Neurons, Lymphatics and Cancer: modelling a dangerous trio

Μαστρογιάννη Μαρία

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Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

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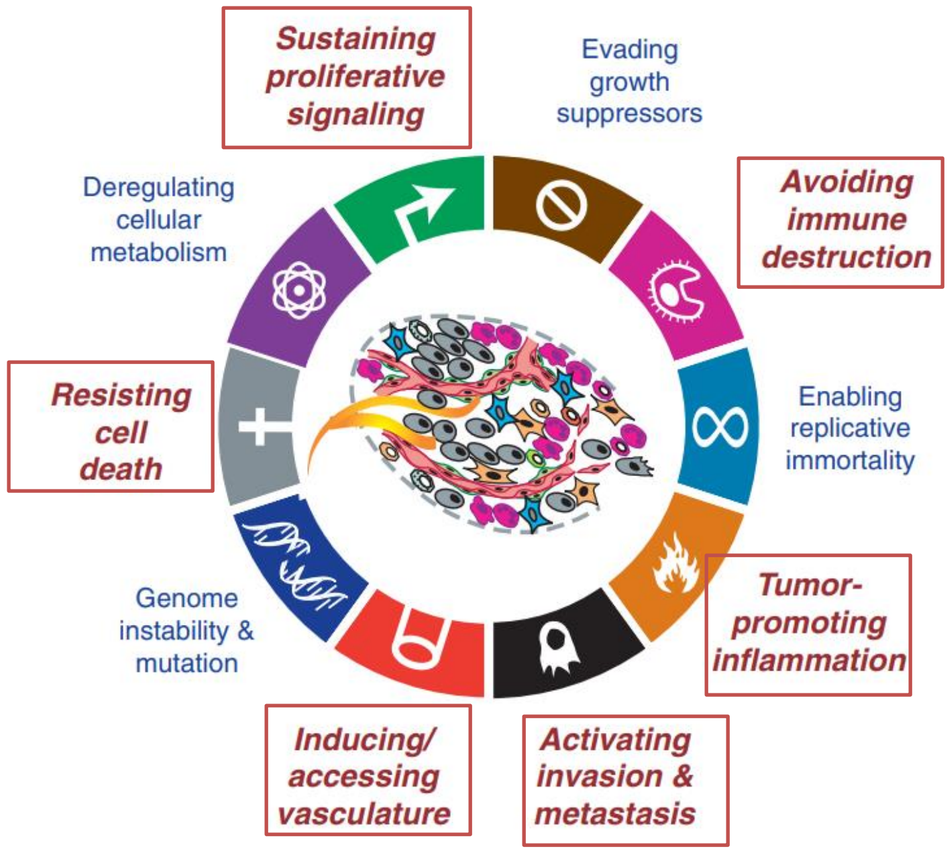
Overview

- Introduction to the field of Cancer Neuroscience
- The role of Perineural Invasion
- Mathematical modelling of Perineural Invasion (PNI)
- Simulations
- Discussion and future direction

Cancer Neuroscience



The nervous system influences six of the fundamental characteristics that make up the core hallmarks[2].

- New field of research entitled cancer neuroscience.
- Recent evidence indicates that the nervous system plays a central role in cancer pathogenesis[2].

