Exergy analysis of pancreas tumor cells behavior: effects of anticancer therapies on life expectancy

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Abstract:
This study investigates the effect of the exergetic dynamics of pancreatic ductal adenocarcinoma (PDAC) through the lens of thermodynamics and systems biology. We employed a mathematical modeling approach from the literature to simulate the tumor microenvironment, incorporating the second law of thermodynamics to quantify the irreversibility associated with the presence of cancerous cells within the organ and the decrease in life expectancy by the "exergetic age". To represent varying degrees of malignancy, the intrinsic growth constant (k_c) was modulated linearly from 0.05 to 0.1, reflecting a transition from low-grade to highly aggressive proliferation. Three distinct therapeutic interventions were evaluated: (1) TGF-β pathway inhibitors, aimed at disrupting the fibrotic signaling between pancreatic cancer cells (PCCs) and stellate cells (PSCs); (2) Synthetic 5'-triphosphate RNA, designed to trigger a RIG-I-mediated immune response by mimicking viral molecular patterns; and (3) a synergistic combined treatment (ppp-TGFβ). Our results demonstrate that the ppp-TGFβ approach was a better treatment, as it effectively decouples the immunosuppressive feedback loops and dampens the entropic surge associated with rapid tumor expansion. Our model predicts that while untreated PDAC leads to critical systemic exhaustion (resilience loss) within approximately 5 years, the ppp-TGFβ intervention can extend the host's thermodynamic viability and life expectancy by more than a decade.

Keywords:
Second Law Thermodynamics, Cancerous cell, Irreversibilities, Life expectancy.

1. Introduction

Classical thermodynamics investigates equilibrium and the macroscopic properties that define a system's state, focusing on the fundamental processes of matter and energy exchange. Each of these changes the quality of the energy, and the second law of thermodynamics is crucial for quantifying how far the process is from the ideal [1]. In the biological sciences, these principles are applied to understand phenomena and evaluate "malfunctions", such as pathologies, with cancer behavior as the focus of several studies in the literature [2], as well as its treatments [3], also focusing on the consequences for life expectancy [4].

The concept of "entropic age" follows two primary paths: in biogerontology, Hayflick [5] established the theoretical foundation by proposing that aging is the biological manifestation of the Second Law of Thermodynamics, in which the loss of molecular complexity represents an inevitable increase in entropy. This is in the same path as earlier studies by Schrödinger [6] and Prigogine [7] on the maximum number of cell divisions over a lifetime. and its relation to entropy.

Luo was one of the first to evaluate the thermodynamics and entropy production of healthy and cancerous cells [8], suggesting that cancer treatments should increase the entropy flow rate of healthy cells. Additionally, the groups of Annamalai [9, 10] and Ozilgen [11, 12] formalized the term quantitatively, using entropy production rate calculations to measure how conditions such as cancer and

lifestyle choices accelerate biological age relative to chronological age and the organism's energetic exhaustion.
A central concept is the analysis of entropy and its transfer. Based on the Second Law of Thermodynamics [13], it is possible to compare the behavior of healthy and cancerous cells [10]. Research indicates that tumor cells generate more entropy than normal cells, suggesting the possibility of early cancer diagnosis by monitoring entropy generation [8]. This idea connects to the concept of entropic age, which relates accumulated metabolic irreversibilities (or destroyed exergy) throughout life to overall lifespan [2].
Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer and is characterized by extremely high mortality when left untreated. This high mortality reflects the difficulty of early diagnosis and the resistance to available treatments, resulting in a survival rate of only 8.5%. Estimates indicate that PDAC is the fourth leading cause of cancer-related death worldwide. The objective of this study is to evaluate the impact of pancreatic cancer on entropy production and, consequently, on life expectancy, while analyzing how the proposed treatments influence the lifespans of females and males.

2. Methods

Pancreatic cancer cells (PCCs) act as central controllers in the tumor microenvironment, secreting signaling factors like TGF-β to drive the activation and proliferation of pancreatic stellate cells (PSCs). These star-shaped cells function as structural actuators, contributing to pancreatic fibrosis and accelerating disease progression. Through the emission of specific cytokines—such as GM-CSF, IL-6, and M-CSF—PCCs and PSCs modulate the system's immune response, forcing a "mode switch" (polarization) in macrophages from the M1 phenotype (anti-tumor/active defense) to the M2 phenotype (pro-tumor/support). This transition functions as a negative feedback loop in the host's defense: it increases IL-10 output while suppressing IL-12, effectively dampening the signaling and activity of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. Consequently, the system's "search-and-destroy" mechanism is neutralized, allowing for unchecked tumor growth [14].
The present article focuses on PDAC and discusses three therapeutic approaches. The first treatment is OH-TGF-β, an inhibitor of the TGF-β pathway, which normally suppresses immune responses and favors tumor progression. Blocking this pathway aims to restore immunity against cancer. The second treatment is ppp-RNA, a synthetic molecule designed to mimic cancer cell RNA and activate the immune system to combat the tumor. Finally, the third treatment, ppp-TGF-β, combines the two previous strategies, promoting an antiviral immune response while eliminating the immunosuppressive effects of the TGF-β pathway [14].
It is important to highlight that only approximately 15% to 20% of patients diagnosed with pancreatic cancer are candidates for surgical organ removal at the time of diagnosis. This low eligibility rate is primarily due to the disease's asymptomatic progression, which often leads to late-stage detection when the tumor has already achieved significant vascular involvement or distant metastasis. For the vast majority of patients—roughly 80%—the cancer is classified as locally advanced or metastatic, making surgical intervention with curative intent unfeasible and shifting the focus toward systemic therapies and palliative care [15].

