Mathematical model of brain tumour

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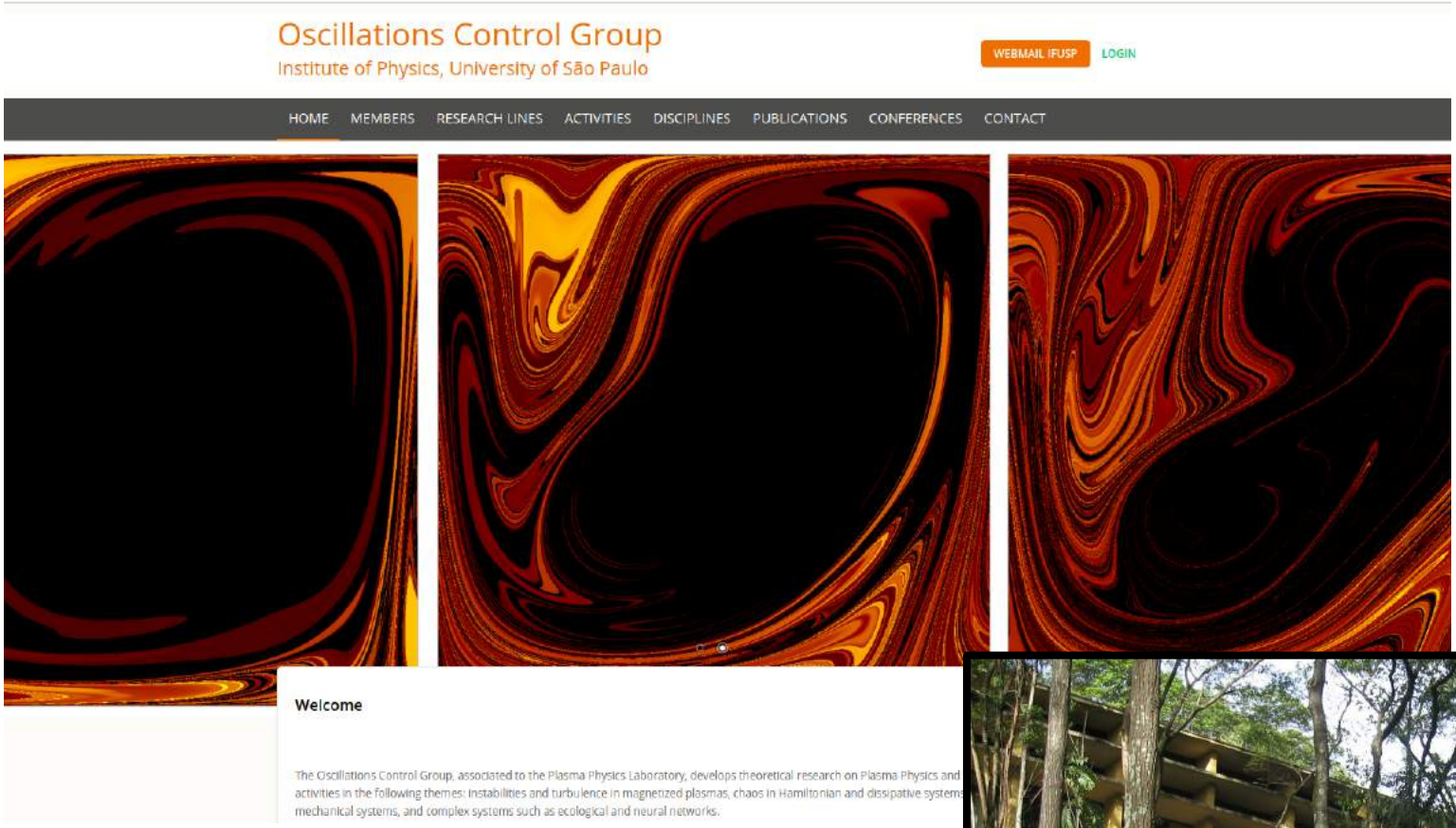
FAPESP SÃO PAULO RESEARCH FOUNDATION



http://portal.if.usp.br/controle/

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https://www.105groupscience.com/about-us

105 GROUP Science

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Alzheimer's and Parkinson's diseases, Epilepsy, Autism

Plasticity (STDP, STP)

Different topologies

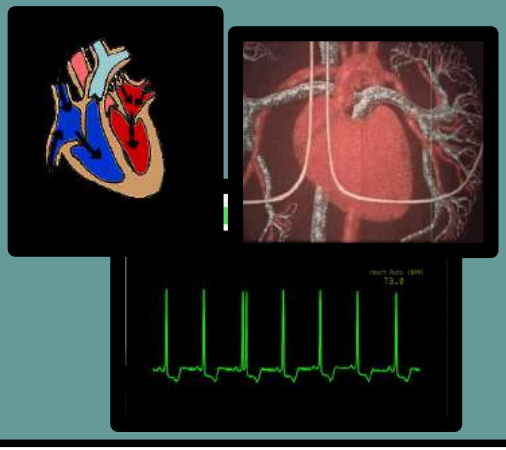
Neuronal models

Cancer models

Cells proliferation

Chemotherapy

Brain tumours

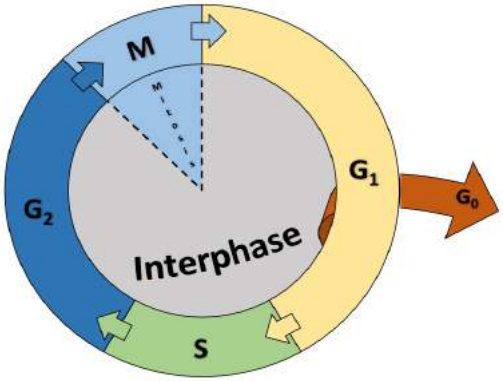


Reconstruction of signals

Electrocardiogram analyzes

Heartbeat models

Mother Cell → 2-cell copies → Normal case (Hayflick Limit (50 x)) / Abnormal case



G1: 12 h
S: 7 - 8 h
G2: 3 - 4 h
M: 1 - 2 h
Total: 24 h

Cicle cell:

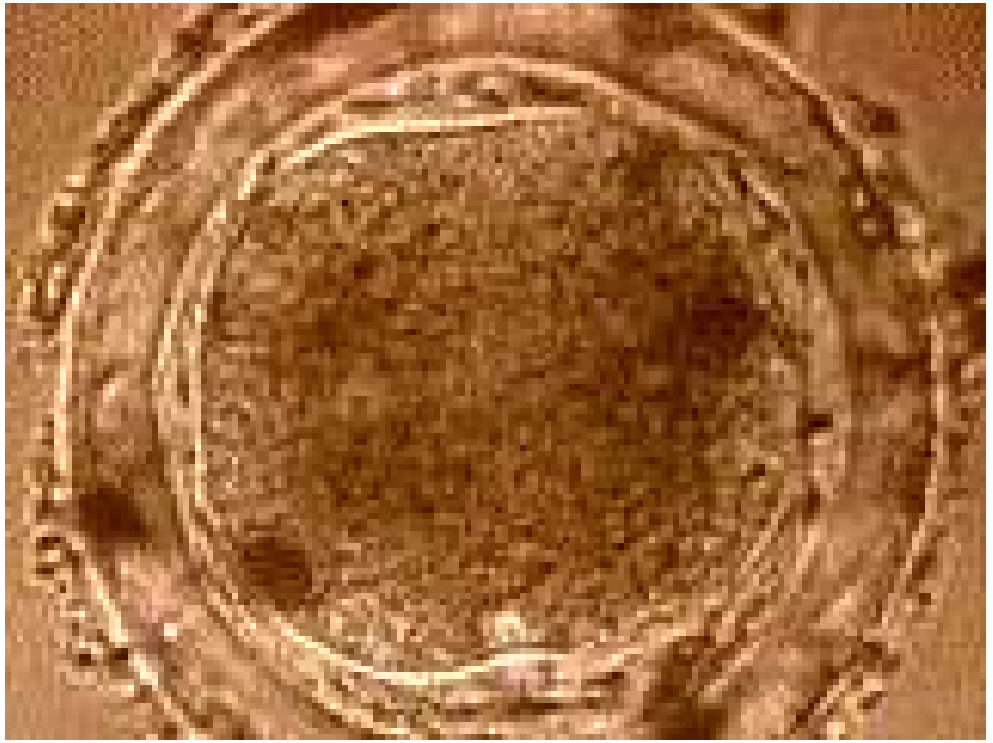
G0 - left the cycle and has stopped dividing.

G1 – Cells increase in size in G1 (control mechanism ensures that everything is ready for DNA synthesis).

S – DNA replication.

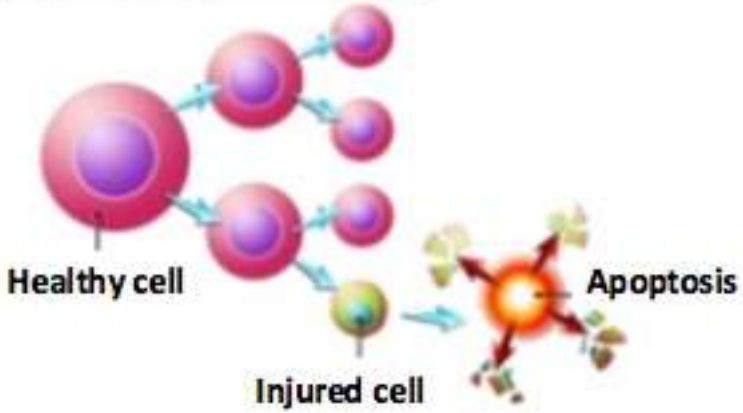
G2 – Cell will continue to grow (control mechanism M phase and divide).

M – Cell growth stops, cellular energy is focused on the orderly division into two daughter cells.

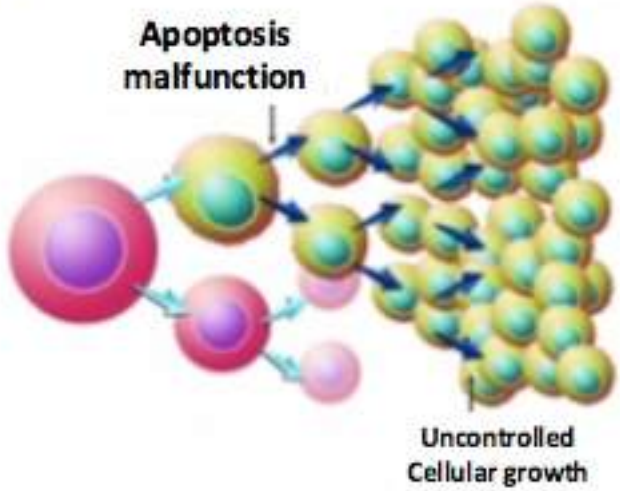


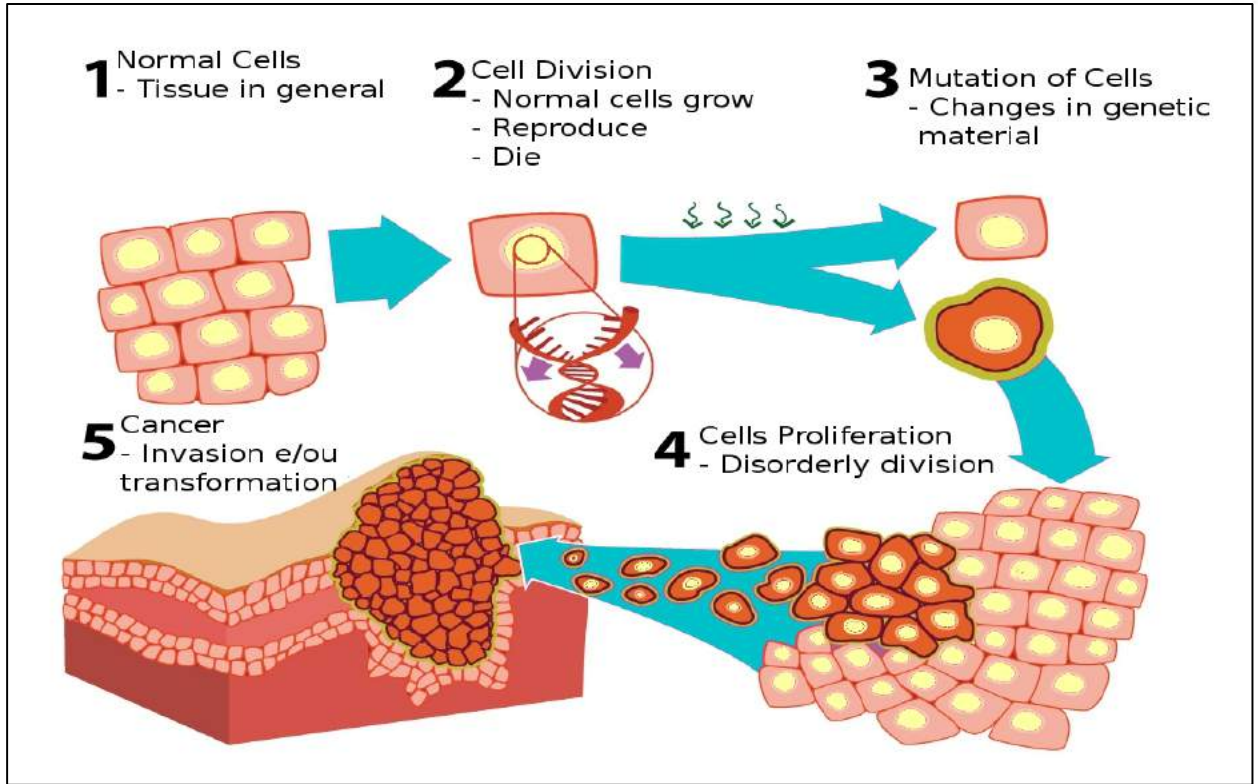
Communications in Nonlinear Science and Numerical Simulations, **v. 70**, p. 307-317, 2019.

