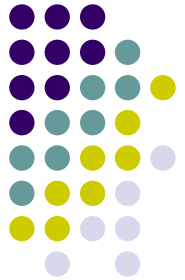

A Model of Angiogenesis by Hybrid Systems with Delay on the Piecewise Constant Part

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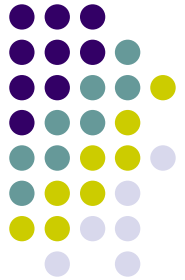
Hybrid Systems:Modelling, Simulation and Optimization, 14-16 May 2008, Istanbul

Outline



Tumor – Induced Angiogenesis

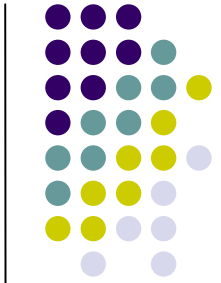
Mathematical Models of Angiogenesis

More on Angiogenesis Models

A Hybrid System Model

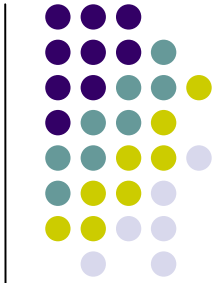
Conclusions

The Body's Control of Angiogenesis



- Angiogenesis occurs in the healthy body for healing wounds and for restoring blood flow to tissues after injury or insult. In females, angiogenesis also occurs during the monthly reproductive cycle (to rebuild the uterus lining, to mature the egg during ovulation) and during pregnancy (to build the placenta, the circulation between mother and fetus).
- The healthy body controls angiogenesis through a series of "on" and "off" switches:
- The main "on" switches are known as angiogenesis-stimulating growth factors
- The main "off switches" are known as angiogenesis inhibitors
- When angiogenic growth factors are produced in excess of angiogenesis inhibitors, the balance is tipped in favor of blood vessel growth. When inhibitors are present in excess of stimulators, angiogenesis is stopped. The normal, healthy body maintains a perfect balance of angiogenesis modulators. In general, angiogenesis is "turned off" by the production of more inhibitors than stimulators.
-

Excessive angiogenesis



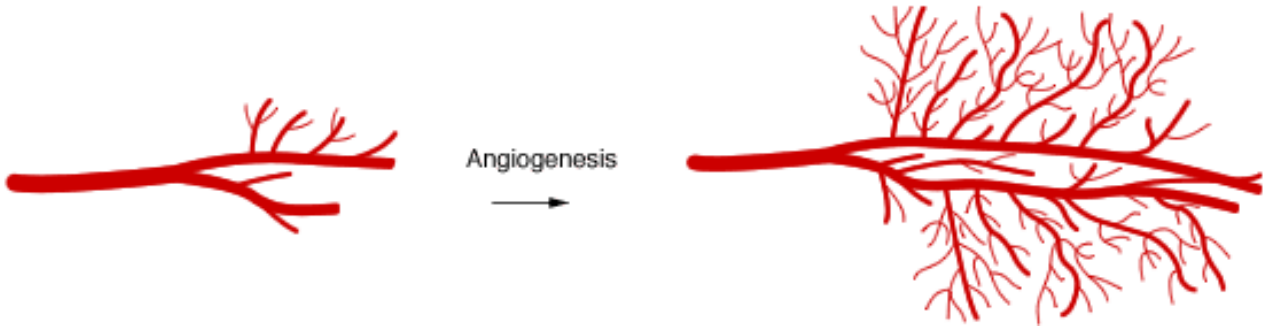
- Occurs in diseases such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis
- Excessive angiogenesis occurs when diseased cells produce abnormal amounts of angiogenic growth factors, overwhelming the effects of natural angiogenesis inhibitors
- Angiogenesis, the growth of new blood vessels, is a “common denominator” shared by diseases affecting many people worldwide, including all cancers, cardiovascular disease, blindness, arthritis, complications of AIDS, diabetes, Alzheimer’s disease.

Tumor–Induced Angiogenesis

Malignant tumor can grow more than 1-2 mm in diameter depending on their neo-vascularization.

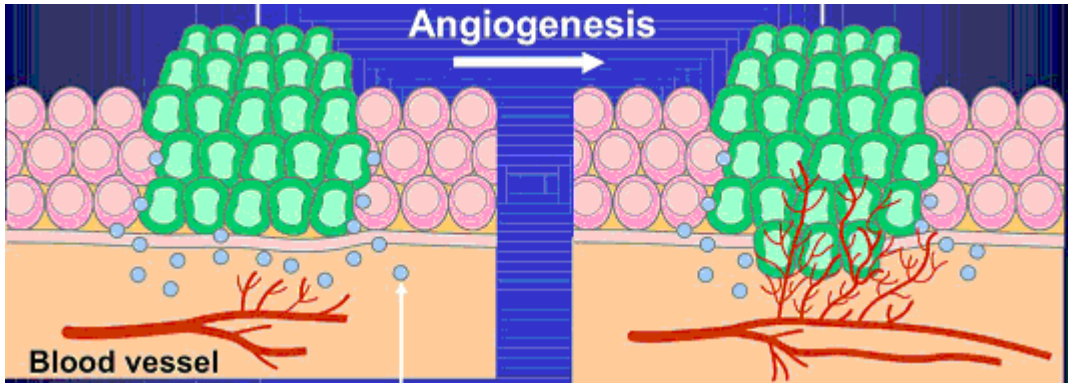
Cancer spreads by *metastasis*, the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade and grow in normal tissues elsewhere. so there is great interest in understanding what makes metastasis possible for a cancerous tumor.

Metastasis Requires Angiogenesis, forming new blood vessels or the growth of a new network of blood vessels.