2.1. Tumor growth and cancer treatment

The simplified model described in Equation 1 to 4 outlines the dynamics between pancreatic cancer cells ($C(t)$ - Eq. 1), pancreatic stellate cells ($P(t)$- Eq. 2), the pro-inflammatory macrophage fraction ($R(t)$ - Eq. 3), and cytotoxic T cells ($T(t)$ - Eq. 4). This entire subsection is constructed from the reference by Louzoun et al. [14].

$$\frac{dC}{dt} = (k_c + \mu_c P)C^{3/4}(1 - (C/C_0)^{1/4}) - \frac{\lambda_c CT}{K_c + (1 - R)} \tag{1}$$

In Equation 1, $(k_c + \mu_c P)C^{3/4}$ represents the growth rate of pancreatic cancer cells. The $C^{3/4}$ power law reflects that tumor growth is limited by surface area or nutrient distribution, not a volumetric problem, k_c is the intrinsic growth rate, $\mu_c P$ is the proliferation boost from pancreatic stellate cells ($P(t)$) via the secretion of growth factors from cancerous cells like EGF (Epidermal Growth Factor). The relation $(1 - (C/C_0)^{1/4})$ is the "braking" term for logistic growth, where C_0 is the carrying capacity or maximum size the environment supports. Next, $\frac{\lambda_c CT}{K_c+(1-R)}$ describes the immune clearing rate, where λ_c is the killing efficiency of T-cells (T). Also, the relation $K_c+(1-R)$ is the denominator representing immune evasion. As R (M1 macrophages) decreases, cells essential to the immune system, the denominator increases, so T-cells become less effective at killing cancer.

$$\frac{dP}{dt} = \left(k_p + \frac{\mu_p C}{K_p + C}\right) P(1 - \frac{P}{P_0}) - \lambda_p P \tag{2}$$

In Equation 2, the relation of pancreatic Stellate Cells (PSCs) $k_p P(1 - \frac{P}{P_0})$ describes the basal growth of PSCs toward their own carrying capacity P_0. The term $\frac{\mu_p C}{K_p+C}P$ explains the recruitment or activation of additional PSCs by the cancer cells. The tumor uses these cells to create a protective fibrous stroma, $\lambda_p P$ describes the natural death (apoptosis) rate of stellate cells.

$$\frac{dR}{dt} = k_r - (\lambda_r + \gamma_p P + \gamma_c C)R \tag{3}$$

Equation 3 concerns pro-inflammatory M1 Macrophages, where k_r is the constant source of recruitment of macrophages into the tissue, $(\lambda_r + \gamma_p P + \gamma_c C)R$ is the inhibition or polarization term, $\gamma_p P$ and $\gamma_c C$ reflect how PSCs (pancreatic Stellate Cells) and cancer cells secrete TGF-β to suppress M1 macrophages or convert them into the "bad" M2 type. This is the "shield" the tumor uses against the immune system.

$$\frac{dT}{dt} = \frac{k_t R}{K_t + (1 - R)} - \lambda_t T \tag{4}$$

Equation 4 involves cytotoxic $T(t)$ cells, where $\frac{k_t R}{K_t+(1-R)}$ is the activation rate and shows that $T(t)$ cell expansion strictly depends on "good" M1 macrophages ($R(t)$). If the tumor suppresses $R(t)$, the production of $T(t)$ drops significantly. $\lambda_t T$ is the natural decay or exhaustion rate of T-cells.
To solve the differential equations, we used the Explicit Euler method, where it was possible to obtain $C(t)$, $P(t)$, $R(t)$, and $T(t)$. After this, all physical and thermodynamic properties were obtained and integrated over time using the trapezoidal method in the Python programming language, programmed by the authors without using any pre-programmed functions from others. Figure 1 shows the results of the application of the model by Louzoun et al. [14] for 3 treatments and the extreme case of no treatment, where it is possible to evaluate that in two scenarios the occupancy limit is achieved. At the moment, there is no space for healthy cells, and vessels are destroyed, which increases hypoxia and anaerobic metabolism.

2.2. Thermodynamics applications in the human body and cells

The oxidation reactions of the nutrients in the human body, when aerobic, are described by Equations 5 to 7, where the variations in enthalpy, Gibbs free energy, and entropy of the reactions are detailed by Mady and Oliveira-Junior [16]

