Modeling Tumor Development

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Outline

- Cancer development overview
- What's been done?

  Overview of mathematical models for tumor growth
- What have we done?

  A cell-based, multiscale model framework
- What can our model do?

  Avascular tumor growth, angiogenesis, vascular growth
- How good is our model?

  Pros and cons
- Where are we going with such a model?

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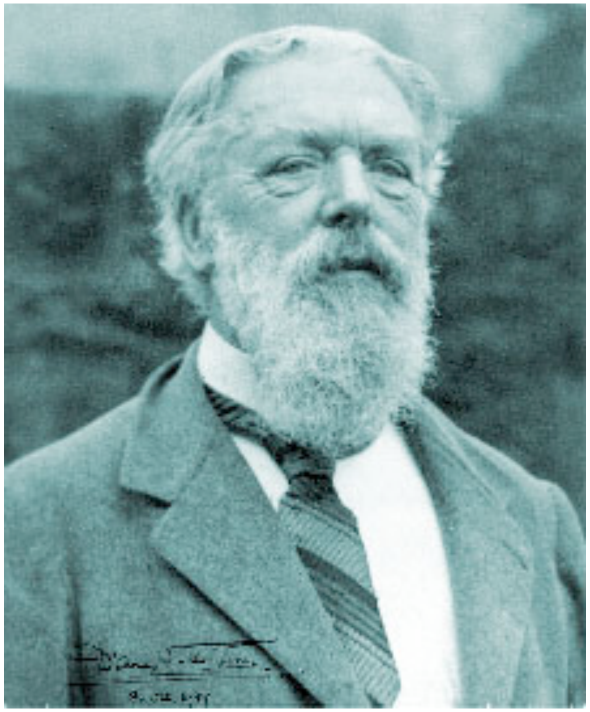
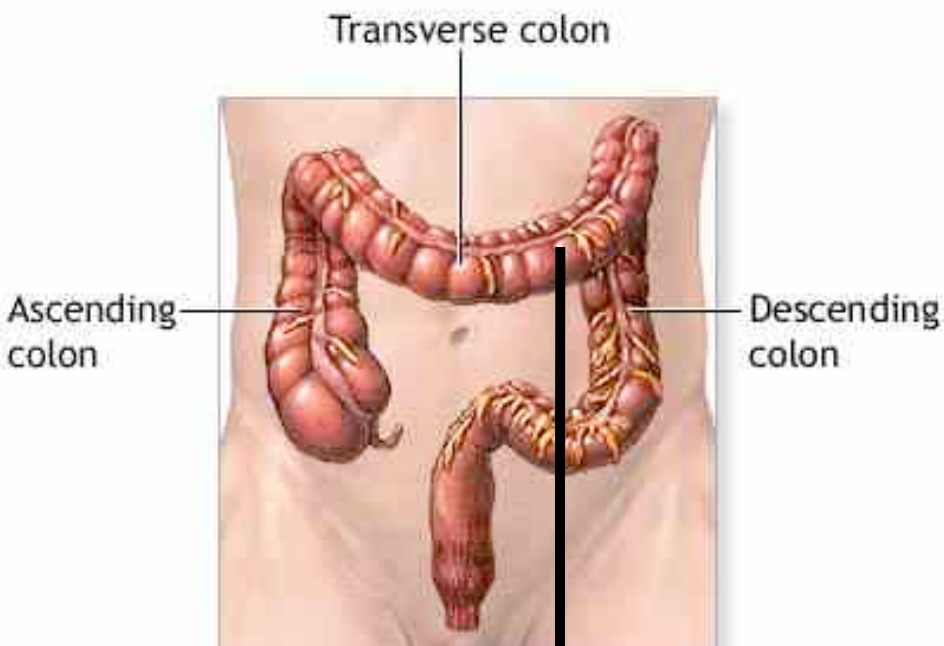
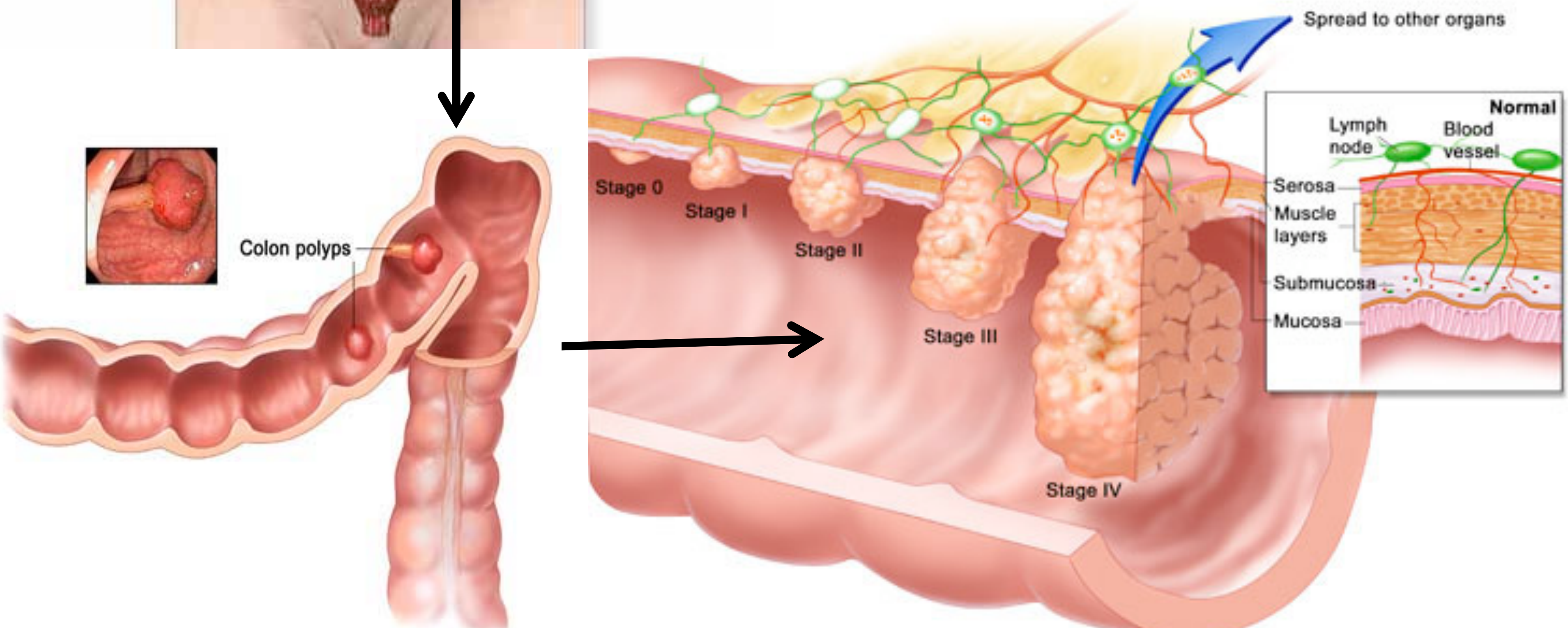
"I know that in the study of material things, number, order and position are the threefold clues to exact knowledge; that these three, in the mathematician's hands, furnish the 'first outlines for a sketch of the Universe'."



On Growth and Form 1917

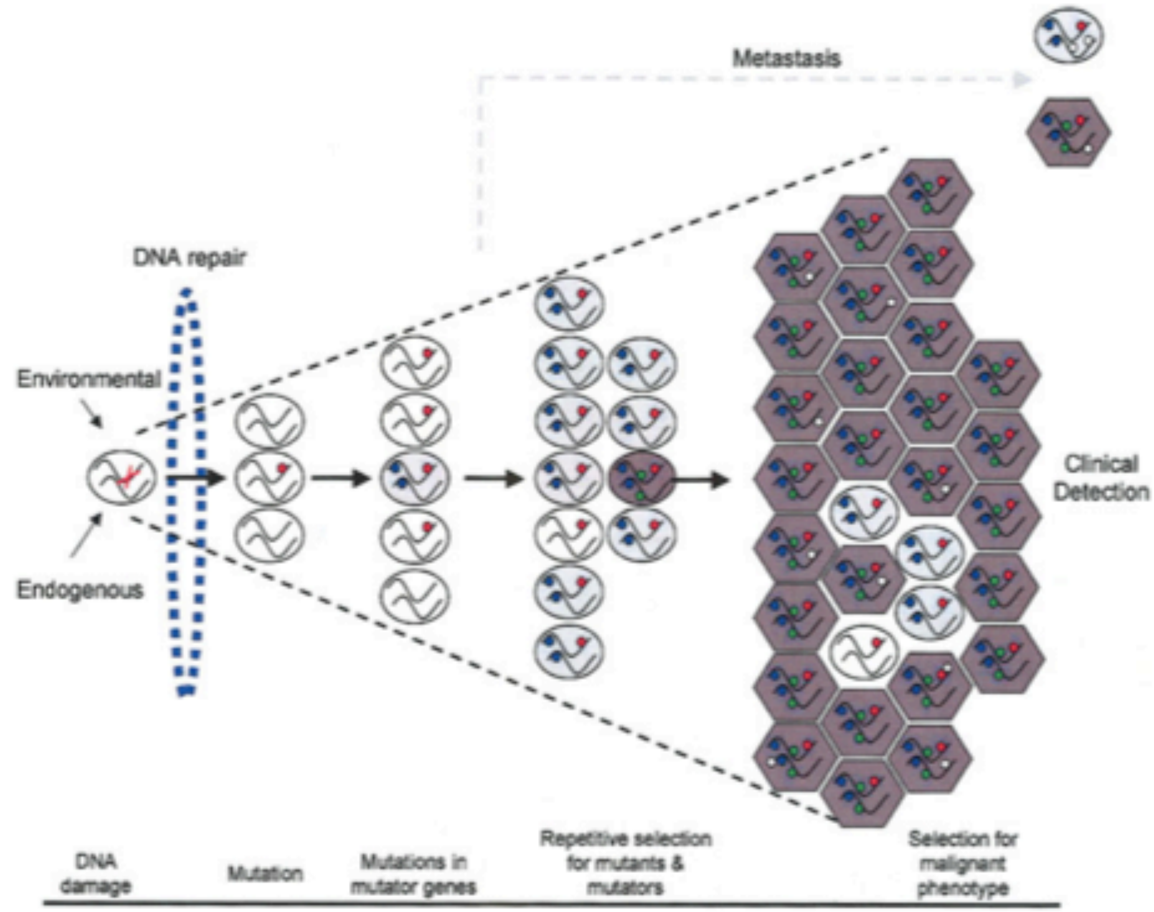
Colon Cancer Development



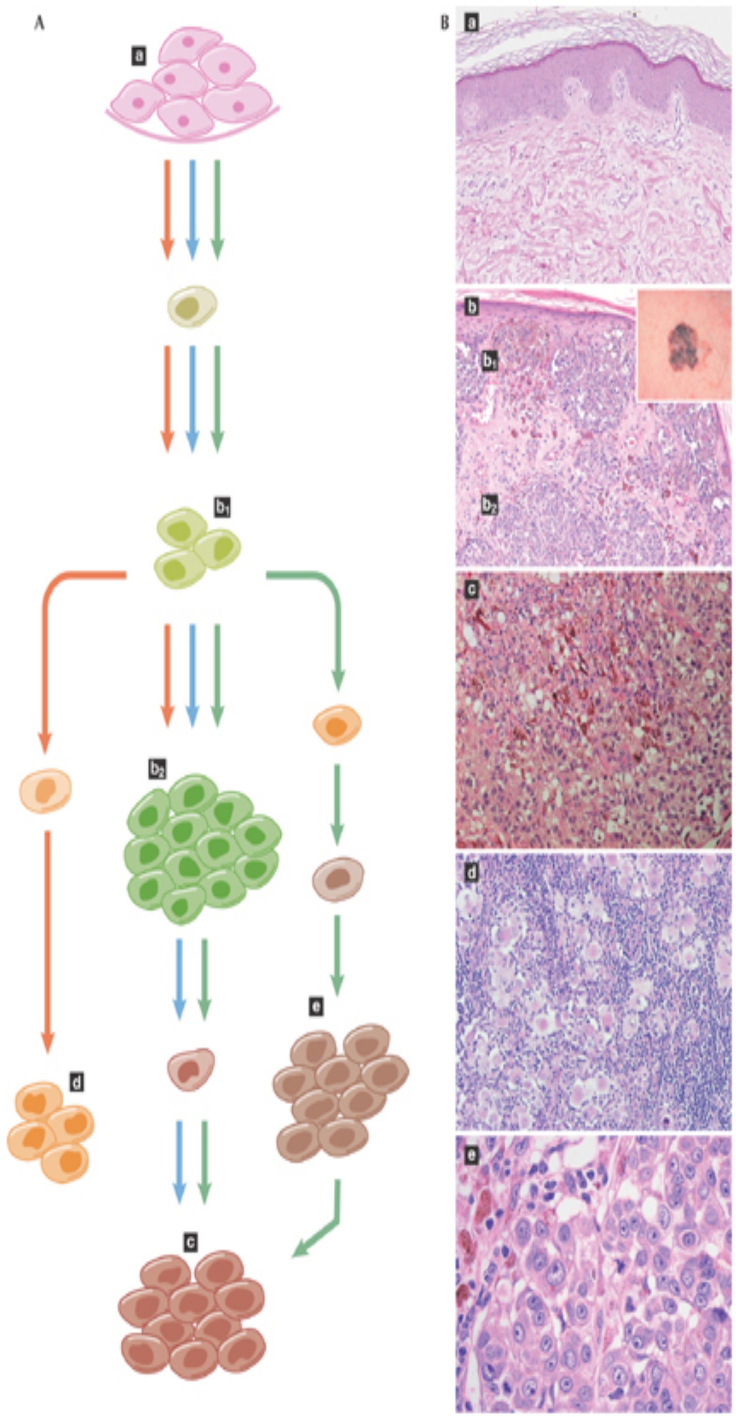


The theory of Multi-Stage Carcinogenesis

- Many waves of Clonal Selection
- Clonal Selection occurs because of gene mutation
- Adaptation produces cells that proliferate more often than normal cells and undergo cell death(apoptosis) less often



Bielas and Loeb, 2005

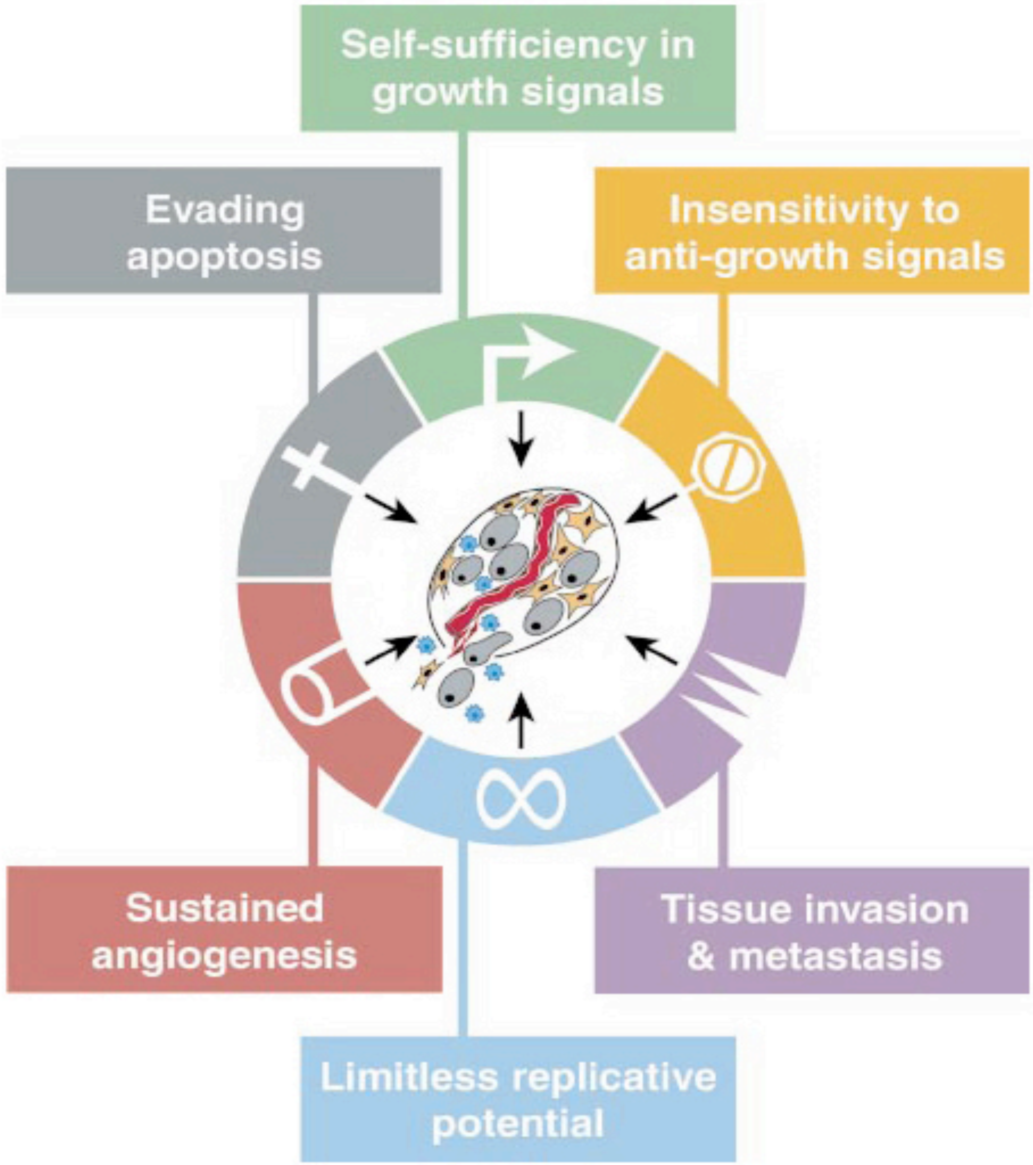


Models of cancer evolution

'clonal selection model' (blue)
'parallel evolution' model (red)
an integrated model of cancer evolution (green)

histological snapshot of normal skin tissue (a), primary tumour (superficial b_1 and deep b_2), subcutaneous metastasis (c), metastasis in the lymph node (d) and metastasis in the lung (e)

Baudo et al. EMBO Reports 2009



Hanahan & Weinberg, Cell 2000

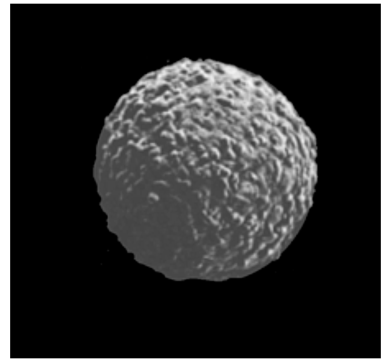
Hallmarks of Cancer

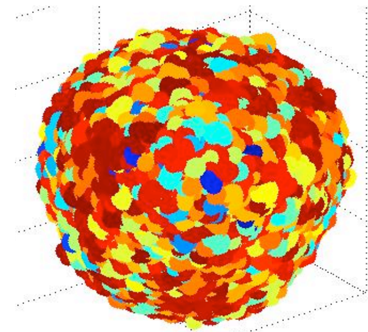
- 6 essential phenotypes
- Many different mutation routes to cancer
- Cancer candidate genes
- Chemotherapies select and kill fast-growing cells
- Radiotherapies kill cells that reproduce more and repair less.

3 Phases of Solid Tumor Growth

Avascular tumor

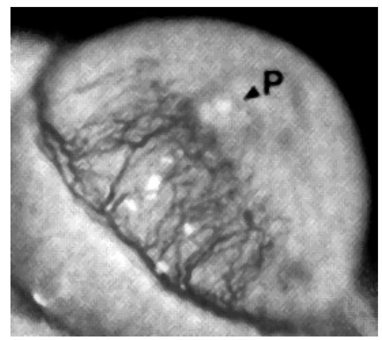
- tumor spheroid 10^6 cells
- maximum diameter ~ 2mm
- necrotic core
- thin proliferating rim

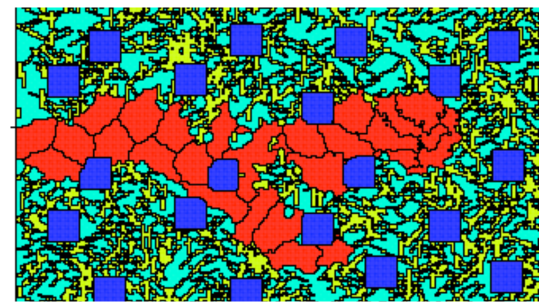




Angiogenesis

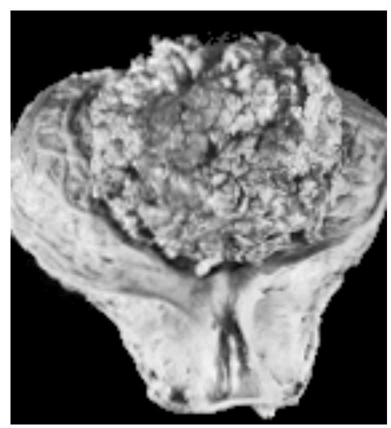
- capillary network formation
- supplies tumor with blood

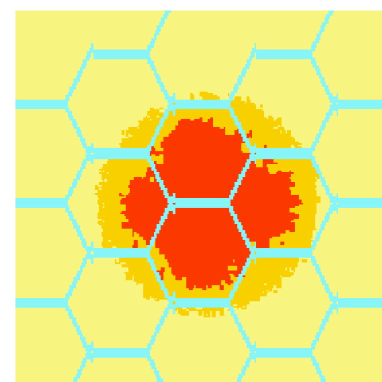




Vascular growth, metastasis

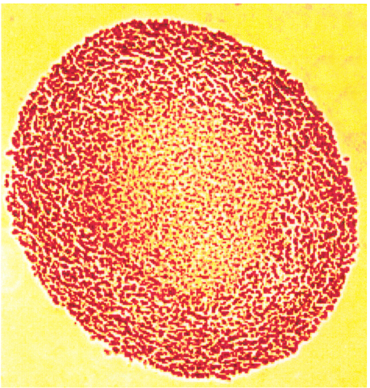
- irregular structure
- highly invasive
- potentially fatal

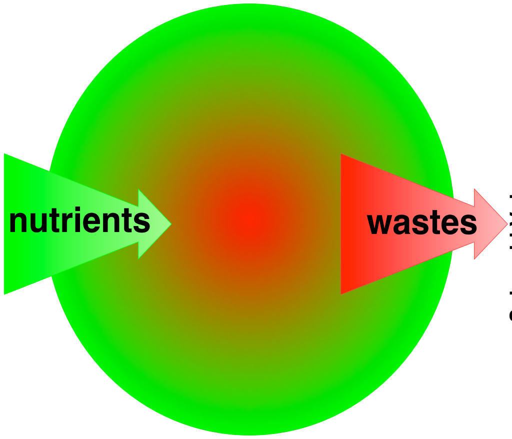


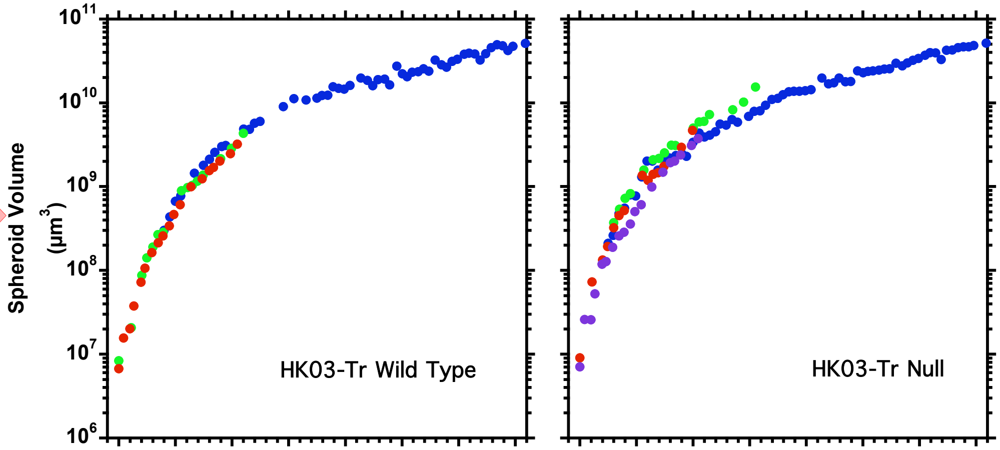


Avascular tumor growth
(Multicellular Tumor Spheroid)

- *In vitro 3D* avascular tumor model.
- Precisely controlled external conditions with realistic tumor microenvironment; assays easy; data rich.
- Mimics growth dynamics of tumor *in vivo*.







Freyer, Sutherland

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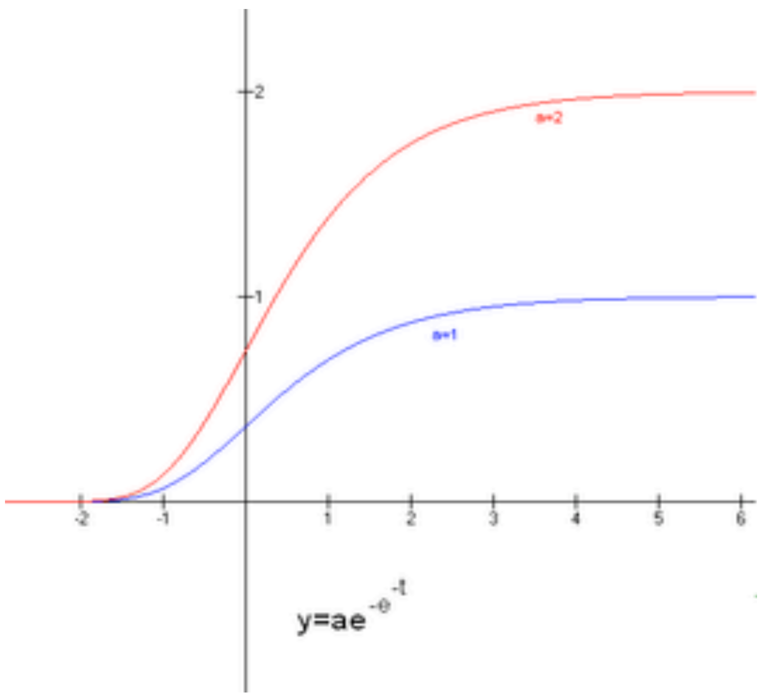
Mathematical Models

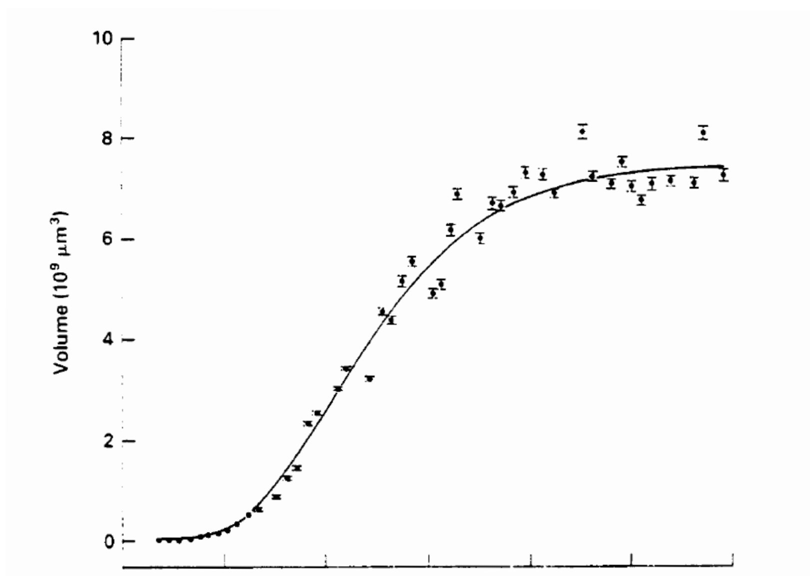
- Empirical data fitting (map)

Gompertz

$$y(t) = a\exp[b\exp(-ct)]$$

$$b = \log(y(0)/a)$$

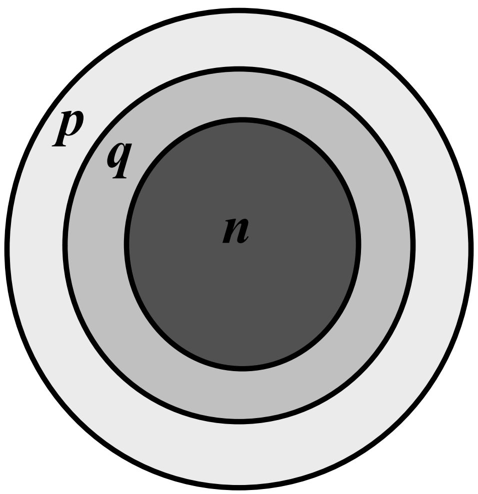




Marusic et al., *Cell Prolif* 1994

Mathematical Models

- Compartmental model (PDEs)



