



**HAL**  
open science

# Dynamic study of carbon-nitrogen competition between the malignant and secondary tumor for breast cancer in the metastasis process

José Alberto Rodrigues, João S Lopes

## ► To cite this version:

José Alberto Rodrigues, João S Lopes. Dynamic study of carbon-nitrogen competition between the malignant and secondary tumor for breast cancer in the metastasis process. 3rd Int'l Conference on Challenges in Engineering, Medical, Economics and Education: Research & Solutions (CEMEERS-24a), International Forum of Engineers & Practitioners, Mar 2024, Porto, France. <10.17758/EIRAI20>. <hal-04664701>

**HAL Id: hal-04664701**

**<https://hal.science/hal-04664701v1>**

Submitted on 31 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

# Dynamic study of carbon-nitrogen competition between the malignant and secondary tumor for breast cancer in the metastasis process

José A. Rodrigues and João S. Lopes

**Abstract** - Metastasis, a major cause of cancer treatment failure, remains poorly understood despite extensive research. This paper employs mathematical modelling to address the crucial question of how tumour cells, including those associated with breast cancer, survive, and initiate secondary growth in nutrient-limited environments. A four-equation model is developed, focusing on the competition between primary and metastatic tumours for carbon and nitrogen. Parameters are estimated from biological data, emphasizing the model's relevance to breast cancer metastasis. Results indicate that the carbon-to-nitrogen (C:N) ratio plays a pivotal role, with tumours having a higher optimal C:N ratio outcompeting others in nutrient-limited conditions. Comparative analyses with existing models are presented, and experimental validations, particularly in the context of breast cancer, are proposed. This study contributes insights into metastasis dynamics, laying the groundwork for further experimental exploration.

**Keywords** - Metastasis; Mathematical Modelling; Carbon-to-Nitrogen Ratio; Breast Cancer

## I. INTRODUCTION

### A. General overview on cancer biology and modelling

In Portugal, the most common cancers are colorectal, breast, and prostate cancer. In addition to being more prevalent, these cancers are responsible for a high number of deaths every year. However, they are not the only ones. Despite being less common, like the global scenario, lung and stomach cancer are among the deadliest cancers in our country. According to the International Agency for Research on Cancer (IARC), the estimated number of new cancer cases in Portugal - excluding non-melanoma skin cancers - was 36,835 in the year 2000, 43,284 in 2008, and increased to 58,199 in 2018. This represents a significant rise in the number of people affected by this disease. The evolution of different types of cancer positions Portugal among the more developed countries. [1]

Biotechnologies like microarray analysis and the Human Genome Project have unveiled traits essential to cancer. The six traits crucial for a cell to turn cancerous, forming the "Hallmarks of Cancer," include independent growth signals, resistance to antigrowth signals, illusion of programmed cell death, sustained angiogenesis, limitless replicative potential, and invasion for secondary growth [Hanahan and Weinberg 2000]. [2]

José Alberto Rodrigues (Author), CIMA and Mathematics Department of Instituto Superior de Engenharia de Lisboa, Portugal Email: Jose.rodrigues@isel.pt

João S. Lopes (Author), Master in Biomedical Engineering, Instituto Superior de Engenharia de Lisboa, Portugal

Optimal functioning of normal cells hinges on a steady supply of reduced carbon sources, essential for ATP production, building block synthesis, and maintaining reducing power. The accelerated growth of tumour cells elevates these fundamental needs, compelling an increased utilization of carbon sources. However, the expansion of solid tumours often outpaces their vascular support, resulting in inadequate carbon and nitrogen sources, as well as limited molecular oxygen availability.

To counter this challenge, angiogenesis emerges as a well-known adaptive strategy, although its heterogeneous nature contributes to uneven blood flow distribution, causing ischemic lesions within solid tumours. Consequently, the adaptation of cellular metabolism to cope with nutrient scarcity becomes a critical determinant in the progression and invasion of tumours. [3]

Tumour cell metabolism is characterized by two prominent features: the Warburg effect, illustrating their reliance on glucose, and glutaminolysis, emphasizing their dependence on glutamine.[4] Understanding and targeting these metabolic adaptations provide valuable insights for developing strategies to impede tumour progression.

