

## THE CONJECTURE OF CARRYING CAPACITY IN CANCER: THERMODYNAMIC IMPLICATIONS

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**ABSTRACT.** In this study, we explore Deisboeck and Z. Wang's conjecture from 2007, which establishes a quantitative relationship between the spatial expansion of tumours and the volume constraints as well as functional variations of the surrounding host tissue. By integrating the physical properties of cells into this mechanistic framework, we provide a robust thermodynamic interpretation based on cellular internal energy. Our findings decisively characterise the conditions that facilitate coexistence between tumours and host organs at first, while also identifying the factors that eventually drive the competitive transformation of tumour cells through spatial dissemination—specifically, local invasion into healthy tissue followed by distant metastasis. We underscore the critical necessity of vascularisation from an energetic perspective and highlight the existence of an 'entropy threshold' for cancer invasion, which mirrors a phase transition in physics, as revealed through the application of the second law of thermodynamics.

### 1. Introduction

In 2020, approximately 10 million people worldwide were diagnosed with cancer, and projections indicate that this number could double by 2030 (Michor *et al.* 2011). Despite advancements in surveillance, diagnosis, and treatment, the prognosis for many advanced cancers remains poor. Therefore, new strategies are urgently needed. Physics is emerging as a new and promising approach to studying cancer progression, particularly through the lens of thermodynamics (Katchalsky and Kedem 1962; Lucia 2013, 2015; Arango-Restrepo and Rubi 2023; Shamsabadipour *et al.* 2023), which offers quantitative models to describe cancer as a complex system.

Since the inception of cancer research, one of the fundamental questions addressed by scientists has been the identification of the growth laws governing tumour behaviour. This inquiry is inherently linked to the objective of modelling the effects of cancer treatments and optimizing therapeutic strategies. Various ordinary differential equation (ODE) models have been proposed, typically categorized as first-order models. These models are named after notable researchers, including Malthus (exponential growth law), Verhulst (logistic growth law), Gompertz, Richards, von Bertalanffy, and West, among others. Most of these models exhibit a 'carrying capacity', which is reached following an initial phase characterized

by either exponential or power growth, subsequently transitioning to a sigmoidal growth pattern. This so-called carrying capacity of a system is the maximum population size that can be sustained by that specific system, given the resources (metabolites, oxygen, etc.) available. As such, the carrying capacity represents the system's maximal load related to the population equilibrium when the number of deaths in a population equals the number of births, which involves a number of intricate traits from proliferation rate and maximum packing density to mechanic and metabolic adaptation. It further implies that the resource extraction is not above the rate of regeneration of the resources and that the waste generated is within the assimilating capacity of the system (Dhondt 1988). Consequently, both tumour and healthy tissue have different carrying capacities; in this paper we focus on that of the healthy tissue and its dynamic relationship with the growing tumour it 'hosts' within its confines.

Tissues can also be modelled as self-organizing structures using a non-equilibrium thermodynamic approach that analyses entropy production and energy dissipation in response to external stimuli (Lucia 2015). Following the work of Zivieri *et al.* (2017), the study of entropy variation resulting from heat fluxes informs the analysis of biochemical reactions occurring in living cells (Zivieri and Pacini 2017, 2018). The concept of entropy production helps to explain the various mechanisms at play within cancerous tissues at different scales and stages of the disease (Arango-Restrepo and Rubi 2023).

In this paper, we will integrate this innovative mechanistic viewpoint with thermodynamic modelling by introducing considerations related to cancer growth and energy management. We will discuss our findings in relation to experimental data reported in the literature and consider their clinical potential.

## 2. Materials and methods

Cancer remains one of the predominant causes of mortality worldwide and, according to the latest global estimates for 2023, constitutes the second leading cause of death after cardiovascular disorders (Force *et al.* (GBD 2023 cancer collaborators) 2025). Reports from the World Health Organization indicate that malignant pathologies were responsible for roughly 16% of total global deaths in 2020, amounting to close to 10 million fatalities. Earlier demographic projections anticipated that annual cancer-related deaths would exceed 11 million by 2030 (Verginadis *et al.* 2012). Updated predictive models now suggest that this burden will continue to intensify, with yearly mortality expected to approach 18.6 million by 2050 (Force *et al.* (GBD 2023 cancer collaborators) 2025). In parallel, accumulating evidence underscores the fundamental role of physical determinants in tumour initiation, evolution, and response to therapy (Clevenger *et al.* 2024; Q. Wang *et al.* 2024). Although significant progress has been achieved in screening, diagnostic techniques, and therapeutic interventions, outcomes for patients with advanced-stage malignancies remain largely unfavourable. This persistent challenge highlights the pressing need for innovative conceptual and methodological approaches. In this context, physics is increasingly recognized as a valuable framework for investigating cancer dynamics, particularly through the lens of thermodynamics (Lucia 2013, 2015; Arango-Restrepo and Rubi 2023), which enables quantitative descriptions of cancer as a complex, non-equilibrium system.

