Angiogenesis

Angiogenesis

A biochemical/mathematical perspective

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with the collaboration of

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Department of Biochemistry, Biophysics and Molecular Biology
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Reference

Reference

Angiogenesis-A Biochemical/Mathematical Perspective

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in

Tutorials in Mathematical Biosciences: Cell Cycle, Proliferation, and Cancer (Vol. 3, Chapter 2) . A. Friedman, ed., Springer-Verlag, Berlin, Heidelberg, New York (2006).

Overview of talk:

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I.

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I. Some of the biological and biochemical underpinnings of angiogenesis.

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I. Some of the biological and biochemical underpinnings of angiogenesis.

II.

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I. Some of the biological and biochemical underpinnings of angiogenesis.

II. The development of a new model for for angiogenesis.

Overview of talk:

I. Some of the biological and biochemical underpinnings of angiogenesis.

II. The development of a new model for for angiogenesis.

III.

Overview of talk:

I. Some of the biological and biochemical underpinnings of angiogenesis.

II. The development of a new model for for angiogenesis.

III. Some results from a model for tumor angiogenesis upon which the new model was based.

Underpinnings

Underpinnings

A.

Underpinnings

A. What is angiogenesis?

Underpinnings

A. What is angiogenesis?

B.

Underpinnings

A. What is angiogenesis?

B. What are the key events in angiogenesis?

Underpinnings

A. What is angiogenesis?

B. What are the key events in angiogenesis?

C.

Underpinnings

A. What is angiogenesis?

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C. What are the chemical and cellular contributions to capillary structure?

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Underpinnings

A. What is angiogenesis?

B. What are the key events in angiogenesis?

C. What are the chemical and cellular contributions to capillary structure?

   1. Endothelial cells form the capillary wall.
   2. Pericytes surround the endothelial cells and provide structural and functional support.
   3. The basal lamina encases the endothelial cells and pericytes.

More underpinnings

More underpinnings

D.

More underpinnings

D. Interaction of endothelial cells with their environment.

More underpinnings

D. Interaction of endothelial cells with their environment.

E.

More underpinnings

D. Interaction of endothelial cells with their environment.

E. What are the extracellular events leading to vascularization?

More underpinnings

D. Interaction of endothelial cells with their environment.

E. What are the extracellular events leading to vascularization?

F.

More underpinnings

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E. What are the extracellular events leading to vascularization?

F. Extracellular soluble proteins that alter the environment and influence EC function: Proteases and protease inhibitors.

More underpinnings

D. Interaction of endothelial cells with their environment.

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G.

More underpinnings

D. Interaction of endothelial cells with their environment.

E. What are the extracellular events leading to vascularization?

F. Extracellular soluble proteins that alter the environment and influence EC function: Proteases and protease inhibitors.

G. Growth and angiogenesis: Factors that stimulate angiogenesis.

Even more underpinnings!

Even more underpinnings!

H.

Even more underpinnings!

H. Inhibitors of angiogenesis.

Even more underpinnings!

H. Inhibitors of angiogenesis.

I.

Even more underpinnings!

H. Inhibitors of angiogenesis.

I. Cellular events that characterize angiogenesis.

Even more underpinnings!

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I. Cellular events that characterize angiogenesis.

1.

Even more underpinnings!

H. Inhibitors of angiogenesis.

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1. Proliferation.

Even more underpinnings!

H. Inhibitors of angiogenesis.

I. Cellular events that characterize angiogenesis.

1. Proliferation.
2.

Even more underpinnings!

H. Inhibitors of angiogenesis.

I. Cellular events that characterize angiogenesis.

1. Proliferation.
2. Apoptosis.

Even more underpinnings!

H. Inhibitors of angiogenesis.

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Even more underpinnings!

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1. Proliferation.
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Even more underpinnings!

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J. Intracellular signals (signal transduction) that regulate cellular events.

Even more underpinnings!

H. Inhibitors of angiogenesis.

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   1. Proliferation.
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   3. Migration.

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Finally! All underpinned! (For this talk anyway.)

Aspects of Angiogenesis:

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Cross sections of capillaries, veins and arteries at various scales as well as the branched network of the vasculature (subfigure at the upper right hand corner).

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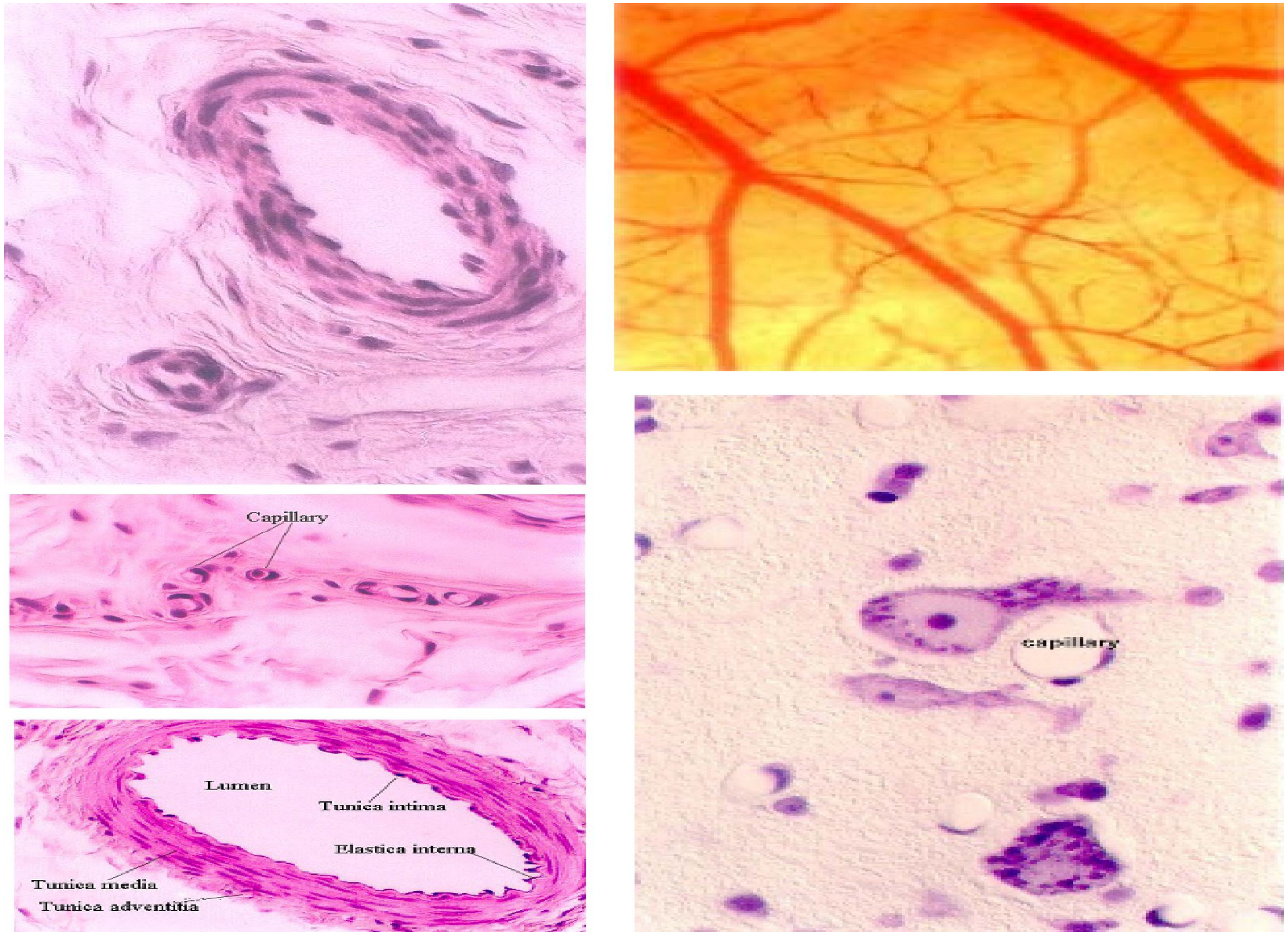
From:

http://cellbio.utmb.edu/microanatomy/cardiovascular/cardiovascular_system.htm


Capillary
Lumen
Tunica intima
Elastica interna
Tunica media
Tunica adventitia
capillary

The local environment of a capillary.

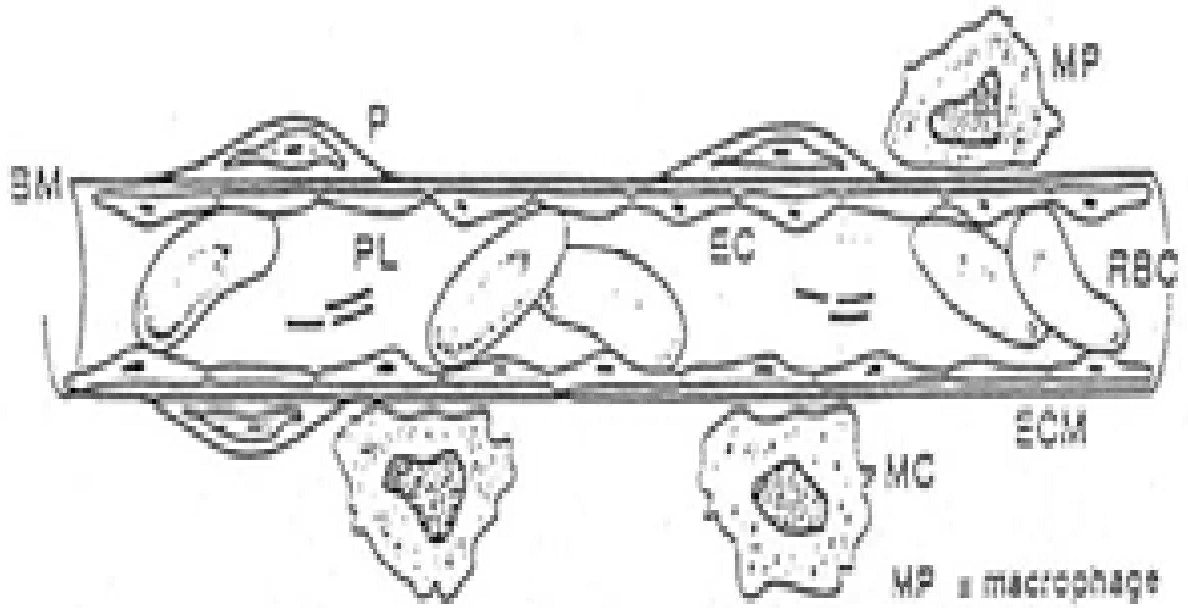
The local environment of a capillary.

Perycites regulate the basement lamina collagens/fibronecten. Macrophages police the local environment for interlopers, Mast cells regulate inflammation. Endothelia line the interior.

II. The capillary and its environment

(From: Rakusan: Coronary Angiogenesis)

Normal capillary.

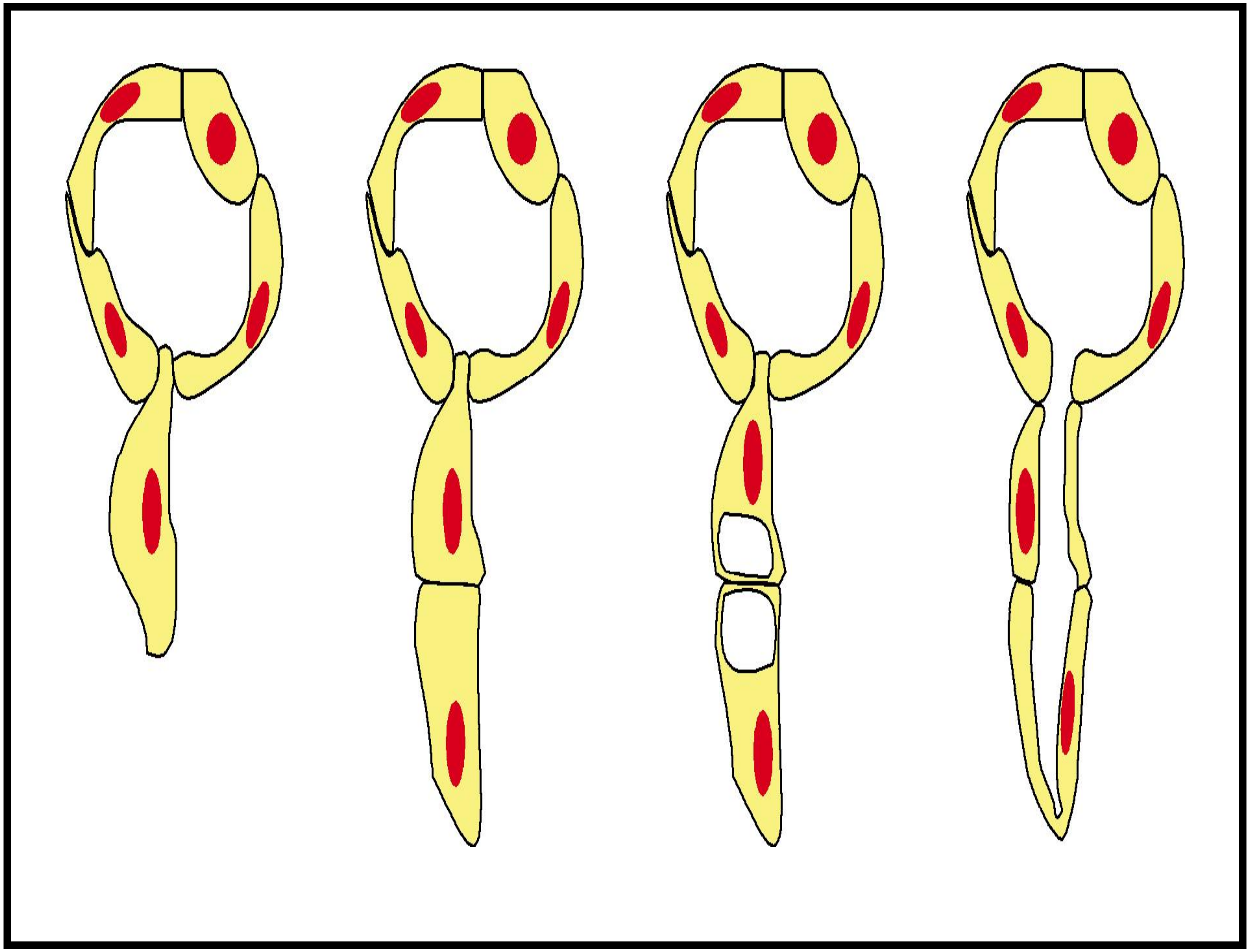


BM = basement membrane
EC = endothelial cell
ECM = extracellular matrix
MC = mast cell
MP = macrophage
P = pericyte
PL = platelet
RBC = red blood cell

Stages of angiogenesis.

Stages of angiogenesis.

Capillary sprouting (cross section). Left to right, the invasion of the endothelial cell into the ECM, cell proliferation, onset of lumen formation, maturation of lumen.



Cell death.

Cell death.

In apoptosis, or programmed cell death, shown on the left, the chromatin condenses and the cell blebs into smaller subunits.

