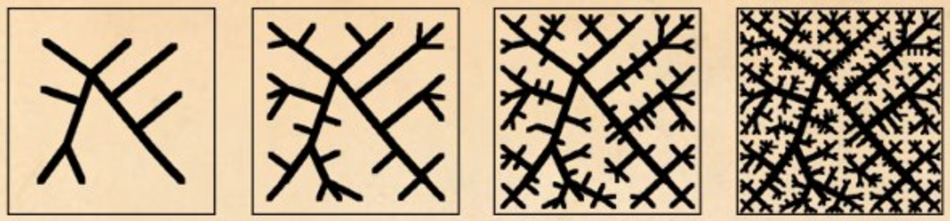
Marc E. Gottlieb, MD, FACS

A Professional Corporation

PLASTIC & RECONSTRUCTIVE SURGERY

Board Certification ••• ••• ••• *Plastic Surgery* ••• *Hand Surgery* ••• *General Surgery*



Specializing in the treatment, reconstruction, and management of
Acute and chronic wounds • Diseases and defects of the soft tissues • Injuries, diseases, and defects of the hand and extremities • Defects of the head and trunk

Office: 1415 N. 7th Avenue • Phoenix, AZ 85007 **Phone 602-252-3354** **Fax 602-254-7891** **megott@arimedica.com**

Marc E. Gottlieb, MD, FACS

1415 N. 7th Avenue
Phoenix, AZ 85007

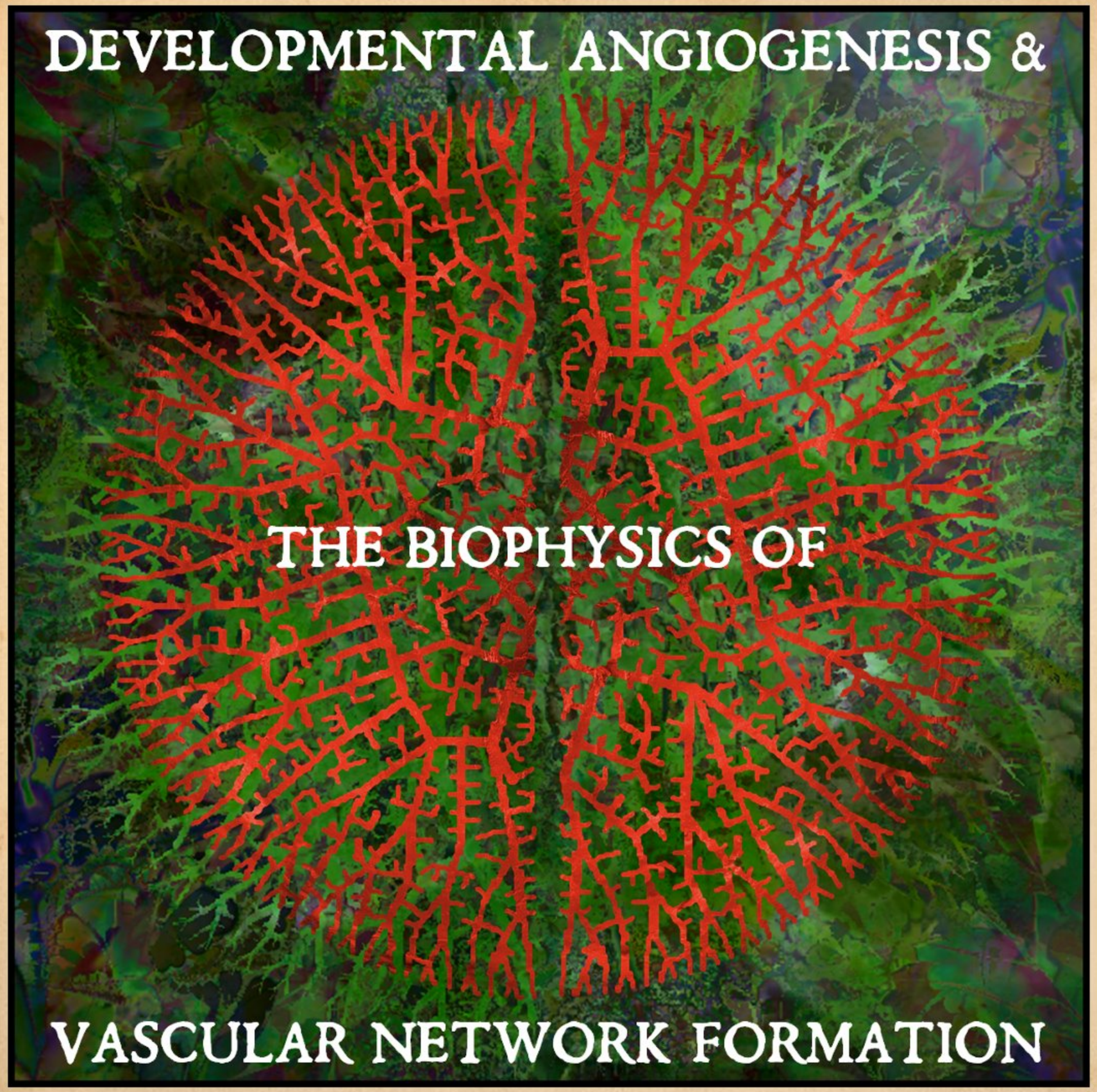
Phone 602-252-3354
Fax 602-254-7891

megott@arimedica.com

DEVELOPMENTAL ANGIOGENESIS & THE BIOPHYSICS OF VASCULAR NETWORK FORMATION

Original presentation May 16, 2006, Scottsdale, AZ
at the annual meeting of the Wound Healing Society

This is the original podium presentation.
Additional annotations pending.



Marc Gottlieb
MD

Phoenix
Arizona

THE CENTURY OF THE SYSTEM

WOUND HEALING - A CLOSED LOOP CONTROL SYSTEM

COAGULOPATHIC ULCERS - CRITERIA & NOMENCLATURE

Bioengineering and Systems Biology

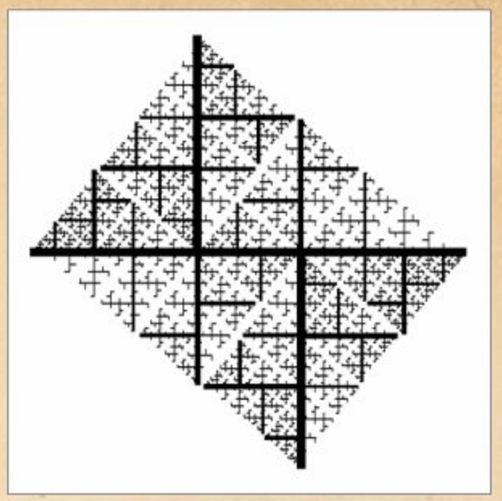
TREY IDEKER,[1] L. RAIMOND WINSLOW,[2] and A. DOUGLAS LAUFFENBURGER[3]

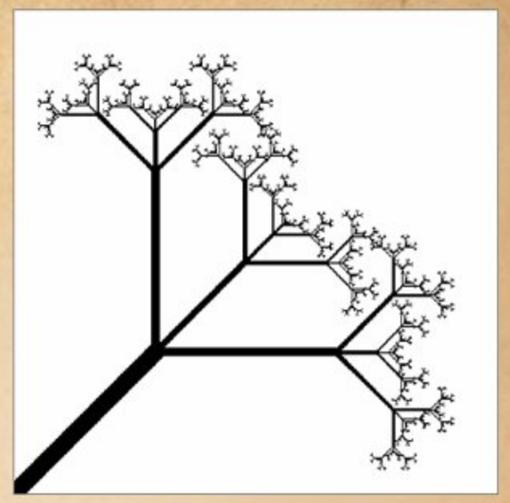
[1]Department of Bioengineering, University of California at San Diego; [2]Department of Biomedical Engineering, The Johns Hopkins University; and [3]Biological Engineering Division, Massachusetts Institute of Technology

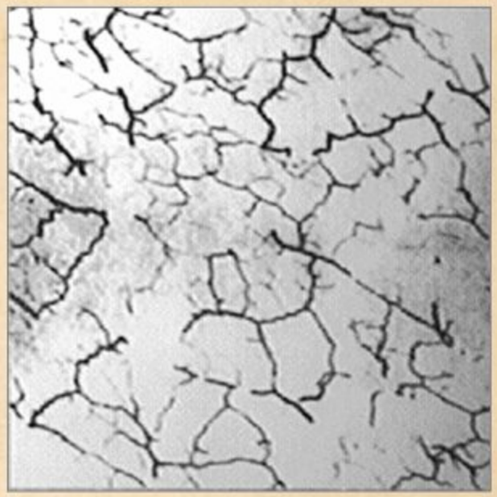
(Received 11 April 2005; accepted 23 November 2005; published online: 11 February 2006)

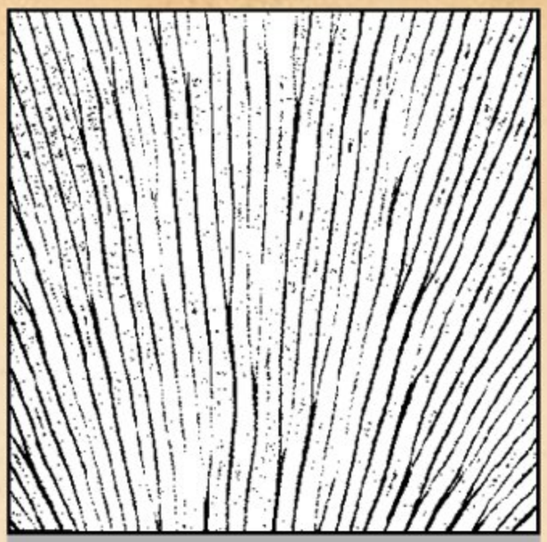
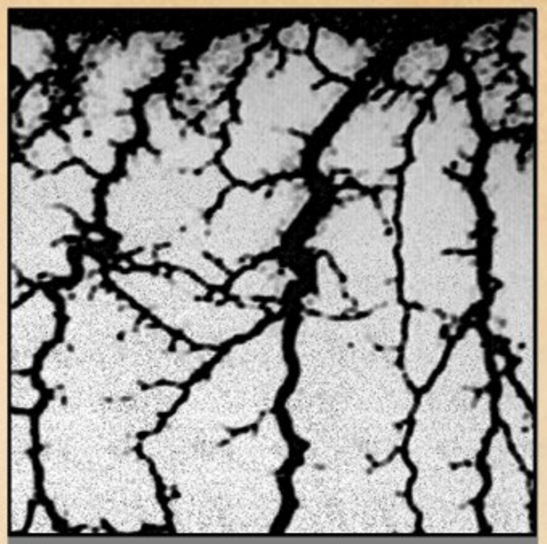
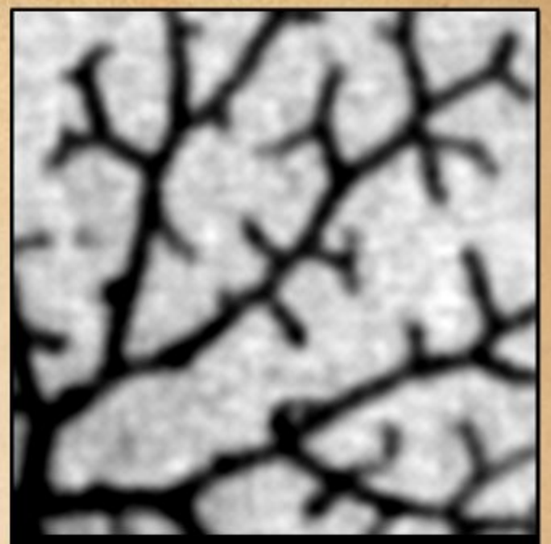
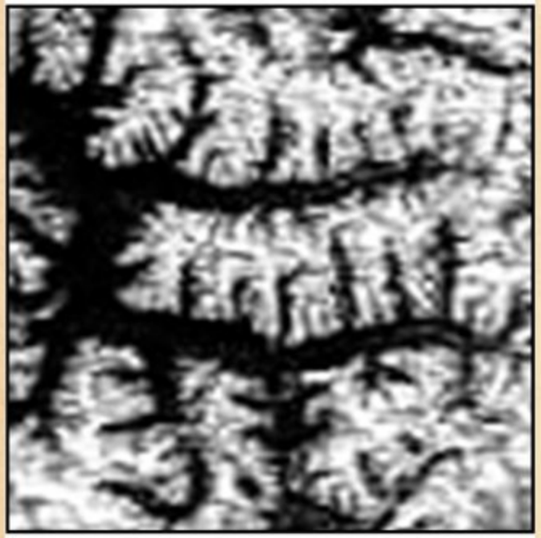
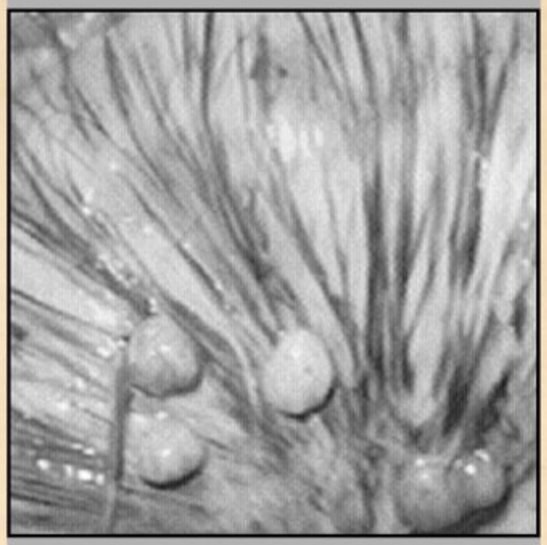
Annals of Biomedical Engineering, February, 2006

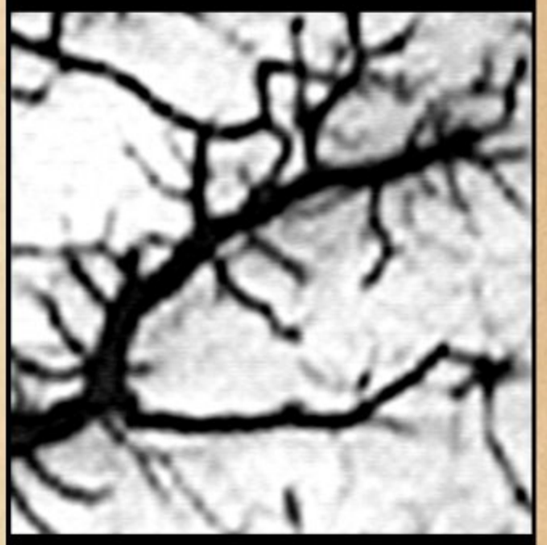
A field known as Systems Biology is emerging, from roots in the molecular biology and genomic biology revolutions—the succession of which has led biomedical scientists to recognize that living systems can be studied not only in terms of their mechanistic, molecular-level components but also in terms of many of them simultaneously. This computational algorithms for Mining the data to generate hypotheses concerning the potential interpretation of these data sets is necessary. In order to consequently develop new predictions for experimental test (or design), computational Modeling is required for similar reason: unaided human intuition likely cannot produce effective predictions concern-



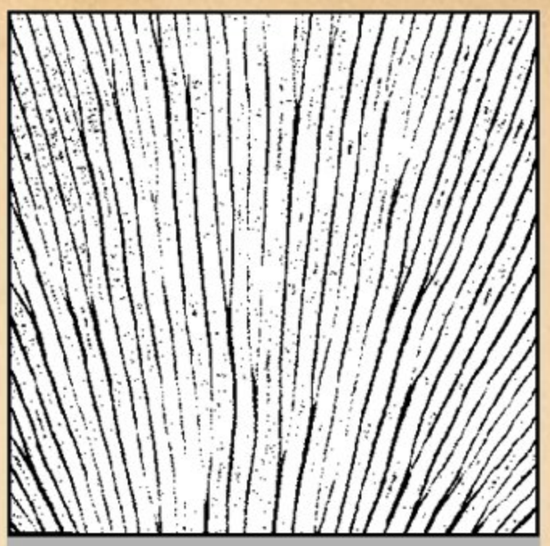


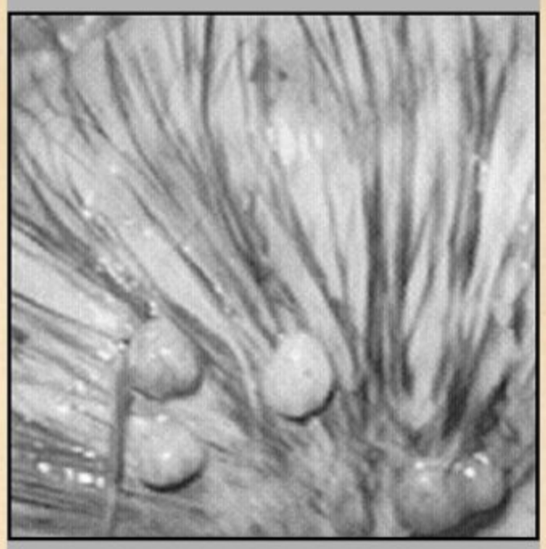






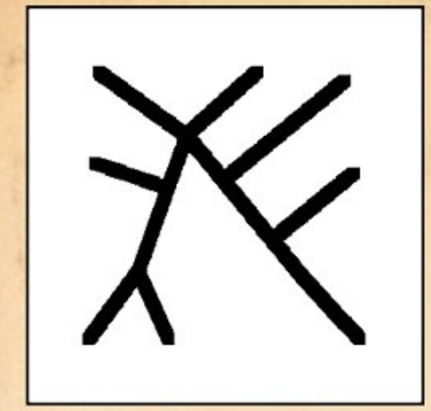


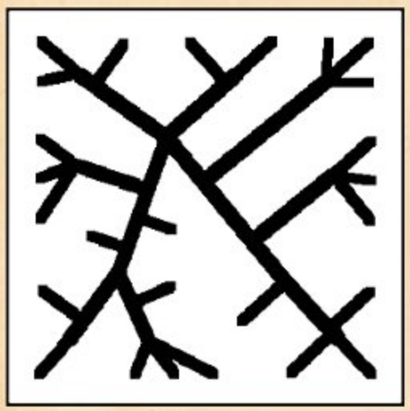


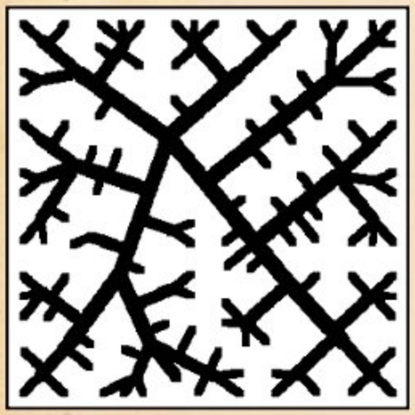
Angiogenesis is a life-and-death critical process.