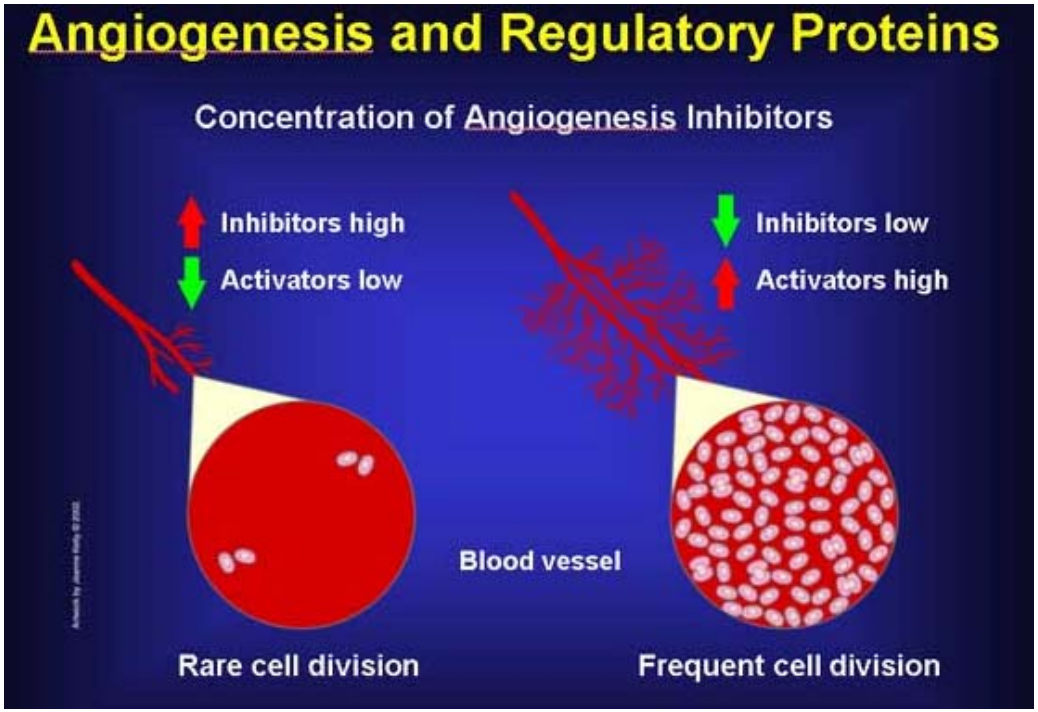
Tumor–Induced Angiogenesis

Tumor Angiogenesis is the proliferation of a network of blood vessels that penetrates into cancerous growths, supplying nutrients and oxygen and removing waste products.

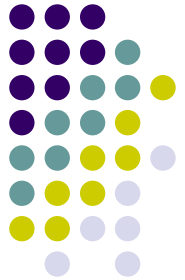


Tumor–Induced Angiogenesis

Angiogenesis is regulated by both *activator* and *inhibitor* molecules. Normally, the inhibitors predominate, blocking growth. Should a need for new blood vessels arise, angiogenesis activators increase in number and inhibitors decrease. This prompts the growth and division of vascular endothelial cells and, ultimately, the formation of new blood vessels.



Tumor–Induced Angiogenesis

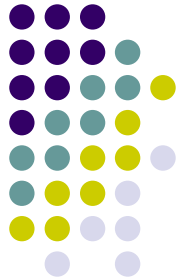


The walls of blood vessels are formed by *vascular endothelial cell*

Vascular Endothelial Growth Factor (VEGF) is a potent stimulator of endothelial cell (EC) proliferation, migration and form new blood vessels.

New blood vessels are formed by increased expression of VEGF and are regressed when VEGF expression is lower then a threshold value.

Tumor–Induced Angiogenesis



Newly formed vessels have highly unstable structure and its stabilization crucially depends on maturation.

The ratio of Ang1 and Ang2, which are angioproteins, determines the dominant process which can be maturation or destabilization.

The effective vessel density (EVD), which is defined as sum of immature vessel (IV) density and mature vessel (MV) density, can exhibit oscilatory behaviour.

Tumor growth is related to effective vessel density.

- **First Description of Tumor Vascularization:**

  Goldman E. The growth of malignant disease in man and the lower animals with special reference to the vascular system. Lancet 1907; ii: 1236-1240.

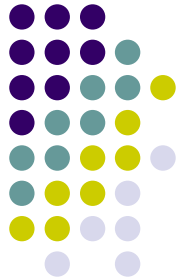
- **Seminal Hypothesis:**

  Folkman J. Tumor angiogenesis: therapeutic implications. New England Journal of Medicine 1971; 285: 1182-1186.

- **First Clinical "Proof of Concept" of Antiangiogenic Therapy for Tumors:**

  Folkman J. Successful treatment of an angiogenic disease. New England Journal of Medicine 1989; 320(18): 1211-1212

Mathematical Models of Angiogenesis

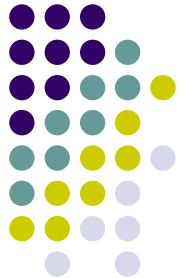


The well - known mathematical model of angiogenesis is the three dimensional model.

Three dimensional model involves the following time dependent variables:

- N: the number of tumor cells or tumor size.
- P: the amount of growth factors known to be involved in angiogenesis supplying the tumor.
- E: the effective vessel density which is calculated by dividing the corresponding vessel volume by the tumor size.