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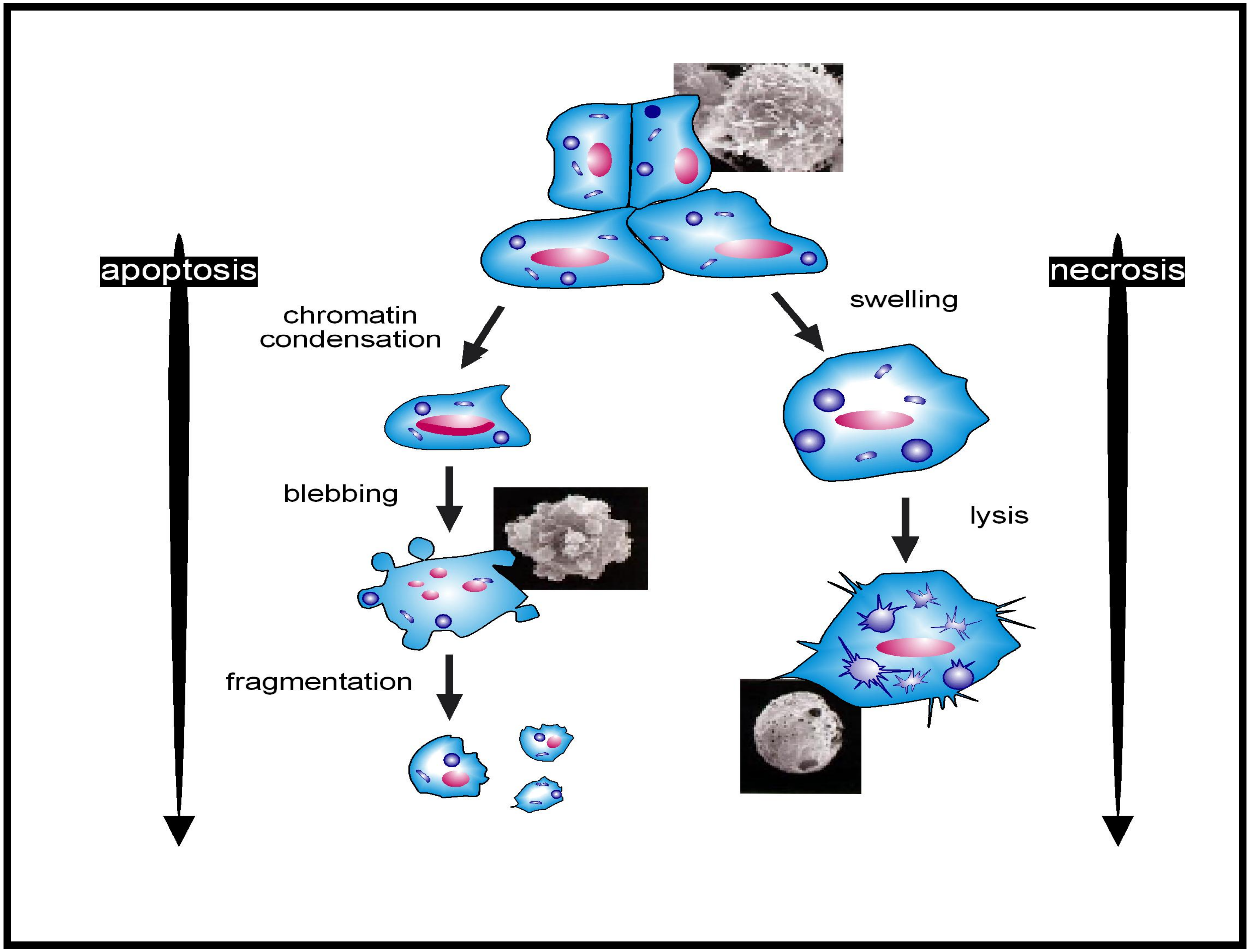
In necrosis, the cell first swells. The cell wall lyses and fragmentation results.


apoptosis
necrosis
chromatin condensation
blebbing
fragmentation
swelling
lysis

Structure of fibronectin.

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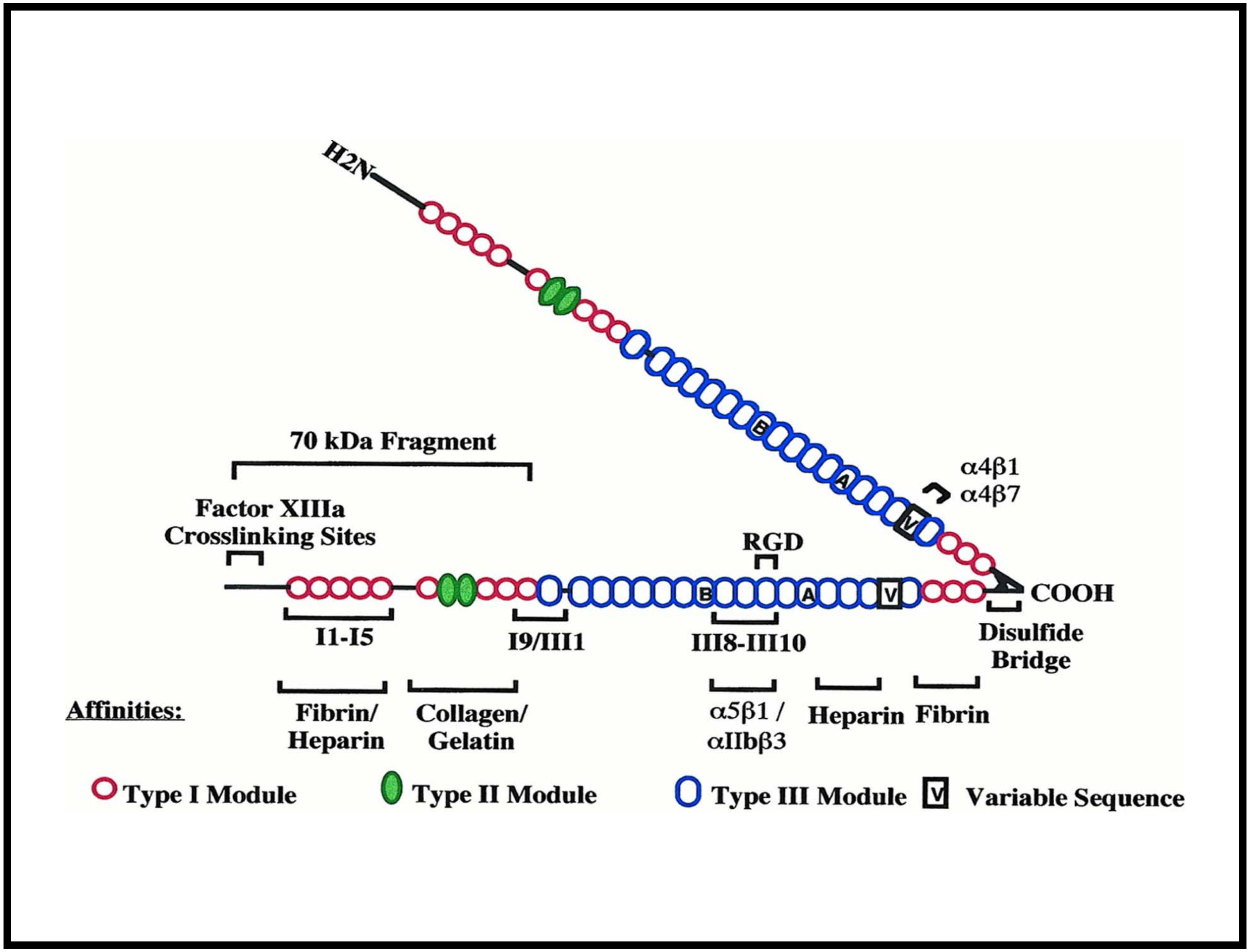
(From Magnusson, and Mosher, 1998 Arteriosclerosis, Thrombosis, and Vascular Biology 18 1363-1370, perm. pending.)



H2N
70 kDa Fragment
Factor XIIIa
Crosslinking Sites
RGD
α4β1
α4β7
B
A
V
COOH
I1-I5
I9/III1
III8-III10
Disulfide
Bridge
Affinities:
Fibrin/
Heparin
Collagen/
Gelatin
α5β1 /
αIIbβ3
Heparin
Fibrin
Type I Module
Type II Module
Type III Module
Variable Sequence

Assembly and structure of collagen.

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Type I collagen chains

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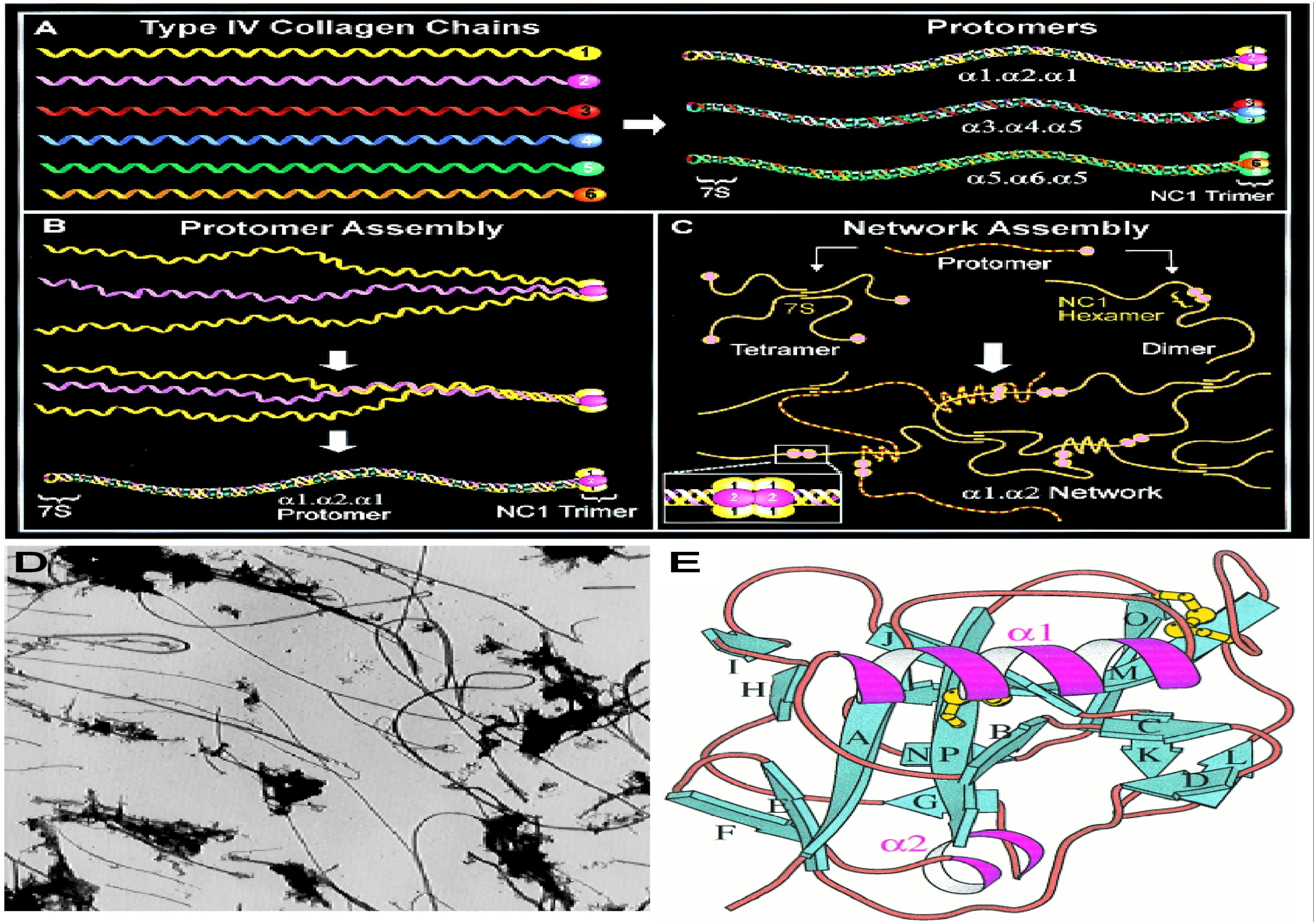
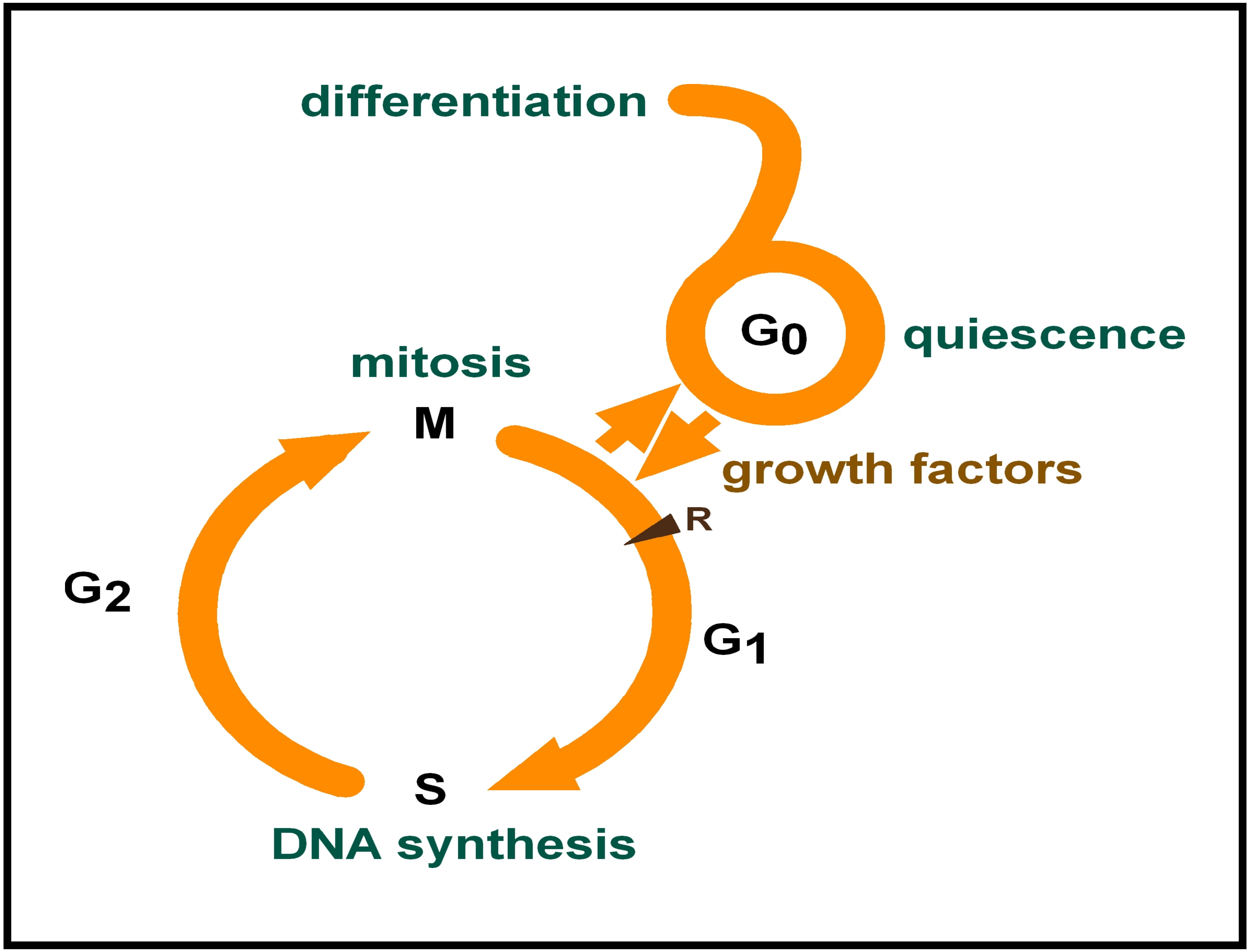
(From Sundaramoorthy etal 2002 JBC 277 31142-53, Btge et al. 1997 J Biochem 122 109-115 Hohenester et al. 1998 EMBO J 17 1656-64, permission pending.)