VEGF & VEGFR genes are highly conserved across major taxa.

Multicellular life is impossible without angiogenesis and VEGF.





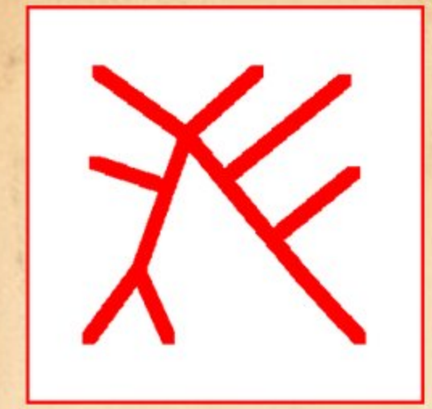


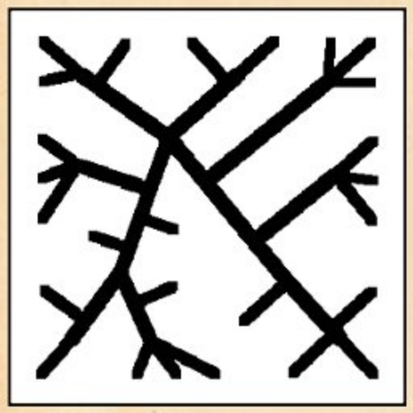
How do VEGF and the machinery of angiogenesis operate to create a vascular network?

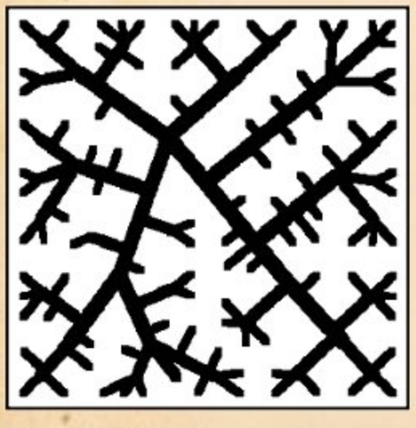
How little information is needed to engineer vascular networks, and how efficient is the process?

How does the system ensure that the life-and-death accuracy of the process is conserved?

What are the geometries and topologies of vascular networks, and why do other structures share them?







How do VEGF and the machinery of angiogenesis operate to create a vascular network?

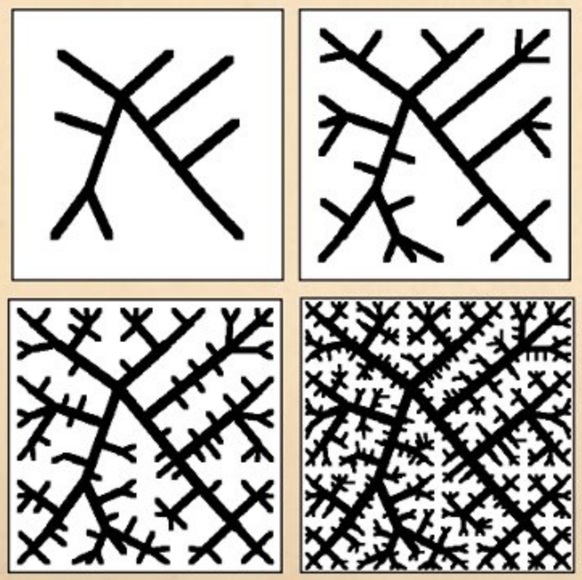
Developmental angiogenesis is a closed loop control system.

It depends on angiocytes, other cells, oxygen, angiogenic factors, and diffusion.

Angiogenesis is a purely reactive process, an error correcting response to perturbations created by growth.

THE VT MODEL OF ANGIOGENESIS

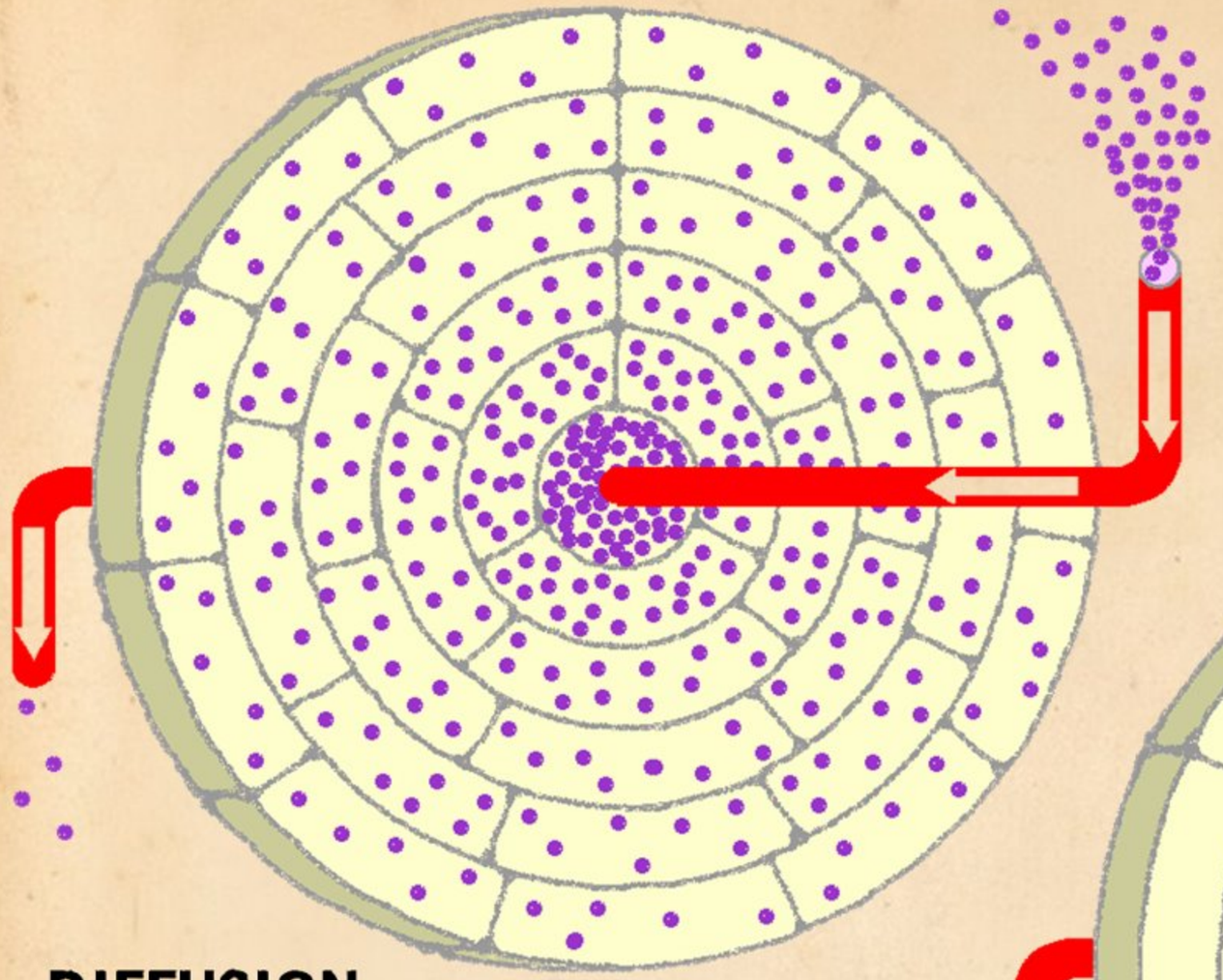
The Vascular neT Model of the Formation of Blood Vessels and Vascular Networks