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O \tag{5}$$

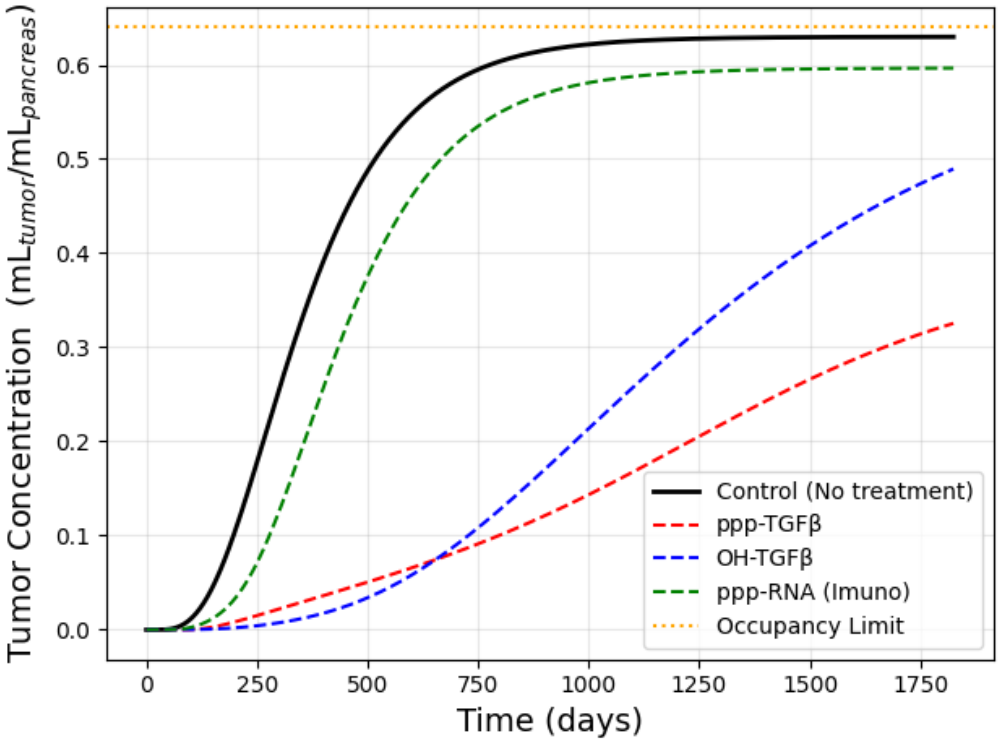

Figure 1: Concentration of cancerous cells as a function time (days) during 5 years of for 3 treatments and no treatment [14].

$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16CO_2 + 16H_2O \tag{6}$$

$$C_{4,98}H_{9,8}N_{1.4}O_{2.5} + 5.13O_2 \rightarrow 4.28CO_2 + 3.5H_2O + 0.7CH_4N_2O \tag{7}$$

These reactions have the objective of producing the molecule responsible for the energy conversion process inside the human body (ATP from ADP). After complete oxidation of the nutrient in the cells, a certain amount of ATP is formed. One mol of glucose forms 32 mols of ATP, 1 mol of palmitic acid forms 106 moles of ATP, and 1 mol of amino acid forms 8 mols of ATP. Reaction 8 shows the production of ATP in the direct reaction and its hydrolysis reverse equation [16]. For the sake of simplicity, it is important to note that $\Delta G = \Delta H - T_0\Delta S \approx \Delta H$, from a biological perspective, where $T\Delta S$ are the most significant terms, showing that this equation is close to reversible [17] .

$$ADP + P_i \leftrightarrow ATP + H_2O \tag{8}$$

Revisiting the article [16], it was possible to upgrade the equations of metabolism on an energy, exergy, and entropy basis from measured carbon dioxide production ($\dot{m}_{CO_2}$) or oxygen consumption ($\dot{m}_{O_2}$). These equations were obtained from the oxidation reactions of nutrients—Equation 5 to 7—and calculated the consumption of glucose, lipids, and amino acids.

$$M = 11224.31 \cdot \dot{m}_{O_2} + 2478.907 \cdot \dot{m}_{CO_2} - 1642.123 \cdot \dot{m}_N \tag{9}$$

$$B_M = 9479.204 \cdot \dot{m}_{O_2} + 4376.781 \cdot \dot{m}_{CO_2} - 5193.885 \cdot \dot{m}_N \tag{10}$$

$$\dot{S}_M = 5.85311 \cdot \dot{m}_{O_2} - 6.3655 \cdot \dot{m}_{CO_2} + 11.9127 \cdot \dot{m}_N \tag{11}$$

Table 1 shows an application of Equations 9 to 11 in an exercise test published by Spanghero et al. [18], where it is possible to obtain the patient metabolism, exergy metabolism, and entropic metabolism. For the first time, it is possible to identify that the entropic metabolism is negative, showing that the considerations of Schrodinger [6] state that "an organism that feeds on negative entropy". Hence, the oxidation reactions responsible for maintaining life create a term that decreases the entropy of the body, making it possible to maintain the disequilibrium with the environment, with $d\mathbf{S}_{body}/dt < 0$. It is possible to analyze this fact in Equation 12.

Table 1: Oxygen consumption and carbon dioxide production from a biceps exercise test in [18]. Calculates metabolism, exergy metabolism and entropic metabolism for each point

Tempo [s]	$\dot{m}_{O_2}$ [kg/s]	$\dot{m}_{CO_2}$ [kg/s]	M [W]	$\dot{B}_M$ [W]	$\dot{S}_M$ [W]
0	0.0000115	0.00001	153.60	151.94	-0.0056
2	0.000012	0.0000098	134.43	112.91	-0.0098
4	0.0000125	0.0000101	140.04	117.65	-0.0108
6	0.0000118	0.0000095	132.18	111.01	-0.0105
8	0.0000115	0.000009	128.75	132.96	-0.0120

The Equation 12 indicates the entropy variation of the body over time, where there is a clear distinction between $\dot{S}_M = \sum(\dot{m}\cdot s)_{product} - \sum(\dot{m}\cdot s)_{reactants}$ and the entropy exchange with the environment ($\dot{S}_{env}$), such as sweating, diffusion, and an increase in the humidity and temperature of the expired air compared with the inspired $\sum(\dot{m}\cdot s)_{in} - \sum(\dot{m}\cdot s)_{out} = \dot{S}_{env}$ [19]. All other articles refer to this energy transfer as a heat transfer to the environment, calculated as $\dot{Q}_i/T_i$, which may reflect erroneous values of entropy generation.

$$\left.\frac{dS}{dt}\right|_{\Delta T} = \dot{S}_M + \dot{S}_{env} + \sum_i \frac{\dot{Q}_i}{T_i} + \dot{\sigma}_{body} \tag{12}$$

The same reasoning can be applied to the exergy analysis according to Equation 13, based in Mady et al. [20], where $\dot{B}_{dest} = T_0 \cdot \dot{\sigma}$ is applicable according to the Gouy-Stodola theorem [21].

$$\left.\frac{dB}{dt}\right|_{\Delta T} = \dot{B}_M - \dot{B}_{env} + \sum_i \dot{Q}_i \left(1 - \frac{T_0}{T_i}\right) - \dot{W}_{body} - \dot{B}_{dest} \tag{13}$$

2.3. Thermodynamic model of tumor growth

The thermodynamic behavior of a cancerous cell is characterized by a significant rise in the rate of irreversibility ($\dot{\sigma}_{body}$), driven by intensified metabolic demands. As the tumor occupies an increasing volume within the tissue, it reaches a critical concentration that leads to mechanical compression and eventual destruction of local blood vessels [22]. This progression, illustrated in Figure 1 according to the model by Louzoun et al. [14], triggers a transition to an environment with low oxygen concentration (hypoxia).