Metastasis, a challenge in cancer treatment, remains mysterious. Mathematical modelling, like Saidel et al.'s [1976] [5], aids experimental research gaps. This paper explores a novel hypothesis, shifting from phosphorus to nitrogen as a limiting nutrient. The C:N ratio sheds light on optimal conditions for tumour growth and metastasis. The model also probes how metastasizing cells compete with those from the primary tumour, considering genotypic differences.

In summary, this paper delves into mathematical modelling to boost our grasp of metastasis, offering insights into tumour growth dynamics for advancements in cancer research and treatment.

### B. Breast Cancer - Challenge

In the intricate landscape of cancer metabolism, parallels between the metabolic profiles of cancer cells and normal proliferating cells have been identified. Both exhibit the use of aerobic glycolysis, selective expression of metabolic enzymes, and heightened amino acid consumption and biosynthesis. Tumor growth, akin to actively dividing tissues, necessitates continuous generation of macromolecule precursors. However, unlike microorganisms capable of synthesizing biomass from a single carbon source, mammalian cells, especially cancer cells, depend on a complex medium of essential carbon and nitrogen sources. The conditional essentiality of certain

substrates, such as glutamine and serine, further complicates the metabolic pathways analysis for cancer cells in both culture and likely in vivo settings. [3]

The central aim of cancer metabolism is to discern selectively activated metabolic pathways in tumor cells, particularly those crucial for biosynthesis, to unveil potential therapeutic targets. Achieving this goal requires quantifying differences in metabolic flux between transformed cells and their differentiated tissues of origin. Experimental approaches, ranging from direct examination of individual metabolite measurements to sophisticated computational models incorporating various data sources, are employed to infer metabolic trends. This challenging task involves exploring the effects of objective functions on metabolic phenotype and assessing the sensitivity of growth rate and other fluxes to perturbations.

## II. MATHEMATICAL METHOD

### A. Model and Equations

The model investigates the growth dynamics of primary  $p(t)$  and secondary  $s(t)$  tumours within a resource-dependent framework. Equations (1) and (2) describe the growth rates of primary and secondary tumours, respectively, influenced by the carbon-to-nitrogen ratio ( $V$ ). The parameter  $\beta_i$  reflects sensitivity to changes in  $V$ , representing the reciprocal of the optimal C:N ratio for tumour growth. Tumour cell death occurs from natural causes ( $\delta$ ) and nutrient-related factors, with the overall death rate ( $\sigma$ ) involving a Michaelis-Menten-like survival assumption tied to carbon concentration. Equations (3) and (4) depict the dynamics of carbon and nitrogen concentrations, incorporating nutrient influx, natural depletion, and tumour cell sequestration. The model assumes constant blood nutrient concentrations maintained by the body. Various parameters, including  $\alpha_i$ ,  $\gamma_i$ ,  $\omega_i$ , and  $\beta_i$ , can be altered to simulate different scenarios and investigate the impact of genotypic differences on tumour growth and competition dynamics. Overall, the model aims to identify key parameters influencing tumour growth and competition for experimental focus.

$$\frac{dp}{dt} = \left[ \alpha_1 V e^{-\beta_1 V} - \left( d_{max,1} - \frac{\sigma_1 c(t)}{K_{d,1} + c(t)} \right) - \delta \right] p(t), \quad (1)$$

$$\frac{ds}{dt} = \left[ \alpha_2 V e^{-\beta_2 V} - \left( d_{max,2} - \frac{\sigma_2 c(t)}{K_{d,2} + c(t)} \right) - \delta \right] s(t), \quad (2)$$

$$\frac{dc}{dt} = \lambda_c [C_B - c(t)] - \gamma_1 (\alpha_1 V p(t) e^{-\beta_1 V}) - \gamma_2 (\alpha_2 V s(t) e^{-\beta_2 V}), \quad (3)$$

$$\frac{dn}{dt} = \lambda_N [N_B - n(t)] - \omega_1 p(t) n(t) - \omega_2 s(t) n(t), \quad (4)$$

$$V = \frac{c(t)}{n(t) + \varepsilon}. \quad (5)$$

**Table 1:** The model's dependent variables, their biological interpretation, and their units.

Variable	Biological Interpretation	Units
$p(t)$	Mass of the primary tumor	grams (g)
$s(t)$	Mass of the secondary tumor	grams (g)
$c(t)$	Carbon concentration	moles per liter (M)
$n(t)$	Nitrogen concentration	moles per liter (M)

