

How can (experimental) data go on tumor growth models?

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CIÊNCIA, TECNOLOGIA
E INOVAÇÕES



① First part:

- Tumor model development (biological motivation)
- Continuous models
- Discrete models (Individual Based Models)
- Hybrid models

② Second part:

- Working with Python
- Solving Ordinary Differential Equations (ODE)

③ Third part:

- Calibration
- Maximum Likelihood Estimation
- Bayesian Approach

Tumor Model Development

Outline

- 1 Tumor modeling
- 2 Model classification
- 3 Continuous models
 - Tumor growth models
 - Therapies
 - Tumor microenvironment
- 4 Individual Based Models
 - Cellular Automata (CA)
 - Agent-Based Model (ABM)
- 5 Hybrid models

Tumor modeling

Increasing number of mathematical, physical, computational and engineering techniques applied to various aspects of tumor growth ¹



With the ultimate goal of understanding the response of the cancer population to clinical intervention

¹ENDERLING, H.; CHAPLAIN, M.A.J. Mathematical modeling of tumor growth and treatment. *Current Pharmaceutical Design*, 20, 4934-4940 (2014). <https://doi.org/10.2174/1381612819666131125150434>

Tumor modeling

- **Mathematical and computational modeling:**

- Test hypotheses
- Confirm experiments
- Indicate new experiments
- Simulate the dynamics of complex systems
- Help understand the mechanistic underpinnings of dynamical systems

In silico trials:

- Reduction and optimization of laboratory experiments
- Invaluable tool to optimize patient-specific care

Model Classification

① Continuos models:

- Ordinary Differential Equation - ODE (continuous time)
- Recursion Equation (discrete time)
- Partial Differential Equation - PDE

② Discrete models:

- Cellular Automata (CA)
- Agent-Based Model (ABM)

③ Hybrid models

Model Classification

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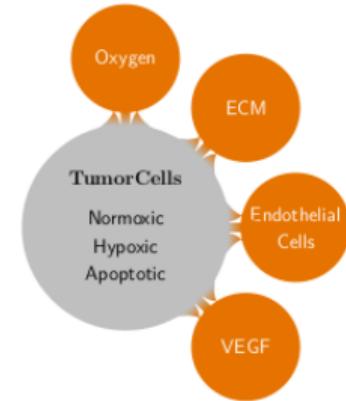
- Cellular Automata (CA)
- Agent-Based model (ABM)

③ Hybrid models

Tumor growth models

- Example of model to describe avascular and vascular phases of the cancer ²:

$$\left\{ \begin{array}{l} \frac{\partial w}{\partial t} = \nabla \cdot (D_w \nabla w) + \alpha_w m(1 - w) - \beta_w(n + h + m)w - \gamma_w w \\ \frac{\partial n}{\partial t} = \nabla \cdot (D_n(\max\{n - \nu_c, 0\} + 1)\nabla n) - \nabla \cdot (n\bar{\chi}_n \nabla f) + \alpha_n n \max\{1 - \nu, 0\} \\ \quad - \alpha_h \mathcal{H}(\omega_h - w)n + h_n \alpha_n \mathcal{H}(w - \omega_h)h \\ \frac{\partial h}{\partial t} = \nabla \cdot (D_h \nabla h) + \alpha_h \mathcal{H}(\omega_h - w)n - h_n \alpha_h \mathcal{H}(w - \omega_h)h - \beta_h \mathcal{H}(\omega_a - w)h \\ \frac{\partial a}{\partial t} = \nabla \cdot (D_a \nabla a) + \beta_h \mathcal{H}(\omega_a - w)h \\ \frac{\partial m}{\partial t} = \nabla \cdot (D_m \nabla m) - \nabla \cdot (m\bar{\chi}_m \nabla g) + \alpha_m m g \max\{1 - \nu, 0\} \\ \frac{\partial f}{\partial t} = -\beta_f n f \\ \frac{\partial g}{\partial t} = \nabla \cdot (D_g \nabla g) + \alpha_g h \max\{1 - g, 0\} - \beta_g m g \end{array} \right.$$

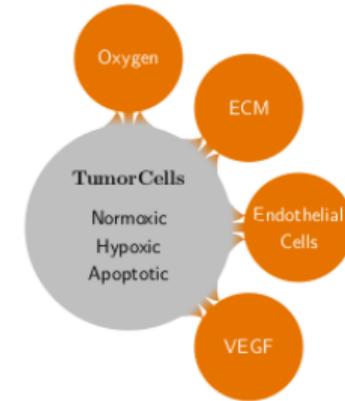


² Resende, A. C. M. de. **Sensitivity Analysis as a Tool for Tumor Growth Modeling**. 2016. 79 p. Dissertation (Mestrado em Modelagem Computacional) - Laboratório Nacional de Computação Científica, Petrópolis, RJ.

Tumor growth models

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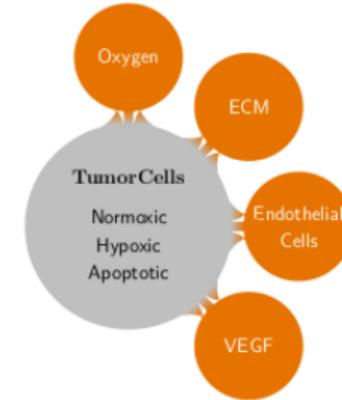


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Choices

What is the best model to describe tumor growth?

- Assessed context:
 - Biological characteristics of the problem (cancer type, stage of growth, ...)
 - Modeling goals
- Model assumptions:
 - Abstraction process (biological and mathematical view)
 - Possibilities and restrictions of the chosen model
- Available data

Tumor growth models

- Dialog between Ecology and Mathematics
- Predictions of different tumor growth models



Figura: GOTELLI, N.J. **Ecologia**. Ed. Planta, 2007. (English and portuguese version)

Murphy et al. BMC Cancer (2016) 16:163
DOI 10.1186/s12885-016-2164-x



RESEARCH ARTICLE

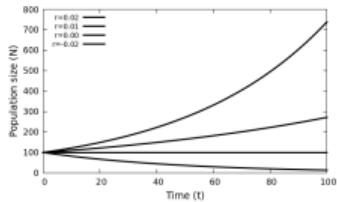
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Differences in predictions of ODE models of tumor growth: a cautionary example

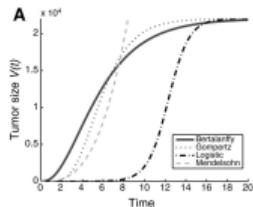
Hope Murphy¹, Hana Jaafari² and Hana M. Dobrovolny^{2*}

Figura: Murphy, H.; Jaafari, H.; Dobrovolny, H.M. Differences in predictions of ODE models of tumor growth: a cautionary example. **BMC Cancer** 16, 163 (2016). <https://doi.org/10.1186/s12885-016-2164-x>

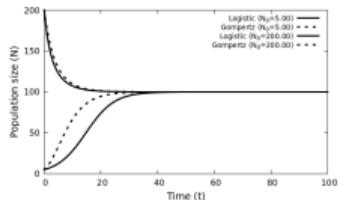


$$\frac{dN}{dt} = rN$$

$$\frac{dN}{dt} = rN^{\frac{2}{3}} - bN$$



$$\frac{dN}{dt} = rN \ln \frac{K}{N}$$



$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K}\right)$$

Exponential

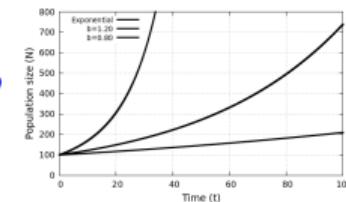
Mendelsohn

$$\frac{dN}{dt} = rN^b$$

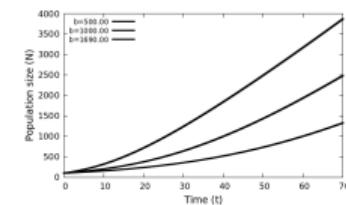
Linear

Tumor growth models

Bertalanffy

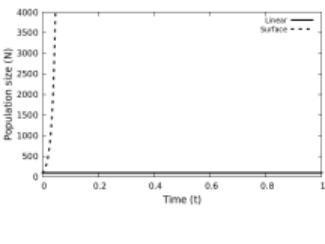
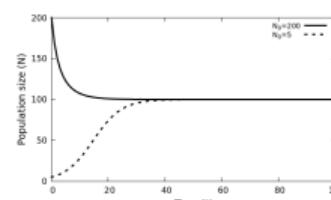


$$\frac{dN}{dt} = \frac{rN}{(N + b)}$$



$$\frac{dN}{dt} = \frac{rN}{(N + b)^{\frac{1}{3}}}$$

Logistic



Population growth models

- **Population** is the group of individuals of the same species that live together and reproduce
- Models of **continuos** and **discrete** time
- All changes in population size can be classified into four categories:
 - Births
 - Deaths
 - Immigration
 - Emigration

Analyzing population growth models

Assumptions:

- Unique population growing in a simple environment
- Closure population (without immigration and emigration)
- Absence of genetic structure
- Absence of age structure

Equilibria and Stability Analyses

- To study the long-term predictions of a mathematical model
- Determining the equilibria of a system is one of the most important steps in analyzing a dynamic model

System at equilibrium

It does not change over time. A particular value of a variable is called an equilibrium value if, when the variable is started at this value, the variable never changes.

- Knowing the equilibria of a model is very useful because these states are good candidates for where a system might eventually end up

Equilibria and Stability Analyses:

- Next step is to determine when each equilibrium is stable or unstable
- If the system starts at equilibrium, it will remain at equilibrium (by definition)

Question:

What if a population starts near, but not exactly at, an equilibrium?

Equilibria and Stability Analyses

- Dialog between Biology and Mathematics
- Additional material and codes (*Mathematica* and *Maxima* software): <https://www.zoology.ubc.ca/biomath/>

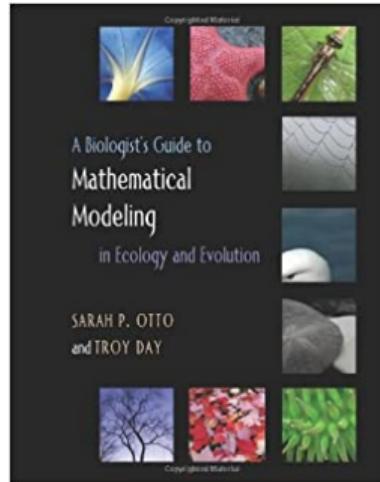


Figura: OTTO, S.P.; DAY, T. **A biologist guide to mathematical modeling in ecology and evolution.** Princeton University Press, 2011.

Equilibria and Stability Analyses

- It explores some themes related to dynamic systems, supported by the computational tool
Maxima

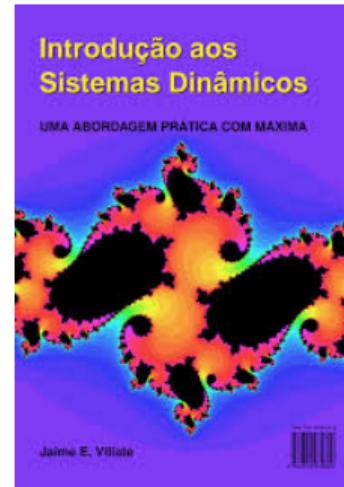


Figura: VILLATE, J.E. **Introdução aos sistemas dinâmicos: uma abordagem prática com Maxima**, 2007.

Exponential model (continuous time) - Malthus

$$\frac{dN}{dt} = rN$$

$\left\{ \begin{array}{l} N : \text{number of individuals in the population at time } t \\ t : \text{time (continuos variable)} \\ r : \text{intrinsic population growth rate } (r = b - d) \end{array} \right.$

Observations:

- **Analytical solution:**

- $N_t = N_0 e^{rt}$

- Population change in the time ($\frac{dN}{dt}$) is proportional to r
- The bigger the population, the faster it grows

- **Main assumption:**

- Resources for population growth are unlimited
- Constant birth and death structure (density independent)

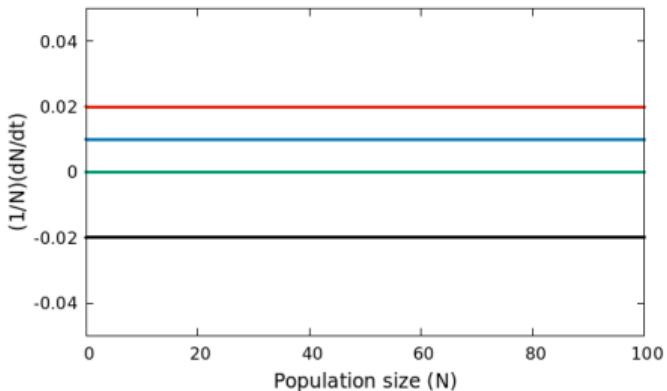
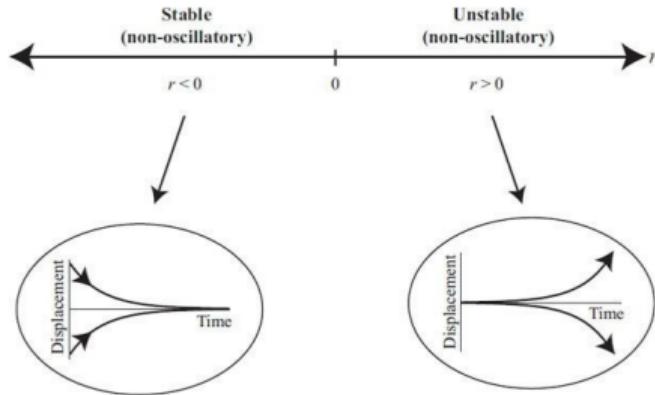
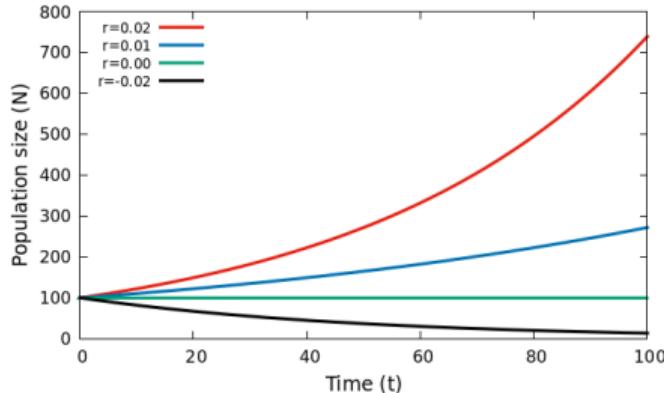


Figura: Continuous exponential model behavior with respect to various values of the parameter r ; equilibria points and their stability [4]; behavior of the population growth rate *per capita*.

Description of tumor growth:

- Best suited for describing early stages of tumor growth (unlimited resources)
- It may fail to describe later stages of tumor growth, when angiogenesis and nutrient depletion start to play a role

Mendelsohn model

- Generalization of the exponential growth model:

$$\frac{dN}{dt} = rN^b$$

Growth is proportional to some power, b , of the population

- Analytical solution:

- $N(t) = [N_0^{1-b} + rt(1-b)]^{\frac{1}{1-b}}$
 $(b \neq 1)$

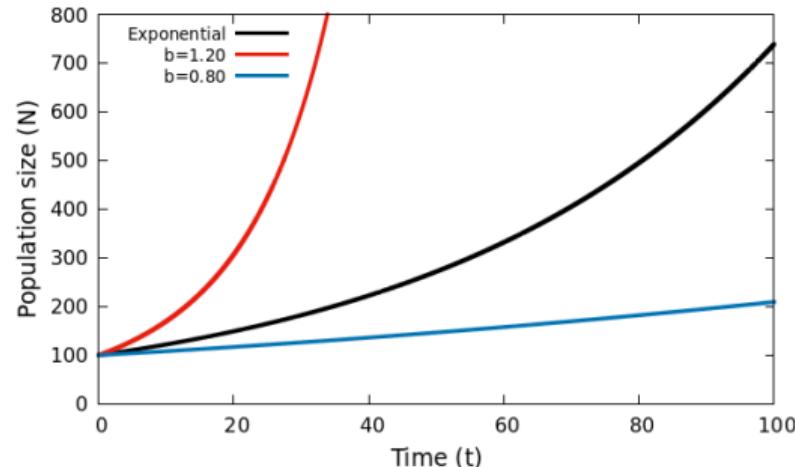


Figura: Mendelsohn model behavior compared to the exponential model ($r = 0.02$ and $N_0 = 100$).

Logistic (continuous time) - Verhulst (1838)

$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K}\right)$$

N : number of individuals in the population at time t
 t : time (continuous variable)
 r : intrinsic population growth rate ($r = b - d$)
 K : environment carrying capacity

- **Analytical solution:**

- $N(t) = \frac{K}{1 + \{[K - N(0)]/N(0)\} e^{-rt}}$

- **Assumptions:**

- Constant carrying capacity
- Linear density dependence

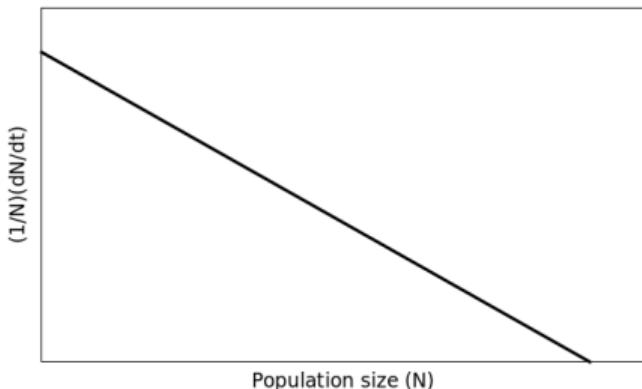
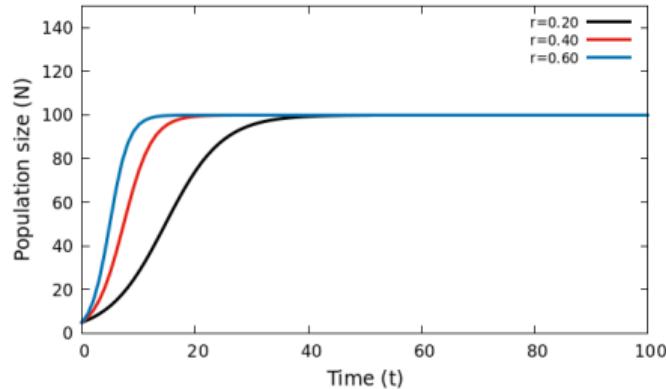
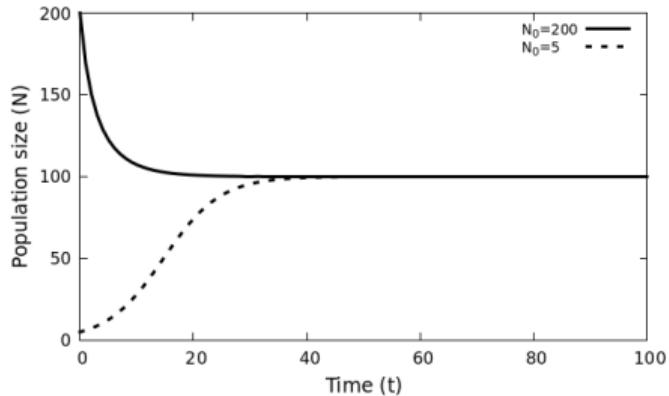


Figura: Continuous logistic model behavior with respect to various values of the initial condition N_0 and parameter r ; behavior of the population growth rate *per capita*

Logistic (discrete time)

$$N_{t+1} = N_t + r_d N_t \left(1 - \frac{N_t}{K}\right)$$

N : number of individuals in the population at time t
 t : time (discrete variable)
 r_d : discrete growth factor
 K : environment carrying capacity

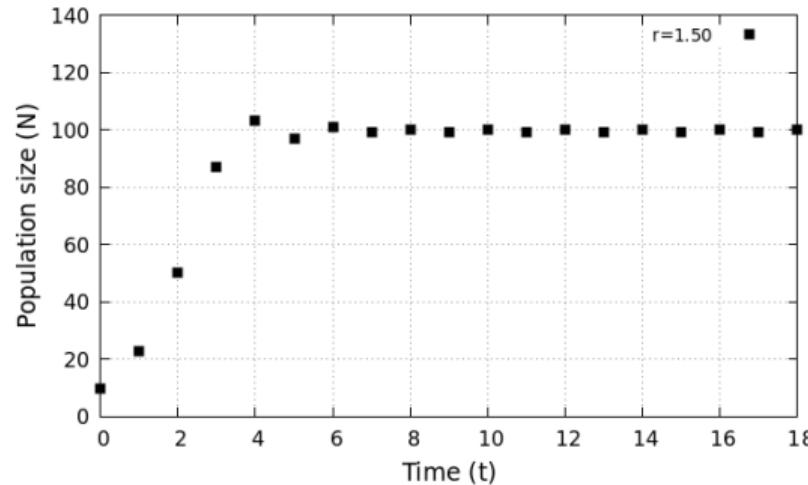


Figura: Discrete logistic model behavior with respect to various values of the parameter r .