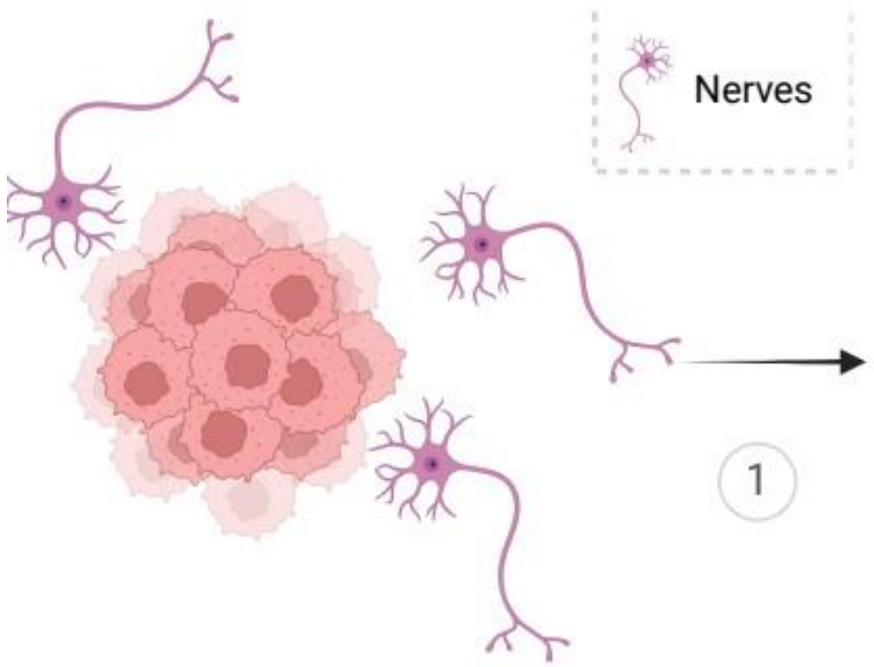
1)Hanahan, D., & Monje, M. (2023). Cancer hallmarks intersect with neuroscience in the tumor microenvironment. *Cancer Cell*, *41*(3), 573-580.
2)Monje, M., Borniger, J. C., D'Silva, N. J., Deneen, B., Dirks, P. B., Fattahi, F., ... & Winkler, F. (2020). Roadmap for the emerging field of cancer neuroscience. *Cell*, *181*(2), 219-222.

Perineural Invasion

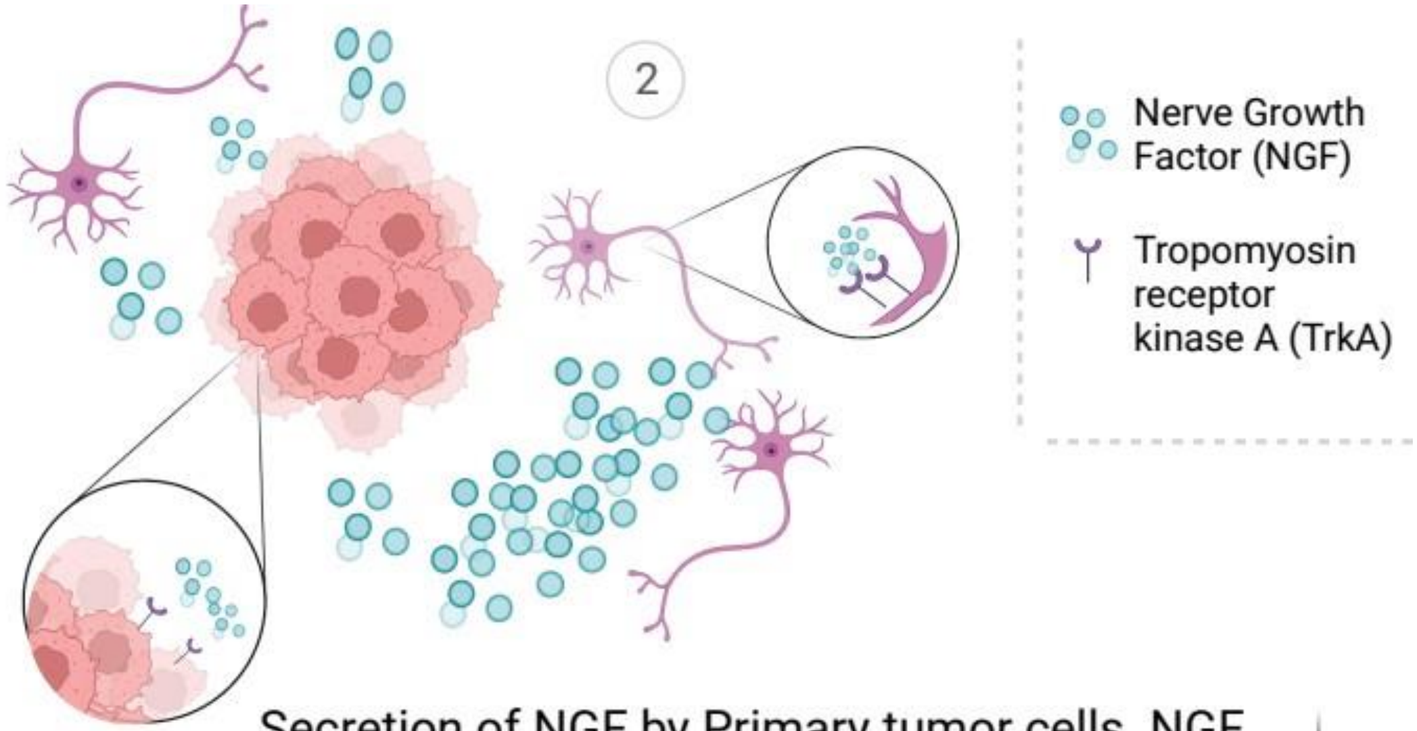
- The ability of tumor cells to proliferate around nerves and to invade them[3]
- Marker of poor prognosis[2]
- Has been reported in a variety[1] of cancers, including colorectal , pancreatic, prostate cancer etc.