As developed by Deisboeck and Z. Wang (2007), at the outset, a host organ can sustain a still relatively small tumour growing locally, i.e.,  $V_{tum}$  is less than (or, at max, equal to) the normal tissue's carrying capacity ( $C_c$ ) which itself is a composite of functionality per unit tissue volume. The authors argued that host tissue functionality exceeds its volume or structural unit and so defined  $C_c \leq 1$  (or  $1/(F_{tis}/V_{tis})$ ). Together, this yields that the 'critical' threshold for a given tumour volume to trigger metastasis outside the host organ is less or equal to 1. Note that in this scenario, the more specialized the tissue's functionality, the smaller it's  $C_c$  and therefore the earlier any tumour would have to metastasize. We summarize this relationship here as:

$$\frac{dV_{tum}(t)}{dt} \leq \frac{dC_c}{dt} \quad (1)$$

where  $C_c = (F_{tis}/V_{tis})^{-1}$  is the tissue carrying capacity,  $V_{tum}$  is the maximum tumour volume that can be sustained by the tissue's composite volume ( $V_{tis}$ ) infrastructure,  $F_{tis} > 1$  represents the level of specialization or functionality of a given tissue, and  $t$  stands for time. The concept implemented here is that anatomical structure and the functionality it enables are necessarily related, but not identical; in fact, based on a complexity perspective, an organ's emergent functionality exceeds the sum of its tissue volume units. As postulated in the aforementioned paper by Deisboeck and Z. Wang (2007), this equation shows that if the growth rate of the tumour is less than or equal to the adjustment rate of the carrying capacity, the host organ's environmental setting remains permissive for on-site tumour growth.

Starting now from Eq. (1) to obtain a thermodynamic relationship, we multiply the two terms of Eq. (1) by  $\rho_{tum} c_{tum} T$ , where  $T$  is the temperature of the composite tissue,  $c_{tum}$  stands for the specific heat of the tumour, and  $\rho_{tum}$  represents the density of the tumour, obtaining:

$$\rho_{tum} c_{tum} T \frac{dV_{tum}(t)}{dt} \leq \rho_{tum} c_{tum} T \frac{dC_c}{dt} \quad (2)$$

which, considering that  $\rho c T V = U$ , with  $U$  being internal energy, we can obtain:

$$\frac{dU_{tum}(t)}{dt} \leq \rho_{tum} c_{tum} T \frac{dC_c}{dt} \quad (3)$$

Taking into account the first law of thermodynamics, i.e.,  $dU/dt = \phi - W_t$ , with  $\phi$  thermal power and  $W_t$  useful work, we can write:

$$(\phi - W_t)_{tum} \leq \rho_{tum} c_{tum} T \frac{dC_c}{dt} \quad (4)$$

Equation (4) points out that up until the temperature of the tumour remains the same as that of the surrounding, non-cancerous host tissue, this organ tissue remains permissive for on-site growth - as the cancer cells' Warburg metabolic cycle is less efficient than the Krebs cycle of the healthy tissue (Warburg 1956; Vander Heiden, Cantley, and Thompson 2009). It is precisely this lower efficiency that requires a greater provision of metabolites (Pavlova and Thompson 2016; Martinez-Outschoorn *et al.* 2017), which can be realised by tumour angiogenesis (Lugano, Ramachandran, and Dimberg 2020), i.e., an increase in vascular supply. Then, as cancer growth continues, the intrinsic tumour temperature increases

due to inflammation and mechanical shifts of exerted stress and sustained strain, through mechanical forces of confinement and cell proliferation-based expansion. Competitive behaviour (versus the surrounding host tissue) ensues as the tumour transitions from locally contained growth to regional (and eventually distant) dissemination, referring to local infiltration, lymph node involvement and systemic metastases via the vascular system.

Following Schrödinger, life is based on entropy decrease, that corresponds to a state of high organization. Entropy outflow can be realised by (Schrödinger 1944):

- absorbing low-entropy nutrients (e.g., glucose, glutamine) and yielding high-entropy waste products (e.g., CO<sub>2</sub> and H<sub>2</sub>O);
- generating heat,

i.e., conditions that are mathematically represented by the following equation (Ozilgen and Oner 2016):

$$\frac{dS}{dt} = \left(\frac{dS}{dt}\right)_{prod} - \left(\frac{dS}{dt}\right)_{out} = \left(\frac{dS}{dt}\right)_{prod} - \left[\frac{\phi}{T} + \left(\frac{dS}{dt}\right)_{exch}\right] \leq 0 \quad (5)$$

where  $dS/dt$  is the rate of entropy change in a living organism, *prod* identifies the rate of internal entropy production due to its metabolic reactions, *out* denotes outflow, which expresses the rate of pumping entropy out,  $\phi$  is the heat power flux, *exch* stands for exchanged, which expresses the rate of entropy change due to the exchange of chemical species between an organism and the environment, and  $T$  [K] is the temperature, and *prod* means produced. Considering Eq. (5) it follows that:

$$\left(\frac{dS}{dt}\right)_{out} \geq \left(\frac{dS}{dt}\right)_{prod} \quad (6)$$