Normal Cell Division



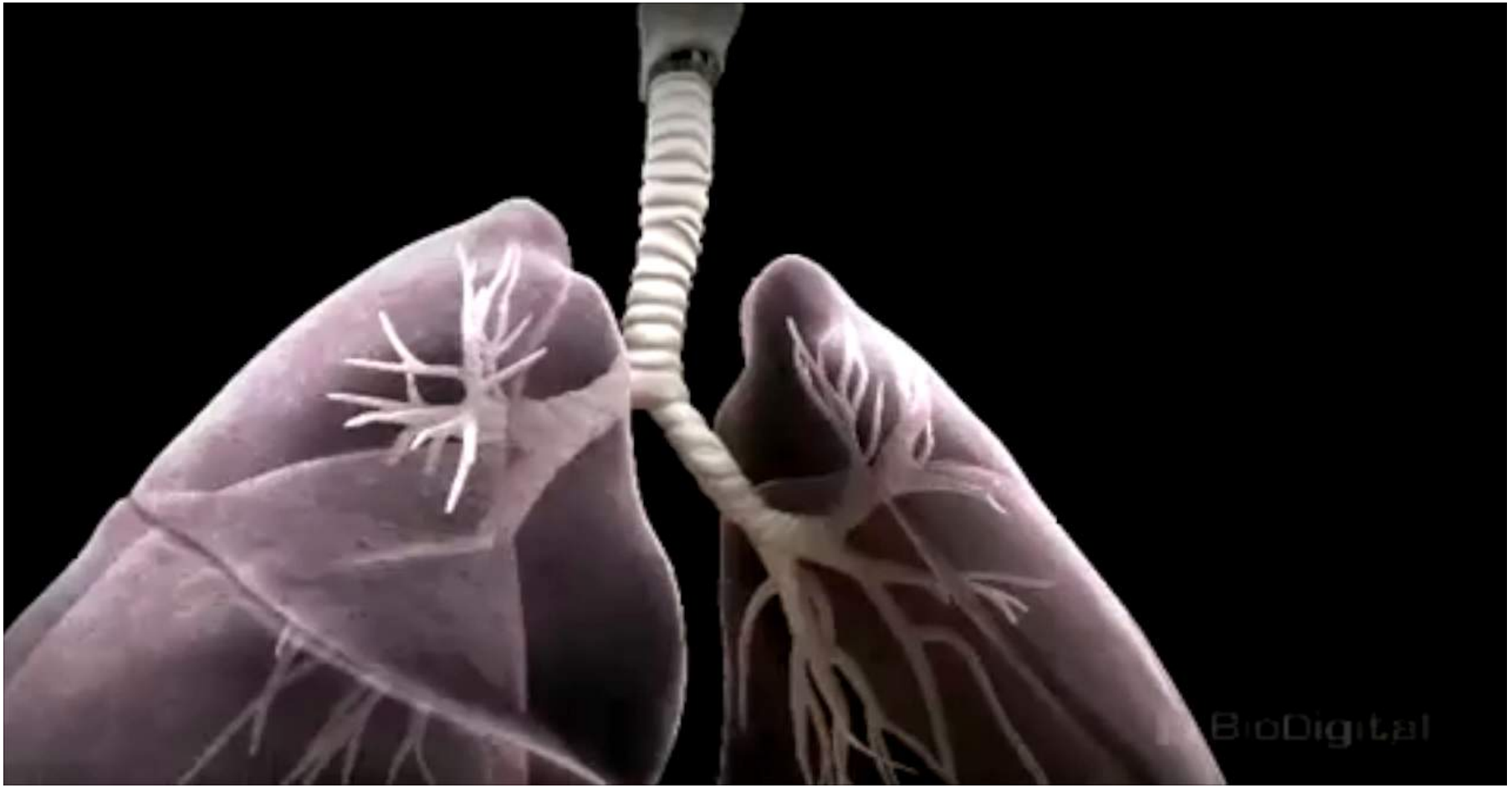
Cancer Cell Division





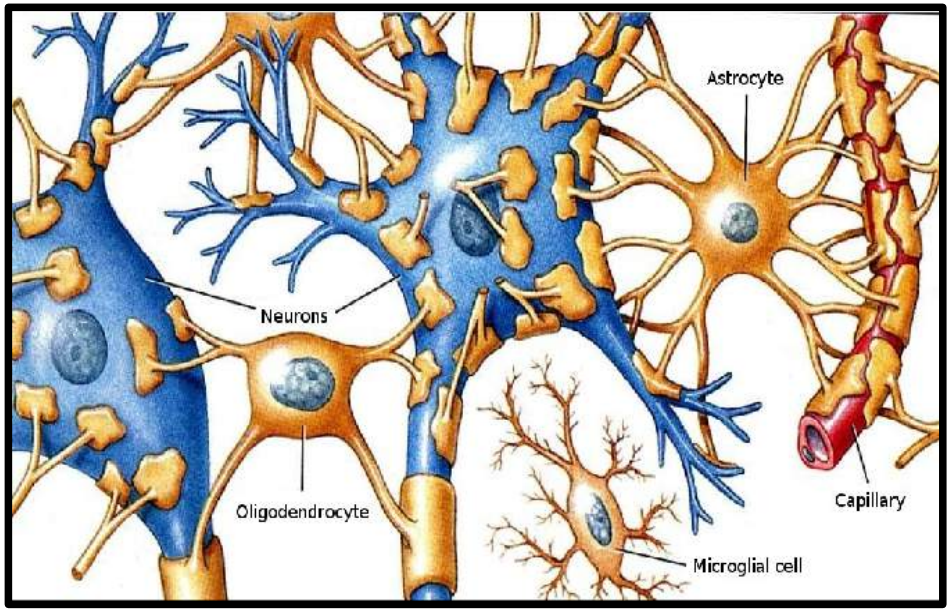
Metastasis (Spread)