$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x}\left[\frac{p}{p+q}\frac{\partial(p+q)}{\partial x}\right] + g(c)p(1-p-q-n) - f(c)p$$

$$\frac{\partial q}{\partial t} = \frac{\partial}{\partial x}\left[\frac{q}{p+q}\frac{\partial(p+q)}{\partial x}\right] + f(c)p - h(c)q$$

$$\frac{\partial n}{\partial t} = h(c)q$$

$$c = \frac{c_0\gamma}{\gamma+p}\left[1-\alpha(p+q+n)\right]$$

Chaplain, Sherratt, Byrne, Anderson, Maini

Compartmental Models

- free boundary problems

$$\frac{\partial P}{\partial t} + \nabla \cdot (\vec{u}_P P) = \big(K_B(C) - K_Q(C)\big)P + K_P(C)Q,$$
$$\frac{\partial Q}{\partial t} + \nabla \cdot (\vec{u}_Q Q) = K_Q(C)P - \big(K_D(C) + K_P(C)\big)Q,$$

$$\nabla^2 C = \mu C,$$

$$\vec{u}_Q = \vec{u}_P + \chi \nabla C,$$

Friedman, Cui, Hu, Byrne

Mathematical Models

- Biochemical kinetics

cancer cell receptor	R, R_a, R_i
fibroblast growth factor, FGF	G
urokinase plasminogen activator, uPA	C
tissue growth factor beta, $TGF\beta$	I_a
latent TGF beta, $TGF\beta_\ell$,	I_i
plasminogen	P_g
plasmin	P_m

$$\frac{\partial\eta}{\partial t}=\nabla\cdot\left\{D_\eta\nabla\left[\eta\ln\left(\frac{\eta}{\tau(g)}\right)\right]\right\}+\phi(g)\eta(1-\eta/\eta_0)-\mu_\eta\eta,$$

$$\partial_t g=D_g\Delta g-\mu_g g+\frac{\sigma_g-\lambda_1 g}{1+\nu_e\iota_a+g/K_m^1}\frac{\eta}{\eta_0},$$

$$\partial_t c=D_c\Delta c-\mu_c c+\frac{\lambda_1 g}{1+\nu_e\iota_a+g/K_m^1}\frac{\eta}{\eta_0},$$

$$\partial_t p_m=D_p\Delta p_m-\mu_p p_m+\lambda_2^p c,$$

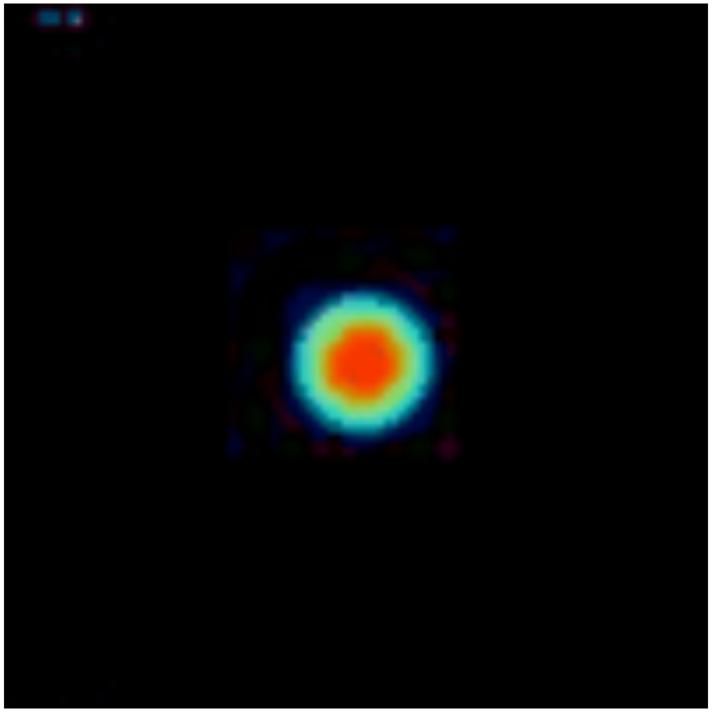
$$\partial_t\iota_a=D_a\Delta\iota_a-\mu_a\iota_a+\lambda_3\iota_i p_m,$$

$$\partial_t\iota_i=D_i\Delta\iota_i-\mu_i\iota_i-\lambda_3\iota_i p_m+\frac{\sigma_i}{1+\nu_e\iota_a+g/K_m^1}\frac{\eta}{\eta_0}$$

Levine, Boushaba

Hybrid Models

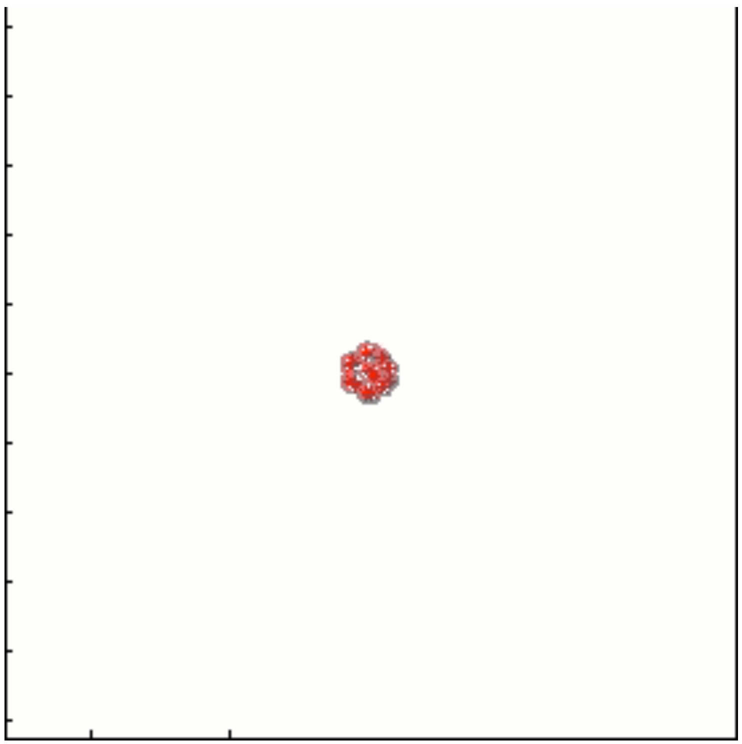
- Cellular automata coupled with PDE for O2, nutrients



Heiko Enderling

Hybrid Models

- Cellular automata coupled with PDEs for O2 dynamics, ECM dynamics, evolution…



Kasia Rajniak
Anderson, Guaranta

Multiscale Models

- John Lowengrub, Vittorio Cristini

http://math.uci.edu/~lowengrb/RESEARCH/tumor.php

- Philip Maini, Helen Byrne, Mark Chaplain

http://people.maths.ox.ac.uk/~maini/

http://www.maths.dundee.ac.uk/mbg/

- Yi Jiang

http://math.lanl.gov/~yi

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Modeling Tumor Development

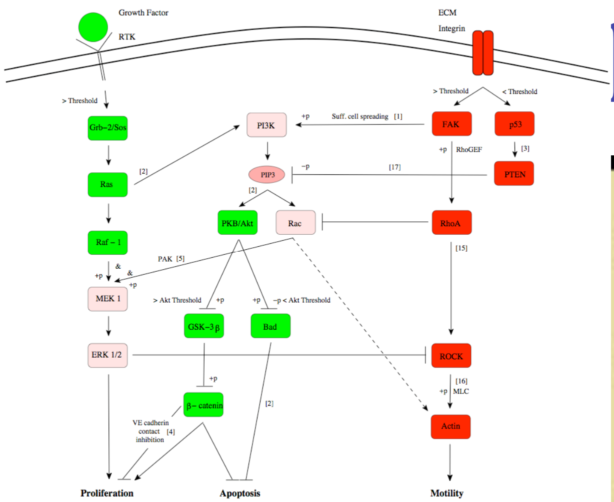
- Cell dynamics: Cell growth and division, death, quiescence = cell cycle arrest, mutation
- Cell-cell interactions: adhesion, competition for space
- Cell-environment interactions

Microenvironment:

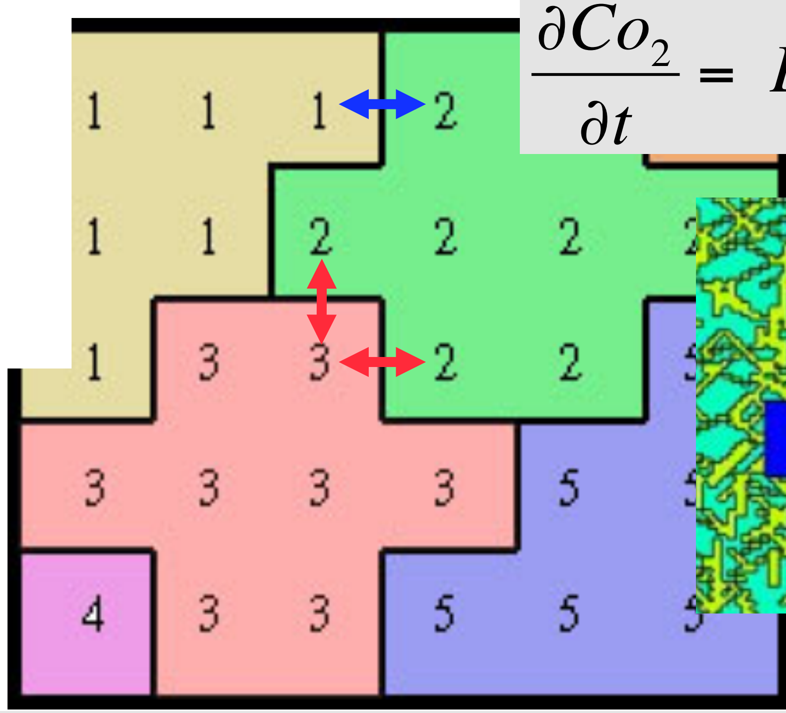
- chemicals (absorption, production, and diffusion) = Nutrients, wastes, growth and inhibitory factors
- ECM/basement membrane – biomechanics
- Stromal cells

Multicellular Multiscale Dynamics

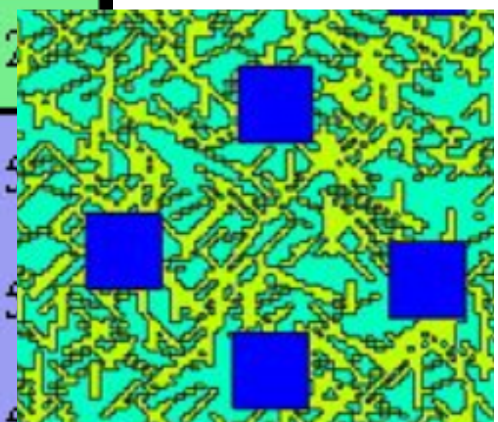
- Complex emergent behavior and patterns
- Begin by using phenomenological descriptions of cell behaviors: biologically based rules, phenomenological terms for equations
- In many cases very complex pathways have fairly simple effects under conditions of interest, cell = blackbox
- Adding regulations back into the cells.



lular Potts Model



$$\frac{\partial Co_2}{\partial t} = D_{O_2}\nabla^2 C_{O_2} + a(x,y,z)$$

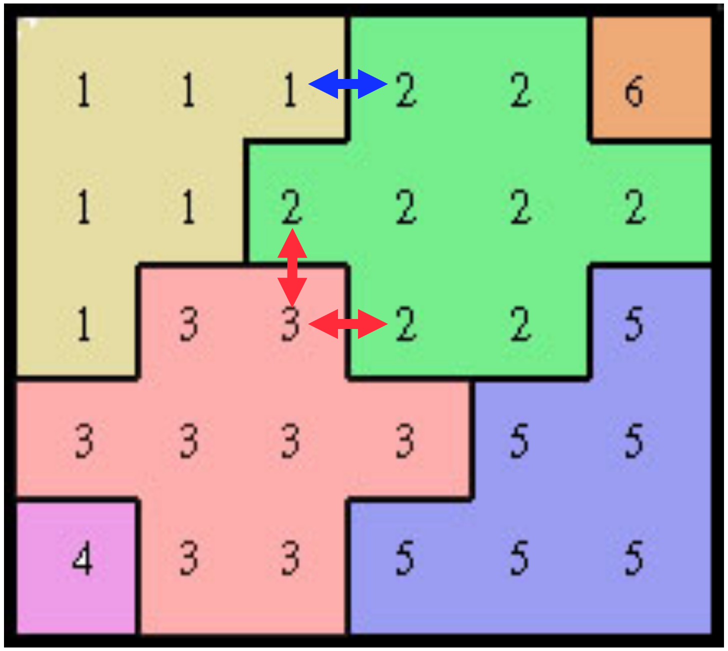


$$E = \sum_{lattice\ sites} J_{\tau(S_1)\tau(S_2)}[1-\delta(S_1,S_2)] + \sum_{cells} \gamma \cdot (v - V^T)^2$$

$$p = \begin{cases} 1 & ,\text{if} \quad \Delta E < 0 \\ e^{-\Delta E/k_bT} & ,\text{if} \quad \Delta E \geq 0 \end{cases}$$

Cellular Potts Model

- Cells are on a 3D lattice
- Each cell has a unique ID: *S*
- Cells have types
- Cells interact at membrane
- Cell keeps a volume.



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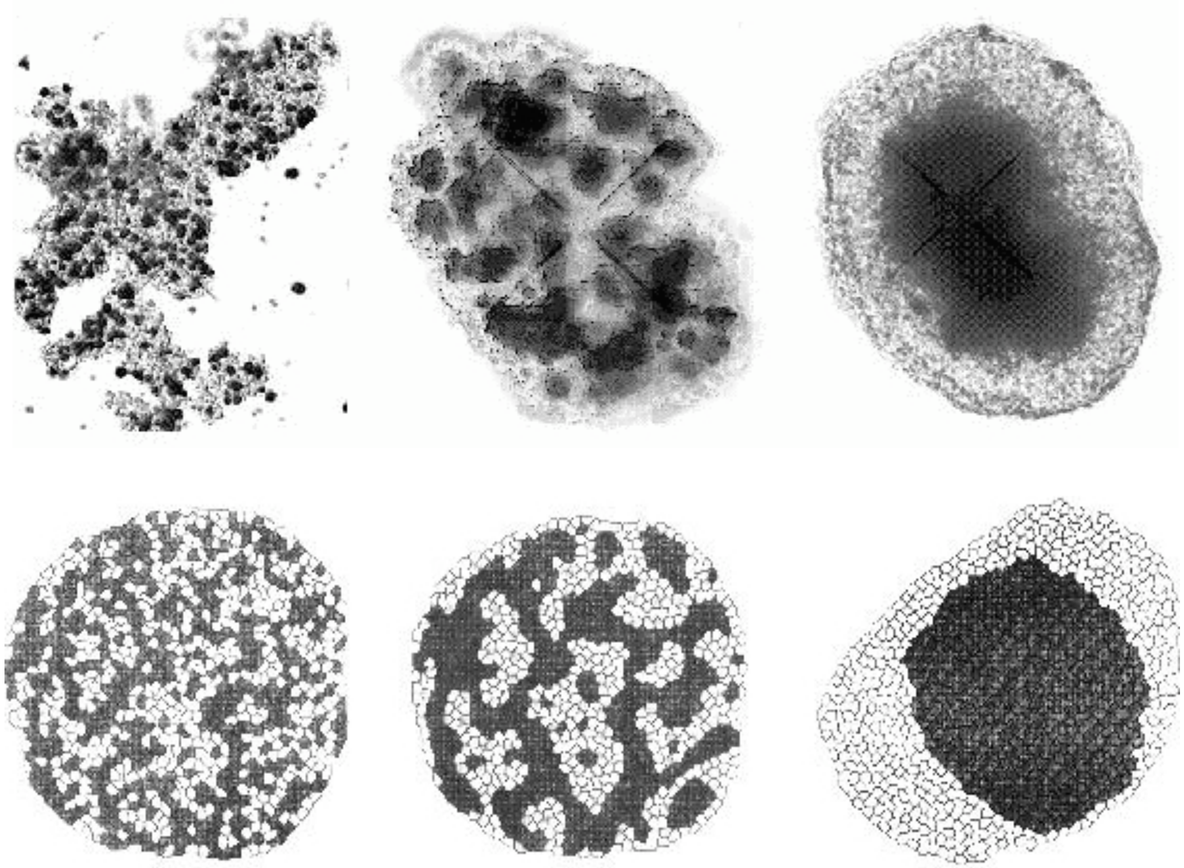
Cell Sorting – differential adhesion



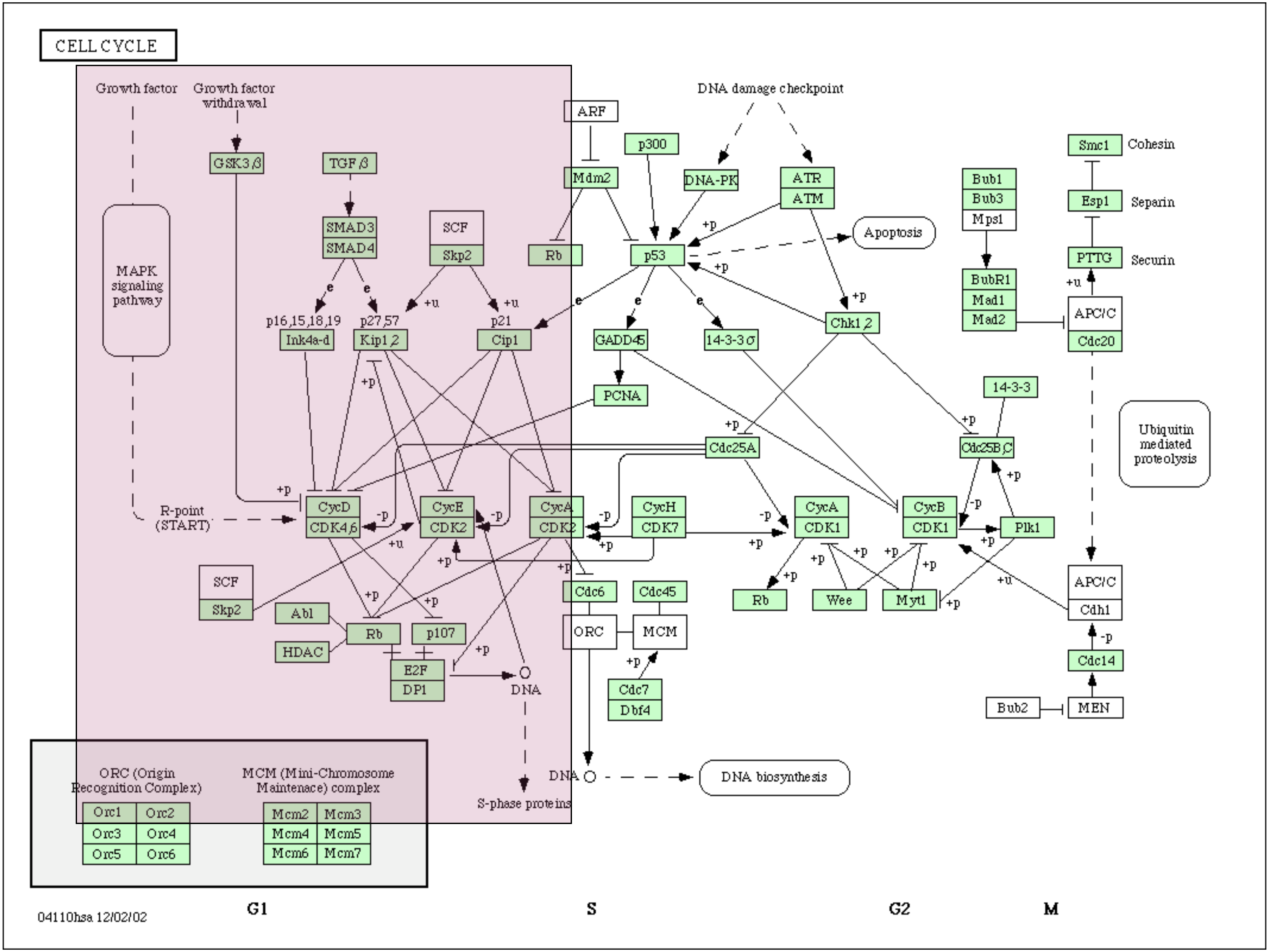
Glazier et al. (1993,1995, 2001)

$$E = \sum_{lattice\ sites} J_{\tau(S_1)\tau(S_2)}[1-\delta(S_1,S_2)] + \sum_{cells} \gamma \cdot (v - V^T)^2$$

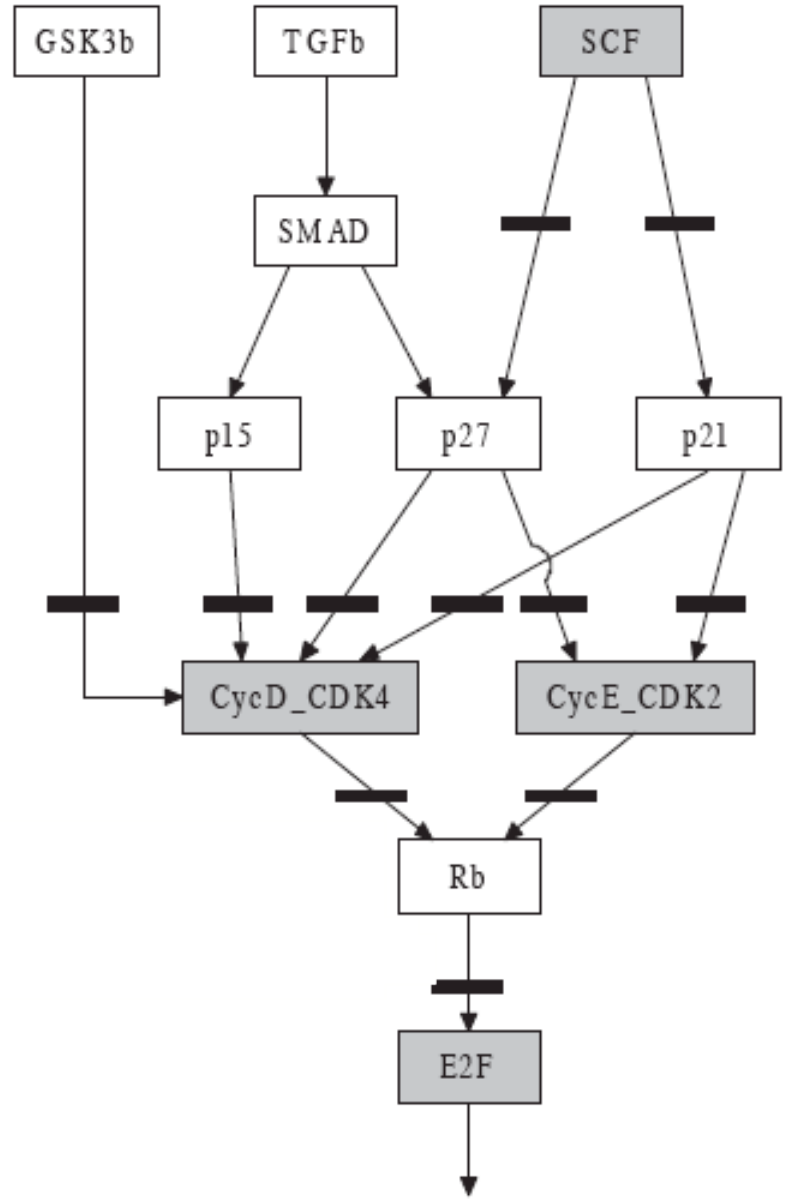
Cell growth: $V^T \sim 2\ V(t=0)$

Cell division —*when cell is ready to divide*—

- half of mother cell is assigned a new ID
- daughter cells inherit all properties of mother cell *(with a probability for mutation)*.


CELL CYCLE
Growth factor
Growth factor withdrawal
GSK3β
TGFβ
SMAD3
SMAD4
SCF
Skp2
MAPK signaling pathway
p16,15,18,19
Ink4a-d
p27,57
Kip1,2
p21
Cip1
ARF
Mdm2
Rb
p300
DNA damage checkpoint
DNA-PK
ATR
ATM
p53
Apoptosis
GADD45
14-3-3σ
Chk1,2
PCNA
Bub1
Bub3
Mps1
BubR1
Mad1
Mad2
Smc1
Cohesin
Esp1
Separin
PTTG
Securin
APC/C
Cdc20
14-3-3
Cdc25B,C
Ubiquitin mediated proteolysis
Cdc25A
R-point (START)
CycD
CDK4,6
CycE
CDK2
CycA
CDK2
CycH
CDK7
CycA
CDK1
CycB
CDK1
Plk1
SCF
Skp2
Abl
HDAC
Rb
p107
E2F
DP1
DNA
Cdc6
Cdc45
ORC
MCM
Cdc7
Dbf4
Rb
Wee
Myt1
APC/C
Cdh1
Cdc14
Bub2
MEN
S-phase proteins
DNA
DNA biosynthesis
ORC (Origin Recognition Complex)
Orc1
Orc2
Orc3
Orc4
Orc5
Orc6
MCM (Mini-Chromosome Maintenace) complex
Mcm2
Mcm3
Mcm4
Mcm5
Mcm6
Mcm7
G1
S
G2
M
04110hsa 12/02/02

Protein Regulatory Network for Cell Cycle: G1→S



- **P15 = p15+p16+p18+p19**
- **P27=p27+p57**
- **Expression level: 0 or 1**
- **Local chemicals modify protein expression**

$$Factor\ level = \left(1 + e^{-\alpha \cdot \left(\frac{gF - ihF}{initGF} - \theta\right)}\right)^{-1}$$

Chemicals: Oxygen, Glucose, Lactate, growth factor, inhibitory factor

$$\frac{\partial Co_2}{\partial t} = D_{O_2}\nabla^2 C_{O_2} + a(x,y,z) \qquad (C_{O_2} = C_0^{O_2} \text{ at boundary})$$

$$\frac{\partial C_n}{\partial t} = D_n\nabla^2 C_n + b(x,y,z) \qquad (C_n = C_0^{n} \text{ at boundary})$$

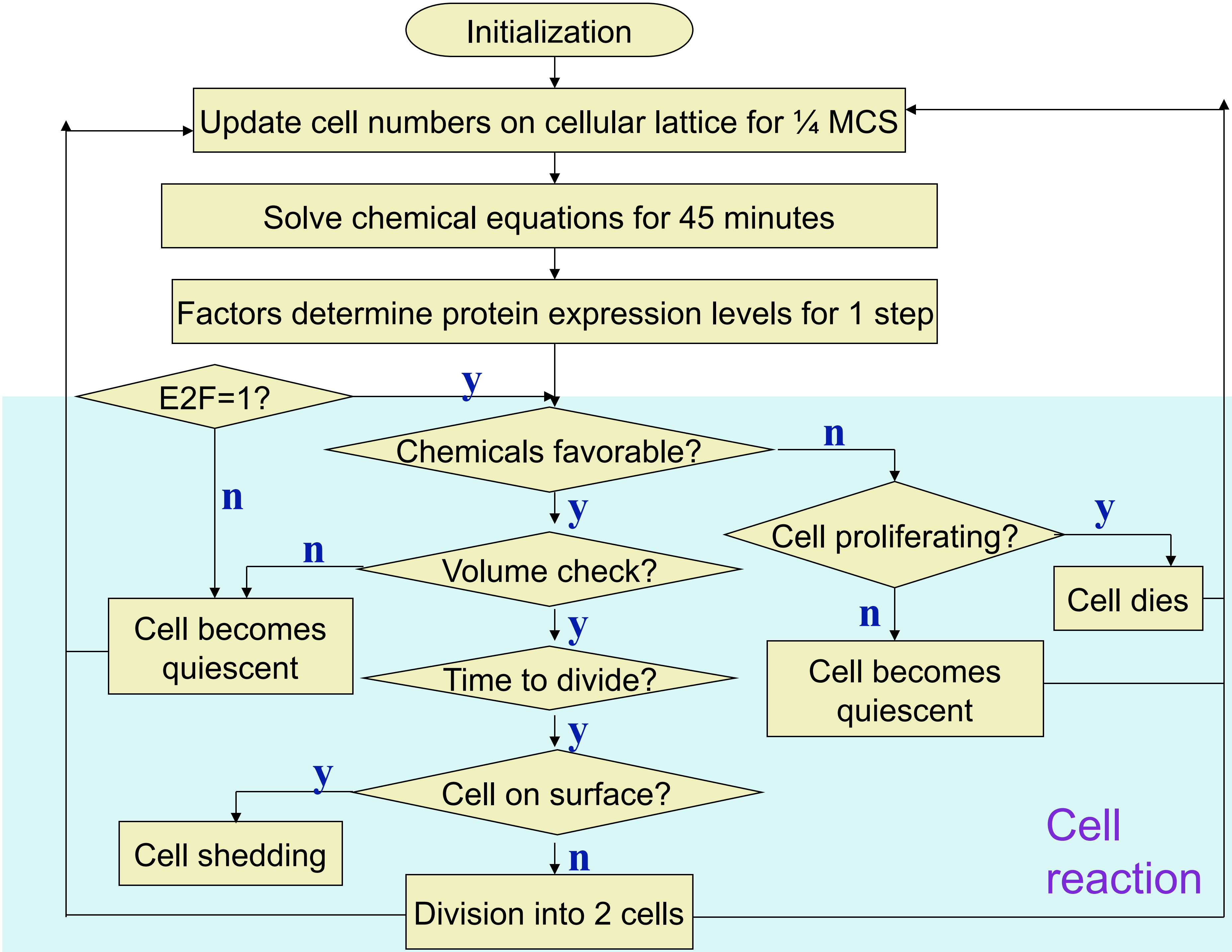
$$\frac{\partial C_w}{\partial t} = D_w\nabla^2 C_w + c(x,y,z) \qquad (C_w = C_0^{w} \text{ at boundary})$$

$$\frac{\partial C_{gf}}{\partial t} = D_{gf}\nabla^2 C_{gf} + e(x,y,z) \qquad (C_{gf} = C_0^{gf} \text{ at boundary})$$

$$\frac{\partial C_{if}}{\partial t} = D_{if}\nabla^2 C_{if} + f(x,y,z) \qquad (C_{if} = C_0^{if} \text{ at boundary})$$

Model details –

- Cells interact through surface adhesion as well as competition for space.
- Outcome of cell regulatory network together with growth (stress) determine quiescence.
- Necrosis condition: below threshold O_2 or glucose or above threshold waste; necrotic cell maintains volume.
- Cells can shed from spheroid surface during mitosis.
- Cell clock. (Mutation)
- 1 cell cycle = 12 hours = 4 Monte Carlo Steps = 16 stages (G1 = 6 , S = 6, G2+M = 4)
- Maximum cell volume = 4x4x4 voxels = 1200 μm^3