Mathematical Models of Angiogenesis



Three dimensional model *with no time delays* is described as:

$$\begin{cases} \dot{N} = f_1(E)N \\ \dot{P} = f_2(E)N - \delta P \\ \dot{E} = f_3(P)E - f_1(E))E. \end{cases}$$

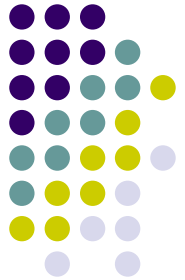
where

$$f_1(E=0) < 0, \lim_{x\to\infty} f_1(x) > 0.$$

$$f_2(x) > 0, \lim_{x\to\infty} f_2(x) = 0.$$

$$f_3(P=0) < 0, \lim_{x\to\infty} f_3(x) > 0.$$

Mathematical Models of Angiogenesis



Three dimensional model *with time delays* is described as:

$$\begin{cases} \dot{N} = f_1(E_{\tau_1})N \\ \dot{P} = f_2(E)N - \delta P \\ \dot{E} = f_3(P_{\tau_2})E - f_1(E_{\tau_1}))E. \end{cases}$$

where

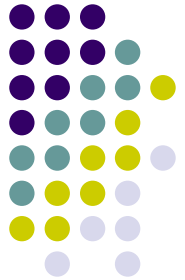
$$E_{\tau_1} = E(t-\tau_1), P_{\tau_2} = P(t-\tau_2),$$

$$f_1(E=0) < 0, \lim_{x\to\infty} f_1(x) > 0.$$

$$f_2(x) > 0, \lim_{x\to\infty} f_2(x) = 0.$$

$$f_3(P=0) < 0, \lim_{x\to\infty} f_3(x) > 0.$$

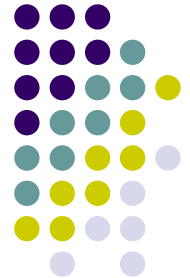
Mathematical Models of Angiogenesis



No Hopf bifurcation points in three dimensional model without time delays.

Three dimensional model with time delays contains Hopf bifurcation points.

Mathematical Models of Angiogenesis



Three dimensional model is numerically (M. Bodnar & U. Forys, 2005)

Their model is described as:

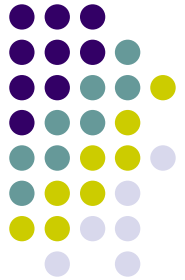
$$\begin{cases} \dot{N} &= \alpha N \left(1 - \dfrac{N}{1 + f_1(E(t-\tau_1))}\right) \\ \dot{P} &= f_2(E)N - \delta P \\ \dot{E} &= \left(f_3(P(t-\tau_2)) - \alpha\left(1 - \dfrac{N}{1 + f_1(E(t-\tau_1))}\right)\right) E\,. \end{cases}$$

where

$$f_1(E) = \frac{b_1 E^2}{c_1 + E^2}\,, \qquad f_2(E) = \frac{a_2}{c_2 + E}\,, \qquad f_3(P) = \frac{(a_3 + b_3)x^2}{\frac{c_3^2 b_3}{a_3} + x^2} - a_3\,.$$

$$c_1 = 5\,, \qquad c_2 = 0.8\,, \qquad a_3 = 2\,, \qquad b_3 = 1\,, \qquad c_3 = 2\,, \qquad \alpha = 1\,, \qquad \delta = 1\,.$$

Mathematical Models of Angiogenesis



Qualitative behaviour varies accordng to b_1 and a_2 in the given model.

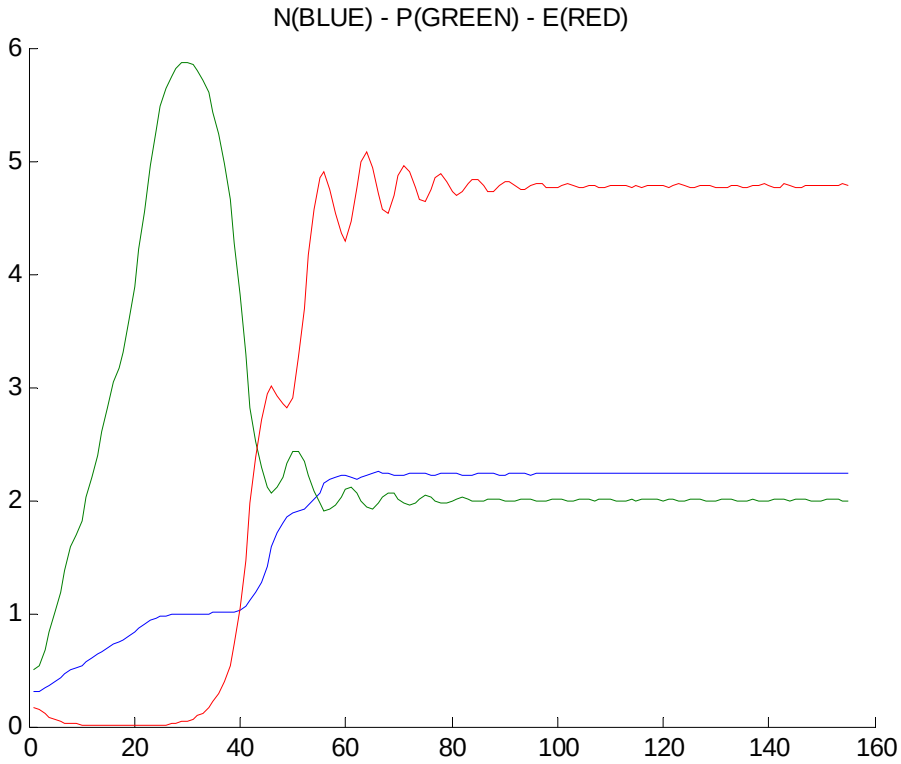
If $b_1 = 1.5$ and $a_2 = 5$ one positive steady state exists.

Qualitative behaviour of the model also depends on delays.

If delay are equal to 1 oscilations dump and if delay are equal to 1.3 undumping oscilations are observed.