Consequently, anaerobic pathways—such as lactic fermentation—become predominant. Due to the significantly lower exergy yield of anaerobic reactions compared to aerobic oxidation, the cell must increase its metabolic rates to satisfy its energetic requirements. This is described by the Warburg-Effect, modeled by Fornalski [23]. Another important issue is that the body requires 6 ATP to convert lactate back into glucose; it is not eliminated, while anaerobic glucose degradation produces only 2 ATP [24]. This may justify weight loss in patients with cancer [24], since there is an increase in the rate of the reaction of Equation 14. Unlike healthy tissue, the tumor microenvironment with hypoxia exhibits an accelerated consumption of nutrients (around 20 times), along with a subsequent release of heat and metabolic products such as lactate ($C_3H_6O_3$) and CO_2—leading to intensified energy release

and exergy destruction (irreversibilities) [8].

$$C_6H_{12}O_6 \rightarrow 2C_3H_6O_3 \tag{14}$$

From the entropy variation of the anaerobic reaction (Equation 14), $\Delta S_{anaerobic,reaction} = 435.2$ [kJ/kgK] is used along with $\Delta G_{ATP} = -56$ [kJ/kmol], where there is a production of 2 ATP. The irreversibilities of a cancer cell can be calculated using Equation 15. Where $S_{M,anaerobic}$ is the metabolic entropy production of the cell, $\dot{Q}_{tumor} = \dot{M}_{anaerobic}$, and T_{tumor} is the temperature of the tumor cell, which is higher than that of a healthy cell. Using the Gouy Stodola Theorem [21] $\dot{W}_{lost} = \dot{B}_{dest} = T_0 \cdot \dot{\sigma}$, it is possible to calculate the destroyed exergy rate over time.

$$\dot{\sigma}_{cancer,cell} = S_{M,anaerobic} - \frac{\dot{Q}_{tumor}}{T_{tumor}} \tag{15}$$

2.4. Anthropometric data of Brazilian society

According to the Brazilian Institute of Geography and Statistics (IBGE), the anthropometric data of Brazilian society are provided by Table 2.4.. It is important to bear in mind that the life expectancy for females is 79.7 years and for males is 72.7 years (an average of 76.2 years). The study by Taneja et al. [25] examined the term biological resilience after stress and concluded that there is a critical age range of 120 to 150 years, indicating an absolute limit to the human lifespan. Herein, it will be considered 120 years old. For that, we suggested a "Carnot" human being that does not take into account the limitations in lifespan due to obesity, heart failure, or other diseases. Although the Bambuí Health and Aging Study and the National Health and Nutrition Examination Survey document that even in healthy elderly people, there is a loss of 1 kg of body mass due to musculoskeletal losses and 1 cm of height per decade, this makes the maximum entropy generation (or destroyed exergy) over life 12750 kJ/kg · K (3801.4 MJ/kg).

Table 2: Anthropometric data of Brazilian society from birth to 80 years (close to national life expectancy

Age [Years]	Mass$_{male}$ [kg]	Height$_{male}$ [m]	Mass$_{female}$ [kg]	Height$_{female}$ [m]
0 (birth.)	3,3	0,5	3,2	0,49
5	18,5	1,1	18,2	1,09
10	32	1,38	33	1,39
15	58	1,67	53	1,6
20	71	1,73	59	1,61
30	76	1,74	64	1,62
40	79	1,73	68	1,61
50	81	1,72	70	1,6
60	78	1,7	69	1,58
70	74	1,68	65	1,56
80	68	1,66	60	1,54

The Mifflin-St Jeor Equations 16 and 17 [26] were utilized to estimate the basal metabolic rate (M) across the subjects' lifespans, differing from the Harris and Benedict equations used in the literature [4, 3]. In these equations, it is possible to estimate the average metabolism ($\dot{M}$), considering age (a), sex (male and female), and height (h). For infants and babies, we used the relations of Silva and Annamalai [10]. The activity level, considering the sedentary level, is $PA = 1.2$.

$$\dot{M}_{male}[kcal/day] = PA \times (10 \cdot m[kg] + 6.25 \cdot h[cm] - 5 \cdot age[years] + 5) \tag{16}$$

$$\dot{M}_{female}[kcal/day] = PA \times (10 \cdot m[kg] + 6.25 \cdot h[cm] - 5 \cdot age[years] - 161) \tag{17}$$

3. Results and discussions

The destroyed exergy rate of a healthy individual is presented for males and females in Figure 3, bearing in mind that there is no effect of cancer on metabolism, as represented in Figure 2. Here, the healthy person's life expectancy and anthropometric data are plotted, showing an increase in the destroyed exergy rate until age 18, followed by a decrease over time. The difference between males and females at this age is around 12%.