Initialization
Update cell numbers on cellular lattice for ¼ MCS
Solve chemical equations for 45 minutes
Factors determine protein expression levels for 1 step
E2F=1?
y
n
Chemicals favorable?
n
y
Cell proliferating?
y
Cell dies
n
Cell becomes quiescent
Volume check?
n
Cell becomes quiescent
y
Time to divide?
y
Cell on surface?
y
Cell shedding
n
Division into 2 cells
Cell reaction

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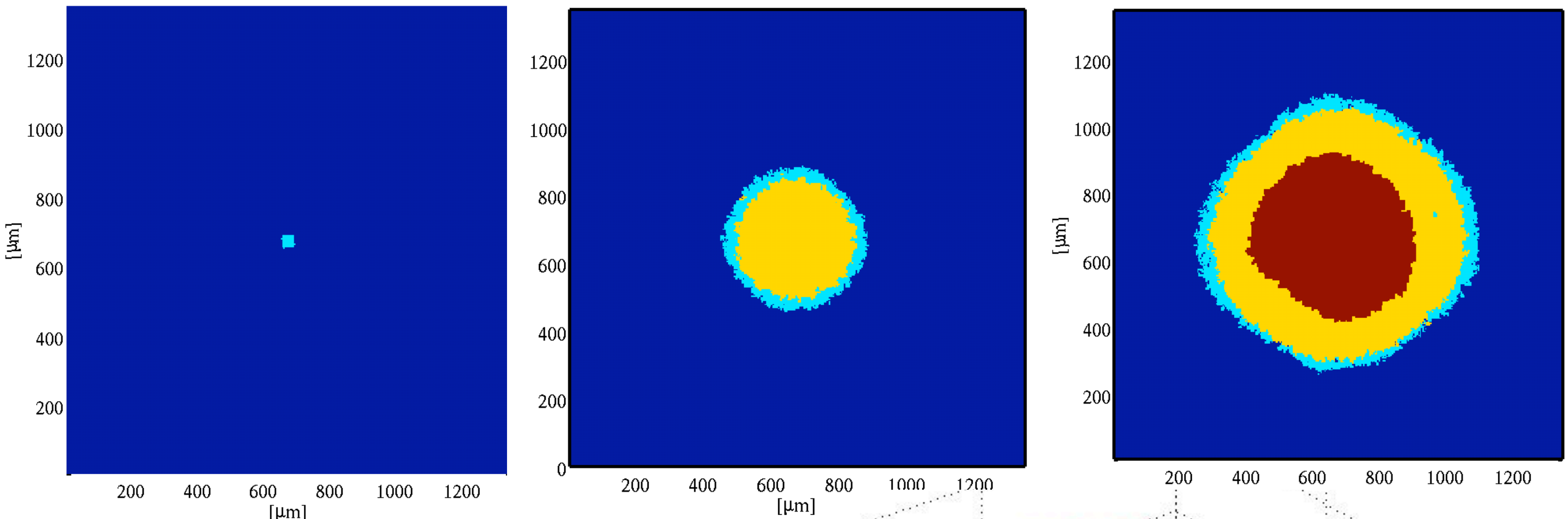
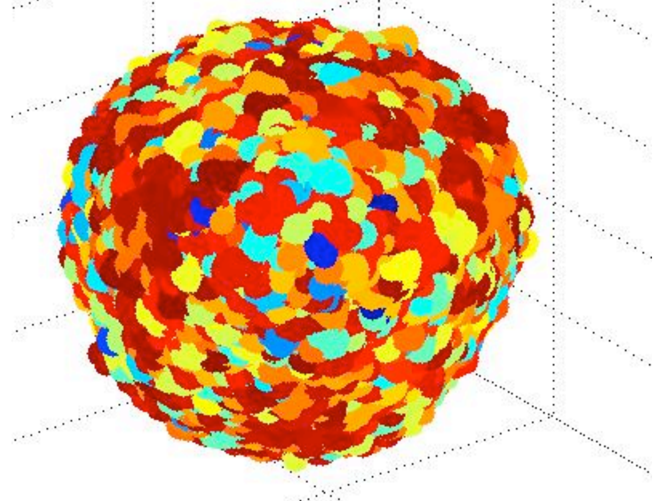
Day 2 **Day 10** **Day 18**



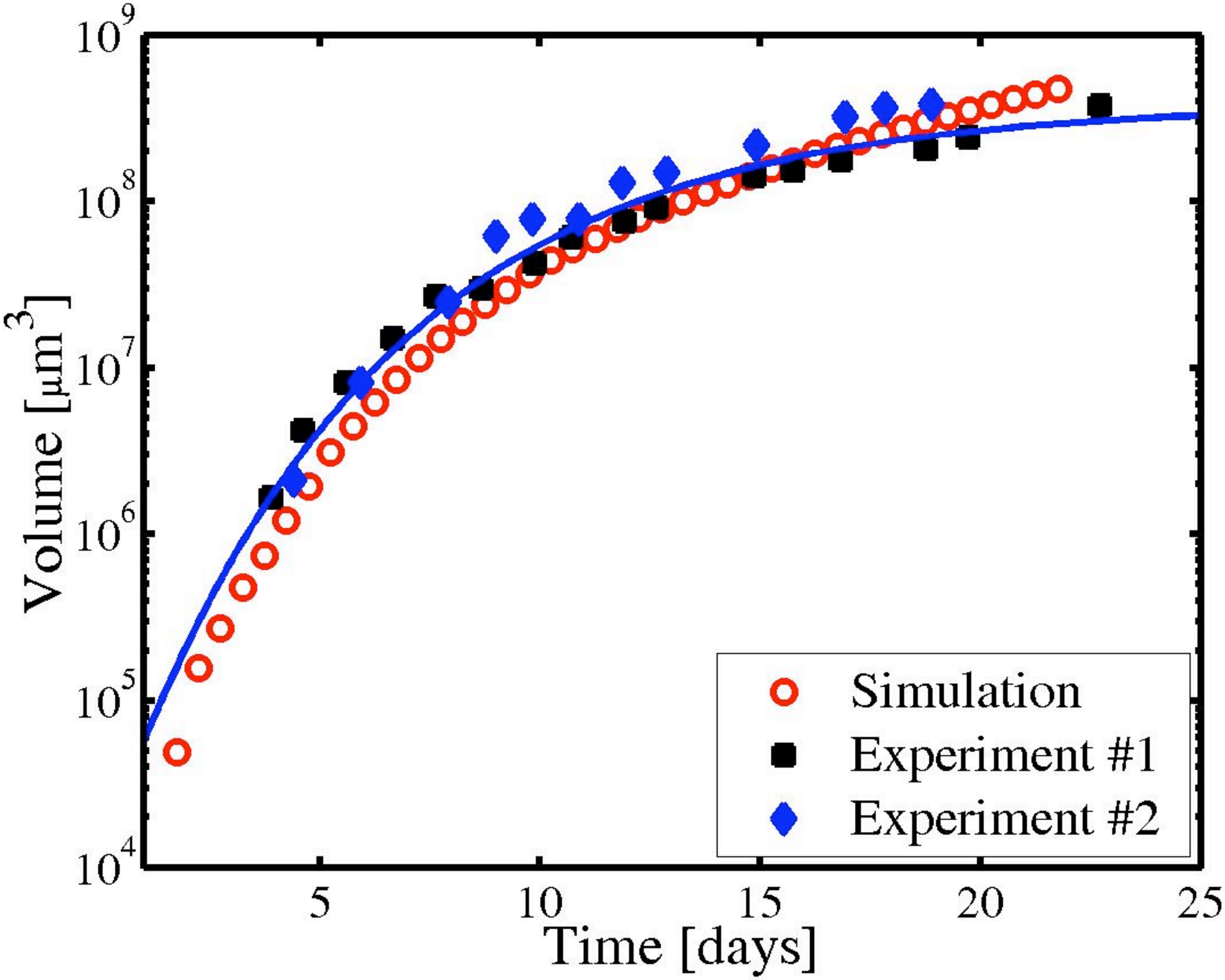


0.08 mM O_2 + 5.5 mM glucose

Jiang et al. 2005

Volume Growth

0.08 mM O_2 + 5.5 mM glucose



- **Necrosis condition for tumor cells:**

  oxygen concentration below 0.02 mM,
  glucose concentration below 0.06 mM,
  waste (lactate) concentration above 8 mM.

Tumor cells can survive in much harsher microenvironment than normal ones.

- ***Diffusion coefficient for growth factor and inhibitors***

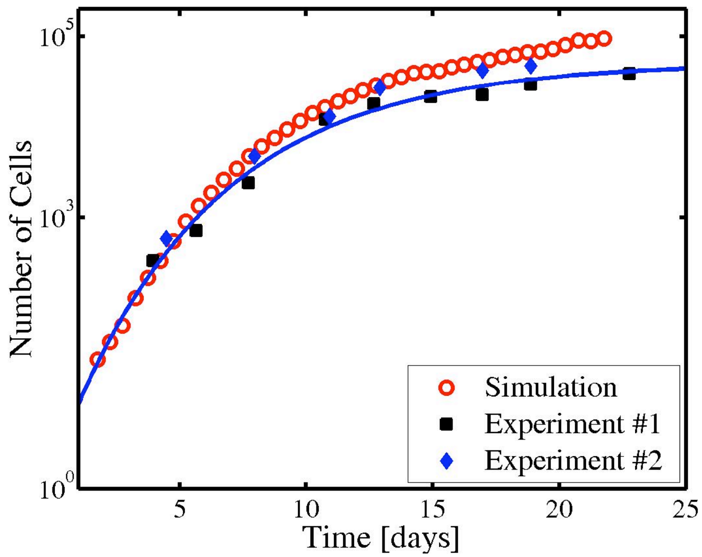
  $10^{-5} - 10^{-6}$ cm^2/hr

Molecular weight ~ 70-100 KDa

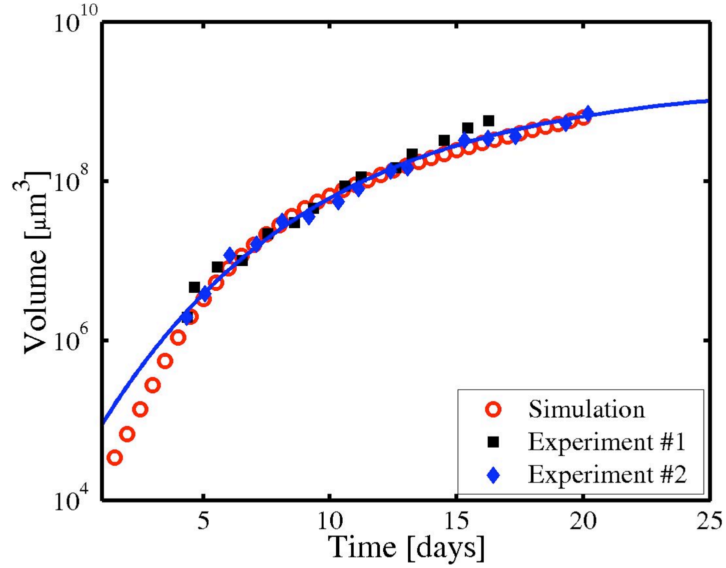
0.08 mM O_2 + 5.5 mM glucose

0.28 mM O_2 + 16.5 mM glucose

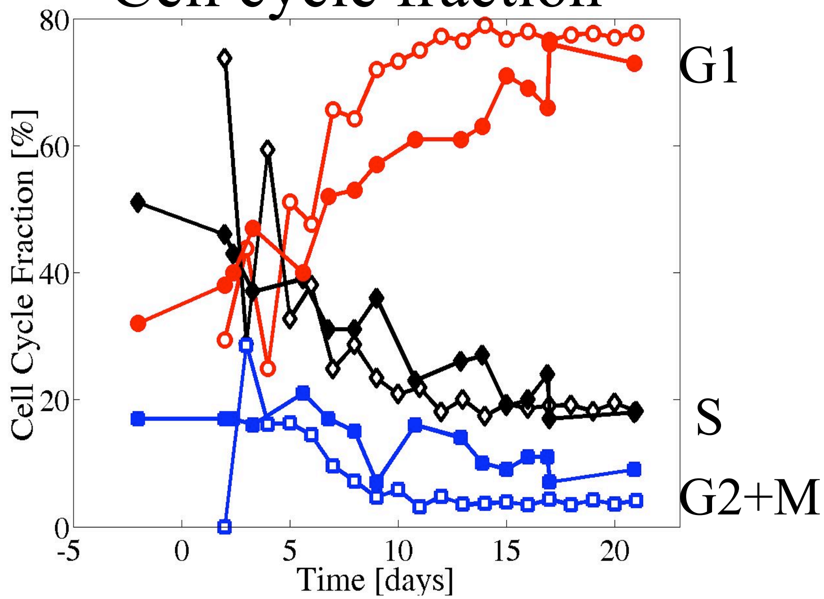
Cell number



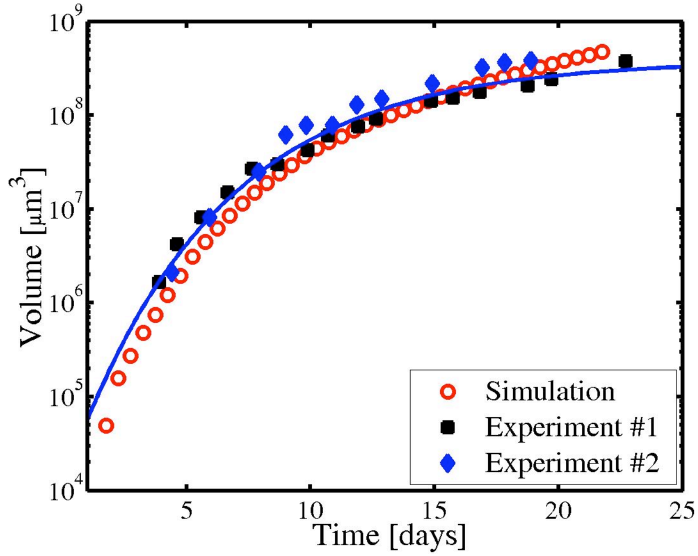
Tumor volume



Cell cycle fraction



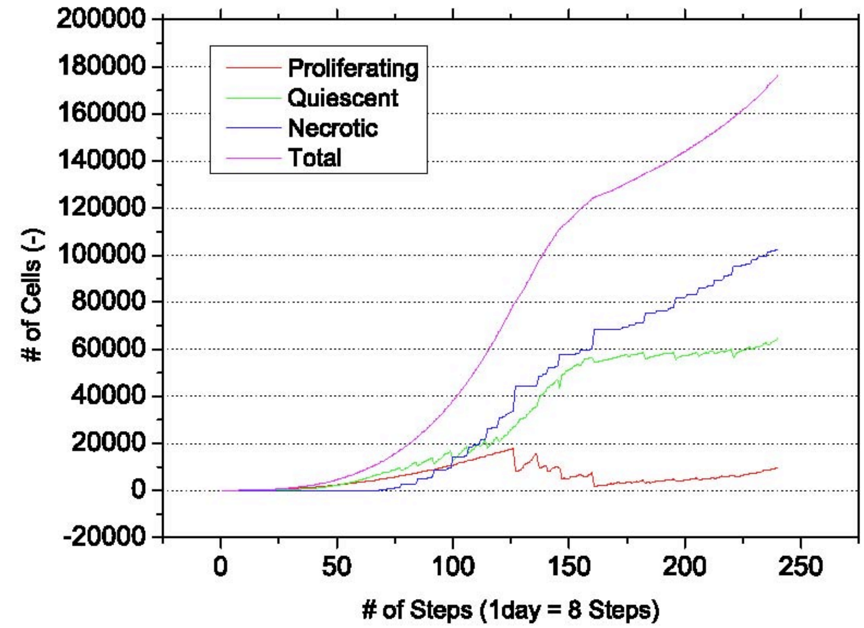
0.08 mM O_2 + 10.5 mM glucose



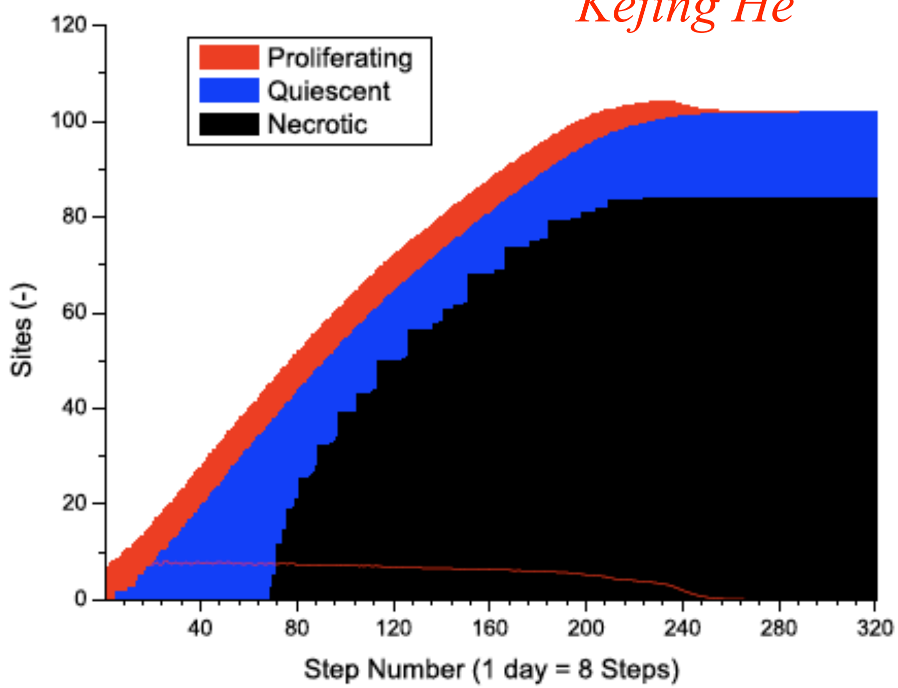
tumor growth saturation

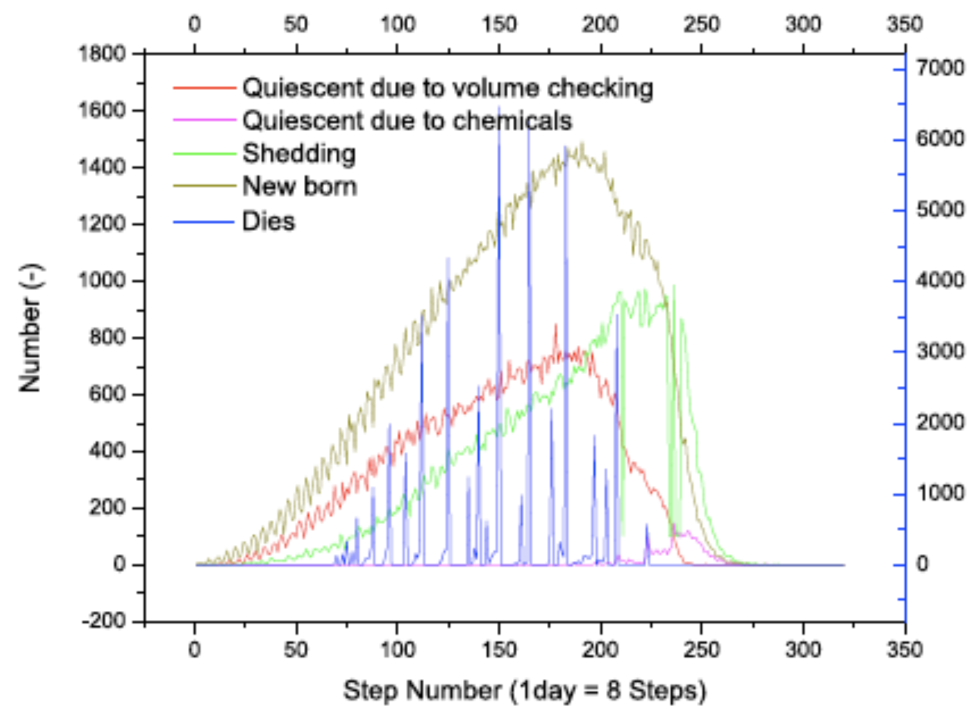
individual mechanisms

- Shedding
- Inhibitors
- Nutrient
- Mechanics



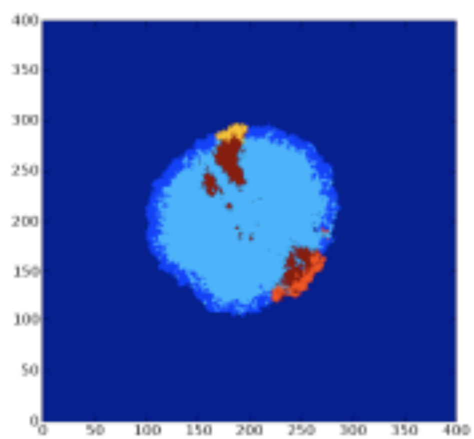
Kejing He

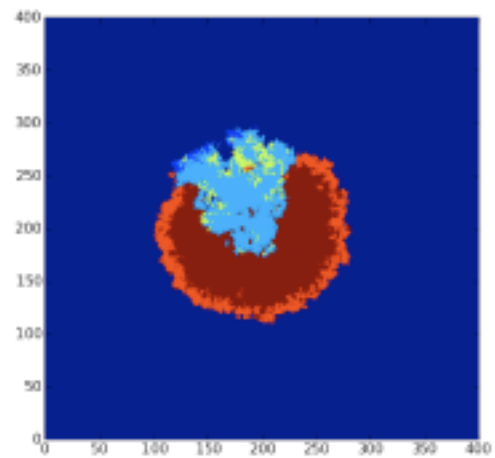




P53 mediated tumor-cell growth competition

- P53 mutation leads to better survival in hypoxic conditions





Kevin Flores

Outline

- Cancer development overview
- What's been done?

  Overview of mathematical models for tumor growth

- What have we done?

  A cell-based, multiscale model framework

- What can our model do?

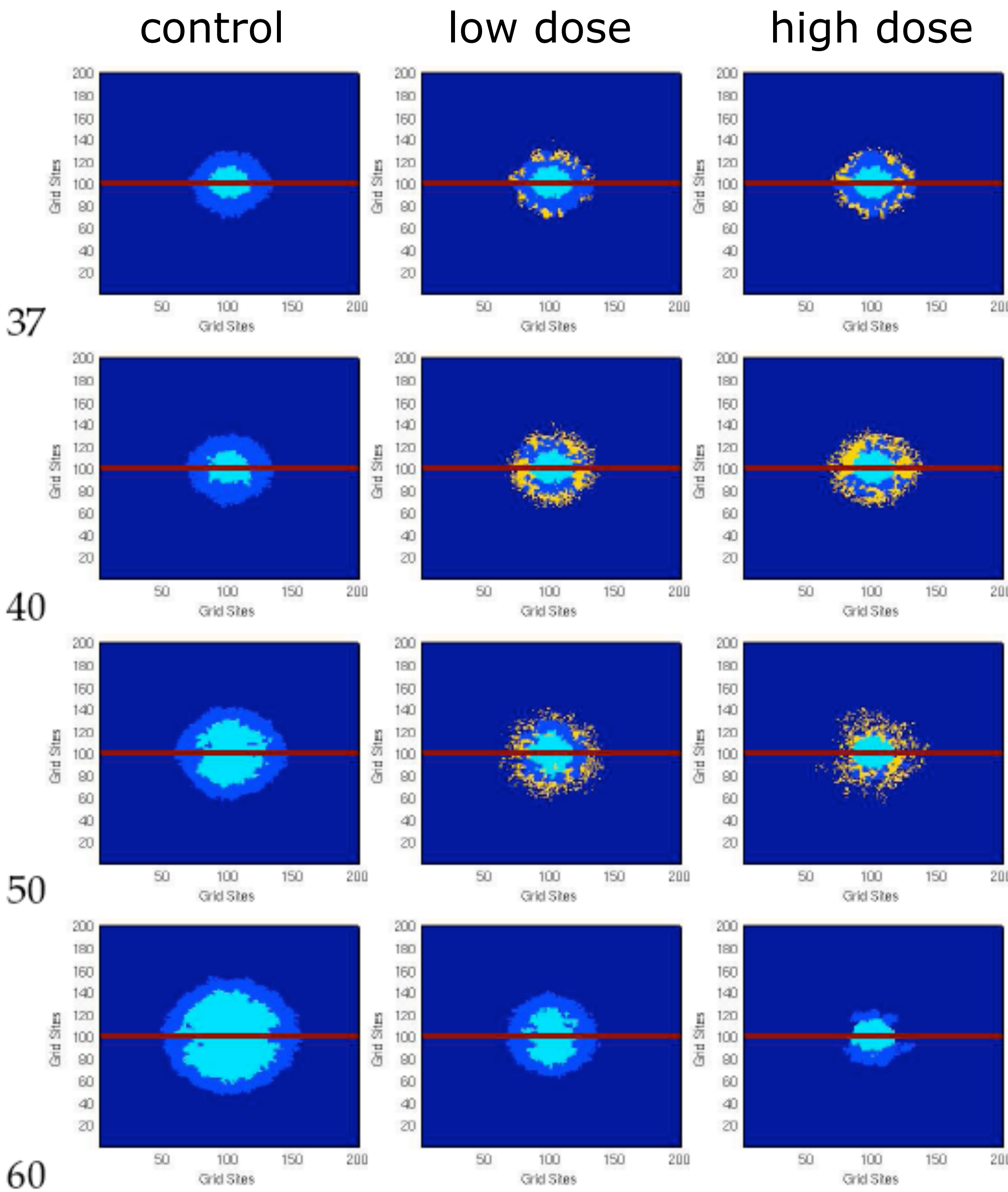
  Avascular tumor growth, angiogenesis, vascular growth

- How good is our model?

  Pros and cons

- Where are we going with such a model?

Pros	Cons
Cell level phenotypes and interactions	Expensive computation
Cellular adhesion	Large scale growth – organ level development
Adding new modules, interactions	Energy based formulation not easy for force based mechanics


control
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high dose
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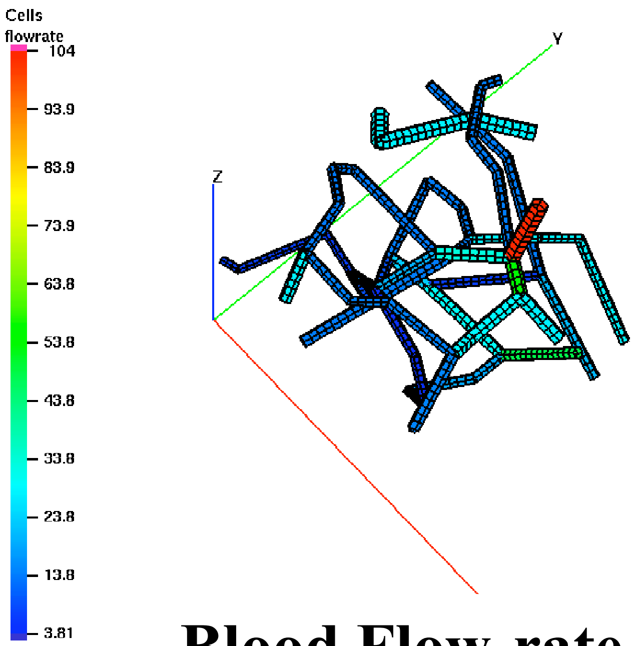
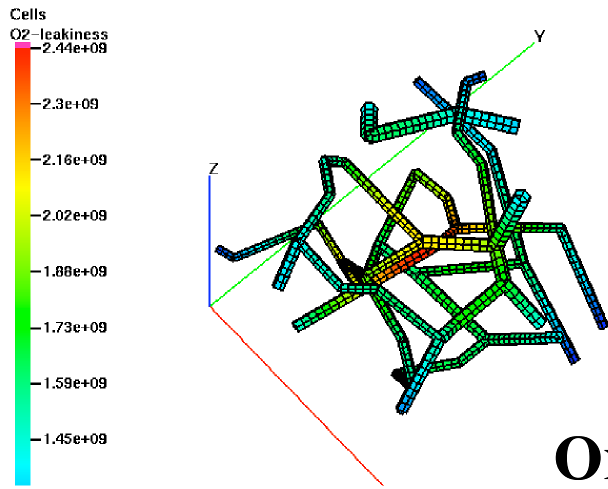
Grid Sites
Grid Sites

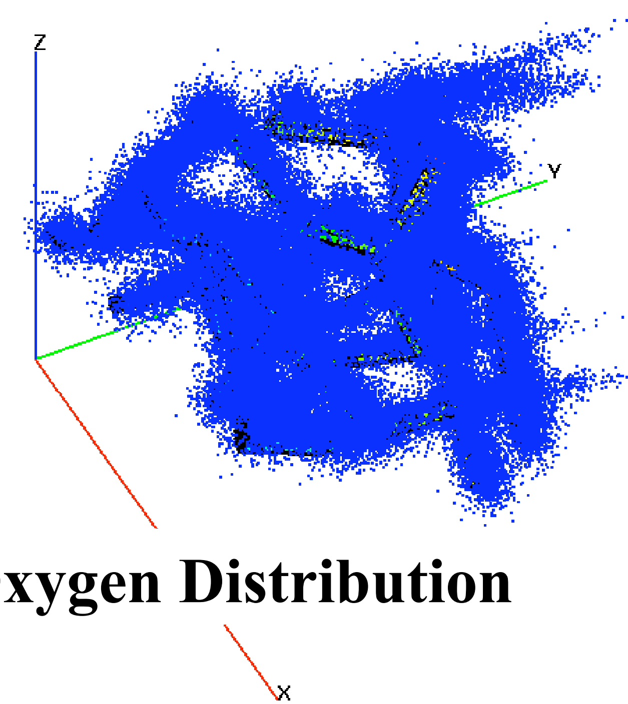
Realistic tumor vessel network



Blood Flow-rate



Oxygen Permeability



Oxygen Distribution

Bryan Travis

Outline

- Cancer development overview
- What's been done?

