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Cancer Metabolism and the Dynamics of Metastasis

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Abstract

Cancer growth dynamics, commonly simulated with a Gompertzian model, is analysed in the framework of a more recent and realistic model. In particular, we consider the setting of a tumor embedded in a host organ and investigate their interaction. We assume that, at least in some cases, tumor metastasis may be triggered by an ‘energetic crisis’, when the tumor exceeds the ‘carrying capacity’ of the host organ. As a consequence, dissemination of clusters of cancer cells is set in motion, with a statistical probability given by a Poisson distribution. The model, although still at a preclinical level, is fully quantitative and is applied, as an example, to the case of prostate cancer. The results confirm that, at least for the more aggressive cancers, metastasis starts very early during tumorigenesis and a quantitative link is found between the tumor’s doubling time, its ‘aggressiveness’ and the metastatic potential.

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1. Introduction

One of the most critical, yet still open questions for cancer therapy and, in particular, for the prevention of metastatic dissemination is whether local control of the primary tumor (i.e. absence of local recurrence) increases long term survival. Experimental in vivo studies, such as those by Ramsay et al. [1], using transplanted squamous cell carcinomas in mice, show a dramatic difference in the development of distal metastasis with and without local control. In fact, only 6.9 % of locally controlled animals developed metastasis, vs. 43% for those that failed local control. Data from human studies (for instance, Fuks et al. [2], Leibel et al. [3]) confirm this trend. Up to now, most of the researchers have focused on the question by investigating whether metastases were generated by the primary tumor or by the recurrent one, or whether tumors responsible for local recurrence were ‘per se’ more aggressive, and therefore equipped with an intrinsically higher metastatic potential.

It is commonly accepted that a ‘critical’ or ‘threshold’ tumor mass for metastatic spread exists, and that this mass varies with the tumor type and may be reached even before the primary tumor is detectable (Tubiana et al. [4]). The prediction of such a ‘critical mass’ has been pursued by many researchers (e.g. Koscielny et al [5] for breast cancer, Yorke et al. [6] for prostate cancer), based on the assumption that tumor growth follows Gompertz’s law and that such a ‘critical mass’ can be deduced from statistical inference on patient datasets.

In recent developments, it has been suggested [7] that Gompertz’s law should be replaced by a more general model, based on the universal law for ontogenetic growth proposed by G.B. West and collaborators [8 a,b]. West’s law is basically an application of energy conservation (or, of the first law of thermodynamics). It includes, however, an extremely important feature, i.e. the fractal nature of the input power term, which is assumed, for all living organisms, to be proportional to their mass m to the power $p=3/4$ (Kleiber scaling law [9]).

In an extension of West’s model to tumors, it is more realistic to assume that p varies through the various phases of tumor growth (avascular, angiogenetic, host tissue invasion, metastasis, etc). Hence a *dynamic* evolution model for the exponent p has been proposed [10]. It may be interesting to note that such an extension fits perfectly

well into the classification scheme for Phenomenological Universalities (PUN) in growth problems [11], and in fact belongs to the class ‘U2’. The class U2 includes, to our knowledge, besides Gompertz as a special case, all the growth models proposed to date in all fields of research, i.e. the exponential, logistic, theta-logistic, potential, von Bertalanffy and, of course, West and collaborators (see De Vladar [12] for a review). It is also possible to include, in the framework of U2, all kinds of cyclical phenomena, which are so important in biology and medicine (e.g. in the choice of protocols for radio- and chemotherapy). For other applications of PUN’s see [13].

In order to provide a more ‘physically-based’ foundation for the concept of a critical tumor mass inducing metastatic spread and defining its aggressiveness, we propose that such an ‘escalation’ starts when the metabolic limit of the harbouring organ is reached and the tumor can no longer be supported by its host.

In the next Section we describe the model following West’s approach, but considering the more complex case of a body (the tumor) surrounded by a ‘host’ organ. The competition between the two allows us to define in a consistent way the organ ‘carrying capacity’ (introduced in [14]). In Sec. 3 the formalism is applied, as an example, to the case of prostate cancer with brief considerations about other more slowly developing neoplasies. The model described in Sec. 2 and illustrated in Sec. 3 relates the tumor growth to the process of metastasis, which is then studied in Sec.4, by means of a Poisson distribution. The relationship between tumor growth and metastasis dissemination is further discussed in the Conclusions.