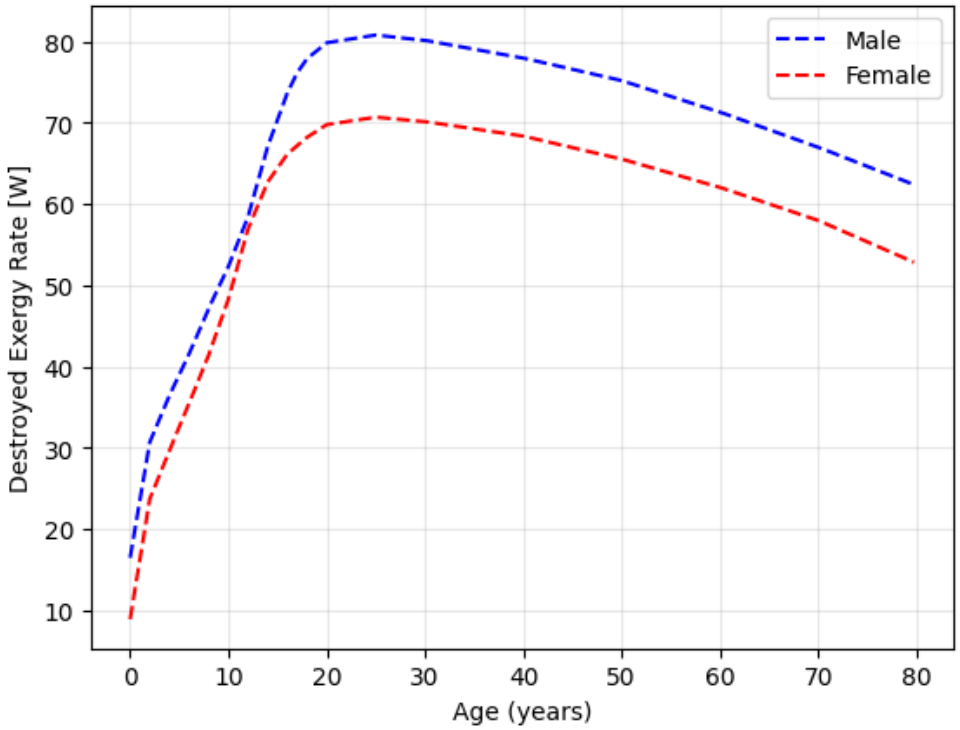

Figure 2: Destroyed exergy rate as a function of time throughout lifespan, considering Brazilian life expectancy

Figure 3 indicates the destroyed exergy integrated from the beginning of cancer cell appearance in the pancreas using Equation 1 to 4, only for the female subject. It is important to highlight that it is impossible to state when the cancer will begin; therefore, we have adopted 40 years as the reference age. There is a small amount of cancer at the beginning, where blood irrigates the cancerous cells (Figure 1) until the vessels are destroyed and there is no space for irrigation with oxygen (hypoxic conditions). The anaerobic conditions become more prominent and occur in a higher rate. In the Louzoun et al. [14] dynamical model, the cancer growth coefficient (k_c) was modulated linearly from 0.05 (representing a lower-grade, less aggressive state) to 0.1 (simulating a high-grade, aggressive malignancy). This linear increase in k_c acts as a driving force that intensifies the system's metabolic demand, and according to the Second Law of Thermodynamics, this increases the irreversibility rate (or destroyed exergy rate). It is important to understand the difference between receiving no treatment and receiving the best available treatment. No treatment offers a life expectancy of nearly 5 years, while the best treatment can extend survival to approximately 12 years.
This value is tracked throughout the lifespan to obtain the cumulative destroyed exergy in MJ/kg, which will be compared to the data on cancerous growth shown in Figure 4, leading to the exergetic age index. It is important to understand the difference between receiving no treatment and receiving the best available treatment. No treatment offers a life expectancy of nearly 5 years, while the best treatment can extend survival to approximately 12 years. The baseline is marked as healthy conditions.

The difference between Figures 4 and 5 is the removal of the cancer effect on the model. As stated,

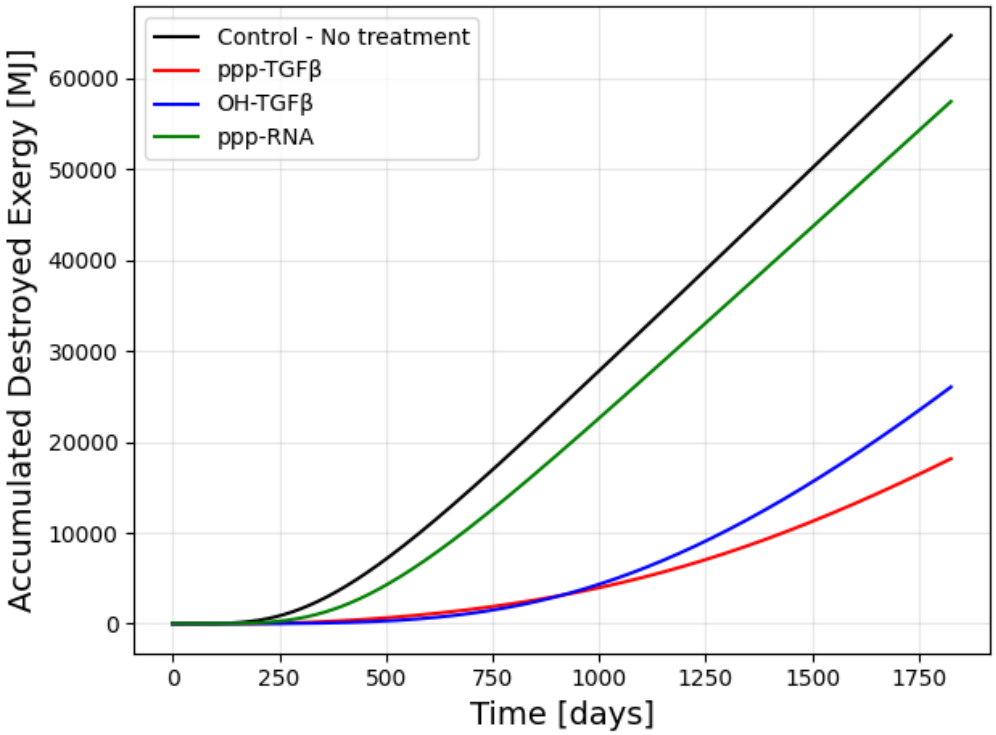

Figure 3: Destroyed exergy as a function of 5 years of four conditions of growth/treatment