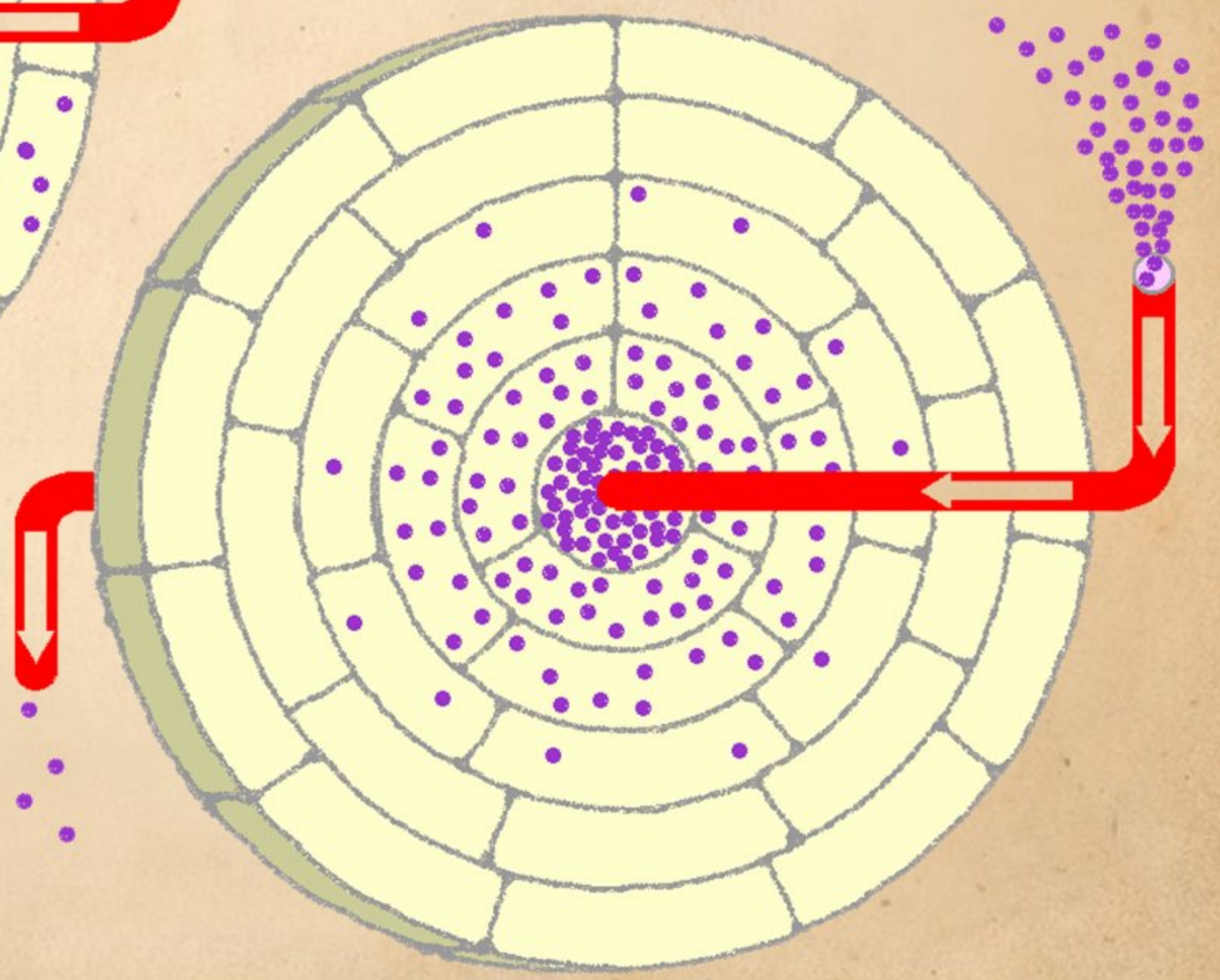
ARIMEDICA

www.arimedica.com

ANGIOGENIC PHYSIOLOGY - THE REAL NATURE

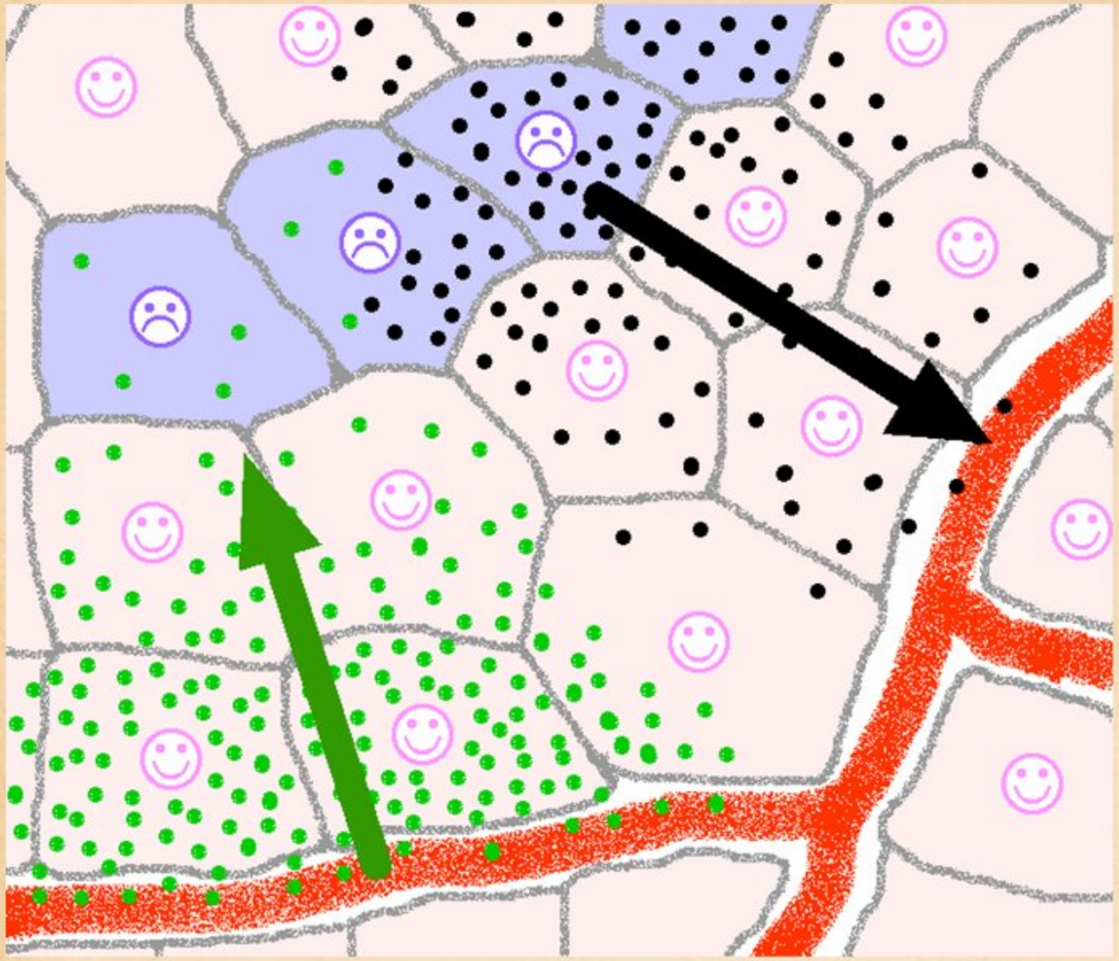


DIFFUSION
WITHOUT
CONSUMPTION



DIFFUSION
WITH
CONSUMPTION

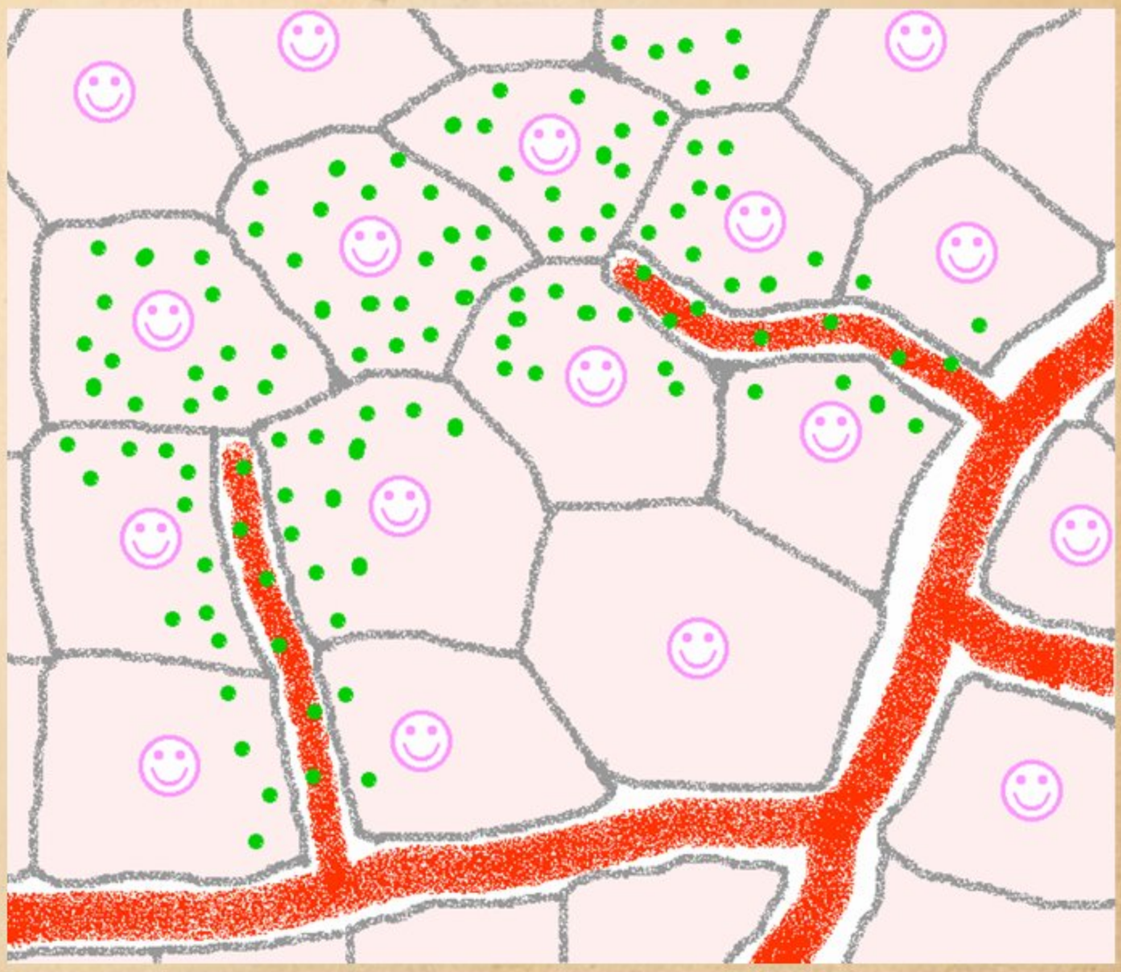
ANGIOGENIC PHYSIOLOGY - THE REAL NATURE



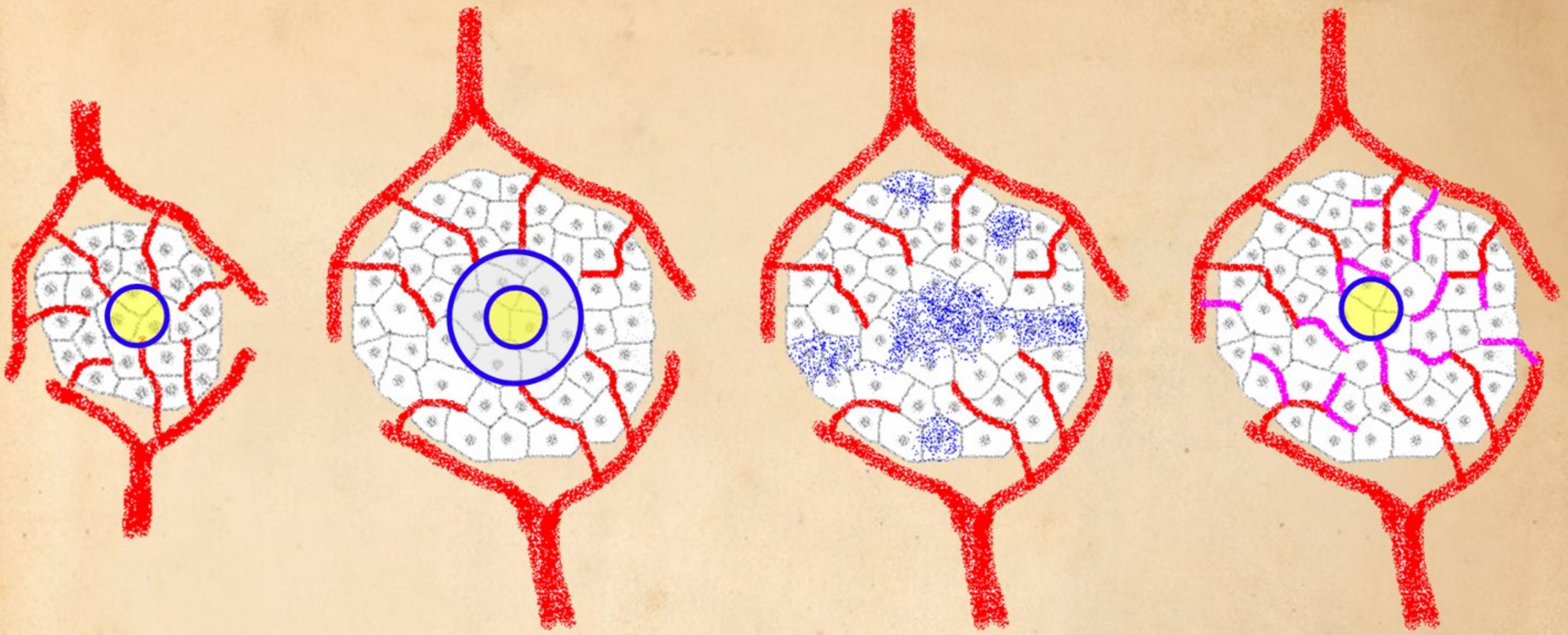
FORWARD DIFFUSION
OF OXYGEN

BACK DIFFUSION OF
ANGIOGENIC FACTORS

NEW
BLOOD VESSELS
RESTORE
OXYGEN SUPPLY



ANGIOGENIC PHYSIOLOGY - THE REAL NATURE

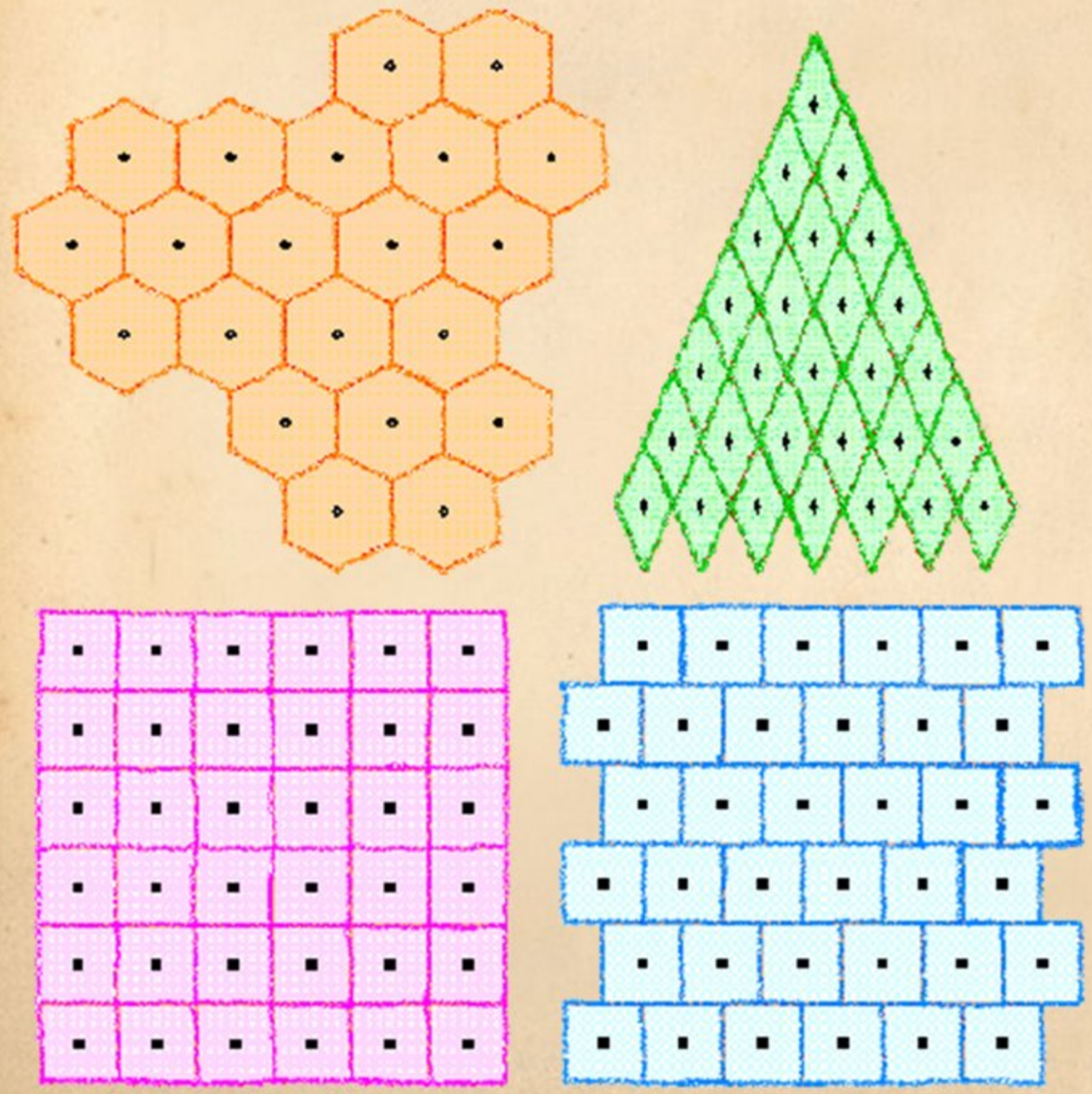


Current vessels	Isauxetic growth	Hypoxic cells	Angiogenic response
Short distances	Increased distances	Release AFs	Restored distances
Adequate oxygen	Inadequate oxygen	Tropic stimulus	Adequate oxygen

COMPUTER ANGIOGENESIS - RECREATING NATURE

STEP 1A

TISSUE & GROWTH MODELS

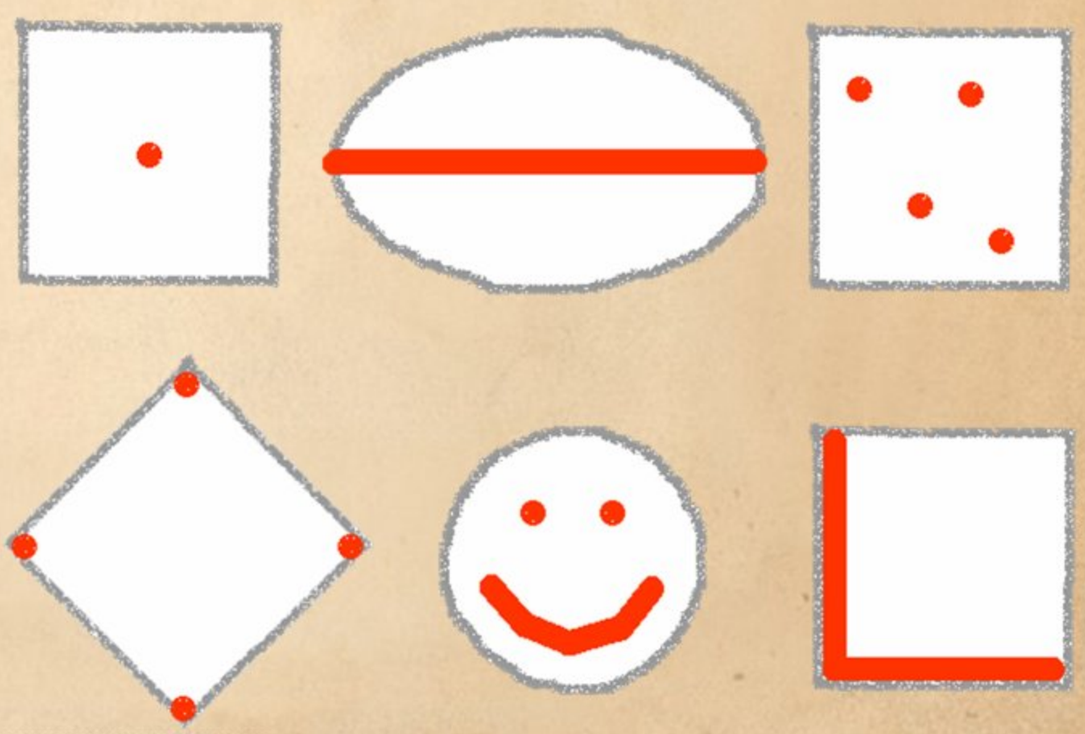


STEP 1

SETUP

Computer modeling of angiogenesis starts here.