Logistic (discrete time)

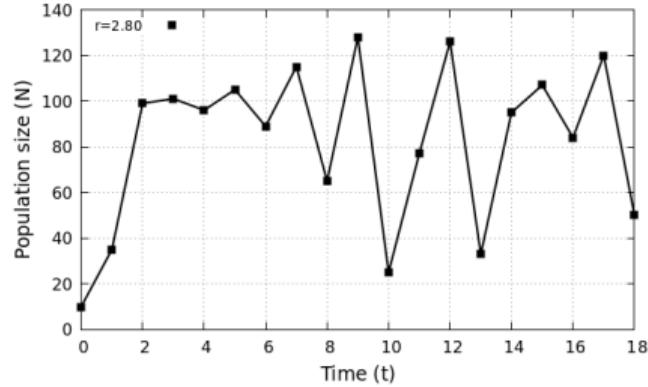
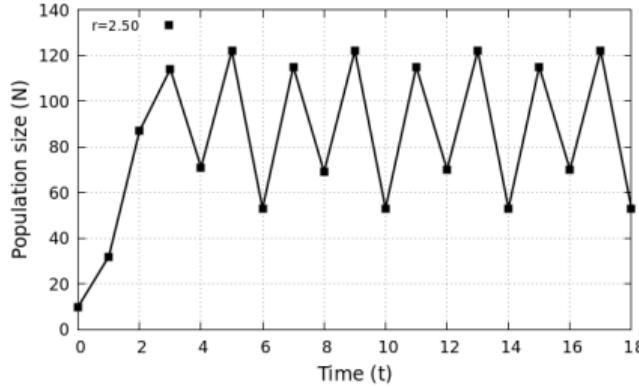
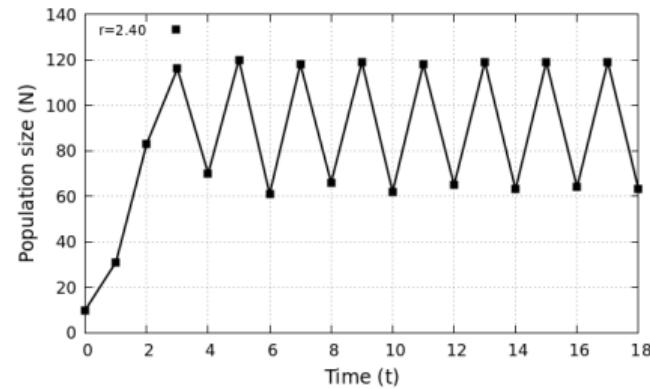
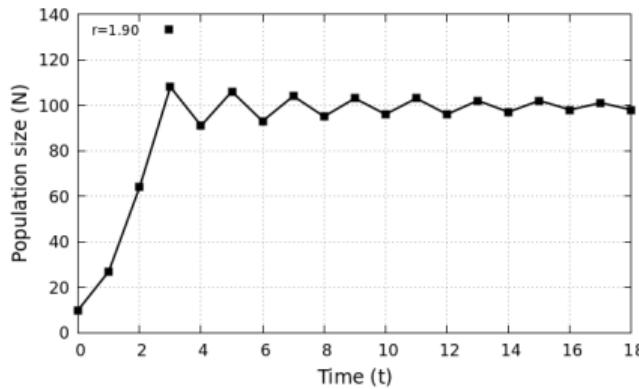


Figura: Behavior of the discrete logistic growth model varying the parameter r ($N_0 = 10$ and $K = 100$).

Logistic (discrete time)

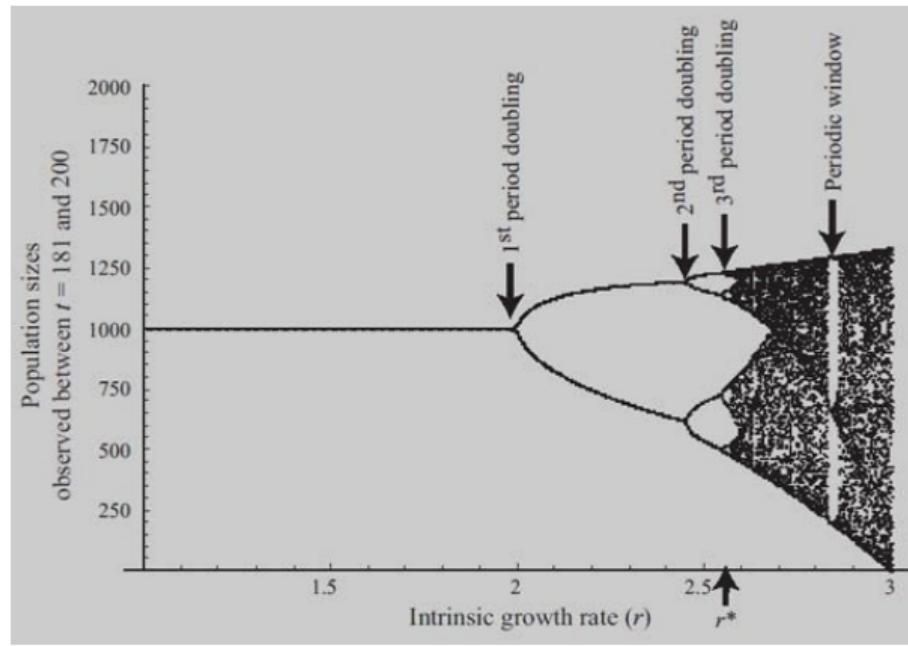


Figura: A bifurcation diagram for the logistic model (discrete) [4].

- Interesting site:

https://pbfy0.github.io/logistic_iterator/#fn=Cosine&wnd=-9.42477796076938,9.42477796076938,18.84955592153876,-18.84955592153876&dk=5.0000&sk=1000&it=3000

RESEARCH ARTICLE

Open Access



Differences in predictions of ODE models of tumor growth: a cautionary example

Hope Murphy¹, Hana Jaafari² and Hana M. Dobrovolny^{2*}

Figura: Murphy, H.; Jaafari, H.; Dobrovolny, H.M. Differences in predictions of ODE models of tumor growth: a cautionary example. **BMC Cancer** 16, 163 (2016).
<https://doi.org/10.1186/s12885-016-2164-x>

Tumor growth models

Article highlights:

- Differences in predictions of tumor growth
- Influence of the amount of data in the calibration process

Tumor growth models

Tabela: Tumor growth models analyzed and their respective equations

Model	Equation
Exponential	$\frac{dN}{dt} = rN$
Mendelsohn	$\frac{dN}{dt} = rN^b$
Logistic	$\frac{dN}{dt} = rN \left(1 - \frac{N}{K}\right)$
Linear	$\frac{dN}{dt} = \frac{rN}{(N + b)}$
Surface	$\frac{dN}{dt} = \frac{rN}{(N + b)^{1/3}}$
Gompertz	$\frac{dN}{dt} = rN \ln \left(\frac{b}{N + c}\right)$
Bertalanffy	$\frac{dN}{dt} = rN^{2/3} - bN$

Tabela: Predicted clinical quantities for each model in the absence of chemotherapy.

Model	Maximum size	Doubling time	Growth condition
Exponential	∞	$\ln 2/r$	$r > 0$
Mendelsohn	∞	$\ln 2/r$	$r > 0$
Logistic	K	$\ln 2/r$	$r > 0$
Linear	∞	$b \ln 2/r$	$\frac{r}{b} > 0$
Surface	∞	$b^{1/3} \ln 2/r$	$\frac{r}{b^{1/3}} > 0$
Gompertz	$b - c$	$\ln 2 / \left(r \ln \left(\frac{b}{c} \right) \right)$	$r \ln \left(\frac{b}{c} \right) > 0$
Bertalanffy	$\left(\frac{r}{b} \right)^3$	$\ln 2 / (r - b)$	$r - b > 0$

Tabela: Predicted clinical quantities for each model with chemotherapy.

Model	Maximum size	Minimum concentration needed to cure
Exponential	∞	$C_0 = r$
Mendelsohn	$\left(\frac{C_0}{r}\right)^{\frac{1}{b-1}}$	$C_0 = r$
Logistic	$\frac{K(r - C_0)}{r}$	$C_0 = r$
Linear	$\frac{r}{C_0} - b$	$C_0 = r/b$
Surface	$\frac{r^3}{C_0} - b$	$C_0 = r/b^{1/3}$
Gompertz	$\frac{b}{e^{C_0/r}} - c$	$C_0 = r \ln\left(\frac{b}{c}\right)$
Bertalanffy	$\left(\frac{r}{b + C_0}\right)^3$	$C_0 = r - b$

Tumor models with chemotherapy:

$$\frac{dN}{dt} = \mathcal{M} - C_0 N$$

\mathcal{M} : tumor growth law

C_0 : constant supply of drug

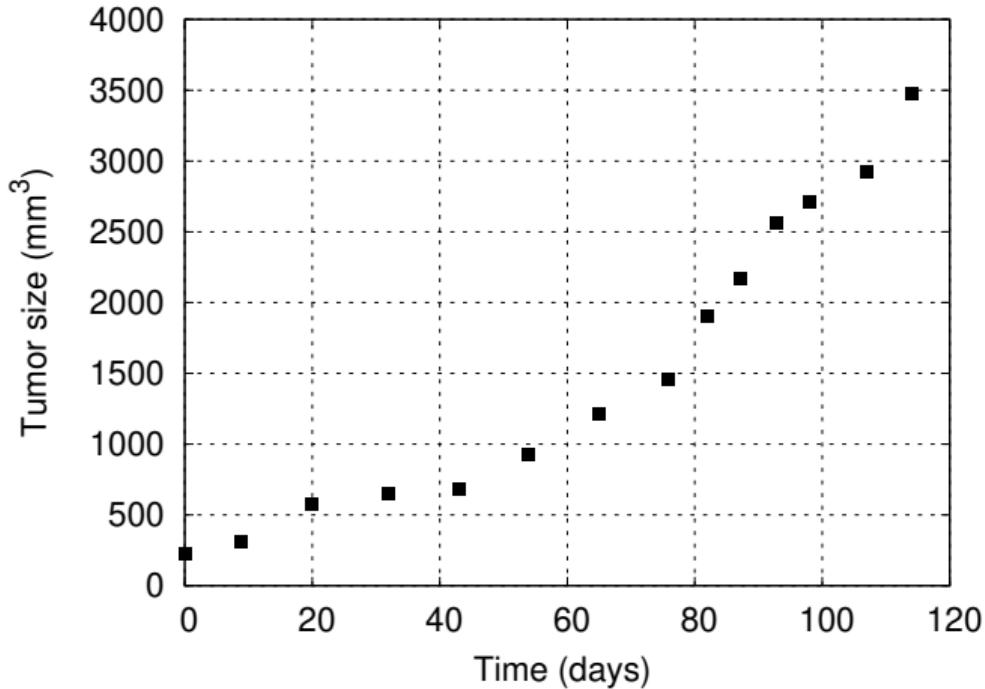


Figura: Experimental data used for calibration process extracted from [7]. The data correspond to breast cancer cell volume growth (GI-101A xenografts) in athymic mice, consisting of 14 tumor volume points (in mm³), distributed over a period of 114 days.

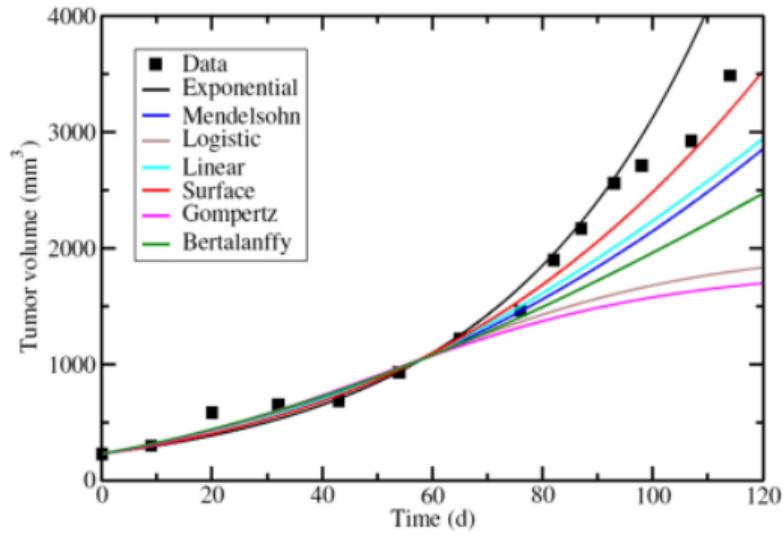
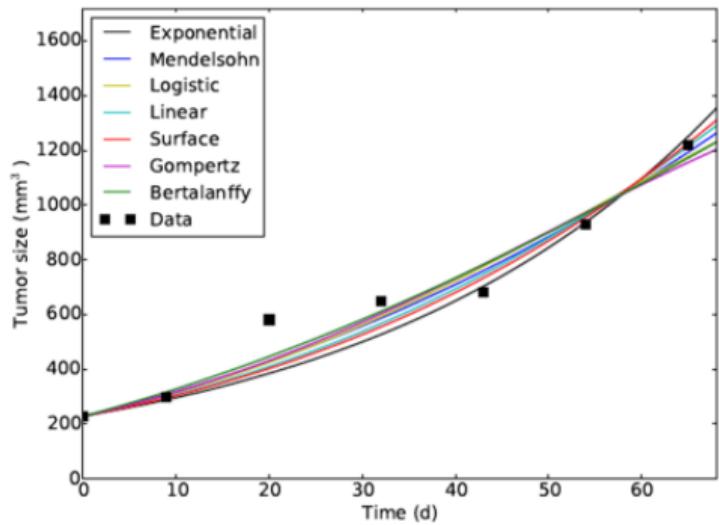


Figura: Fits of the ODE tumor growth models to the first half of the experimental data from Worschech et al. [43]. Each model was fit to the first seven time points and parameter estimates were used to extrapolate the remaining seven time points.

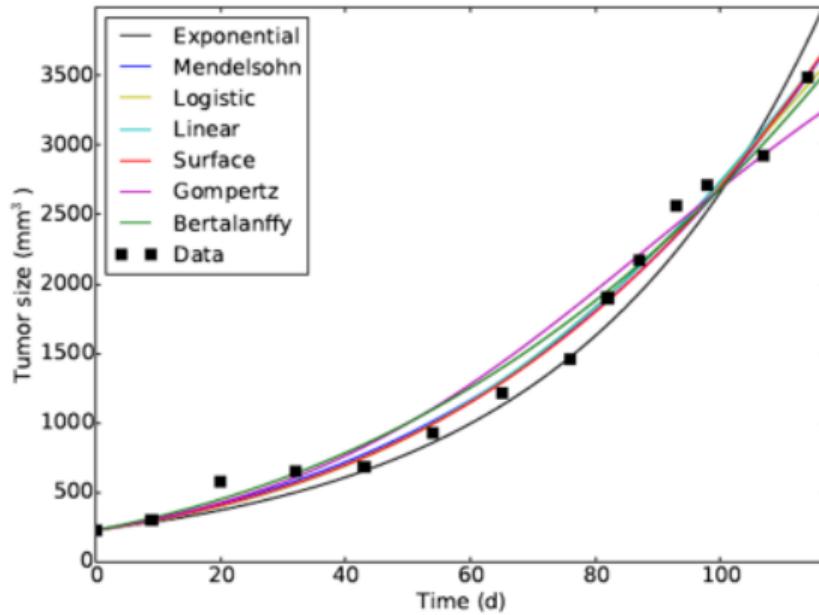


Figura: Fits of the ODE tumor growth models to the all data from Worschech et al. [43]

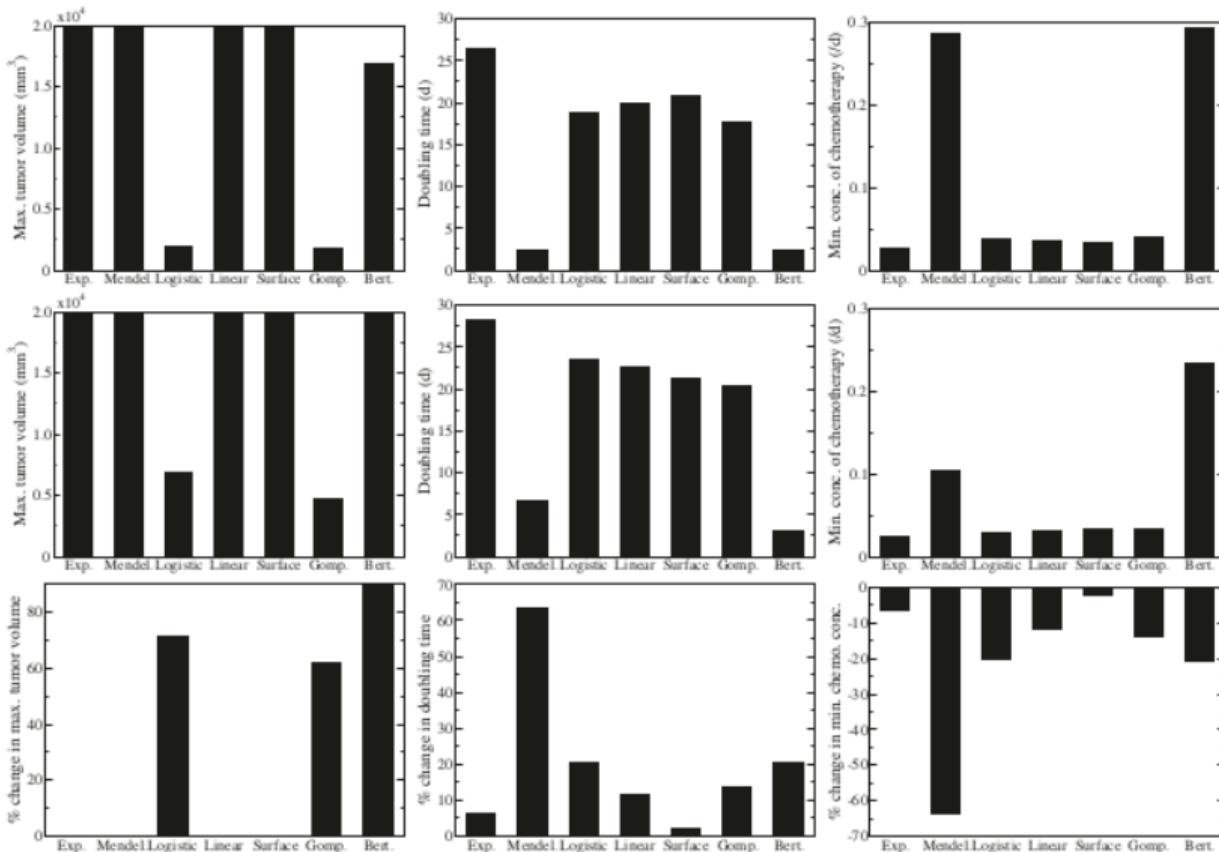


Figura: Estimates of clinically important measurements for the half or full data set and the percent change in each of the predictions.

Tumor growth models (Murphy et al., 2016)

- “The results highlight the need for careful consideration of model assumptions when developing mathematical models for use in cancer treatment planning”

Attention

“While models have great potential to improve development and implementation cancer treatment, they will only realize this potential if they provide accurate predictions”



Trends in Computational and Applied Mathematics, 22, N. 3 (2021), 1-20
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www.scielo.br/tcam
doi: 00001

Model Comparison and Uncertainty Quantification in Tumor Growth

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M. P. C. MENEZES⁴ and R. C. ALMEIDA⁵

Received on January 15, 2020 / Accepted on March 10, 2021

Figura: Paixão, E. A.; Naozuka, G. T.; Silva, J. V. O.; Menezes, M. P. C.; Almeida, R. C. Model comparison and uncertainty quantification in tumor growth. **TEMA** 22(3), 495-514 (2021).

Therapies

Incorporation of therapies into tumor growth modeling:

- **Type of therapy**

- Chemotherapy [6]
- Radiotherapy [2]
- Immunotherapy (CAR-T cells, ...) [5]

- **Operating mechanism of therapy**

- Cell cycle dependent
- The effects of therapy are instantaneous
- Existence of memory effects...

Chemotherapy

- **Ways to model chemotherapy action**
- As a death term³:

How cells grow and die under treatment

$$\frac{dN}{dt} = f(N, t) = G(N, t) - D(N, t)$$

G: net growth function (difference between natural growth and natural death)

D: drug-induced decay function

³ Resende, A. C. M. de. **Toward Predictive Computational Models of Breast Cancer Development and Treatment**. 2020. 113 p. Tese (Doutorado em Modelagem Computacional) - Laboratório Nacional de Computação Científica, Petrópolis, RJ.

Chemotherapy

- **Ways to model chemotherapy action**
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Murphy et al. (2016)

$$\frac{dN}{dt} = G(N, t) - C_0 N$$

Chemotherapy

- As a separate equation:

ODE System

$$\begin{cases} \frac{dN}{dt} = rN \left(1 - \frac{N}{K}\right) - fCN \\ \frac{dC}{dt} = a - bC - gNC \end{cases}$$

r : tumor growth rate

K : environmental carrying capacity

f : tumor death rate due to the drug

a : drug delivery

b : drug natural decay

g : drug consumption rate

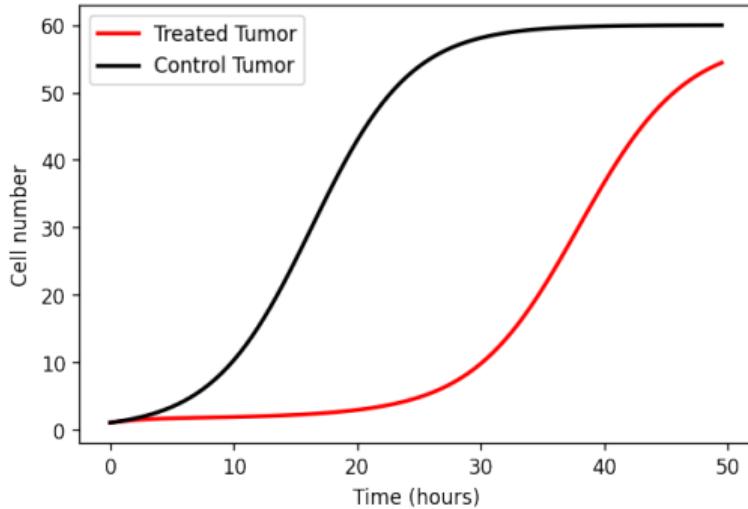
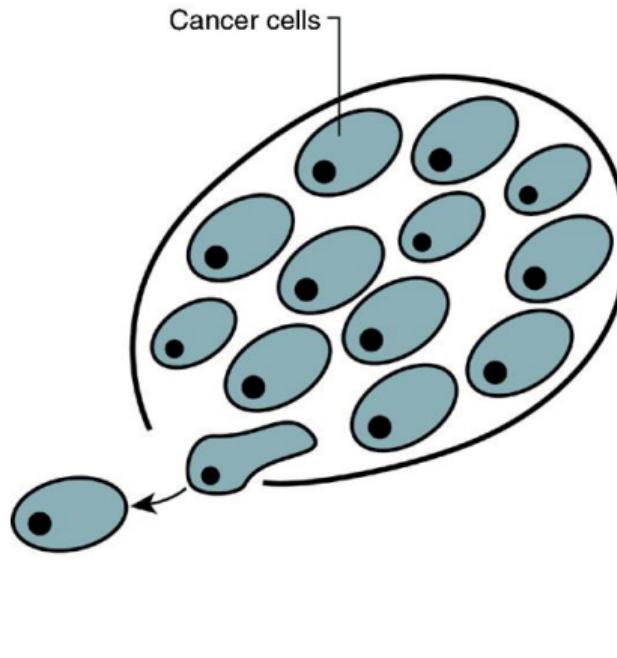


Figure: Tumor cell dynamics without and with chemotherapy.