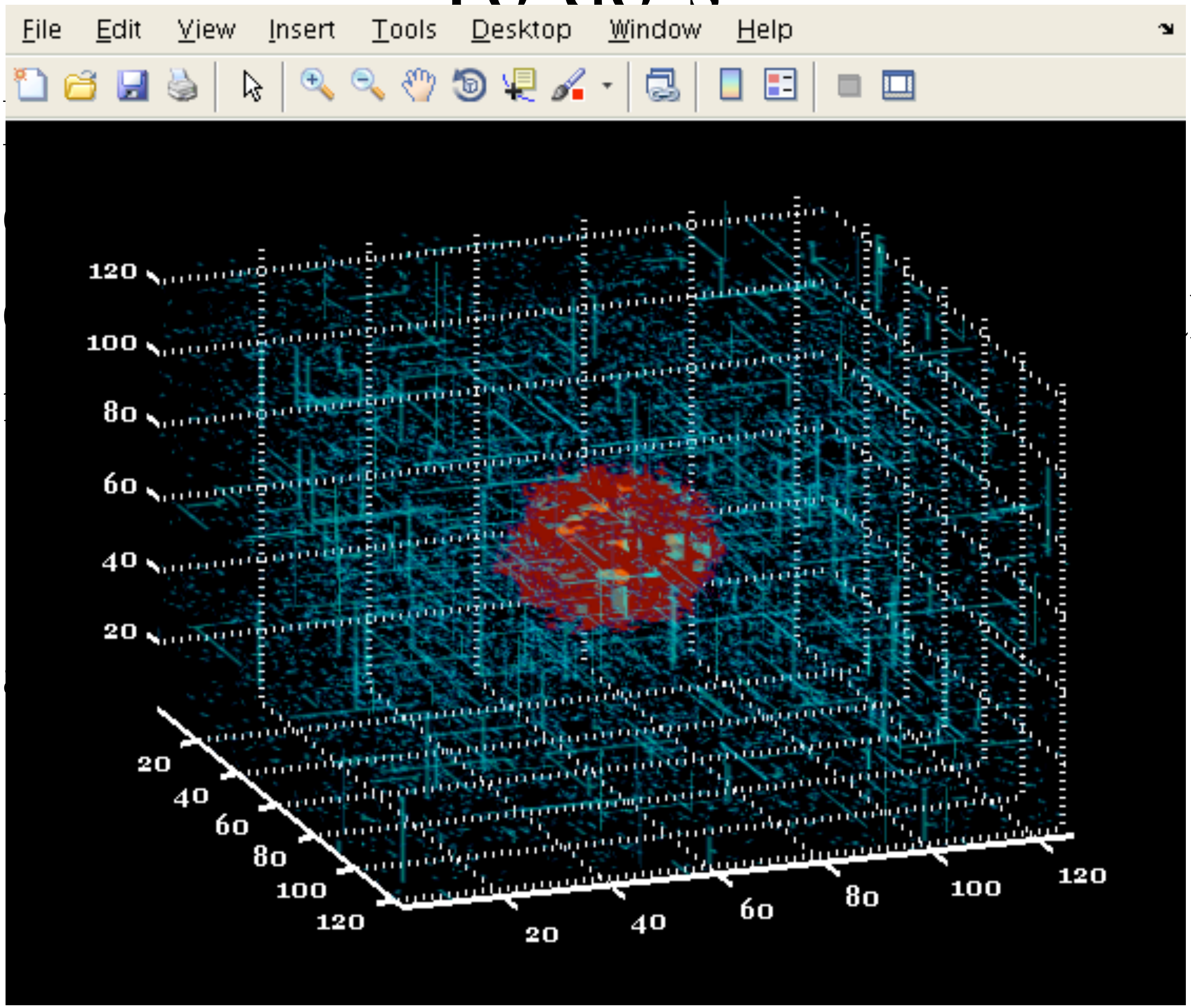
  Overview of mathematical models for tumor growth
- What have we done?

  A cell-based, multiscale model framework
- What can our model do?

  Avascular tumor growth, angiogenesis, vascular growth
- How good is our model?

  Pros and cons
- Where are we going with such a model?

To-do's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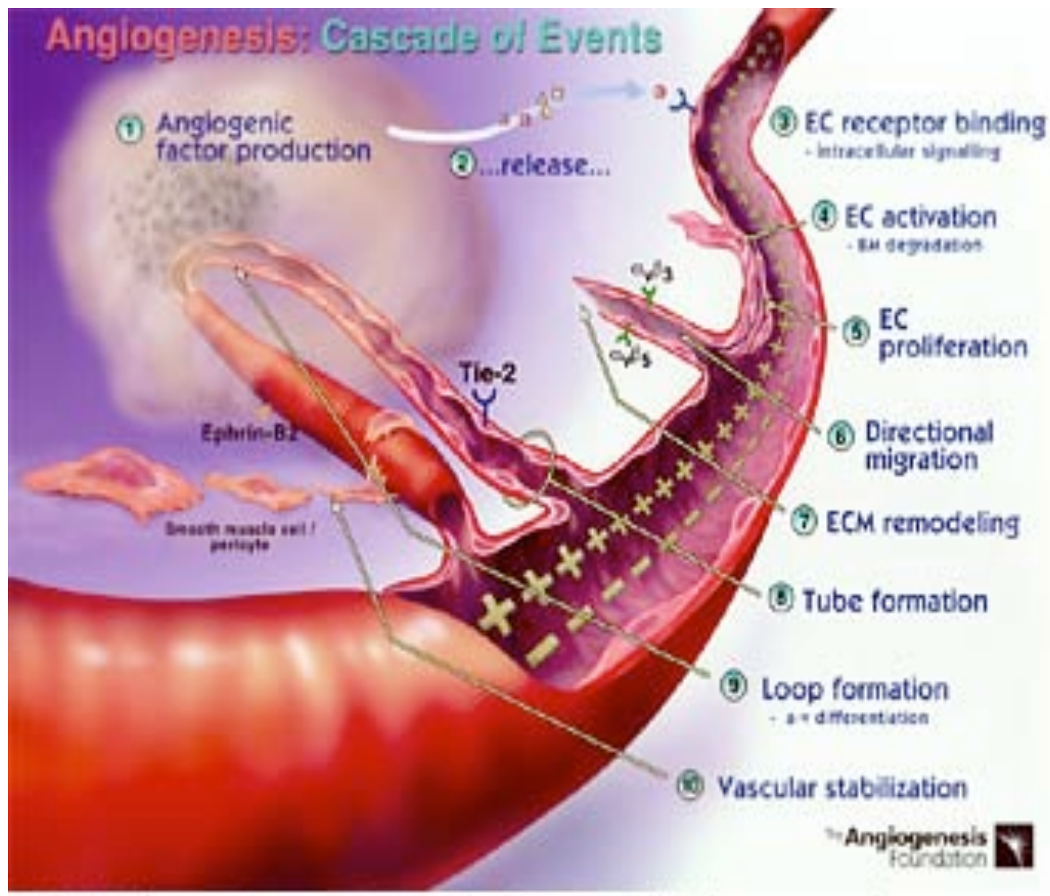
Summary I (Tumor Growth)

- Cell-based approach
- Multiscale modeling
- Experimental data – starting point and validation
- Experimentally testable predictions and hypotheses
- Mechanistic understanding

Tumor Induced Angiogenesis

- Secretion and diffusion of TAFs (VEGF)
- Endothelial cell activation: proliferation and migration
  - Signaling pathways
  - Chemotaxis
  - EC-ECM interactions
  - ECM remodeling
- Vasculature formation

http://www.angio.org/



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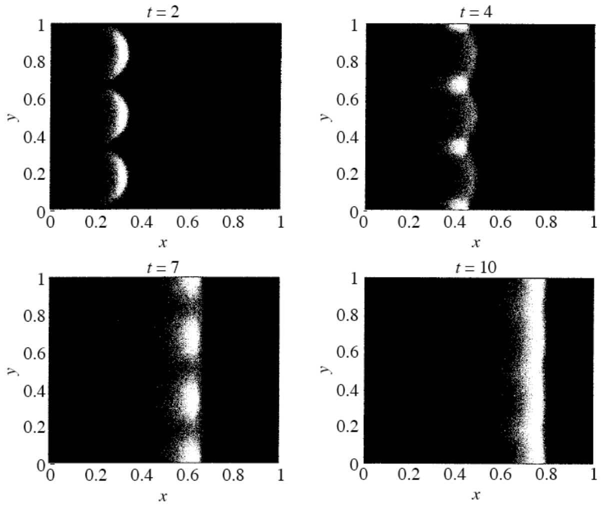
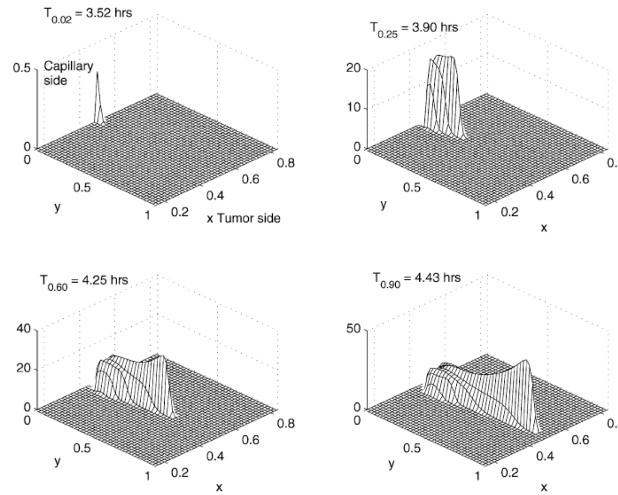
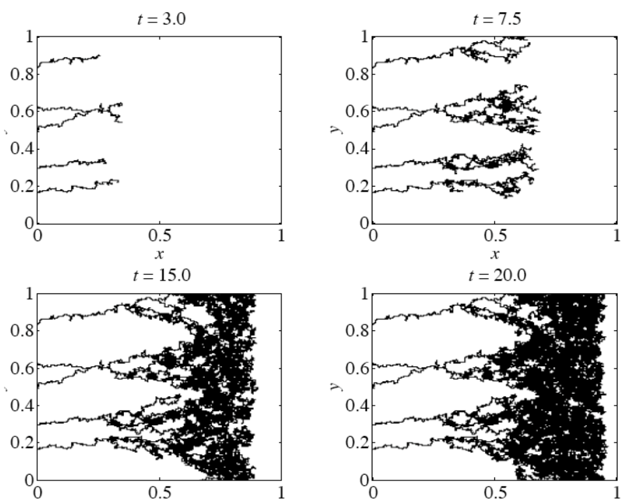
Continuous

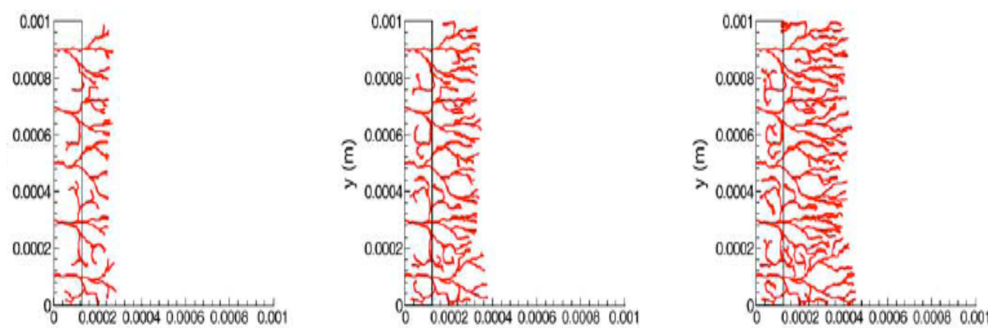
Anderson & Chaplain, *Bull. Math. Biol.* (1998)





Levine, et.al., *Bull. Math Biol.* (2001)

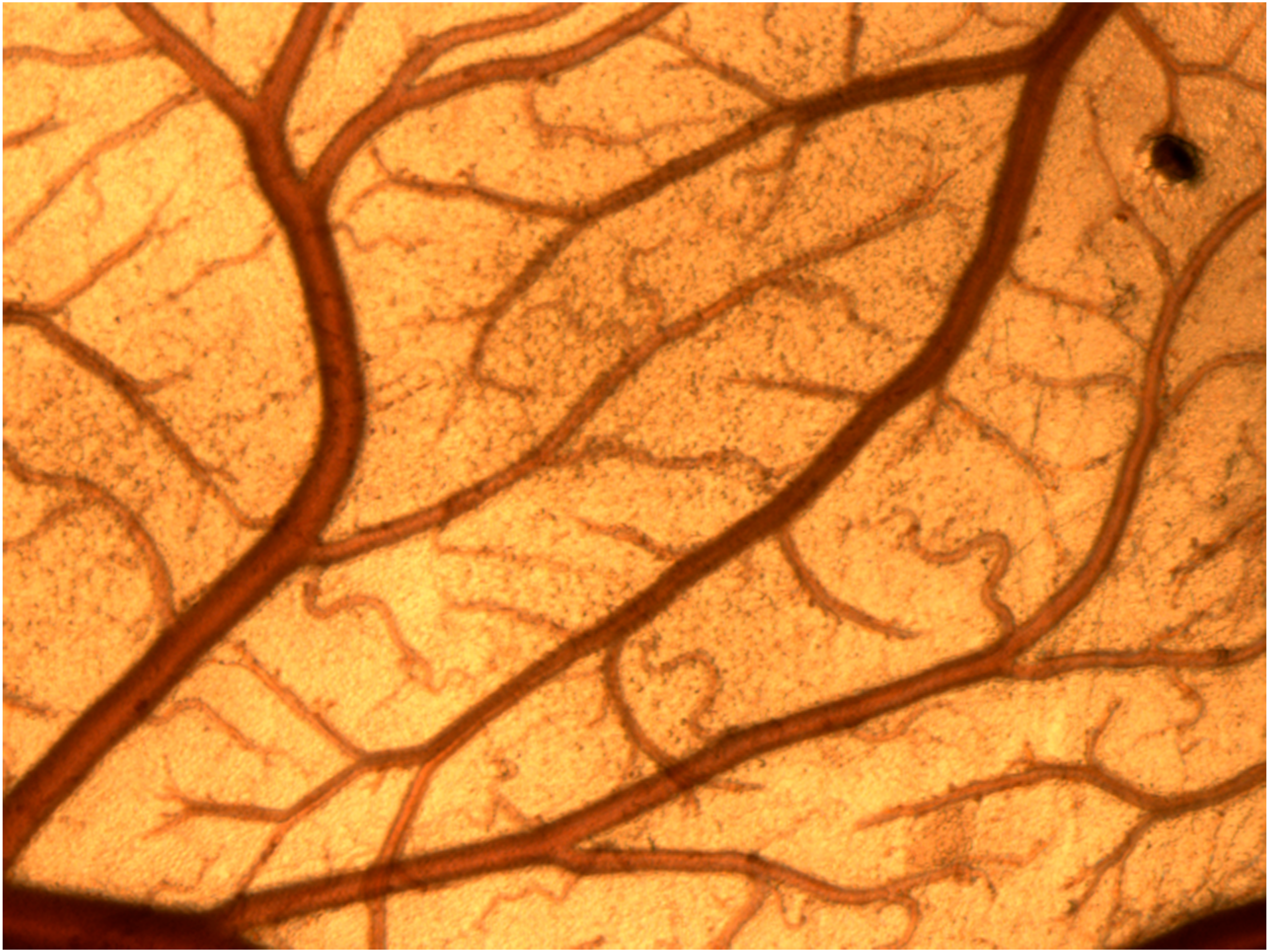




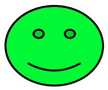
Wheeler, et.al., *Bull. Math. Biol.* (2005)

Discrete Treatment of Cells

Continuous + Binary Capillary Indicator Fcn



Hypotheses/Assumptions



- VEGF acts as chemo-attractant for EC.

?

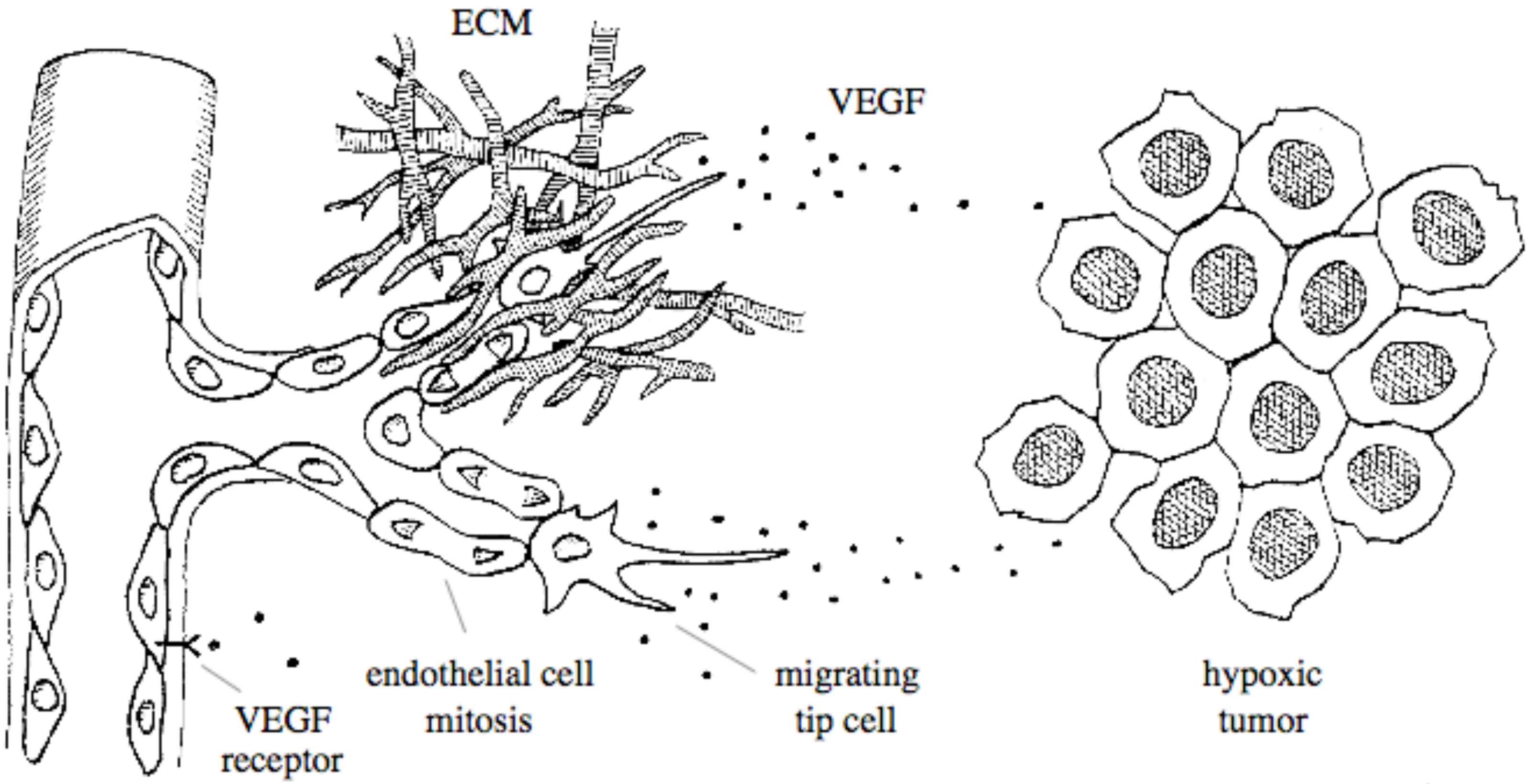
- Freely diffusing VEGF
- **“Go or grow”**
- Proliferation region:

?

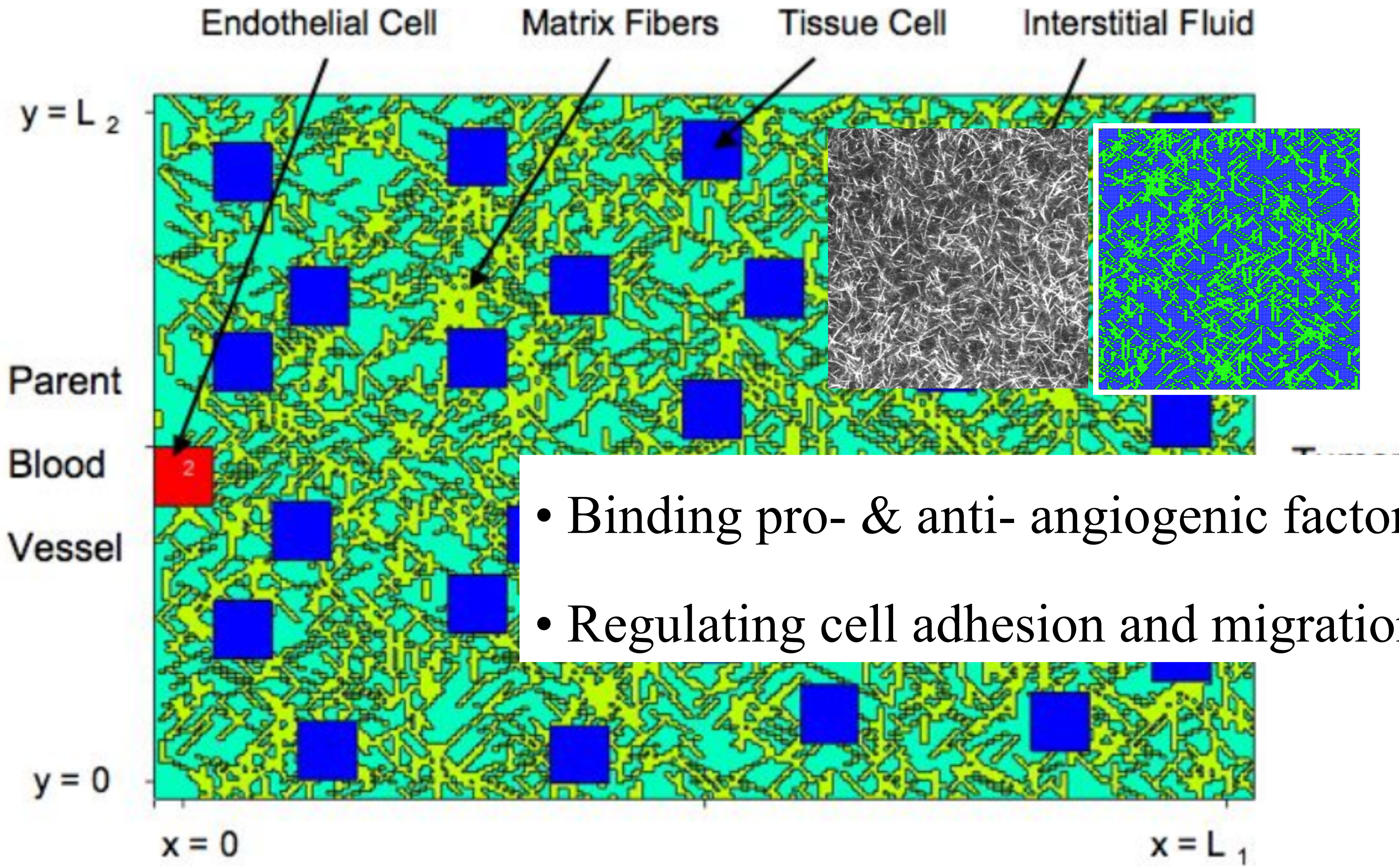
1. right behind the tip
2. all activated cells except for tip cell
3. at the base of the sprout

?

- ECs degrade ECM or secrete fibronectin
- Sprout tip secretes MMPs that degrade ECM.



- Binding pro- & anti- angiogenic factors
- Regulating cell adhesion and migration



- Binding pro- & anti- angiogenic factors
- Regulating cell adhesion and migration

Bauer et al. Biophys J. 2007

Cellular model:

- Cell types: endothelial, normal, extracellular matrix, interstitial fluid

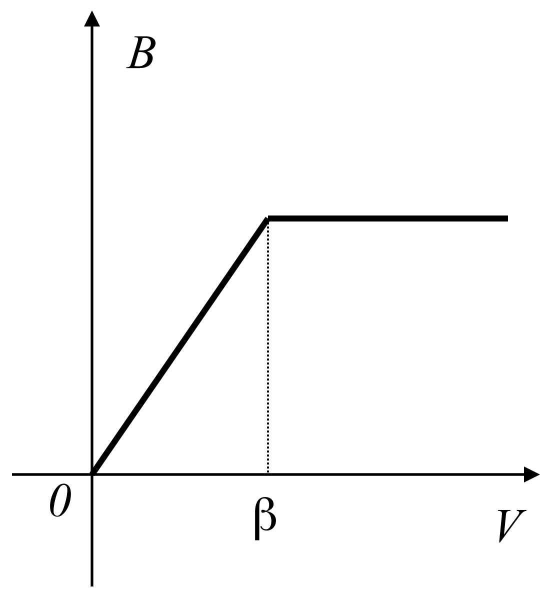
$$E = \sum_{lattice\ sites} J_{\tau(S_1)\tau(S_2)}[1-\delta(S_1,S_2)] + \sum_{cells} \gamma \cdot (v - V^T)^2 + \sum_{EC} \mu C + \sum_{cells} \gamma'[1-\delta(v,v')]$$

- Cell-matrix interaction: adhesion (haptotaxis), secretion and degradation, remodel and reorganizing
- Cell-VEGF interaction: binding, activation, sprout tip vs. proliferating vs. dormant; chemotaxis
- EC cell cycle = 18 hours = 5 MCS
- EC size = 16 x 16 = 100 μm^2

VEGFA Dynamics

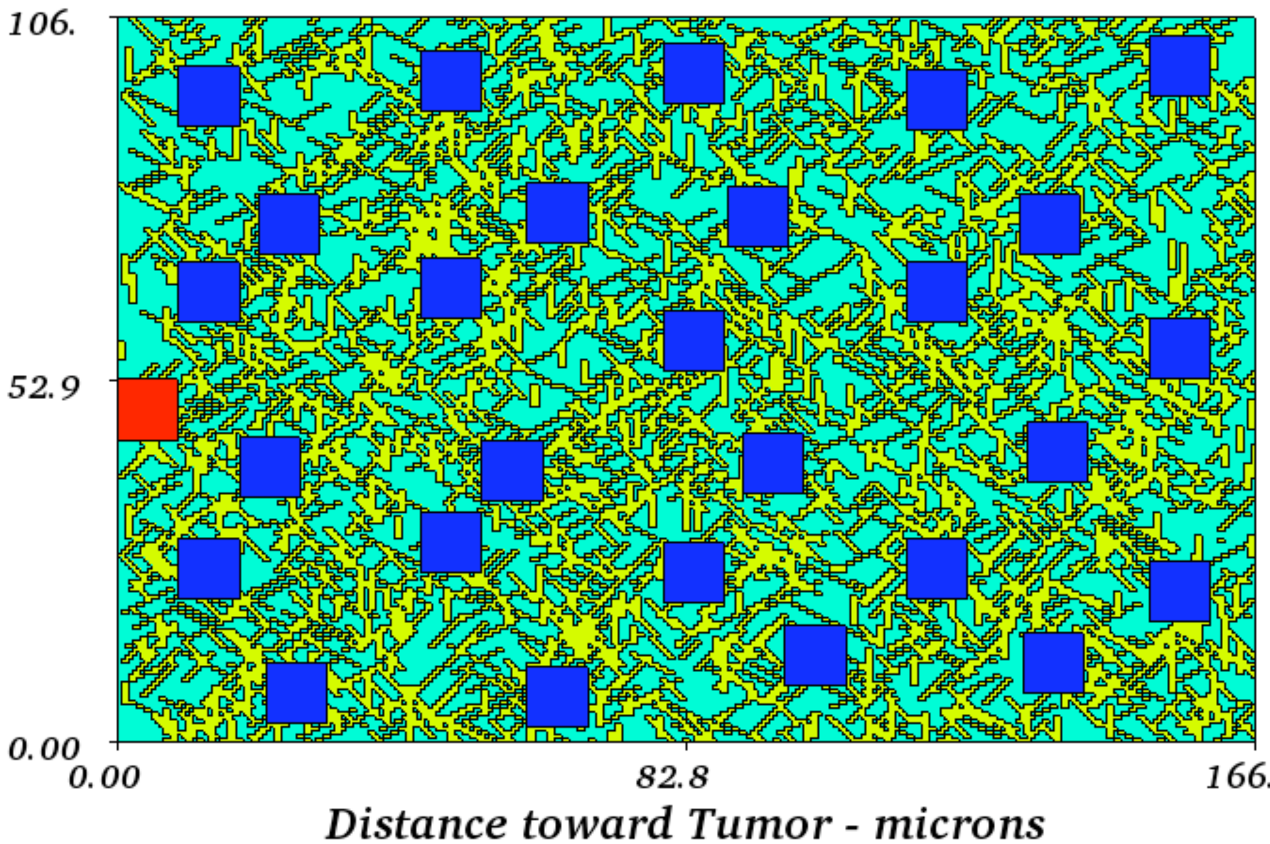
$$\frac{\partial V}{\partial t} = D\nabla^2 V - \lambda V - B(x,y)$$

$$B(x,y) = \begin{cases} \beta, & \text{if } \beta \le V \text{ and } \{(x,y) \subset \text{EC}\}; \\ V, & \text{if } 0 \le V < \beta \text{ and } \{(x,y) \subset \text{EC}\}; \\ 0, & \text{if } \{(x,y) \not\subset \text{EC}\}. \end{cases}$$