This approach can also be rewritten in terms of Gibbs free energy  $\Delta G$ , introducing the hypothesis that life is the sum of catabolic and anabolic reactions in a system of constant composition (the cell), which can analytically be expressed by the following equation (von Stockar and van der Wielen 2013):

$$\Delta G_m = \Delta H_m - T \Delta S_m \quad (7)$$

where  $\Delta G_m$  is the Gibbs free energy related to the production of one mole of new biomass,  $\Delta H_m$  is the enthalpy variation due to the production of one mole of new biomass, and  $\Delta S_m$  depicts the entropy variation due to consumption of nutrients to generate one mole of new biomass. It emerges that Gibbs' free energy of the living environment presents two different processes:

- heat generation by the living organism ( $\Delta H$ );
- the increase of entropy ( $\Delta S$ ) due to the production of waste molecules of higher entropy value than the ingested nutrients (Ghuchani 2019).

If we introduce the hypothesis of stationary states for the cells, both for cancer and healthy tissue, the internal entropy production rate ( $S_{prod}$ ), in the absence of mechanical work, can be obtained in terms of this biochemical reaction  $\dot{\xi}$  (von Stockar *et al.* 2006):

$$\dot{\xi} \cdot \Delta G_m = -T \left(\frac{dS}{dt}\right)_{prod} \quad (8)$$

Considering that  $(dS/dt)_{prod}$  is always positive for living cells (von Stockar *et al.* 2006), it follows that  $\Delta G_m$  turns negative, with the consequence that living cells are able to maintain their internal low-entropy state by increasing the entropy of their environment.

### 3. Results

Our main result consists of Eq. (4), which states that a ‘threshold’ exists for entropy production, as obtained in Eq. (6); here, tumour ‘behaviour’ switches from non-competitive, co-existing to competitive, expansive growth versus normal cells in the surrounding host tissue, in agreement with the expectation of Davies, Demetrius, and Tuszyński (2011) and confirming Deisboeck & Z. Wang’s earlier mechanistic concept (2007). Specifically, Eq. (4) highlights that if, in a given tumour, the entropy outflow exceeds entropy production, a slower proliferating, more stationary tumour coexists with the normal tissue. However, if the entropy outflow is lower than the entropy production, Eq. (4) describes a rapidly proliferating tumour, where such local entropy increase leads to excess internal cell energy and thus higher tumour temperature: the consequence is both, the need for increased neo-vascularization (to increase nutrient supply and provide flow for cooling) and eventually, competitive (local) invasion as well as (distant or systemic) metastasis. Considering Eq. (4) under equilibrium condition (sign =), we see the following two extreme cases:

- $W_t = 0$ , i.e., cancer does not exhibit any thermodynamic work, and fails to grow; cancer carrying capacity has a positive sign because the tumour cell must process heat outflow to live; in this case cancer does not compete with its environment;
- $\phi = 0$ , i.e., cancer is converting all its energy into molecular production during growth; in this case, cancer competes with normal cells for metabolites and energy.

Of course, these two cases cannot occur, while heat transfer and work performance must occur together to allow for viability. But, if there is an excess of energy present it must be converted into other forms, i.e., work. So, when cancer increases its growth, the carrying capacity of the system decreases. These considerations agree with the results of Gerlee and Anderson (2015). From here, our approach focuses on the concept of carrying capacity related to the host tissue.

Now, considering Eqs. (4), (5), (7), and (8), it is possible to obtain the following relation:

$$\frac{dC_c}{dt} \geq \frac{1}{\rho_{tum} c_{tum}} \left[ \xi \Delta S_m - \left( \frac{dS}{dt} \right)_{exch} \right] - \frac{1}{\rho_{tum} c_{tum} T} \left( \xi \Delta H_m + W_{tum} \right) \quad (9)$$

Based on the definition of carrying capacity ( $C_c = V_{tis}/F_{tis}$ ) it follows:

$$\begin{aligned} \frac{dC_c}{dt} &= \frac{1}{F_{tis}} \frac{dV_{tis}}{dt} - \frac{V_{tis}}{F_{tis}^2} \frac{dF_{tis}}{dt} = \frac{1}{F_{tis}} \frac{dV_{tis}}{dt} \left( 1 - \frac{V_{tis}}{F_{tis}} \frac{dF_{tis}}{dV} \right) \geq \\ &\geq \frac{1}{\rho_{tum} c_{tum}} \left[ \xi \Delta S_m - \left( \frac{dS}{dt} \right)_{exch} \right] - \frac{1}{\rho_{tum} c_{tum} T} \left( \xi \Delta H_m + W_{tum} \right) \end{aligned} \quad (10)$$