1) Amit, M., Na'Ara, S., & Gil, Z. (2016). Mechanisms of cancer dissemination along nerves. Nature reviews Cancer, 16(6), 399-408
2) Magnon C. Role of the nerves in the tumor microenvironment. Prog Mol Biol Transl Sci. 2015;131:151-175
3) Wang, W., Li, L., Chen, N., Niu, C., Li, Z., Hu, J., & Cui, J. (2020). Nerves in the tumor microenvironment: origin and effects. Frontiers in Cell and Developmental Biology, 8, 601738

Mechanism of Perineural Invasion

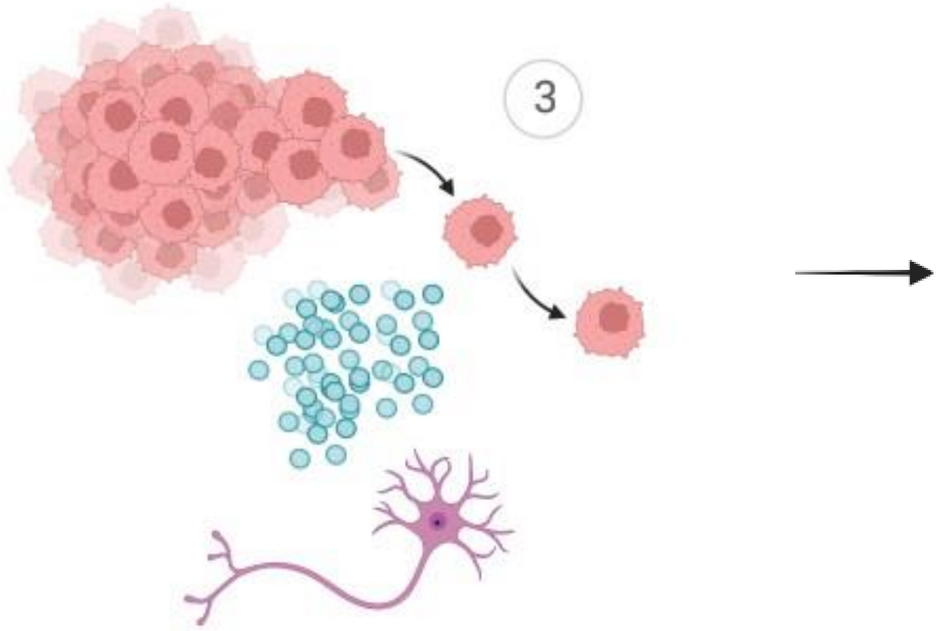


Nerves around tumor microenviroment.