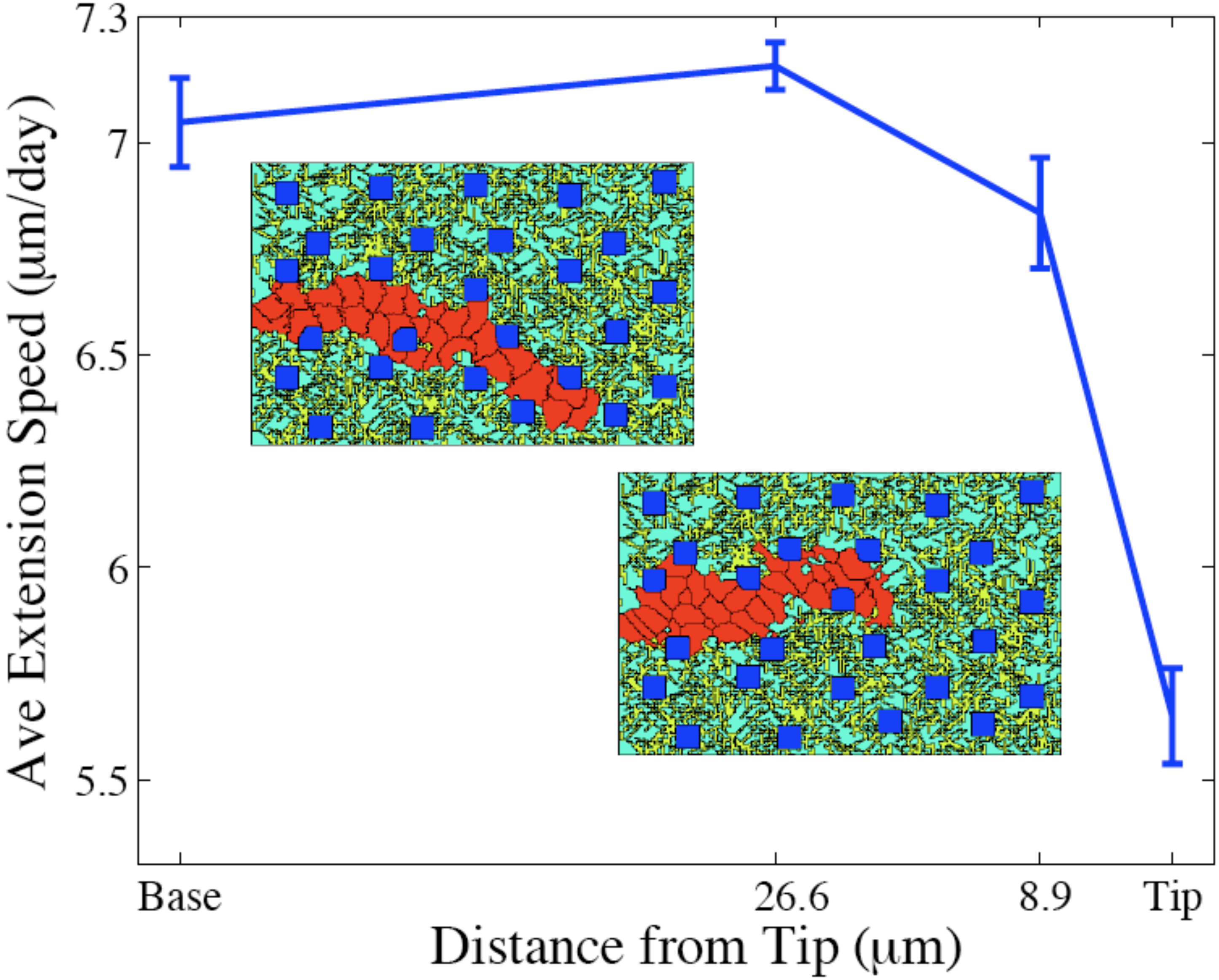


β = maximal amount of VEGF bound by EC
= total available receptor numbers

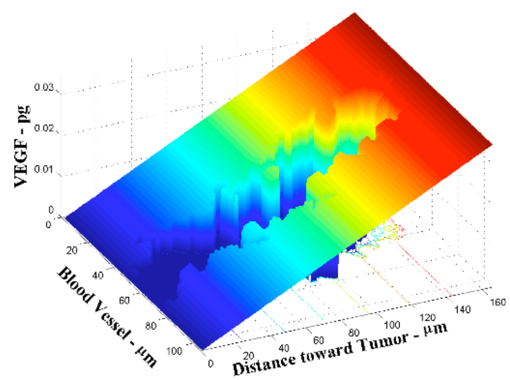
Bauer, et al, Biophys J. (2007)

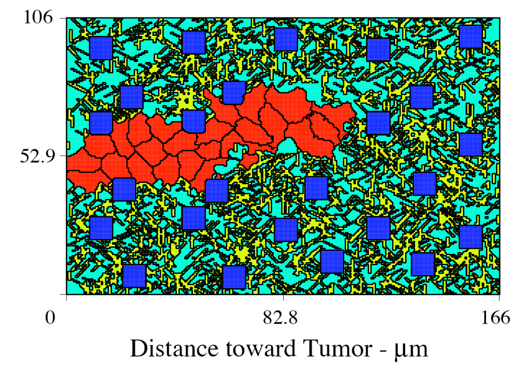


Proliferating region:

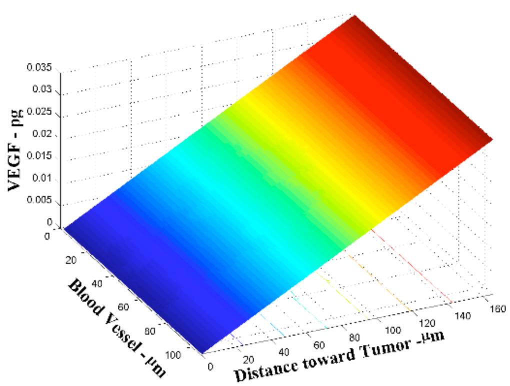


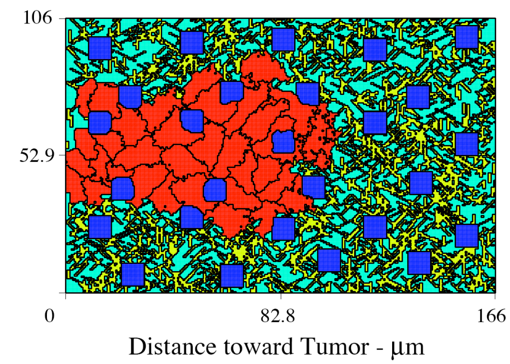
VEGF Gradient Profiles



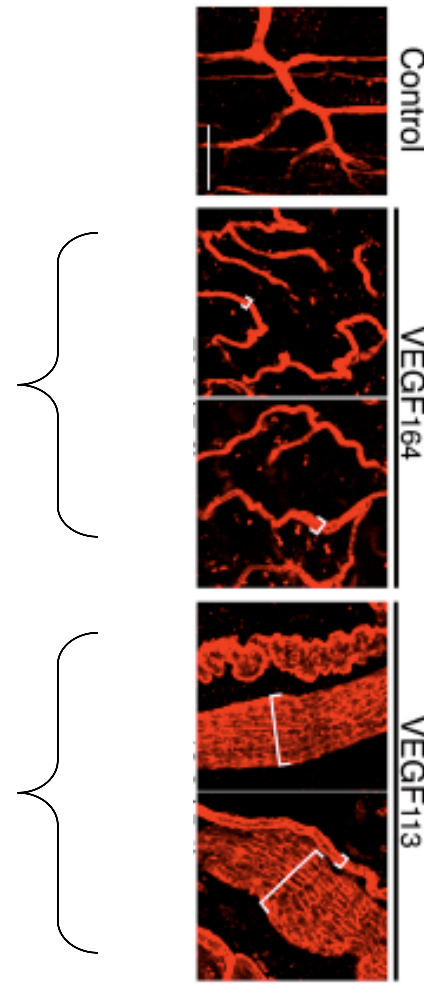


a)

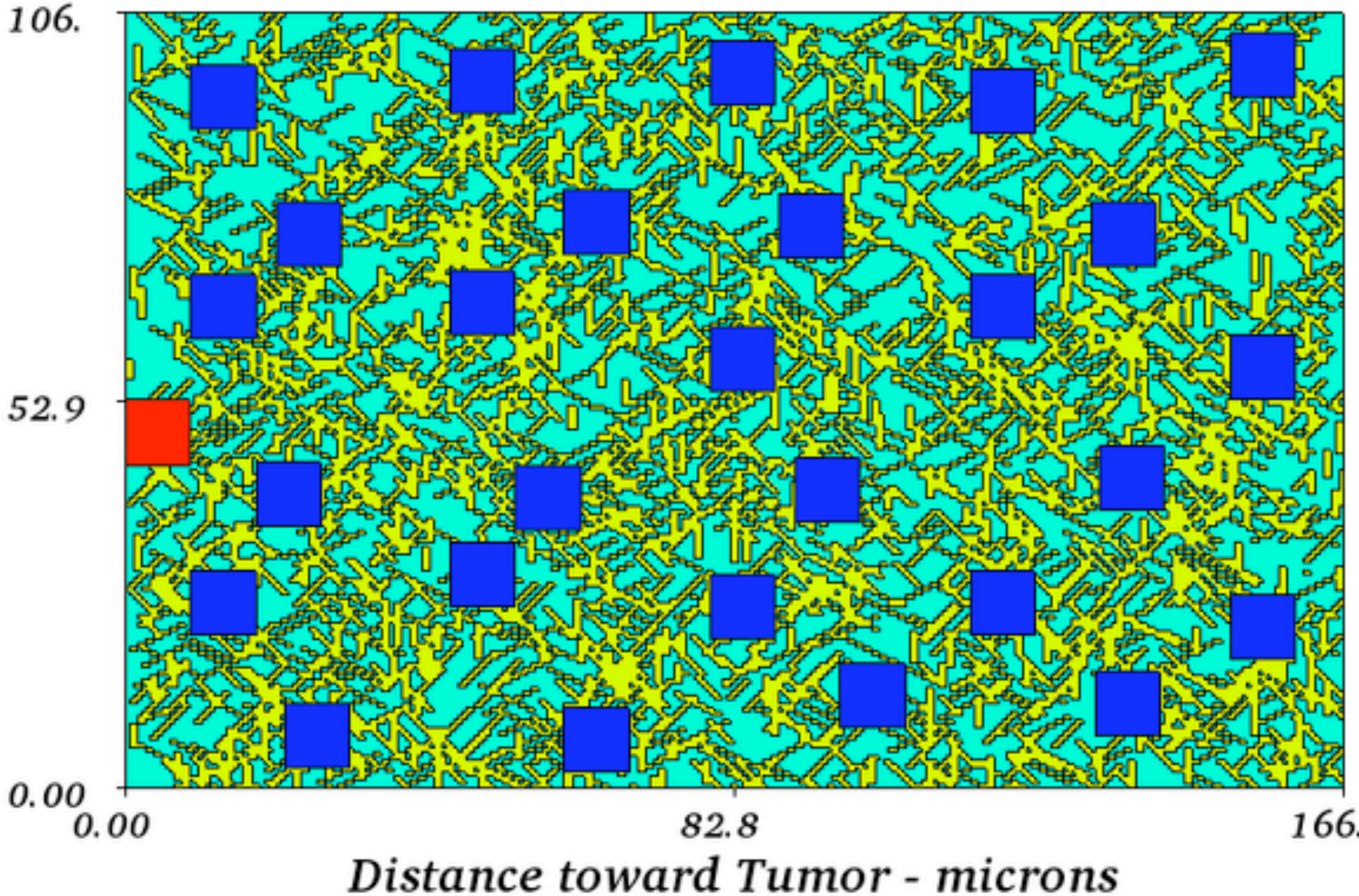




b)



Iruela-Arispe, et. al. *J. Cell Biol.* (2005)



106.
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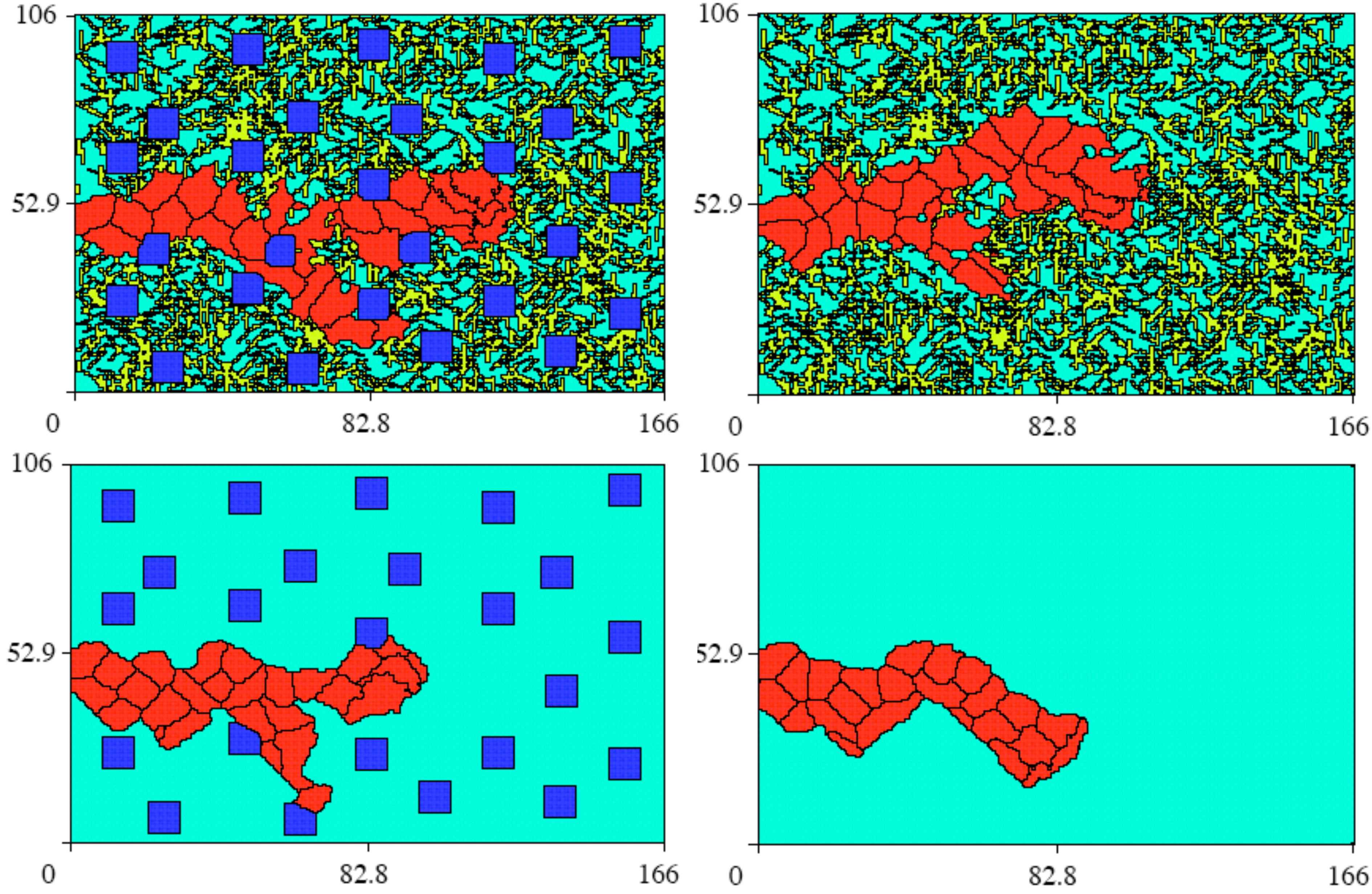
0.00
82.8
166.
Distance toward Tumor - microns

Branching?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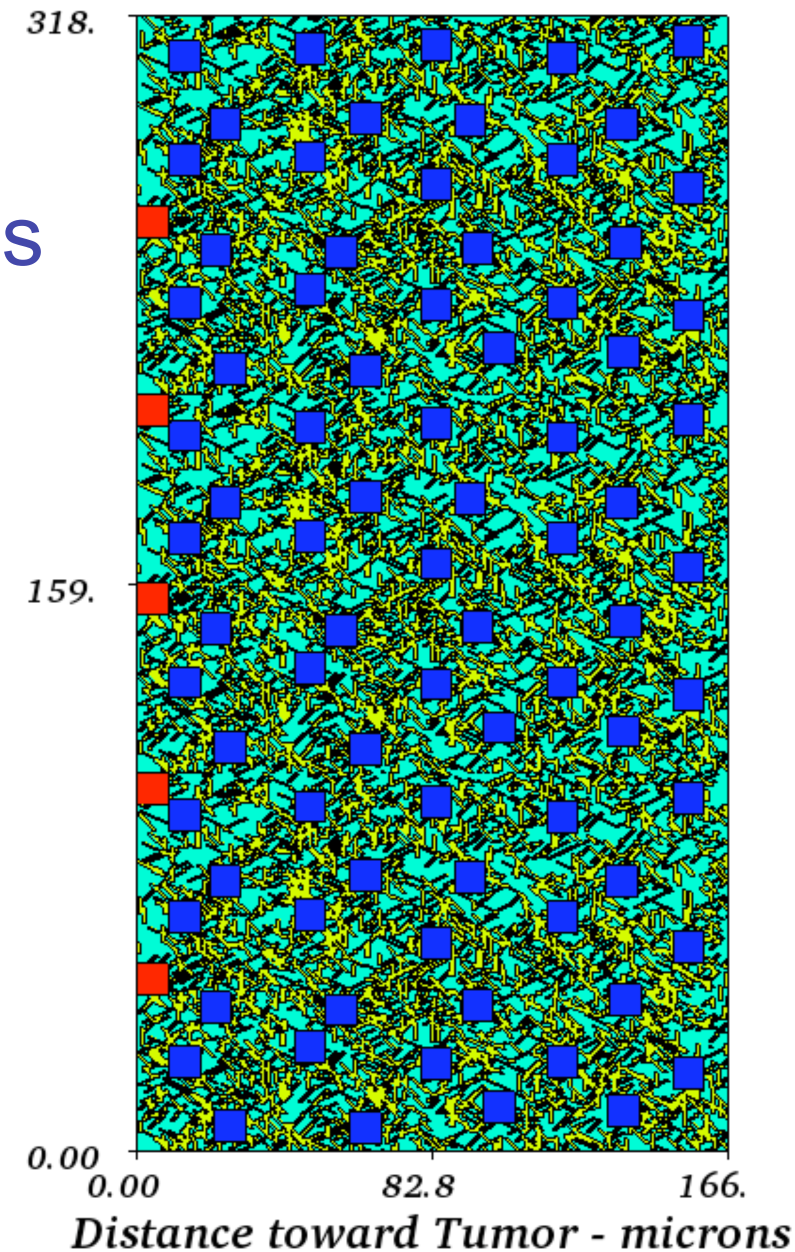
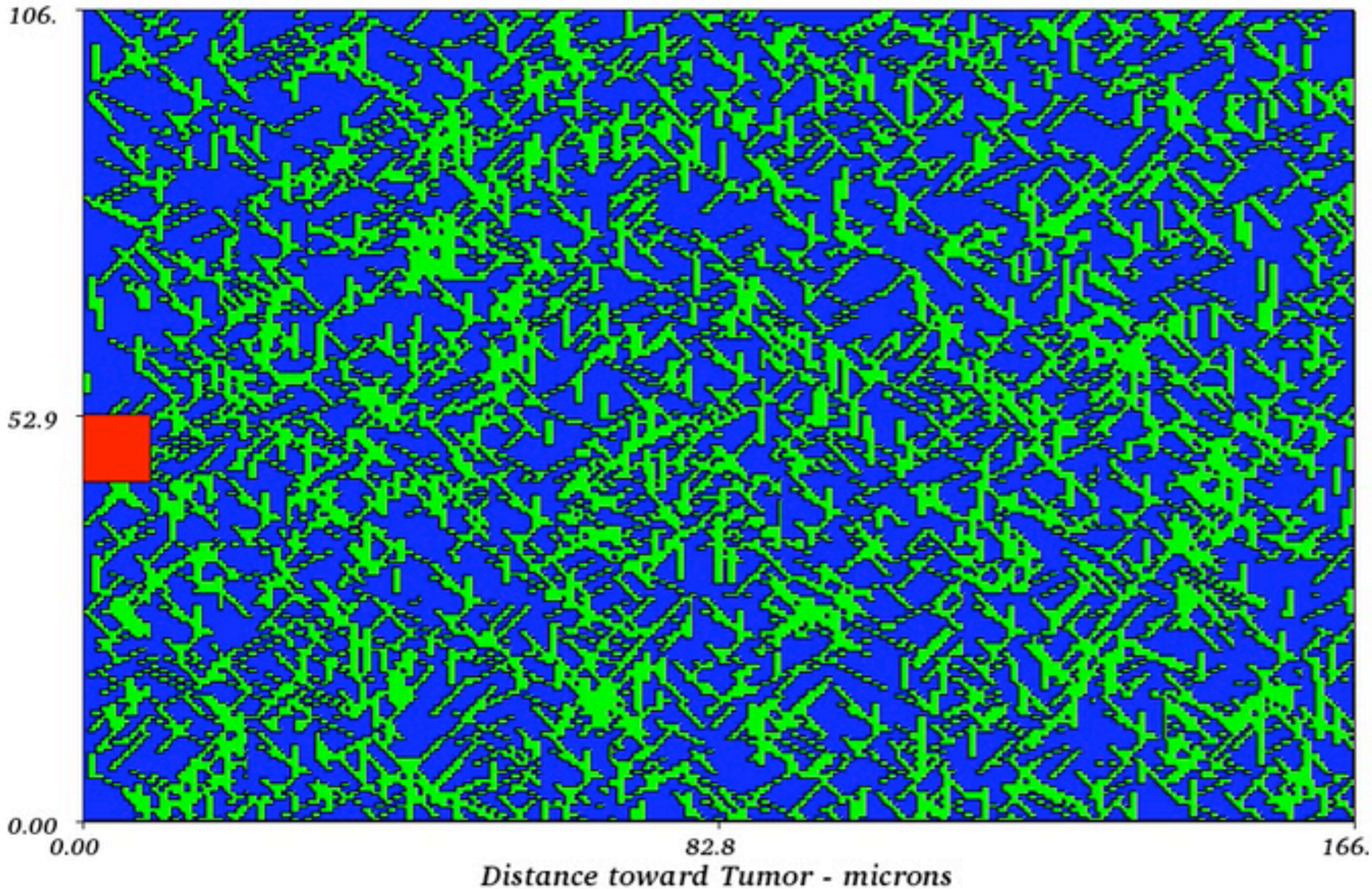
Anastomosis




106.
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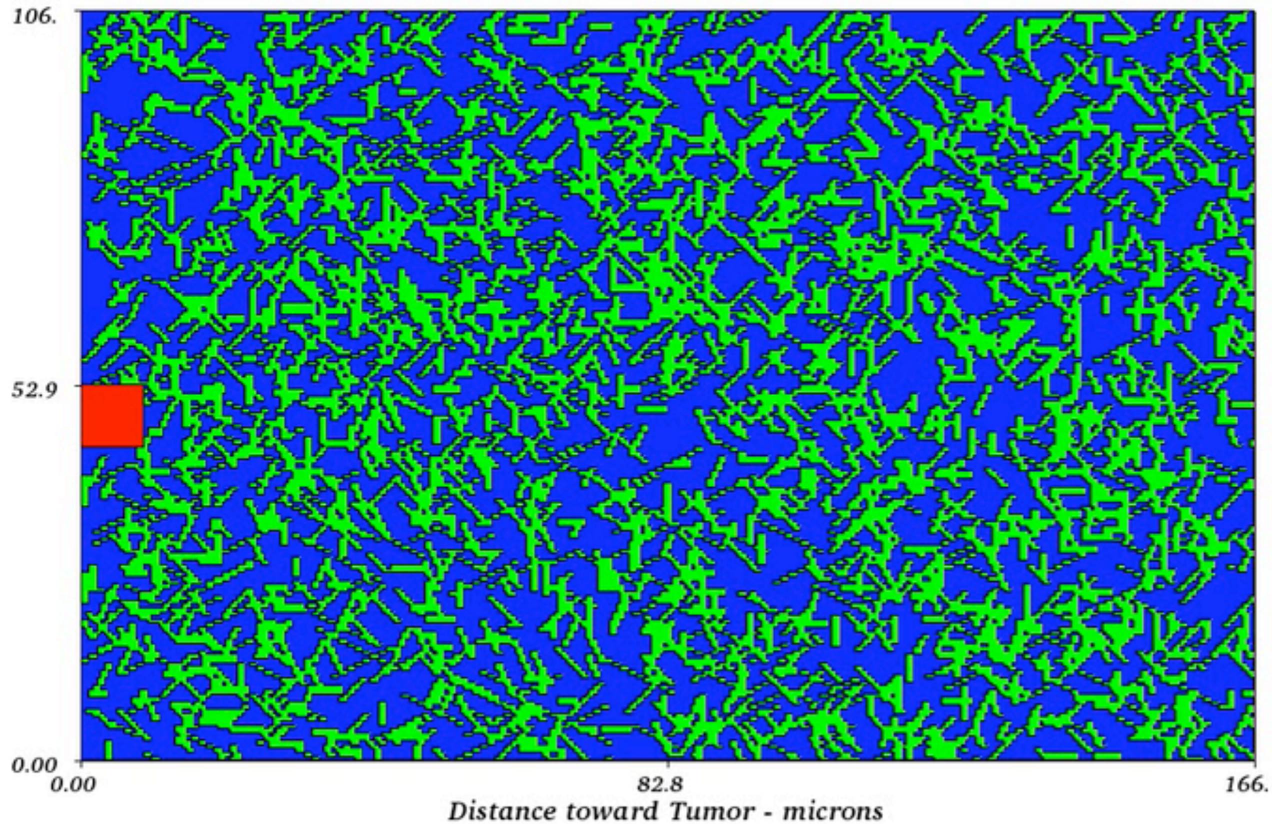
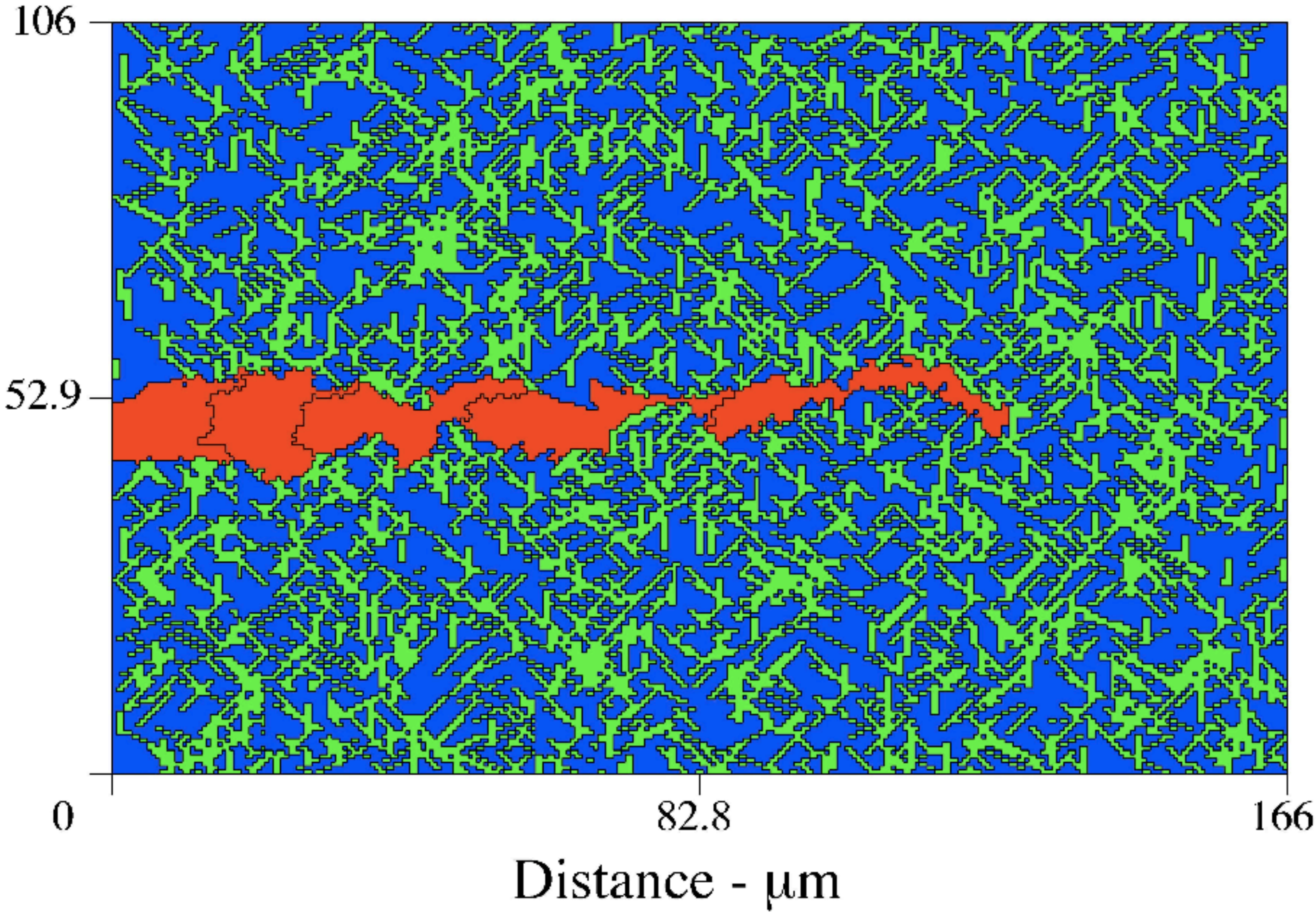
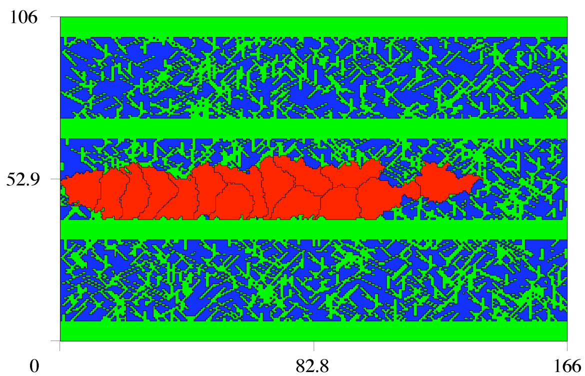
82.8
166.
Distance toward Tumor - microns