approximately 15% to 20% of patients diagnosed with pancreatic cancer are candidates for surgical organ removal at the time of diagnosis. This low eligibility rate is primarily due to the disease's asymptomatic progression, which often leads to late-stage detection when the tumor has already achieved significant vascular involvement or distant metastasis. The results shown in Fugue 5 indicate that if the cancer is discovered and the treatments are conducted over 5 years, surgery for pancreas removal would increase lifespan by decades. No treatment in this case is considered as if the person did not discover the cancer. the cancer during this period would lead to a chronological death around 60 years old.

Based on the results of Henriques and Oliveira-Junior [4], we proposed Figures 6 and 7, where it is possible to compare the effect of cancer with no treatment (worst case), ppp-TGFβ (best treatment), and the normal development of a person without any pathology until the end of life expectancy (79.7 for females and 72.2 for males). These two figures are the same as Figures 4 and 5, but they show the effect of the second law on life expectancy for males and females. The justification for ppp-TGFβ treatment was that it is the optimal strategy to mitigate pancreatic cancer growth. It addresses the thermodynamic coupling between the malignant cells and their surrounding stroma (a dense, fibrous "shield" of connective tissue, cells, and extracellular matrix, collagen, that surrounds the tumor) as discussed by Liot et al. [27]. By inhibiting the TGF-β signaling axis, the treatment effectively exhausts the feedback loops that accelerate the k_c transition, thereby minimizing the 'entropic age' acceleration and preserving the structural and immunological resilience of the host system. Therefore, this treatment may be suggested as the best option when cancer is diagnosed and before surgery if the person is eligible.

4. Concluding remarks

In this work, we propose a thermodynamic model of human body metabolism over time and the effect of cancer growth on lifespan. Where it was possible to evaluate the cancer growth equations in the literature [14] with a complete thermodynamic model based on the second law of thermodynamics and its effect on chronological age and entropic (or exergetic) age. From this model, it was possible to conclude that:

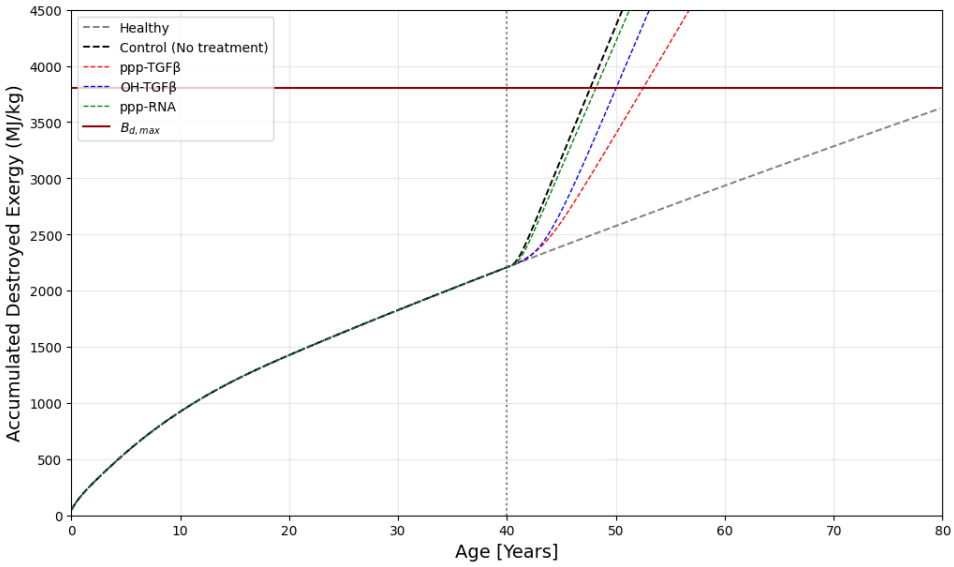

Figure 4: Destroyed exergy and a function of time of four conditions of growth/treatment

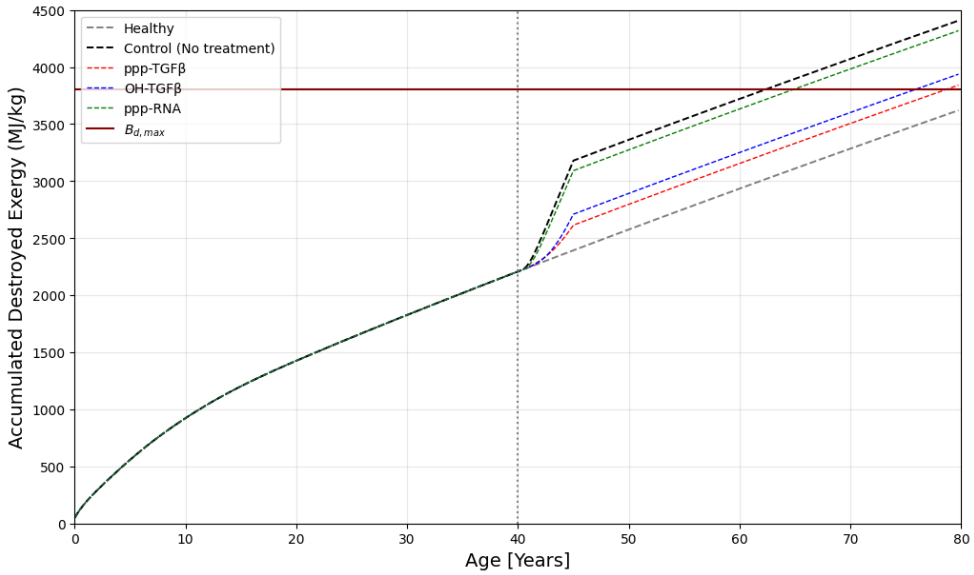

Figure 5: Destroyed exergy and a function of time of four conditions of growth/treatment and the effect of pancreas surgery removal on lifespan