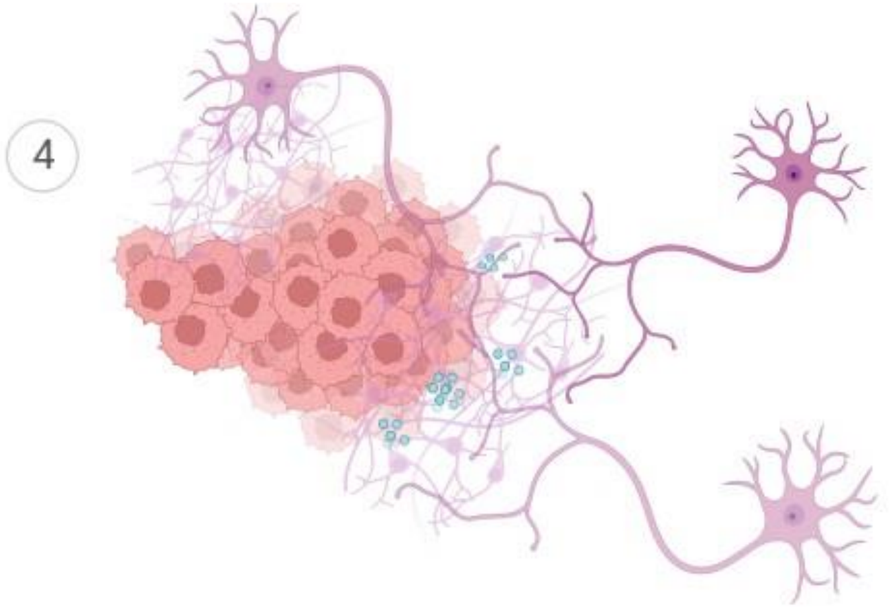


Secretion of NGF by Primary tumor cells. NGF binds to the receptors of both Nerves and Primary tumor cells enhancing PNI.

Mechanism of Perineural Invasion



Tumor cells detatching from the main mass and circulating the nerve whilst proliferating.



Cancer cells spread along and through nerves.

Mathematical Model

$$\frac{dG}{dt} = s_P T_p + s_i T_i N - d_G\, G - \gamma_T (T_p + T_i) G - \gamma_N N G$$

$$\frac{dTi}{dt} = pi(\mu_0 + \mu_1 G) T_p - d_T Ti$$

$$\frac{dTp}{dt} = (r_{Tp} + \frac{G}{\tau_1 + \tau_2 G}) T_p - pi(\mu_0 + \mu_1 G) T_p - d_T T_p$$

$$\frac{dN}{dt} = \nu_N G N + r_N \left(1 - \frac{N}{K_n}\right) N - d_N (T_p + T_i) N$$