Concerning this inequality, we can argue that:

$$1 - \frac{V_{tis}}{F_{tis}} \frac{dF_{tis}}{dV} < 0 \quad (11)$$

then  $F_{tis}$  exceeds  $V_{tis}$ , and  $C_c$  is below 1; consequently, for evolved, highly specialized human tissues, such as the brain parenchyma for instance, the tumour volume that can be sustained would have to be smaller and as such spatial tumour expansion would start relatively sooner. Conversely, if

$$1 - \frac{V_{tis}}{F_{tis}} \frac{dF_{tis}}{dV} > 0 \quad (12)$$

then  $F_{tis}$  remains smaller than  $V_{tis}$ , and  $C_c$  is greater than 1. In reality, the applicable medical scenario would include for instance already tumour-infiltrated tissues and/or surrounding areas post-treatment such as after surgery, radiation- and chemo-therapy impact where the tissue oedema or swelling is common (hence, increasing  $V_{tis}$ ) (Solar *et al.* 2022)). In either case, a compromised organ architecture – and thus, concomitantly, an even more rapidly decaying functionality or  $F_{tis}$  – permits a comparatively larger, recurrent tumour volume prior to a secondary spatial expansion wave.

It is sensible to understand both these cases as a dynamic sequence: After malignant transformation, the still small neoplasm grows within a  $C_c < 1$  host setting while, at  $C_c > 1$ , the altered environment later on inevitably fuels further tumour progression of on-site growth and spatial expansion. Note that, as an analytical inequality, the carrying capacity threshold  $C_c$  implies the aforementioned entropy threshold. Using this result we can also state that the temperature must be highest in the centre of the tightly packed tumour, where motility and invasion are reduced, while it is lower at the boundary, where malignant cells are shed and invasion increases. This result is also in agreement with the results presented by Shimatani *et al.* (2021).

#### 4. Discussion and conclusions

Cancer should be conceptualized as a complex and dynamic biosystem possessing self-organizing capabilities at both the cellular and tissue levels. During the process of tumour growth, heat is transferred from the tumour to the surrounding host tissue. Due to the less efficient metabolic processes in cancer cells, the variation in entropy within these cells is lower than that in healthy tissue. Consequently, cancerous tissues must enhance their heat transfer mechanisms (Lucia 2012). This ability to generate heat is a dynamic characteristic that evolves throughout the progression of the tumour, influenced by two primary factors:

- biochemical reactions;
- neovascularisation, which provides essential oxygen and nutrients to support the metabolism of rapidly proliferating tumour cells (Sherwood, Parris, and Folkman 1971). Indeed, neovascularization is a critical physiological process that drives the growth and metastasis of malignant tumours (Gimbrone *et al.* 1972), depending on a range of proangiogenic cues, some of which have already served as therapeutic targets such as its vascular endothelial growth factor for instance (Jain 2005).

When the blood supply is inadequate or co-opted, tumour growth is limited to approximately 1–2 mm<sup>3</sup> in diameter. Hypoxia can then trigger an angiogenic switch, leading to the formation of new blood vessels. This neovascularisation facilitates tumour growth while maximizing heat generation. However, the rapid expansion of the tumour mass may induce mechanical constraints on these newly formed blood vessels, resulting eventually

in a diminished nutrient supply. This leads to local hypoxia, followed by apoptosis at the cellular level and irreversible central necrosis at the tissue level. Consequently, the reduction in metabolic activity within the tumour ultimately results in a decrease in its temperature.

We have commenced our analysis with Eq. (1), which builds upon previous conceptual work characterizing the relationship between volumetric tumour growth and the mechanistic constraints and functional variations of the surrounding host tissue (Deisboeck and Z. Wang 2007). Furthermore, we have introduced some thermo-physical properties of cells into Eq. (1) and obtained its thermodynamic interpretation in terms of cellular internal energy (Eq. (3)). By applying the first law of thermodynamics, we have incorporated the heat exchanged and functions performed by the cells themselves (Eq. (4)).

The analytical results highlight the conditions for tumour-host tissue coexistence, as well as those that favour the onset of invasion of tumour cells into the surrounding healthy tissue. Additionally, the necessity of tumour vascularization emerges from an energetic perspective. Specifically, our findings suggest the existence of an entropy production inequality (Eq. (6)) as a threshold for triggering cancer invasion, akin to a phase transition in physics (Davies, Demetrius, and Tuszynski 2011). The presence of a threshold in a thermodynamic potential - here, entropy - correlates with results from studies of potential functions in dynamical systems (Fuchs 2011), where a threshold manifests in the analysis of stable and unstable fixed points, indicating the evolution towards a local minimum or maximum of the potential functions associated with the control or expansion of cancer discussed in this paper.

Moreover, we note that conceptually, this entropy threshold is likely related to the ‘carrying capacity’ referenced in the paper by Deisboeck and Z. Wang (2007) as both a mechanical and structural aspect of the host environment; this suggests that the threshold may be not only tumour-specific but also organ-specific. Ultimately, this could provide opportunities to incorporate factors like comorbidities and ageing, which may have significant implications for clinical translation. Future work will aim to investigate this in greater detail.

