[2] The elastic component of the deformation $\mathbf{F}_e$ plays here the same role as in equation 1 and we purposely adopt the same notation. As a matter of fact, a unifying theory of growth and elastoplastic deformation is cumbersome, but possible (3; 17).

representing the maximum shear stress occurring in the plane orthogonal to
$\mathbf{n}$. It can be explicitly calculated that f is half of the difference between the
maximum and the minimum eigenvalue of $\mathbf{T}$.

When the tension overcomes the yield stress in terms of the stipulated
measure f, energy is no longer elastically stored. The extra energy possibly
provided by the work of external and internal forces is spent in unbinding at
the cellular scale, i.e. material rearrangement at the macroscopic scale. Cells
flow in mutual direction, dissipating energy, and determining an evolution
of the intermediate configuration. In such a regime the material behaves as
a viscous fluid, with the theoretical complication that an amount of strain
energy remain stored during flow. Such a pictorial description is put into
formal terms by the following constitutive equation

$$\mathbf{L}_p = \frac{1}{2\eta} \left[1 - \frac{\tau}{f(\mathbf{T})} \right]_+ \mathbf{F}_e^T \mathbf{T} \mathbf{F}_e^{-T} \tag{13}$$

where the symbol $[\cdot]_+$ denotes the positive part of the argument, η is a posi-
tive constant, with the physical meaning of a dynamic viscosity. Neglecting
the mappings by $\mathbf{F}_e$ and its inverse, due to the existence of an intermediate
configuration, basically at the right hand side of Equation (13) there is the
tensor deformation rate, i.e. the stress tensor that characterizes the viscous
fluids. After some calculations, an evolution equation for $\mathbf{F}_p$ can be obtained.
Therefore, in the present framework, (13) provides the evolution equation for
the relaxed configuration.
The positive part function that appears at the right hand side of (13), de-
pending on the value of the yield stress τ, distinguishes between the elastic
(reversible) behavior and the viscous (irreversible) behavior of cell aggre-
gates. In Eq. (13), if the body undergoes a deformation corresponding to
a stress below the yield stress, then the square parenthesis vanishes and $\mathbf{F}_p$
does not change; the natural configuration does not evolve and all the energy
is stored elastically. If the measure of tension f takes a value larger than the
yield stress, then the reference configuration changes to release the stress in
excess, until the yield condition defined by f is reached again. An example
of specific constitutive equation for this problem is reported in (17).

The complexity of the system of equations that models the growth of
a solid tumor with non trivial mechanical behavior is currently treatable
just in very simple geometries, i.e. when radial symmetry makes the prob-
lem one–dimensional. In case of arbitrary geometries, the complexity of the

mathematical problem makes attractive the idea to reconsider the model in terms of a cell-based point of view. In such an approach, single cells are individually discretized in their position and in their own interaction with the surrounding ones. The number of tumor cells in a multicell spheroid is large, but the number of degrees of freedom can be numerically afforded. The drawback of a cell-based approach is known: without the powerful tools of differential calculus, no predictions can be done about qualitative behavior and stability of the system. In a pure cell-based perspective, the dependence of the solution on parameters can be just explored by sampling numerically the space of the parameters. The most convenient strategy (continuum vs. cellular) is still matter of debate.

Final remarks

The formal representation of tumour growth reported in this paper owns a specific characteristics: the mathematical model starts from conservation principles of mechanical quantities (mass, momentum) that are encoded in classical mechanics since centuries. However, it turns out that usual models, based on the standard forces that characterize engineering problems are too poor to account for the richness of the behavior of living matter, and some new ingredients are to be included in the mathematical description, using arguments based on the experimental observation. This way to proceed, starting from very fundamental questions, has one main advantage, in our opinion. As far as as no new effects are included, one can straightforwardly inherit the general results in terms of well posedness, frame indifference, stability, that have been collected in the classical literature for inert matter. Then the new non-standard elements, like the stress–modulated growth for instance, can be possibly stated in some known framework, or they simply offer new challenging mathematical questions. Constitutive equations are here conjectured on the basis of experiments, while abiding the due mathematical properties (frame indifference, thermodynamical admissibility).

Whatever the mathematical model adopted, the numerical simulation of solid tumor growth (in its avascular or vascular phase) is still in its infancy. One open question is the statement of the mathematical laws that rule the interplay between growth and mechanics; as discussed above, this aspect is less relevant than the biochemical factors, but not negligible. Equation (4) has been successful in other contexts, but tumors are in some sense the distinguished system where homeostatic self–regulation does not work. The

interplay between nutrients, kinetics of growth factors and cell proliferation is much better understood, but the complexity of such relations make quantitative predictions difficult.

Another important ingredient that is still missing in the mathematical modelling of cell aggregates is the active stress generation. In this review we have mainly focussed on the tension generated by growth: cell proliferation and death produce an incompatibility in the equilibrium configuration of the cell aggregate that induces a stress, then possibly relaxed by material rearrangement. However cells are also able to originate forces directly, irrespective of growth. A nice example in this respect is reported in embryogenesis, where actin fibers organized at the surface of the cells slide mutually under the action of myosin motors and produce a local rearrangement of cells that reflects in a global displacement of the aggregate, likely in view of shape and functions of the emerging organ (16). From a continuum mechanics point of view, this self ability to produce stress could be modeled in terms of an active stress term, sometimes by an active strain, with the due mathematical prescriptions (1). At the best of our knowledge, the role of active stress in tumor cell migration and organization is still unexplored.

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