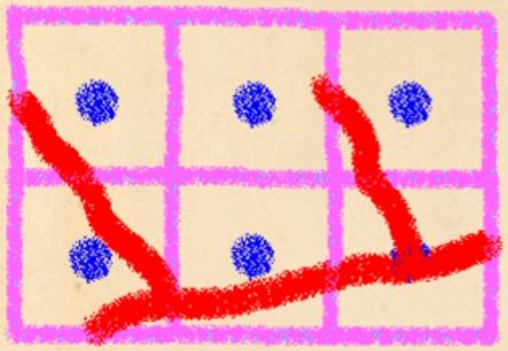
STEP 1B SEED VESSELS



COMPUTER ANGIOGENESIS - RECREATING NATURE

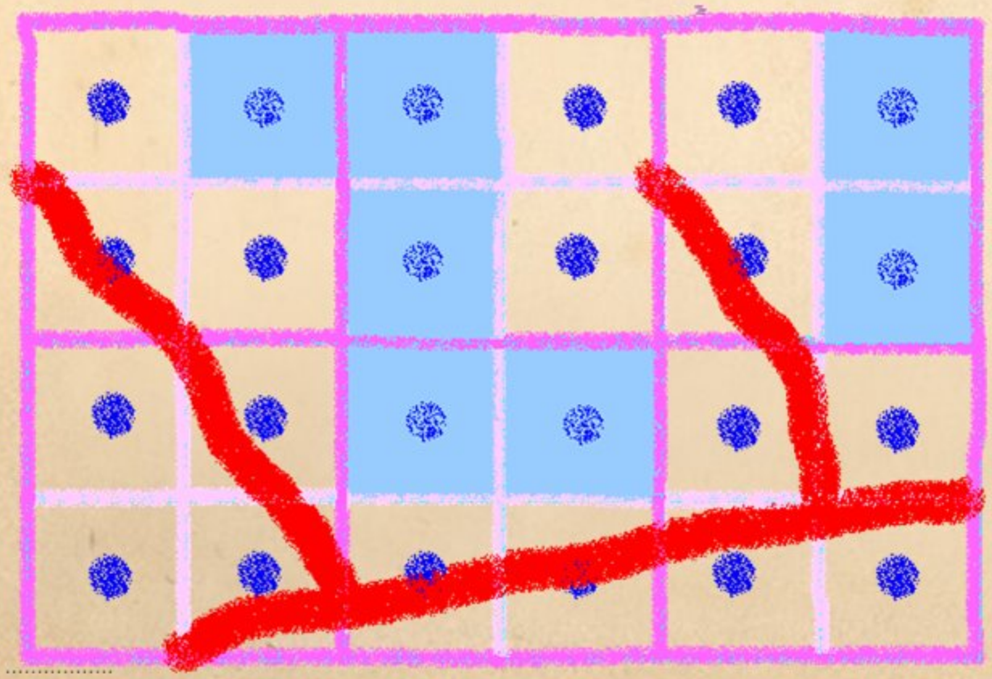
STEP 2 GROWTH

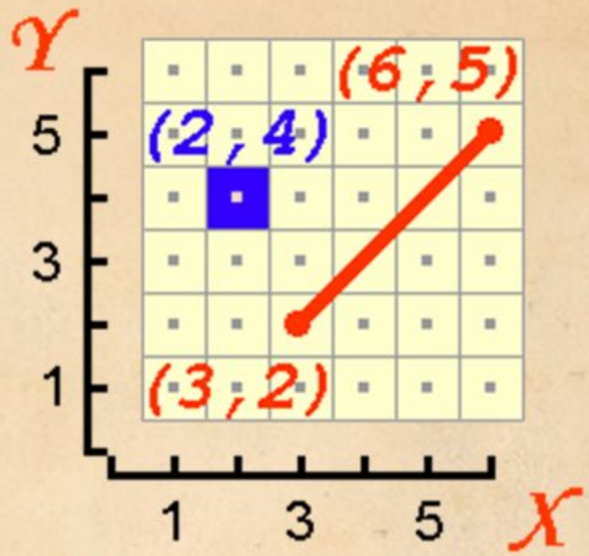
This is the start of the Main Loop
"ISAUXESIS"