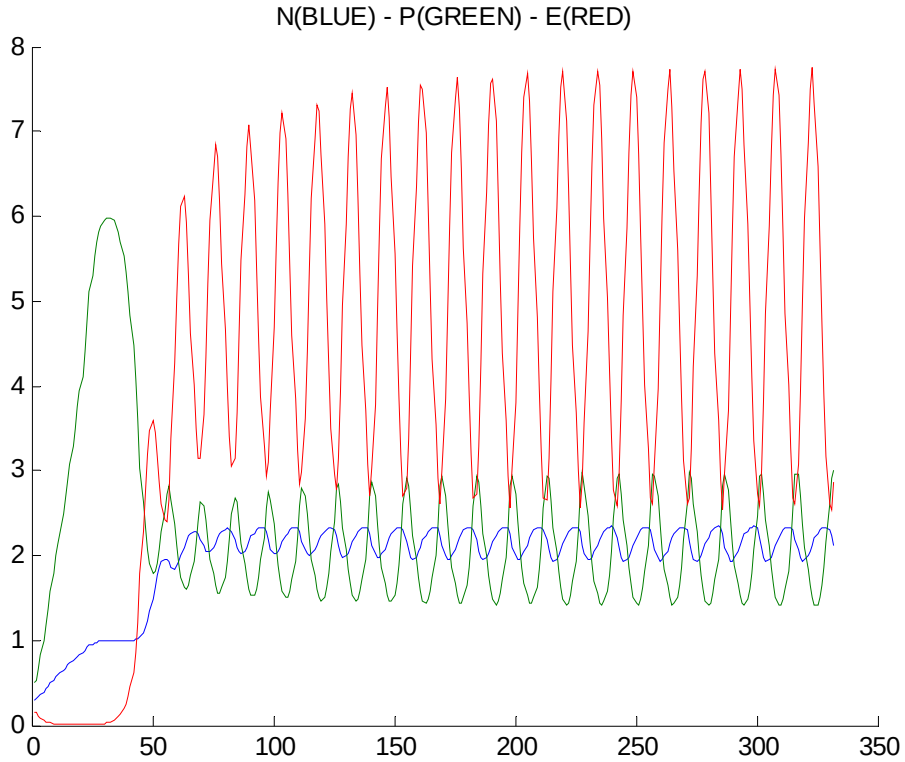
Mathematical Models of Angiogenesis

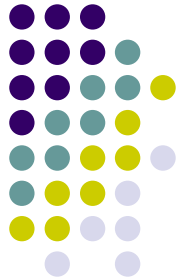
Delays equal to 1:



Mathematical Models of Angiogenesis

Delays equal to 1.3:

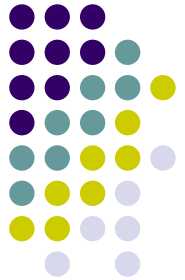




This model is based on a simple tumor growth model and simplifications on the more detailed process description. Substituting the related variables, ignoring the phases of dormancy period (the period before the start of rapid grow) and metastasis (the slowing down of tumor growth after a proper size) a 3-variable model of angiogenesis was formed. This model can efficiently demonstrate the oscillatory behaviour. The authors also showed that stable steady states can exist under some circumstances.

The model is mainly aimed at basic understanding and qualitative analysis.

More on Angiogenesis Models



Three dimensional model can be expanded to five dimesional model to make the model more more elaborate and realistic. In this model immature and mature vessel volumes denoted by V_1 and V_2, respectively. Additionally, the general term protein, denoted P, is now replaced by two specific proteins VEGF, denoted P_1 and Ang1, denoted P_2. The five dimensional model:

$$\begin{cases} \dot{N} = f_1(E_{\tau_1})N \\ \dot{P}_1 = f_2(E)N - \delta_1 P_1 \\ \dot{P}_2 = \alpha N - \delta_2 P_2 \\ \dot{V}_1 = f_3(P_{1\tau 2})V_1 - f_4(P_2)V_1 + f_5(P_{2\tau_3})V_2 \\ \dot{V}_2 = f_4(P_2)V_1 - f_5(P_{2\tau_3})V_2 \end{cases}$$

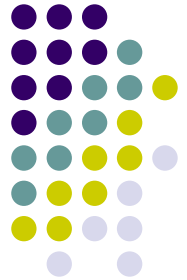
where

f_4 is maturation rate, it is positive increasing function of P_2,

f_5 is the destabilization rate, it is positive decreasing function of P_2 and satisfies

$$\lim_{x \to \infty} f_5(x) = 0.$$

More on Angiogenesis Models



After making the substitutions

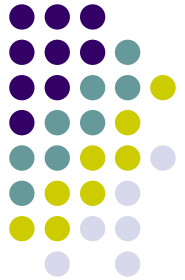
$$V_i \to E_i = \frac{V_i}{N}$$
$$E_2 \to E = E_1 + E_2$$

the system

$$\begin{cases} \dot{N} = f_1(E_{\tau_1})N \\ \dot{P}_1 = f_2(E)N - \delta_1 P_1 \\ \dot{E} = f_3(P_{1\tau_2})E_1 - f_1(E_{\tau_1})E \\ \dot{P}_2 = \alpha N - \delta_2 P_2 \\ \dot{E}_1 = f_3(P_{1\tau_2})E_1 - f_4(P_2)E_1 + f_5(P_{2\tau_3})(E - E_1) - f_1(E_{\tau_1})E_1. \end{cases}$$

İs obtained.

More on Angiogenesis Models



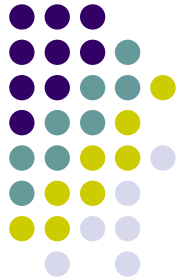
A computer algorithm describing tumor induced angiogenesis

(L. Arekelyan, V. Vainstein , Z. Agur, 2002)

They described three interconnected processes the influence tumor and vascular dynamics:

- Tumor cell proliferation,
- Formation of mature vessels, regression of immature vessels, maturation of immature vessels, destabilization of mature vessels into immature vessels.