2. The Model

Following the approach of West and collaborators [8a, b], and extended by Guiot et al [7] to the case of tumors, we write the power conservation law as

$$\frac{B_0 m_c}{E_c} m^p = \frac{dm}{dt} + \frac{B_c}{E_c} m \quad (1)$$

which implies that the input energy (first term) is split into two parts. The first part corresponds to tumor growth (dm/dt), while the second one refers to tumor metabolism. In Eq. (1), m is the tumor mass, m_c the mass of a single tumor cell, E_c is the energy required to generate a new cell, p is the ‘fractal’ exponent (which has been discussed in

the Introduction ($p=3/4$ in West's model)), B_0 is a constant that depends on the particular tumor type and B_c the metabolic power of a single cell. For cell mass and energy, we will use in the following the reference values $m_c \equiv 3 \cdot 10^{-9} g$ and $E_c \equiv 2.1 \cdot 10^{-5} J$ (see refs. [7, 8]).

The condition $\frac{dm}{dt} = 0$ yields the equilibrium (or asymptotic) mass

$$m_\infty = \left(\frac{B_0 m_c}{B_c} \right)^4 \quad (2)$$

The general solution of Eq. (1) is,

$$m(t) = m_\infty \left[4 \sqrt[4]{\frac{m_0}{m_\infty}} e^{-\frac{t}{\tau_1}} + 1 - e^{-\frac{t}{\tau_1}} \right]^4, \quad (3)$$

where

$$\tau_1 = \frac{4 E_c}{B_c}$$

defines the growth time scale. Both τ_1 and m_∞ are quantities that may be obtained from experimental data (see e. g. [15]). They can be used to infer the values of the model parameters B_0 and B_c , which are linked to the other parameters by

$$\begin{aligned} B_0 &= \frac{a E_c}{m_c}, \\ B_c &= \frac{B_0 m_c}{\sqrt[4]{m_\infty}}, \\ a &= \frac{4 \sqrt[4]{m_\infty}}{\tau_1} \end{aligned} \quad (4)$$

At very small times ($t \ll \tau_1$) the tumor mass is minuscule ($m \ll m_\infty$) and almost all the available power is used up to increase it. From Eq. (3) it follows that the corresponding power is then given by

$$P_T \equiv \frac{1}{4^3} \frac{P_c^4}{E_c^3} t^3, \quad (5)$$

where

$$P_c = B_0 m_c^{\frac{3}{4}} \quad (6)$$

represents the metabolic power¹ of a single tumor cell.

We note that the Kleiber scaling has been proven to hold even at the cellular level [8 a,b]). Although Eq. (6) is valid only at early stages, we use this fairly simple relationship to get a first, albeit approximate, understanding of the energetic aspects of the process. It has already been remarked [16] that, in the absence of sufficient nutrient supply, some cancer cells start to migrate looking for ‘greener pastures’. If cells diffuse into the lymphatic or vascular systems a satellite or metastatic colony may be seeded elsewhere in the body [17]. Although the insufficient supply of nutrients may be due to a variety of reasons, including early necrotization, we assume that such a problem arises whenever the tumor’s metabolic needs, P_T , become comparable with the intrinsic metabolic power, P_0 , of the host organ.

If the mass of the tumor is sufficiently large compared to the mass M of the organ in which it is embedded or, more precisely, if the interaction of the former with the latter is not negligible, then a second equation for the host organ must be considered:

$$\frac{dM}{dt} = \frac{B_0^{org} m_c}{E_c} (M + m)^{\frac{3}{4}} - \frac{B_0 m_c}{E_c} m^{\frac{3}{4}} - \frac{B_0^{org}}{E_c} M \quad (7)$$

where we have assumed that the masses of both host organ and tumor cells, are the same, and likewise for their respective cell proliferation ‘costs’, E_c . In Eq. (7) we have assumed an energy input through the surface of the organ with the tumor inside (mass $M+m$) and an energy output through the surface of the tumor (mass m), both with the same exponent $3/4$. For consistent treatment, the two equations (1) and (7) should be coupled, e.g. through the addition of a term (in Eq. (1)) that corresponds to the effect of the organ metabolism; the coefficient B_0 should depend e.g. on the availability of nutrients in the surrounding microenvironment through an exponentially decreasing term of the kind $\exp(-\gamma \frac{m}{M})$. For a sufficiently small m the above equations can, however, be considered uncoupled.

¹ This ‘power’ is used to maintain the metabolism of the cell and to allow for replication.