A
Type IV Collagen Chains
Protomers
α1.α2.α1
α3.α4.α5
α5.α6.α5
7S
NC1 Trimer
B
Protomer Assembly
7S
α1.α2.α1
Protomer
NC1 Trimer
C
Network Assembly
Protomer
7S
Tetramer
NC1
Hexamer
Dimer
α1.α2 Network
D
E
α1
α2

The cell cycle.

Current thinking is that cell differentiation is preceded by cell entry into the G_0 or quiescent state. Also, cells that move are in G_0 phase and cells in the active phase do not move.


differentiation
G0
quiescence
mitosis
M
growth factors
R
G2
G1
S
DNA synthesis

VEGF signalling.

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A molecule of VEGF is shown bound to its dimeric receptor (blue).

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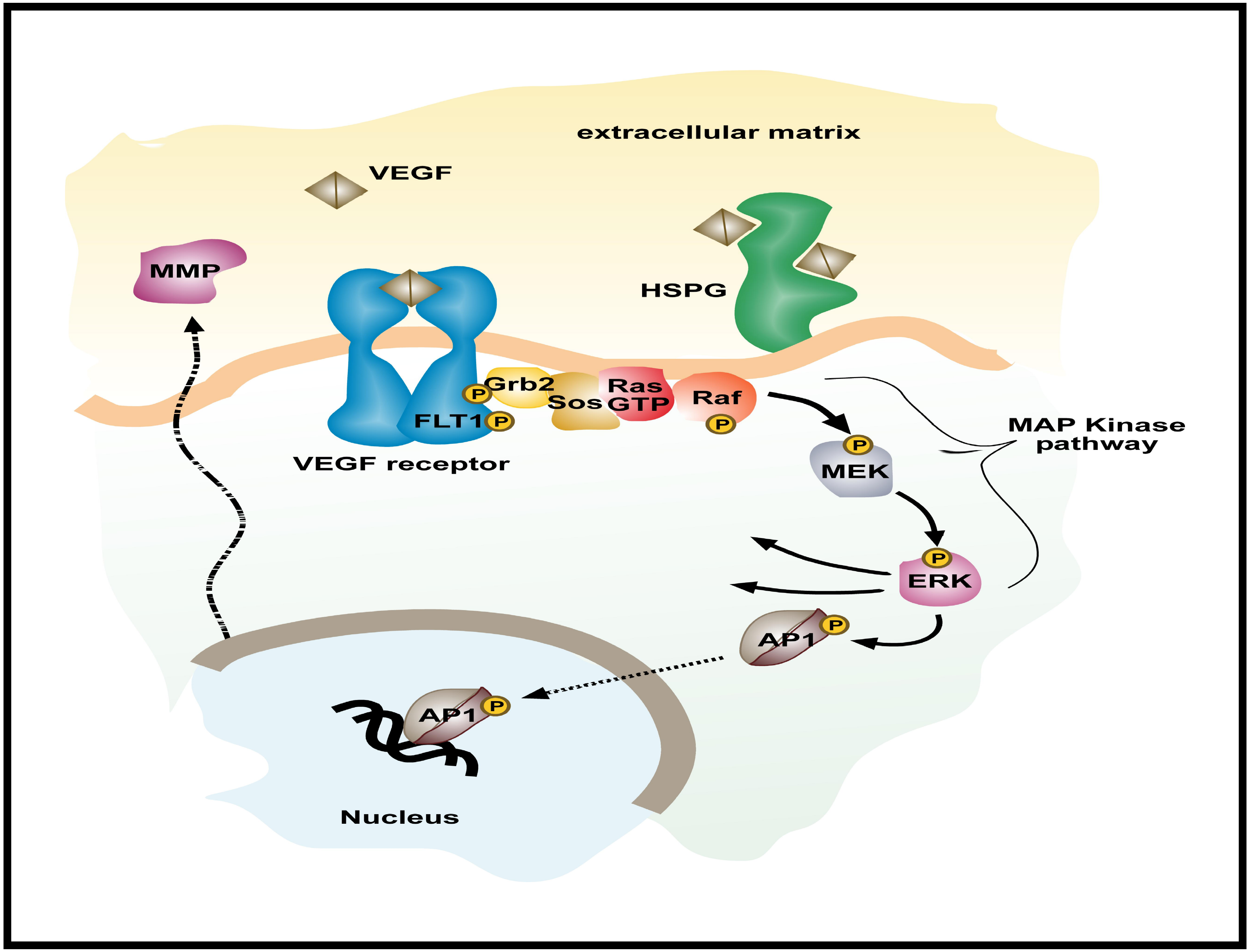
Within the cell cytoplasm a signal transduction cascade activates a transcription factor (AP1).

This enters the nucleus to begin the transcription of the MMP gene.

This results in cellular expression of the protease.


extracellular matrix
VEGF
MMP
HSPG
P
Grb2
Sos
Ras
GTP
Raf
P
FLT1
P
VEGF receptor
MAP Kinase
pathway
P
MEK
P
ERK
AP1
P
AP1
P
Nucleus

VEGF receptors.

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In the next figure, classes of tyrosine kinase receptors are displayed.

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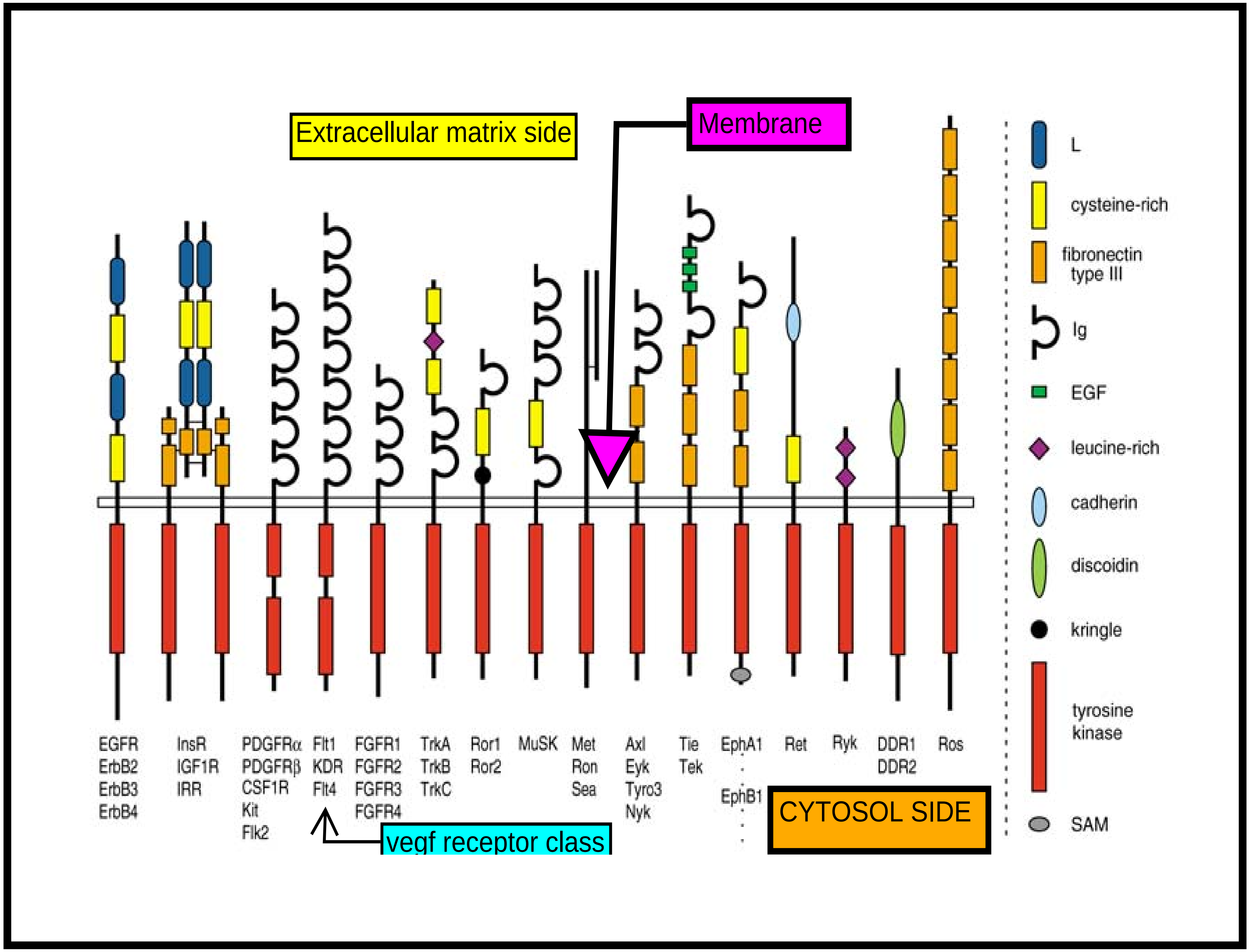
(From Hubbard and Till Annu Rev Biochem 2000;69:373-98, permission pending.)


Extracellular matrix side
Membrane
L
cysteine-rich
fibronectin type III
Ig
EGF
leucine-rich
cadherin
discoidin
kringle
tyrosine kinase
SAM
EGFR
ErbB2
ErbB3
ErbB4
InsR
IGF1R
IRR
PDGFRα
PDGFRβ
CSF1R
Kit
Flk2
Flt1
KDR
Flt4
FGFR1
FGFR2
FGFR3
FGFR4
TrkA
TrkB
TrkC
Ror1
Ror2
MuSK
Met
Ron
Sea
Axl
Eyk
Tyro3
Nyk
Tie
Tek
EphA1
EphB1
Ret
Ryk
DDR1
DDR2
Ros
CYTOSOL SIDE
vegf receptor class

VEGF-receptor binding.

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”A ribbon diagram . . . with the two protomers of disulfide-linked VEGF shown in orange and purple, and Ig-like domain 2 of Flt1 shown in green. The view in the bottom panel is orthogonal to that in the top panel, as indicated.”

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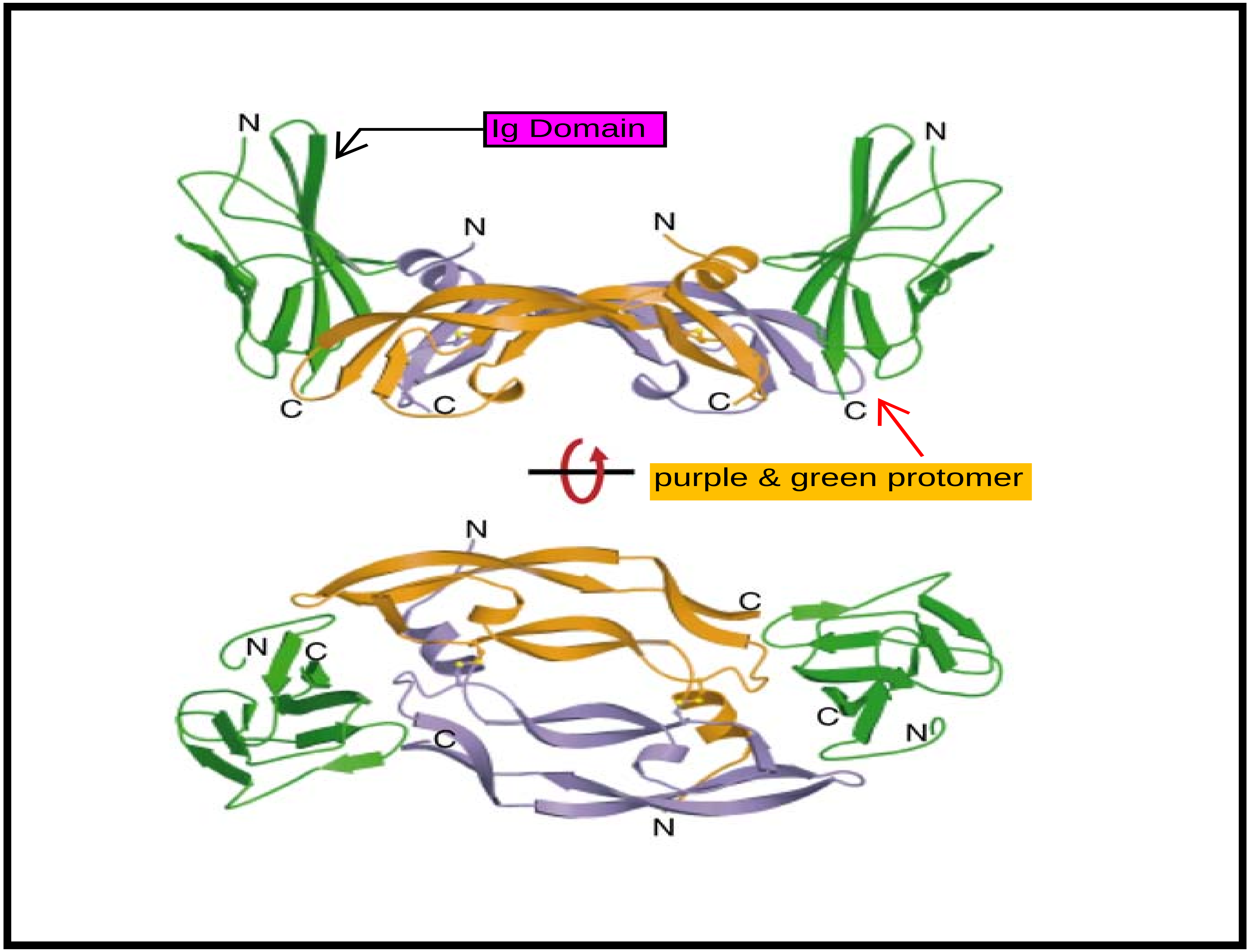
From Hubbard and Till Annu Rev Biochem 2000;69:373-98 Figure 3, permission pending.


Ig Domain
purple & green protomer
N
N
N
N
C
C
C
C
N
C
N
C
C
N
C
N
N

Inhibition Sites.

Potential sites for inhibiting tumor induced angiogenesis:

1.

2.

3.

4.

5.

6.

Inhibition Sites.

Potential sites for inhibiting tumor induced angiogenesis:

1. protease inhibitors.
2.
3.
4.
5.
6.

Inhibition Sites.