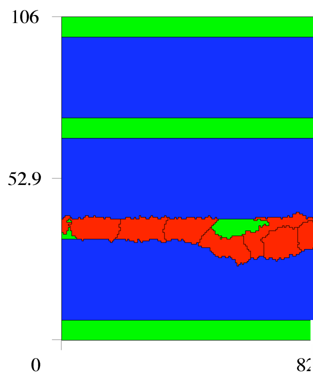
cell recruitment from sprout base

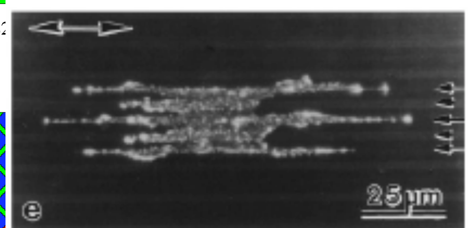


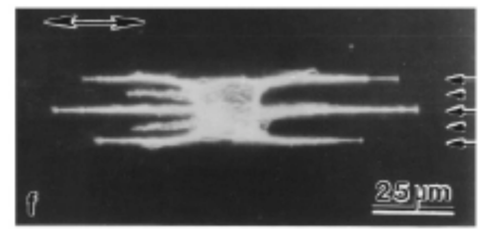

106
52.9
0
82.8
166
Distance - μm

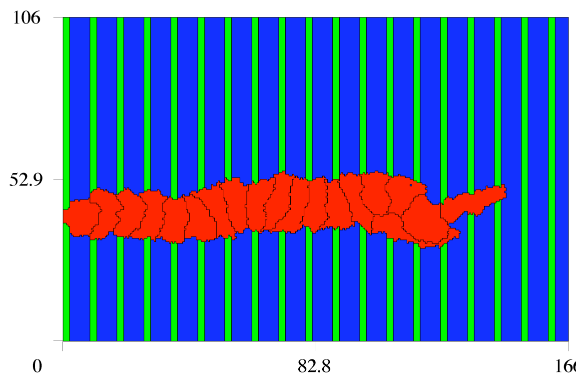
Matrix fiber alignment

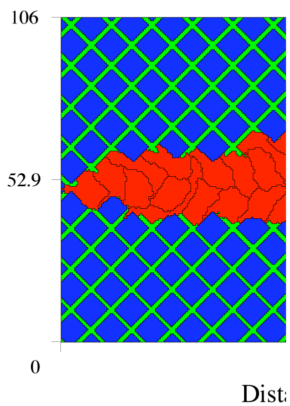


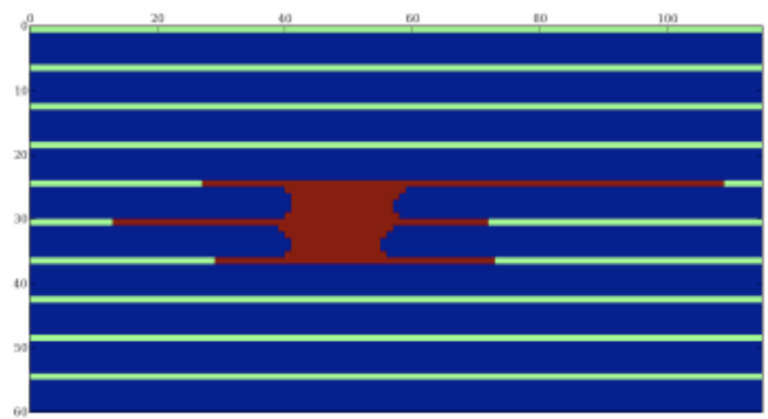




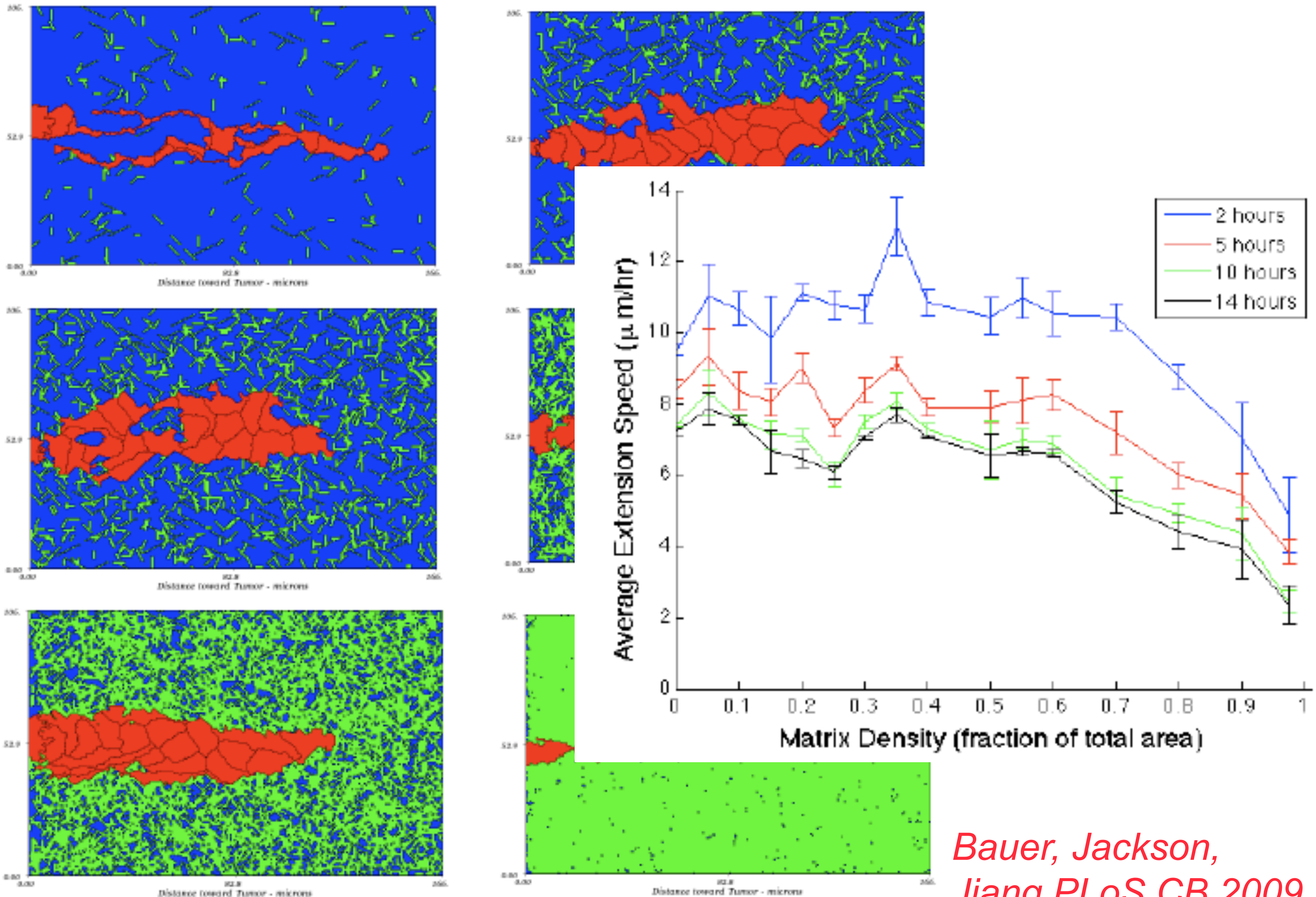








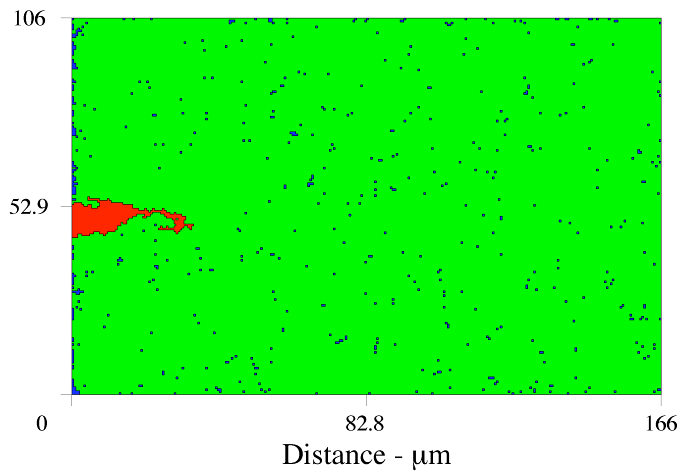
Effects of matrix density on sprout extension



Bauer, Jackson, Jiang PLoS CB 2009

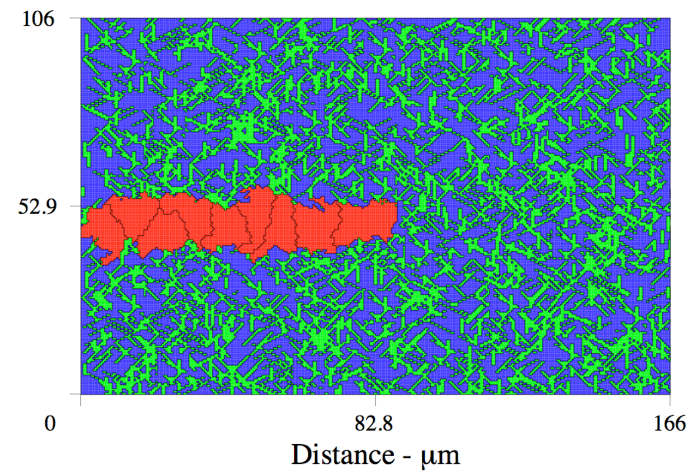
Interruption of Angiogenesis

ρ = 0.99

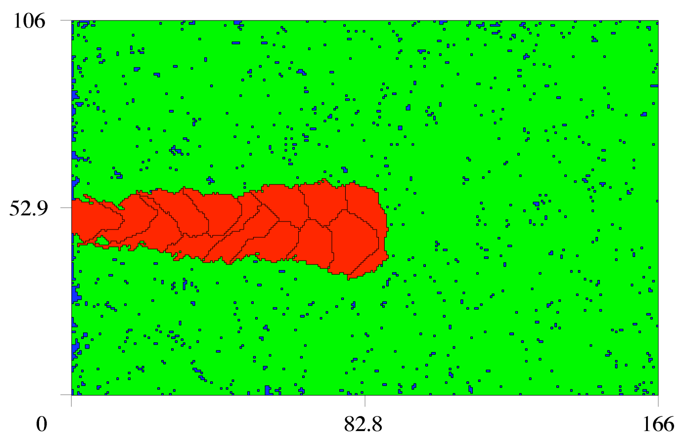


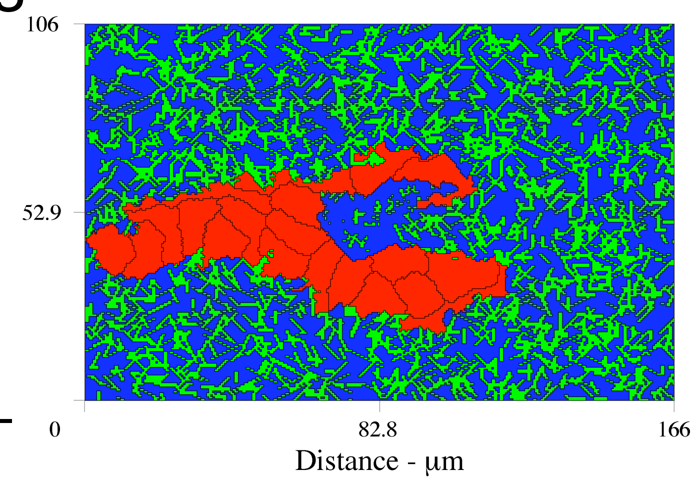
High Anisotropy Induces Branching

ρ = 0.4



With matrix degradation

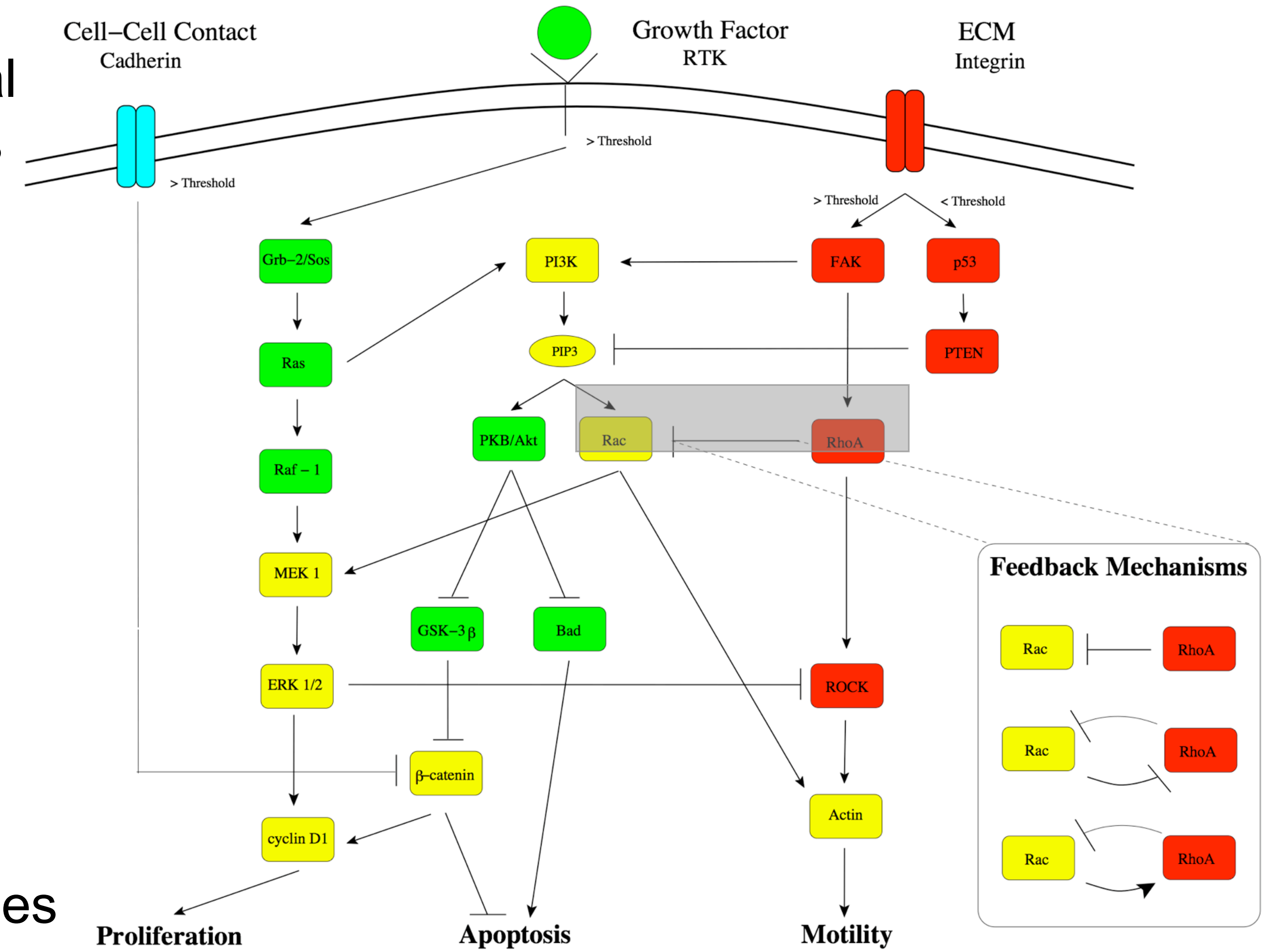




Intracellular Signaling Network

Bauer et al. 2009

External signals



Output phenotypes

Glass-type model

- State transition dynamics

  → Signal transduction

Glass, JTB, 1973.
Glass, JCP, 1975.

$$x_i(t) \in [0,\ 1], \qquad X_i(t) = H(x_i - \theta)$$

$$X_i(t) = \begin{cases} 1, & x_i(t) \geq 1/2 \\ 0, & x_i(t) < 1/2 \end{cases}$$

•Variables in biological systems are usually continuous
•There are few mechanisms for synchronous updating of the state

Discrete Boolean

$$X_i(t+1) = f_i(X(t))$$

$$f_H = \frac{\lambda x^n}{\theta^n + x^n}$$

Continuous Boolean

$$\frac{dx_i(t)}{dt} = f_i(X_{r_i}{}^1(t), \ldots, X_{r_i}{}^{k_i}(t)) - x_i(t)$$

Continuous Stochastic Boolean

$$\frac{dx_i(t)}{dt} = \left| f_i(X_{r_i}{}^1(t), \ldots, X_{r_i}{}^{k_i}(t)) - \delta(t) \right| - x_i(t)$$

$$\delta(t) = \begin{cases} 1, \text{ with probability } p \\ 0, \text{ with probability } 1-p \end{cases}$$

Glass-type model

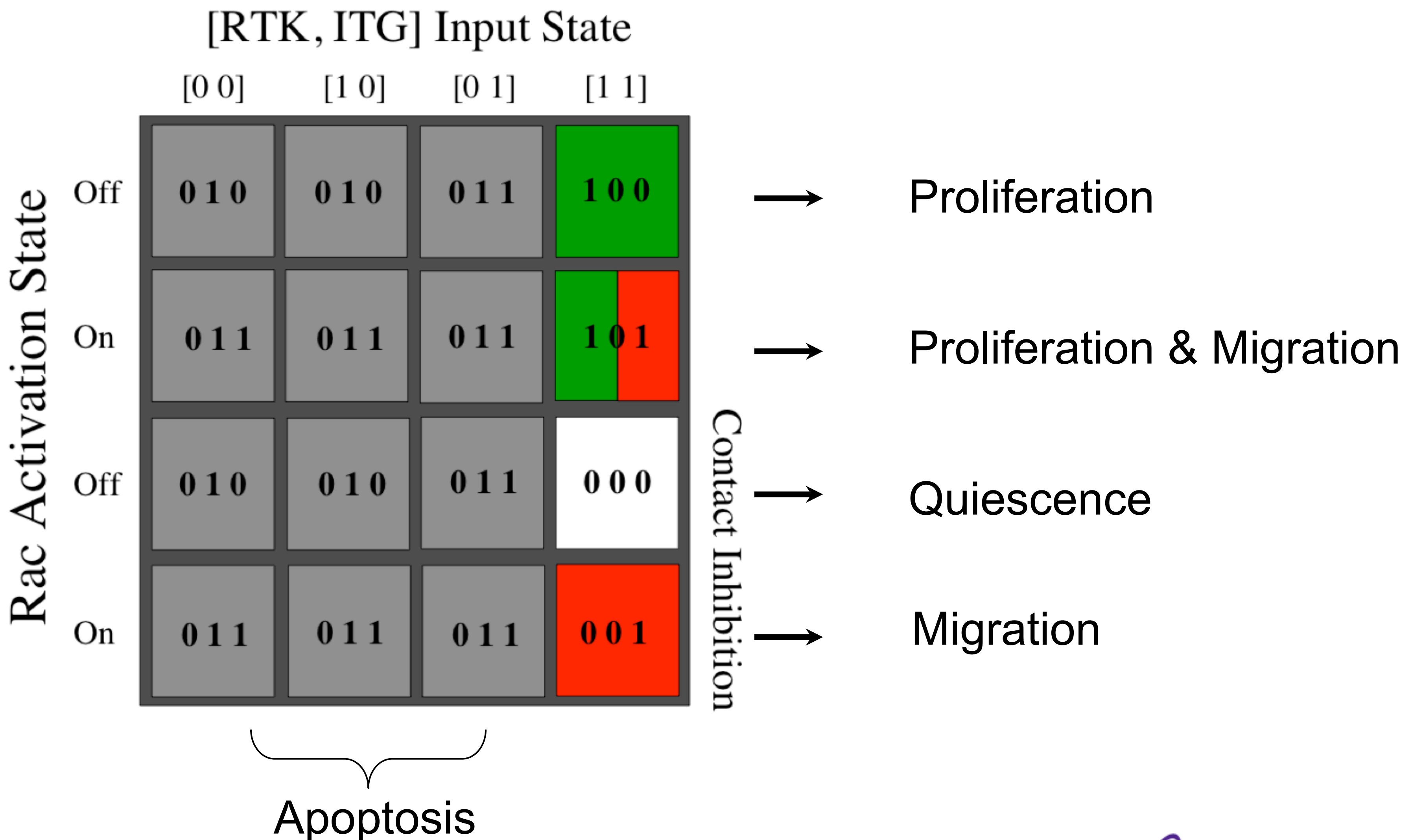
- Boolean dynamics $f_i(X_{r_i}{}^{1}(t), \ldots, X_{r_i}{}^{k_i}(t))$

ECM-Integrin = ITG
VEGF- VEGFR2 = RTK
VE-cadherin = cadherin

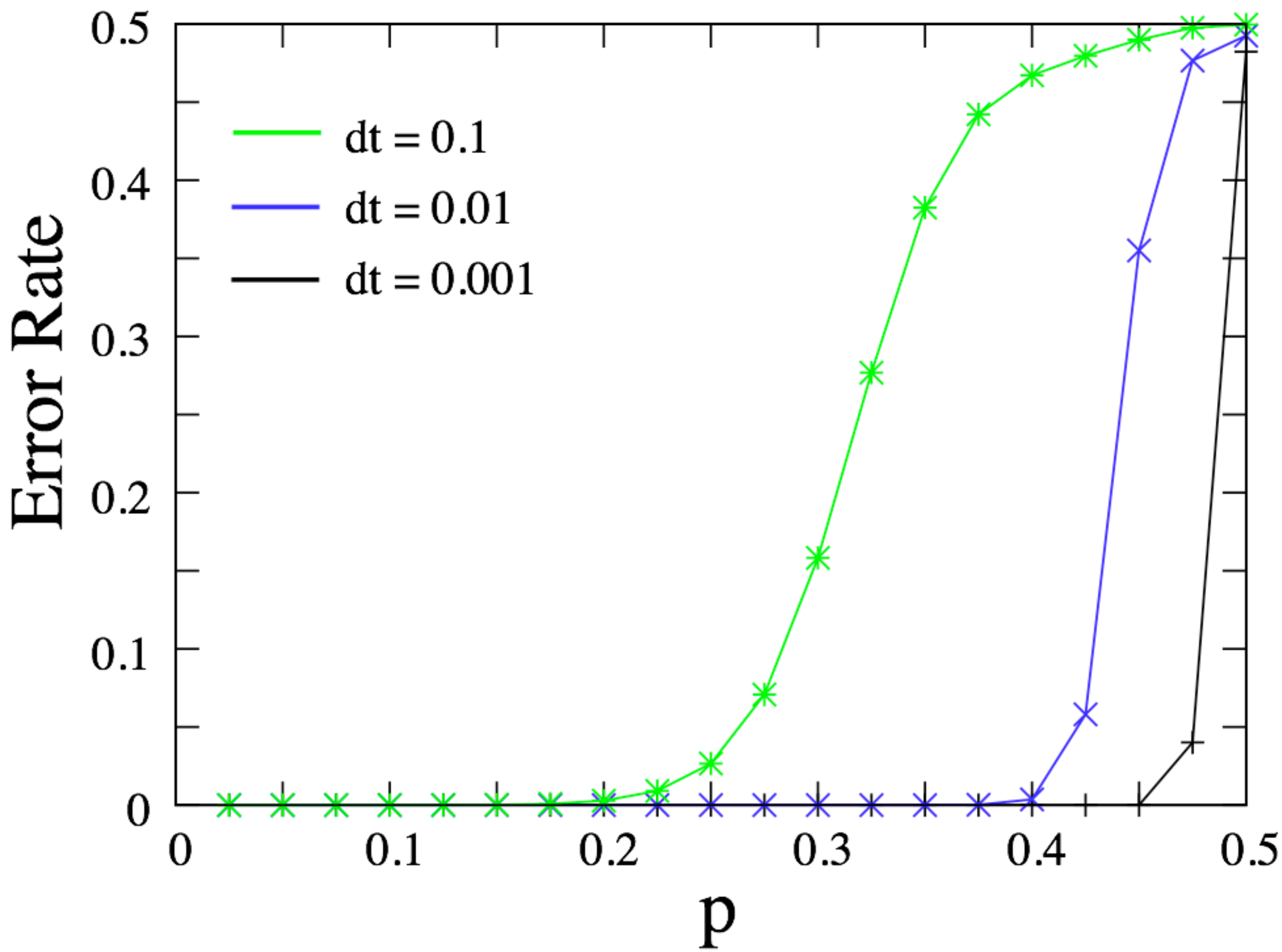
p53 = !ITG
PIP3 = PI3K && ! PTEN
Rac1 = PIP3 && ! RhoA
MEK1 = Raf-1 || Rac1
…