**Table 2:** The model's parameters, their biological interpretation, and their units.

Parameter	Value	Units
$\alpha_1$	0.05	(days) <sup>-1</sup>
$\alpha_2$	0.05	(days) <sup>-1</sup>
$d_{max,1}$	1.00	(days) <sup>-1</sup>
$d_{max,2}$	1.00	(days) <sup>-1</sup>
$\sigma_1$	1.00	(days) <sup>-1</sup>
$\sigma_2$	1.00	(days) <sup>-1</sup>
$K_{d,1}$	0.5	moles per liter (M)
$K_{d,2}$	0.5	moles per liter (M)
$\delta$	0.01	(days) <sup>-1</sup>
$\lambda_c$	19.0	(days) <sup>-1</sup>
$\lambda_N$	6.4	(days) <sup>-1</sup>
$\varepsilon$	0.00001	adimensional

**Table 3 - Fixed parameters, their value, and their units.**

Parameter	Biological Interpretation	Units
$\alpha_i$	Per capita growth rate of tumor i	(days) <sup>-1</sup>
$\beta_i$	Sensitivity of growth rate of tumor i to variations in the C:N ratio	adimensional
$d_{max,i}$	Maximum death rate due to nutrient limitation for tumor i	(days) <sup>-1</sup>
$\sigma_i$	Per capita death rate due to nutrient limitation for tumor i	(days) <sup>-1</sup>
$K_{d,i}$	Nutrient concentration at half the maximum death rate for tumor i	moles per liter (M)
$\delta$	Death rate due to causes unrelated to nutrient deprivation for tumor i	(days) <sup>-1</sup>
$\lambda_c$	Rate of carbon influx into the environment	(days) <sup>-1</sup>
$\lambda_N$	Rate of nitrogen influx into the environment	(days) <sup>-1</sup>
$C_B$	Interstitial carbon concentration	moles per liter (M)
$N_k$	Interstitial nitrogen concentration	moles per liter (M)
$\gamma_i$	Carbon sequestration rate for tumor i	moles per (g-liter)
$\omega_i$	Nitrogen sequestration rate for tumor i	(g-days) <sup>-1</sup>

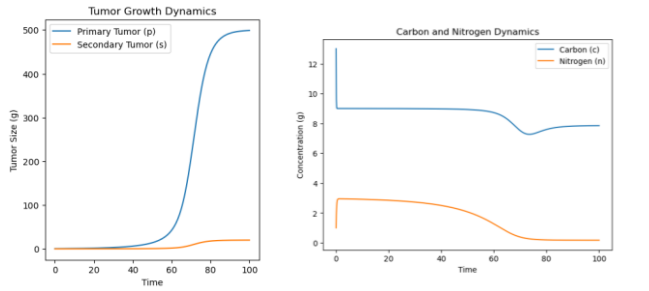
### B. Parameterization and Numerical investigation

In the numerical investigation of the model, specific parameters were kept constant, including an initial primary tumor size of 0.5 g and an initial secondary tumor size of 0.02 g, following previous studies and the assumption that the mass of the secondary tumor will not be very large, but sufficient to enter the competition model [6]. The smaller size of the secondary tumor is assumed to reflect its later development.

Initial carbon and nitrogen concentrations were set to achieve a percentage of 13:1 of total biomass, respectively, based on human body glutamine contribution evidence and its uptake on the Human body. [4] The reciprocal of the optimal C:N ratio for growth ( $\beta_i$ ) was initially set at 0.077. Per capita growth rates for both tumors were initially assumed to be 0.05, later adjusted based on evidence suggesting different growth rates. Carbon influx into the body ( $\lambda_C$ ) was assumed to be three times greater than nitrogen influx ( $\lambda_N$ ), supported by protein composition data. Speculative values for other parameters were within an order of magnitude of known values from relevant literature.