Most common case: from the lung to the brain



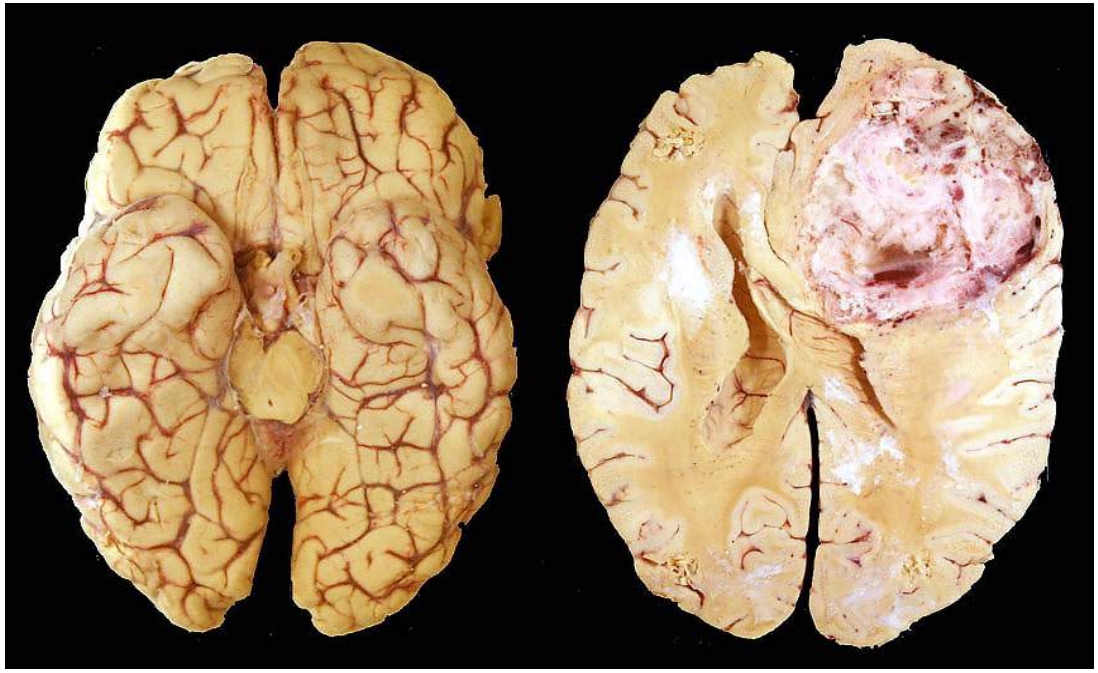
BioDigital, Inc.
https://www.youtube.com/user/biodigitalsystems/about

Gliomas x Neurons



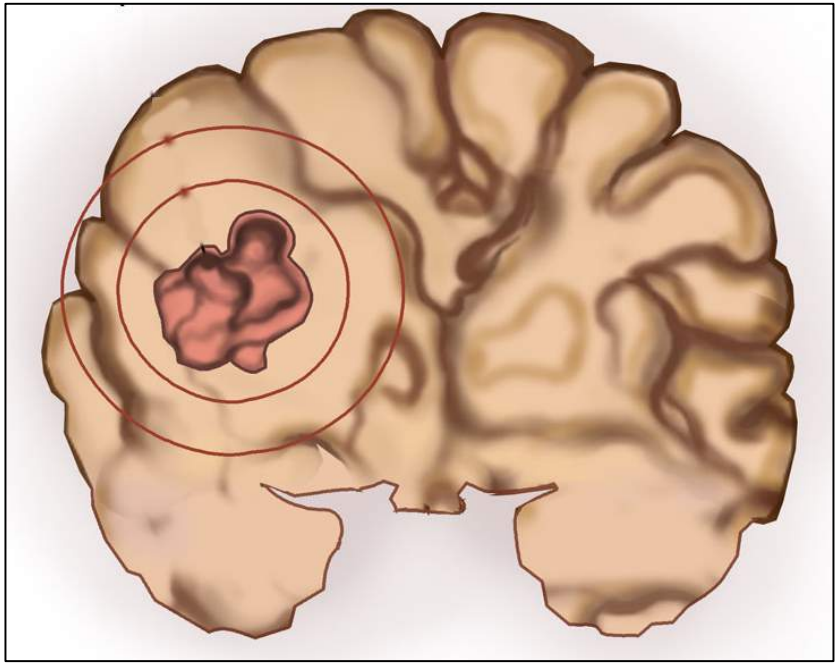
Glial cells	Neurons
• Primarily as the physical support for neurons • Provide nutrients to neurons • Regulate the extracellular fluid of the brain, especially surrounding neurons and their synapses • Migration of neurons and produce molecules that modify the growth of axons and dendrites • Development of the nervous system and in processes such as synaptic plasticity and synaptogenesis • Regulation of repair of neurons after injury • Central Nervous System, suppress repair • Neurotransmission	• Receive signals (or information) • Integrate incoming signals (to determine whether or not the information should be passed along) • Communicate signals to target cells (other neurons or muscles or glands)

Eric R. Kandel, ed. (2006). Principles of neural science (5. ed.). Appleton and Lange: McGraw Hill. ISBN 978-0071390118.



Teaching website for Pathology, Neuropathology & Neuroimaging – UNICAMP

<http://anatpat.unicamp.br>



- Disruptions of glial cells affect the neurons, because they are responsible for delivering nutrients, to provide structural support to them (Glees, 1955), and to control the biochemical compositions of the fluid surrounding the neurons.

Chemotherapy (not only)

- Hospital
- Specialized clinics

- Protocol for Drugs
- Agent chemotherapic infusion

- Wait

Anemia	Infection	Central nervous system	Pain
Infertility	Constipation	Mouth and throat	Diarrhea
Sexual	Appetite	Urinary systems	Nausea
Fatigue	Bleeding	Skin and nails	**Hair loss**

Brazil: Portaria 874/2013 (“Extended Network”) - National Policy on Cancer Prevention and Control
https://www.inca.gov.br/onde-tratar-pelo-sus

Suppresion

SUPRESSÃO DE CÉLULAS CANCERÍGENAS EM AUTÔMATO CELULAR

SUPPRESSION OF CANCEROUS CELLS IN CELLULAR AUTOMATON

RESUMO

2010

Immune System

Sodebras

Revista SODEBRAS – Volume 9 Nº 102 – JUNHO 2014

MODELO DE INTERAÇÃO TUMOR-SISTEMA IMUNOLÓGICO

2014

Glia-Neuron-Chem.