- The model of cancer cell concentration over time indicates that the best treatment is the ppp-TGFβ. It does not allow 1 mL of tissue to be saturated with cancerous cells over 5 years.
- If the patient receives treatment, it can increase life expectancy by decades compared with no treatment, which is around 5 to 7 years.
- The combination of treatment and surgery is the best method to avoid cancer growth; the removal of an organ may lead to several other problems that are outside the scope of this article. The results indicate that there is less expenditure of exergetic age if the patient adopts this route, thereby decreasing life expectancy by a few years.

5. Acknowledgments

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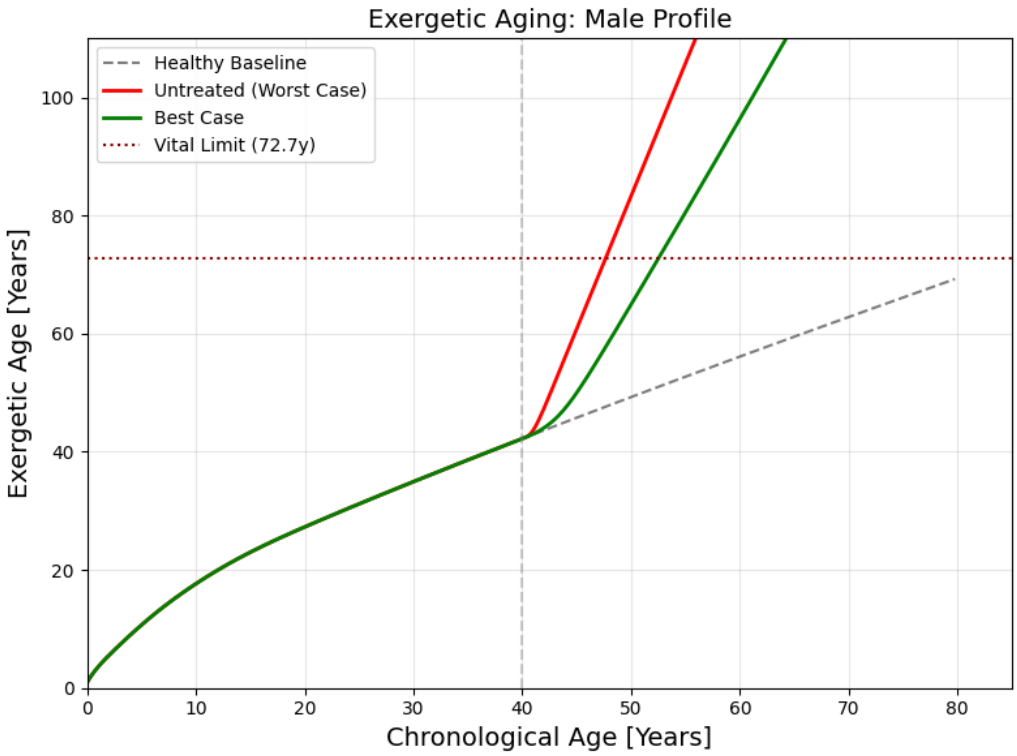