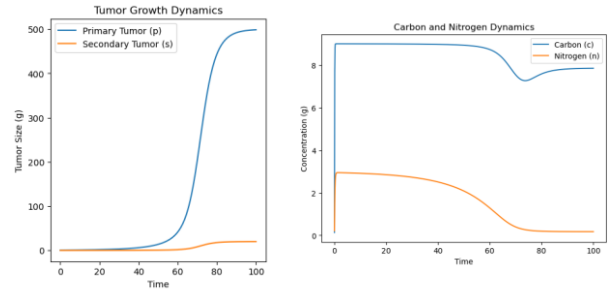
The chosen method to study the model dynamics involved changing various parameters to observe their impact on overall tumour dynamics. While assessing the overall effects of one parameter, other values were held steady. This approach aimed to identify crucial parameter values influencing tumour growth and competition dynamics.

### C. Simulated Data - Breast Cancer

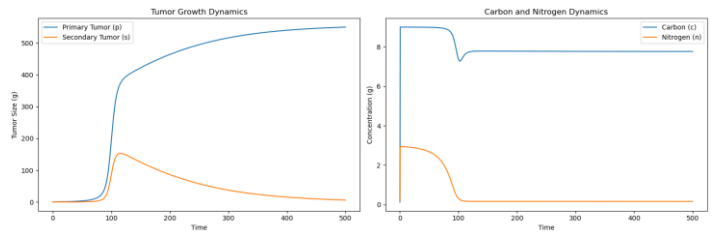


**Figure 1** - Tumour competition occurs within a framework of homeostatic C:N ratios at 3:1 (equivalent to 9.0 for carbon and 3.0 for nitrogen). This competition is characterized by the interplay of (a) tumour growth dynamics, (b) carbon dynamics, and nitrogen dynamics. The dynamics are further delineated as follows ( $\beta_1 = \beta_2 = 0.077$ ,  $\gamma_1 = \gamma_2 = 0.20$ ,  $\omega_1 = \omega_2 = 1$ ).

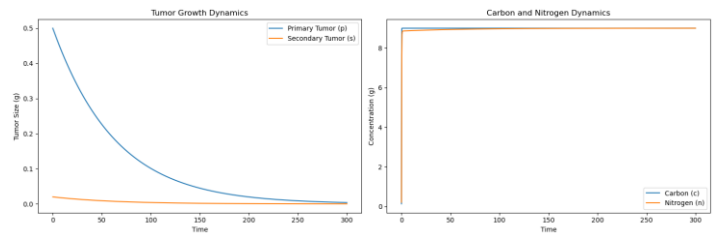
The initial composition of total biomass involved carbon and nitrogen concentrations, designed to reflect a specific percentage distribution. In accordance with evidence related to glutamine contribution in the human body and its uptake, the concentrations were established at 25.7% for carbon and 41.6% for nitrogen, aiming to achieve a proportional ratio in the total biomass [7], particularly relevant in the context of breast cancer research.



**Figure 2** – Breast tumour competition occurs within C:N percentages of 25.7% and 41.6% of total biomass, respectively. This competition is characterized by the interplay of (a) tumour growth dynamics, (b) carbon dynamics, and nitrogen dynamics. The dynamics are the same as figure 1.



**Figure 3** – Breast tumour competition occurs within C:N ratio similar to figure 2. This competition is characterized by the interplay of (a) tumour growth dynamics, (b) carbon dynamics, and nitrogen dynamics. The dynamics are further delineated as follows  $\beta_1 = 0.0693$ ,  $\beta_2 = 0.077$ ,  $\alpha_1 = 0.4$ ,  $\alpha_2 = 0.5$ .



**Figure 4** – Breast tumour competition occurs C:N ratio similar to figure 2. This competition is characterized by the interplay of (a) tumour growth dynamics, (b) carbon dynamics, and nitrogen dynamics. The dynamics are the same as figure 2, except  $C_B = N_k = 9$

#### D. Discussion

The drop in carbon concentration at 70 days as seen in Figure 1 and 2 is likely due to the competition between the two tumors for nutrients. As the primary tumor grows, it consumes more and more carbon and nitrogen, leaving less for the secondary tumor. This can lead to a decrease in the carbon concentration of the medium, which can in turn slow down the growth of the secondary tumor.