STEP 2A

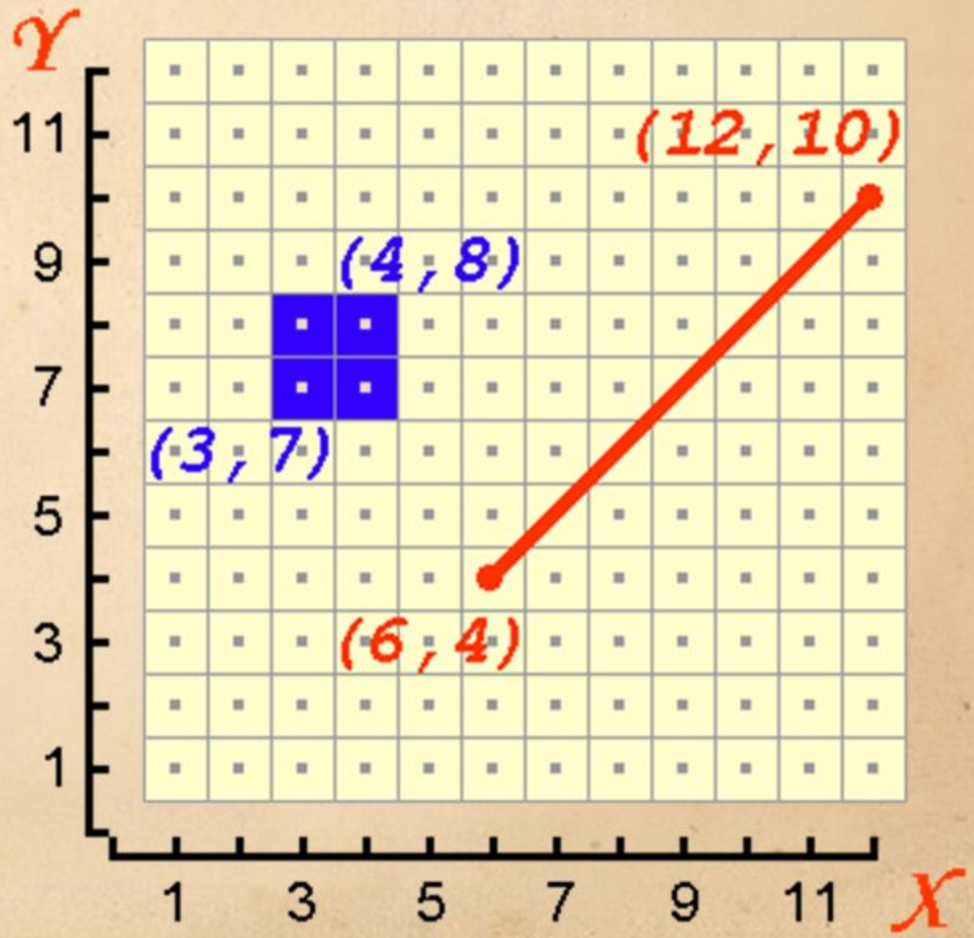
GROW THE TISSUE





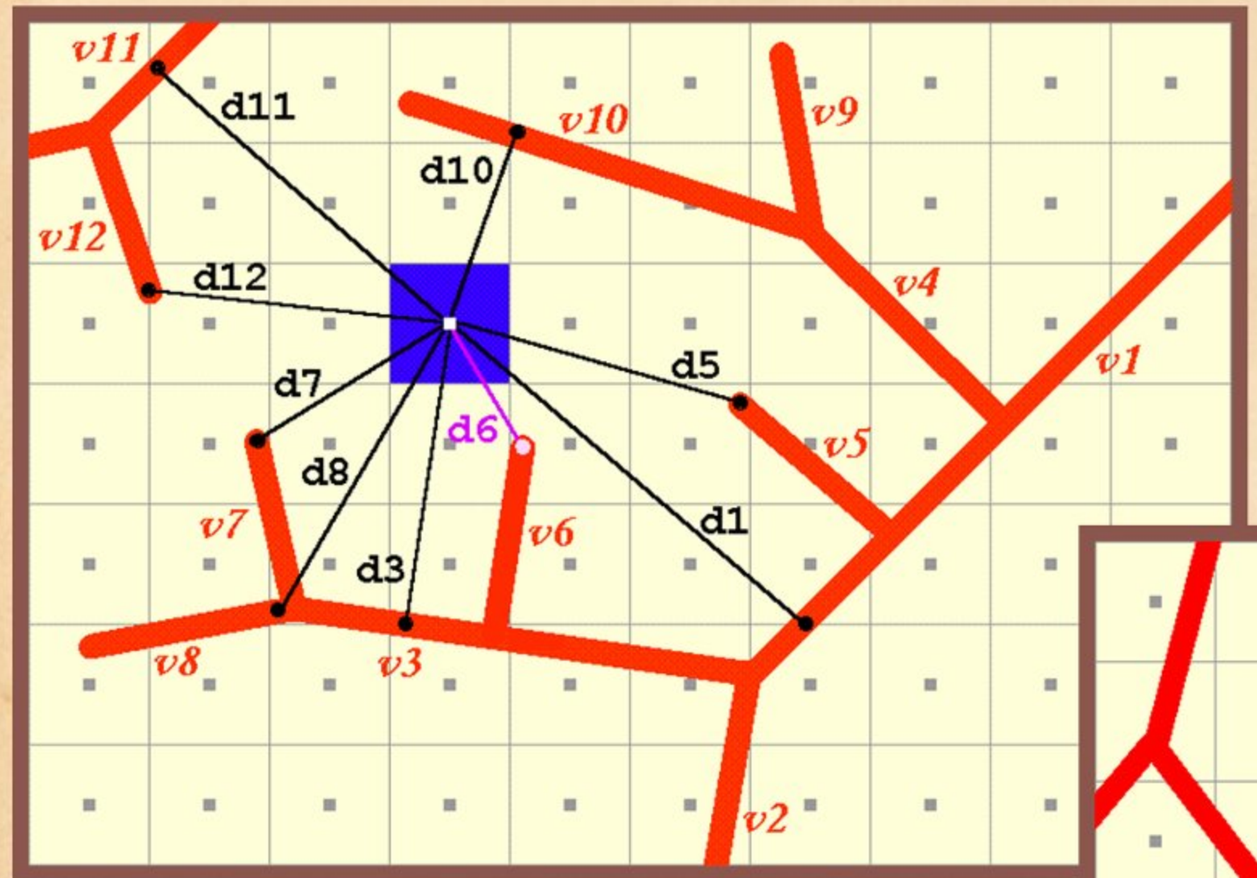
STEP 2B

MATCHING VESSEL GROWTH



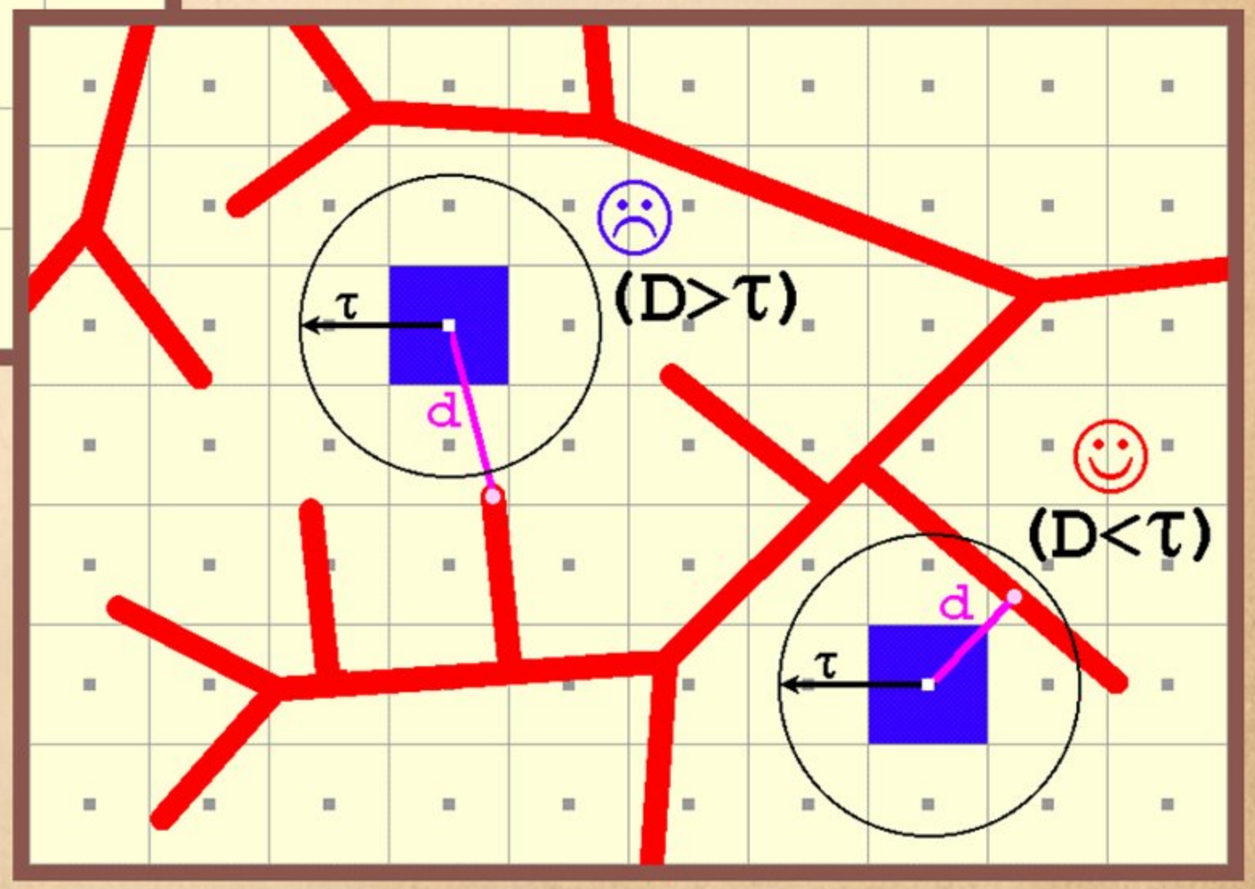
COMPUTER ANGIOGENESIS - RECREATING NATURE

STEP 3A FIND DISTANCE



STEP 3
ISCHEMIA TESTING

STEP 3B TEST FOR ISCHEMIA



Intrinsic Parameter # 1

τ

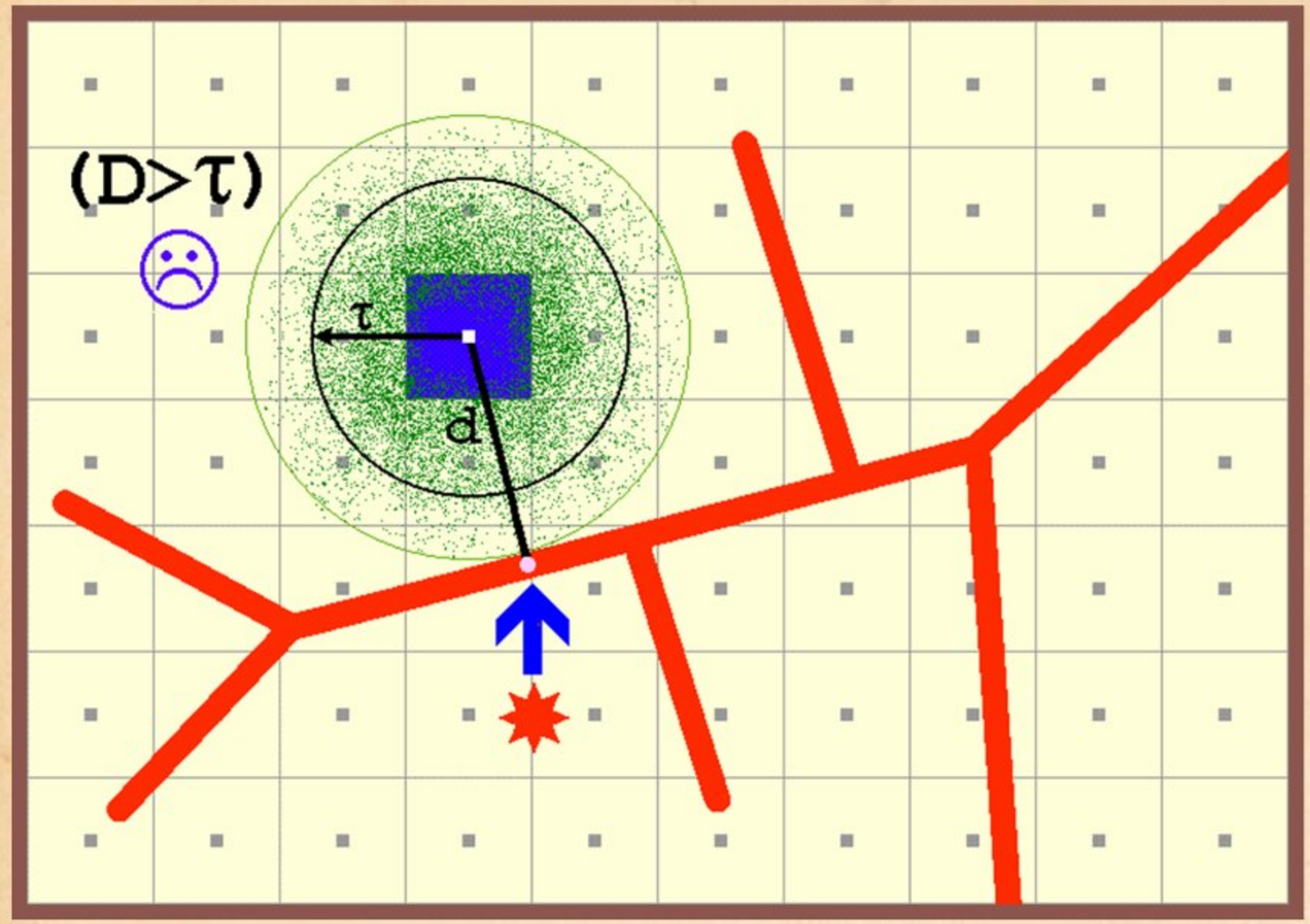
ischemia threshold

$D > \tau$

=

ischemia

COMPUTER ANGIOGENESIS - RECREATING NATURE



STEP 4
SPROUTING

STEP 4A **ORIGINATE**

parameters

=

one + *three*

G Extrinsic Element # 0
growth model

τ Intrinsic Parameter # 1
ischemia threshold

R Intrinsic Parameter # 2
vessel reach

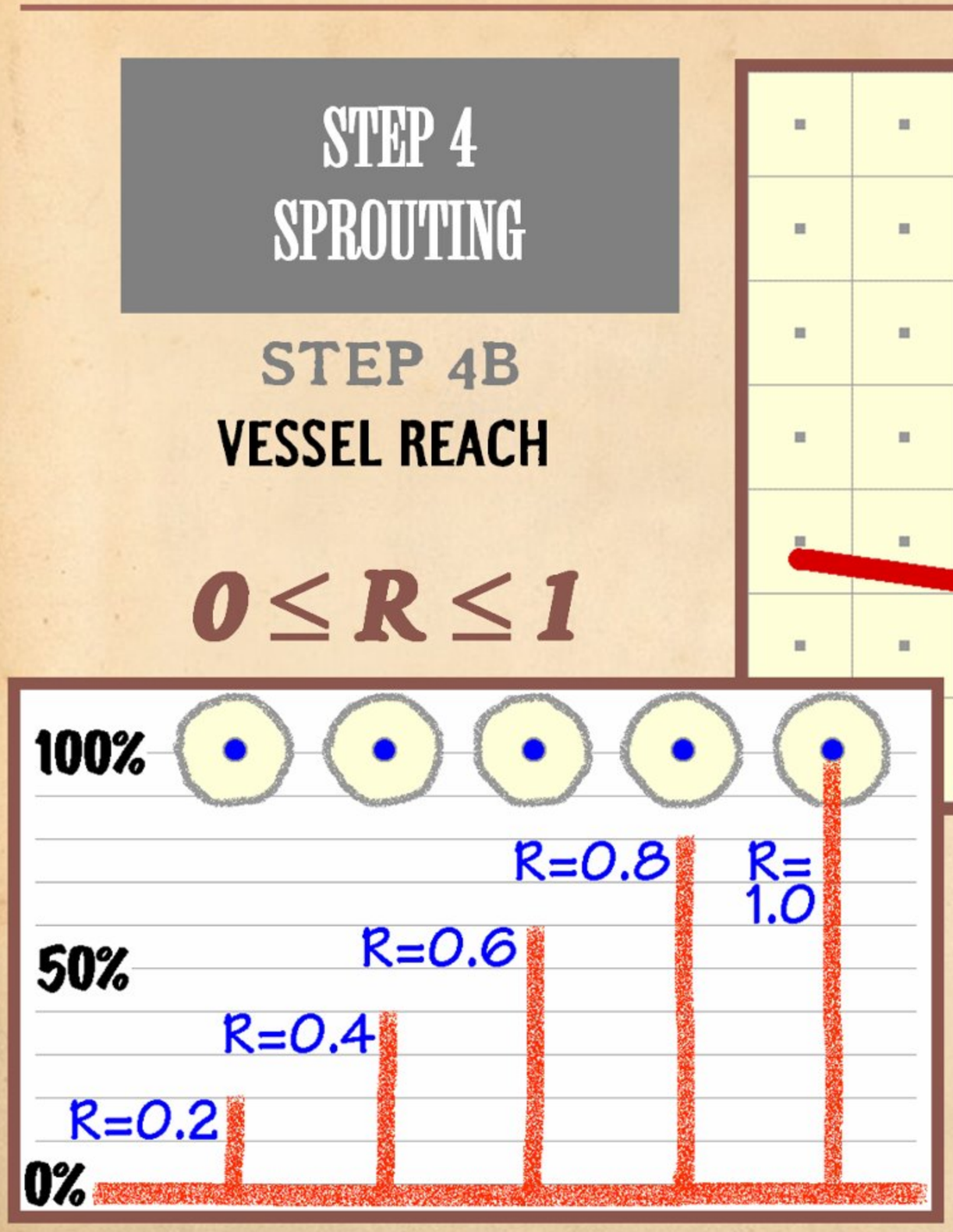
A Intrinsic Parameter # 3
multiple sprout zone