Importantly, our theoretical findings are already supported by experimental data in the literature. The murine melanoma B16-F10 cell line is an established, rapidly metastasizing variant of the parental B16 cell line (Hart and Fidler 1980). Recent studies (Shao *et al.* 2023) have shown that this cell line develops central necrosis and exhibits a higher tumour temperature compared to surrounding tissue in a preclinical subcutaneous mouse model. The authors reference earlier work suggesting that increased mitochondrial heat generation occurs during apoptosis, a state preceding central necrosis. They also examined other tumour cell lines that exhibit lower temperatures compared to body temperature, which according to our model, might indicate a less aggressive tumour type or earlier stage where entropy outflow still surpasses its generation.

Our results align with the conclusions of Stein *et al.* (2007), which highlight how differences in tumour cell dispersion are influenced by the chemical factors produced by the cells. This study, focused on Glioblastoma Multiforme tumour spheroids, considers four parameters of brain cancer growth: undirected and directed movement, cell shedding rate from the spheroid, and proliferation rate. Additionally, Nousi *et al.* (2021) demonstrated that invasion involves the cooperative transport of groups of cells. In the presence of a non-zero extracellular matrix concentration, the volume of an invading spheroid is larger than that of a non-invading spheroid, indicating not only that they invade but also that they remodel the surrounding matrix which presumably had constrained the emerging mass. We

argue that enabling continued on-site proliferation such a rapidly growing mass would then max out the host tissue's carrying capacity even faster, in turn accelerating invasion and remodelling, and so on - which together supports seeing the concept of 'limited carrying capacity' as a key to understanding the dynamics of malignant progression and systemic expansion.

Mark *et al.* (2020) demonstrated that the collective forces exerted by tumour spheroids reflect the contractility of individual cells for up to one hour following seeding, with these forces being influenced by mechanical feedback from the extracellular matrix over extended timescales. These experimental findings underscore the active role of tumours as they become increasingly competitive with normal cells, in stark contrast to their cooperative behaviour observed during the initial stages of progression. Furthermore, Lucia (2013) provides theoretical evidence for the existence of a maximum value - or threshold - of volumetric growth, beyond which tumours invade other regions of the body, a conclusion that is supported numerically through data from existing literature (Mark *et al.* 2020; Huang *et al.* 2024).

We acknowledge that additional experimental data are essential to ascertain whether the theoretical framework proposed here can be generalized beyond selected contexts and may ultimately facilitate the differentiation of tumour types or stages based on metabolic requirements and energetic constraints. Should these ideas be corroborated, they may present significant opportunities for the development of novel therapeutic strategies against cancer, including immunotherapy. For instance, as reported by Knapp *et al.* (2022), the efficacy of oncolytic viruses is sensitive to temperature fluctuations. While tumour angiogenesis appears to be a logical therapeutic target, the reduction in metabolite supply to the tumour core due to anti-angiogenic treatments also results in decreased entropy outflow. Should the decrease in entropy outflow occur prior to or at a greater rate than the reduction in metabolite supply, such treatments could inadvertently facilitate tumour dissemination and recurrence. And indeed, the clinical administration of the vascular endothelial growth factor (VEGF) antibody, bevacizumab (Avastin<sup>®</sup>), has failed to demonstrate any significant improvement in outcomes for patients with glioblastoma (Gramatzki *et al.* 2018). Additionally, tumour evasion from bevacizumab has been partly attributed to the adaptation of recurrent glioma cells to a more infiltrative phenotype, utilizing endothelial cells as structural conduits (Falchetti *et al.* 2019).

A noteworthy theoretical byproduct of the identified non-linearity in entropy generation-which exhibits a threshold function triggering the onset of spatial dissemination-is that minor, therapeutically induced changes in entropy might exert considerable influence on the control or mitigation of tumour aggression. Consequently, innovative practical approaches such as tumour cooling may warrant consideration where and when feasible. This concept could be effectively realized through the application of external fields, such as extremely low-frequency electromagnetic or ultrasound fields, under resonant conditions (Lucia and Grisolia 2020a,b, 2022).

Therefore, the results of this inquiry are of considerable interest from both a fundamental biophysics perspective and a medical standpoint. If spatial cancer progression can be analytically correlated with the crossing of a threshold of measurable temperature changes in situ, such data could enhance the efficacy of diagnostic procedures and lead to the

formulation of innovative therapeutic regimens tailored to specific tumour types and patient characteristics.

### Conflicts of interest

The authors declare that they have no known conflicts of interest.

### Author contributions

G.G.: Conceptualization; Investigation; Methodology; Data Curation; Writing - Original Draft; Writing - Review & Editing; Writing - Original Draft; Writing - Review & Editing.

U.L.: Conceptualization; Investigation; Methodology; Formal analysis; Funding acquisition; Writing - Original Draft; Writing - Review & Editing; Supervision; Validation; Project administration; Funding acquisition; Resources.

T.S.D.: Conceptualization; Investigation; Writing - Original Draft; Writing - Review & Editing; Validation.