More on Angiogenesis Models

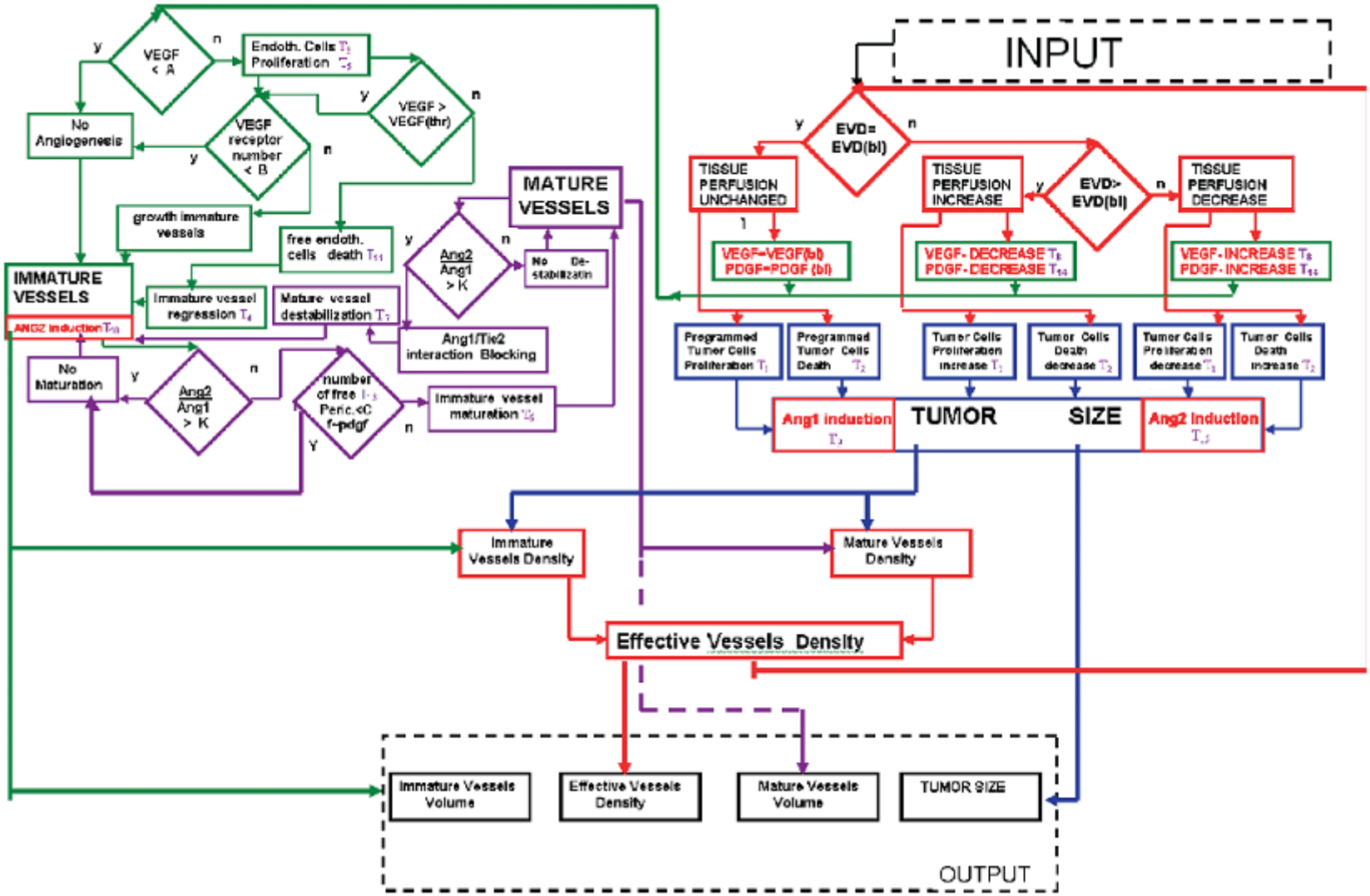


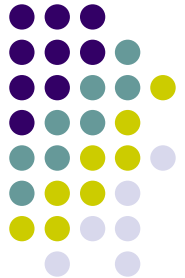
They included more variables in their algorithm. These variables are:

- Ang1: Angioprotein,
- Ang2: Angioprotein,
- EC: Endothelial cells,
- EVD: Effective vascular density,
- IV: Imature vessels,
- MV: Mature vessels,
- VEGF: Vascular endothelial growth factor,
- PDGF: Platelet – derived growth factor.

The algorithm is described in a diagram.

More on Angiogenesis Models



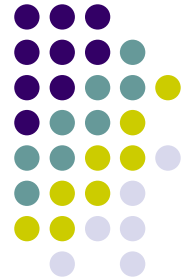


This model have been implemented by a well defined computer algorithm. However, a formal mathematical model was not introduced. The delays were not considered in the model and the dormancy period was not covered by the model. The model simulations exhibit a very close dynamics to the experimental results of Gilead and Neeman.

Even the model simulations are similar to experimental observations the importance of delays in angiogenesis and tumor growth was already showed in the work of Bodnar and Forys.

There exist developed numerical methods for simulations of DDE's. However, they are efficient for a small number of variables and relatively simple initial functions. Therefore, some alternative model classes can be considered for a more descriptive model of angiogenesis involving delays.

A Model by Hybrid Systems



Hybrid (in particular piecewise linear) dynamical systems with delay on piecewise constant part can also be used to model tumor induced angiogenesis.

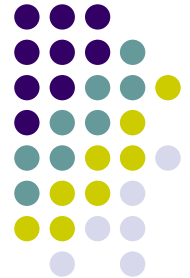
Piecewise linear dynamical systems with delay on piecewise constant part can be defined as:

$$\frac{dy}{dt} = M_{s(t)}y(t) + N_{s(t)}x_e(t) + k_{s(t)}$$

$$s_i(t) = F_i(Q([y_1(t-\tau_{1i}), y_2(t-\tau_{2i}), ..., y_n(t-\tau_{ni})]))$$

$$Q_j(y(t)) = \{ \begin{matrix} 1 \; if \; y_j(t) \geq h_j \\ 0 \; if \; y_j(t) < h_j \end{matrix}$$

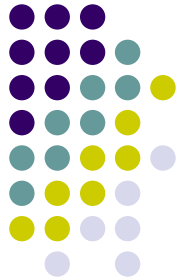
A Model by Hybrid Systems



The qualitative behaviour of piecewise linear dynamical systems with delay on piecewise constant part can be described as:

- The system can converge to or diverge from a convegent focal point,
- The system can converge to a cyclic periodic attractor,
- The system can exhibit cycles with exponentially growing magnitude
- Since a graph might have multiple number of circuits and multiple number of subspaces might have their own focal point within its invariant set this class of systems can exhibit multistationary behavior.