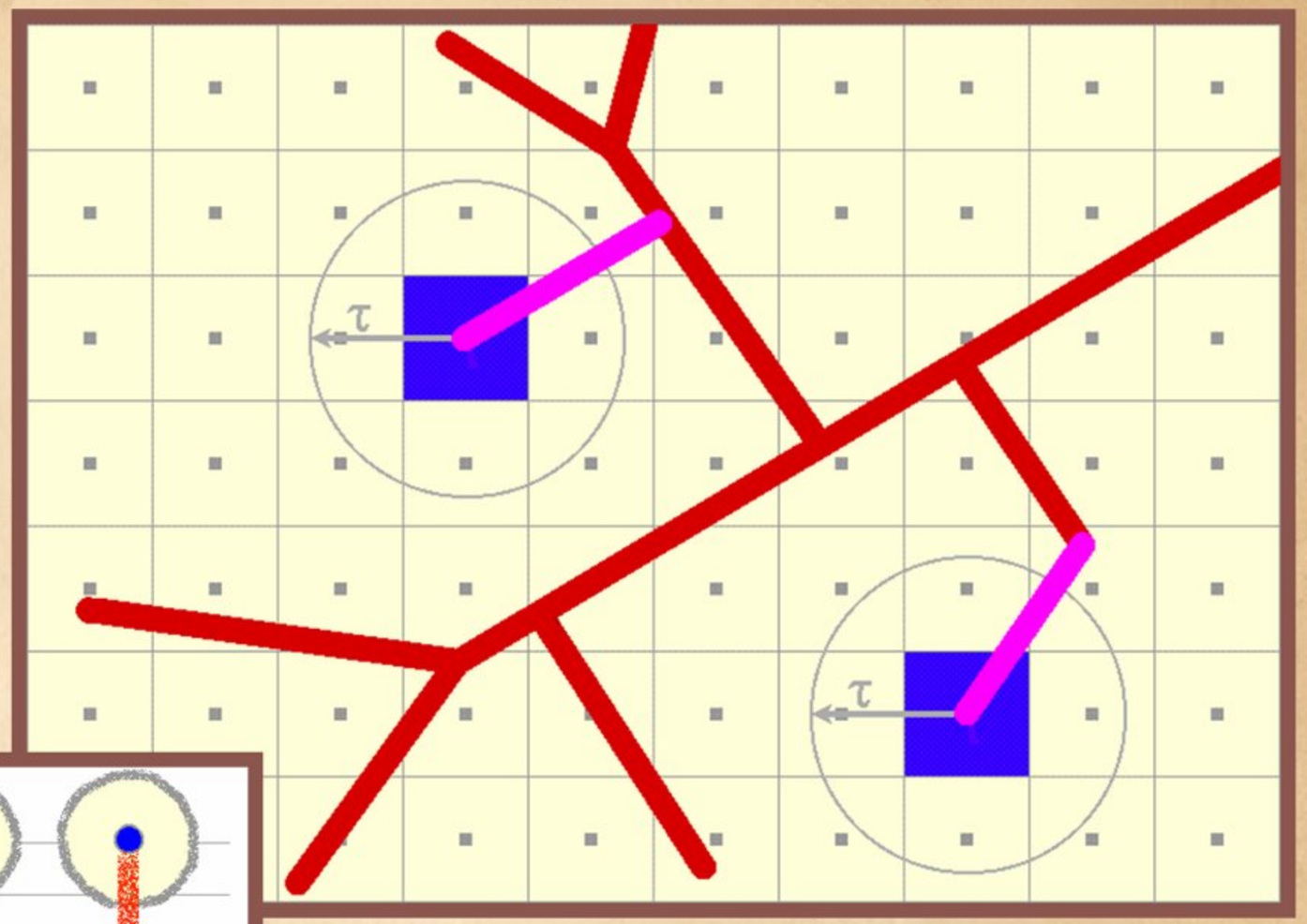
COMPUTER ANGIOGENESIS - RECREATING NATURE

STEP 4
SPROUTING

STEP 4B
VESSEL REACH

$0 \leq R \leq 1$





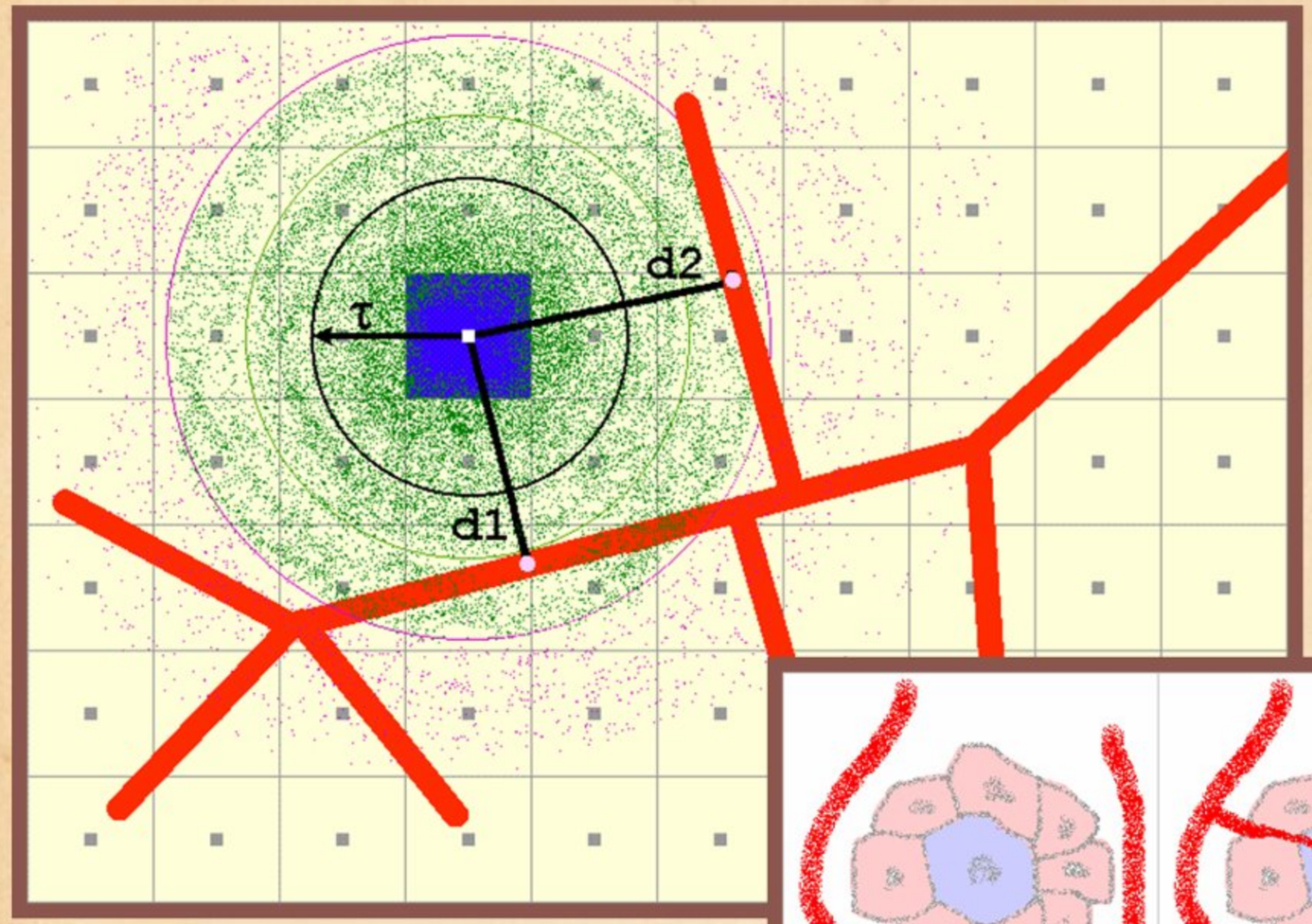
two constructs

Intrinsic Parameter # 2

R

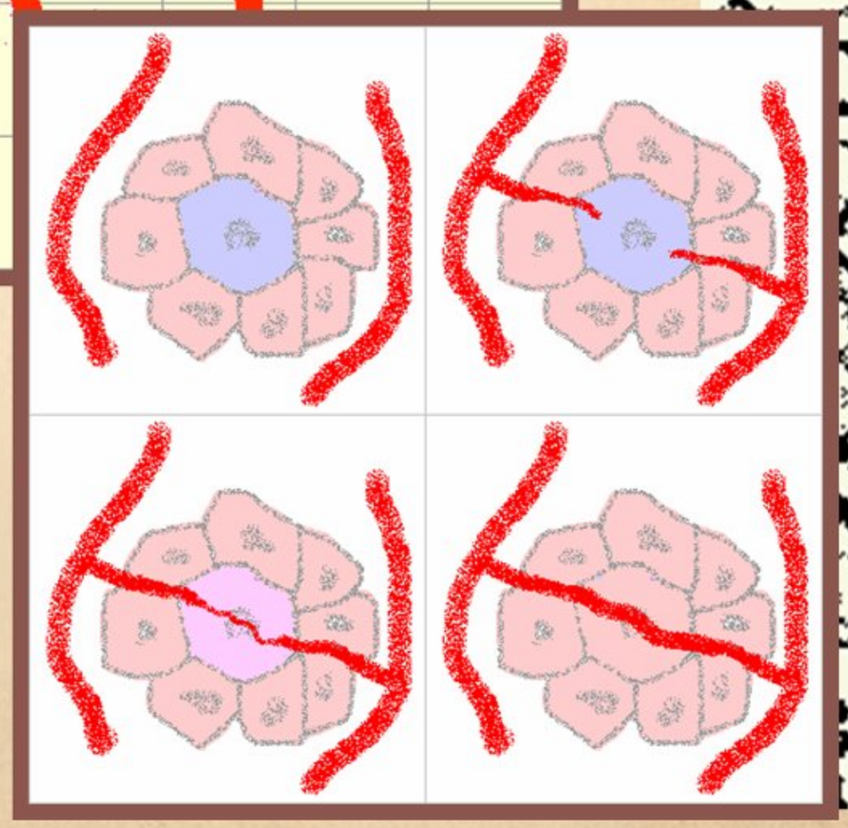
vessel reach

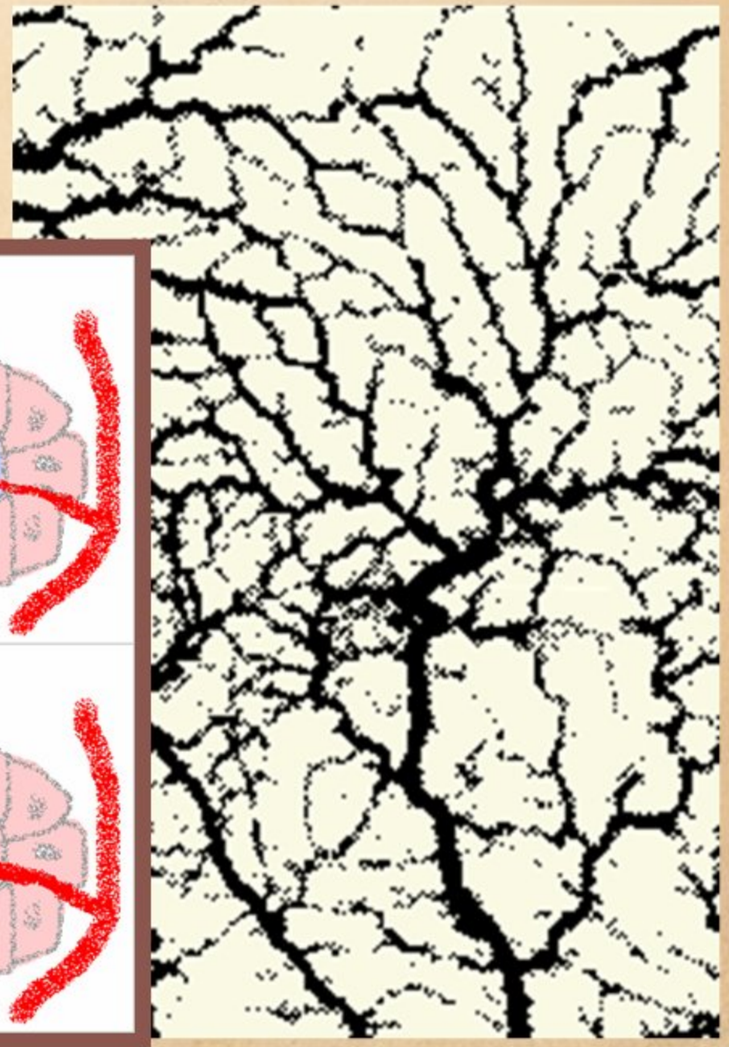
COMPUTER ANGIOGENESIS - RECREATING NATURE



STEP 4
SPROUTING

STEP 4C MULTIPLES





anastomoses

Intrinsic Parameter # 3

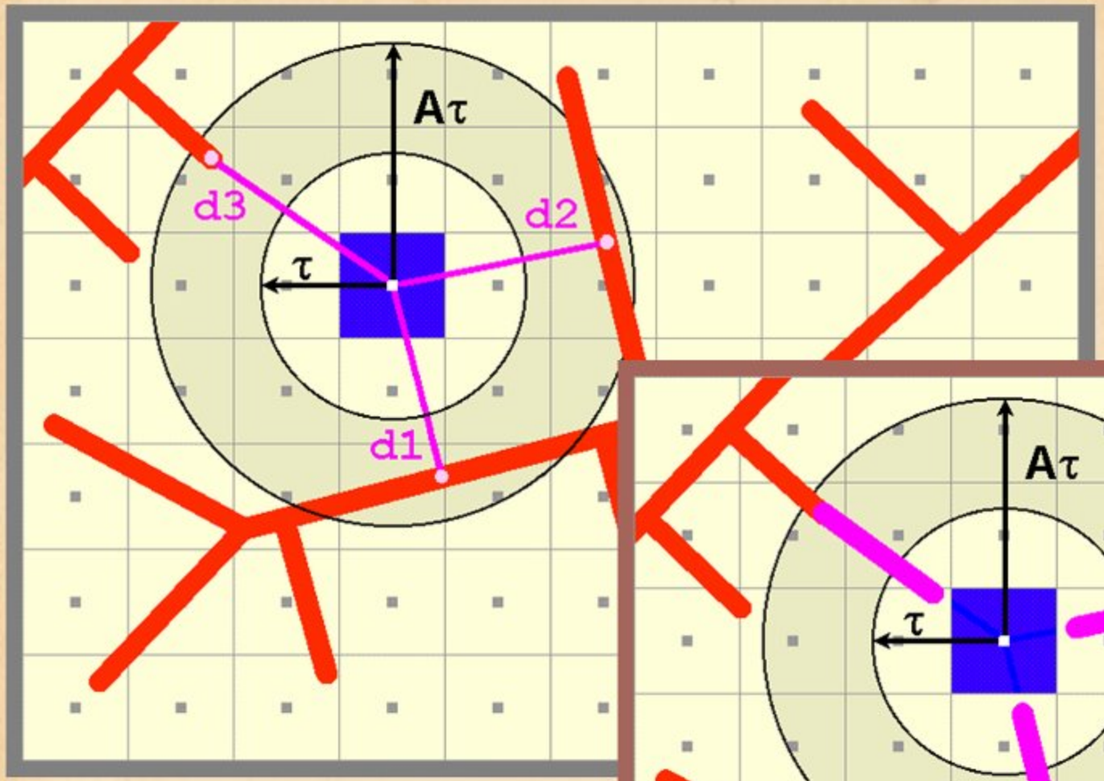
A

multiple sprout zone

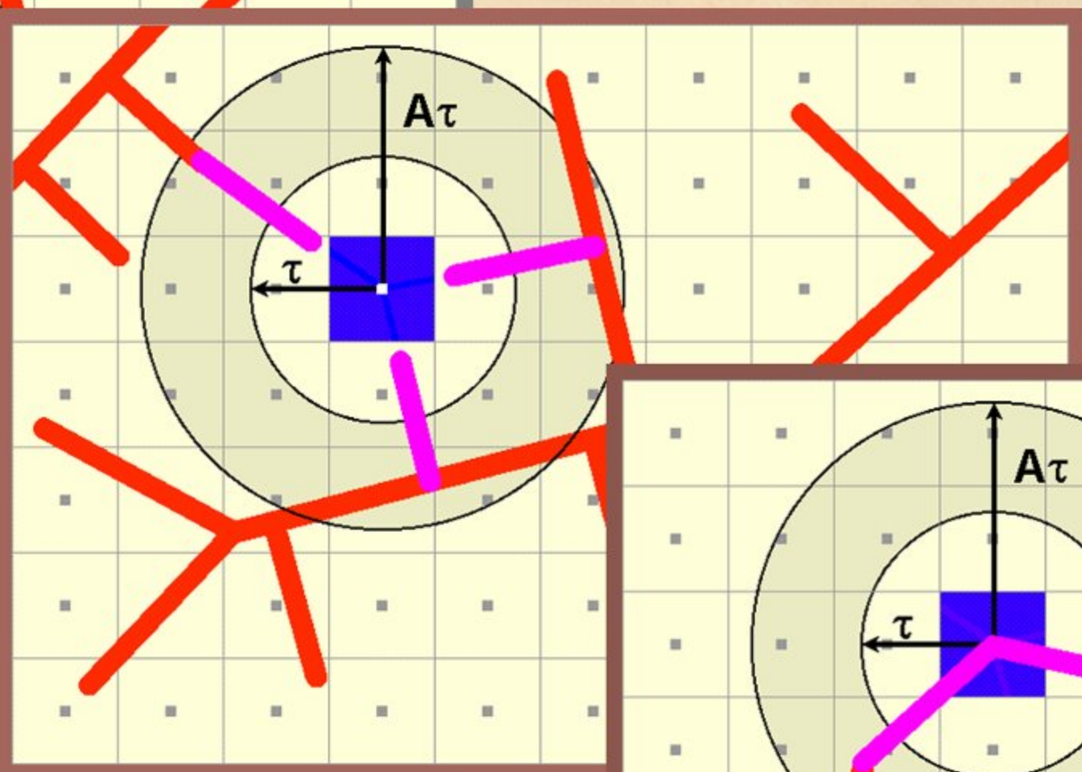
COMPUTER ANGIOGENESIS - RECREATING NATURE

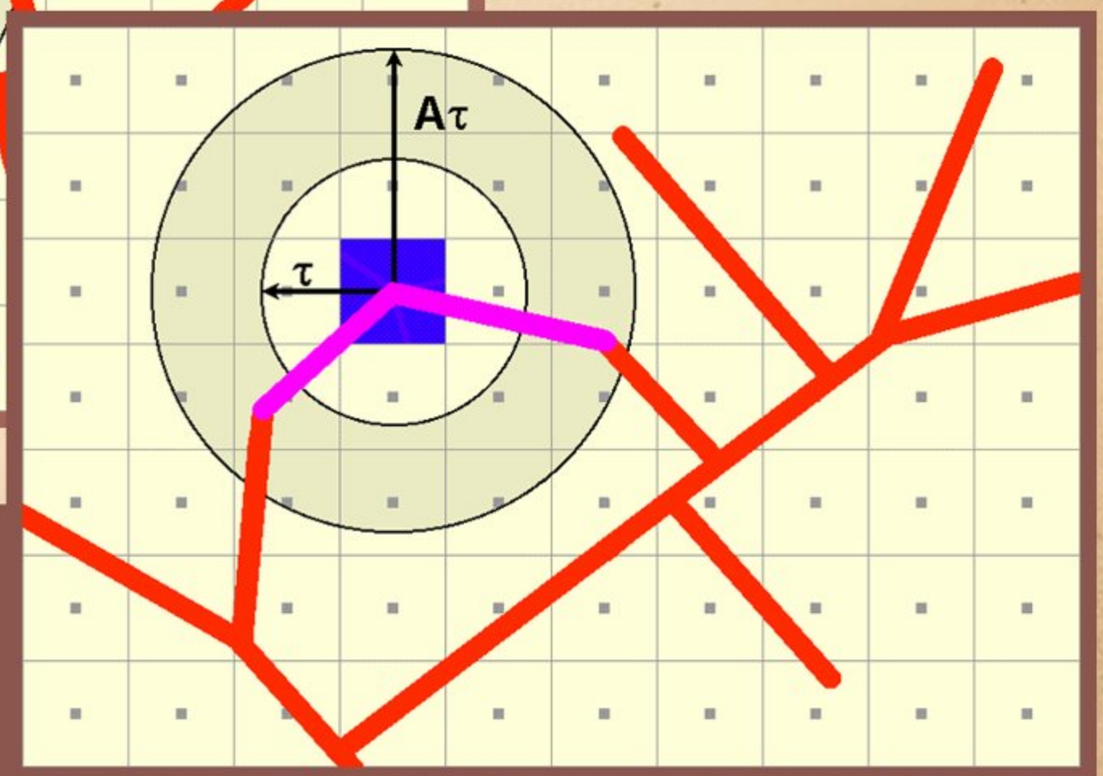
STEP 4 SPROUTING

STEP 4D ANASTOMOSES



R < 1

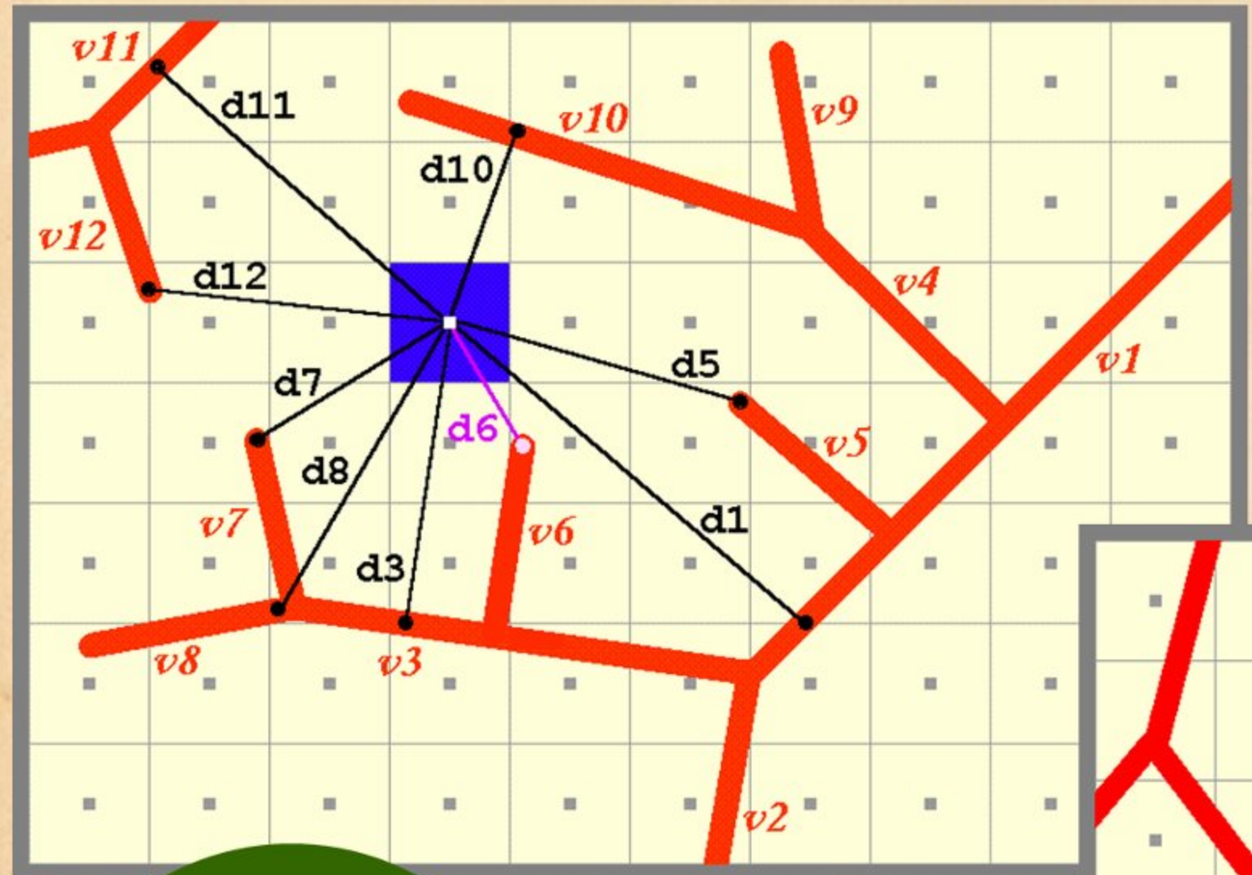




R = 1

COMPUTER ANGIOGENESIS - RECREATING NATURE

STEP 3A FIND DISTANCE