Initial Conditions	
T_p	5000
T_i	0
G	0
N	2.575

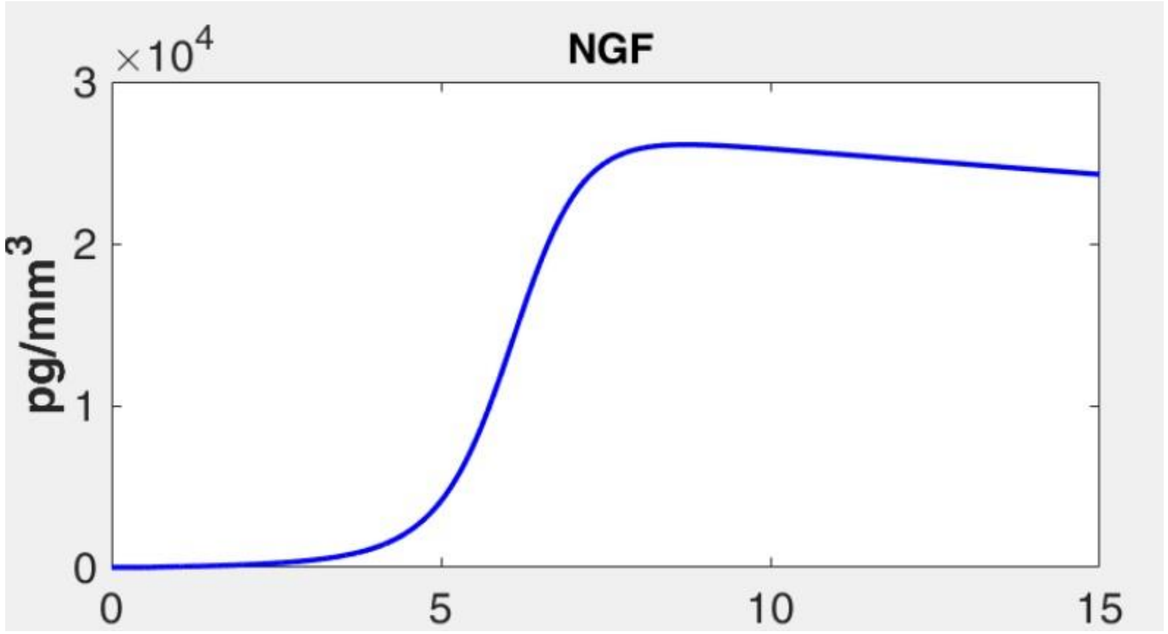
Parameters Estimation

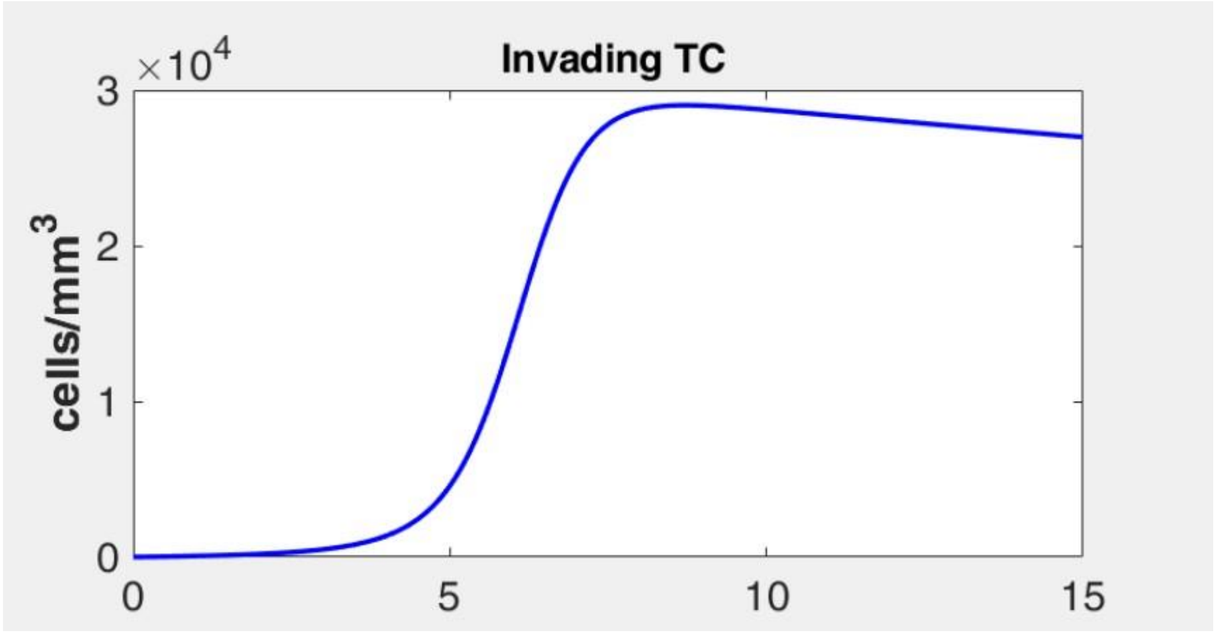
Parameter [1]	Value	Units
s_p	$2.22\text{x}10^{-3}$	pg $cell^{-1}day^{-1}$
s_i	4.5x10-2	$pgmm^3(daycell^2)^{-1}$
d_G	22.18	day^{-1}
γ_T	$5.57\text{x}10^{-5}$	$cells^{-1}\ day^{-1}$
γ_N	$5\text{x}10^{-2}$	$cells^{-1}\ day^{-1}$
p_i	0.05	
μ_0	0.22	day^{-1}
μ_1	0.00173	$mm^3\ day^{-1}\ pg^{-1}$

Parameter [1]	Value	Units
d_T	$1.27\text{x}10^{-2}$	day^{-1}
r_{Tp}	$4.81\text{x}10^{-4}$	day^{-1}
τ_1	134.27	$pgday(mm^3)^{-1}$
τ_2	2.39	day
ν_n	10.85	$pg(daymm^3)^{-1}$
r_n	0.06	day^{-1}
k_n	0.26	$(cells/mm^3)^{-1}$
d_N	0.0000035	$(cells/mm^3)^{-1}day^{-1}$

1) Lolas, G., Bianchi, A., & Syrigos, K. N. (2016). Tumour-induced neoneurogenesis and perineural tumour growth: a mathematical approach. *Scientific reports*, *6*(1), 1-10.