Journal of Theoretical Biology

Mathematical model of brain tumour with glia-neuron interactions and chemotherapy treatment

2015

Norton-Simon hypothesis

Commun Nonlinear Sci Numer Simulat

Nonlinear cancer chemotherapy: Modelling the Norton-Simon hypothesis

2019

Resistance

Mathematical model of brain tumour growth with drug resistance

Sub.

2011

On a cellular automaton with time delay for modelling cancer tumors

Delay

2014

BioSystems

Model for tumour growth with treatment by continuous and pulsed chemotherapy

Chemotherapy (C/P)

2017

Journal of Theoretical Biology

The dose-dense principle in chemotherapy

Dose-dense-Chem.

2019

Commun Nonlinear Sci Numer Simulat

The role of dose density in combination cancer chemotherapy

Rules: Dose-dense

Journal of Theoretical Biology 368 (2015) 113–121

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journal homepage: www.elsevier.com/locate/yjtbi

Mathematical model of brain tumour with glia–neuron interactions and chemotherapy treatment

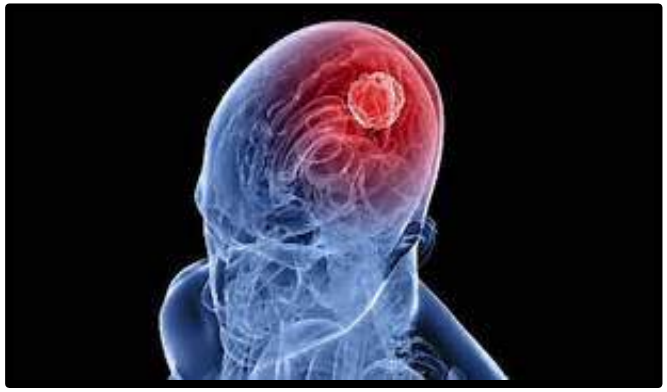
$$\frac{dG(t)}{dt} = \Omega_1 G(t)\left(1-\frac{G(t)}{K}\right) - \Psi_1 G(t)C(t) - \frac{P_1 G(t)Q(t)}{A_1+G(t)},$$

$$\frac{dC(t)}{dt} = \Omega_2 C(t)\left(1-\frac{C(t)}{K}\right) - \Psi_2 G(t)C(t) - \frac{P_2 C(t)Q(t)}{A_2+C(t)},$$

$$\frac{dN(t)}{dt} = \psi \dot{G}(t)H(-\dot{G})N(t) - \frac{P_3 N(t)Q(t)}{A_3+N(t)},$$

$$\frac{dQ(t)}{dt} = \Phi - \zeta Q(t),$$

+



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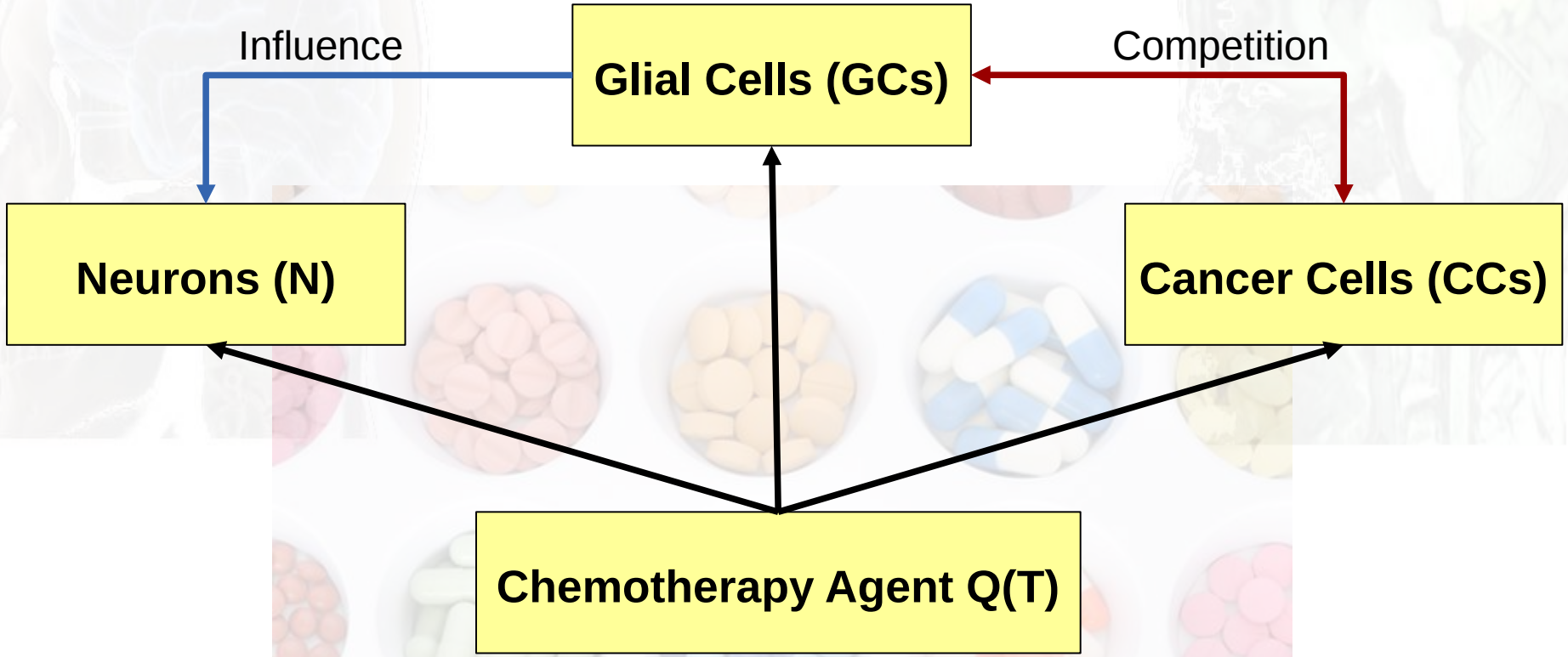
General ideia



Schematic representation of the agents, and their interactions (links) considered in our model.

Journal of Theoretical Biology, **368**, 113-121, 2015.