Figure 6: Exergetic age as a function of the physiological age for males

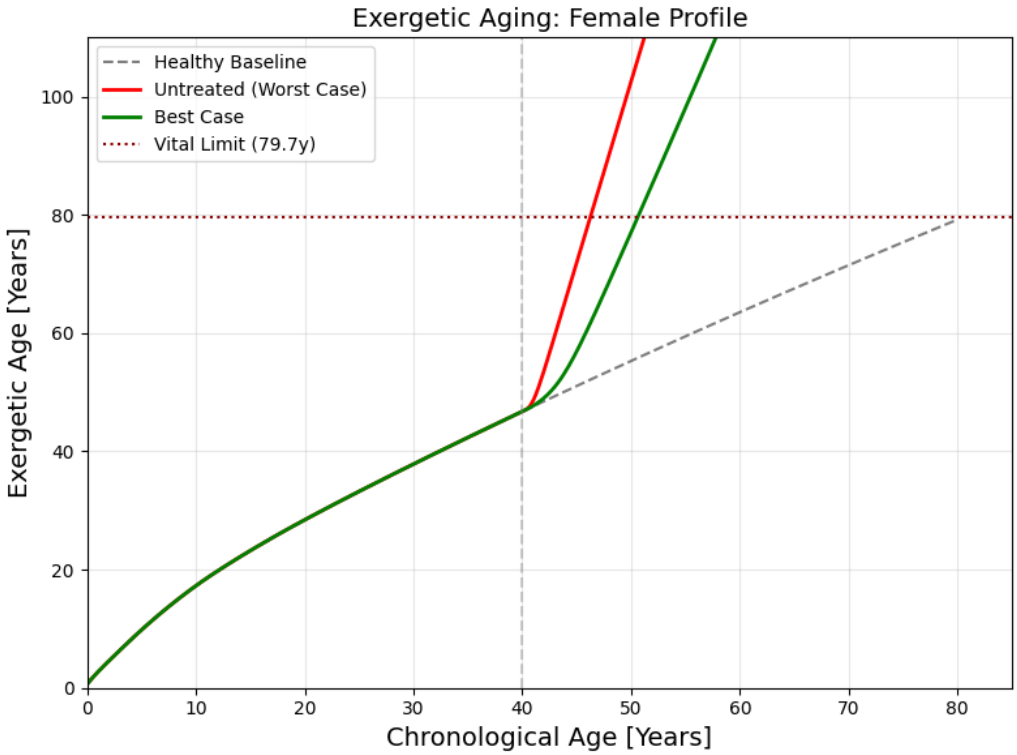

Figure 7: Exergetic age as a function of the physiological age for females

References

1. Mady CEK. Exergy Analysis: From Cells to Societies: A Unified Approach. Springer Nature, 2025
2. Lucia U, Grisolia G, Ponzetto A, and Deisboeck TS. Thermodynamic considerations on the role of heat and mass transfer in biochemical causes of carcinogenesis. Physica A: Statistical Mechanics and its Applications 2018; 490:1164–70
3. Silva ARd and de Oliveira Junior S. Exergy Analysis Applied to Tumor Growth. *Proceedings of ECOS 2022 - The 35th International Conference on Efficiency, Cost, Optimization, Simulation and Environmental Impact of Energy Systems*. Copenhagen, Denmark, 2022 Jul
4. Henriques IB and De Oliveira S. Tumour cells and life expectancy: an exergy approach. International Journal of Exergy 2020; 31:103–19
5. Hayflick L. Biological aging is no longer an unsolved problem. Annals of the New York academy of Sciences 2007; 1100:1–13
6. Schrodinger E. What is life?: With mind and matter and autobiographical sketches. Cambridge, UK: Cambridge University Press, 2012
7. Prigogine I and Wiame JM. Biologie et thermodynamique des phénomènes irréversibles. Experientia 1946; 2:451–3
8. Luo L. Entropy production in a cell and reversal of entropy flow as an anticancer therapy. Frontiers of Physics in China 2009; 4:122–36
9. Silva C and Annamalai K. Entropy generation and human aging: lifespan entropy and effect of physical activity level. Entropy 2008; 10:100–23
10. Annamalai K, Silva C, and Puri IK. Thermodynamics of biological systems. International Journal of Thermodynamics 2008; 11:25–37
11. Öngel ME, Yildiz C, Yilmaz B, and Özilgen M. Nutrition and disease-related entropy generation in cancer. International Journal of Exergy 2021; 34:411–23
12. Yildiz C, Semerciöz AS, Yalçınkaya BH, Ipek TD, Ozturk-Isik E, and Özilgen M. Entropy generation and accumulation in biological systems. International Journal of Exergy 2020; 33:444–68
13. Shamsabadipour A, Pourmadadi M, Davodabadi F, Rahdar A, and Ferreira LFR. Applying thermodynamics as an applicable approach to cancer diagnosis, evaluation, and therapy: A review. Journal of Drug Delivery Science and Technology 2023; 86:104681
14. Louzoun Y, Xue C, Lesinski G, and Friedman A. A mathematical model for pancreatic cancer growth and treatments. Journal of Theoretical Biology 2014; 351:74–82
15. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, Choné L, Francois E, Artru P, Biagi JJ, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. New England Journal of Medicine 2018; 379:2395–406
16. Mady C and Oliveira-Junior S. Human body exergy metabolism. International Journal of Thermodynamics 2013; 16:73–88
17. Alberty R. Thermodynamics of the Hydrolysis of Adenosine Triphosphate. Journal of Physical Chemistry 1994; 98:10281–7
18. Spanghero G, Albuqerque C, Lazzaretti T, Hernandez A, and Mady C. Exergy analysis of the musculoskeletal system efficiency during aerobic and anaerobic activities. Entropy 2018; 20:119
19. Alves EC and Mady CEK. Thermodynamic assessment of therapeutic hypothermia techniques for rehabilitation of post-cardiac arrest patients. Case Studies in Thermal Engineering 2020; 22:100752
20. Mady CEK, Albuquerque C, Fernandes TL, Hernandez AJ, Saldiva PHN, Yanagihara JI, and Oliveira Jr S de. Exergy performance of human body under physical activities. Energy 2013; 62:370–8

21. De Nevers N and Seader J. Lost work: A measure of thermodynamic efficiency. Energy 1980; 5:757–69
22. Chen M and Holmes K. Microvascular contributions in tissue heat transfer. Annals of the New York Academy of Sciences 1980; 335:137–50
23. Fornalski K. Non-equilibrium thermodynamics of cancer: Entropy dynamics and metastatic growth. Biochimica et Biophysica Acta (BBA) - General Subjects 2026; 1870:130898
24. Gold J. Cancer cachexia and gluconeogenesis. Annals of the New York Academy of Sciences 1974; 230:103–10
25. Pyrkov TV, Avchaciov K, Tarkhov AE, Menshikov LI, Gudkov AV, and Fedichev PO. Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts ultimate limit of human lifespan. bioRxiv 2019 :618876
26. Mifflin M, St Jeor S, Hill L, Scott B, Daugherty S, and Koh Y. A new predictive equation for resting energy expenditure in healthy individuals. The American Journal of Clinical Nutrition 1990; 51:241–7
27. Liot S, Balas J, Aubert A, Prigent L, Mercier-Gouy P, Verrier B, Bertolino P, Hennino A, Valcourt U, and Lambert E. Stroma involvement in pancreatic ductal adenocarcinoma: an overview focusing on extracellular matrix proteins. Frontiers in immunology 2021; 12:612271