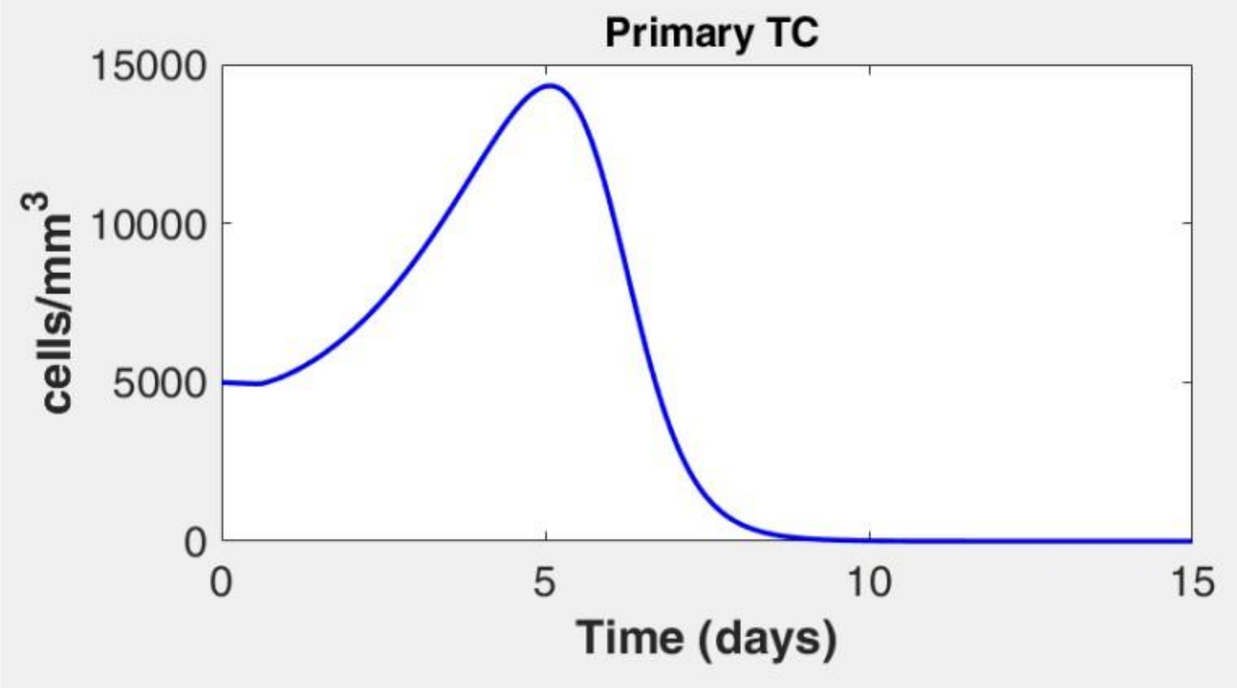
Simulations – “go or grow” hypothesis

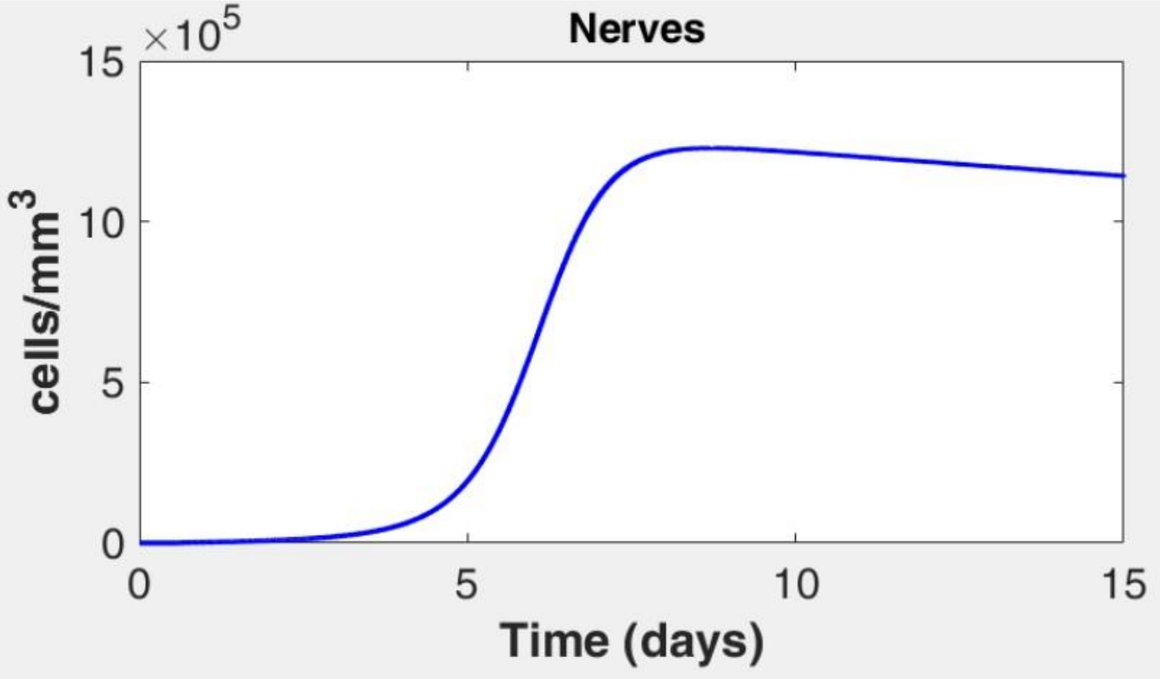




Similar pattern between Invading tumor cells and Nerve growth factor as a result of the secretion of NGF by Primary tumor cells.

Simulations – “go or grow” hypothesis





Primary tumor cells are over proliferating until day 5 (go or grow hypothesis) and then decrease due to migration. The pattern of nerves seen in the graph suggests that nerves initially increase in density in response to the presence of cancer cells (Neurogenesis). After that, the density of nerves begins to decline slightly, possibly due damage caused by the invasion of cancer cells.

Mathematical Model - Adding Lymphatics

$$\frac{dG}{dt} = s_P T_p + s_i T_i N - d_G\, G - \gamma_T (T_p + T_i) G - \gamma_N N G$$

$$\frac{dTi}{dt} = pi(\mu_0 + \mu_1 G) T_p - d_T Ti \boxed{+\mu_2 L T p}$$

$$\frac{dTp}{dt} = (r_{Tp} + \frac{G}{\tau_1 + \tau_2 G}) T_p - pi(\mu_0 + \mu_1 G) T_p - d_T T_p \boxed{-\mu_2 L T p}$$

$$\frac{dN}{dt} = \nu_N G N + r_N \left(1 - \frac{N}{K_n}\right) N - d_N (T_p + T_i) N$$

$$\frac{dL}{dt} = r_L \left(1 - \frac{L}{k_L}\right) + \frac{V}{\lambda_1 + \lambda_2 V} L$$