Potential sites for inhibiting tumor induced angiogenesis:

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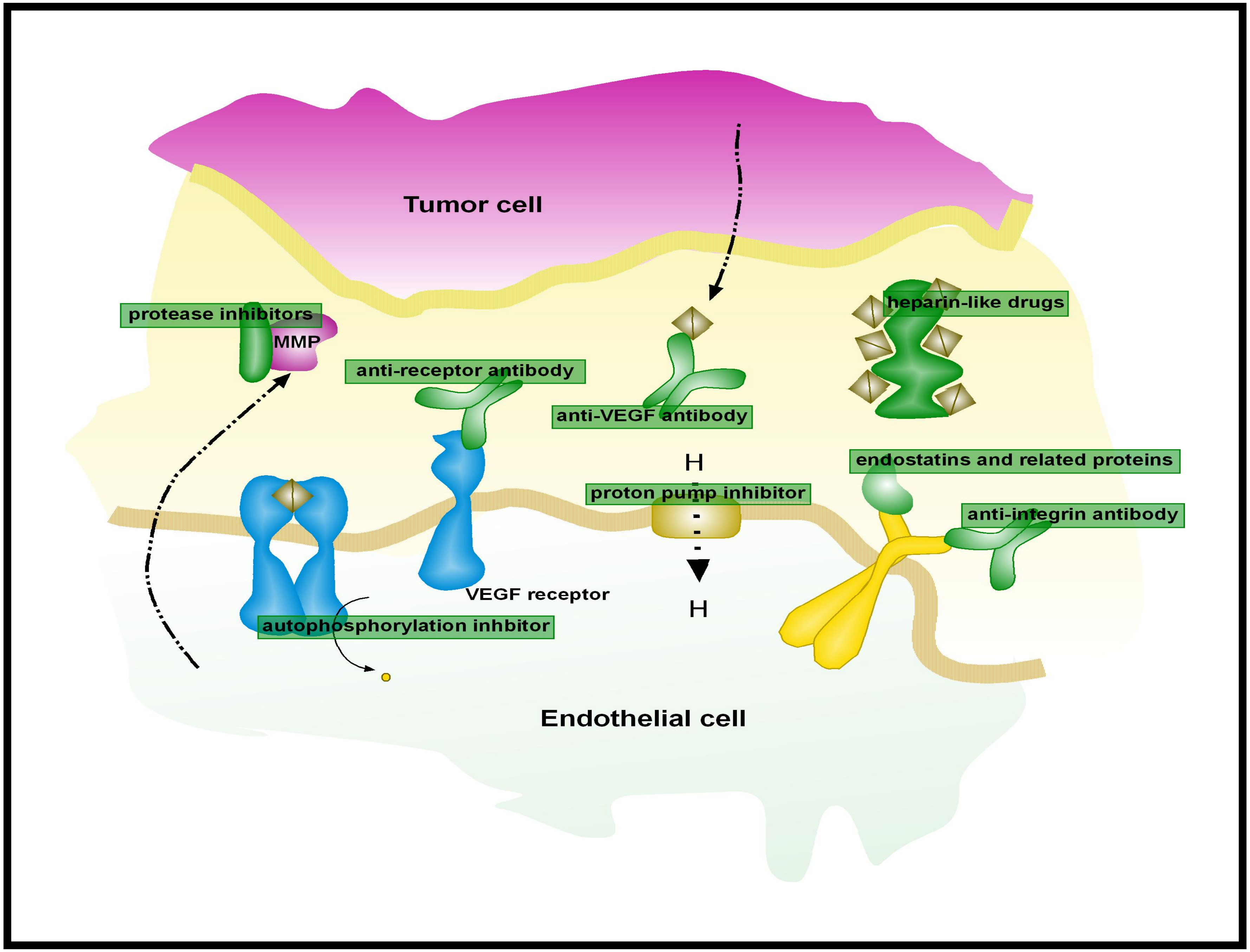
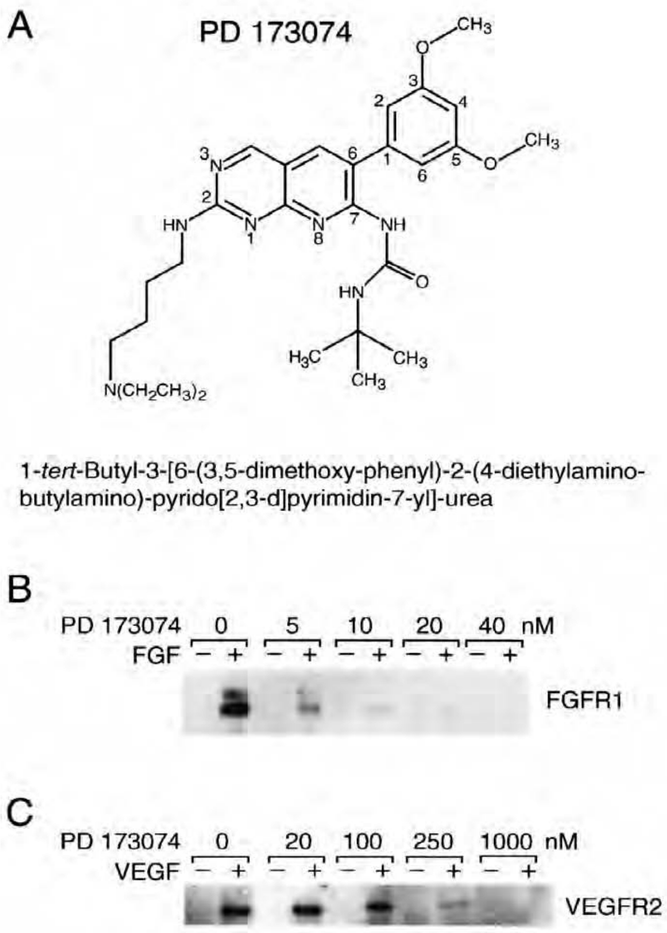
2. antibodies against VEGF, VEGF receptors and integrins.
3. inhibitors of the autophosphorylation of the VEGF receptor.
4. heparin-like drugs that soak up the VEGF.
5. endostatins and related angiogenesis inhibitors.
6. inhibitors of certain general cell functions associated with angiogenesis such as an inhibitors of proton pumps.



Tumor cell
protease inhibitors
MMP
anti-receptor antibody
anti-VEGF antibody
heparin-like drugs
endostatins and related proteins
anti-integrin antibody
H
proton pump inhibitor
H
VEGF receptor
autophosphorylation inhbitor
Endothelial cell

Inhibition of receptors

Growth factor receptor blocking by inhibition of tyrosine kinase activity.



Angiogenesis inhibitors that specifically inhibit tyrosine kinase activity of the FG and VEGF receptors

Mohammadi et al. 1998 EMBO J 17,5896-5904

II.The development of a new model for for angiogenesis.

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- cell density as a probability density.

Model constituents:

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A.

Model constituents:

A. The role of chemical kinetics in the simplification of the intracellular events.

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A. The role of chemical kinetics in the simplification of the intracellular events.

B.

Model constituents:

A. The role of chemical kinetics in the simplification of the intracellular events.

B. The role of the cell cycle.

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C. The role of chemotaxis, haptotaxis and chemokinesis in modeling cell movement.

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D.

Model constituents:

A. The role of chemical kinetics in the simplification of the intracellular events.

B. The role of the cell cycle.

C. The role of chemotaxis, haptotaxis and chemokinesis in modeling cell movement.

D. Contact inhibition, crowding and one way to model them.

Biochemical ingredients

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  -
-
-

Biochemical ingredients

- Growth factor, G, binds to a receptor, R, forms an intermediate, $\{GR\}$ that initiates an intracellular signal cascade that results in:
  -
-
-

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- Inhibitors may be also introduced into the system intravenously.

If a molecule .

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If a molecule X is in an active state, we write X_a.

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$$G_a + R_a$$

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$$Y + \{G_a R_a\}$$

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The relationship of receptor density to endothelial cell density.

1. $\rho = \#$ of receptors/cell.
2. $r(x, y, z, t) = \#$ of receptors in micro moles/liter.
3. $N(x, y, z, t) =$ EC density in cells/liter.
4. $\rho = r/N = \#$ of receptors/cell in micro moles/cell.
5. $1/N_{max}$ cell volume.
6. Then $r_{max} = \rho N_{max}$.
7. Thus $r = r_{max} N/N_{max}$.

An estimate for r_{max}.

1. For many GF's, there are roughly 10^5 receptors/EC.
2. The volume of a typical EC $\approx 10^3$ cubic microns $\approx 10^{-15} m^3$.
3. Thus there are roughly 10^{20} receptors/m^3 or $\approx 10^{17}$/liter.
4. Dividing by Avogadro's number, 6×10^{23}, there are 1.2×10^{-6}moles/l or 1.2μM.
5. Typically $r_{max} \approx 1.0 \mu M$.

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Cell movement partial differential equations

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$$\frac{\partial N_a}{\partial t}$$

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$$+\lambda \frac{g_a}{K + g_a} N_a \left(1 - \frac{N_a + N_i}{N_{max}} \right) - \mu N_a$$

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These lead to

Algebraic relationships

The active protease and active growth factor are related to g, c by

$$g = g_a(1 + \nu_g i_g + r_a/K_m^1)$$

and

$$c = c_a(1 + f/K_m^2)$$

where

$$r_a = r_{max}(N/N_{max})/(1 + g_a/K_m^1).$$

These lead to

$$g = g_a(1 + \nu_g i_g + r_{max}(N/N_{max})/(g_a + K_m^1)) \equiv F(g_a)$$

.

Biochemical partial differential equations

Biochemical partial differential equations

$$\frac{\partial g}{\partial t}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t}$$

$$\frac{\partial c}{\partial t}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t}$$

$$\frac{\partial c}{\partial t}$$

$$\frac{\partial f}{\partial t}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t}$$

$$\frac{\partial c}{\partial t}$$

$$\frac{\partial f}{\partial t}$$

$$\frac{\partial i_g}{\partial t}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g$$

$$\frac{\partial c}{\partial t}$$

$$\frac{\partial f}{\partial t}$$

$$\frac{\partial i_g}{\partial t}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g$$

$$\frac{\partial c}{\partial t} = D_c \Delta c$$

$$\frac{\partial f}{\partial t}$$

$$\frac{\partial i_g}{\partial t}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g$$

$$\frac{\partial c}{\partial t} = D_c \Delta c$$

$$\frac{\partial f}{\partial t} =$$

$$\frac{\partial i_g}{\partial t}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g$$

$$\frac{\partial c}{\partial t} = D_c \Delta c$$

$$\frac{\partial f}{\partial t} =$$

$$\frac{\partial i_g}{\partial t} = D_{i_g} \Delta i_g$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g + \left(\sigma_g - \frac{k_2 g_a}{K_m^1 + g_a} \right) \frac{N_a}{N_{max}}$$

$$\frac{\partial c}{\partial t} = D_c \Delta c$$

$$\frac{\partial f}{\partial t} =$$

$$\frac{\partial i_g}{\partial t} = D_{i_g} \Delta i_g$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g + \left(\sigma_g - \frac{k_2 g_a}{K_m^1 + g_a} \right) \frac{N_a}{N_{max}}$$

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$$\frac{\partial f}{\partial t} =$$

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$$\frac{\partial c}{\partial t} = D_c \Delta c + \frac{k_2 g_a}{K_m^1 + g_a} \frac{N_a}{N_{max}}$$

$$\frac{\partial f}{\partial t} = \frac{4}{T_f} f \left(1 - \frac{f}{f_M}\right) \frac{N_a + N_i}{N_{max}}$$

$$\frac{\partial i_g}{\partial t} = D_{i_g} \Delta i_g$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g + \left(\sigma_g - \frac{k_2 g_a}{K_m^1 + g_a}\right)\frac{N_a}{N_{max}}$$

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$$\frac{\partial i_g}{\partial t} = D_{i_g} \Delta i_g + \frac{k_4 c_a f}{K_m^2} + \sigma_i \frac{N_a + N_i}{N_{max}}$$

Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g + \left(\sigma_g - \frac{k_2 g_a}{K_m^1 + g_a} \right) \frac{N_a}{N_{max}} - \mu_g g_a,$$

$$\frac{\partial c}{\partial t} = D_c \Delta c + \frac{k_2 g_a}{K_m^1 + g_a} \frac{N_a}{N_{max}}$$

$$\frac{\partial f}{\partial t} = \frac{4}{T_f} f \left(1 - \frac{f}{f_M} \right) \frac{N_a + N_i}{N_{max}}$$

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Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g + \left(\sigma_g - \frac{k_2 g_a}{K_m^1 + g_a}\right)\frac{N_a}{N_{max}} - \mu_g g_a,$$

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Biochemical partial differential equations

$$\frac{\partial g}{\partial t} = D_g \Delta g + \left(\sigma_g - \frac{k_2 g_a}{K_m^1 + g_a}\right) \frac{N_a}{N_{max}} - \mu_g g_a,$$

$$\frac{\partial c}{\partial t} = D_c \Delta c + \frac{k_2 g_a}{K_m^1 + g_a} \frac{N_a}{N_{max}} - \mu_c c_a,$$

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$$\frac{\partial i_g}{\partial t} = D_{i_g} \Delta i_g + \frac{k_4 c_a f}{K_m^2} + \sigma_i \frac{N_a + N_i}{N_{max}}$$

Biochemical partial differential equations

$$
\begin{aligned}
\frac{\partial g}{\partial t} &= D_g \Delta g + \left(\sigma_g - \frac{k_2 g_a}{K_m^1 + g_a} \right) \frac{N_a}{N_{max}} - \mu_g g_a, \\
\frac{\partial c}{\partial t} &= D_c \Delta c + \frac{k_2 g_a}{K_m^1 + g_a} \frac{N_a}{N_{max}} - \mu_c c_a, \\
\frac{\partial f}{\partial t} &= \frac{4}{T_f} f \left(1 - \frac{f}{f_M} \right) \frac{N_a + N_i}{N_{max}} - \frac{k_4 c_a f}{K_m^2}, \\
\frac{\partial i_g}{\partial t} &= D_{i_g} \Delta i_g + \frac{k_4 c_a f}{K_m^2} + \sigma_i \frac{N_a + N_i}{N_{max}} - \mu_{i_g} i_g.
\end{aligned}
$$

III. Some results for a tumor induced angiogenesis model.

Literature for this model

H.A. Levine, S. Pamuk, B. D. Sleeman and M. Nilsen-Hamilton, J. Math. Biol. 63(2001) 801-863.