Brain Tumour model

Logistic growth

Interactions

$$\frac{dg(t)}{dt} = \Omega_1 g(t)(1-g(t)) - \beta_1 g(t)c(t) - \frac{p_1 g(t)Q(t)}{a_1 + g(t)}$$

} **Glial cells concentration**

Proliferation rate

Interaction coefficients

Logistic growth

Interactions

$$\frac{dc(t)}{dt} = \Omega_2 c(t)(1-c(t)) - \beta_2 g(t)c(t) - \frac{p_2 c(t)Q(t)}{a_2 + c(t)}$$

} **Glioma cells concentration**

Interaction coefficient

$$\frac{dn(t)}{dt} = \alpha \dot{g}(t)H(-\dot{g})n(t) - \frac{p_3 n(t)Q(t)}{a_3 + n(t)}$$

} **Neurons cells concentration**

Decrease “n” due to glial cells death

$$\frac{dQ(t)}{dt} = \Phi - \zeta Q(t)$$

} **Concentration of the chemotherapeutic agent**

Chemotherapy agent rate (infusion)

Chemotherapy agent rate (decrease of chemotherapy that is delivered to the cells)

Behaviour of the glioma without the infusion of a chemotherapeutic agent.

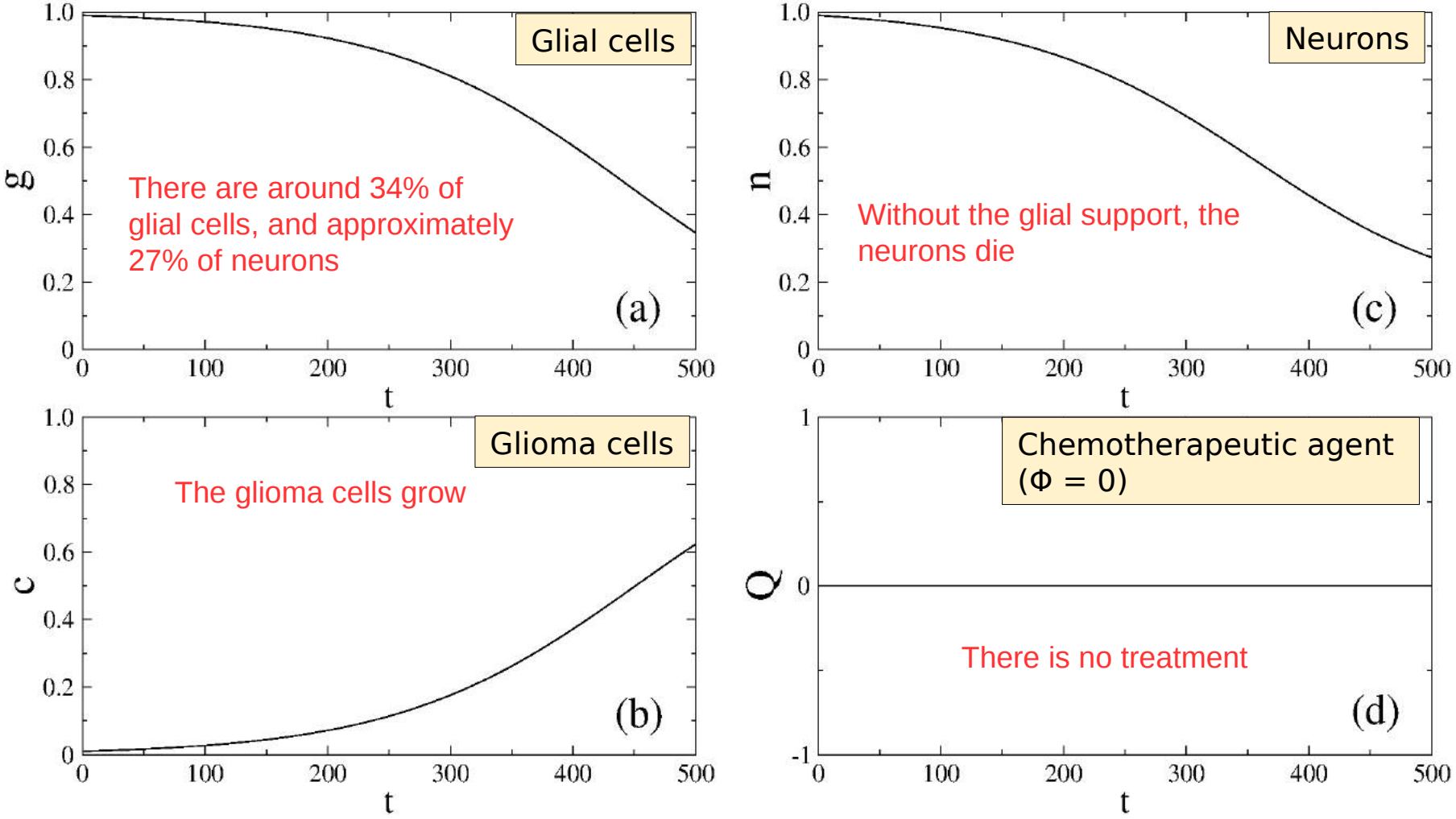


Fig 1 - Temporal evolution of the concentration of (a) glial cells, (b) glioma cells, (c) neurons and (d) chemotherapeutic agent (=0).