A Model by Hybrid Systems



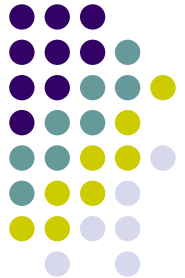
The general assumption of previous angiogenesis models is sigmoid transitions.

This behaviour can be approximated by steplike transitions. This abstraction will also allow embedding the delays into the piecewise constant part of the system. i.e. between subspace crossings and state transitions

In this work, a hybrid dynamical system model of angiogenesis is studied.

We studied a modular model with some assupmtions satisfying previous works on the subject.

A Model by Hybrid Systems



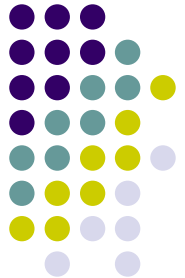
• TS (tumor size) increases if EVD(t-τ) is above a threshold value and decreases if EVD(t-τ) is below a threshold value.
• Exit of tumor from dormancy depends on a threshold value of mature vessel volume.

Tumor Size Module

$$\frac{dTS}{dt} = m_{s(t)}TS + k_{s(t)}$$

$$s(t) = \begin{cases} s_1 \ if \ EVD(t-\tau) < h_{EVD} \ \ and \ MV < h_{MV} \\ s_2 \ if \ EVD(t-\tau) \geq h_{EVD} \ and \ MV < h_{MV} \\ s_3 \ if \ EVD(t-\tau) < h_{EVD} \ and \ MV \geq h_{MV} \\ s_4 \ if \ EVD(t-\tau) \geq h_{EVD} \ and \ MV \geq h_{MV} \end{cases}$$

A Model by Hybrid Systems



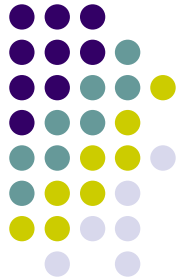
- VEGF density is directly related to EVD

VEGF Module

$$\frac{dVEGF}{dt} = m_{s(t)} VEGF$$

$$s(t) = \begin{matrix} s_1 \; if \;\; EVD(t) < h_{EVD} \\ s_2 \; if \;\; EVD(t) \geq h_{EVD} \end{matrix}$$

A Model by Hybrid Systems



•Ang1 concentration increases if the derivative of TS is greater than zero and decreases if the derivative of TS is below or equal to zero.
•Ang2 concentration increases if the derivative of IV volume is greater than zero and decreases if the derivative of IV volume is below or equal to zero.

Ang1 Module

$$\frac{dAng1}{dt} = m_{s(t)}Ang1 + k_{s(t)}$$

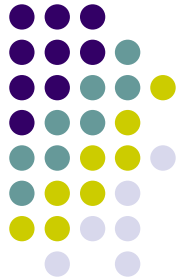
$$s(t) = \begin{matrix} s_1 \; if \; \dfrac{dTS}{dt} \le 0 \\ s_2 \; if \; \dfrac{dTS}{dt} > 0 \end{matrix}$$

Ang2 Module

$$\frac{dAng2}{dt} = m_{s(t)}Ang2 + k_{s(t)}$$

$$s(t) = \begin{matrix} s_1 \; if \; \dfrac{dIV}{dt} \le 0 \\ s_2 \; if \; \dfrac{dIV}{dt} > 0 \end{matrix}$$

A Model by Hybrid Systems



•IV volume increases if VEGF density is above a threshold value and decreses if VEGF density is below a threshold value.
•MV volume increases if Ang2/Ang1 is above a threshold value and decreases if Ang2/Ang1 is below a threshold value.
•EVD = (IV+MV)/TS.

MV Module

$$\frac{dMV}{dt} = m_{s(t)} MV$$

$$s(t) = \begin{cases} s_1 \ if \ \dfrac{Ang2}{Ang1} \geq h_{\frac{Ang2}{Ang1}} \\ s_2 \ if \ \dfrac{Ang2}{Ang1} < h_{\frac{Ang2}{Ang1}} \end{cases}$$