I. J. Folkman's Model

(From: Angiogenesis:Key Principles-Science-Technology-Medicine)

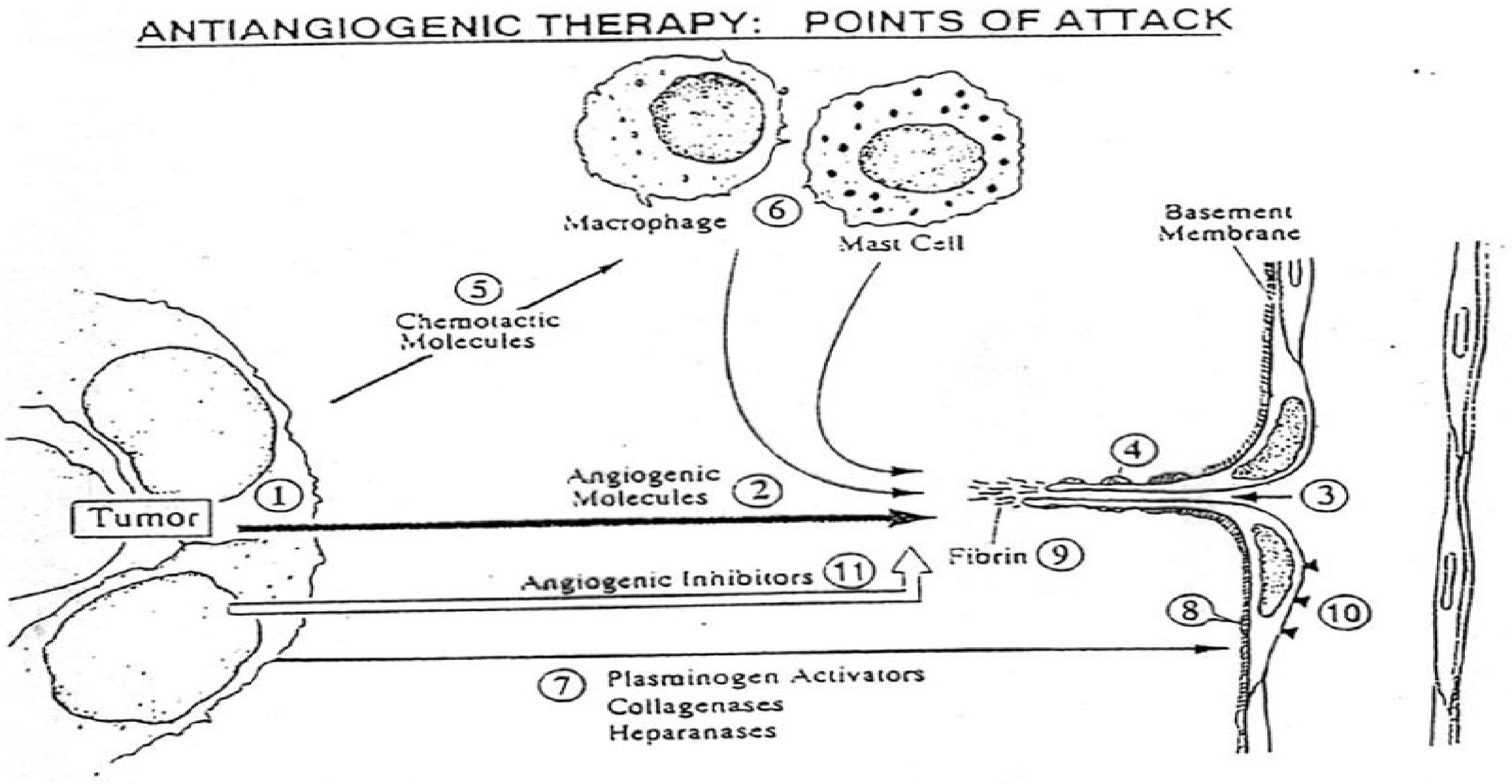
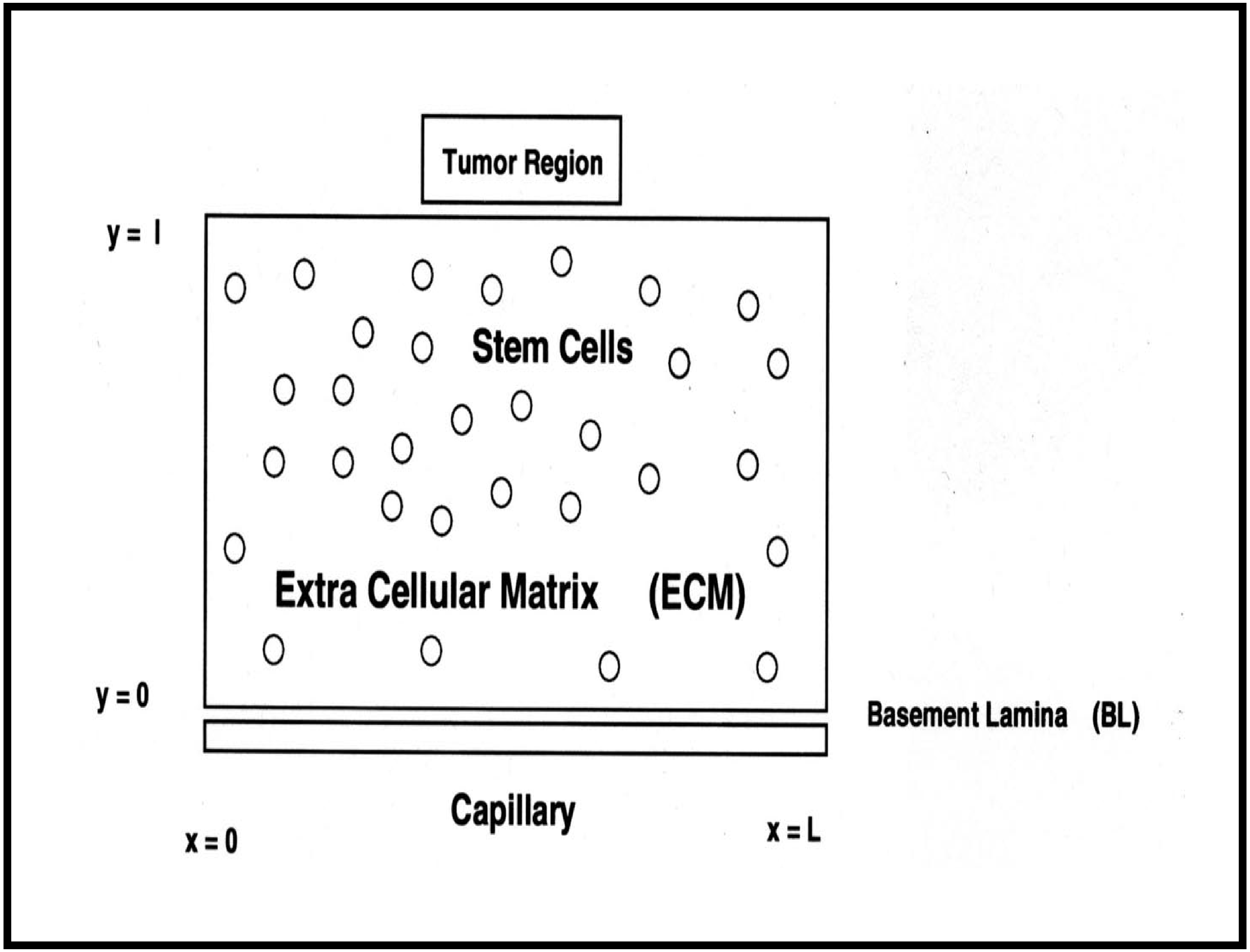


Diagram of different targets for antiangiogenic therapy.

A segment of capillary wall of fixed length L on the x axis at $y = 0$.
A tumor is located at $y = \ell$.


Tumor Region
y = l
Stem Cells
Extra Cellular Matrix (ECM)
y = 0
Basement Lamina (BL)
Capillary
x = 0
x = L

Notation for the capillary wall:

$$
\begin{aligned}
v(x,t) &= \text{angiogenic factor, } V, \\
c(x,t) &= \text{total available proteolytic enzyme, } C, \\
c_a(x,t) &= \text{free active proteolytic enzyme, } C_{act}, \\
c_i(x,t) &= \text{inhibited proteolytic enzyme, } C_I, \\
\tilde{c_a}(x,t) &= \text{total available active enzyme, } \tilde{C}_{act}, \\
f(x,t) &= \text{fibronectin, } F, \\
a(x,t) &= \text{angiostatin as inhibitor, } A, \\
\eta(x,t) &= \text{endothelial cell density.}
\end{aligned}
$$

In the ECM, the notation becomes:

$$
\begin{aligned}
V(x,y,t) &= \text{angiogenic factor, } V, \\
C(x,y,t) &= \text{proteolytic enzyme, } C, \\
C_a(x,y,t) &= \text{free active proteolytic enzyme, } C_{act}, \\
C_i(x,y,t) &= \text{inhibited proteolytic enzyme, } C_I, \\
\tilde{C}_a(x,y,t) &= \text{total available active enzyme, } \tilde{C}_{act}, \\
F(x,y,t) &= \text{fibronectin, } F, \\
A(x,y,t) &= \text{angiostatin as inhibitor, } A, \\
N(x,y,t) &= \text{endothelial cell density.}
\end{aligned}
$$

Results and conclusions:

Results and conclusions:

I.

Results and conclusions:

I. No angiostatin case:

Results and conclusions:

I. No angiostatin case:

A.

Results and conclusions:

I. No angiostatin case:

   A. The onset of sprouting time and the onset of vascularization time, when scaled up to one or two mm. are in very good agreement with the experimental results of Folkman and his colleagues as well as with CAM assay experiments.

Results and conclusions:

I. No angiostatin case:

A. The onset of sprouting time and the onset of vascularization time, when scaled up to one or two mm. are in very good agreement with the experimental results of Folkman and his colleagues as well as with CAM assay experiments.

B.

Results and conclusions:

I. No angiostatin case:

A. The onset of sprouting time and the onset of vascularization time, when scaled up to one or two mm. are in very good agreement with the experimental results of Folkman and his colleagues as well as with CAM assay experiments.

B. The channel widths are in agreement with the known (6-10 μmm) widths for capillary diameters.

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  C. EC proliferation is a maximum a little behind the moving tip.

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C. EC proliferation is a maximum a little behind the moving tip.

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D. The tip speed increases as the forming capillary approaches the tumor source.

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E.

Results and conclusions:

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A. The onset of sprouting time and the onset of vascularization time, when scaled up to one or two mm. are in very good agreement with the experimental results of Folkman and his colleagues as well as with CAM assay experiments.

B. The channel widths are in agreement with the known (6-10 μmm) widths for capillary diameters.

C. EC proliferation is a maximum a little behind the moving tip.

D. The tip speed increases as the forming capillary approaches the tumor source.

E. The model predicts the onset of sprouting without EC movement into the ECM when one allows for protease diffusion in the ECM.

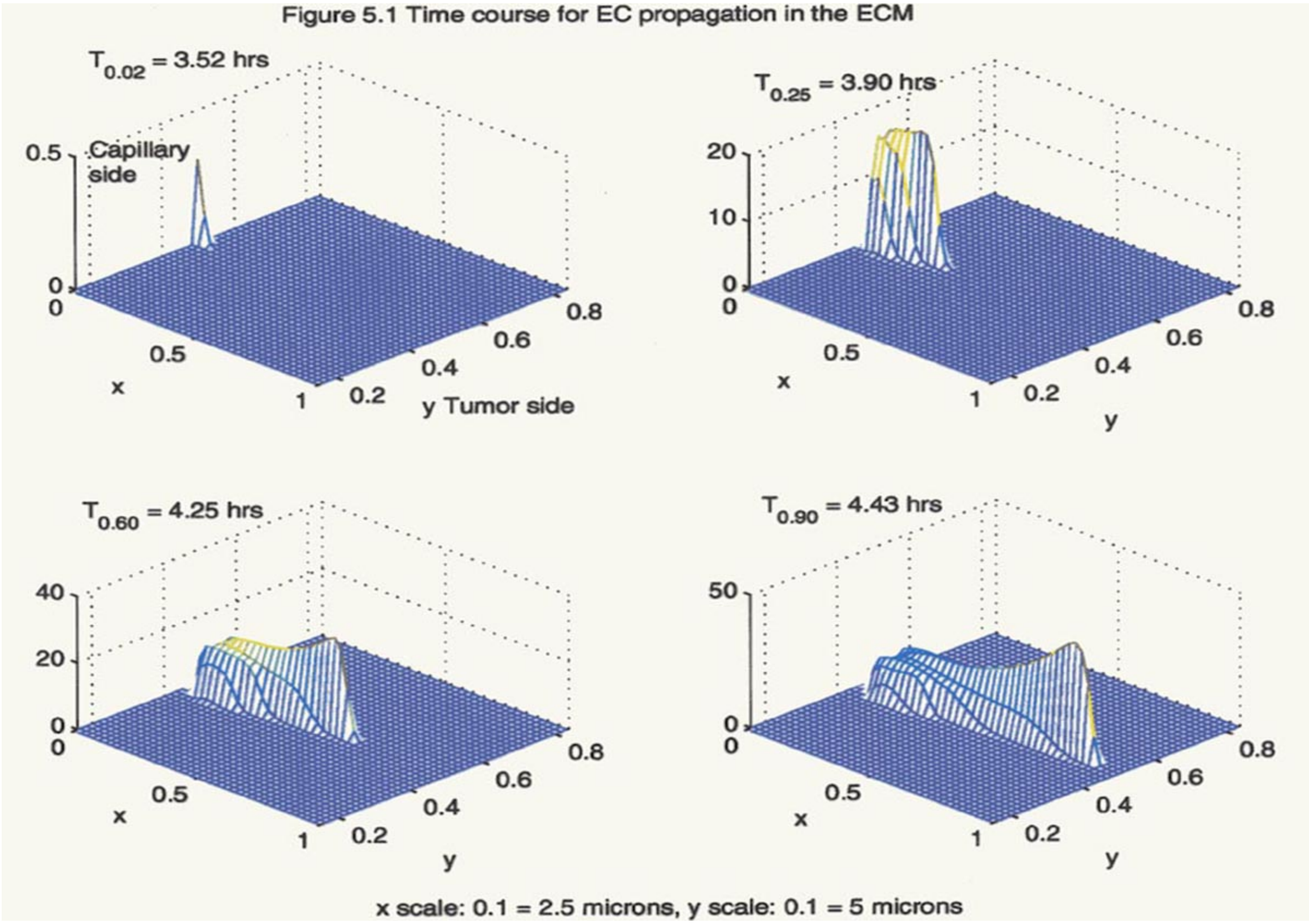
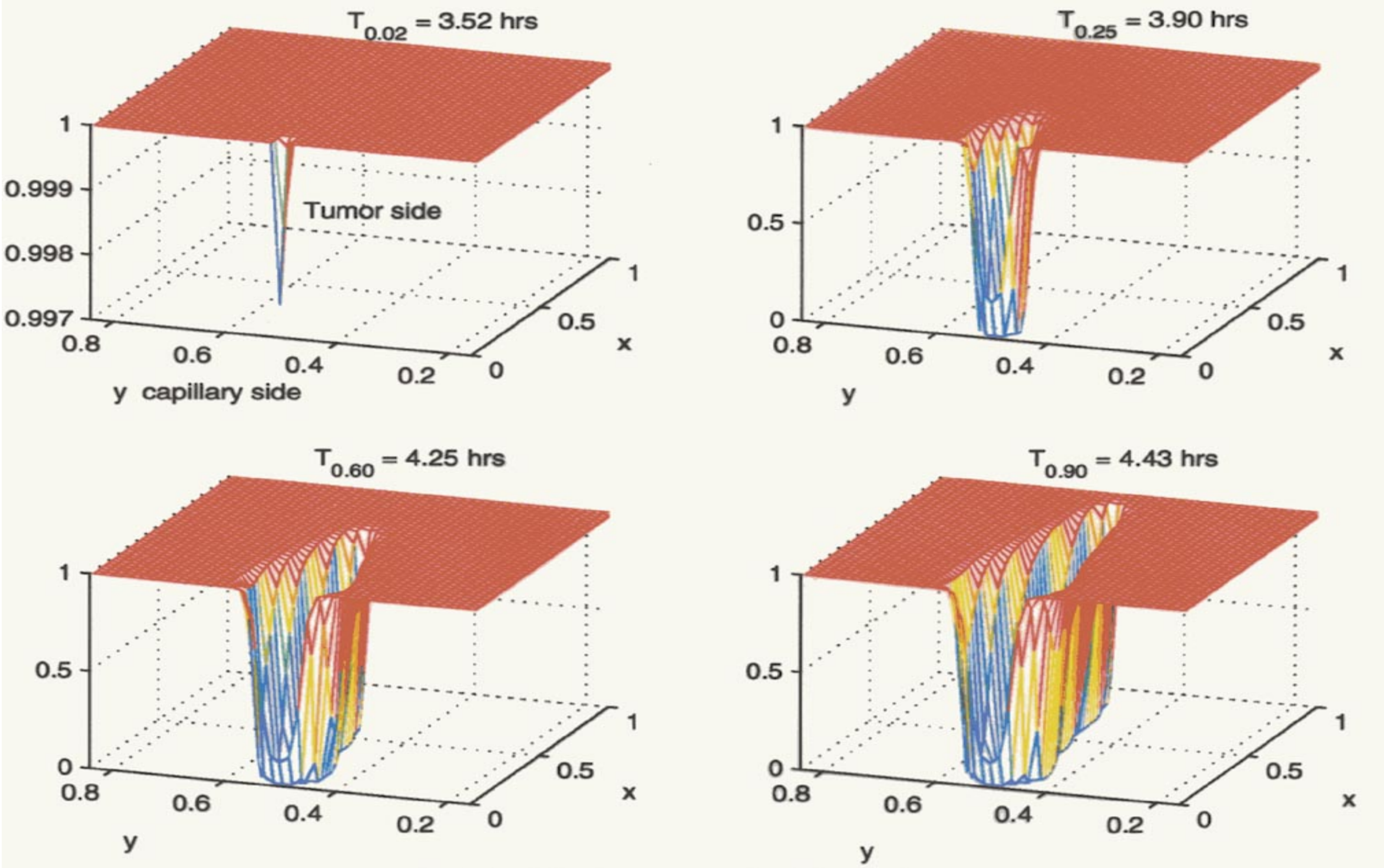