### References

- Arango-Restrepo, A. and Rubi, J. M. (2023). “Predicting cancer stages from tissue energy dissipation”. *Scientific Reports* **13**, 15894. DOI: [10.1038/s41598-023-42780-0](https://doi.org/10.1038/s41598-023-42780-0).
- Clevenger, A. J., McFarlin, M. K., Gorley, J. P. M., Solberg, S. C., Madyastha, A. K., and Raghavan, S. A. (2024). “Advances in cancer mechanobiology: Metastasis, mechanics, and materials”. *APL Bioengineering* **8**(1). DOI: [10.1063/5.0186042](https://doi.org/10.1063/5.0186042).
- Davies, P. C. W., Demetrius, L., and Tuszynski, J. A. (2011). “Cancer as a dynamical phase transition”. *Theoretical Biology and Medical Modelling* **8**, 30. DOI: [10.1186/1742-4682-8-30](https://doi.org/10.1186/1742-4682-8-30).
- Deisboeck, T. S. and Wang, Z. (2007). “Cancer dissemination: A consequence of limited carrying capacity?” *Medical Hypotheses* **69**, 173–177. DOI: [10.1016/j.mehy.2006.11.007](https://doi.org/10.1016/j.mehy.2006.11.007).
- Dhondt, A. A. (1988). “Carrying capacity: a confusing concept”. *Acta Oecologica. Oecologia Generalis* **9**(4), 337–346.
- Falchetti, M. L., D’Alessandris, Q. G., Pacioni, S., Buccarelli, M., Morgante, L., Giannetti, S., Lulli, V., Martini, M., Larocca, L. M., Vakana, E., Stancato, L., Ricci-Vitiani, L., and Pallini, R. (2019). “Glioblastoma endothelium drives bevacizumab-induced infiltrative growth via modulation of PLXDC1”. *Molecular Cancer Biology* **144**, 1331–1444. DOI: [10.1002/ijc.31983](https://doi.org/10.1002/ijc.31983).
- Force *et al.* (GBD 2023 cancer collaborators) (2025). “The global, regional, and national burden of cancer, 1990–2023, with forecasts to 2050: a systematic analysis for the Global Burden of Disease Study 2023”. *The Lancet* **406**(10512), 1565–1586. DOI: [10.1016/s0140-6736\(25\)01635-6](https://doi.org/10.1016/s0140-6736(25)01635-6).
- Fuchs, A. (2011). “Dynamical Systems in One and Two Dimensions: A Geometrical Approach”. In: *Nonlinear Dynamics in Human Behavior*. Ed. by H. Huys and V. K. Jirsa. Berlin, Heidelberg: Springer Berlin Heidelberg, pp. 1–33. DOI: [10.1007/978-3-642-16262-6\\_1](https://doi.org/10.1007/978-3-642-16262-6_1).
- Gerlee, P. and Anderson, A. R. A. (2015). “The evolution of carrying capacity in constrained and expanding tumour cell populations”. *Physical Biology* **12**(5), 056001. DOI: [10.1088/1478-3975/12/5/056001](https://doi.org/10.1088/1478-3975/12/5/056001).
- Ghuchani, M. S. (2019). “Thermodynamic Modeling of the Competition. Between Cancer and Normal Cells”. *Journal of Non-Equilibrium Thermodynamics* **45**, 19–25. DOI: [10.1515/jnet-2019-0037](https://doi.org/10.1515/jnet-2019-0037).
- Gimbrone, M. A., Leapman, S. B., Cotran, R. S., and Folkman, J. (1972). “Tumor Dormancy in Vivo by Prevention of Neovascularization”. *Journal of Experimental Medicine* **136**, 261–276. DOI: [10.1084/jem.136.2.261](https://doi.org/10.1084/jem.136.2.261).