Tumor complexity

The Reductionist View



A Heterotypic Cell Biology

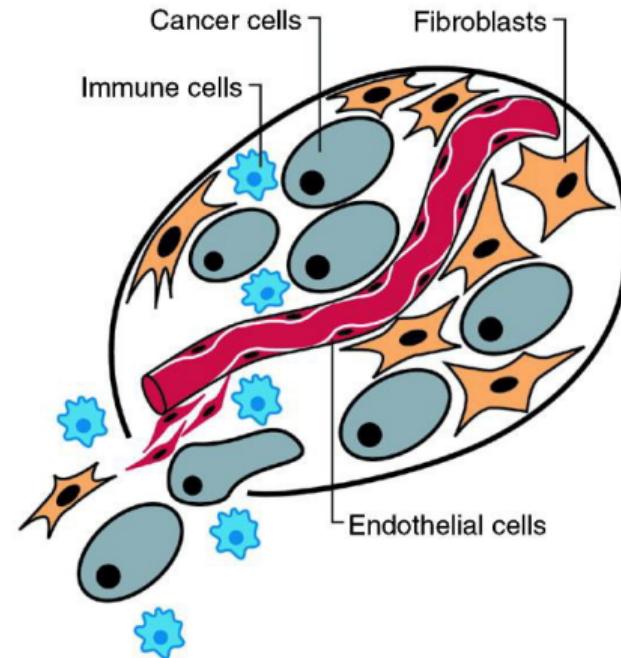


Figura: Tumors as complex tissues [1].

Avascular and vascular phases of the cancer

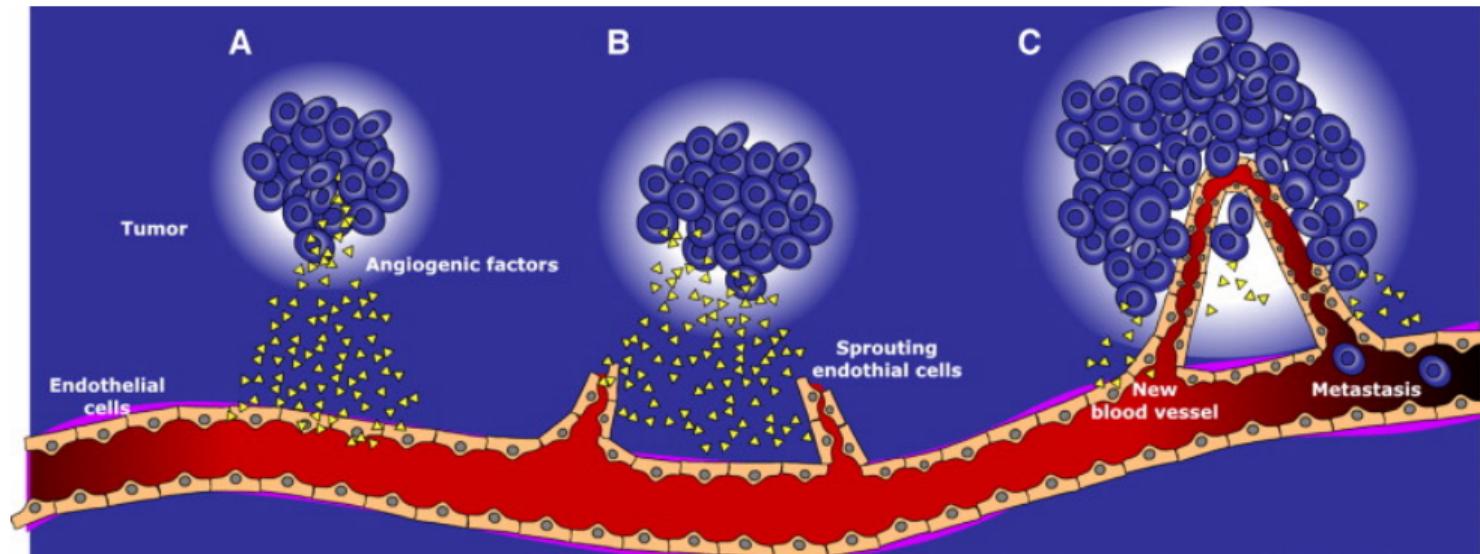


Figura: Scheme of the angiogenesis process (Griffioen, 2007).

Tumor complexity

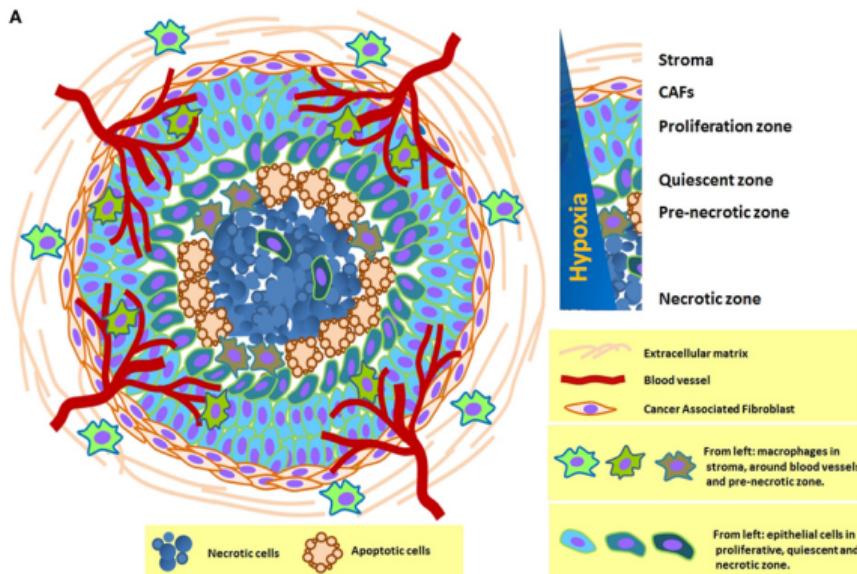
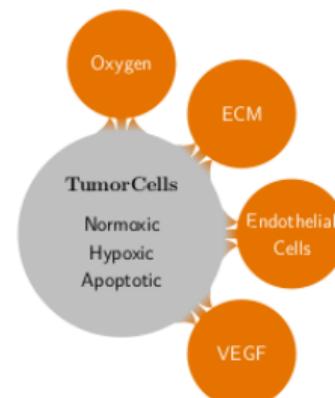


Figura: Schematic formation of a distinct necrotic zone in carcinoma [3].

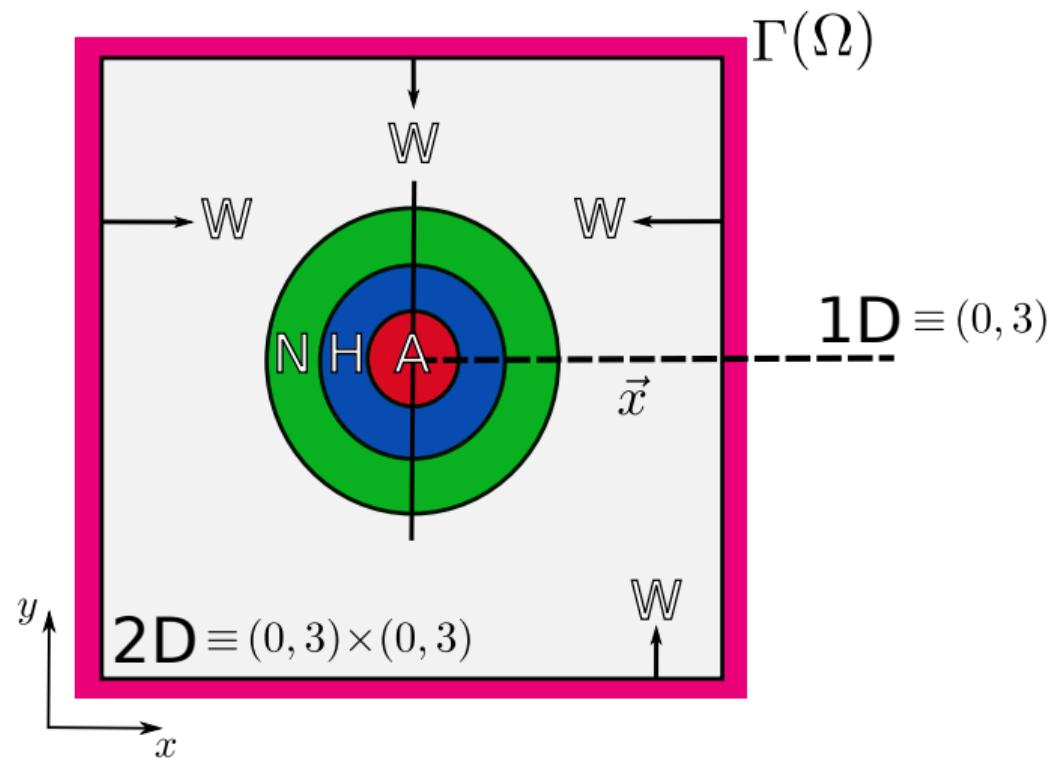
Model to describe avascular and vascular phases of the cancer

Resende, A. C. M. de. **Sensitivity Analysis as a Tool for Tumor Growth Modeling**. 2016. 79 p. Dissertation (Mestrado em Modelagem Computacional) - Laboratório Nacional de Computação Científica, Petrópolis, RJ.

$$\left\{ \begin{array}{l} \frac{\partial w}{\partial t} = \nabla \cdot (D_w \nabla w) + \alpha_w m(1-w) - \beta_w(n+h+m)w - \gamma_w w \\ \frac{\partial n}{\partial t} = \nabla \cdot (D_n (\max\{n-\nu_c, 0\} + 1) \nabla n) - \nabla \cdot (n \bar{\chi}_n \nabla f) + \alpha_n n \max\{1-\nu, 0\} \\ \quad - \alpha_h \mathcal{H}(\omega_h - w)n + h_n \alpha_n \mathcal{H}(w - \omega_h)h \\ \frac{\partial h}{\partial t} = \nabla \cdot (D_h \nabla h) + \alpha_h \mathcal{H}(\omega_h - w)n - h_n \alpha_h \mathcal{H}(w - \omega_h)h - \beta_h \mathcal{H}(\omega_a - w)h \\ \frac{\partial a}{\partial t} = \nabla \cdot (D_a \nabla a) + \beta_h \mathcal{H}(\omega_a - w)h \\ \frac{\partial m}{\partial t} = \nabla \cdot (D_m \nabla m) - \nabla \cdot (m \bar{\chi}_m \nabla g) + \alpha_m m g \max\{1-\nu, 0\} \\ \frac{\partial f}{\partial t} = -\beta_f n f \\ \frac{\partial g}{\partial t} = \nabla \cdot (D_g \nabla g) + \alpha_g h \max\{1-g, 0\} - \beta_g m g \end{array} \right.$$



Computational domain



Numerical experiments:

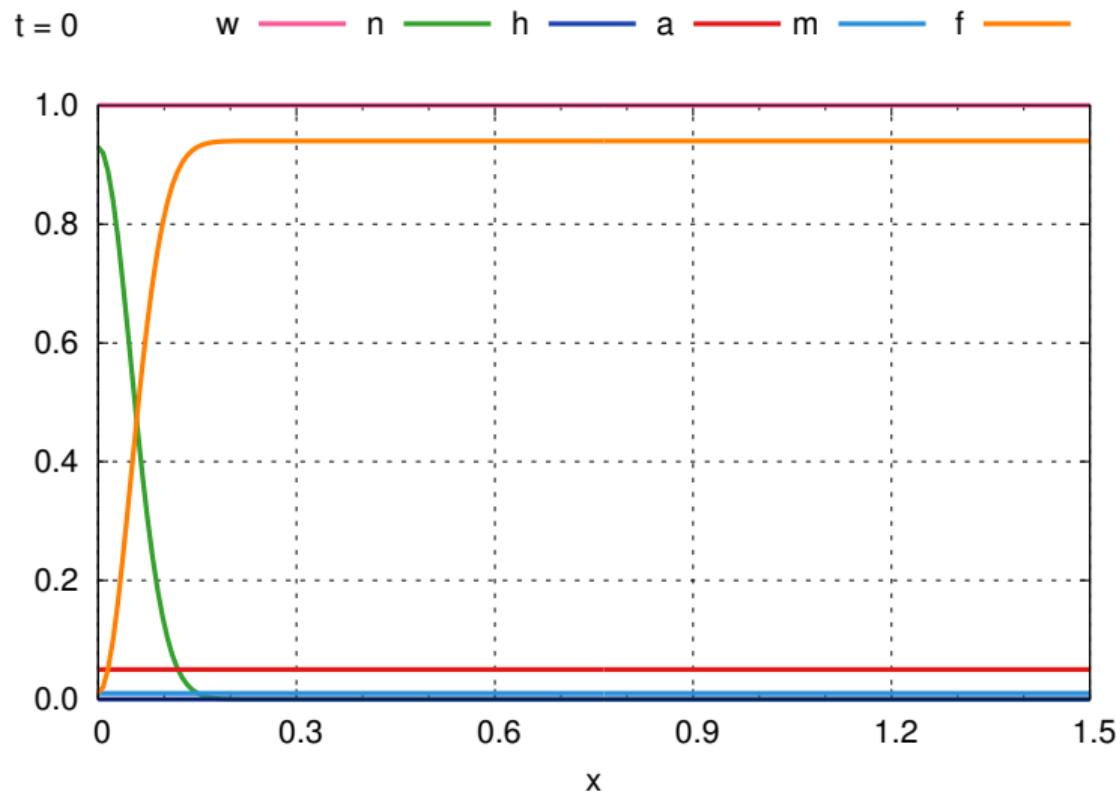


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

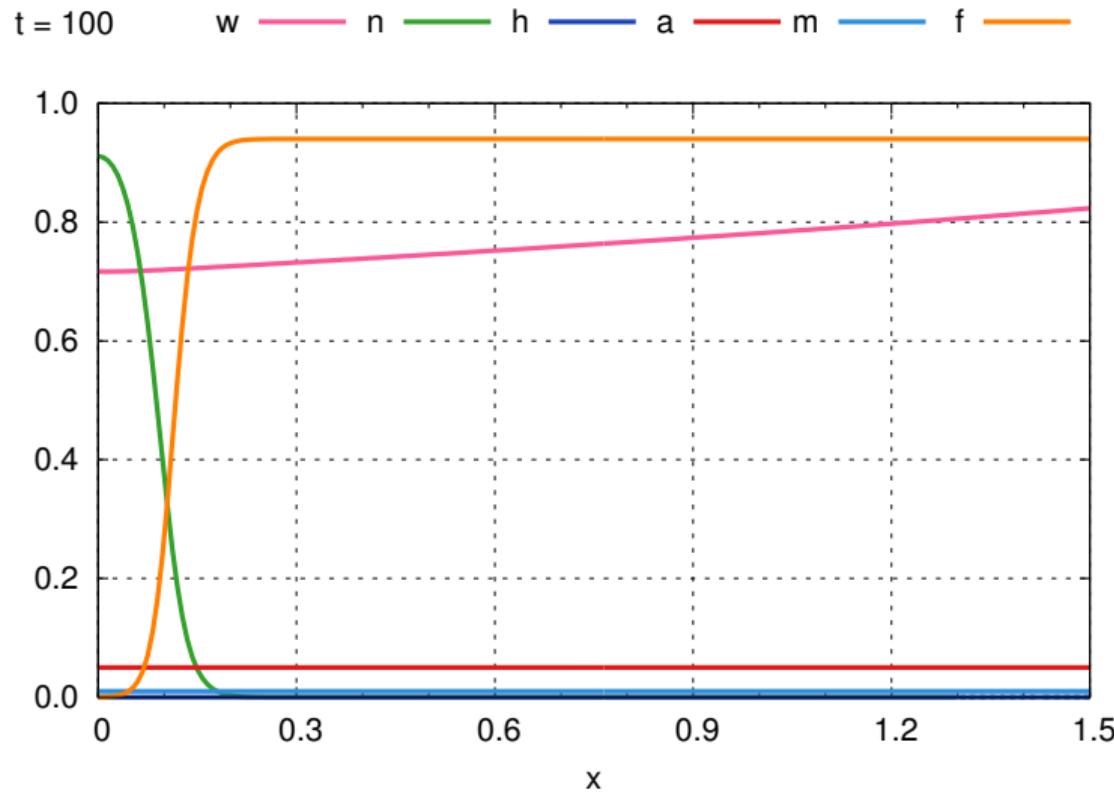


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

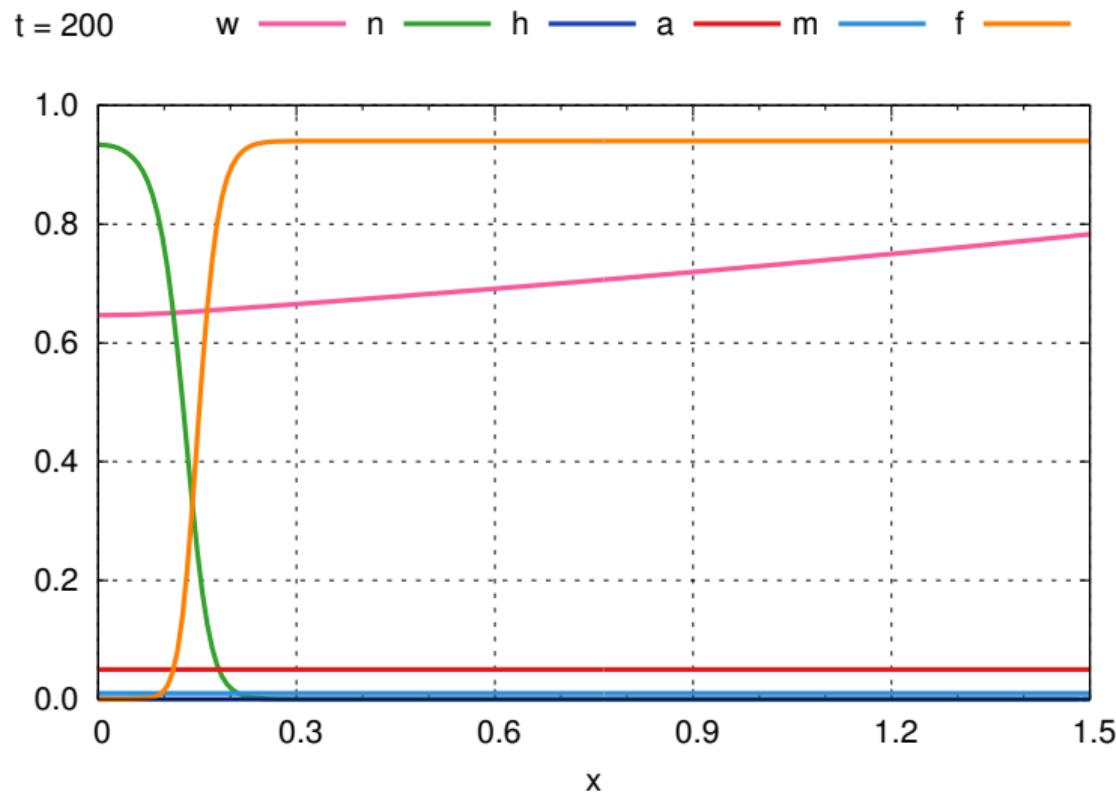


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

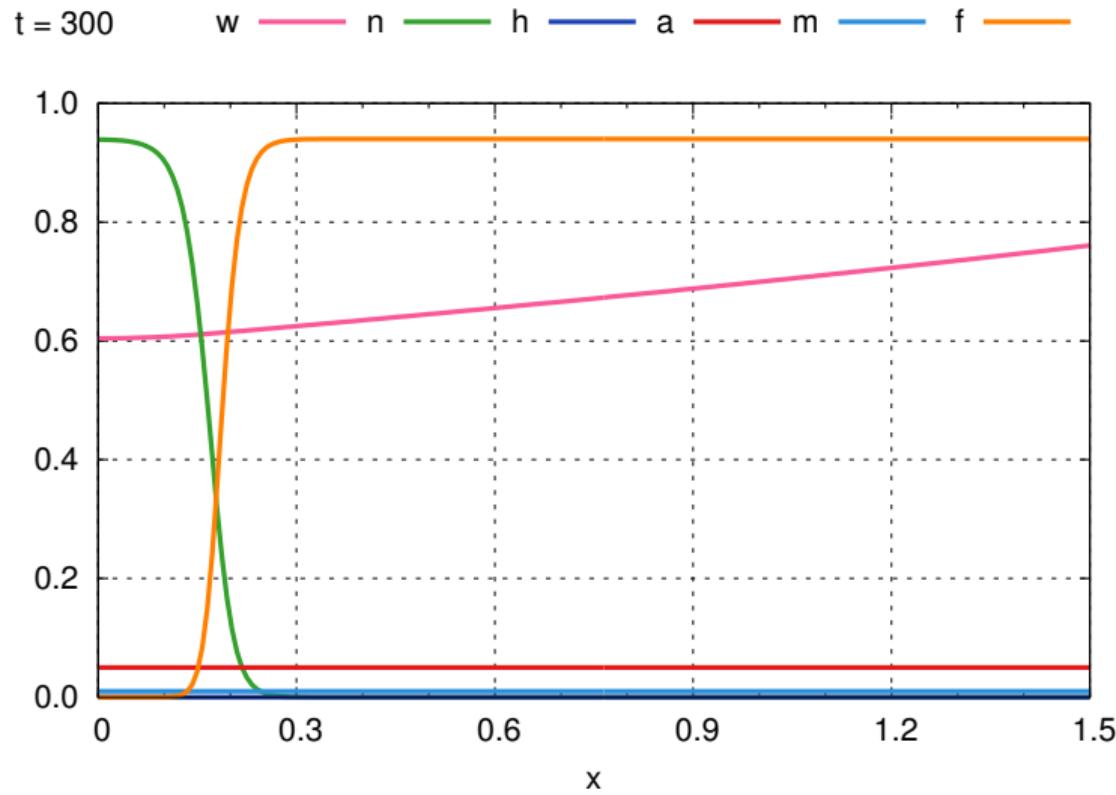


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

$t = 400$

w — n — h — a — m — f —

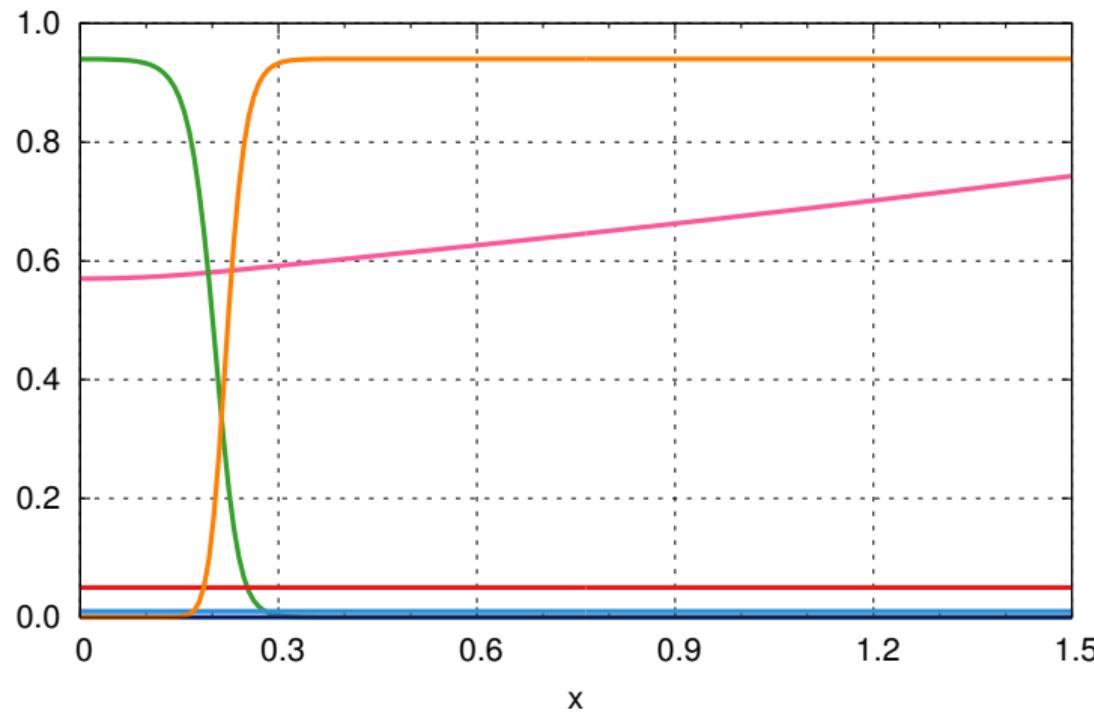


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

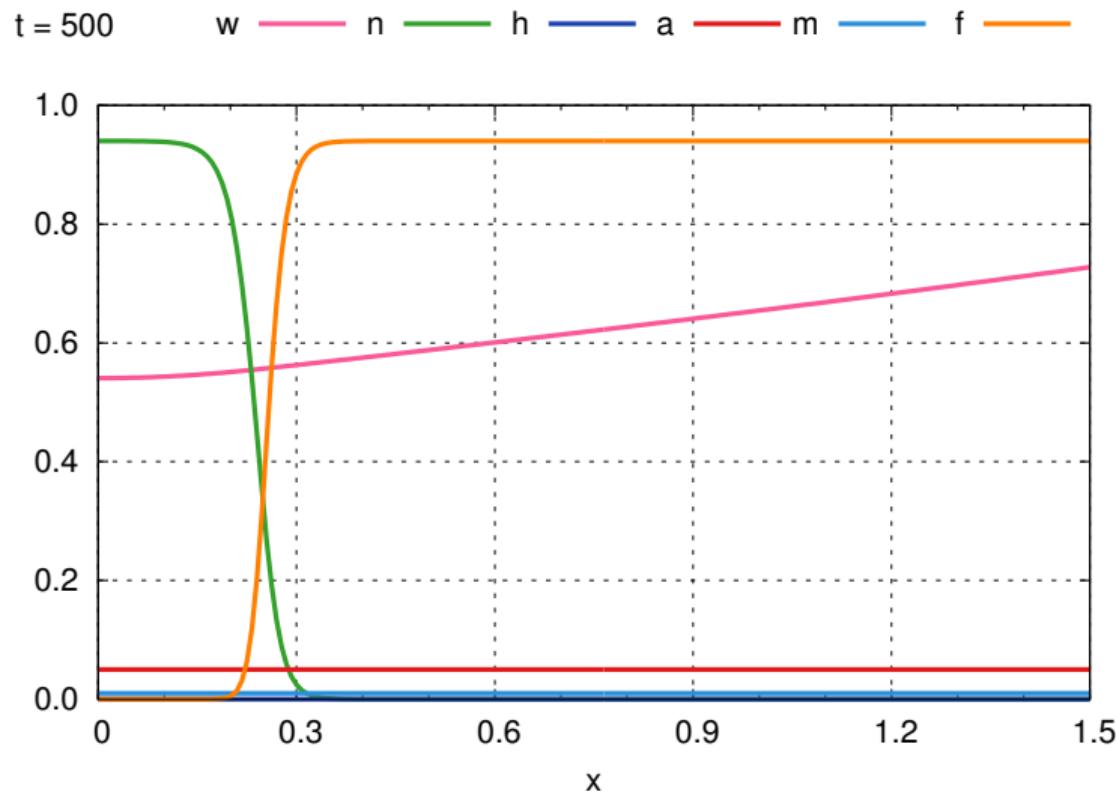


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

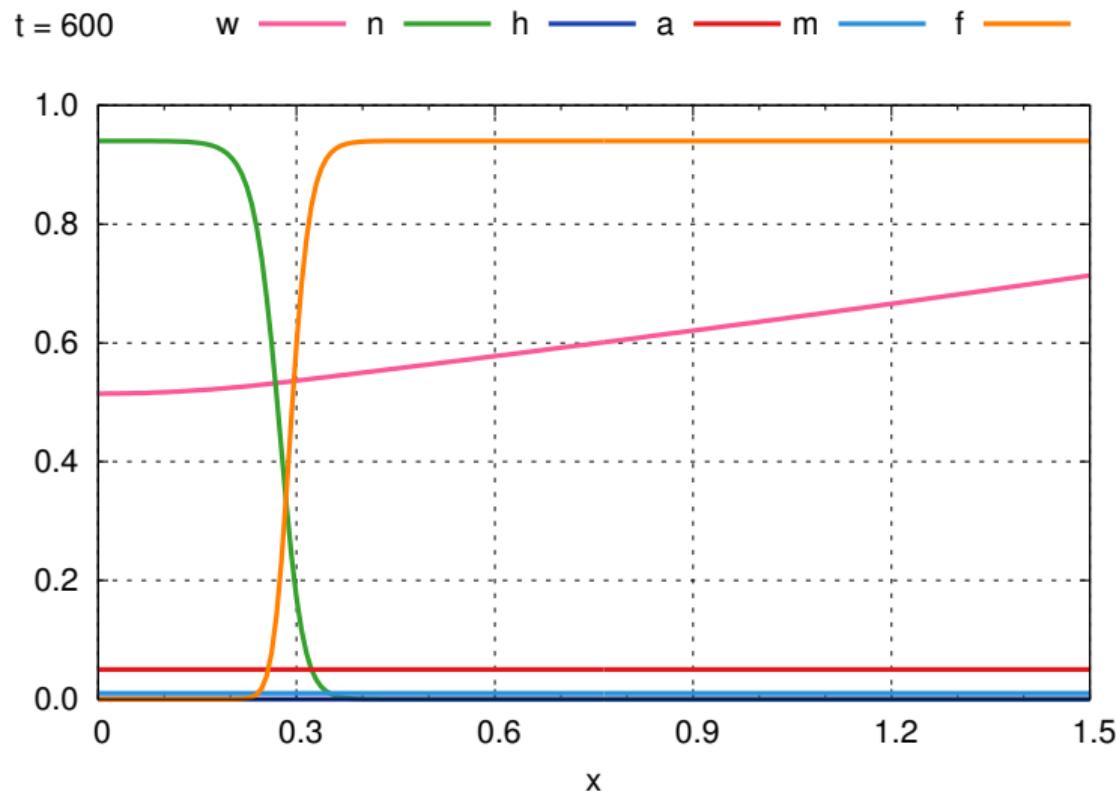


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

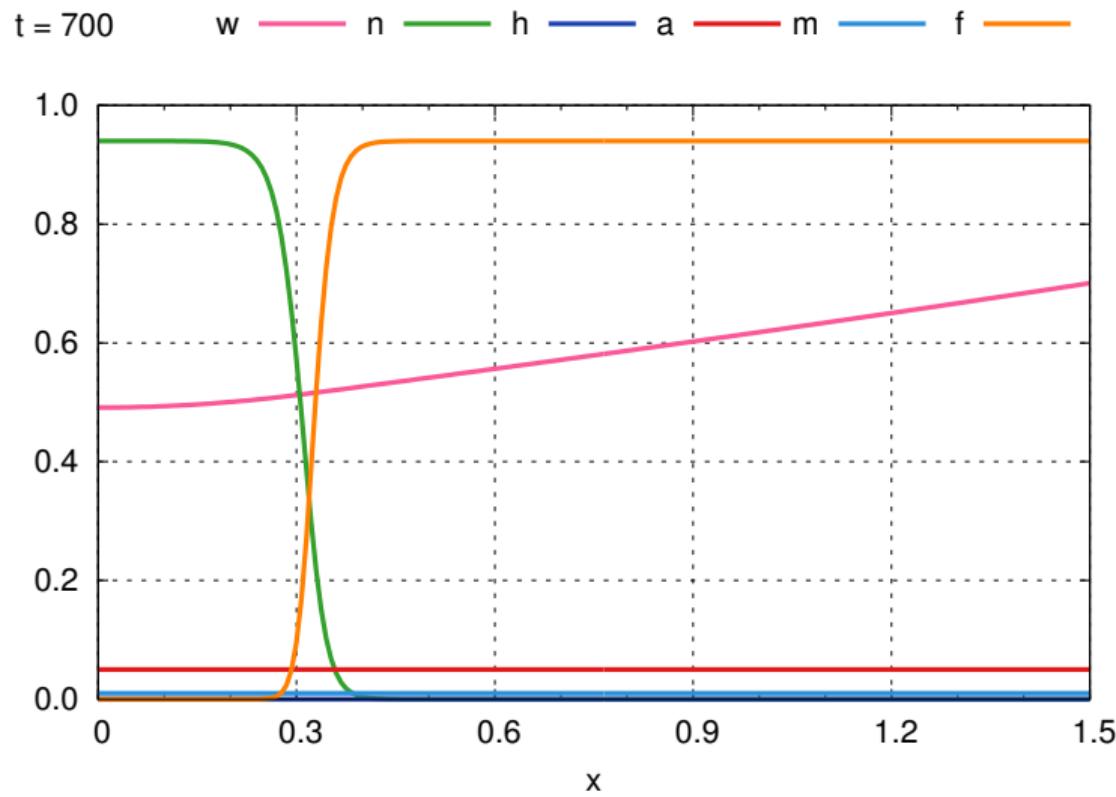


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

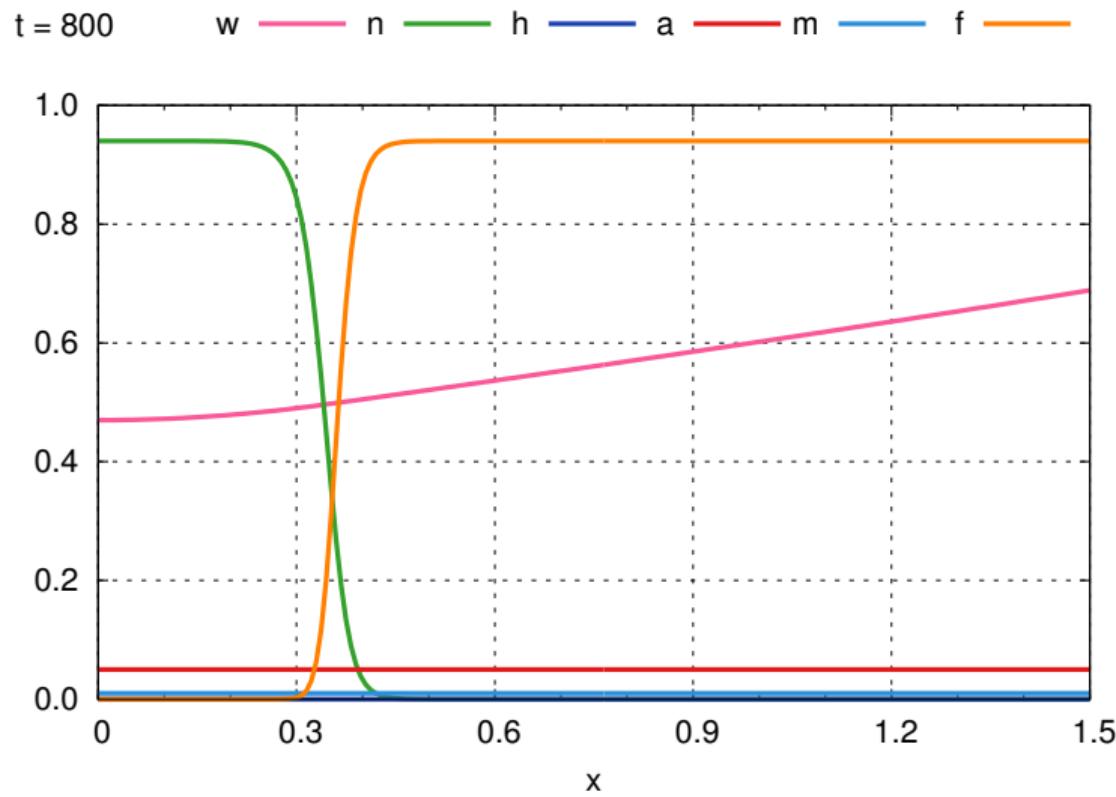


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

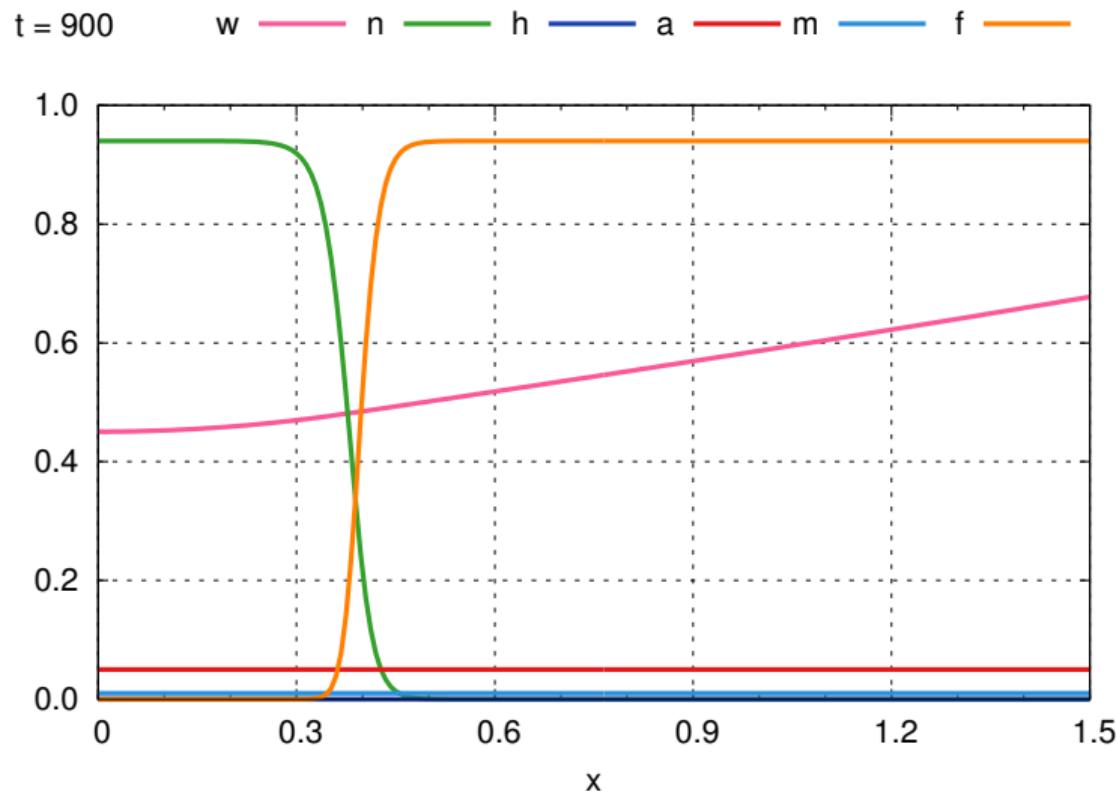


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