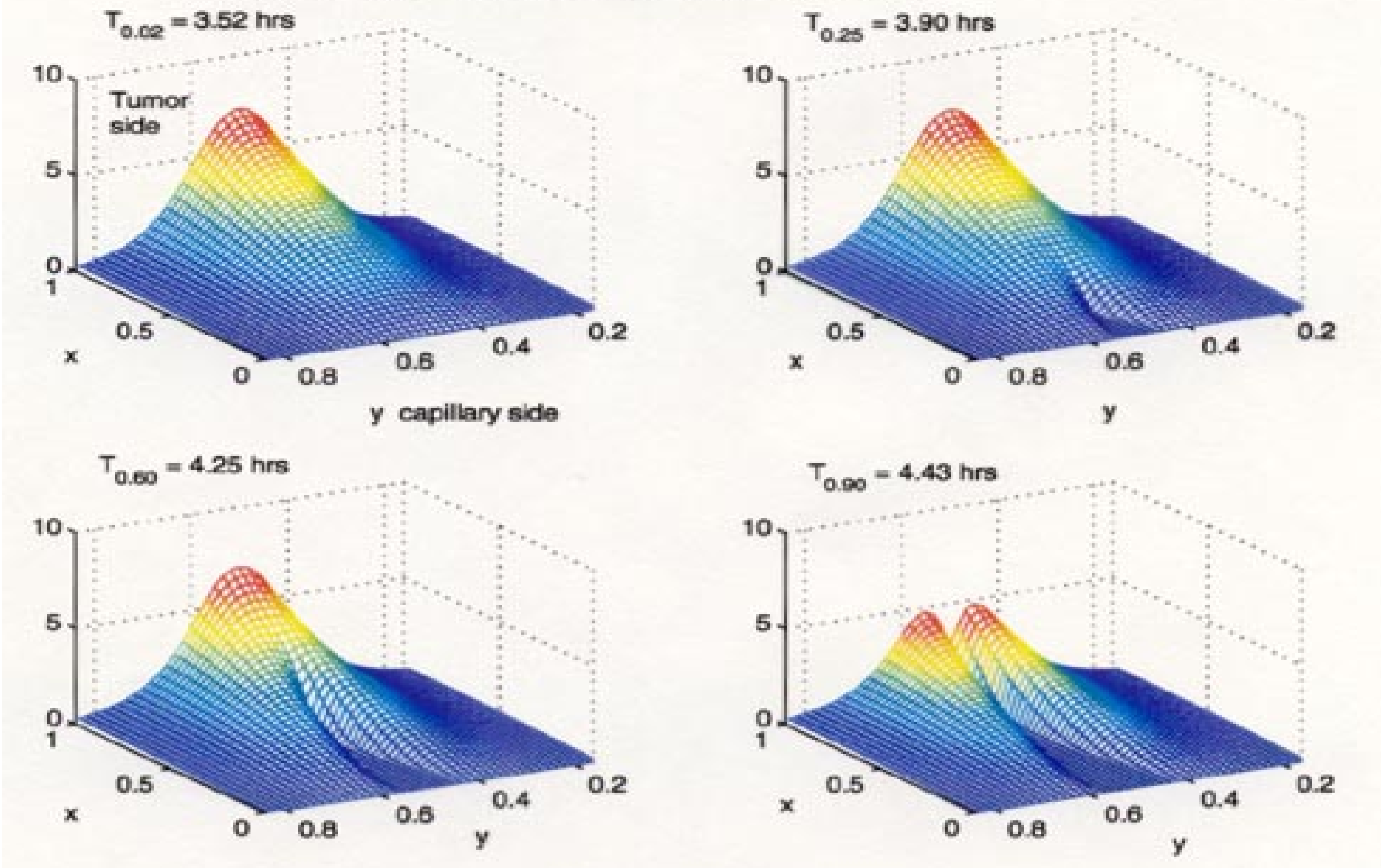
Figure 5.1 Time course for EC propagation in the ECM
T0.02 = 3.52 hrs
Capillary side
y Tumor side
T0.25 = 3.90 hrs
T0.60 = 4.25 hrs
T0.90 = 4.43 hrs
x
y
x scale: 0.1 = 2.5 microns, y scale: 0.1 = 5 microns

Figure 5.3 Time course for fibronectin propagation in the ECM



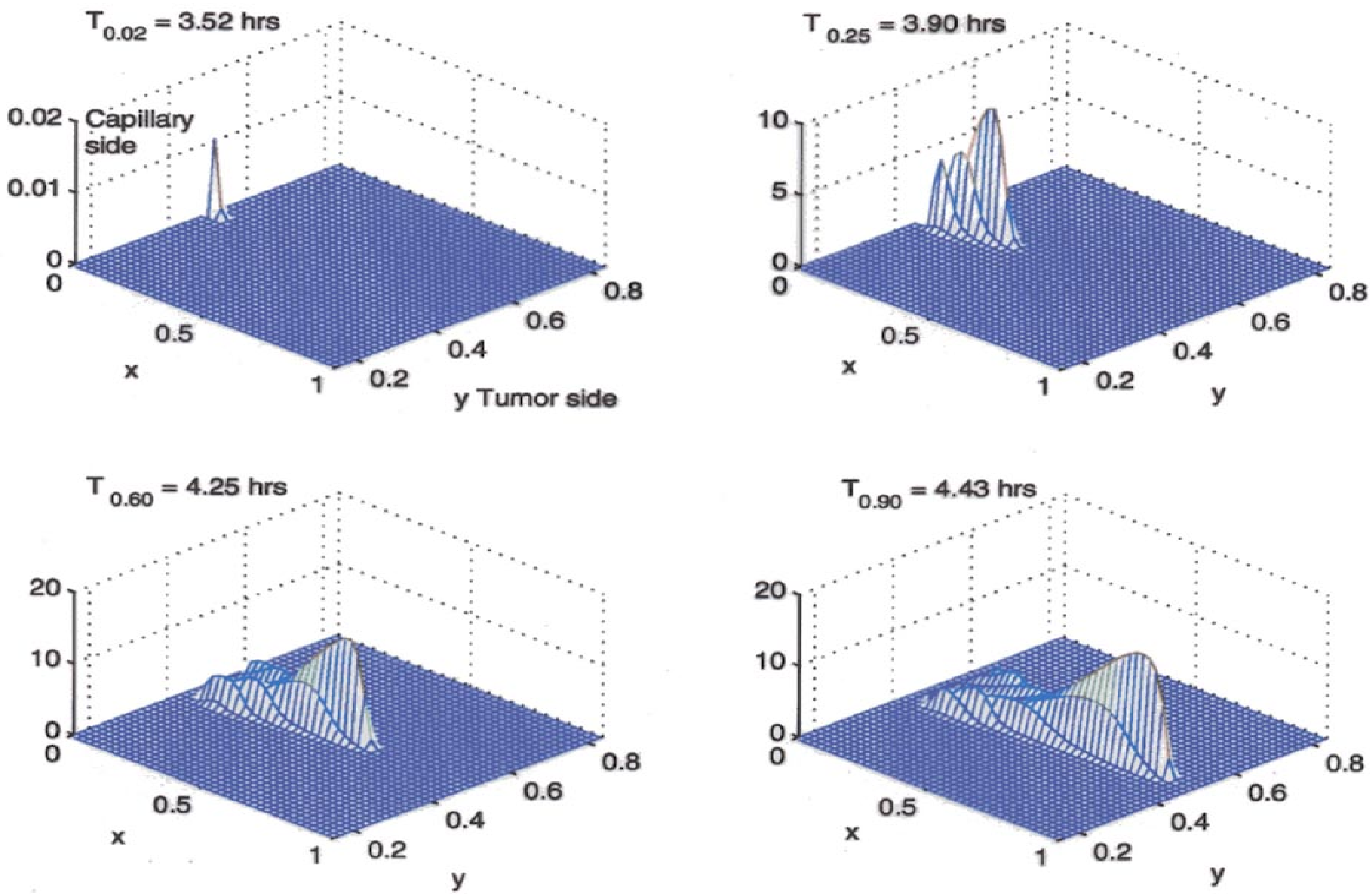
x scale: 0.1 = 2.5 microns, y scale: 0.1 = 5 microns

Figure 5.5 Time course for VEGF propagation in the ECM



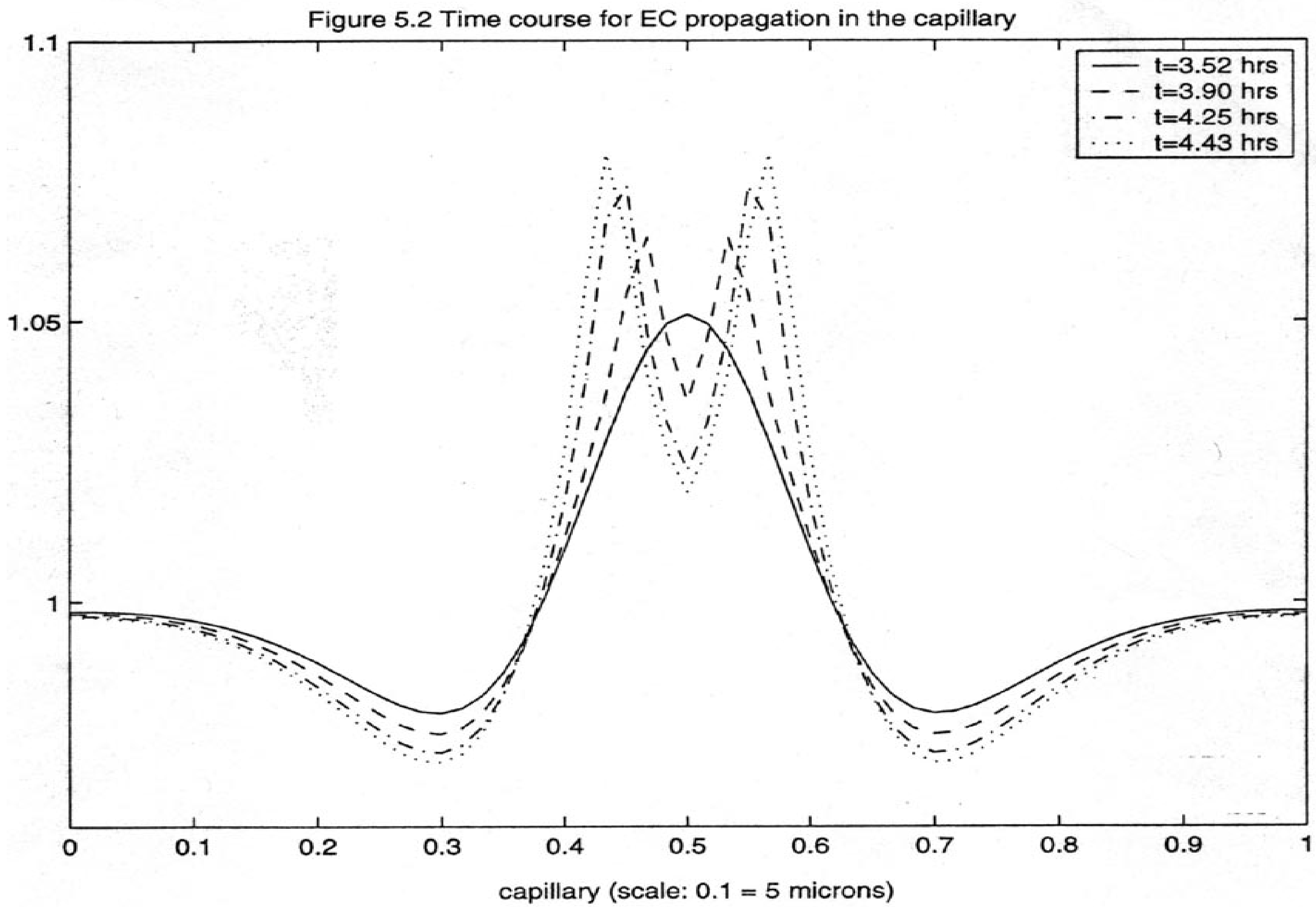
x scale: 0.1 = 2.5 microns, y scale: 0.1 = 5 microns

Figure 5.6 Time course for protease propagation in the ECM

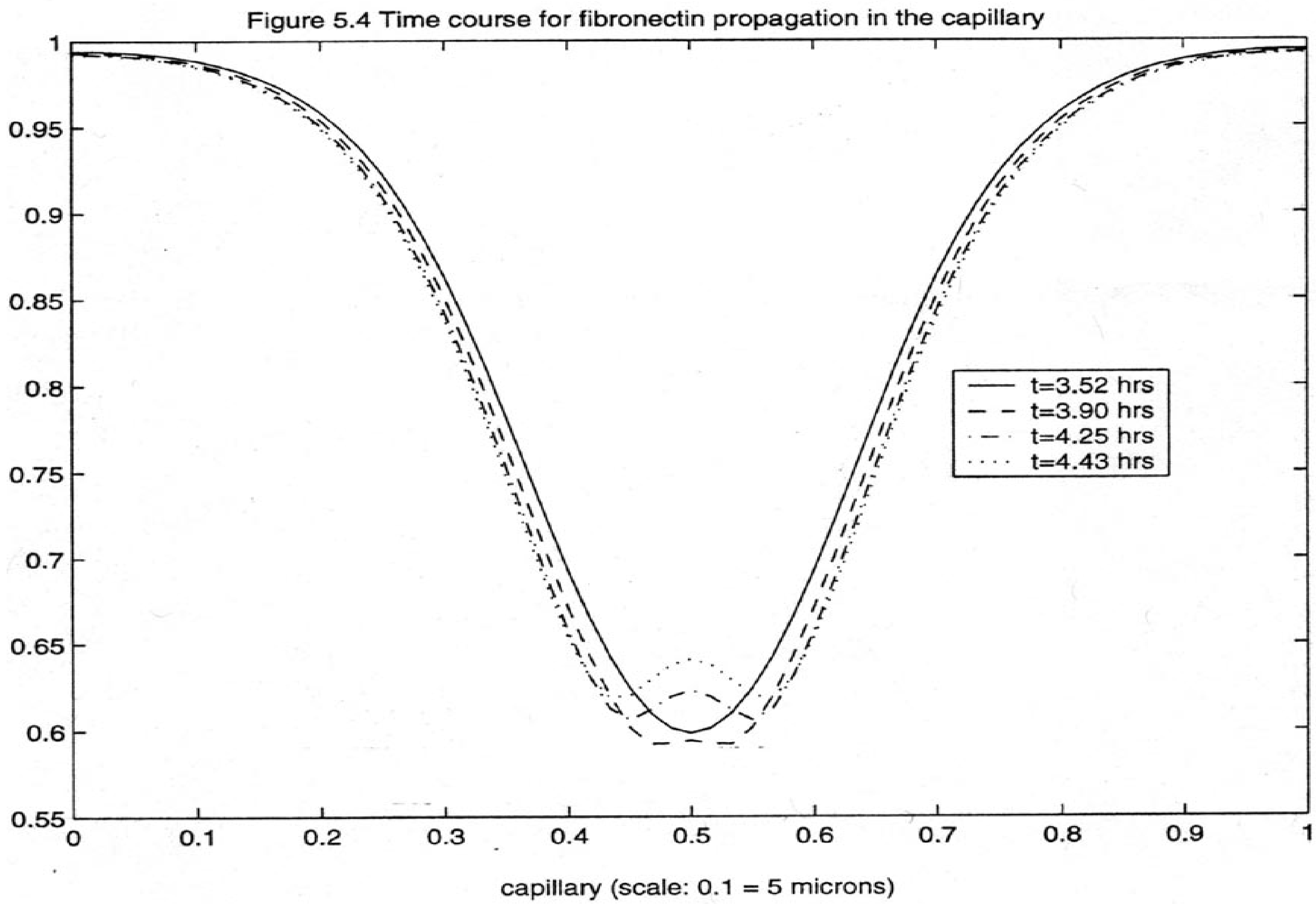


x scale: 0.1 = 2.5 microns, y scale: 0.1 = 5 microns

Cell density in the capillary



Fibronectin density in the capillary



II.