$$\frac{dV}{dt} = s_V T_p - d_V V - \gamma_V L V$$

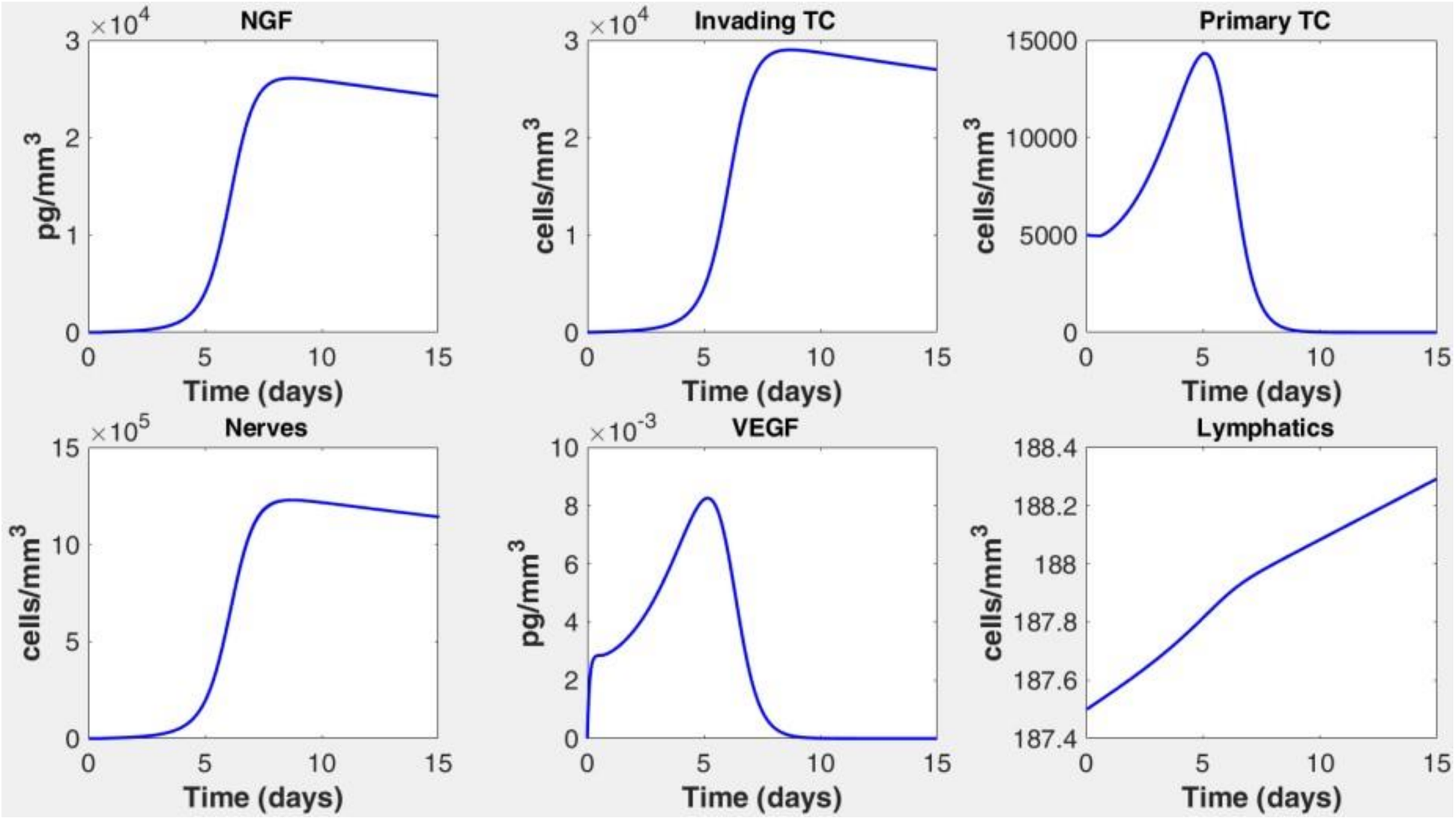
We add the term $-\mu_2 L T p$ to the Tp equation and $+\mu_2 L T p$ to the Ti equation, in order to represent tumor cells escaping the primary site through the lymphatics.

Parameters Estimation

Parameter [1]	Value	Units
s_V	6.5×10^{-6}	pg $cell^{-1} day^{-1}$
d_V	11	day^{-1}
γ_V	1.4×10^{-3}	$mm^3 cells^{-1}\ day^{-1}$
r_L	0.042	day^{-1}
k_L	18.52×10^5	cells day $(mm^3)^{-1}$
μ_2	4.8×10^{-8}	$cell day^{-1}$
λ_1	42	day
λ_2	4.1	pg day mm^3

1) Bianchi, A., Painter, K. J., & Sherratt, J. A. (2015). A mathematical model for lymphangiogenesis in normal and diabetic wounds. *Journal of theoretical biology*, *383*, 61-86.

Results after the addition of VEGF (V) and Lymphatic Endothelial Cell (L)



Discussion and future directions

- We presented the first attempt of modelling tumor cells, nerves and lymphatics interactions in PNI
- We managed to capture the *go or grow* hypothesis of the tumor cells based upon the interactions with the neurons
- We will further investigate these interactions by including other tumor microenviromental factors such as macrophages, fibroblasts etc.
- Provides a fundamental basis for further examination of the interactions that occur during perineural invasion

Acknowledgments

Dr. Arianna Bianchi , Dr. Georgios Lolas
and Prof. Konstantinos Syrigos

Thank you for your attention!