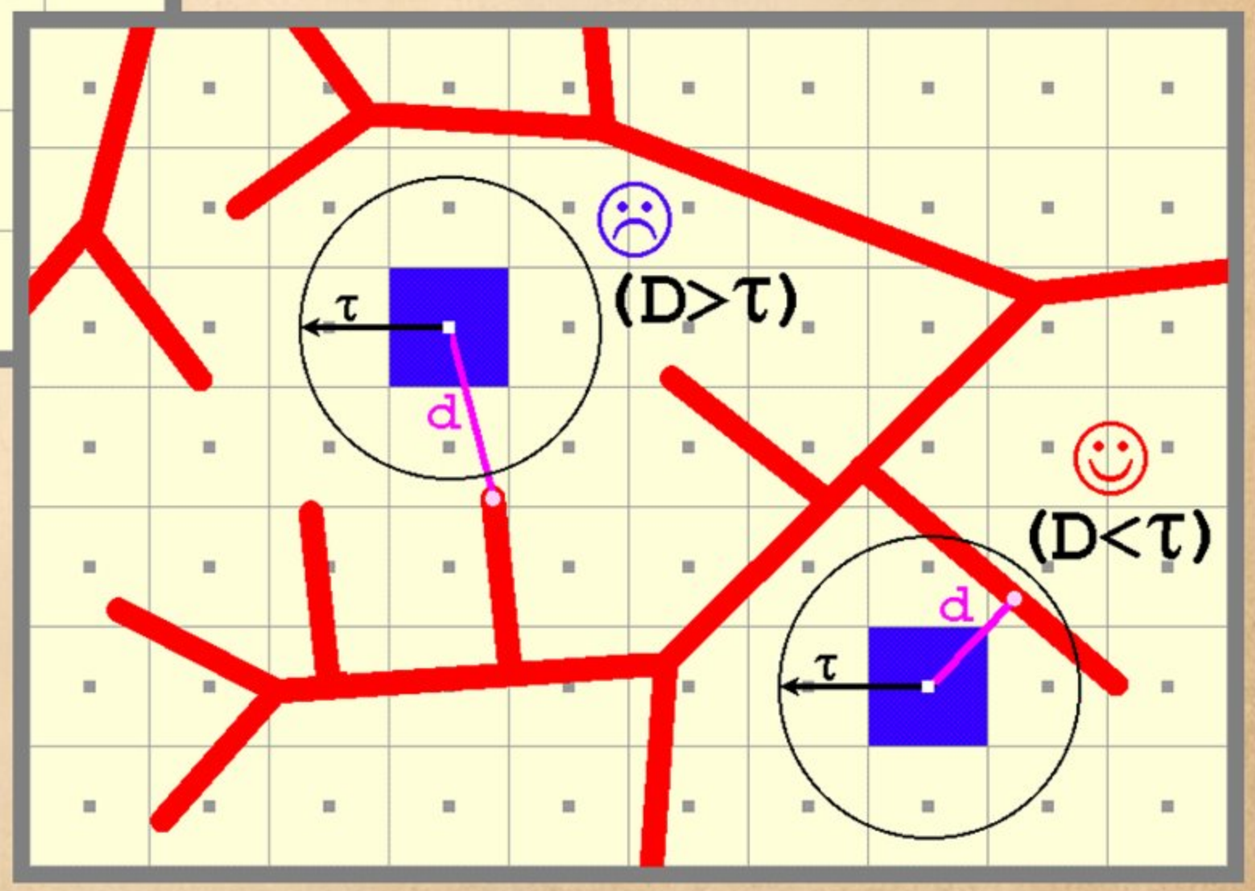
repeat for each cell

$D > \tau$ = ischemia

STEP 3 ISCHEMIA TESTING

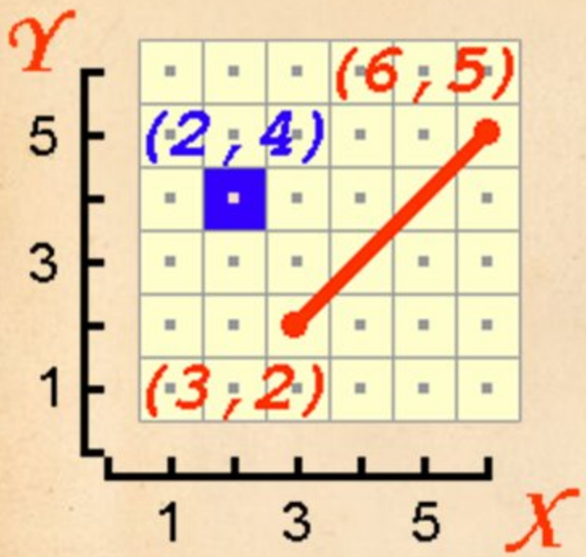
iterate: cell - by - cell

STEP 3B TEST FOR ISCHEMIA



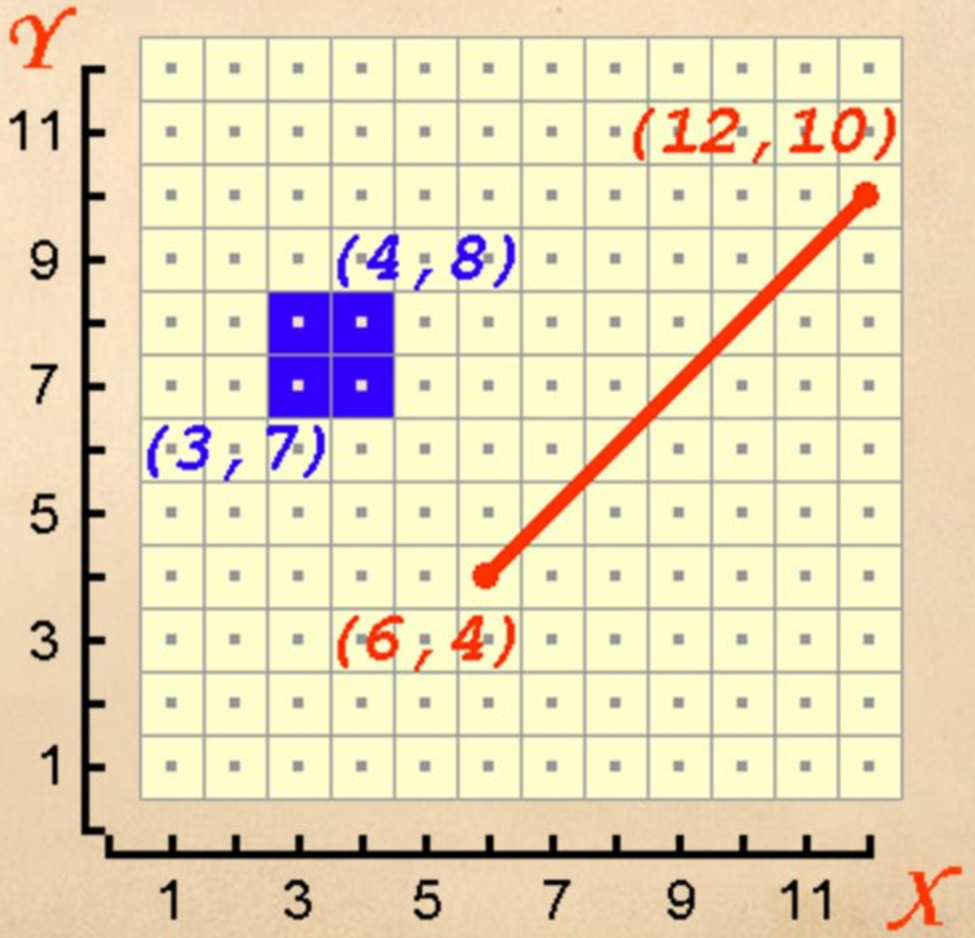
COMPUTER ANGIOGENESIS - RECREATING NATURE

Back to the start of the Main Loop



iterate the growth cycle

STEP 2 GROWTH

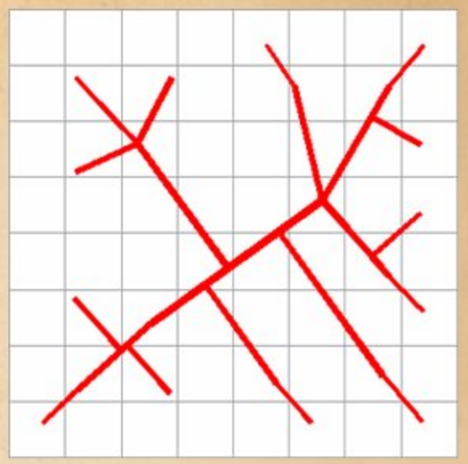


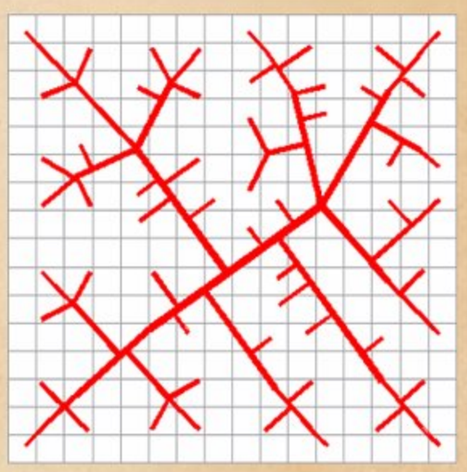
STEP 2A

GROW THE TISSUE

STEP 2B

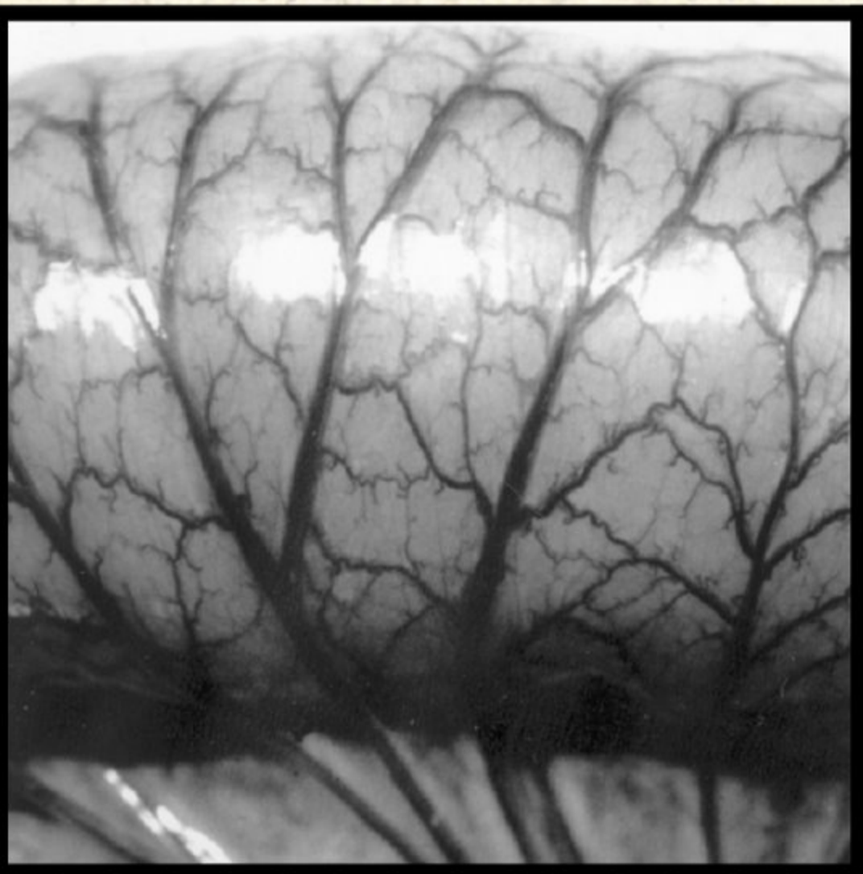
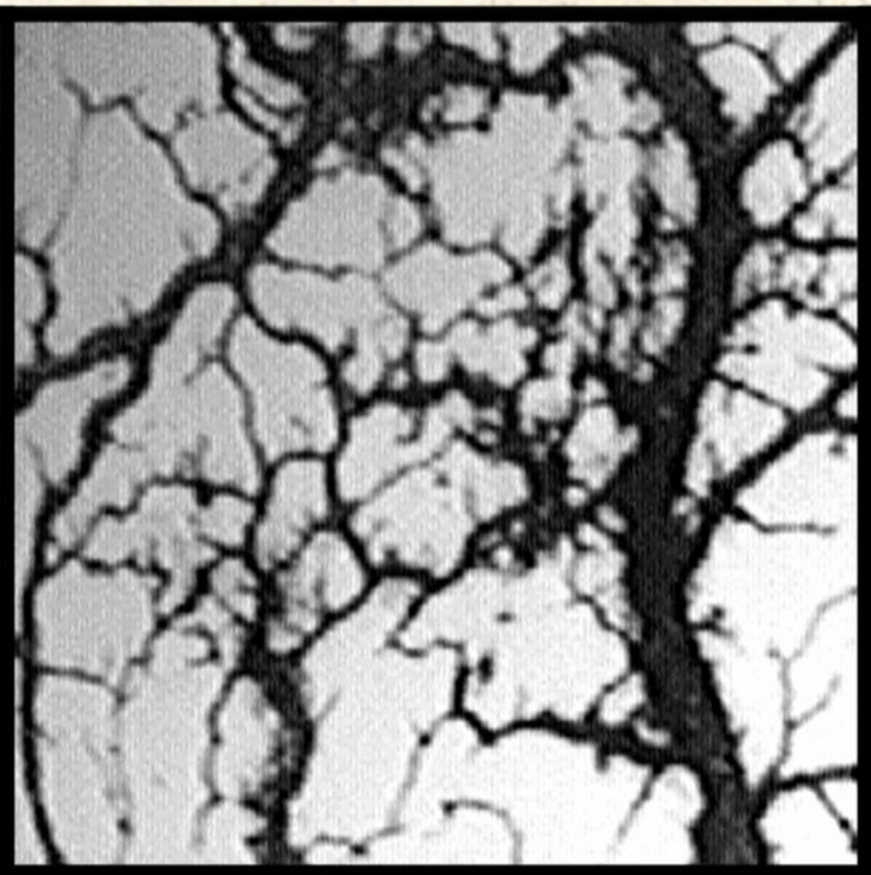
MATCHING VESSEL GROWTH





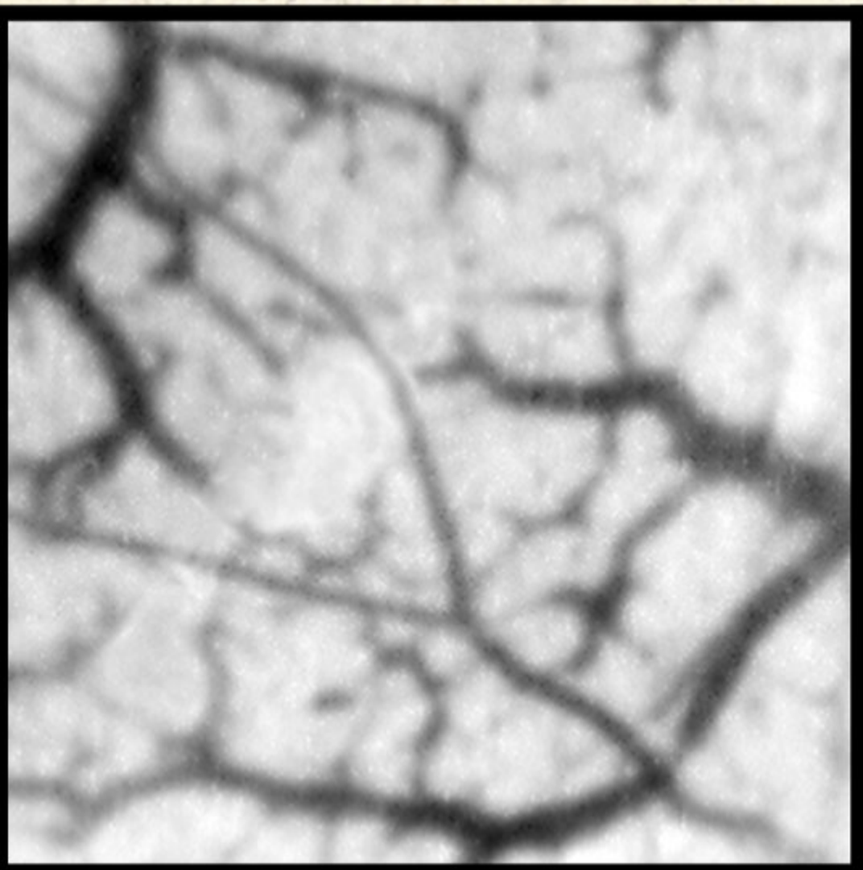
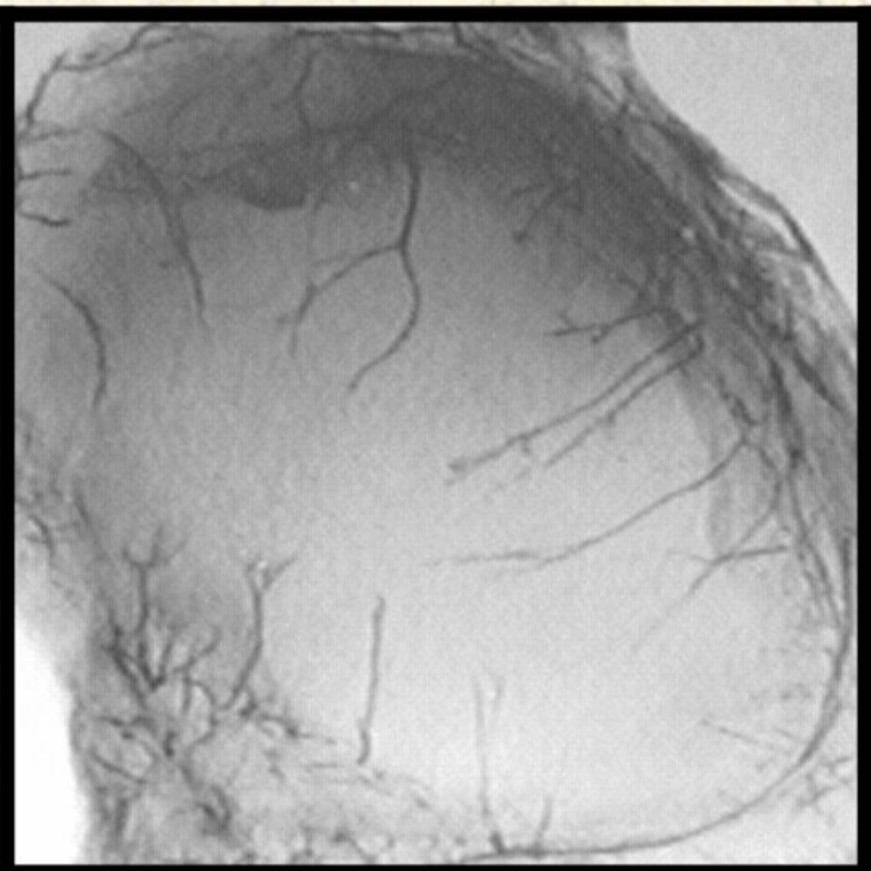
repeat a new generation

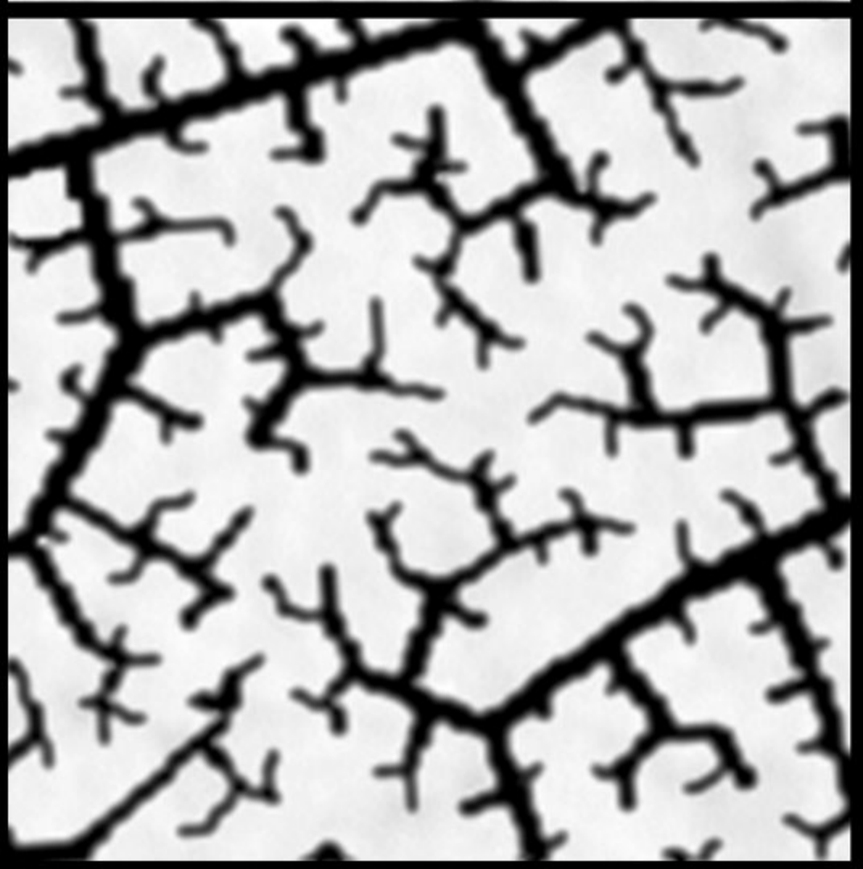
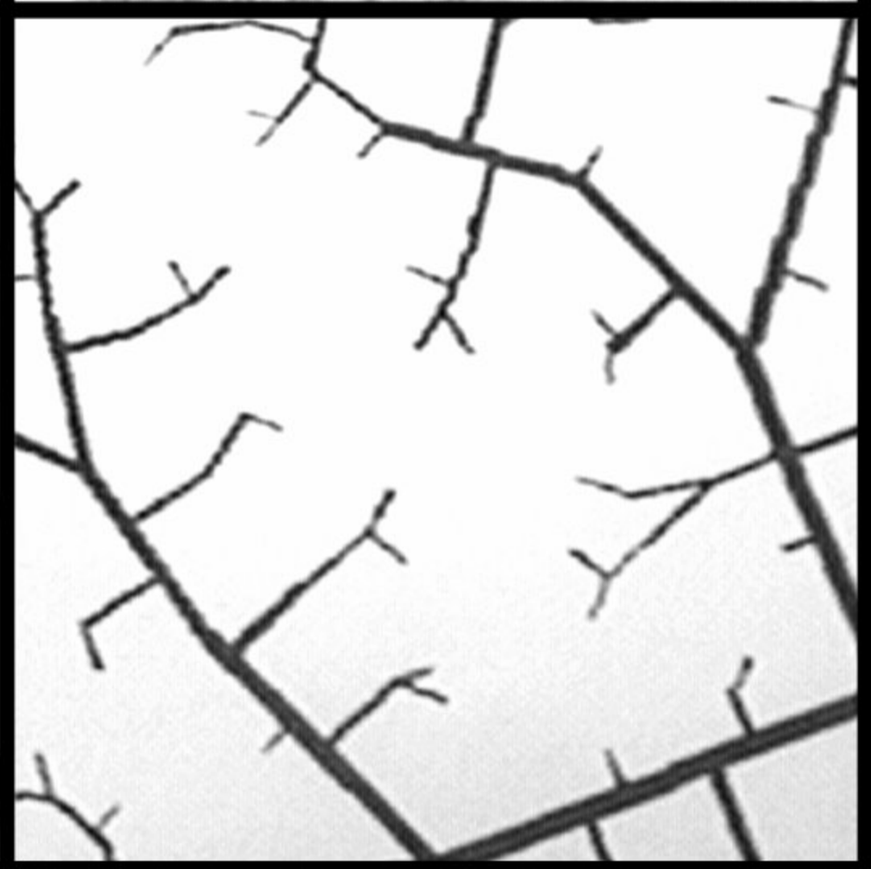
Real Vessels & Computer Vessels :: Side-by-Side