II. Angiostatin case with high protease affinity:

II. Angiostatin case with high protease affinity:

A.

II. Angiostatin case with high protease affinity:

A. The opening from the mother capillary closes.

II. Angiostatin case with high protease affinity:

A. The opening from the mother capillary closes.

B.

II. Angiostatin case with high protease affinity:

A. The opening from the mother capillary closes.

B. The EC density in the daughter capillary drops.

II. Angiostatin case with high protease affinity:

A. The opening from the mother capillary closes.

B. The EC density in the daughter capillary drops.

C.

II. Angiostatin case with high protease affinity:

A. The opening from the mother capillary closes.

B. The EC density in the daughter capillary drops.

C. The tip retreats and the channel closes.

II. Angiostatin case with high protease affinity:

A. The opening from the mother capillary closes.

B. The EC density in the daughter capillary drops.

C. The tip retreats and the channel closes.

D.

II. Angiostatin case with high protease affinity:

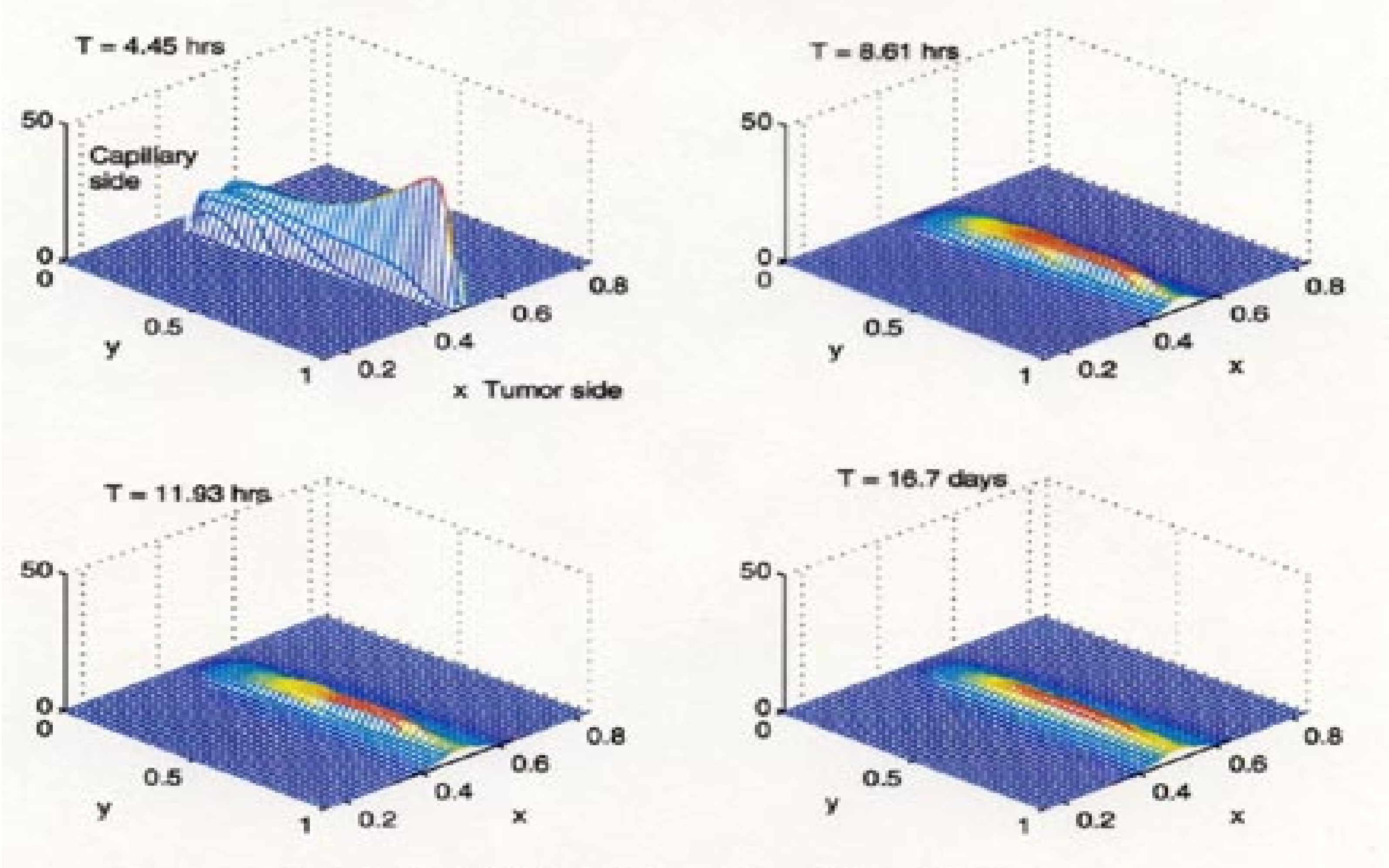
A. The opening from the mother capillary closes.

B. The EC density in the daughter capillary drops.

C. The tip retreats and the channel closes.

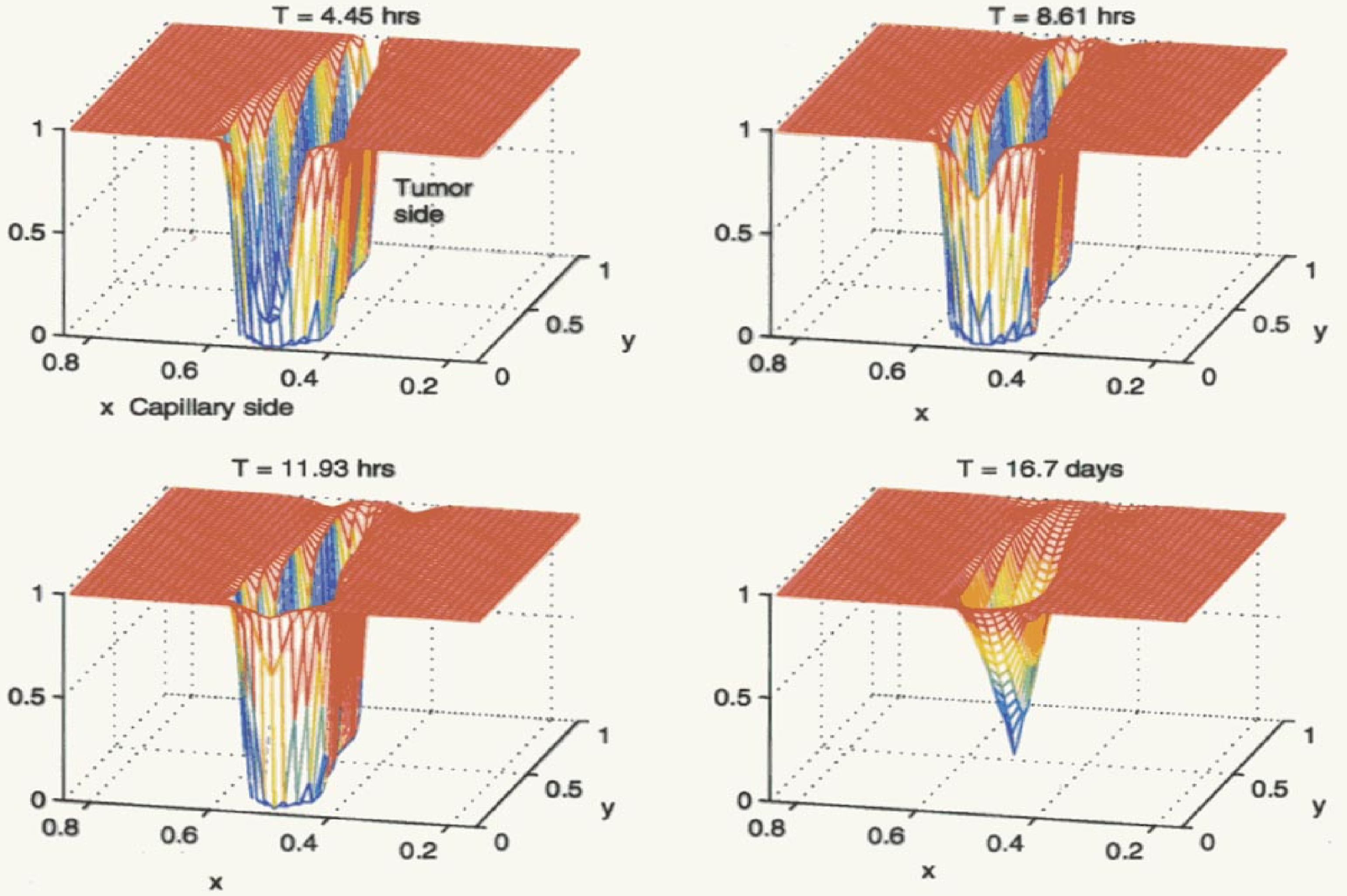
D. It takes much longer for the channel to close completely than for the EC density to fall to negligible values.

Figure 6.1 Time course for EC propagation in the ECM

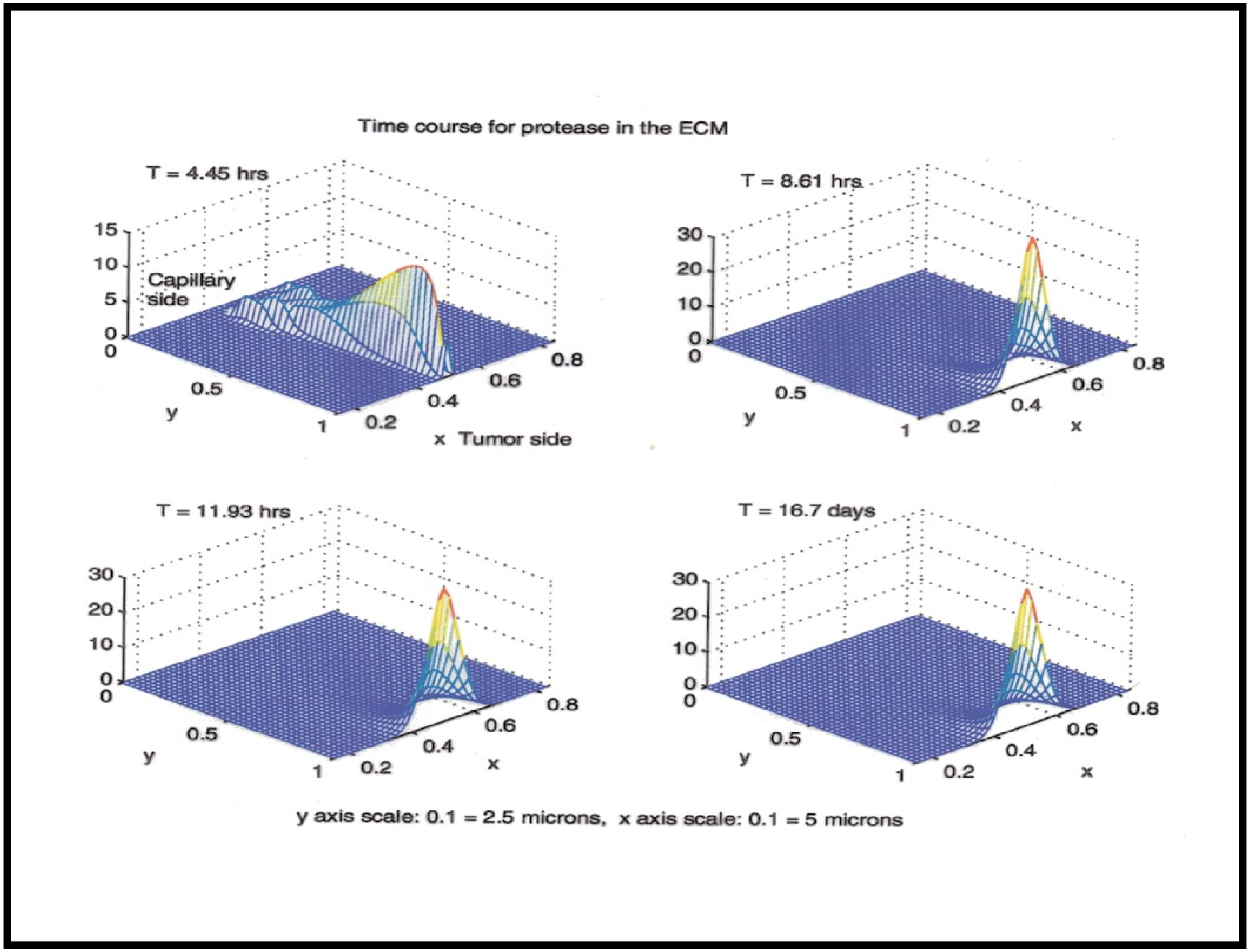


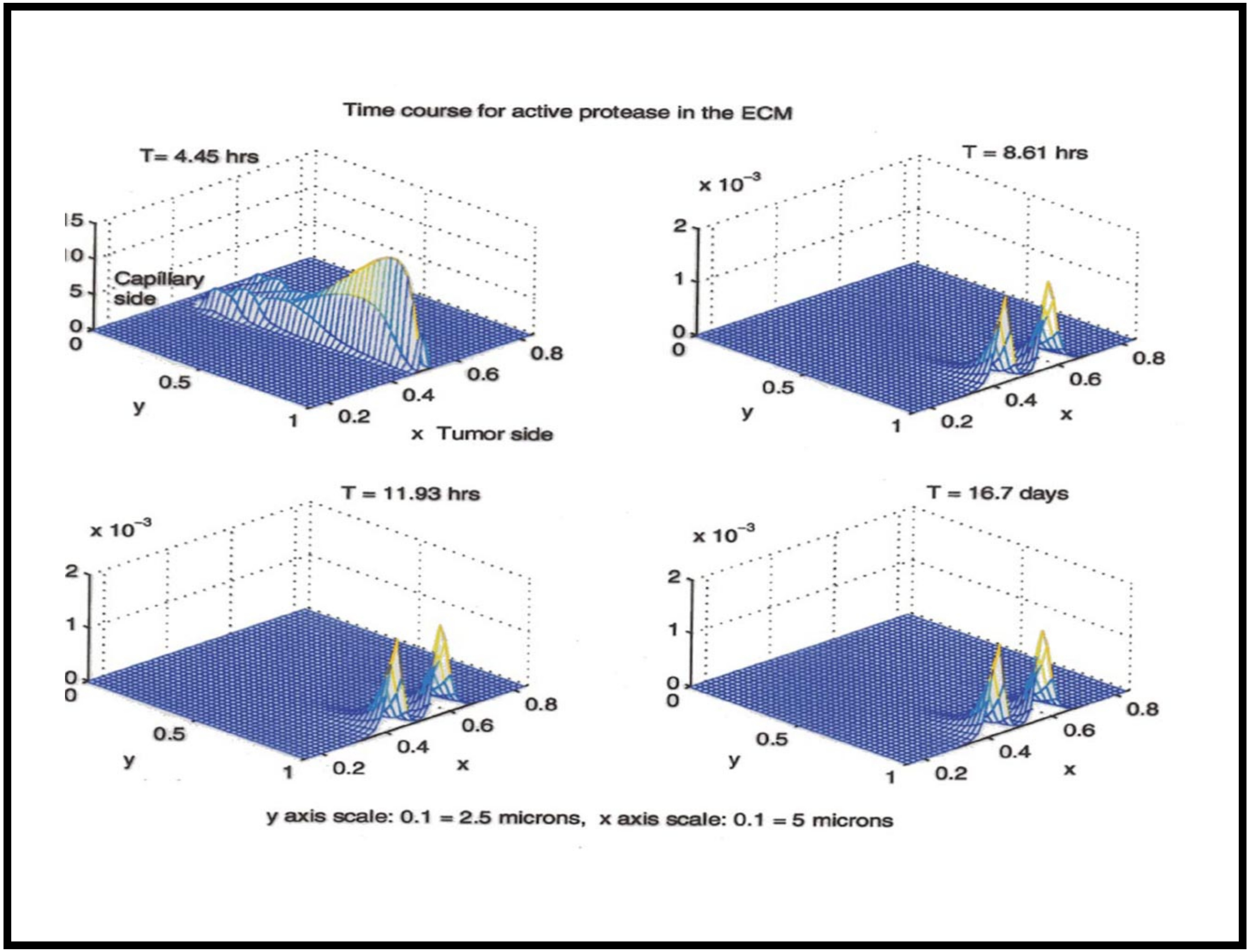
y axis scale: 0.1 = 2.5 microns, x axis scale: 0.1 = 5 microns