The infusion of a chemotherapeutic agent - suppress the glioma growth

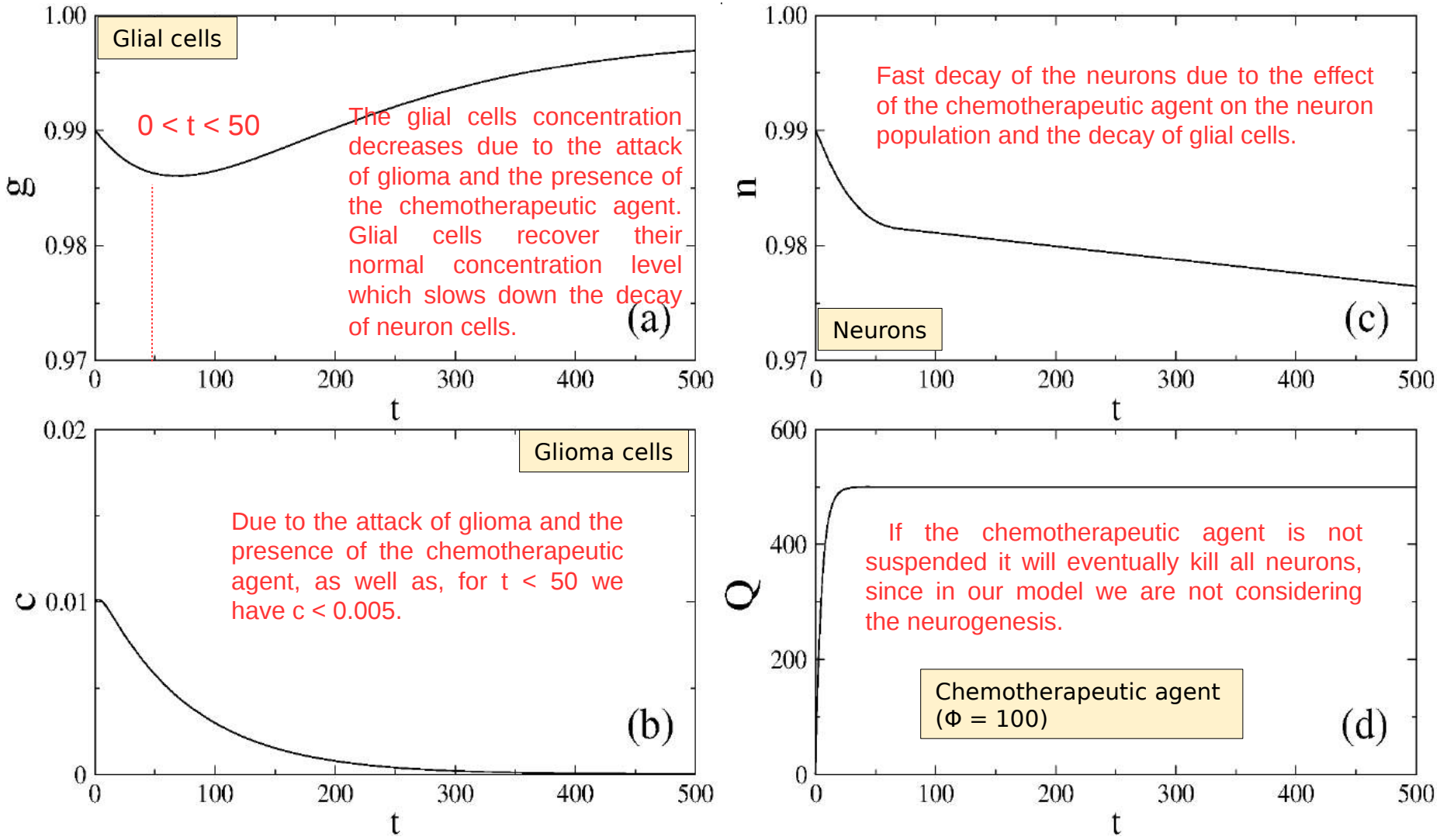


Fig 2 - Temporal evolution of the concentration of (a) glial cells, (b) glioma cells, (c) neurons and (d) chemotherapy, continuous treatment ($\neq 0$).

Glioma Elimination

Here, we study the performance of our model to understand what are the conditions such that glioma concentration in the normalised model reaches levels related to no glioma ($c \leq 10^{-11}$), while glial and neuron cell concentrations are kept high.

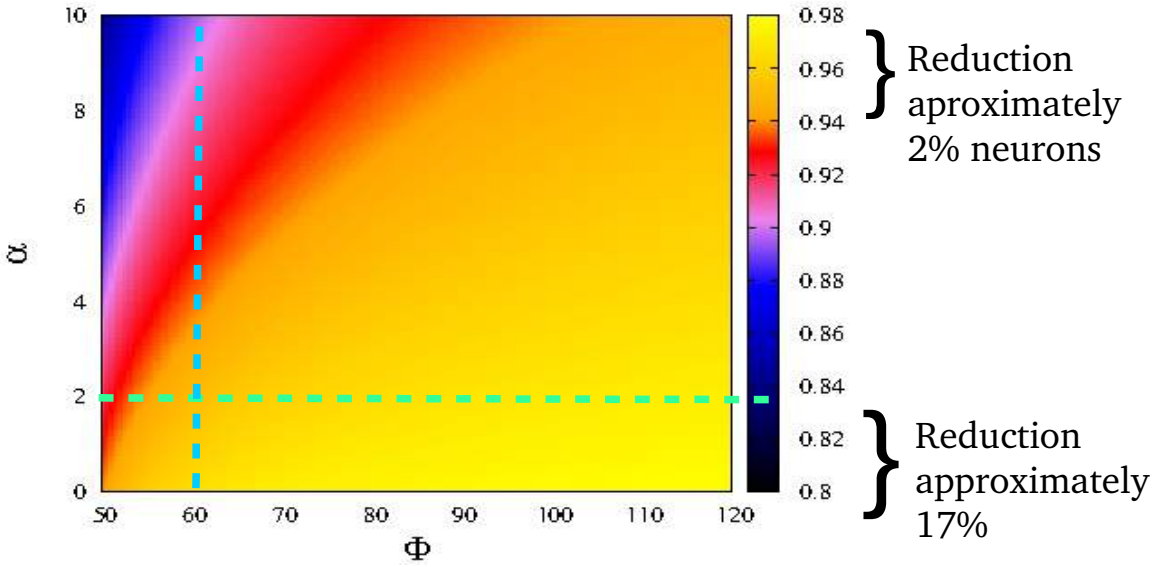


Fig 4 - Neuron concentration as a function of α versus Φ, where g (0) = 0.99, c (0) = 0.01, n (0) = 0.99, and Q (0) = 0.0. The colour bar represents the value of the neuron concentration (n) after a successful chemotherapy.

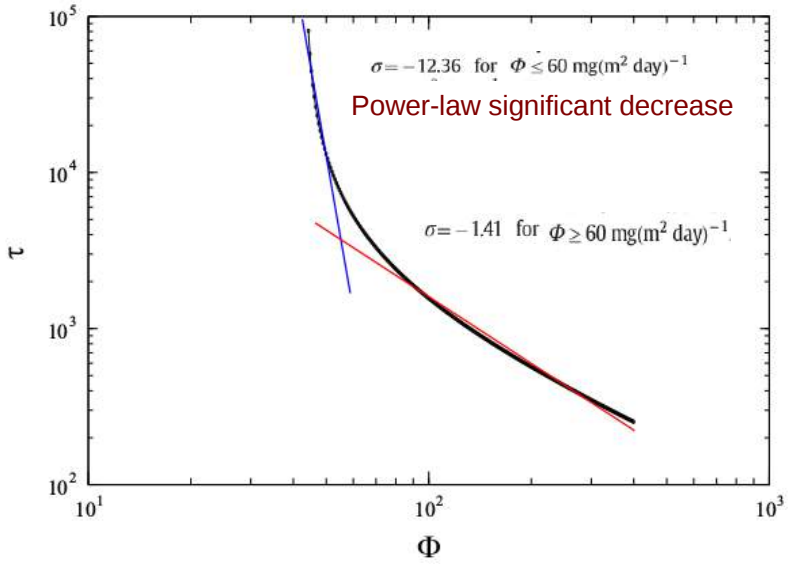


Fig 5 - Time (τ) to achieve suppression of glioma. Looking at Fig. 4, neurons will also be significantly preserved if $\alpha \leqslant 2$.

$$\alpha = \psi K_1,$$

Loss influences

Carrying capacity

Case: glioma x Temozolomide, after radiation therapy. Protocol Drug: 5 days on and 23 days off.