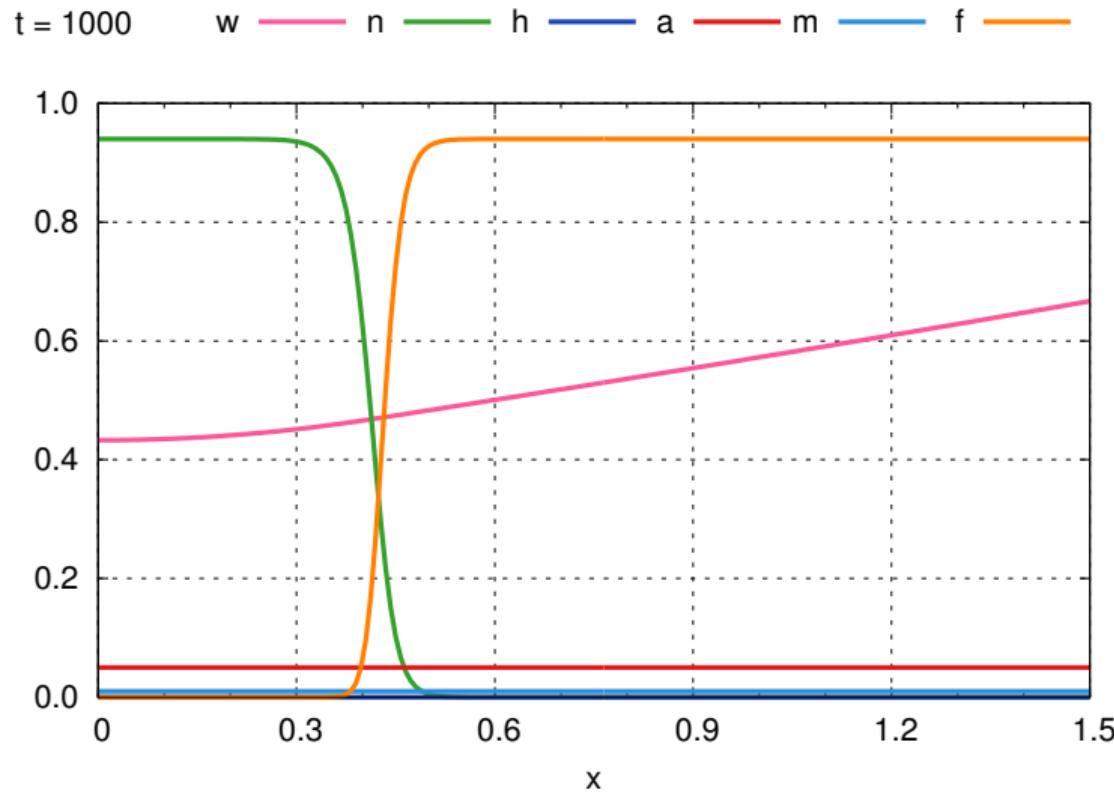


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

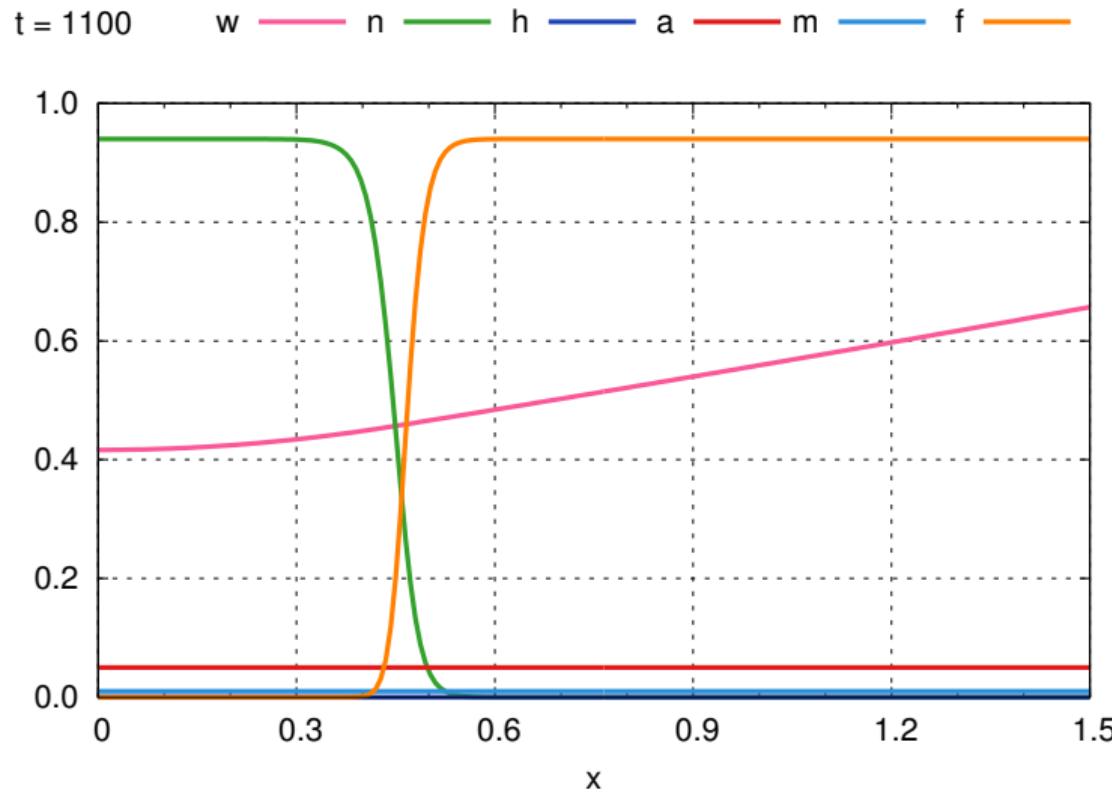


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

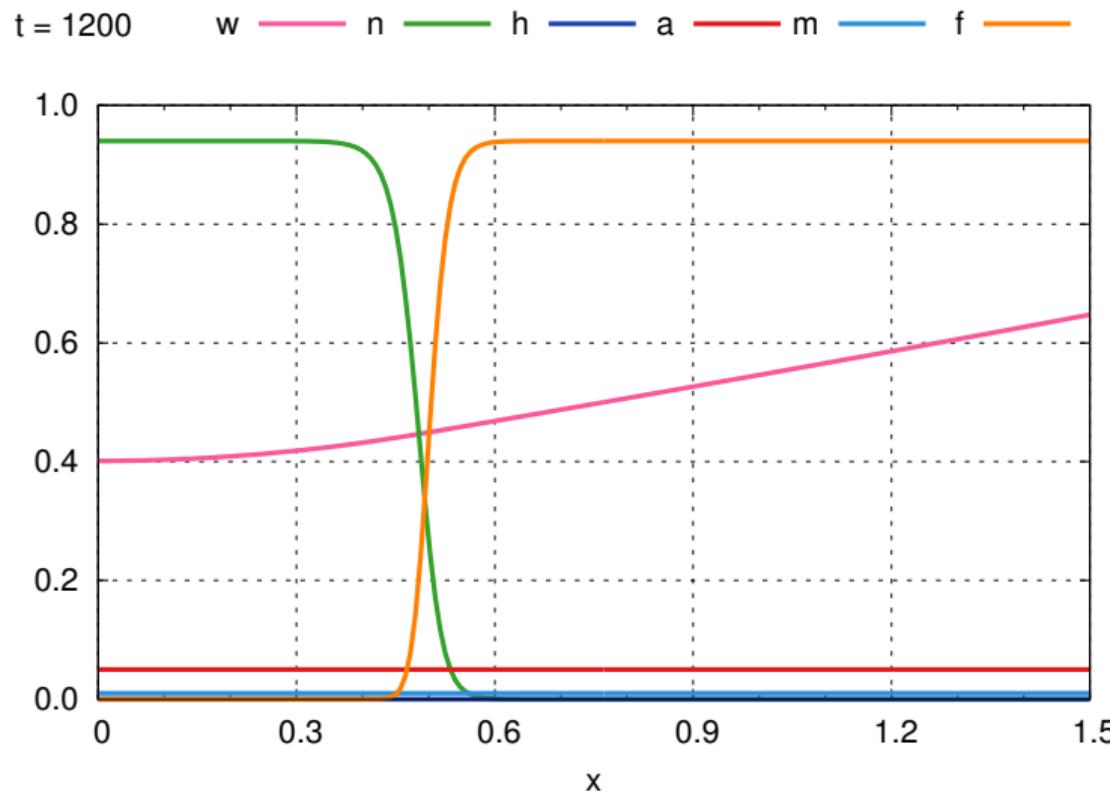


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

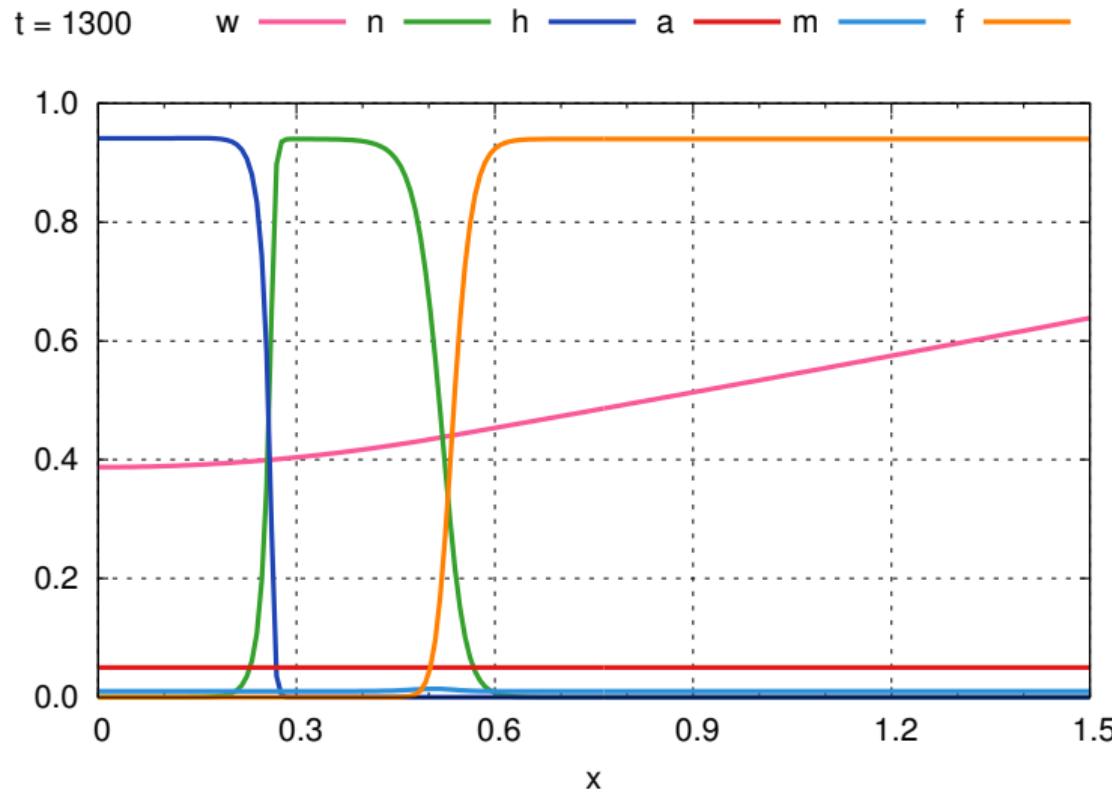


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

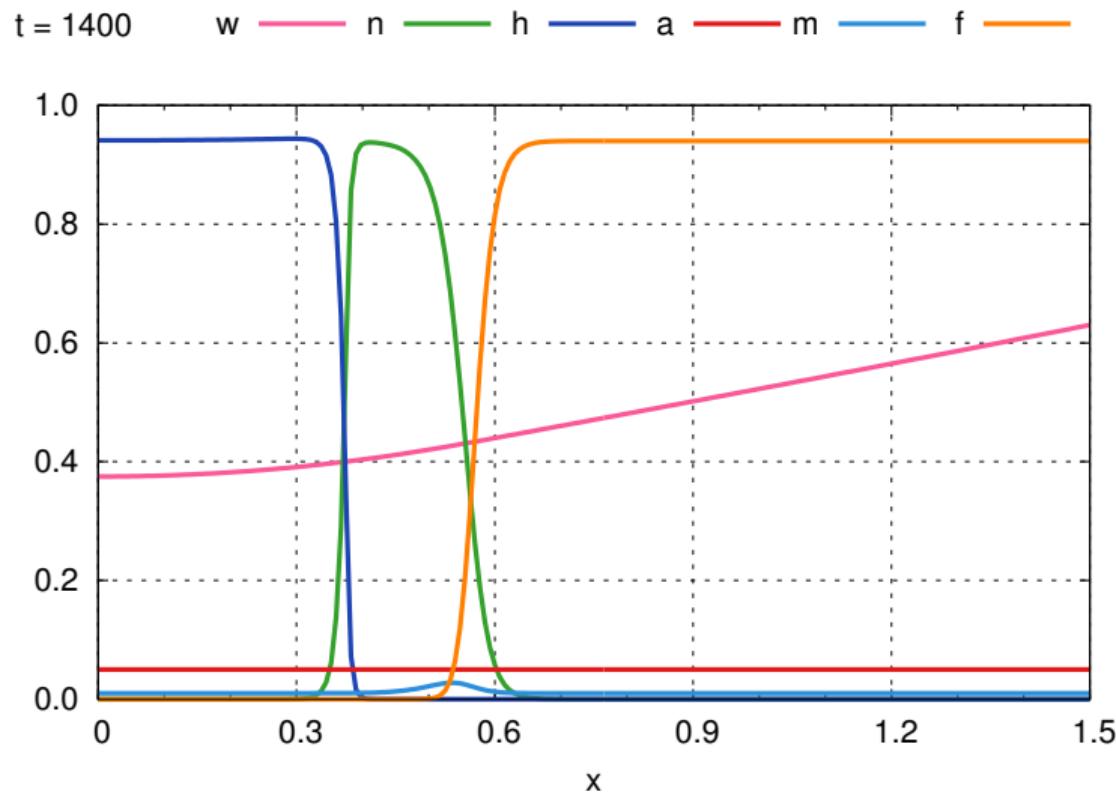


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Numerical experiments:

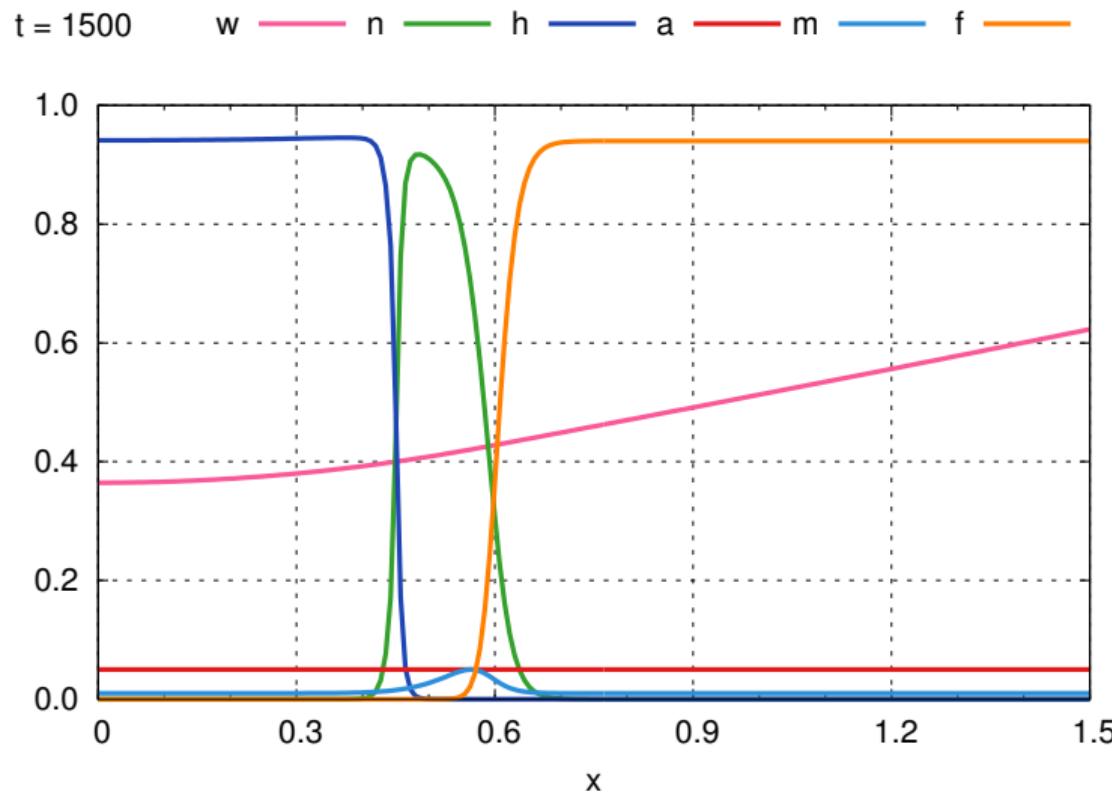


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Numerical experiments:

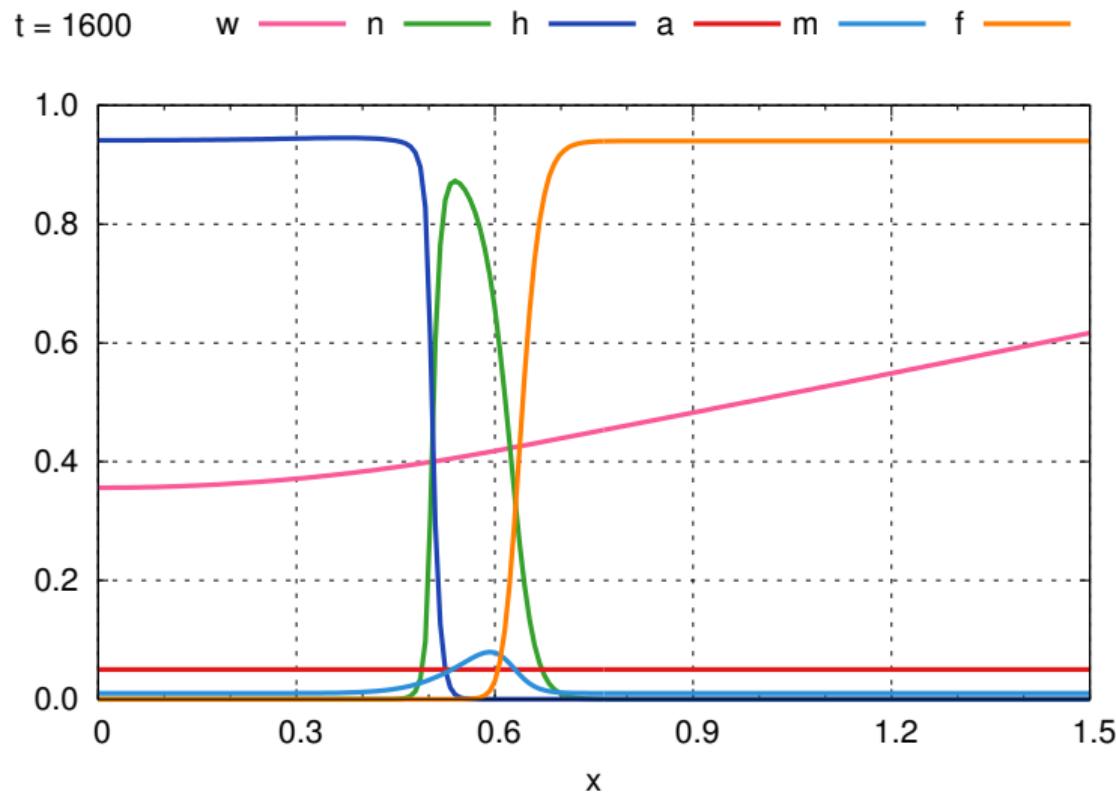


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Numerical experiments:

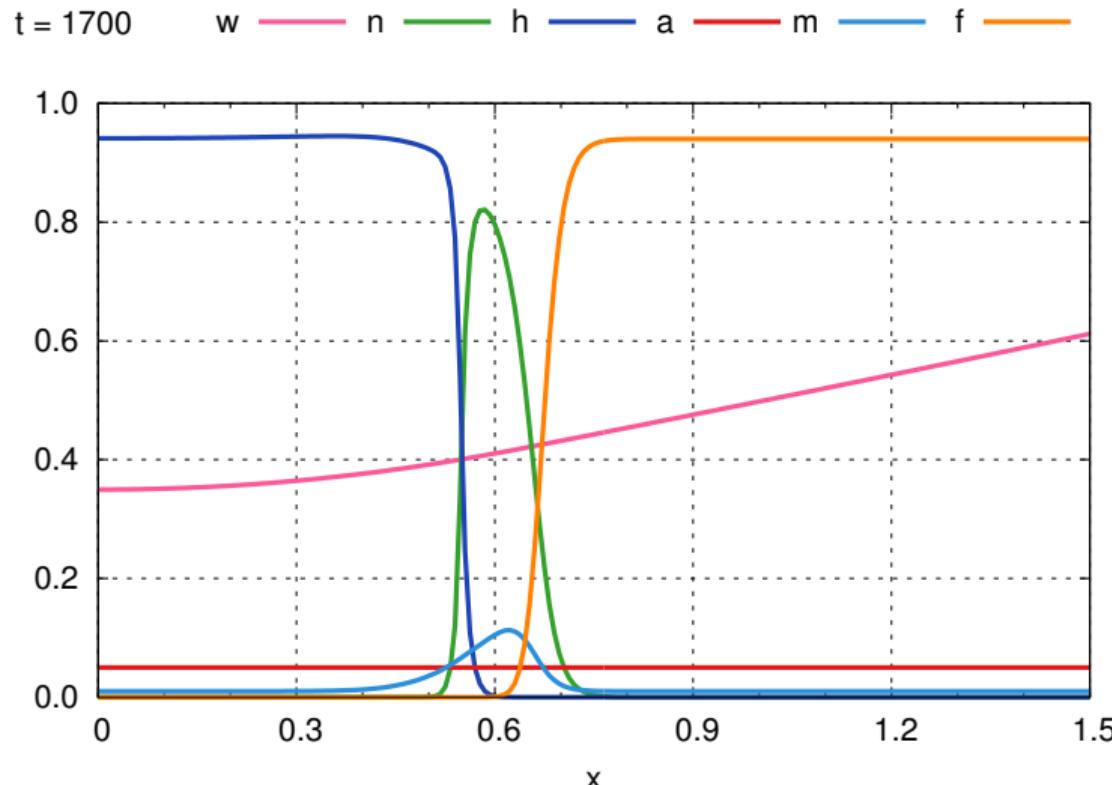


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Numerical experiments:

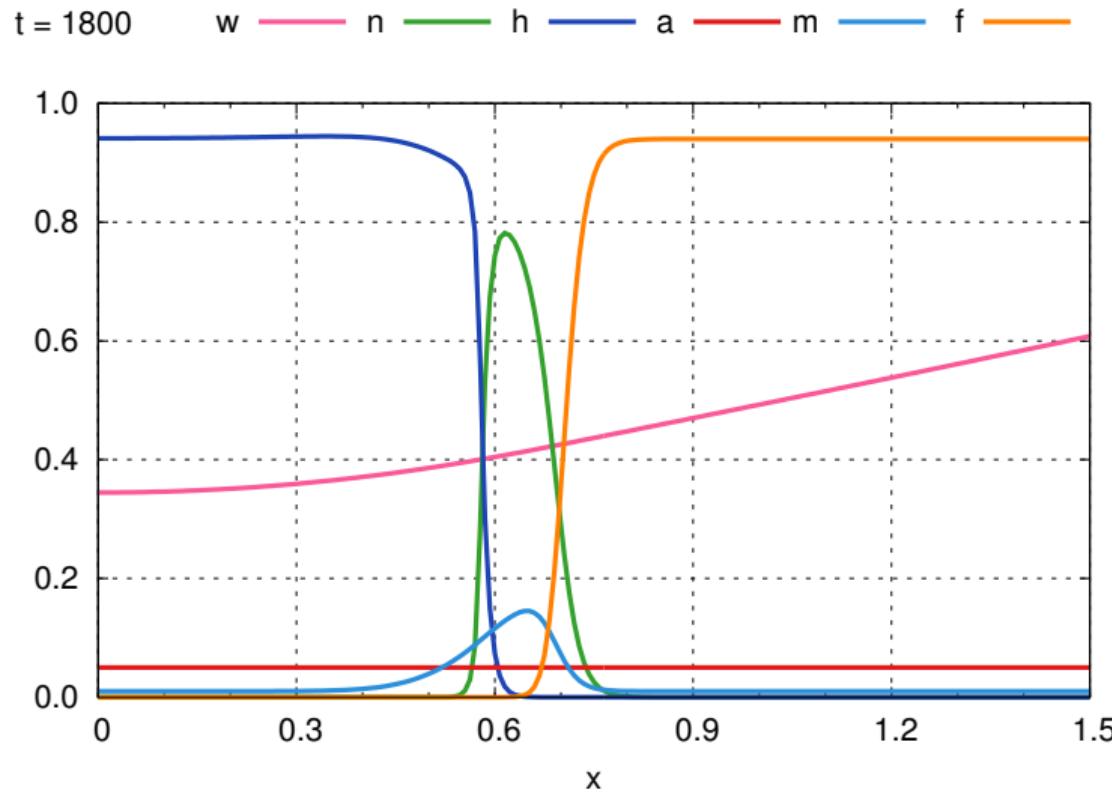


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Numerical experiments:

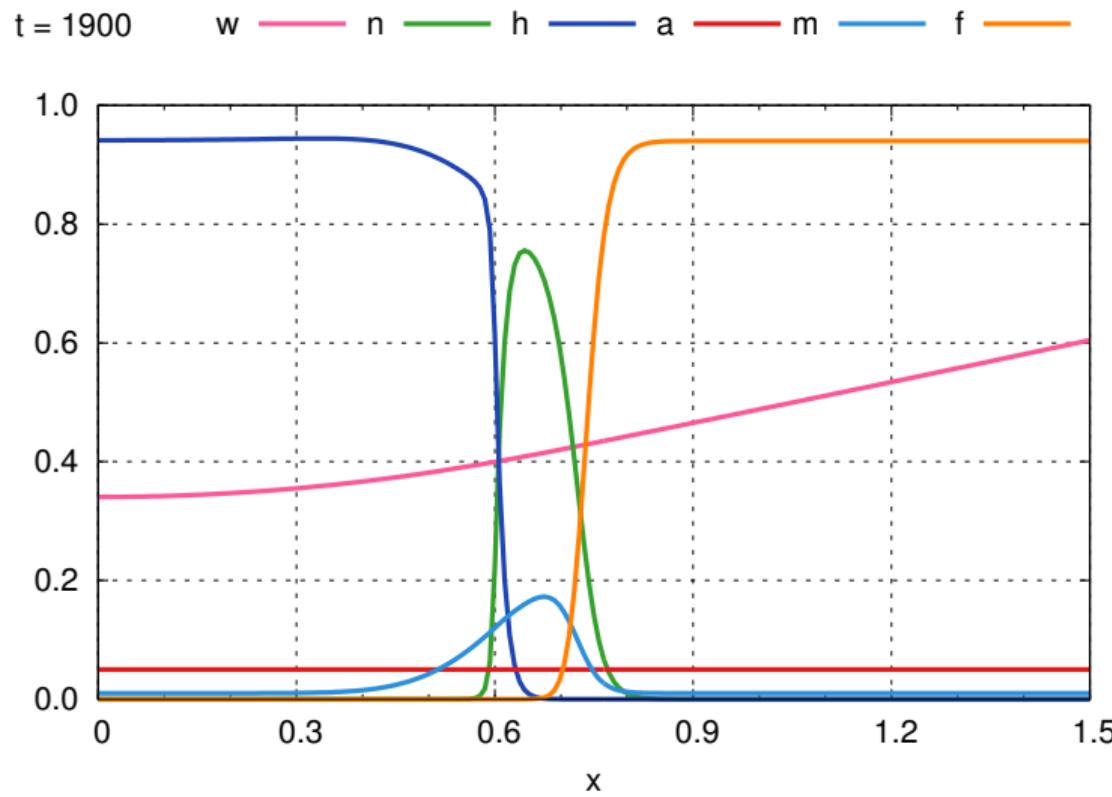


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

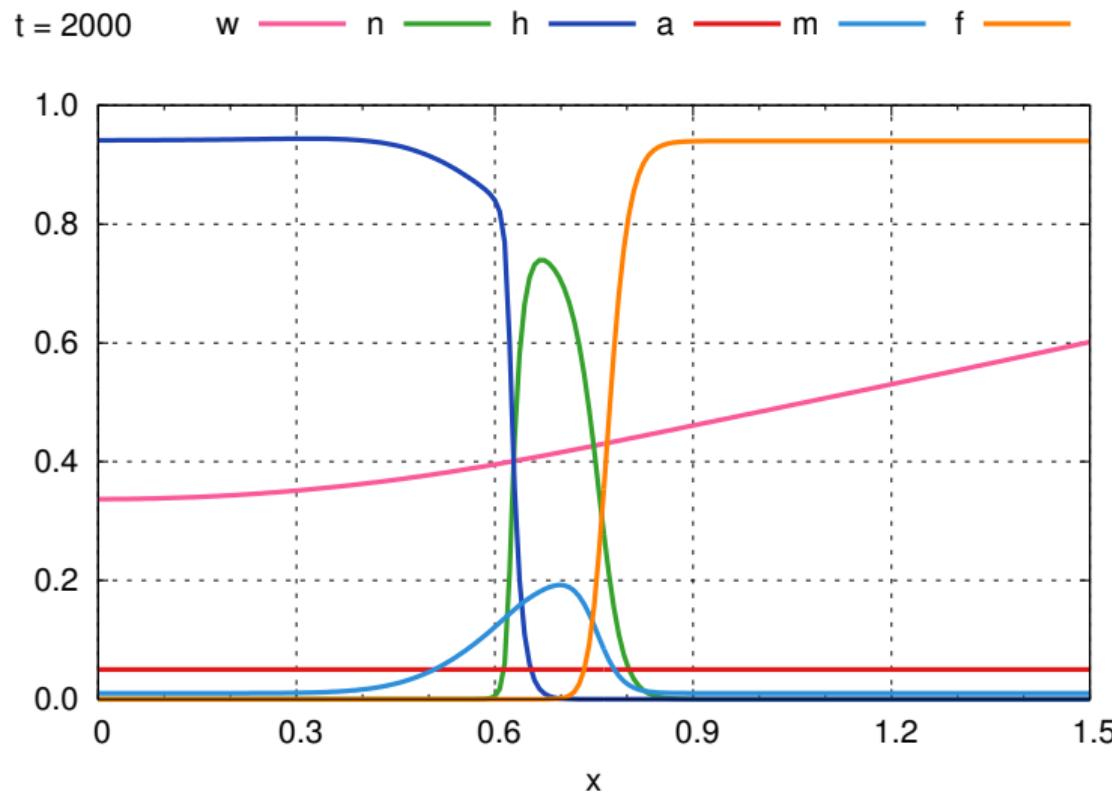


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

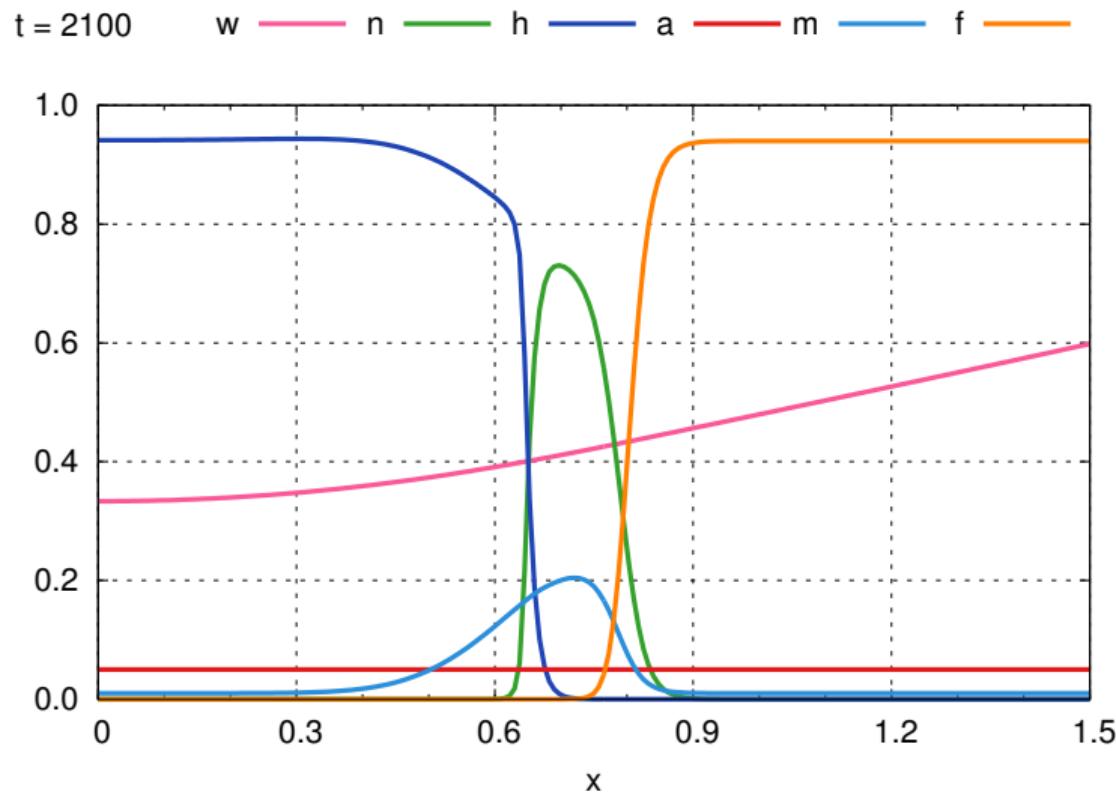


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

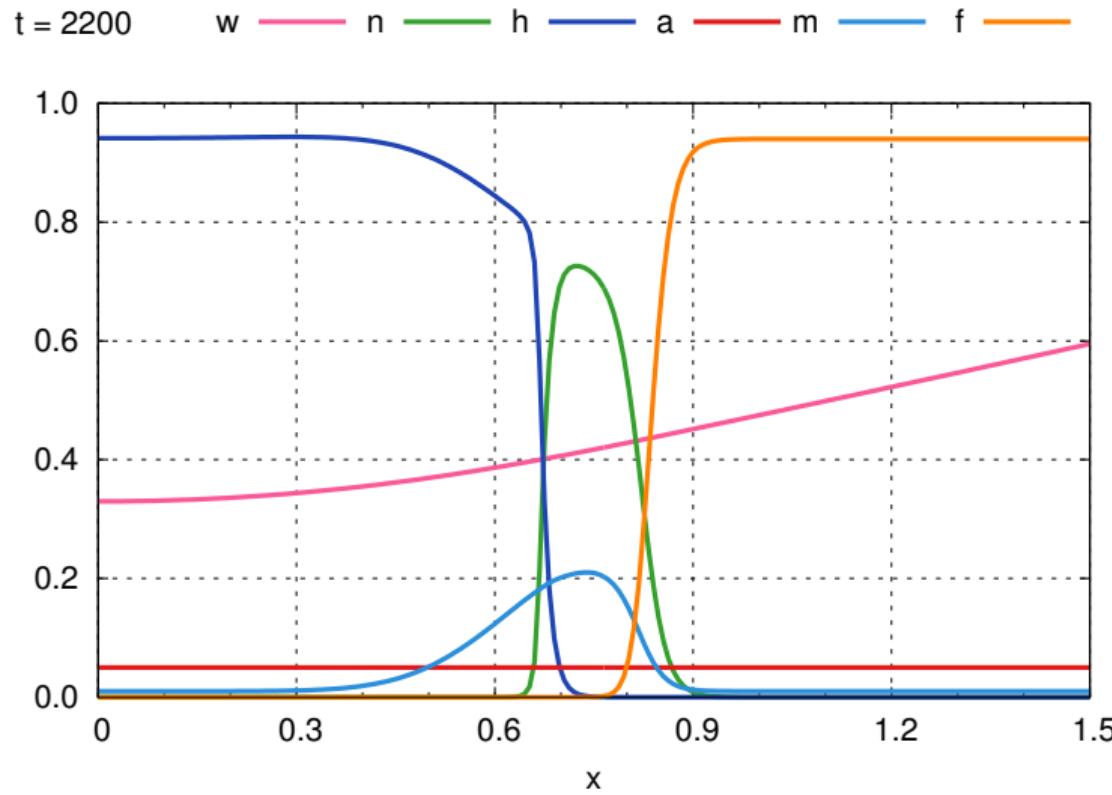


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Numerical experiments:

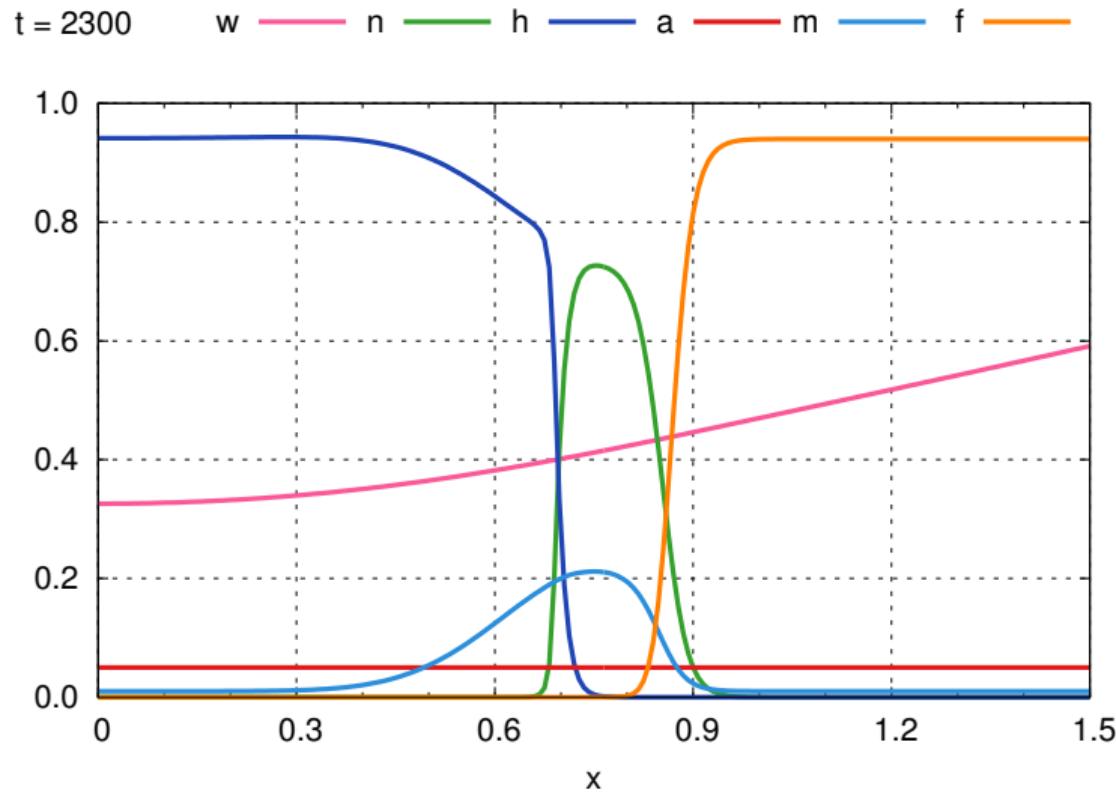


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Numerical experiments:

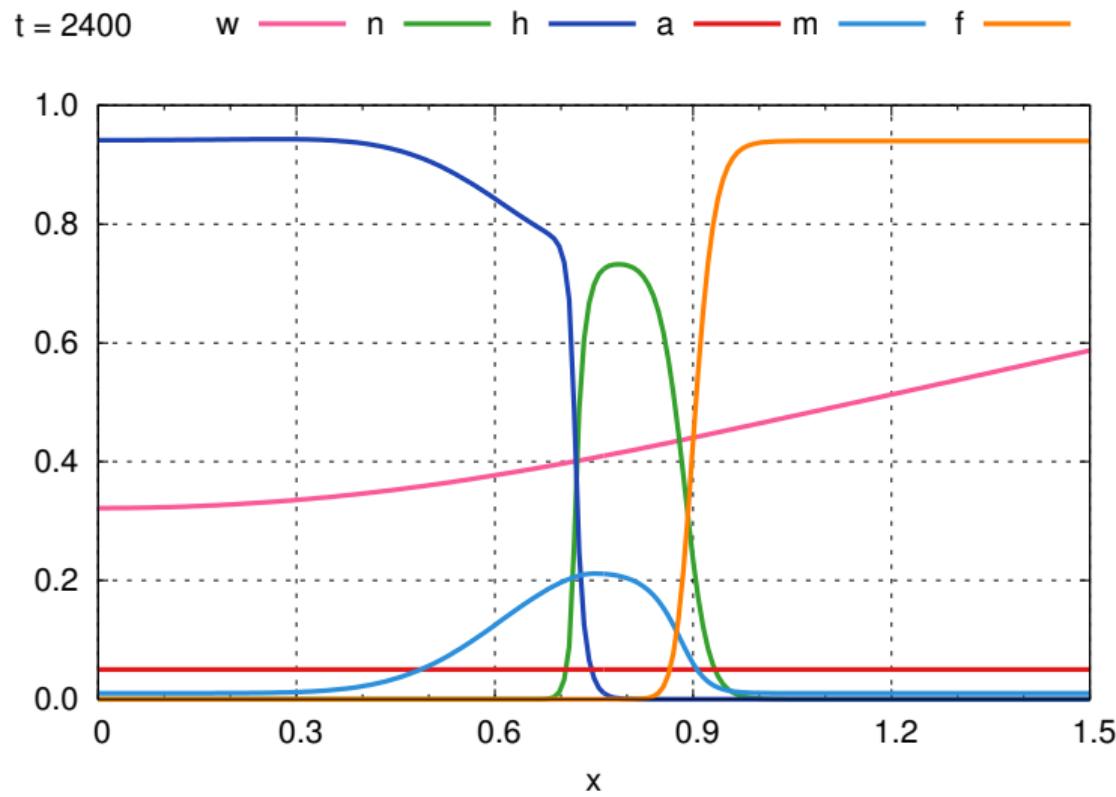


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Numerical experiments:

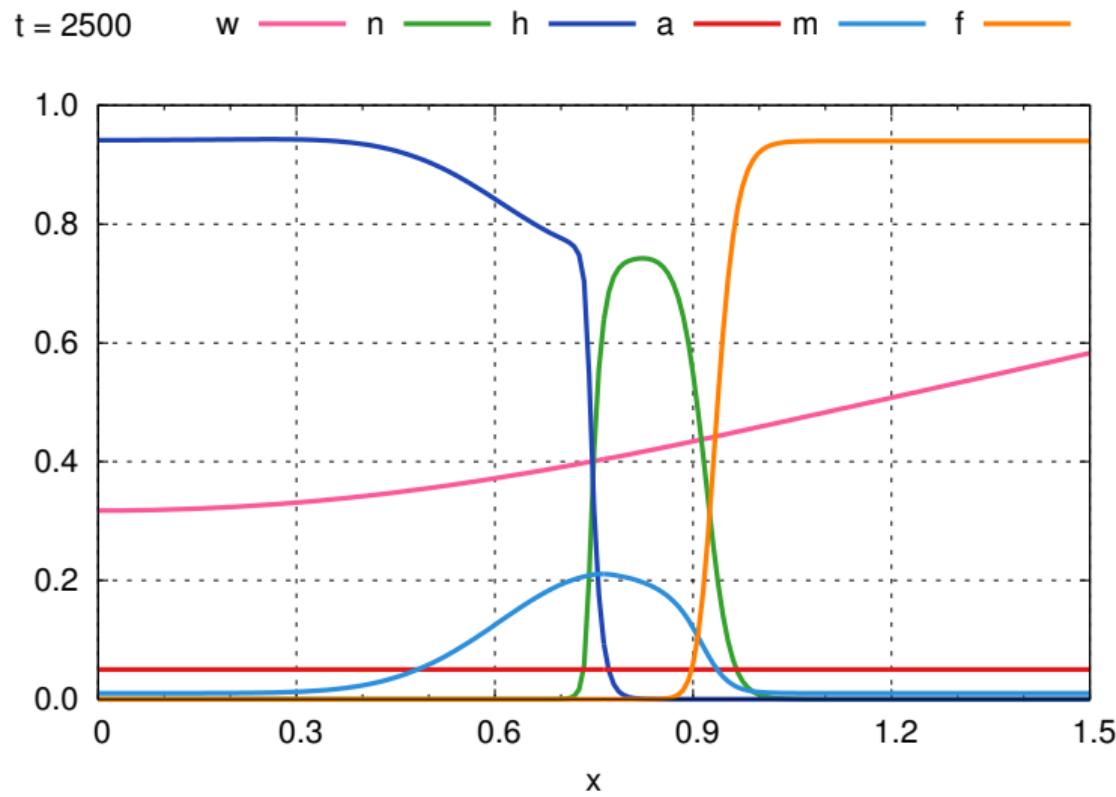


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

$t = 2600$

w — n — h — a — m — f —

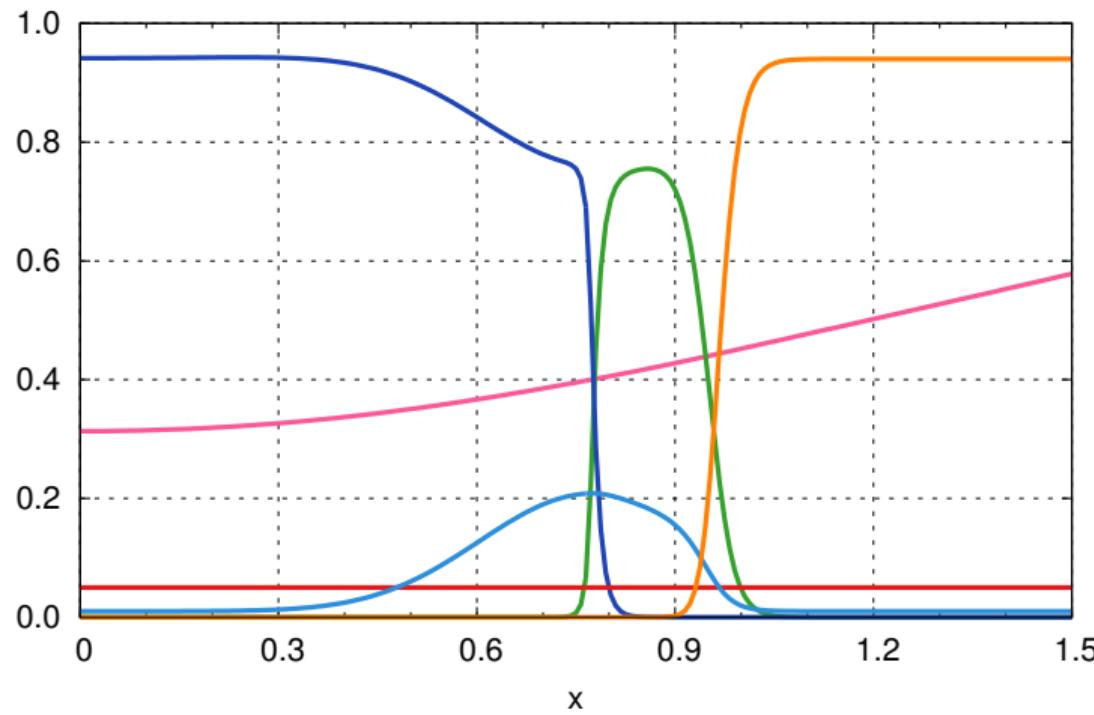


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

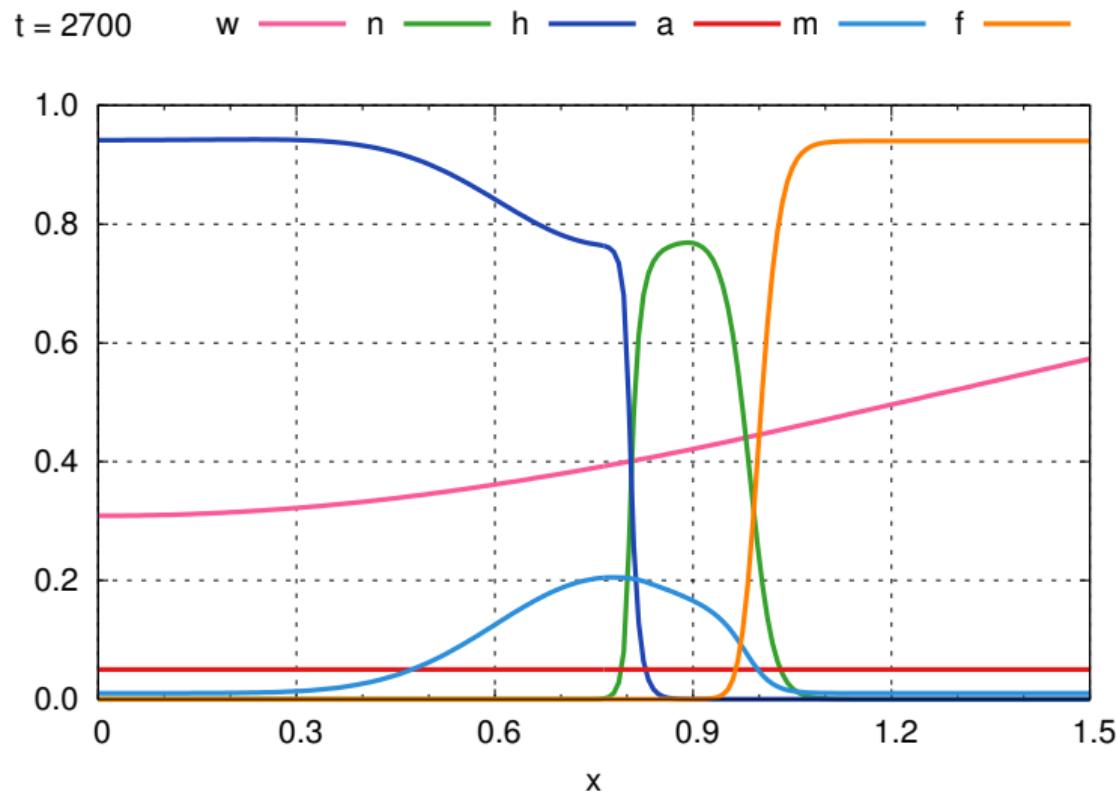


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

$t = 2800$

w — n — h — a — m — f —

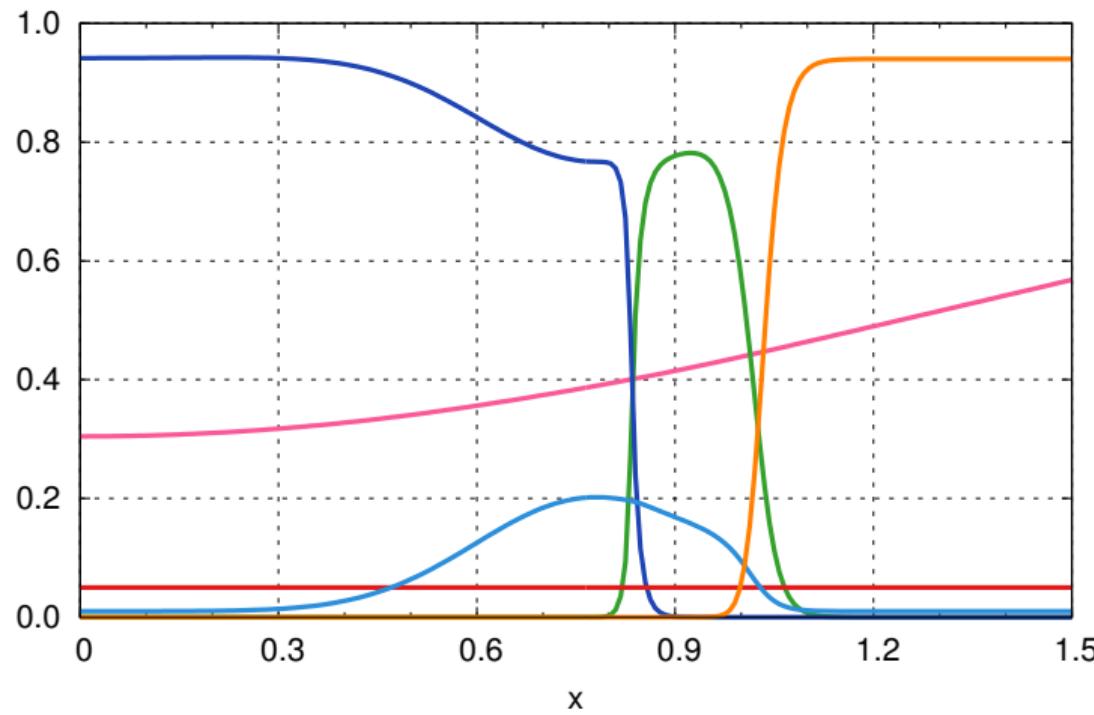


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

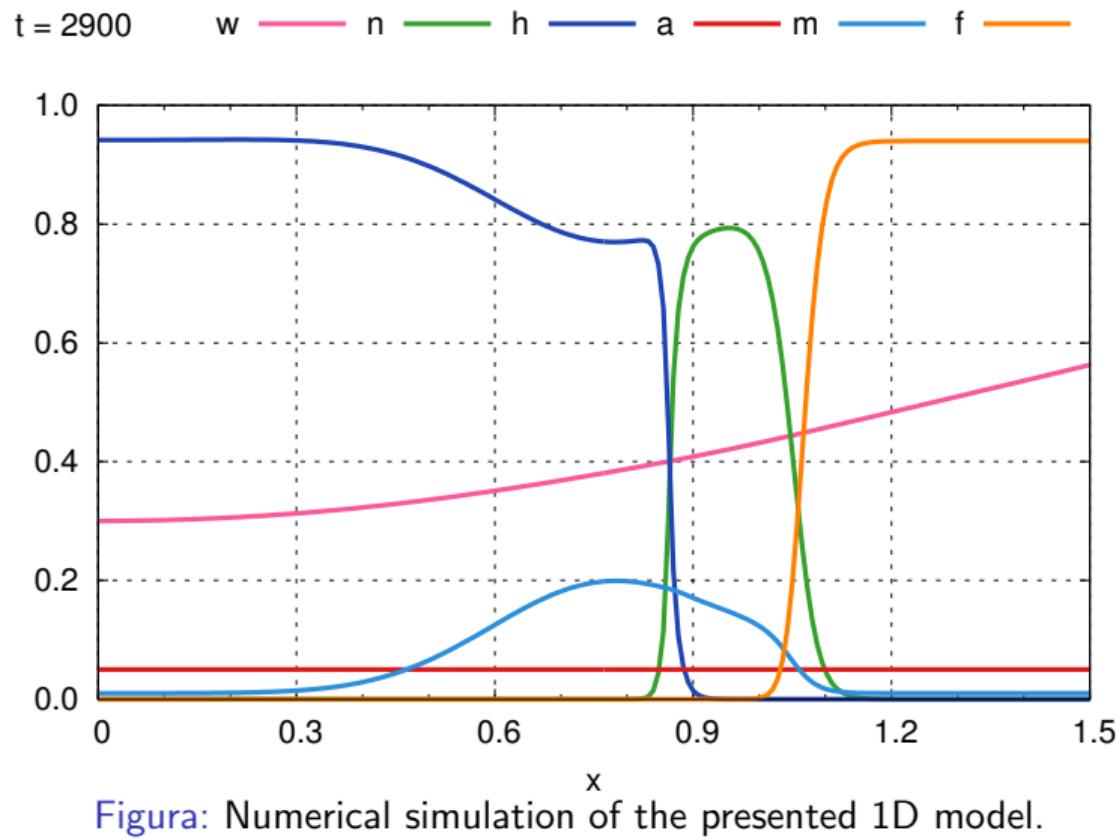


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

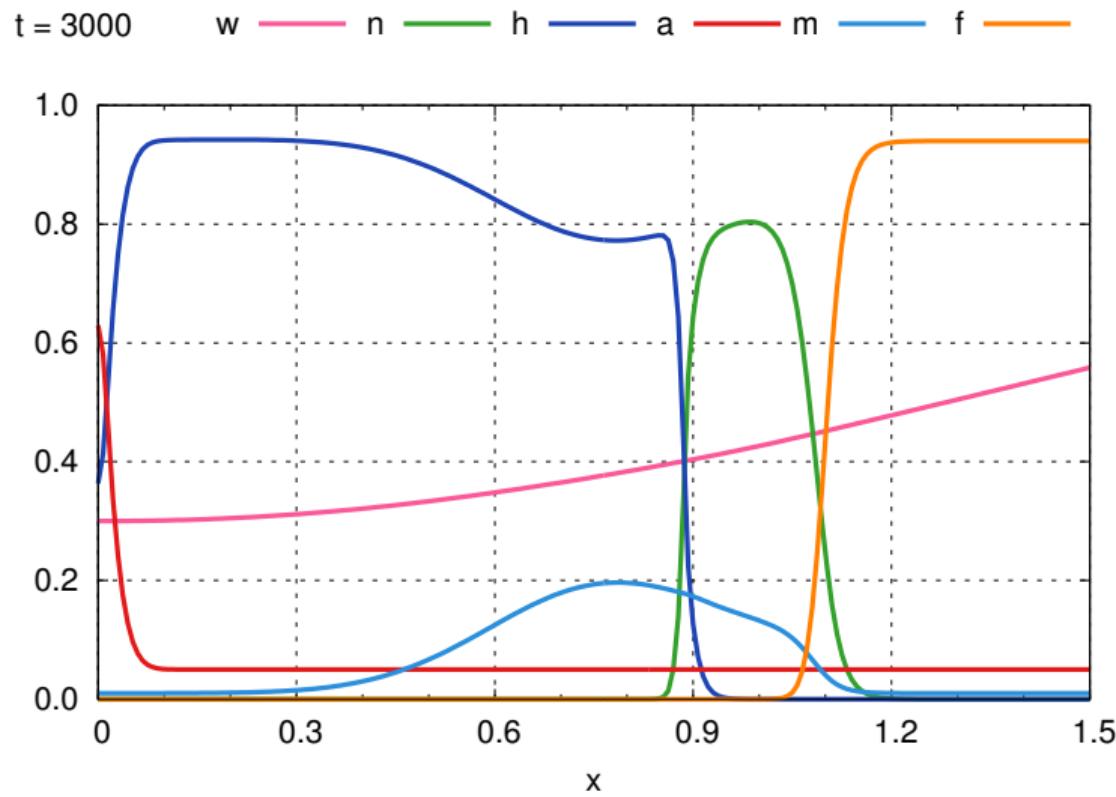


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

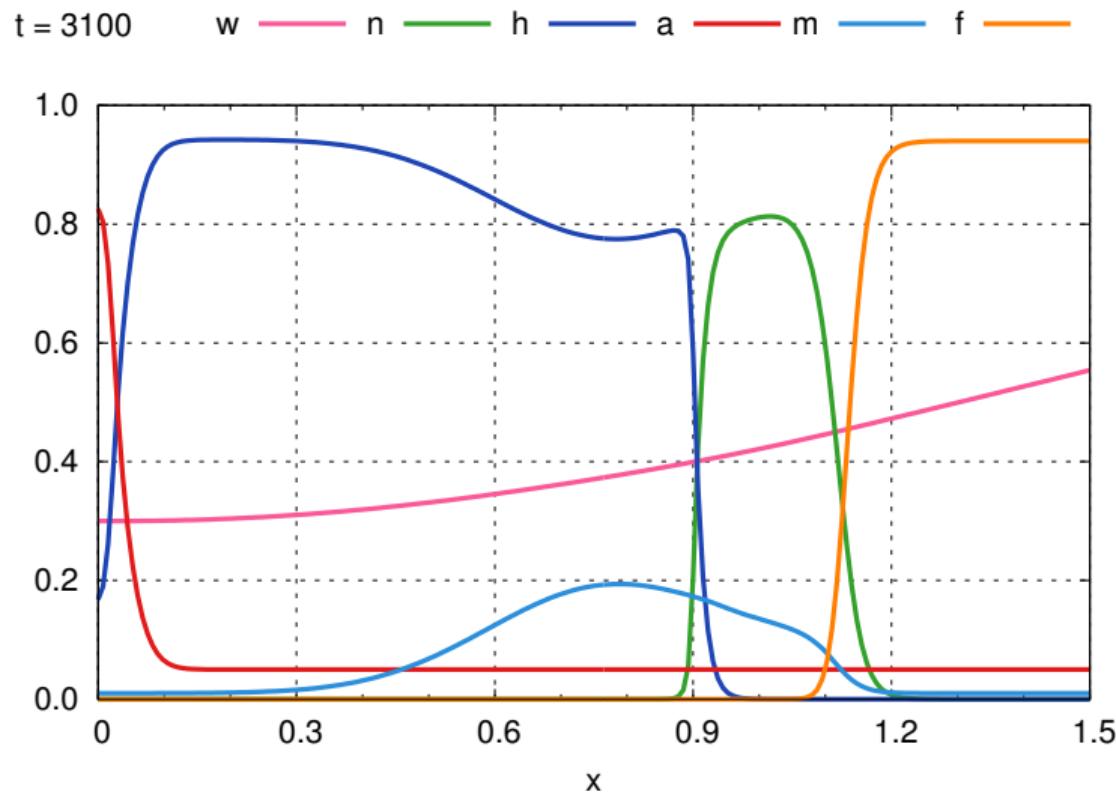


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:

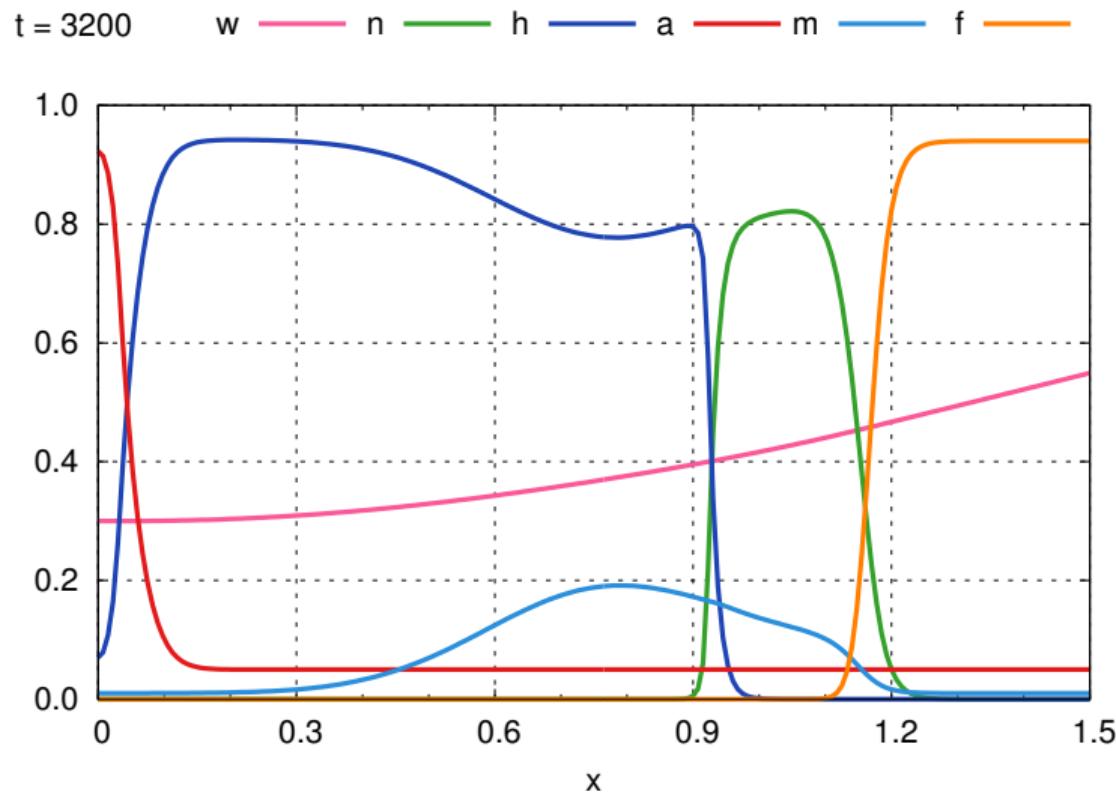
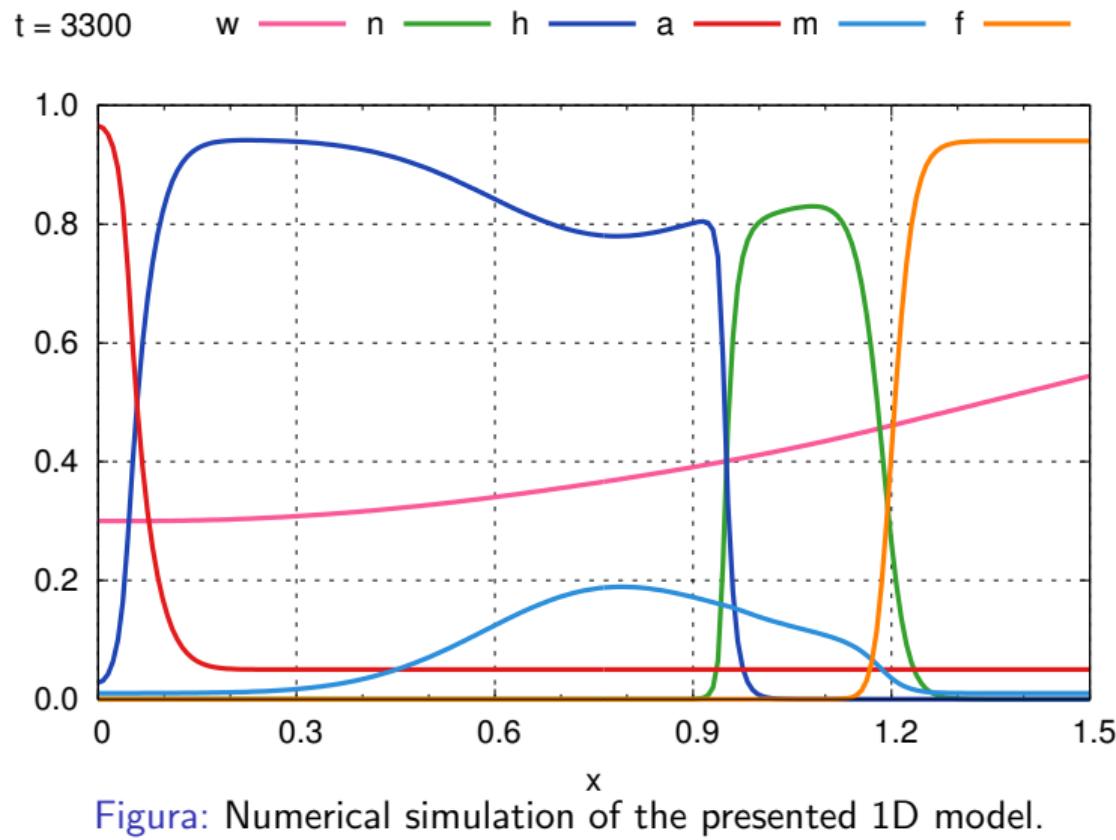


Figura: Numerical simulation of the presented 1D model.

Numerical experiments:



Numerical experiments:

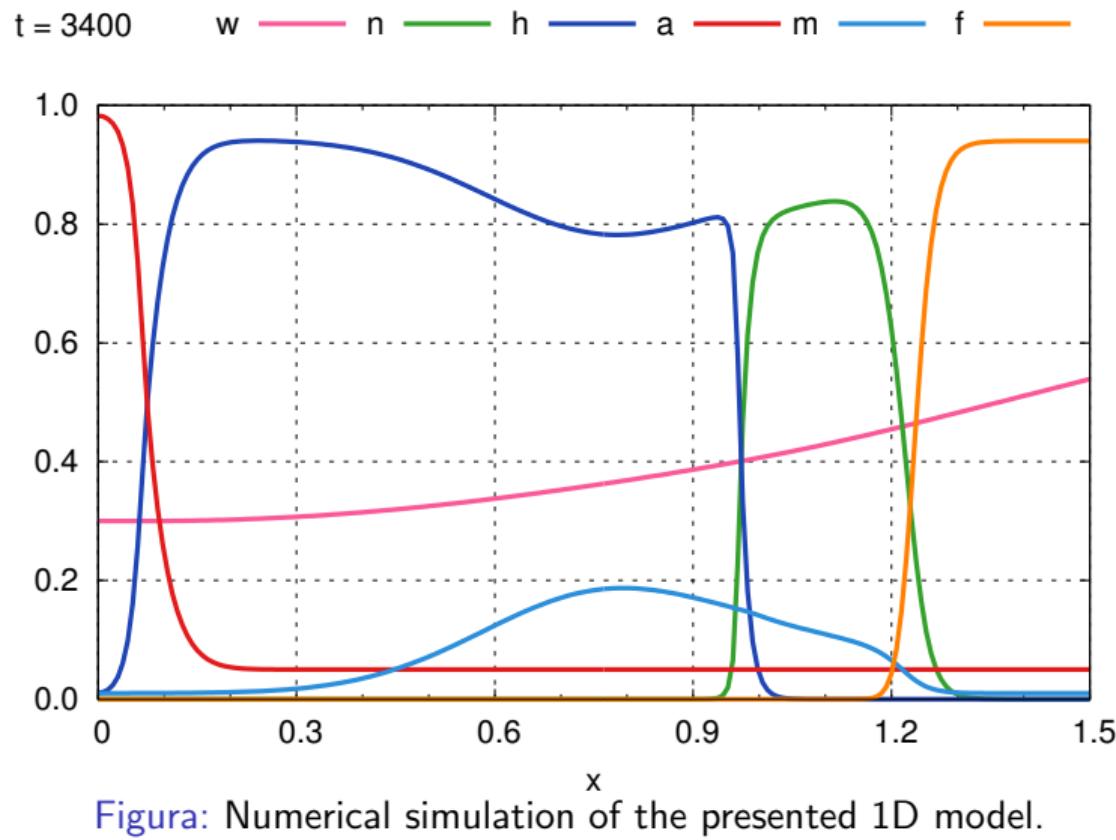


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Numerical experiments:

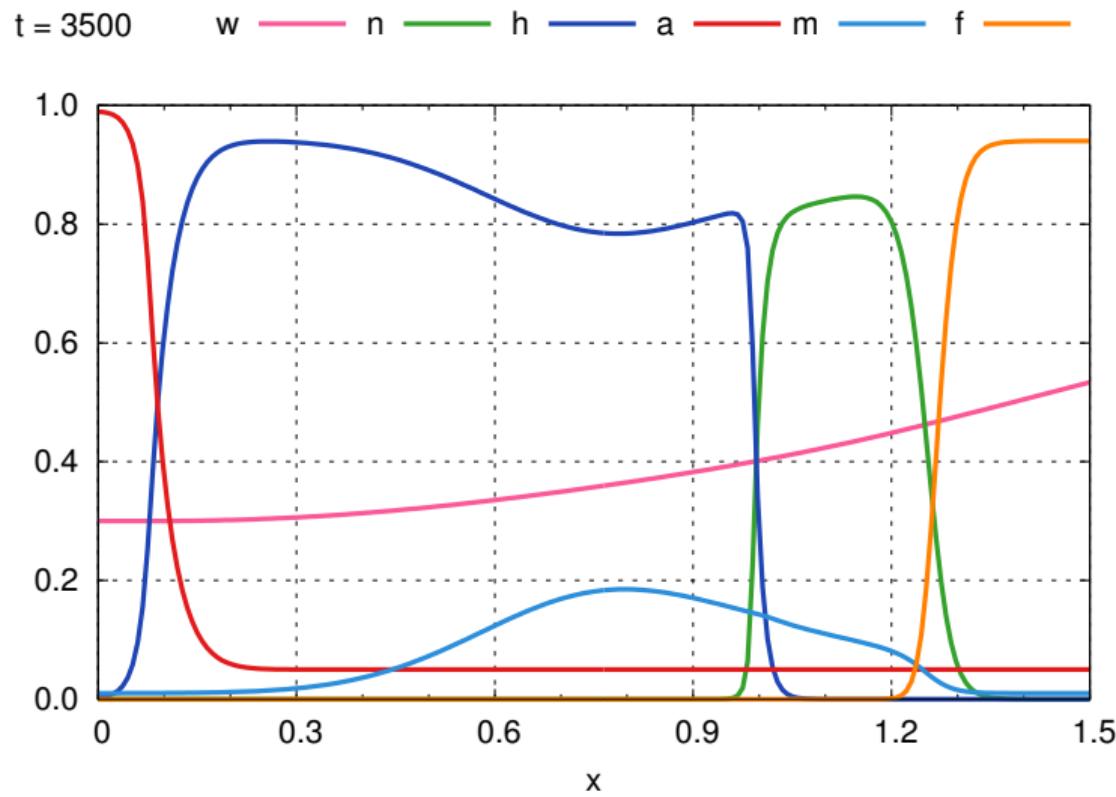


Figura: Numerical simulation of the presented 1D model.