Under these assumptions we can argue that a *coexistence* condition between tumor and organ holds. Only when m becomes comparable with M , their mutual *competition* (for limited resources) becomes important, and the metabolic parameters change according to the overall nutrient distribution. To render this concept quantitative, we define the dimensionless quantity

$$C = \frac{P_T}{P_0} \quad (8)$$

where we have assumed that P_0 is constant even when the mass of the tumor becomes relevant. The inequality $C < Q$, where Q represents a reference value depending on the cancer type considered, yields a condition of coexistence between the tumor and the host organ. When $C > Q$ we may expect that the tumor enters an energetic crisis of sorts. C is conceptually equivalent to the organ *Carrying Capacity* already introduced in [14], as a critical element controlling metastasis. If we use the condition $C = Q$ (in the following we will assume $Q=1$ for simplicity), we can define a kind of critical time for the onset of metastasis, namely

$$t^* \cong \frac{4 E_c}{P_c} \sqrt[3]{\frac{P_0}{P_c}} \quad (9)$$

which should be understood as a reference value and not as a threshold time.

According to this equation, the time of dissemination is reached *earlier* in organs with *lower* intrinsic metabolic power or energy supply. We also note that an increase in metabolic rate in the same, less nourished organ would accelerate the onset of metastasis. These conclusions are based on the tacit assumption that the tumor is competing with the hosting organ, which acts as an energy reservoir.

3. Application to Prostate Cancer

As an example of application of the model described in Sec. 2, we consider here the case of prostate cancer, whose specific characteristic parameters are well documented in the literature [18] and have been employed in [19] to infer that

$$a \cong 0.42 \text{ g}^{\frac{1}{4}} / \text{day} \text{ and therefore}$$

$$P_c \cong 1.192 \cdot 10^{-3} \frac{J}{day} \quad (10)$$

Assuming for the prostate a metabolic power of 0.2 W (17000 J/day), we find that metastasis starts at a critical time of about two or three weeks after a malignant transformation of the parental tumor. However, since t^* depends on $(P_0)^{\frac{1}{3}}$, its dependence on the intrinsic metabolic power of the organ is rather weak. Indeed (see Fig. 1), if the metabolic power is reduced by a factor 2, the critical time decreases by less than a factor of 1.3.

From Eq. (1,5) we obtain, in correspondence of t^* see Eq. 9, the critical mass².

$$m^* \cong \sqrt[3]{\left(\frac{P_0}{B_0}\right)^4}, \quad (11)$$

Using for prostate cancer the values $B_0 \cong 2.93 \cdot 10^3 J \cdot g^{3/4} / day$, $P_0 = 0.2 W^{(3)}$, we can compute a critical mass of about 10 g, (corresponding roughly to $10^9 - 10^{10}$ cells).

The previous semi-quantitative analysis seems to indicate that metastasis starts very early in a tumor's evolution, in the case of prostate cancer. This fact should be stressed, because our conclusions strongly depend on the value of the hosting organ's metabolic rate. Consequently, if we assume for the prostate $P_0 \cong 0.1 W$, we obtain even earlier critical times at parental tumor dimensions which are barely clinically detectable. Starting from a single cell, the time necessary to yield a given tumor mass m_0 is

$$T = \left| \tau_1 \left[\ln \left(\frac{m_0}{m_\infty} \right) \right]^{1/4} \right| \cong \frac{4 E_c}{B_0 m_c^4} \sqrt[3]{n_0} \quad (12)$$

The saturation mass corresponds to a cancer cell number of the order of $10^{11} - 10^{12}$, usually called the lethal level [18]. In Figs. 2 we have reported three evolution assumptions for the number of cells corresponding to tumors with different growth times τ_1 . The parallel lines intercept three different stages of tumor development,

² For the critical radius we find from Eq. (11) (spherical shape) $r^* = \left(\frac{3}{4\pi\rho} \right)^{1/3} \left(\frac{P_0}{B_0} \right)^{4/9}$ where ρ is the tumor density.

³ The value of B_0 has been inferred from analysis of the growth curves, while P_0 refers to the metabolic power consumption of the prostate; the latter, however, is not well defined and thus, the relevant estimates range between 0.1-0.2 W.

corresponding to the preclinical phase, the threshold of clinical diagnostics [18], and the clinical phase where the evolution of the tumor should be studied (since the preclinical evolution is simply a matter of extrapolation).

There are tumors that develop over a long time frame, with years between diagnosis and lethal stage (among them some types of lung cancer [18]), (see Fig. 3).

In conclusion, if we trust the extrapolation and assume that the tumor starts at the beginning of the preclinical phase from a single cell (monoclonal hypothesis)⁴ [21 *and references therein*], the disease had to be present at sub-clinical levels at least ten years before it may be clinically diagnosed. In the meanwhile, one wonders whether the tumor has already started to spread, i.e., to disseminate metastases to other organs.