IV Module

$$\frac{dIV}{dt} = m_{s(t)} IV + k_{s(t)}$$

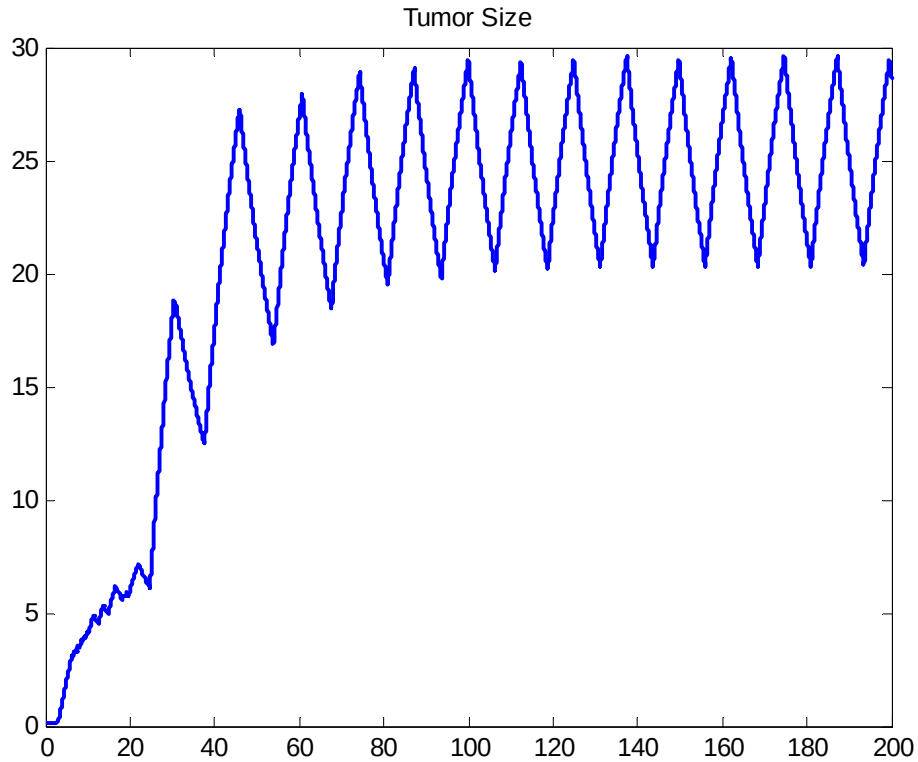
$$s(t) = \begin{cases} s_1 \ if \ VEGF \leq h_{VEGF} \\ s_2 \ if \ VEGF > h_{VEGF} \end{cases}$$

EVD Module

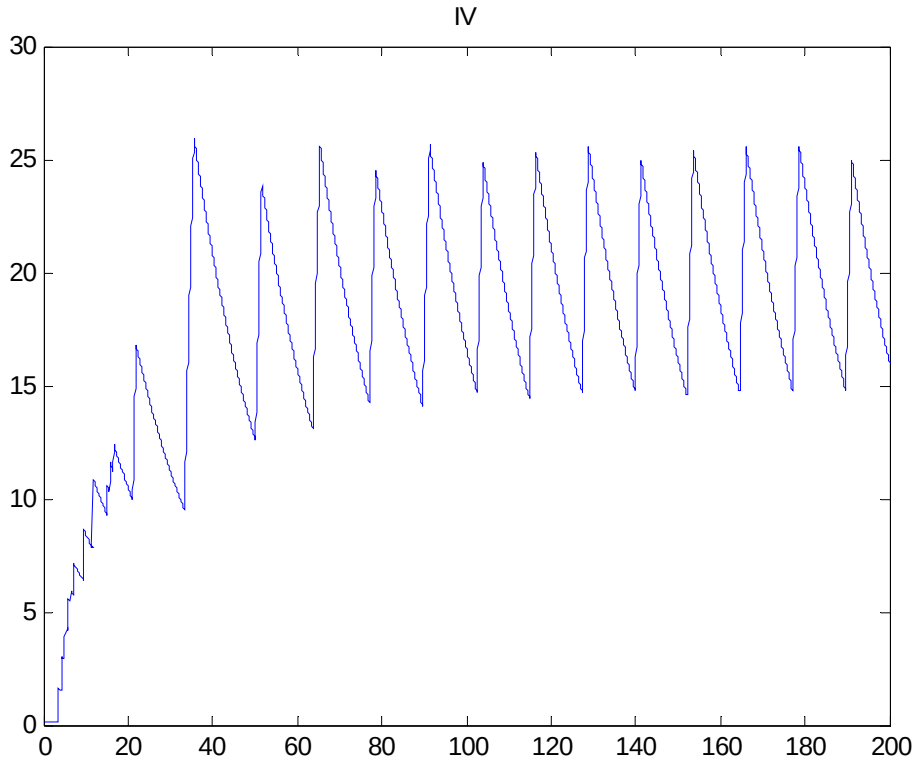
$$EVD = \frac{MV + IV}{TS}$$

A Model by Hybrid Systems

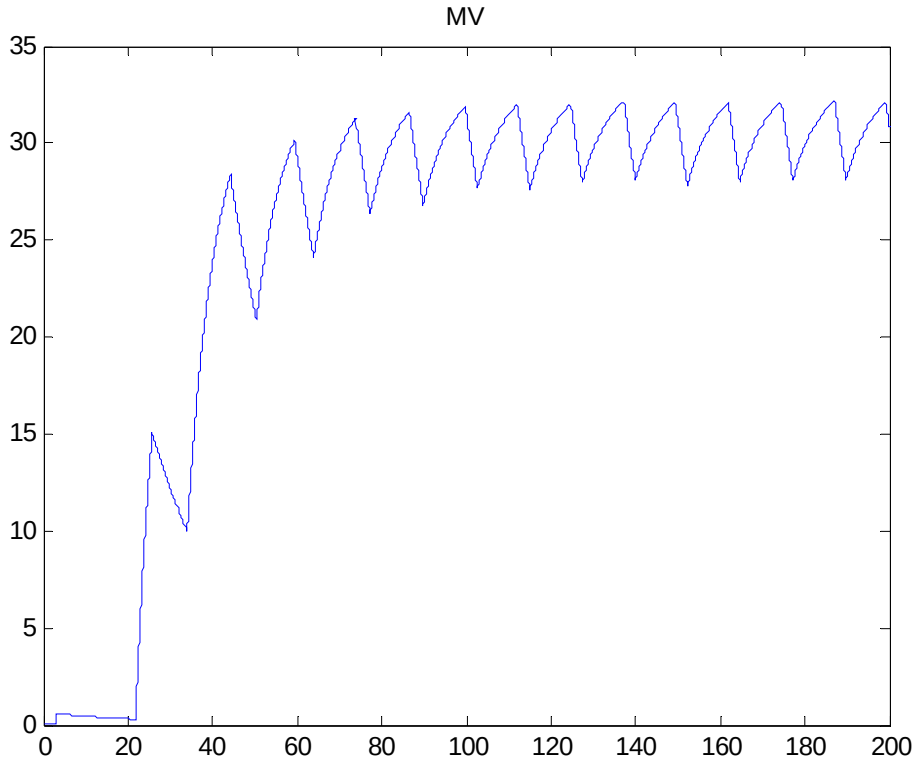
Results obtained by simulating the modules:



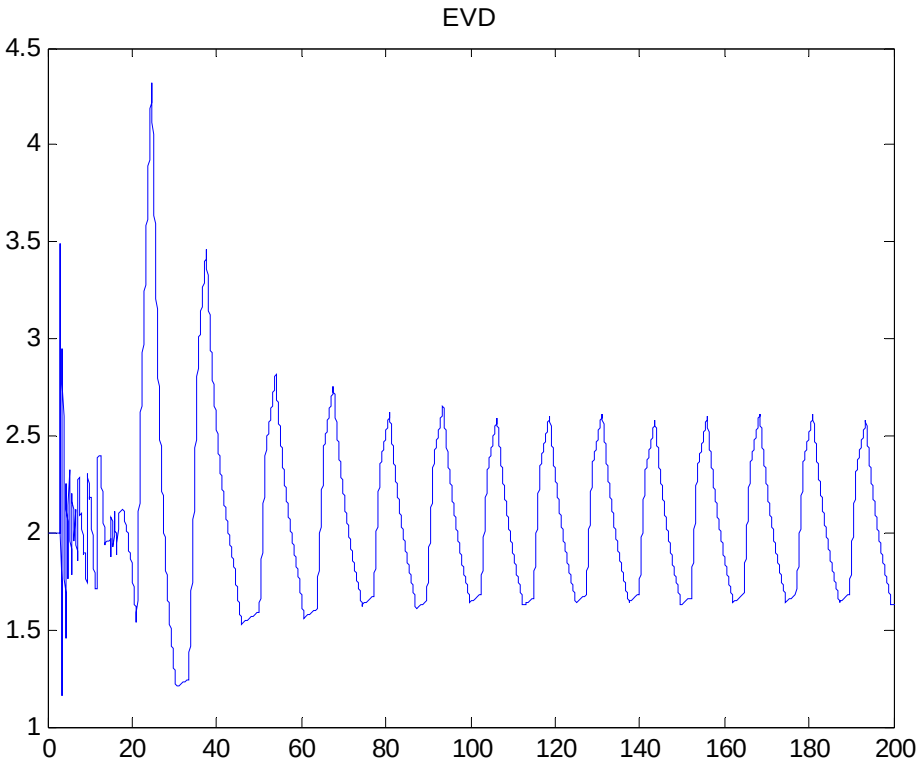
A Model by Hybrid Systems



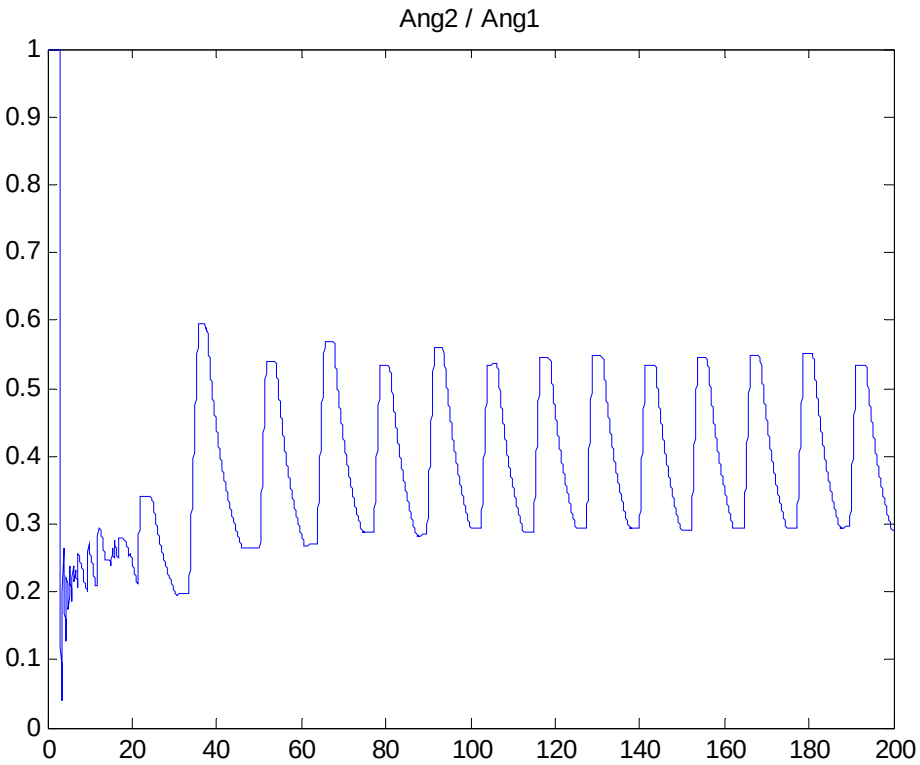
A Model by Hybrid Systems



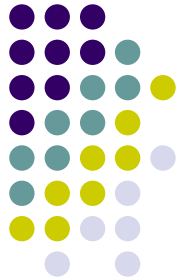
A Model by Hybrid Systems



A Model by Hybrid Systems



Conclusions



- In this work we modeled angiogenesis by using a piecewise linear system with delay on the piecewise constant part. We approximated sigmoid transitions by step functions. The simulations of our model exhibited an oscillatory Gompertz growth which is suggested by many researchers.

- The models of angiogenesis are studied for efficient therapy planning. Therefore, collaboration with the clinical studies is required for further steps. The structure of piecewise linear systems allow incorporation of therapatic interventions as external inputs and further knowledge on the system can easily be incorporated.

- The process naturally can be subject to random perturbations and response of immune system. Therefore, the model can be improved by involving different factors which are not considered here.

Thank you...