5 days on with Φ = 400 mg$(m^2 day)^{-1}$, and 23 days off.

But the concentration of glioma cells is going to a suppressed state.

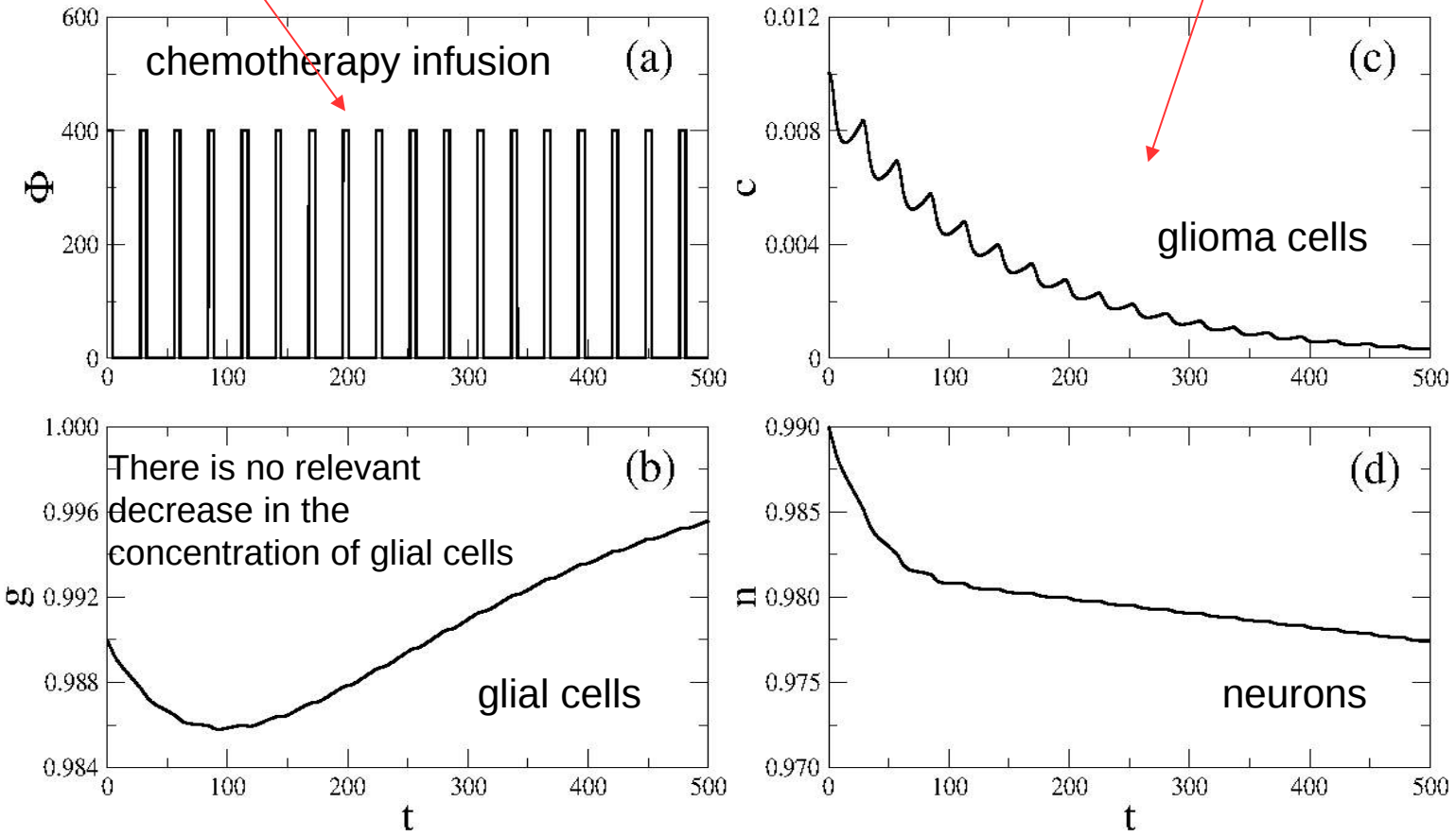


Fig 6 - There is no relevant decrease in the concentration of glial cells, but the concentration of glioma cells is going to a suppressed state (Fig. 6c) "Norton–Simon hypothesis". Whereas, the concentration of neuron decreases around only slightly (Communications in Nonlinear Science and Numerical Simulation, **70**, 307-317, 2019).

Concluding Reflections

- We proposed a mathematical model for the evolution of a brain tumour under the attack of chemotherapeutic agents.

- We studied some aspects of the dynamics of glioma growth, suppression and elimination.

- A successful chemotherapy: eliminates all the glioma cells minimising the neurons and glial cells injury.

- Through local stability we found a range of values for the infusion rate that allows for the elimination of glioma, as well as, the glioma will not return. Our results are in line with this experimental/medical observation. The tumour is not eliminated, but reduced.

- Temozolomide (1998), according to our model the rate would kill all the glioma cells, and in addition, it would preserve high levels of neural population. The range of the values for the infusion rate is clinically relevant because it reveals the effectiveness of the treatment strategies by the administration of chemotherapeutic drugs. New strategies have been developed aiming health benefits of patients, that is the elimination of glioma cells. Regardless of whether doctors will use the optimal rates obtained from our model, our work can help doctors to access the risks of a treatment on an individual basis.

- We realised numerical simulations and obtained values of the infusion of chemotherapeutic agents in that the glioma growth is eliminated within the shortest time. Continuous infusion x Pulsed infusion.

- Our main result was to show that chemotherapy can be applied mitigating the side effects of drugs on the neurons death, if the appropriated rate is used. In 2011 (Gong et al.) analysed the neurotoxicity due to chemotherapy against glioma. They concluded that newer chemotherapy agents (proteasome inhibitor bortezomib, and epidermal growth factor receptor tyrosine kinase inhibitor erlotinib) are effective against glioma cells, producing minimal effects on neurons. Older drugs (temozolomide and cisplatin) are more toxic for neurons than for glioma cells.

CANCER ETIOLOGY

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti[1]* and Bert Vogelstein[2]*

Some tissue types give rise to human cancers millions of times more often than other tissue types. Although this has been recognized for more than a century, it has never been explained. Here, we show that the lifetime risk of cancers of many different types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis. These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions. The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells. This is important not only for understanding the disease but also for designing strategies to limit the mortality it causes.

Science 2 January 2015: Vol. 347 no. 6217 pp. 78-81

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Words: why and Carcinogenesis

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