Model Classification

① Continuos models:

- Ordinary Differential Equation - ODE (continuous time)
- Recursion Equation (discrete time)
- Partial Differential Equation - PDE

② Discrete models:

- Cellular Automata (CA)
- Agent-Based Model (ABM)

③ Hybrid models

Discrete Models

Advantage

They capture interactions between cells

Disadvantage

High computational cost: $1\text{mm}^3 = 10^6$ cells

Cellular Automata

- CA are simple mathematical models composed of a large number of identical elements that interact with each other through well-defined rules
- These components are arranged in a network and are associated with each network site an automata that is represented by a variable discrete, which can assume a finite set of values.
- The time steps that describe the evolution are discrete and defined based on the update of the automata states.

Cellular Automata

Common features in CA models:

- ① Mesh
- ② Homogeneity
- ③ Discrete states
- ④ Local interactions
- ⑤ Discrete dynamic

Agent-Based Model

- A typical ABM has three elements:
 - Agents
 - Relations between agents
 - Environmental information

Agent Based Model

- **What is an agent?**

- A discrete entity with its own goals and behaviors
- Autonomous, with a capability to adapt and modify its behaviors
- Can be heterogeneous

- **Assumptions/Rules:**

- Key aspects of behaviors are described
- Description of interaction mechanisms
- Agents can move in a lattice-free space

Agent Based Model

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What is an agent?

Cell: autonomous decision-making unit

Agent-Based Model x Cellular Automata

- **CA and ABM are quite different yet similar:**
 - CA are discrete in space and finite in cardinality (fixed number of cells)
 - ABM can be continuous in space and the cardinality of agents can be infinite since the agents can sprout other agents

More information (www.tmg.lncc.br):

- “Modelagem Matemática do Câncer”, P.F.A. Mancera & D. Rodrigues
VI Em²c²T (2020)
- “Modelos Matemáticos & Computacionais em Câncer”, R.C. Almeida & H. Rocha
IV Em²c²T (2018)
- “Modelos Matemáticos em Câncer”, R.C. Almeida & E.B. Lima
I Em²c²T (2014) (not available yet)

Model Classification

① Continuos models:

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- Recursion Equation (discrete time)
- Partial Differential Equation - PDE

② Discrete models:

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③ Hybrid models

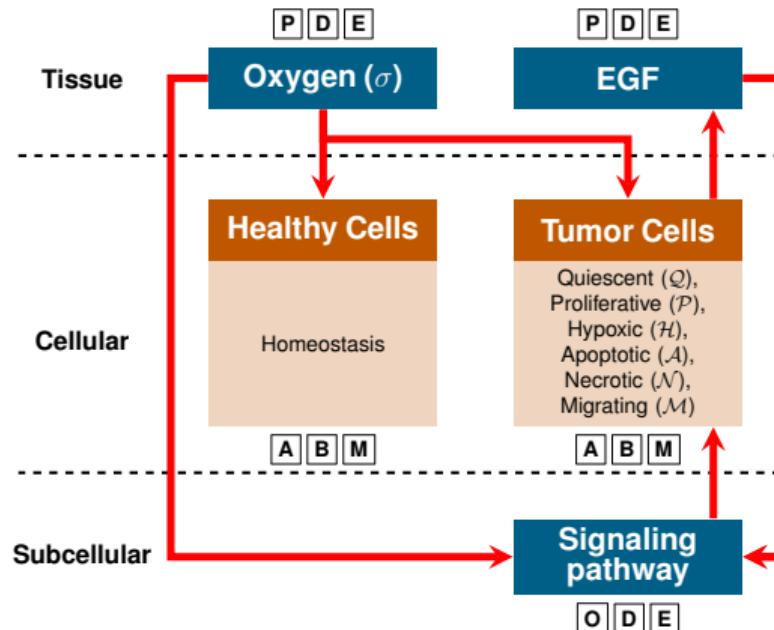
Integrate both continuum and discrete approaches

Advantages

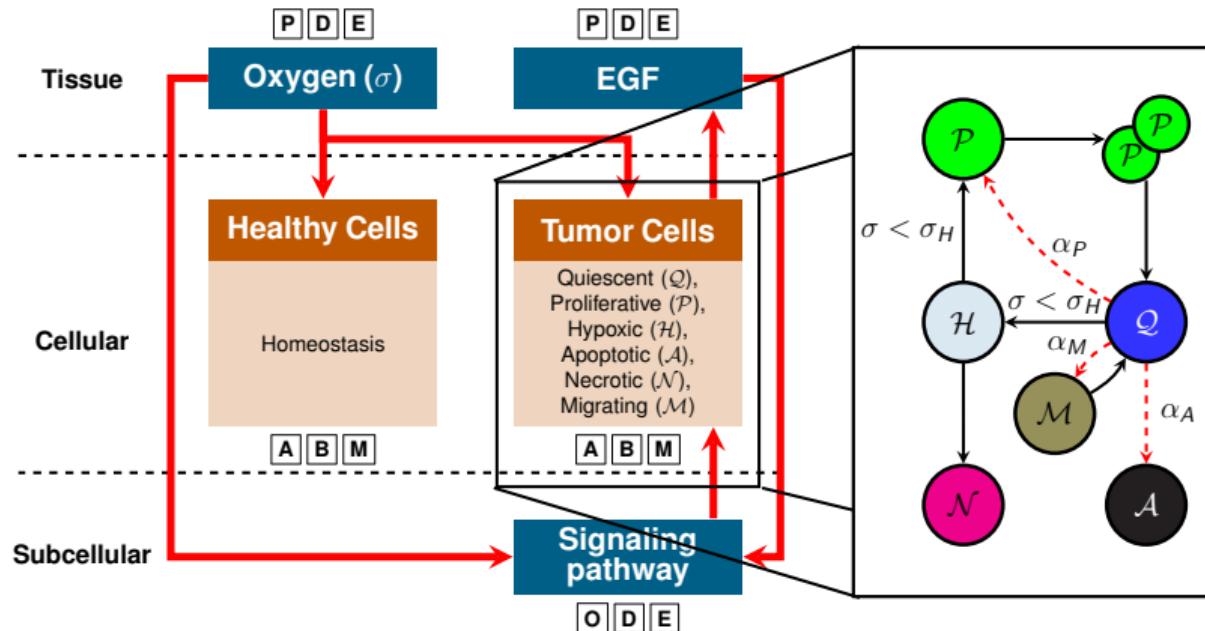
Hybrid models can capture the diffusion of nutrients, oxygen, proteins and subcellular events *via* PDEs and ODEs while the cell heterogeneity may be tracked through a discrete model

Example of hybrid model

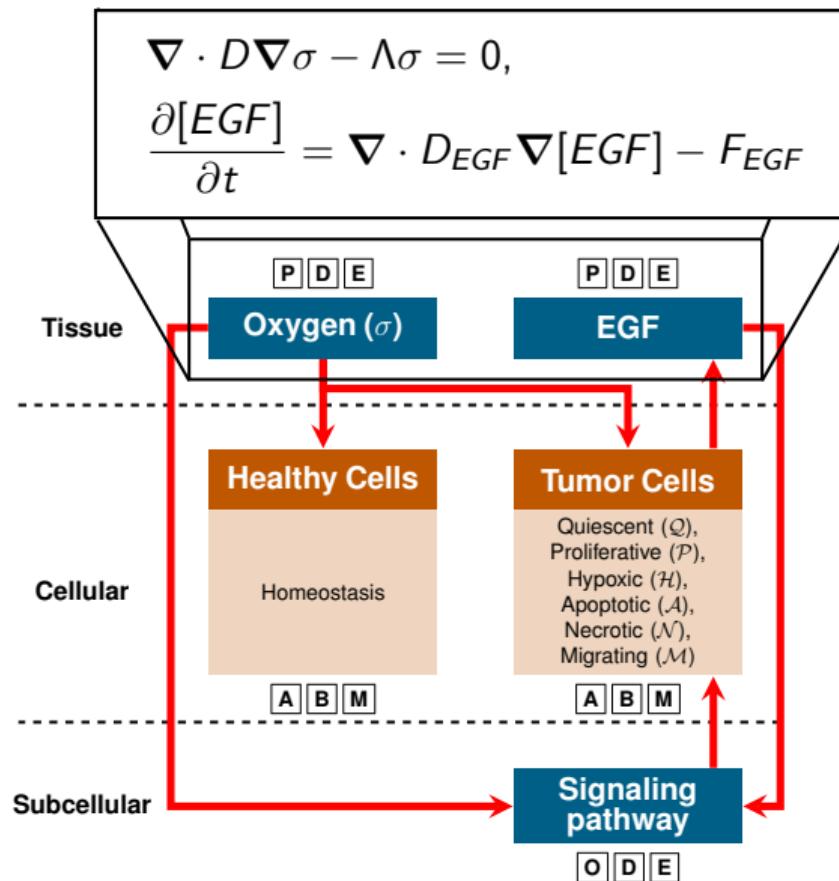
Rocha, H.L., Almeida, R.C., Lima, E.A.B.F., Resende, A.C.M., Oden, J.T. and Yankeelov, T.E., 2018. A hybrid three-scale model of tumor growth. Mathematical Models and Methods in Applied Sciences, 28(01), pp.61-93.



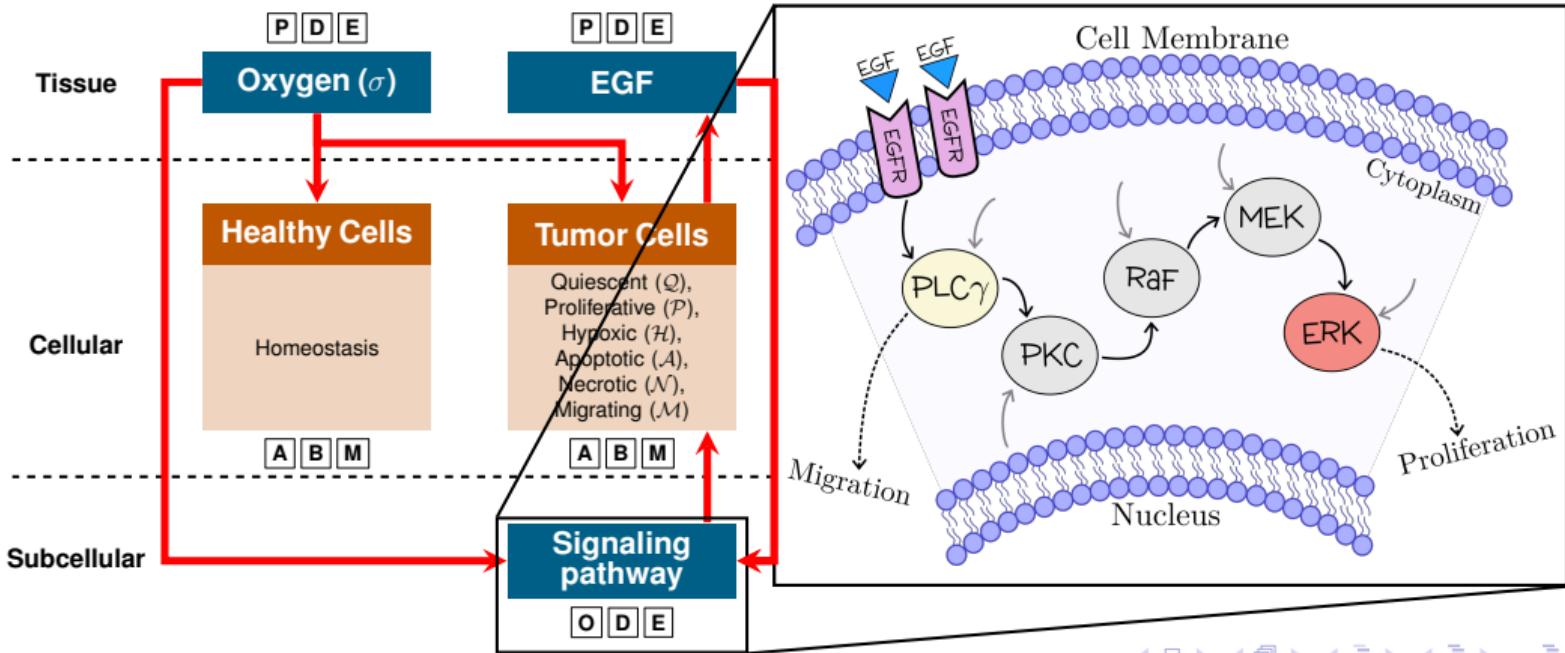
Example of hybrid model



Example of hybrid model



Example of hybrid model



Example of hybrid model

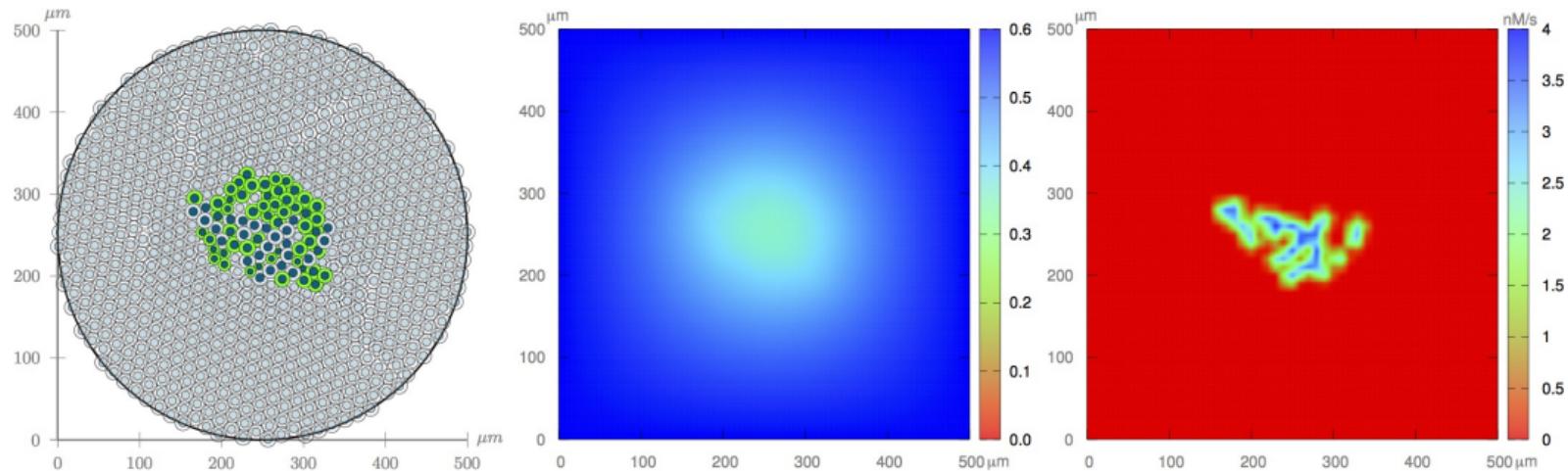


Figura: Simulation at 4.17 days. ABM model (left), oxygen dispersion (middle), and EGF dispersion (right).

Example of hybrid model

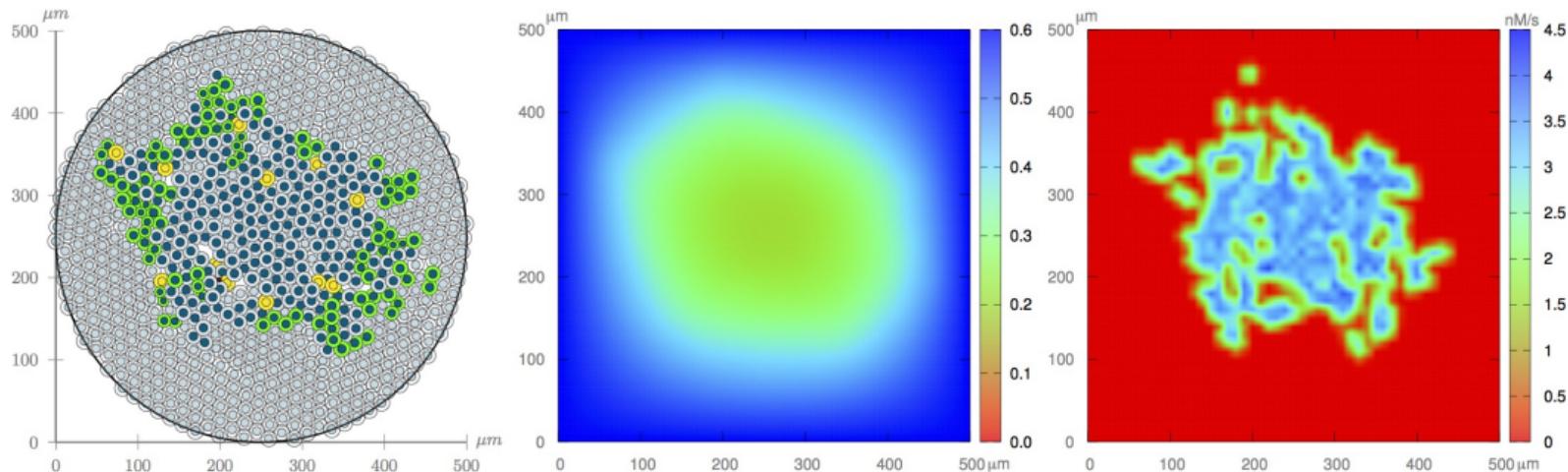


Figura: Simulation at 8.33 days. ABM model (left), oxygen dispersion (middle), and EGF dispersion (right).

Example of hybrid model

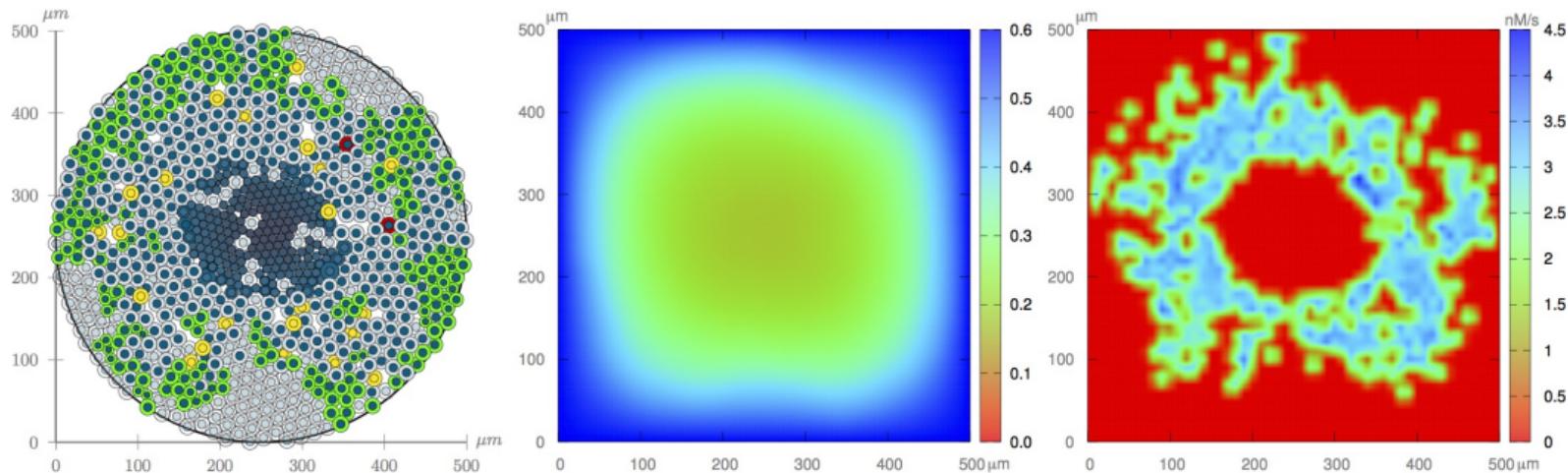


Figura: Simulation at 12.5 days. ABM model (left), oxygen dispersion (middle), and EGF dispersion (right).

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Cancers 13, 12 (2021).
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Toward Predictive Computational Models of Breast Cancer Development and Treatment.
PhD thesis, Laboratório Nacional de Computação Científica, 12 2020.
-  WORSCHECH, A., CHEN, N., YU, Y. A., AND ET AL.
Systemic treatment of xenografts with vaccinia virus GLV-1h68 reveals the immunologic facet of oncolytic therapy.
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Thank you very much!



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