4. Metastasis Dissemination

In the previous section we have assumed that the increase in tumor mass is governed by Eq. (2), which, as already remarked in [19], shares significant analogies with optical coherent amplifiers. The tumor mass evolution can therefore be viewed as the consequence of a coherent mechanism in which malignant cells grow, like physical systems with a natural counteracting feedback. The latter has been extensively studied, e.g. in laser devices. As an example of cross-fertilization among different fields, we can transfer ‘mutatis mutandis’ some of the results learned in other fields [19] into our present study.

The process of metastasis dissemination can then be understood, in statistical terms, as the probability that the tumor dispatches a colony of cells which, through a rather complex process of adhesion, migration, angiogenesis and extravasation [22], sets up a new secondary cancer ‘satellite’ in a local lymphatic node or in a different organ, or both. The prerequisite for the formation of metastasis is, however, that a certain number of cells leaves the primary tumor. We assume that the probability that a cluster of s cells leaves the primary tumor follows a Poisson distribution, i.e.

$$P_s(t) = \frac{[\mathcal{E}n(t)]^s}{s!} \exp(-\mathcal{E}n(t)) \quad (13)$$

⁴ The monoclonal hypothesis is in the present context a non-crucial assumption and we can relax it without any prejudice to the presented conclusions.

where $n(t)$ is the number of cells of the primary tumor and ε is a phenomenological term, ranging from 0 to 1, accounting for the distinct (genetic and epigenetic) ability of the tumor to metastasize and $n(t)$ is calculated with the model developed in the previous section. The time has been properly rescaled to account for the critical time at which the metastasis actually started developing (see eq. (9)).

The assumption that the probability distribution is given by (13) amounts to requiring that the spread out of cells at a given time t is independent on the spread at previous times.

We can define the level of aggressiveness of a tumor in terms of the two phenomenological quantities ε and τ_1 . Larger values of ε mean that a larger number of malignant cells leave the primary tumor, while smaller values of τ_1 mean that the primary tumor is proliferating at higher rates. A more detailed discussion of the process involved is given in the Appendix.

In Fig. (4), we have plotted the probability $P_s(t)$ vs. time for different values of s , for tumors with different levels of aggressiveness.

It is worth noting that the probability of disseminating metastases is maximal for times around the critical time t^* (see Eq. 9), even though dissemination may occur earlier.

According to this rather simple picture, it seems probable that, in the case of fast growing hence locally aggressive tumors, metastasis starts prior to the ‘clinical’ phase, while for slow growing tumors the dissemination may occur at later times in the course of tumorigenesis (see also [16]).

5. Concluding Remarks

In this paper we have treated the problem of cancer and metastatic dissemination using energetic and statistical arguments. The occurrence of a ‘threshold’ tumor mass for the development of metastasis has been computed based on the assumption that, as long as the dimension of the ‘in situ’ tumor remains negligible, it grows according to its ontogenetic law and ‘coexists’ with the host without interfering with its nutrient distribution. However, when the tumor mass increases, competition with the hosting

organ starts and different strategies for generating metastases may become energetically favourable.

As an example, we have investigated prostate tumors and their metastatic patterns. Provided reasonable metabolic estimates are used for the parameters of the prostate, a ‘threshold mass’ of around 10 g is obtained, which to detect clinically with conventional tools appears to be rather challenging. We note that such a value seems to be realistic also for breast cancer. For instance, Tubiana et al. [4] found metastases in 50% of the women whose primary tumor had a diameter of 3.5 cm (i.e. $m = 22$ g, approximately). The ‘pessimistic’ conclusion is then that tumors can start developing metastasis very early, i.e. before they may even become clinically detectable, metastatic cells should be able to shed from the primary tumor and start migration to other organs.

Our discussion of metastatic dissemination as presented in Sec. 4, may appear simplistic with respect to the complexity of the underlying phenomenology. Metastasis is indeed a multi-step process promoted by mutations in many genes, and the phenotypic changes that these mutations triggers with regards to adhesion, initiation of motility and proteolysis of the extracellular matrix. Together, these changes promote the spread of cancer cells through the membrane surrounding the initial tumor, their invasion into and dispersion throughout the vascular and lymphatic systems [22, 23]. The metastatic potential and associated parameters are merely phenomenological tools to quantify some of these complex biological mechanisms in terms of macroscopic quantities.

What we emphasize in this work is that tumors may start to disseminate very early, prior to becoming visible on conventional imaging, yet post angiogenesis. We have put the value obtained for prostate cancer in context to data from the literature investigating metastatic breast cancer. Our work supports the notion of biomarker assessments (detecting proteins secreted by occult metastases) aiding imaging studies.