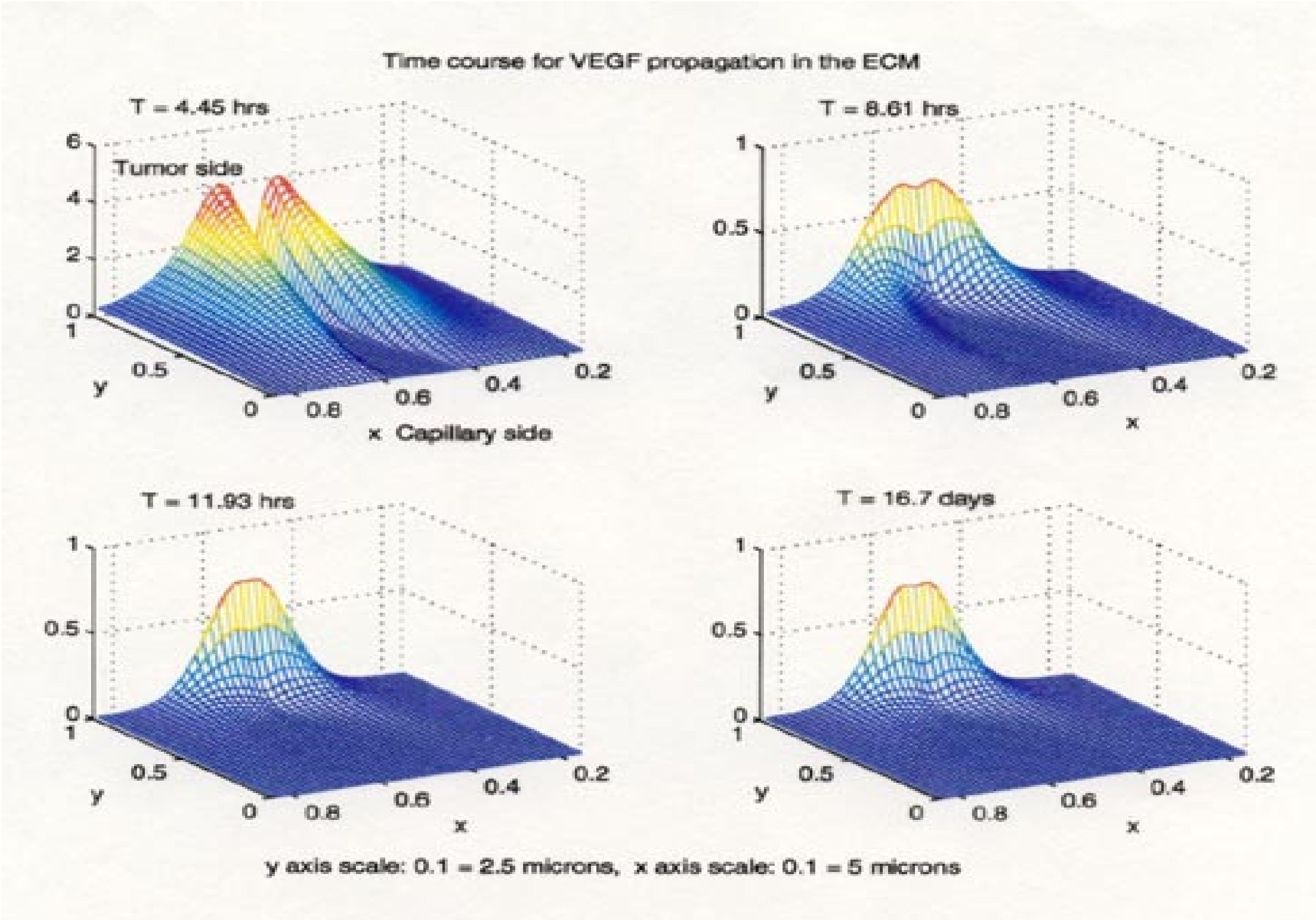
Figure 6.3 Time course for fibronectin propagation in the ECM



y axis scale: 0.1 = 2.5 hrs, x axis scale: 0.1 = 5 microns

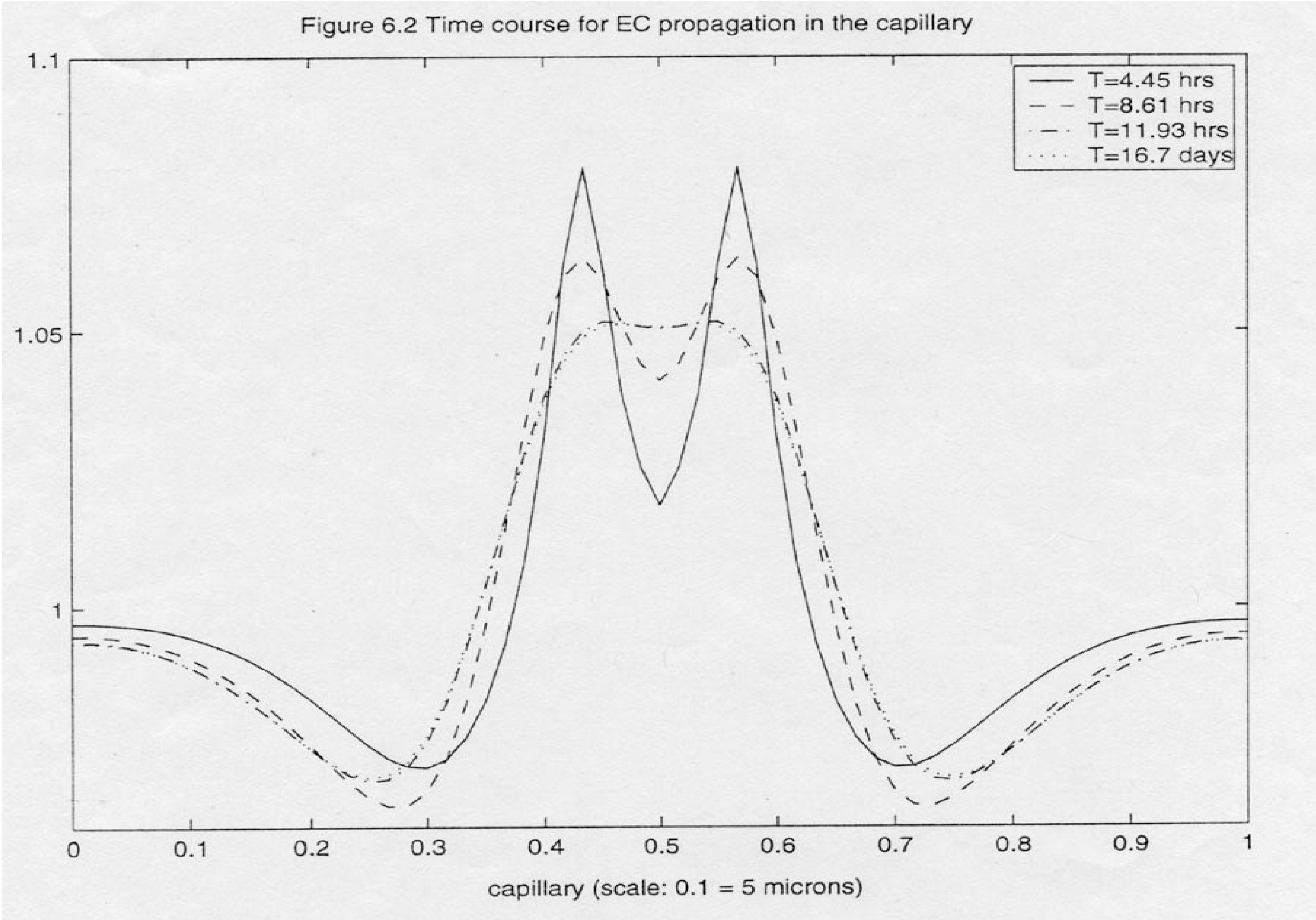

Time course for protease in the ECM
T = 4.45 hrs
Capillary side
x Tumor side
T = 8.61 hrs
T = 11.93 hrs
T = 16.7 days
y
x
y axis scale: 0.1 = 2.5 microns, x axis scale: 0.1 = 5 microns


Time course for active protease in the ECM
T= 4.45 hrs
Capillary side
x Tumor side
T = 8.61 hrs
T = 11.93 hrs
T = 16.7 days
y axis scale: 0.1 = 2.5 microns, x axis scale: 0.1 = 5 microns

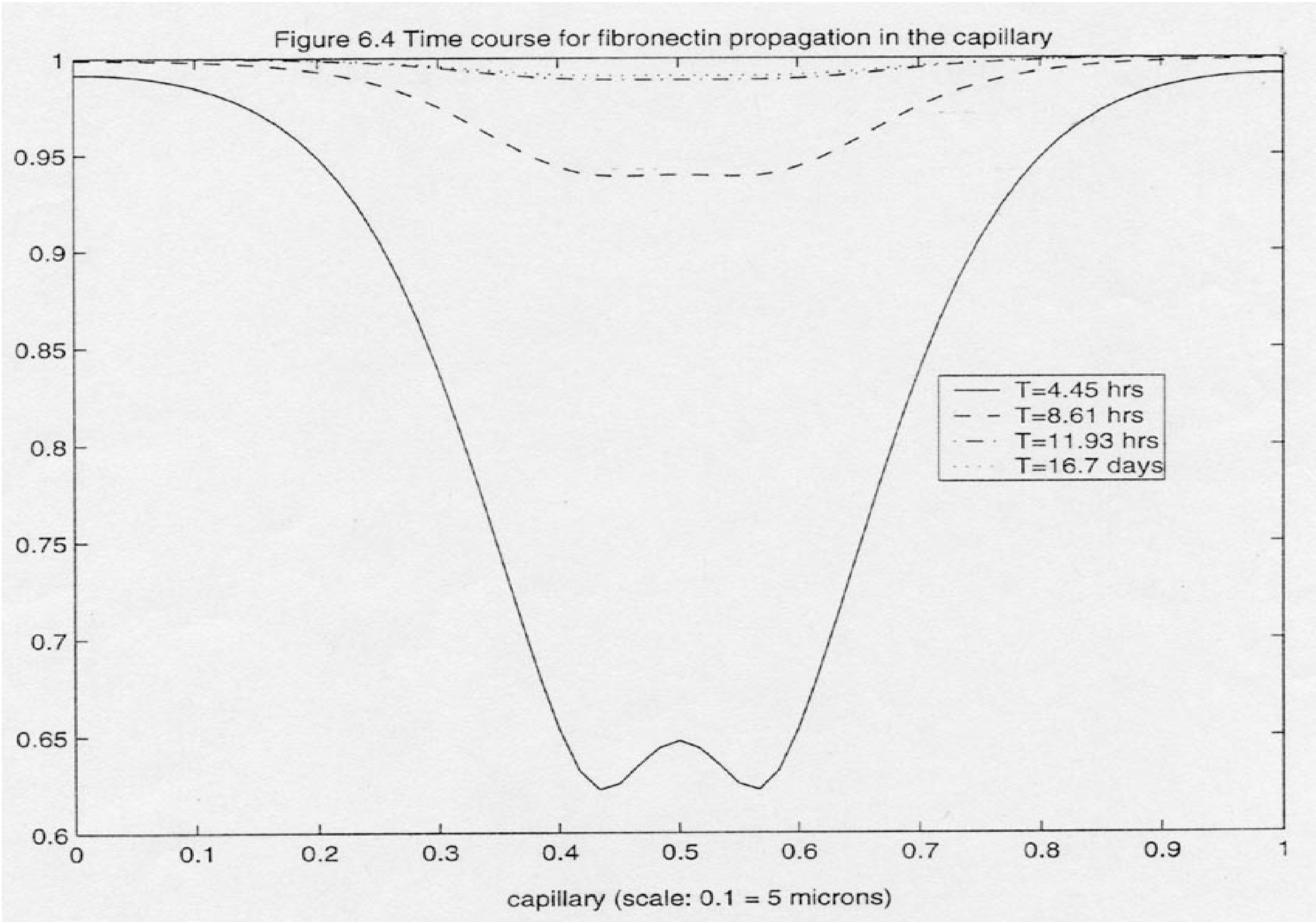


Time course for VEGF propagation in the ECM
T = 4.45 hrs
Tumor side
x Capillary side
T = 8.61 hrs
T = 11.93 hrs
T = 16.7 days
y axis scale: 0.1 = 2.5 microns, x axis scale: 0.1 = 5 microns

Cell density in the capillary



Fibronectin density in the capillary



Travel times and tip speeds

Distance from capillary to tumor in microns	Time in hours	Mean velocity (mm/day)	Extrap. times in days for 1 mm	Extrap. times in days for 2 mm
0.00	3.49		5.817	11.633
2.50	3.74	0.242	6.817	13.633
5.00	3.88	0.436	7.317	14.633
7.50	3.99	0.545	7.650	15.300
10.00	4.09	0.580	7.900	15.800
12.50	4.18	0.703	8.100	16.200
15.00	4.25	0.831	8.267	16.533
17.50	4.32	0.914	8.410	16.819
20.00	4.38	1.015	8.535	17.069
22.50	4.43	1.015	8.646	17.291

($\ell = 25\mu$mm, $L = 50\mu$mm)

The End

Any Questions?