- Gramatzki, D., Roth, P., Rushing, E. J., Weller, J., Andratschke, N., Hofer, S., Korol, D., Regli, L., Pangalu, A., Pless, M., Oberle, J., Bernays, R., Moch, H., Rohrmann, S., and Weller, M. (2018). “Bevacizumab may improve quality of life, but not overall survival in glioblastoma: an epidemiological study”. *Annals of Oncology* **29**, 1431–1436. DOI: [10.1093/annonc/mdy106](https://doi.org/10.1093/annonc/mdy106).
- Hart, I. R. and Fidler, I. J. (1980). “Role of Organ Selectivity in the Determination of Metastatic Patterns of B16 Melanoma”. *Cancer Research* **40**(7), 2281–2287.
- Huang, Y., Liu, L., Gan, Q., Shen, Z., Yao, Y., Liao, C., Lu, S., zou, Y., Huang, Y., Kong, J., and Fan, X. (2024). “Estimation of the tumor size at cure threshold among adult patients with adrenocortical carcinoma: A populational-based study”. *Heliyon* **10**, e28160. DOI: [10.1016/j.heliyon.2024.e28160](https://doi.org/10.1016/j.heliyon.2024.e28160).
- Jain, R. K. (2005). “Antiangiogenic therapy for cancer: current and emerging concepts”. *Oncology (Williston Park)* **19** (4 Suppl 3), 7–16.
- Katchalsky, A. and Kedem, O. (1962). “Thermodynamics of Flow Processes in Biological Systems”. *Biophysical Journal* **2**(2), 53–78. DOI: [10.1016/s0006-3495\(62\)86948-3](https://doi.org/10.1016/s0006-3495(62)86948-3).
- Knapp, J. P., Kakish, J. E., Bridle, B. W., and Speicher, D. J. (2022). “Tumor Temperature: Friend or Foe of Virus-Based Cancer Immunotherapy”. *Biomedicines* **10**(8), 2024. DOI: [10.3390/biomedicines10082024](https://doi.org/10.3390/biomedicines10082024).
- Lucia, U. (2012). “Irreversibility in biophysical and biochemical engineering”. *Physica A: Statistical Mechanics and its Applications* **391**, 5997–6007. DOI: [10.1016/j.physa.2012.07.018](https://doi.org/10.1016/j.physa.2012.07.018).
- Lucia, U. (2013). “Thermodynamics and cancer stationary states”. *Physica A: Statistical Mechanics and its Applications* **392**, 3648–3653. DOI: [10.1016/j.physa.2013.04.033](https://doi.org/10.1016/j.physa.2013.04.033).
- Lucia, U. (2015). “Bioengineering thermodynamics of biological cells”. *Theoretical Biology and Medical Modelling* **12**, 29. DOI: [10.1186/s12976-015-0024-z](https://doi.org/10.1186/s12976-015-0024-z).
- Lucia, U. and Grisolia, G. (2020a). “Resonance in thermal fluxes through cancer membrane”. *Atti della Accademia Peloritana dei Pericolanti. Classe di Scienze Fisiche, Matematiche e Naturali* **98**(1), SC1. DOI: [10.1478/AAPP.981SCI](https://doi.org/10.1478/AAPP.981SCI).
- Lucia, U. and Grisolia, G. (2020b). “Thermal resonance and cell behaviour”. *Entropy* **22**, 774–785. DOI: [10.3390/e22070774](https://doi.org/10.3390/e22070774).
- Lucia, U. and Grisolia, G. (2022). “Thermal resonance in living cells to control their heat exchange: Possible applications in cancer treatment”. *International Communications in Heat and Mass Transfer* **131**, 105842. DOI: [10.1016/j.icheatmasstransfer.2021.105842](https://doi.org/10.1016/j.icheatmasstransfer.2021.105842).
- Lugano, R., Ramachandran, M., and Dimberg, A. (2020). “Tumor Angiogenesis: Causes, Consequences, Challenges and Opportunities”. *Cellular and Molecular Life Sciences* **77**, 1745–1770. DOI: [10.1007/s00018-019-03351-7](https://doi.org/10.1007/s00018-019-03351-7).
- Mark, C., Grundy, T. J., Strissel, P. L., Böhringer, D., Grummel, N., Gerum, R., Steinwachs, J., Matthias W. Beckmann, C. C. H. and, Eckstein, M., Strick, R., O’Neill, G. M., and Fabry, B. (2020). “Collective forces of tumor spheroids in three-dimensional biopolymer networks”. *eLife* **9**, e51912. DOI: [10.7554/eLife.51912](https://doi.org/10.7554/eLife.51912).
- Martinez-Outschoorn, U. E., Peiris-Pages, M., Pestell, R. G., Sotgia, F., and Lisanti, M. P. (2017). “Cancer metabolism: a therapeutic perspective”. *Nature Reviews Clinical Oncology* **14**, 11. DOI: [10.1038/nrclinonc.2016.60](https://doi.org/10.1038/nrclinonc.2016.60).
- Michor, F., Liphardt, J., Ferrari, M., and Widom, J. (2011). “What does physics have to do with cancer?” *Nature Reviews Cancer* **11**, 657–670. DOI: [10.1038/nrc3092](https://doi.org/10.1038/nrc3092).
- Nousi, A., Søggaard, M. T., Audoin, M., and Jauffred, L. (2021). “Single-cell tracking reveals super-spreading brain cancer cells with high persistence”. *Biochemistry and Biophysics Reports* **28**, 101120. DOI: [10.1016/j.bbrep.2021.101120](https://doi.org/10.1016/j.bbrep.2021.101120).
- Ozilgen, M. and Oner, E. S. (2016). *Biothermodynamics: Principles and Applications*. Boca Raton: CRC Press.
- Pavlova, N. N. and Thompson, C. B. (2016). “The emerging hallmarks of cancer metabolism”. *Cell Metabolism* **23**, 27–47. DOI: [10.1016/j.cmet.2015.12.006](https://doi.org/10.1016/j.cmet.2015.12.006).