However, since the complexity of the biochemical process involved has yet to be fully deciphered and because the nature of cell dissemination is non-deterministic, a statistical approach combined with an appropriate analysis of the evolution of the number of cells of the primary tumor, as well as with experimental observations, may eventually provide useful information even at the clinical level.

APPENDIX

The idea that the metastasis formation follows a Poisson distribution is by no means new. In fact, it was already proposed in [24-27], which assumed that similar events are rare but occur with a certain probability, proportional to the number of cells of the primary tumor. Accordingly, the probability of forming s metastatic colonies at time t can be written as

$$\begin{aligned}\Pi_s(t) &= \frac{[A(t)]^s}{s!} e^{-A(t)}, \\ A(t) &= \frac{\eta}{\lambda} (n(t) - n(t_0))\end{aligned}\tag{A1.1}$$

and $n(t)$ is the number of cells of the primary tumor whose growth has been assumed to be exponential with rate λ [24]. Furthermore $t - t_0$ is the time when the event occurs. The difference with respect to Eq. (13) refers to the formation of a certain number of colonies or metastases and not to the number of cells per colony. The quantity η plays a role analogous to ε and is essentially the metastatic potential, a concept introduced in clinical oncology [17], and is linked to the rate of colony formation.

It is evident that $\tilde{\varepsilon} = \frac{\eta}{\lambda}$ can be understood as a kind of metastatic *efficiency*, since it has the “dimensions” of the number of secondary colonies formed by the primary tumor. Its numerical value can be estimated by means of a very crude argument. That is, a value of $\eta \cong 5 \cdot 10^{-3}$ for the metastatic potential is currently quoted in the literature as being consistent with experimental observations [22]. Assuming that a tumor increases with a rate of $\lambda \cong 5 \cdot 10^6$ (corresponding to 170 days to reach the clinical detectable size) we get $\tilde{\varepsilon} \cong 10^{-9}$. In Fig. 5 we have reported the probability of disseminating metastases vs. time, along with the number of primary tumor cell growth. Here too is evident that metastasis may occur even prior to the tumor reaching a clinically detectable size.

The influence of $\tilde{\varepsilon}$ on the metastasis dissemination is shown in Fig. 6, where we have plotted the probability vs. time, for different values of $\tilde{\varepsilon}$. It is evident that more aggressive tumors tend to seed *more* metastases at *earlier* times in the course of tumorigenesis.

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Figure Captions

Fig. 1 - Prostate cancer, metabolic rate (J/day) vs. time (day)

- a) Full time course of tumor growth, starting from a very small mass (dotted line 0.2 W, dashed line 0.1W)
- b) Tumor evolution around the critical time.

Fig. 2 - Evolution vs. time (in days) of the cancer cell number assuming $m_{\infty}=671g$ and $\tau_1 = 12 days$ (solid), $\tau_1 = 48 days$ (dotted), and $\tau_1 = 144 days$ (dashed). The 0.1-0.2 W levels refer to the intrinsic metabolic power of the host organ.

Fig. 3 - Evolution vs. time (in years) of the cancer cell number for cases with $m_{\infty}=671g$ and $\tau_1 = 6.5 years$.

Fig. 4 – Propability vs. time ($days$) that s-malignant cells leaves the primary tumor, $s=10$ cells (solid line), $s = 50$ cells (dashed line), $s = 130$ cells (dotted line) for $m_{\infty} = 671g$ a) $\tau_1 = 144 days$, $\epsilon = 10^{-3}$; b) $\tau_1=6.5 years$, $\epsilon = 10^{-6}$.

Fig. 5 - Probability of metastatic sites vs. time (days) for a tumor with $\tau_1 = 120 days$ and $\tilde{\epsilon} = 10^{-9}$ 1 colony (solid line), 10 colonies (dotted line), 50 colonies (dashed line), number of cells normalized to the saturation number (dashed-dotted), the parallel line corresponds to the clinical level (10^9 cells).

Fig. 6 - Probability of forming 30 metastatic sites for a tumor with $\tau_1 = 144 days$ $m_{\infty}=671g$ and $\tilde{\epsilon} = 10^{-8.5}$ (dotted line) $\tilde{\epsilon} = 10^{-9}$ (solid line) $\tilde{\epsilon} = 10^{-9.5}$ (dashed line).

Fig. 1a

Fig. 1a

Fig. 1b **Fig. 1b**

Fig. 2

Fig. 2

Fig. 3 **Fig. 3**

Fig. 4a **Fig. 4a**

Fig. 4b **Fig.4b**

Fig. 5

Fig. 5

Fig. 6

Fig. 6