Figure 3 unveils a compelling dynamic where in the primary tumor, marked by a slower growth rate and a heightened optimal C:N ratio relative to the secondary tumor, exhibits a noteworthy survival advantage. In simpler terms, although the primary tumor grows more gradually, it displays a superior nutrient efficiency with reduced nitrogen requirements per unit of carbon. The secondary tumor's accelerated growth proves advantageous in environments with a smaller C:N ratio, but it plateaus at 150 g, succumbing to an unfavorable C:N ratio that hampers sustained growth. Meanwhile, the primary tumor steadily progresses, reaching 580 g and maintaining its mass, owing to its ability to thrive with lower nitrogen levels due to its higher optimal C:N ratio. The results underscore the significance of a tumor's optimal C:N ratio over its per capita growth rate in determining survival outcomes.

Figure 4 demonstrates that when the levels of carbon and nitrogen in the surroundings are equal, the tumor's utilization of nitrogen becomes notably inefficient. Tumor cells expend substantial energy while eliminating excess nitrogen that they cannot effectively utilize. The inefficiency in this process leads to the rapid demise of the tumors. This inference is drawn from the fact that the carbon-to-nitrogen ratio in the environment is 1.0, contrasting with the tumors' optimal C:N ratio, which is significantly higher than 1.0 due to the small value of  $\beta_i$ . This inefficiency can be exploited to treat tumors with inhibitors. Inhibitors are drugs that can block the enzymes that tumors use to process nitrogen. By blocking these enzymes, we can make it even more difficult for tumors to utilize nitrogen, which can lead to their death.

### III. CONCLUSION

In conclusion, this paper utilizes mathematical modelling to explore the dynamics of metastasis, with a specific emphasis on breast cancer. By investigating the competition between primary and secondary tumours for nutrients, the study underscores the pivotal role of the carbon-to-nitrogen (C:N) ratio in influencing tumour growth. The findings offer insights into breast cancer progression, revealing those tumours with a higher optimal C:N ratio demonstrate a survival advantage. This focused analysis contributes to the broader understanding of breast cancer metabolism and provides a foundation for potential therapeutic interventions. The study's implications extend to advancements in breast cancer research, offering a tailored perspective on the metabolic adaptations of tumour cells in nutrient-limited environments.

#### APPENDIX

Simulation data and analysis on :  
<https://github.com/joaoslopes11/Study-of-Malignant-and-Secondary-Tumor-Dynamics-effect-on-the-metastasis-process> (Jupyter - Python)

#### ACKNOWLEDGMENT

This research was partially sponsored with national funds through the Fundação Nacional para a Ciência e Tecnologia, Portugal-FCT, under projects UIDB/04674/2020 (CIMA).

<https://doi.org/10.54499/UIDB/04674/2020>

#### REFERENCES

- [1] Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.
- [2] Hanahan, D., Weinberg, R. (2000). The hallmarks of cancer. *Cell* 100, 57-70
- [3] Bartlome, S., Berry, C.C. Recent insights into the effects of metabolism on breast cancer cell dormancy. *Br J Cancer* 127, 1385–1393 (2022).
- [4] Winkler, Jonathan Alexander. "A mathematical model of competition for nutrients between malignant and secondary tumors." Arizona State University (2005).
- [5] Sidel, G., Liotta, L., Kleinerman, J. (1976). System dynamics of a metastatic process from an implanted tumor. *Journal of Theoretical Biology* 56, 417-434
- [6] Pescarmona, G.P., Scalerandi, M., Delsanto, P.P., Condat, C.A. (1999) Non-linear model of cancer growth and metastasis: a limiting nutrient as a major determinant of tumor shape and diffusion. *Medical Hypotheses* 53, 497-503
- [7] Keibler, M.A., Wasylenko, T.M., Kelleher, J.K. *et al.* Metabolic requirements for cancer cell proliferation. *Cancer Metab* 4, 16 (2016).