Motility = Actin
Proliferation = cyclin D1
Apoptosis = Bad && !b-catein

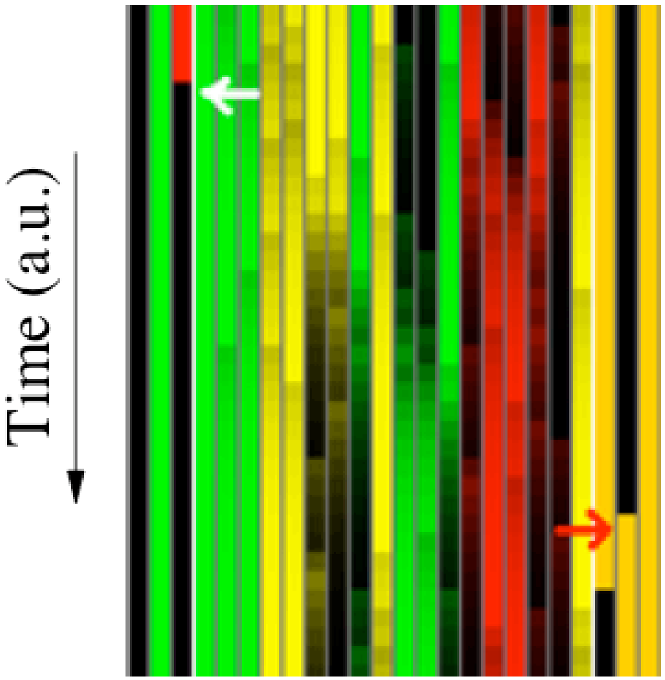
cell phenotypes

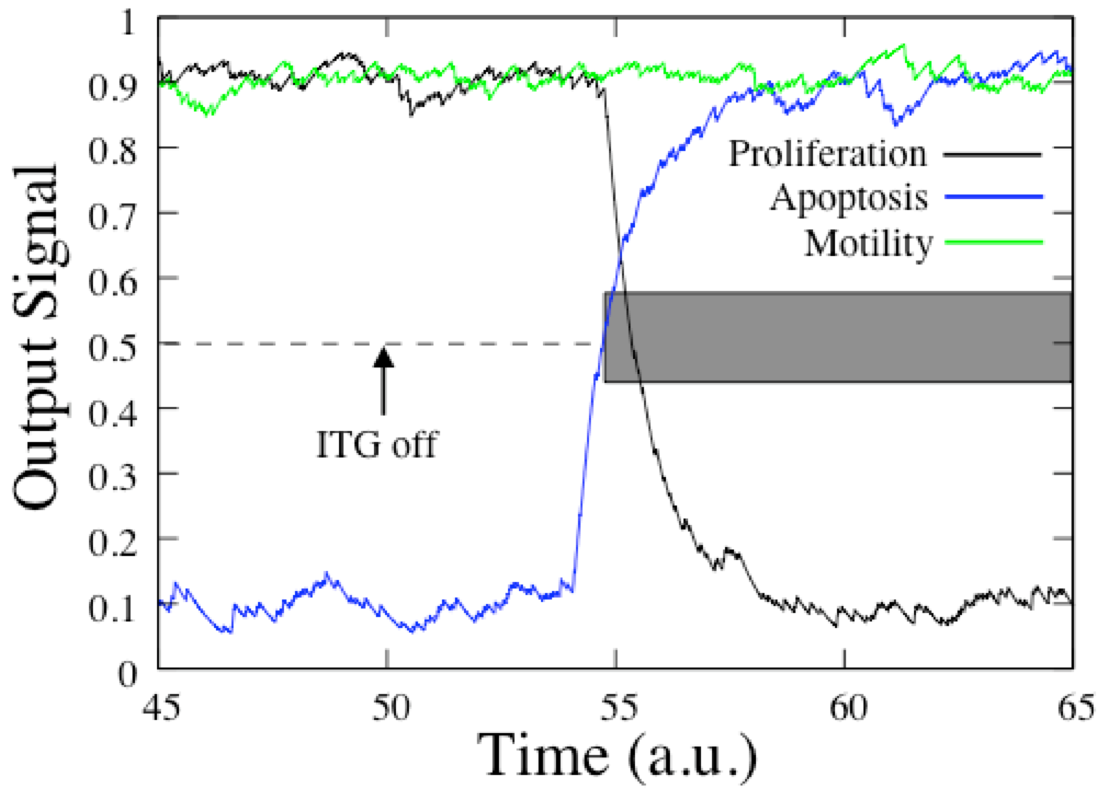


Robust to internal noise

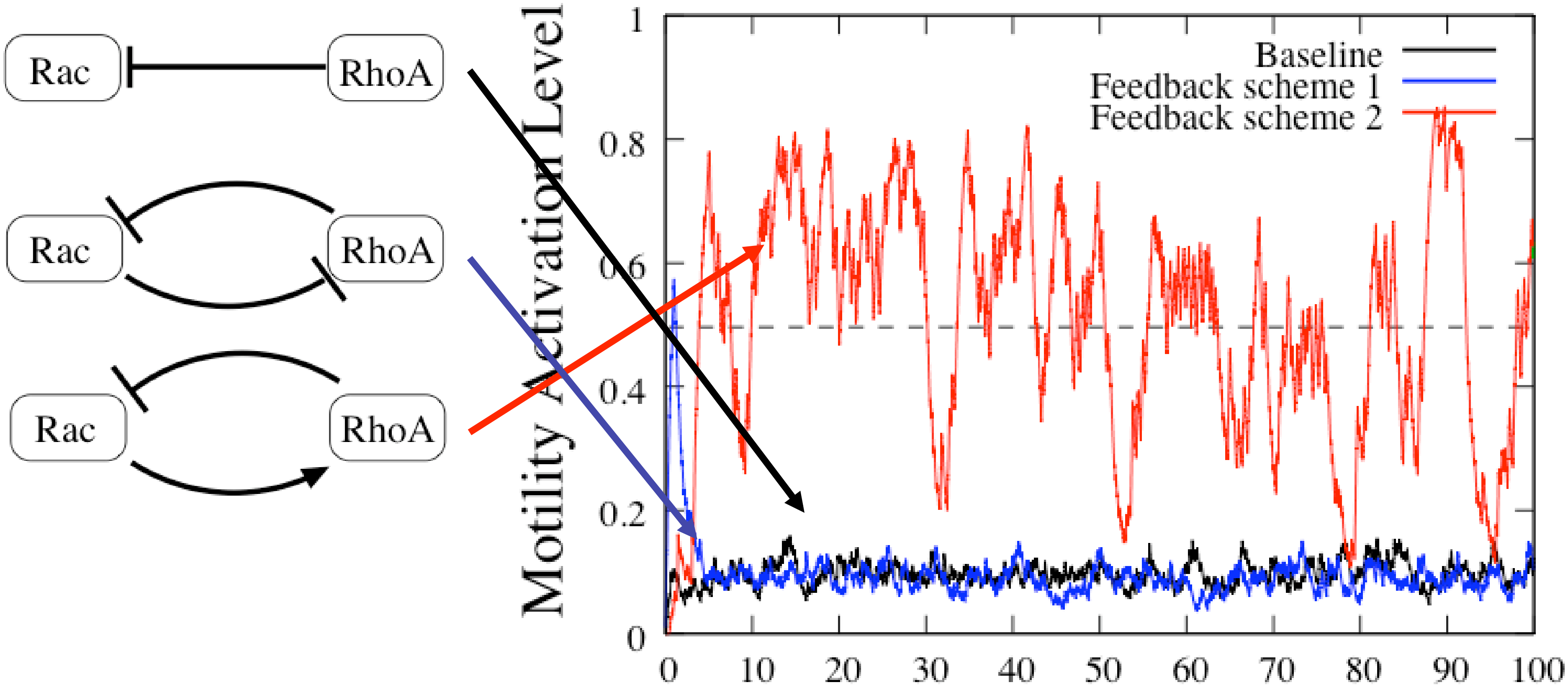


Fast response to signals

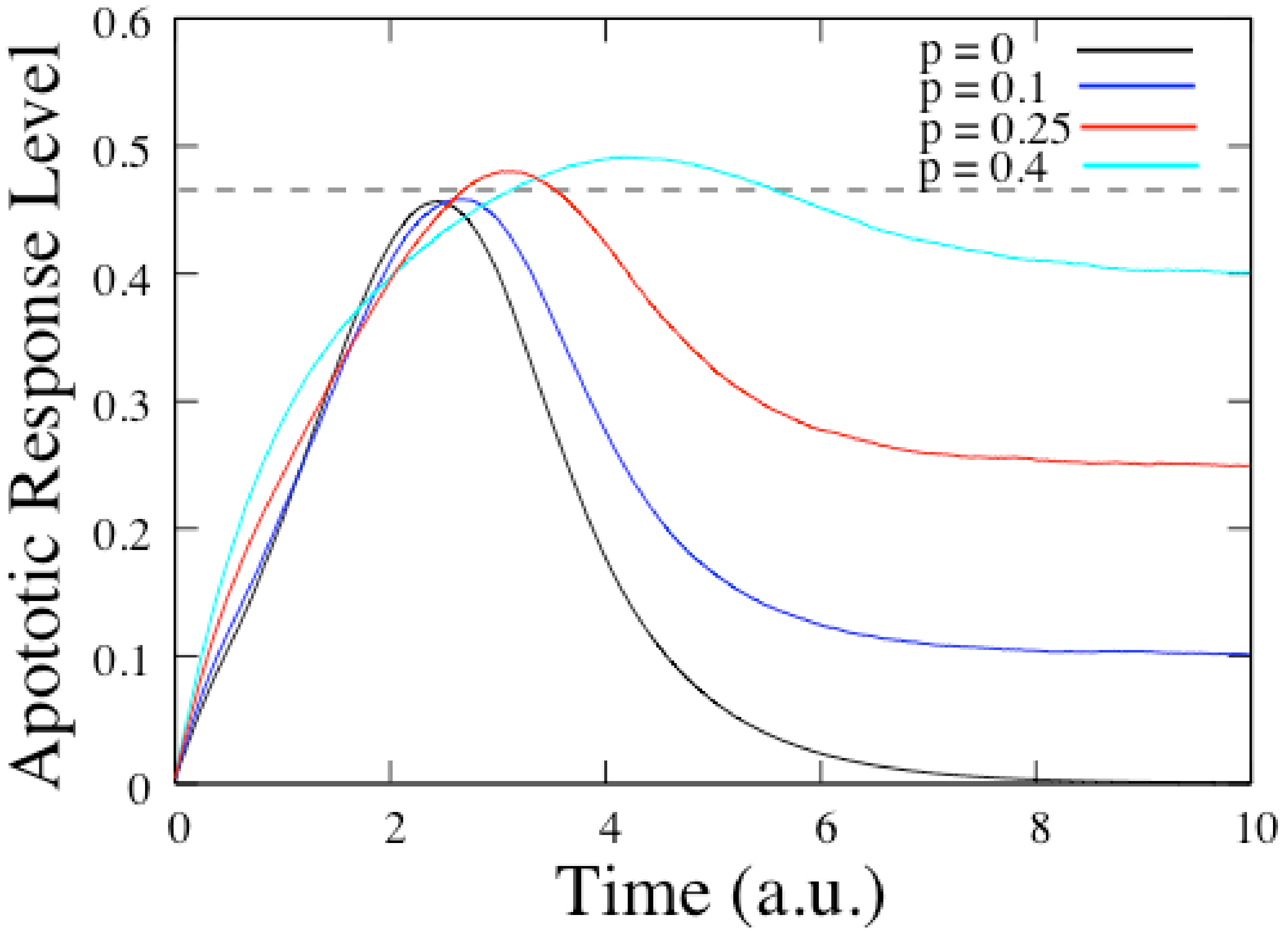




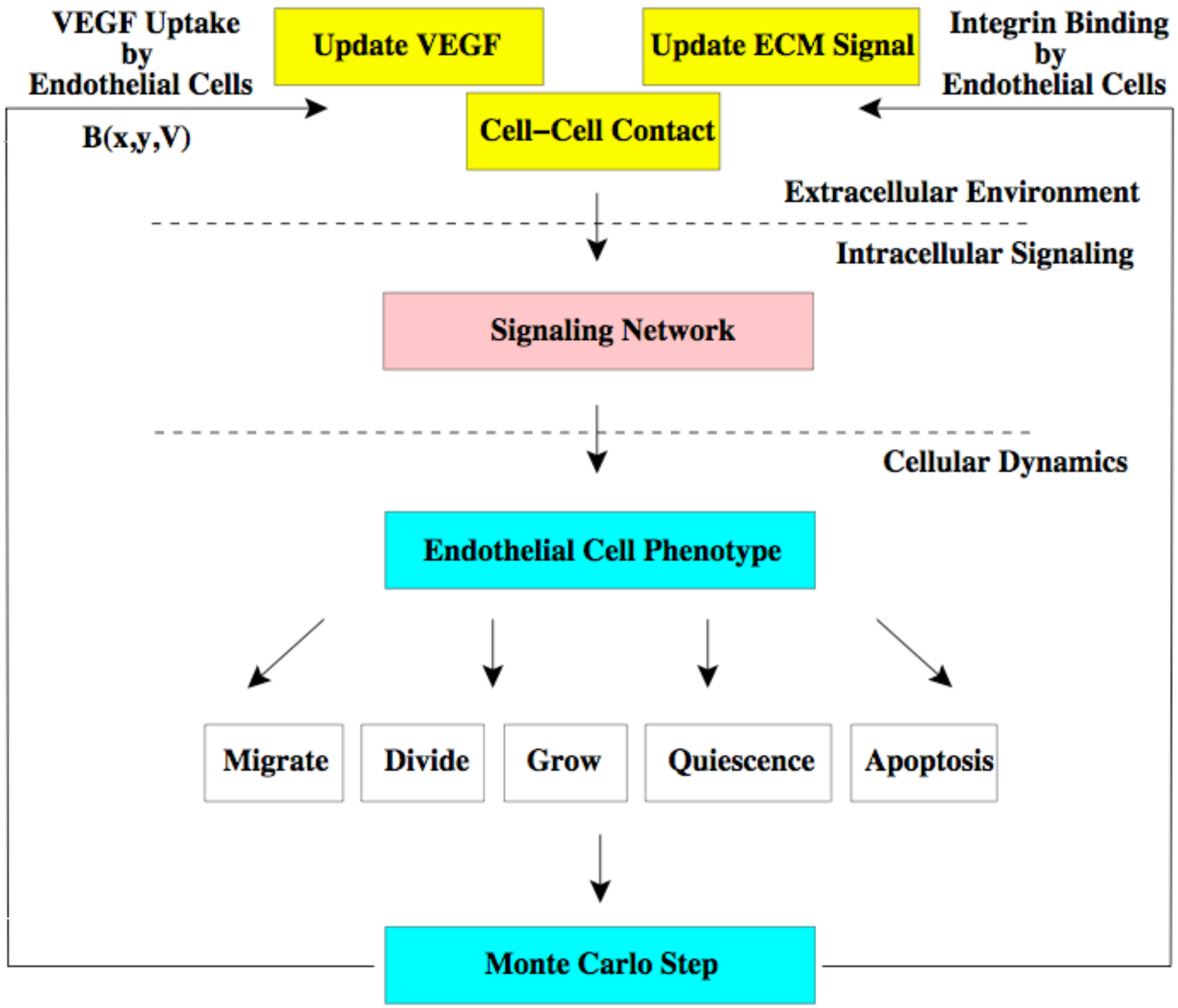
Feedback scheme 2 unstable



Apoptotic switch sensitive



Multi-Scale Model of Tumor Angiogenesis



Cellular model

- Cell types: endothelial, normal, extracellular matrix, interstitial fluid

$$E = \sum_{lattice\ sites} J_{\tau(S_1)\tau(S_2)}[1-\delta(S_1,S_2)] + \sum_{cells} \gamma \cdot (v - V^T)^2 + \sum_{EC} \mu C + \sum_{cells} \gamma'[1-\delta(v,v')]$$

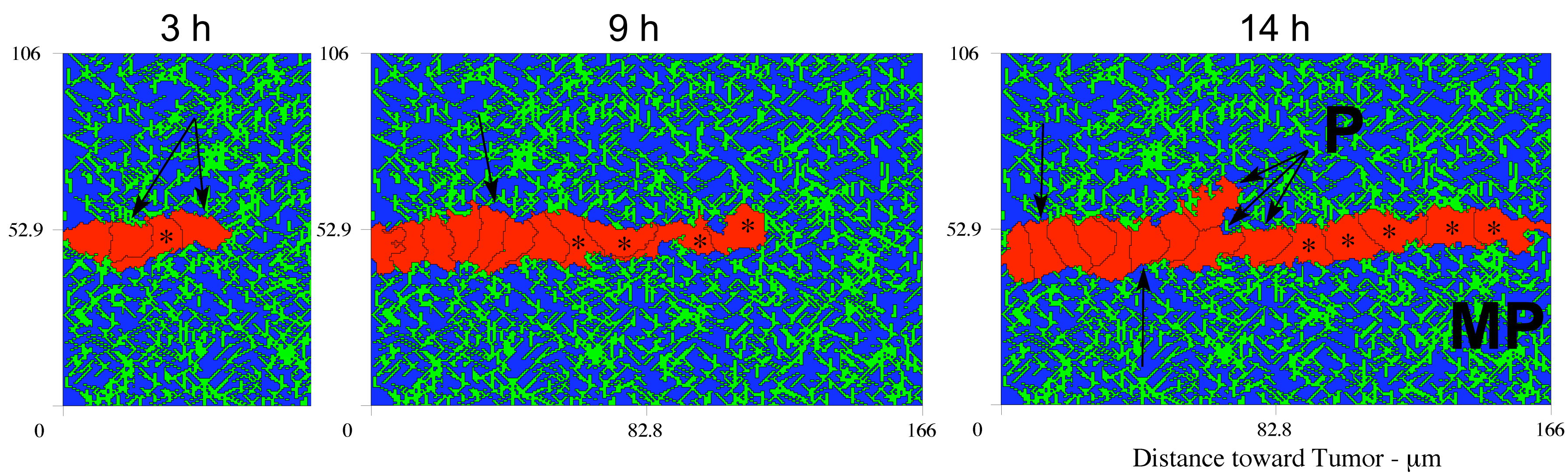
haptotaxis, chemotaxis

ExtraCellular chemical

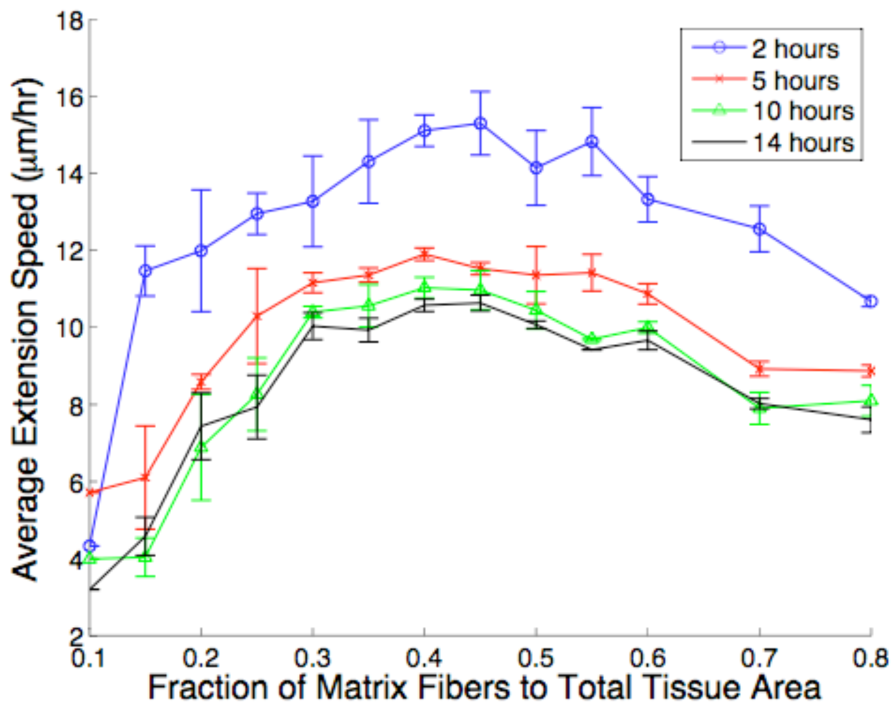
$$\frac{\partial V}{\partial t} = D\nabla^2 V - \lambda V - B(x,y)$$

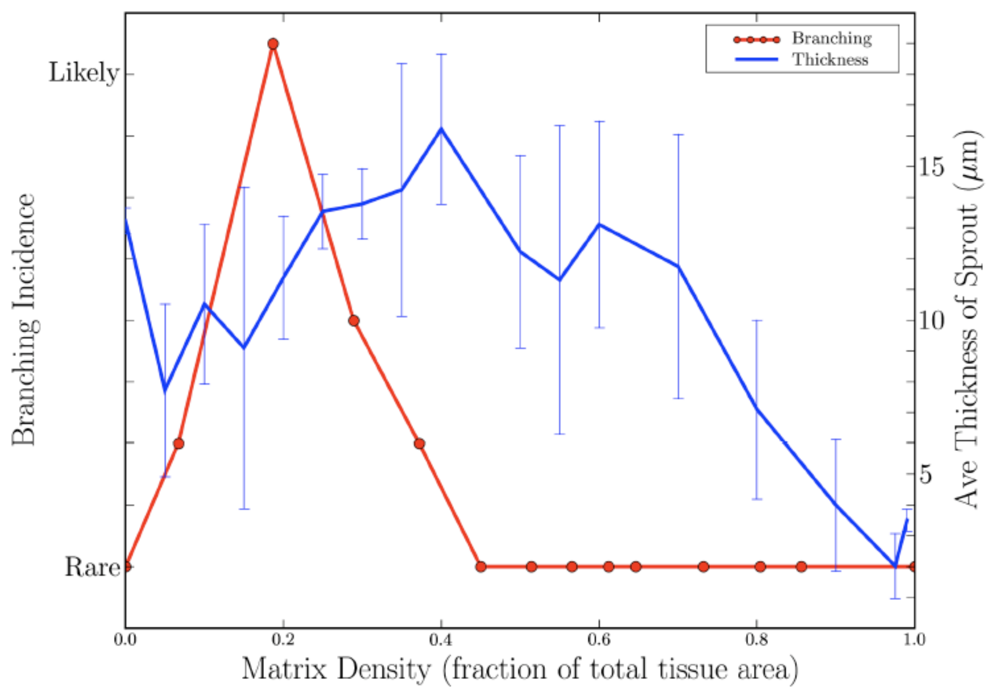
Static ECM

Phenotype Distribution

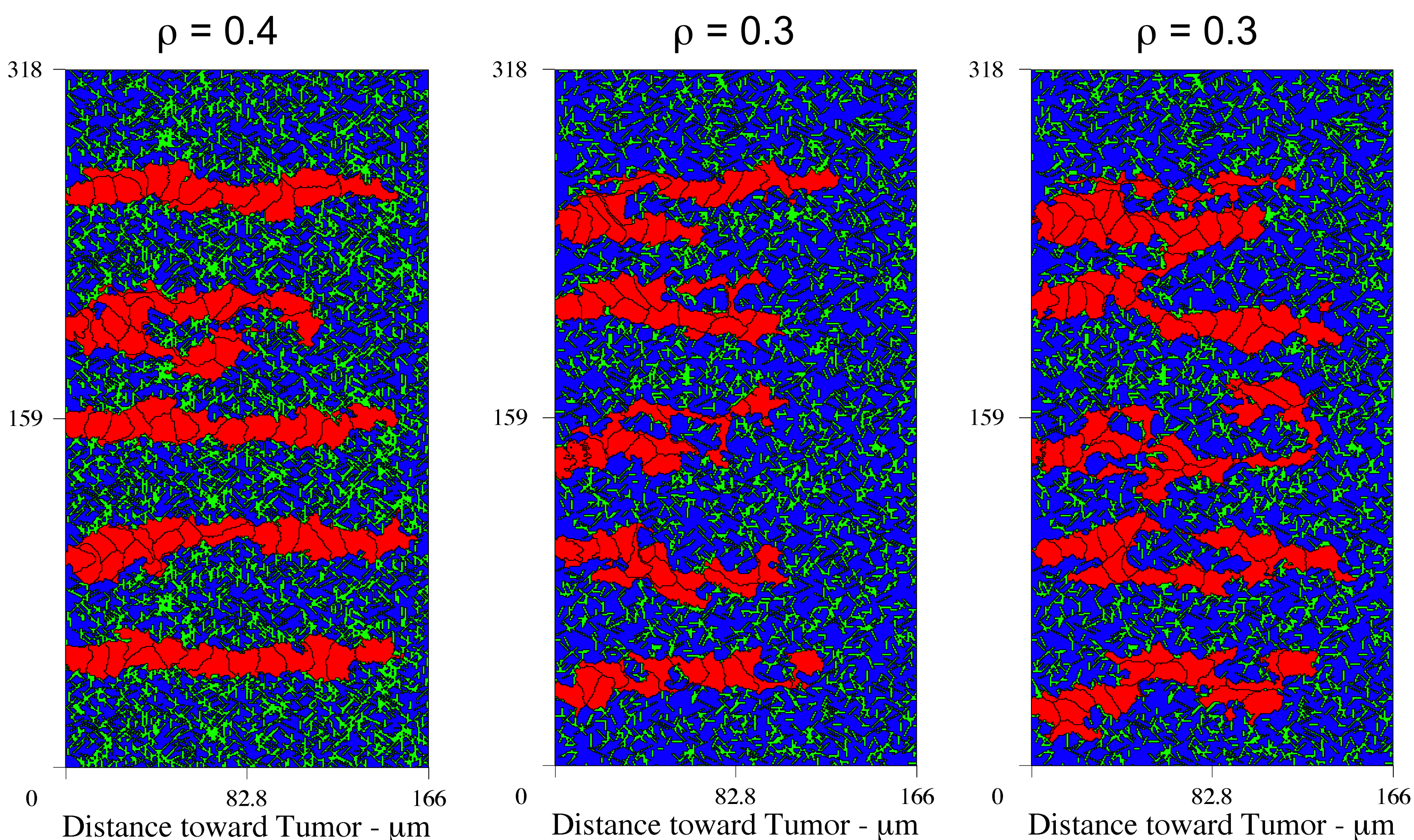


Extension Speed and Branching Mediated by Matrix Density



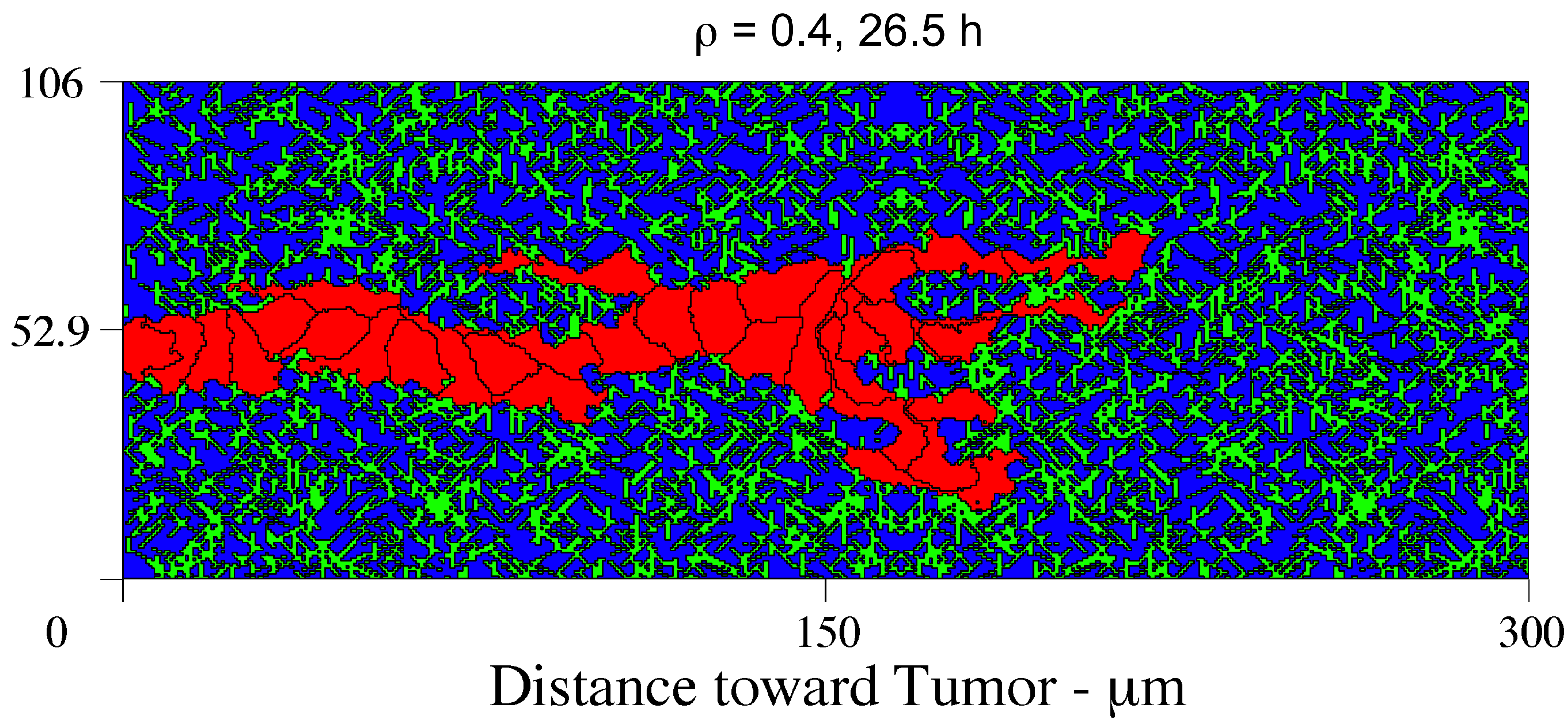


Branching & Anastomosis



NNSA Los Alamos

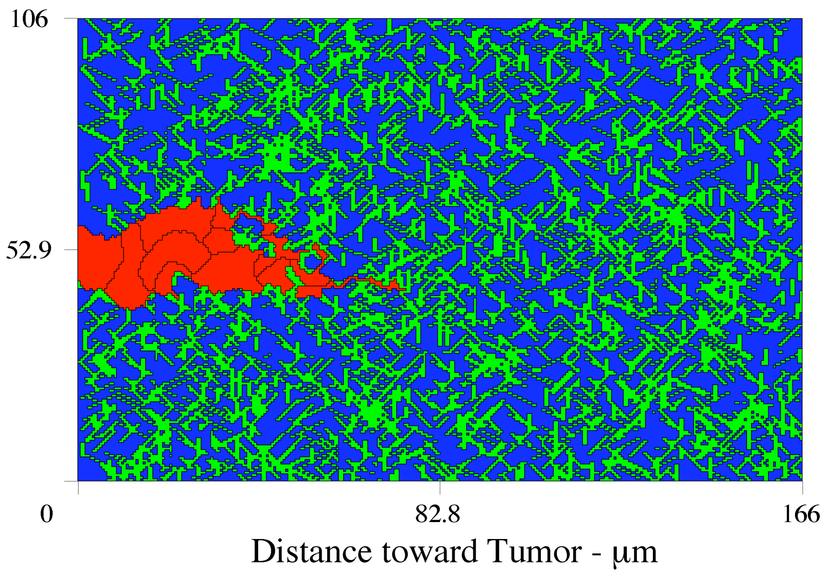
Emergent Phenomenon:
Brush Border Effect



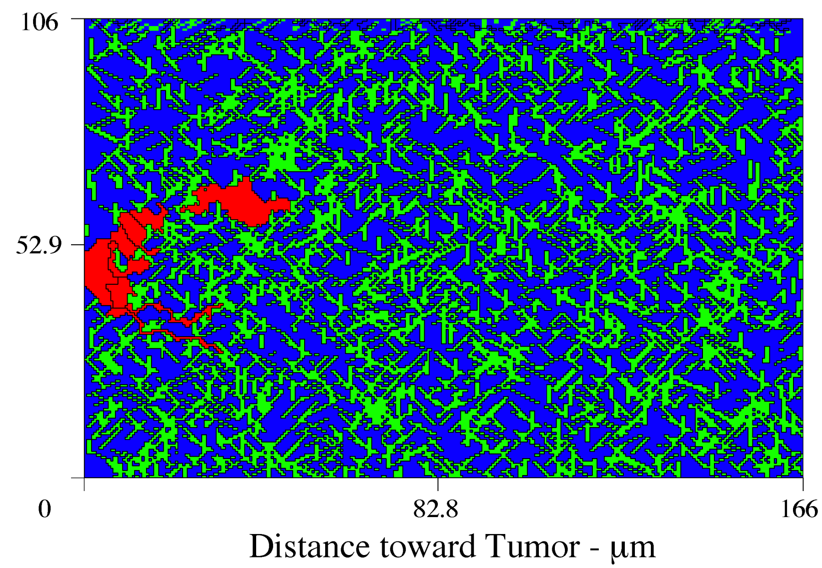
Bauer Thesis 07

Apoptosis:

Receptor dialing as Pro- and Anti-angiogenic therapy



↑ T_I → ↑ Apoptosis

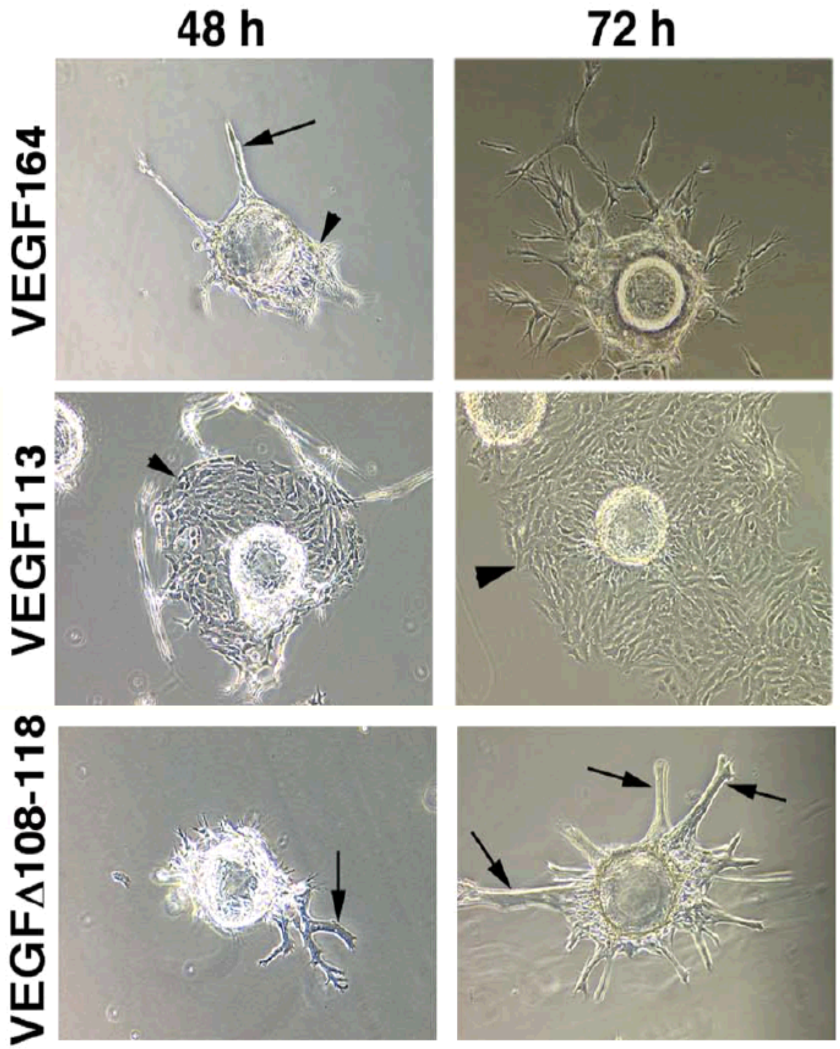


↑ T_R → ↑ Apoptosis

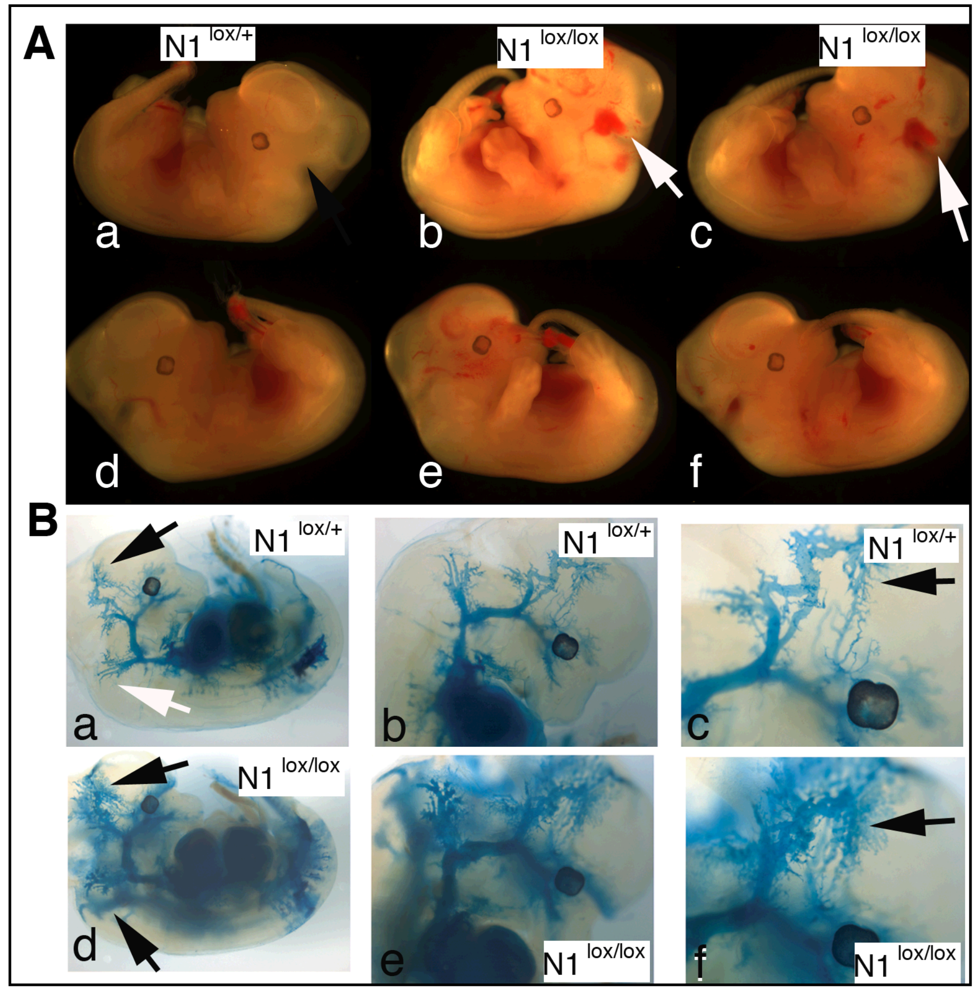
Avasin
PTK787/ZK222584

Experimental validation

Luisa Arispe lab

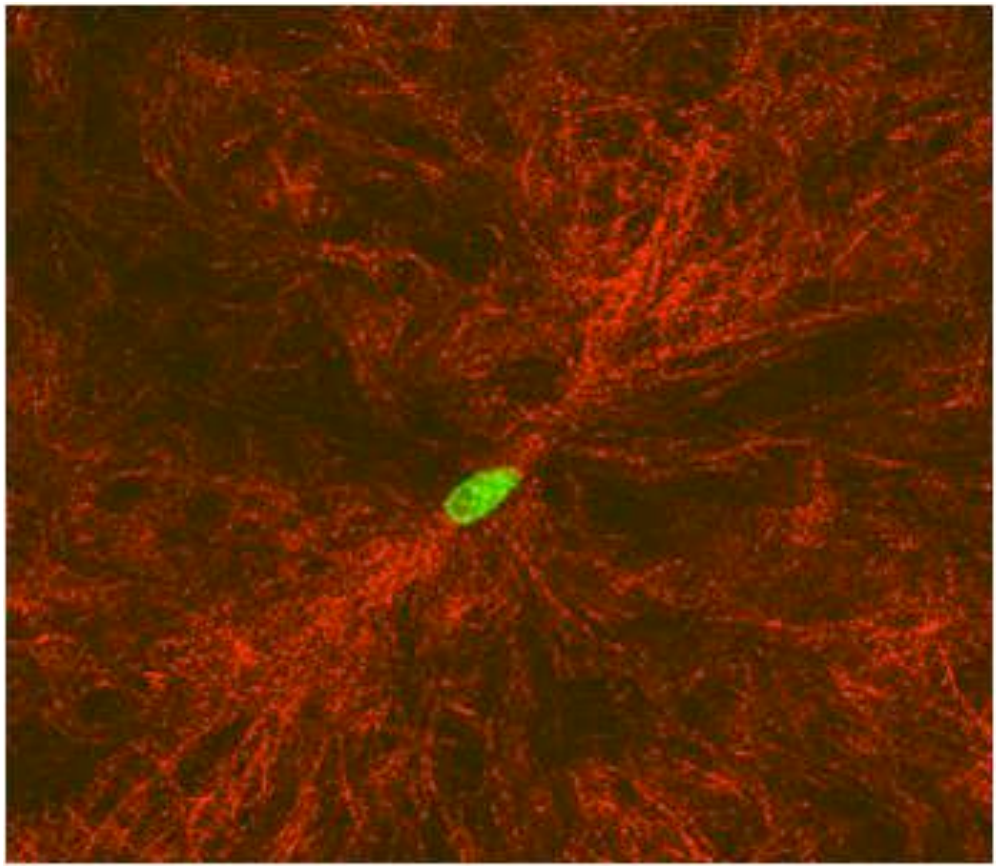


In vitro



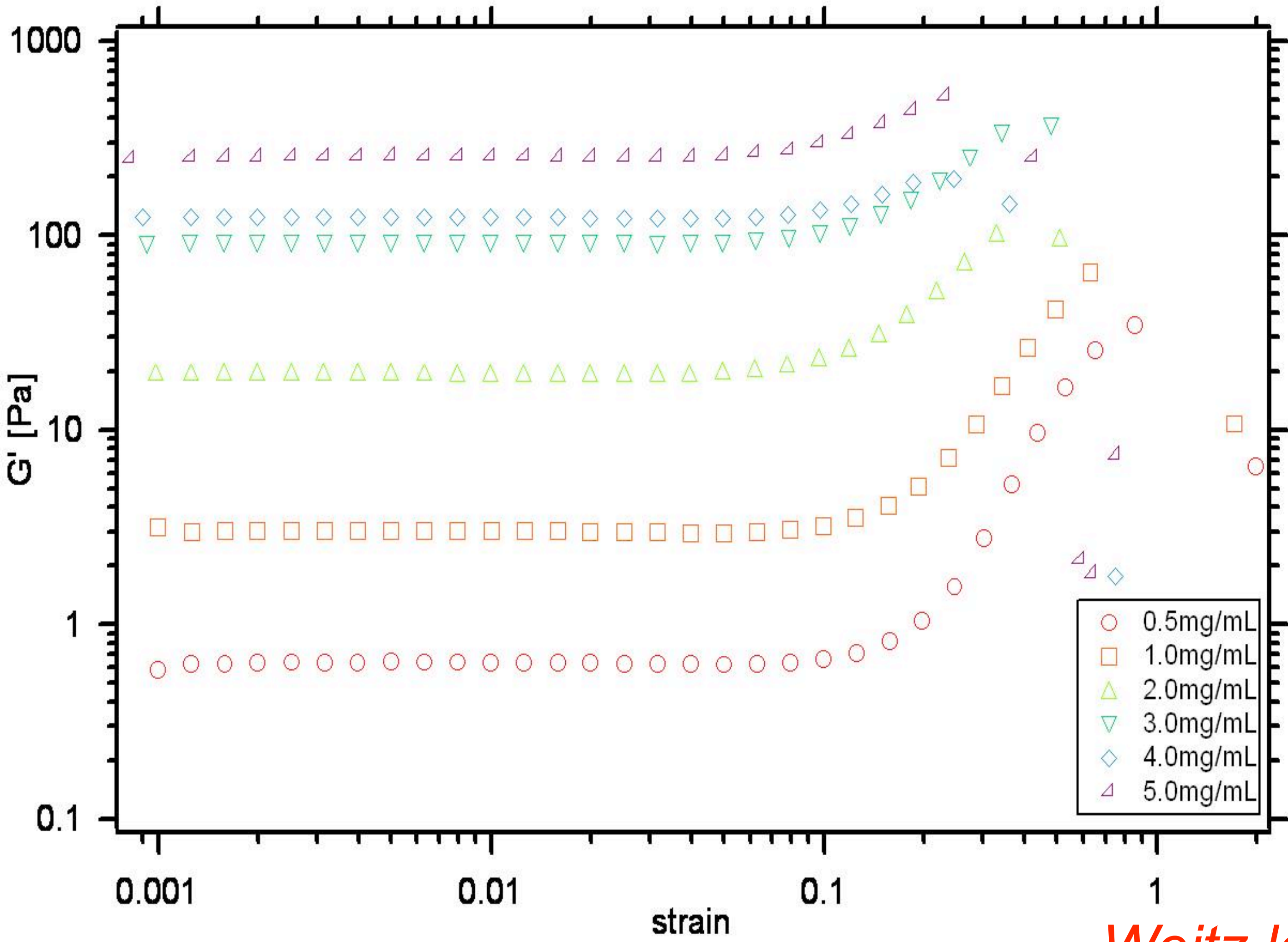
In vivo

Cell-ECM Interactions



David Weitz lab

ECM Mechanics



Weitz lab

Integrins

- 17 Integrin-α chains + 8 Integrin-β chains
  → 25 Integrins
- each integrin selectively binds ECM proteins
  ITG-α1/β1: collagen-I, collagen-IV and laminin; ITG-α5β1: fibronectin
- each integrin is expressed differently in different cell types

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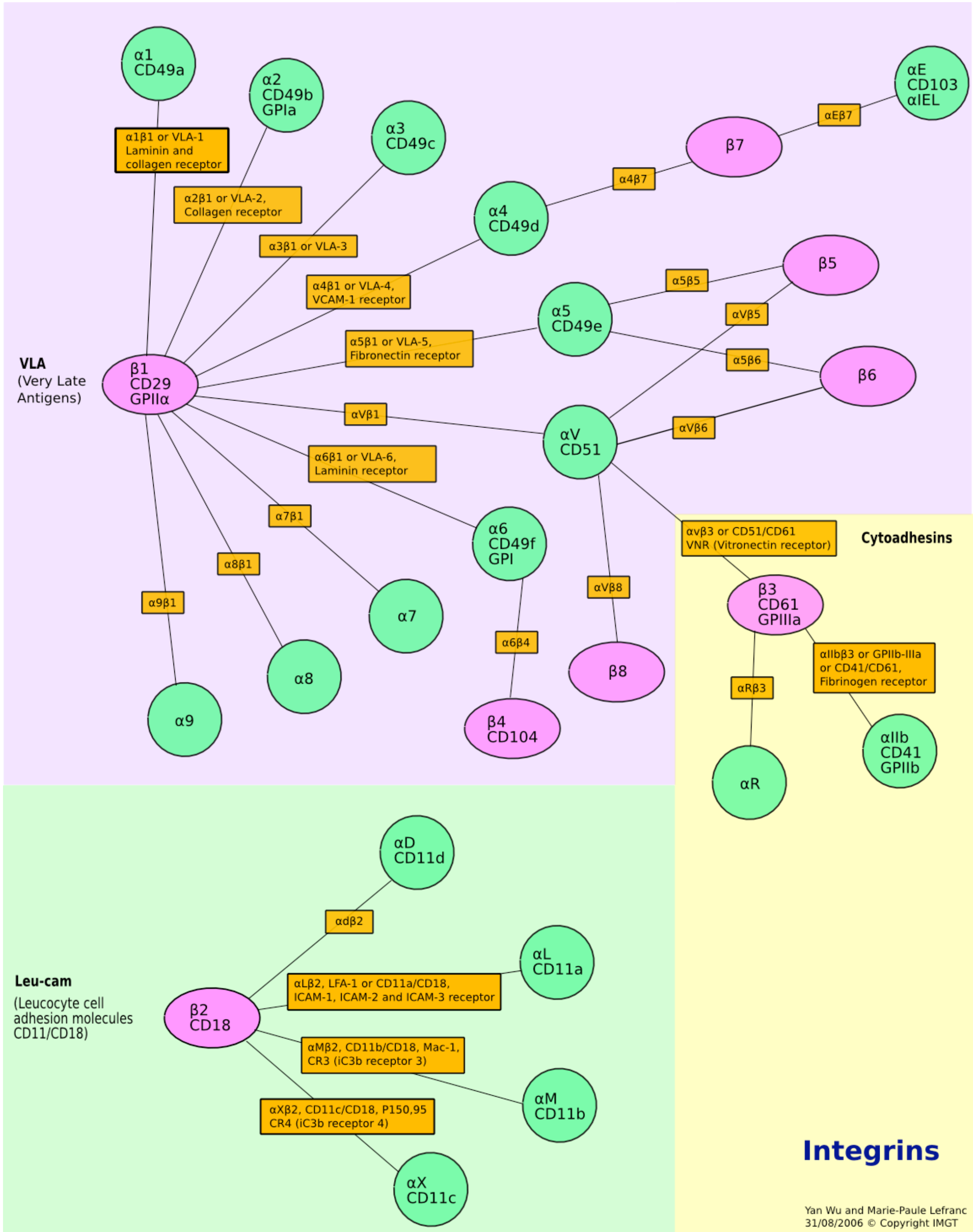
VLA
(Very Late Antigens)
α1 CD49a
α2 CD49b GPIa
α3 CD49c
α4 CD49d
α5 CD49e
α6 CD49f GPI
α7
α8
α9
αV CD51
αE CD103 αIEL
β1 CD29 GPIIα
β4 CD104
β5
β6
β7
β8
α1β1 or VLA-1 Laminin and collagen receptor
α2β1 or VLA-2, Collagen receptor
α3β1 or VLA-3
α4β1 or VLA-4, VCAM-1 receptor
α5β1 or VLA-5, Fibronectin receptor
αVβ1
α6β1 or VLA-6, Laminin receptor
α7β1
α8β1
α9β1
α4β7
αEβ7
α5β5
αVβ5
α5β6
αVβ6
αVβ8
α6β4
Cytoadhesins
αvβ3 or CD51/CD61 VNR (Vitronectin receptor)
β3 CD61 GPIIIa
αIIbβ3 or GPIIb-IIIa or CD41/CD61, Fibrinogen receptor
αRβ3
αR
αIIb CD41 GPIIb
Leu-cam
(Leucocyte cell adhesion molecules CD11/CD18)
β2 CD18
αD CD11d
αdβ2
αL CD11a
αLβ2, LFA-1 or CD11a/CD18, ICAM-1, ICAM-2 and ICAM-3 receptor
αM CD11b
αMβ2, CD11b/CD18, Mac-1, CR3 (iC3b receptor 3)
αX CD11c
αXβ2, CD11c/CD18, P150,95 CR4 (iC3b receptor 4)
Integrins
Yan Wu and Marie-Paule Lefranc
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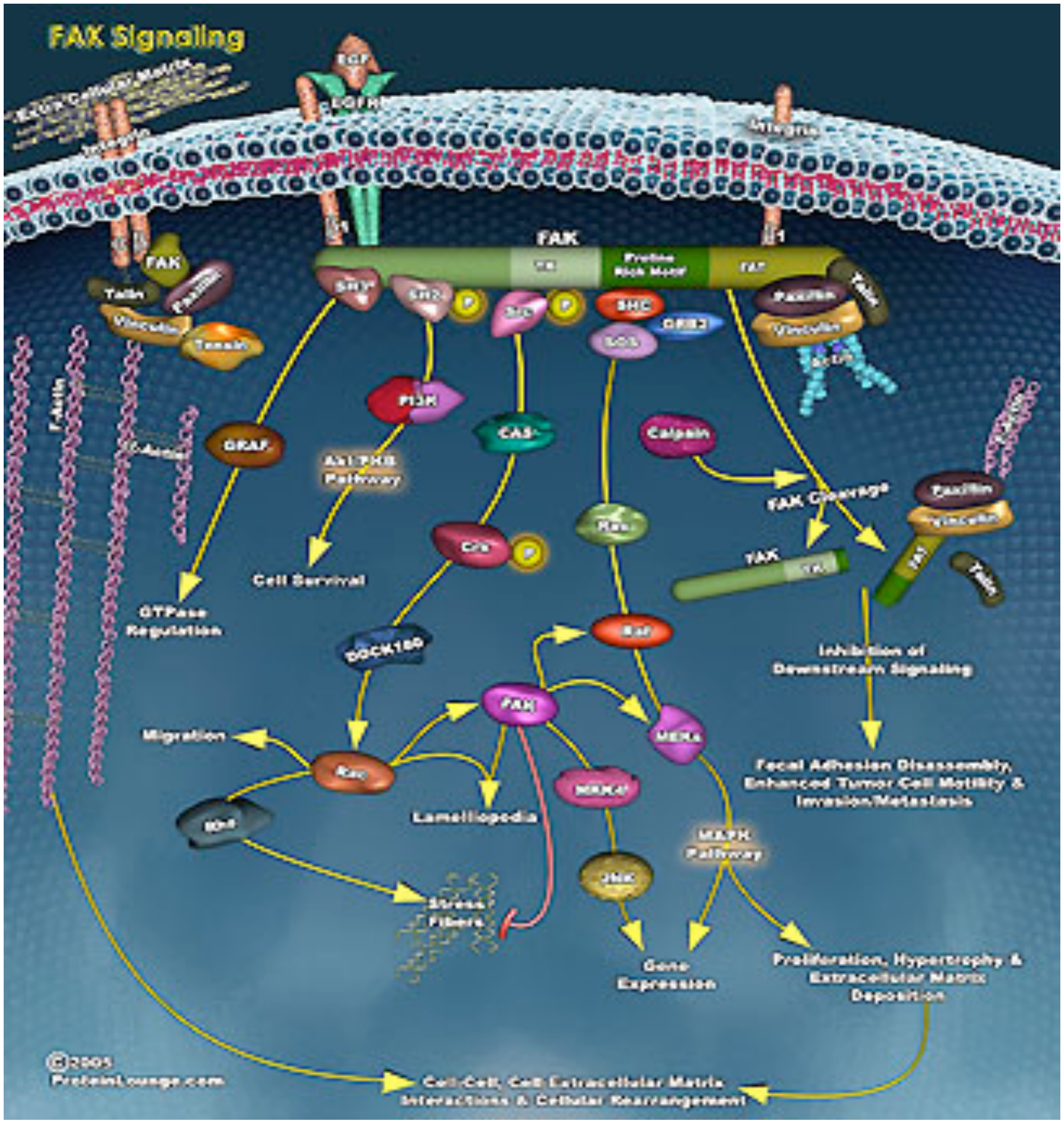
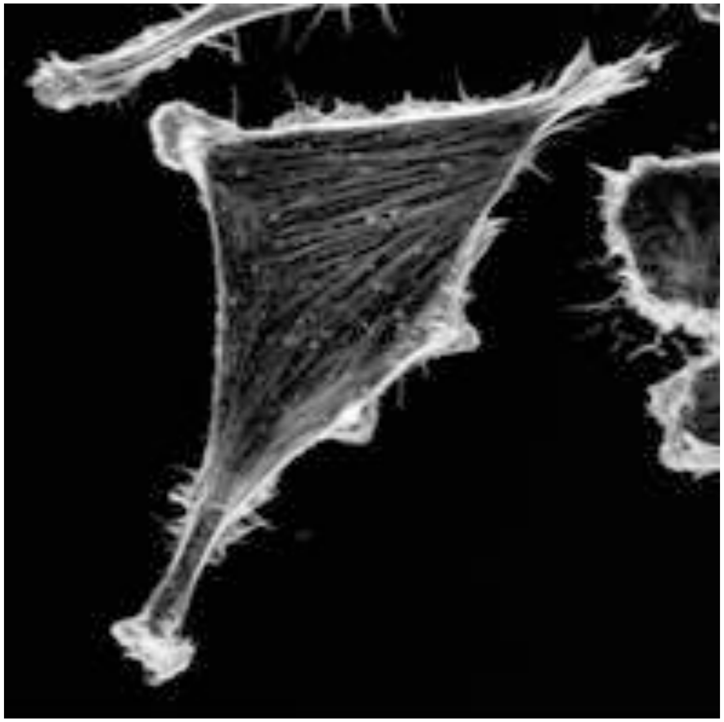
FAK Pathway



ProteinLaunge.com

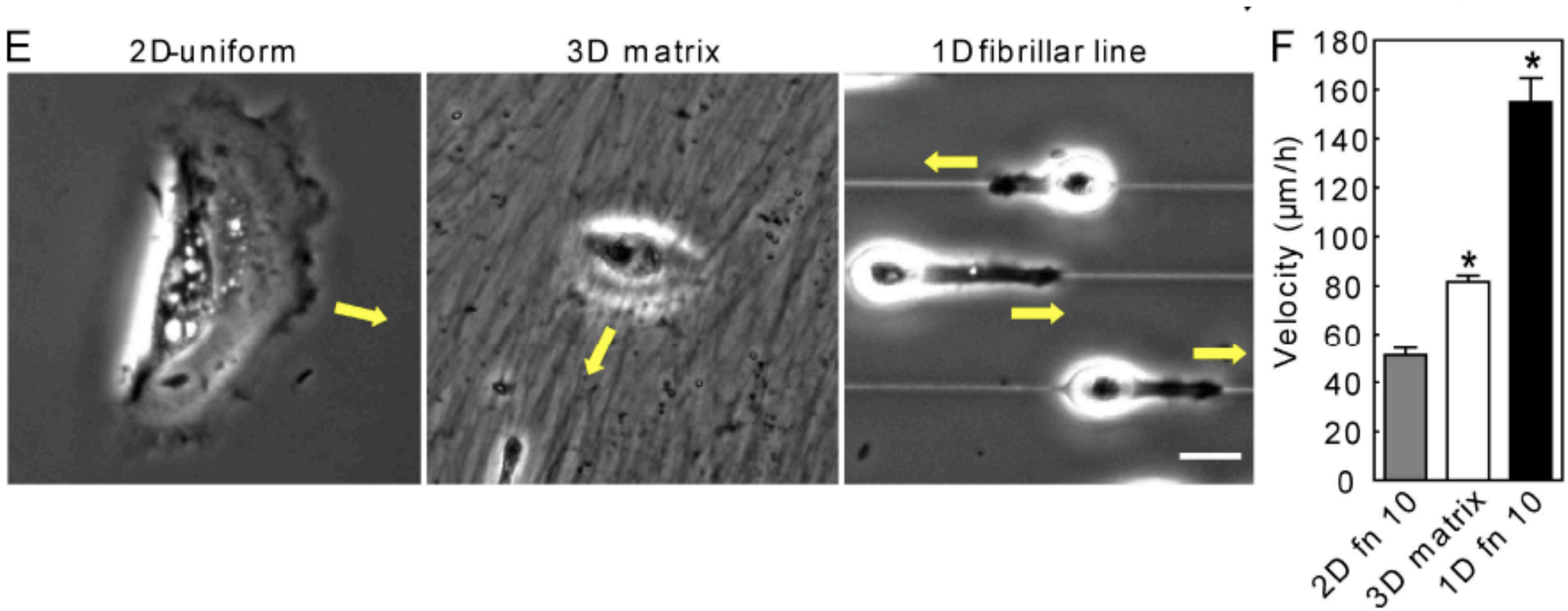
Mechano-transduction



Weitz lab

Growth, proliferation, polarization, migration, regulation of MMPs, cadherins…

Dimensionality



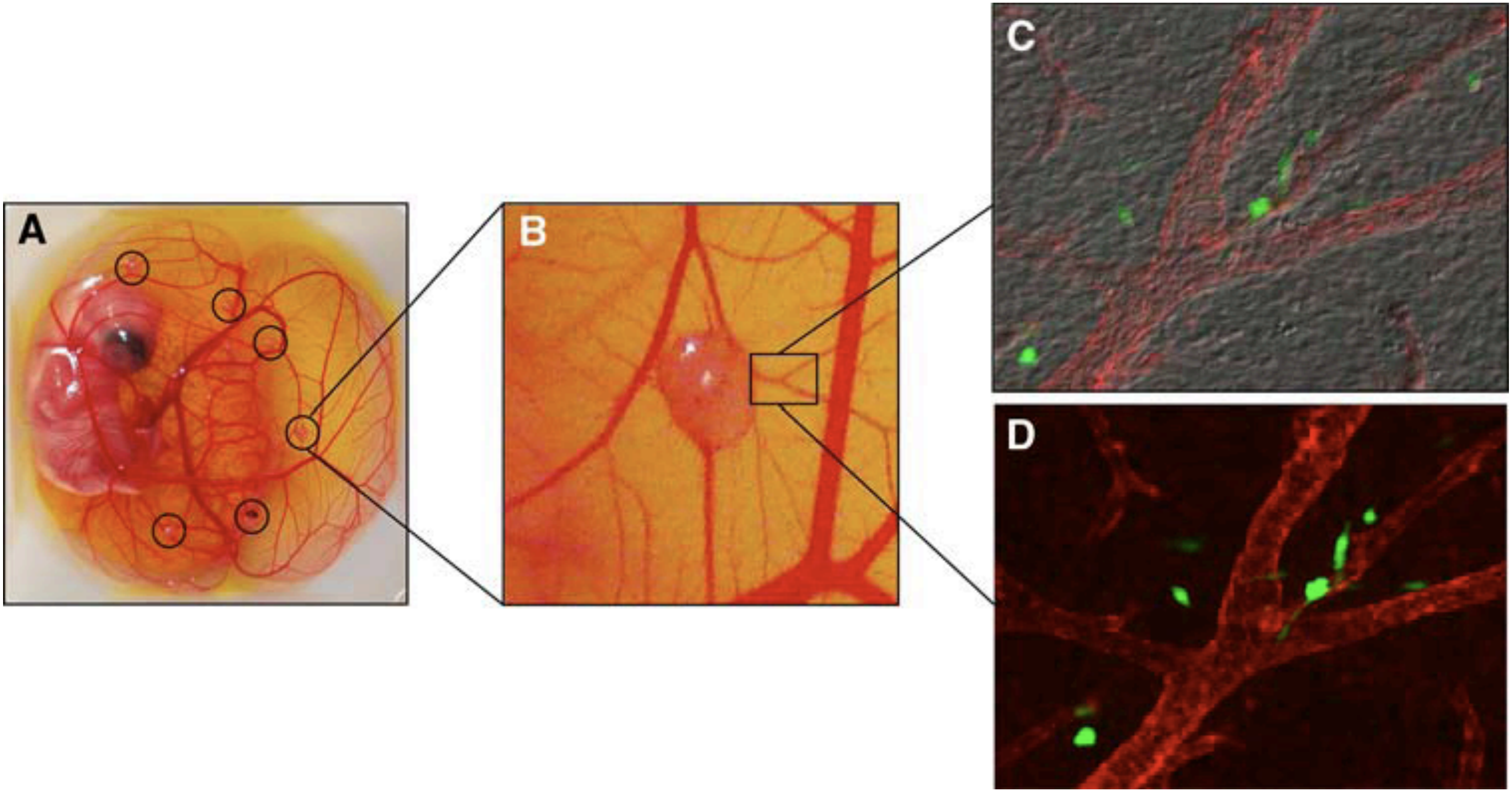
Doyle et al. JCB Report, 2009

Cell-Migration Hike at q-Bio 09

<u>when:</u> Friday afternoon (8/7/09)
<u>where:</u> Santa Fe ski basin day hike trail, meet at St. John's College
<u>who:</u> anyone interested

Tumor Invasion

- Migration: brain tumor (glioma, glioblastoma), breast cancer…
- http://www.youtube.com/marcuslab



Deryugina & Quigley, 2008

Summary

- Cell – tissue – organ level mechanistic study
- Cell-based, multiscale modeling framework for tumor growth and angiogenesis.
- Test hypotheses and generate hypotheses that can be tested experimentally
- Mathematical Model vs. in vitro model vs. in vivo animal model vs. in vivo human (model) vs. clinical cases
- ‘Simple but not simpler’

Los Alamos National Laboratory

Jim Freyer, Bryan Travis

Jelena Pjesivac, Charles Cantrell,

Amy Bauer, Kejing He,

Kevin Flores, Zhiying Sun

Trace Jackson, Jacques Nor

Amy Bauer

Tom Chen, Luisa Iruela-Arispe

Evan Zamir