- Schrödinger, E. (1944). *What's life? The Physical Aspect of the Living Cell*. Cambridge: Cambridge University Press.
- Shamsabadipour, A., Pourmadadi, M., Davodabadi, F., Rahdar, A., and Ferreira, L. F. R. (2023). "Applying thermodynamics as an applicable approach to cancer diagnosis, evaluation, and therapy: A review". *Journal of Drug Delivery Science and Technology* **86**, 104681. DOI: [10.1016/j.jddst.2023.104681](https://doi.org/10.1016/j.jddst.2023.104681).
- Shao, Q., Lundgren, M., Lynch, J., Jiang, M., Mir, M., Bischof, J., and Nelson, M. (2023). "Tumor therapeutic response monitored by telemetric temperature sensing, a preclinical study on immunotherapy and chemotherapy". *Scientific Reports* **13**, 7727. DOI: [10.1038/s41598-023-34919-w](https://doi.org/10.1038/s41598-023-34919-w).
- Sherwood, L. M., Parris, E. E., and Folkman, J. (1971). "Tumor Angiogenesis: Therapeutic Implications". *The New England Journal of Medicine* **285**, 1182–1186. DOI: [10.1056/nejm197111182852108](https://doi.org/10.1056/nejm197111182852108).
- Shimatani, A., Hoshi, M., Oebisu, N., Takada, N., Ban, Y., and Nakamura, H. (2021). "An analysis of tumor-related skin temperature differences in malignant soft-tissue tumors". *International Journal of Clinical Oncology* **27**, 234–243. DOI: [10.1007/s10147-021-02044-1](https://doi.org/10.1007/s10147-021-02044-1).
- Solar, P., Hendrych, M., Barak, M., Valekova, H., Hermanova, M., and Jancalek, R. (2022). "Blood-Brain Barrier Alterations and Edema Formation in Different Brain Mass Lesions". *Frontiers in Cellular Neuroscience* **16**, 922181. DOI: [10.3389/fncel.2022.922181](https://doi.org/10.3389/fncel.2022.922181).
- Stein, A. M., Demuth, T., Mobley, D., Berens, M., and Sander, L. M. (2007). "A Mathematical Model of Glioblastoma Tumor Spheroid Invasion in a Three-Dimensional In Vitro Experiment". *Biophysical Journal* **92**(1), 356–365. DOI: [10.1529/biophysj.106.093468](https://doi.org/10.1529/biophysj.106.093468).
- Vander Heiden, M. G., Cantley, L. C., and Thompson, C. B. (2009). "Understanding the Warburg effect: the metabolic requirements of cell proliferation". *Science* **324**, 1029–1033. DOI: [10.1126/science.1160809](https://doi.org/10.1126/science.1160809).
- Verginadis, I., Velalopoulou, A., Karagounis, I., Simos, Y., Peschos, D., Karkabounas, S., and Evangelou, A. (2012). "Beneficial Effects of Electromagnetic Radiation in Cancer". In: *Electromagnetic Radiation*. Ed. by S. O. Bashir. London: IntechOpen. Chap. 11. DOI: [10.5772/35456](https://doi.org/10.5772/35456).
- von Stockar, U., Maskow, T., Liu, J., Marison, I. W., and Patino, R. (2006). "Thermodynamics of microbial growth and metabolism: an analysis of the current situation". *Journal of Biotechnology* **121**, 517–533. DOI: [10.1016/j.jbiotec.2005.08.012](https://doi.org/10.1016/j.jbiotec.2005.08.012).
- von Stockar, U. and van der Wielen, L. A. M., eds. (2013). *Biothermodynamics: The Role of Thermodynamics in Biochemical Engineering*. Lausanne: EPFL Press. DOI: [10.1201/b15428](https://doi.org/10.1201/b15428).
- Wang, Q., Yin, X., Ding, Y., Zhao, H., and Luo, Y. (2024). "Application of biomechanics in tumor epigenetic research". *Mechanobiology in Medicine* **2**(4), 100093. DOI: [10.1016/j.mbm.2024.100093](https://doi.org/10.1016/j.mbm.2024.100093).
- Warburg, O. (1956). "On the origin of cancer cells". *Science* **123**, 309–314. DOI: [10.1126/science.123.3191.309](https://doi.org/10.1126/science.123.3191.309).
- Zivieri, A. and Pacini, N. (2017). "Is an Entropy-Based Approach Suitable for an Understanding of the Metabolic Pathways of Fermentation and Respiration?" *Entropy* **19**, 662. DOI: [10.3390/e19120662](https://doi.org/10.3390/e19120662).
- Zivieri, A. and Pacini, N. (2018). "Entropy Density Acceleration and Minimum Dissipation Principle: Correlation with Heat and Matter Transfer in Glucose Catabolism". *Entropy* **20**, 929. DOI: [10.3390/e20120929](https://doi.org/10.3390/e20120929).
- Zivieri, A., Pacini, N., Finocchio, G., and Carpentieri, M. (2017). "Rate of entropy model for irreversible processes in living systems". *Scientific Reports* **7**, 9134. DOI: [10.1038/s41598-017-09530-5](https://doi.org/10.1038/s41598-017-09530-5).

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