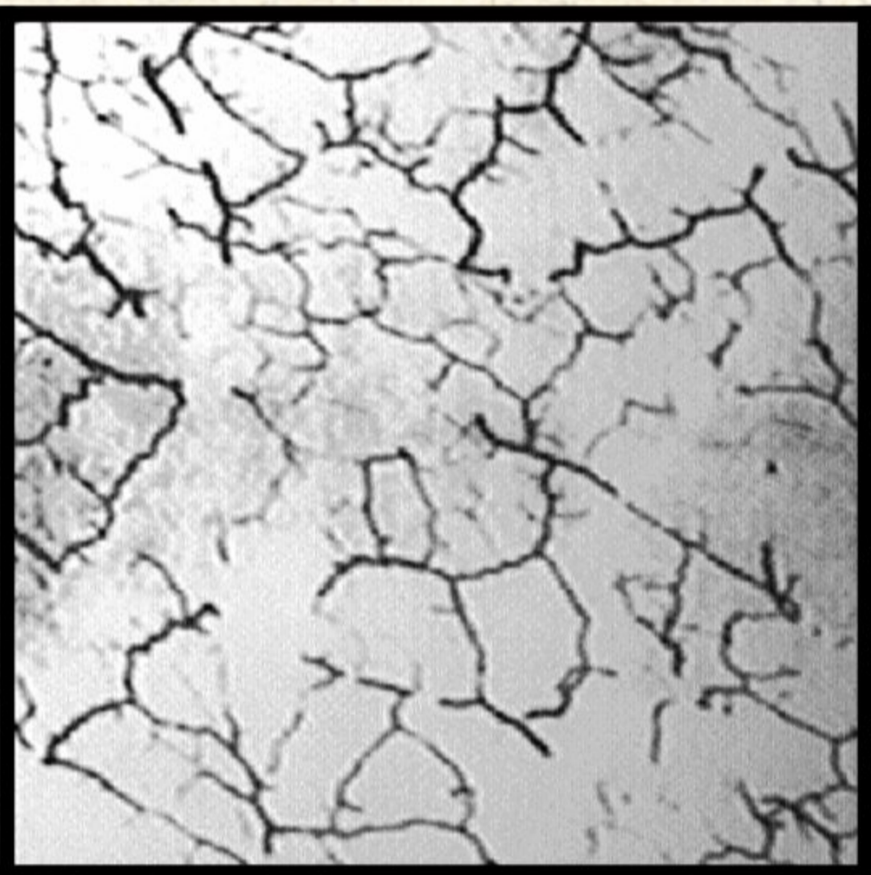
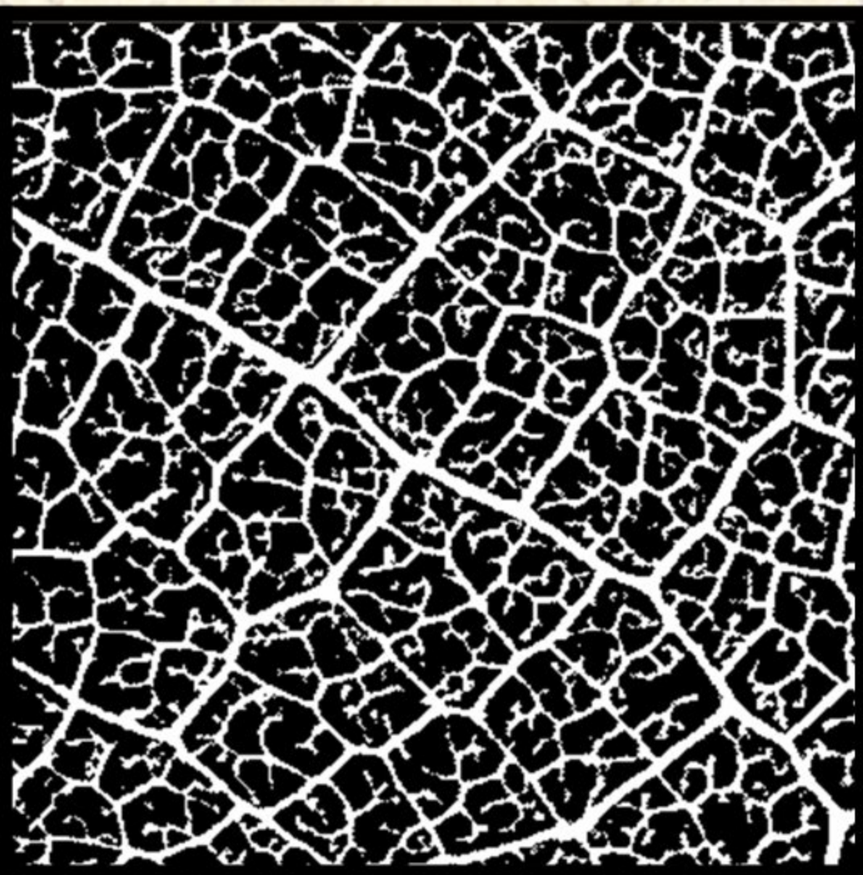


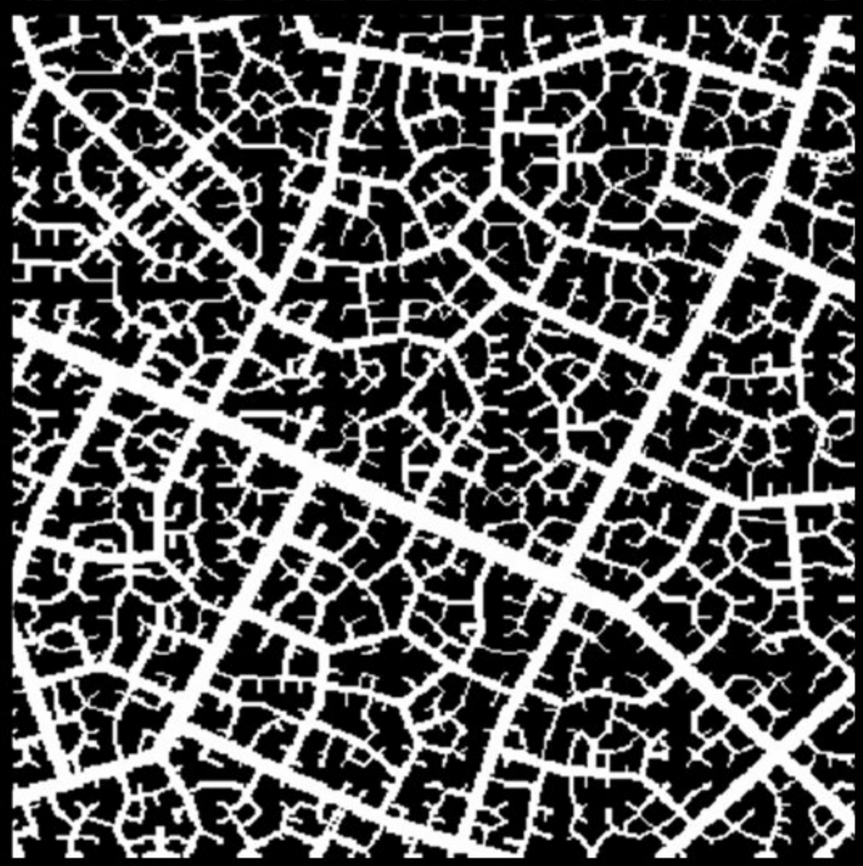
Real Vessels & Computer Vessels :: Side-by-Side

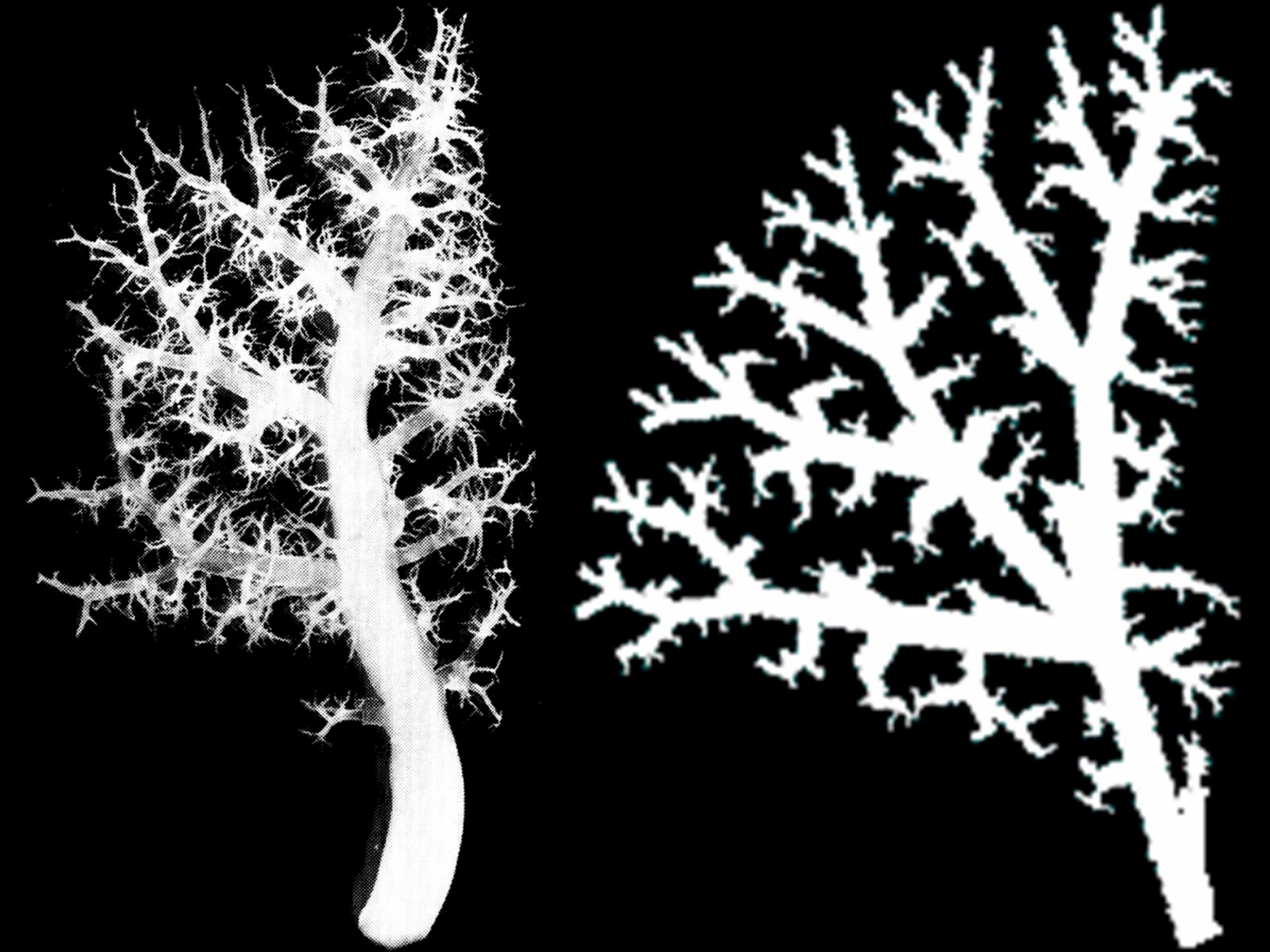




Real Vessels & Computer Vessels :: Side-by-Side

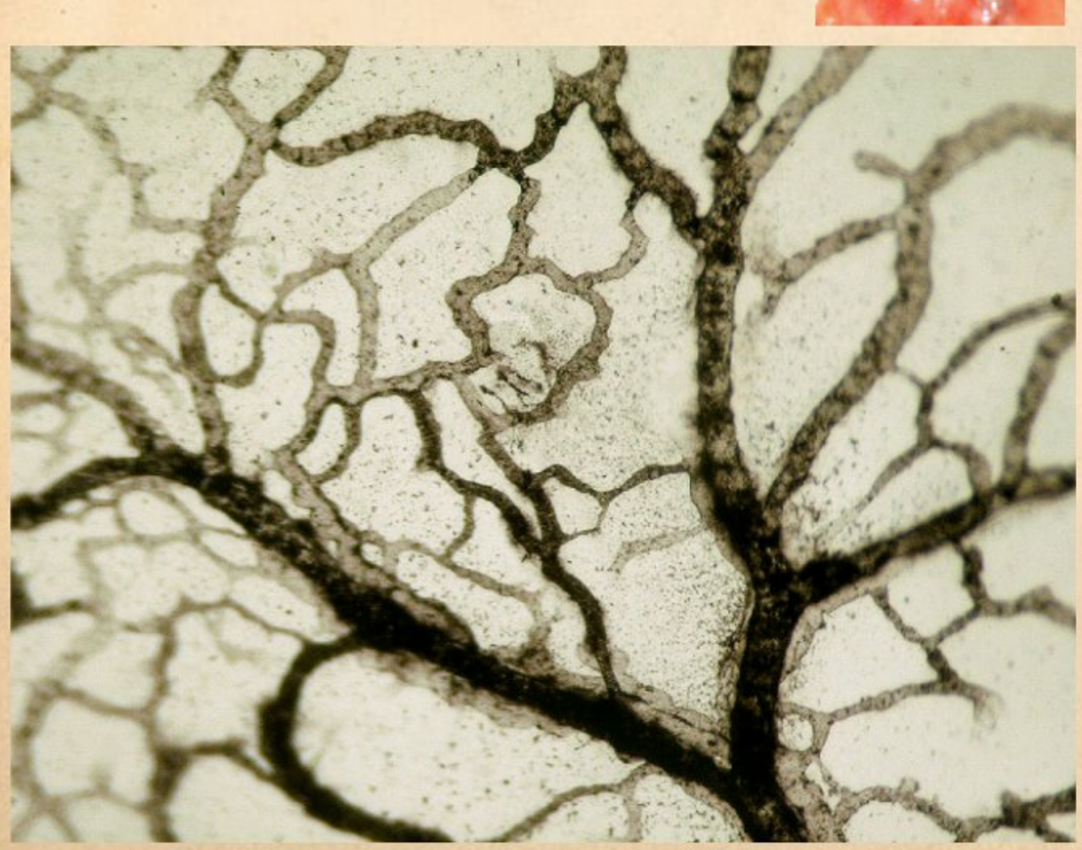


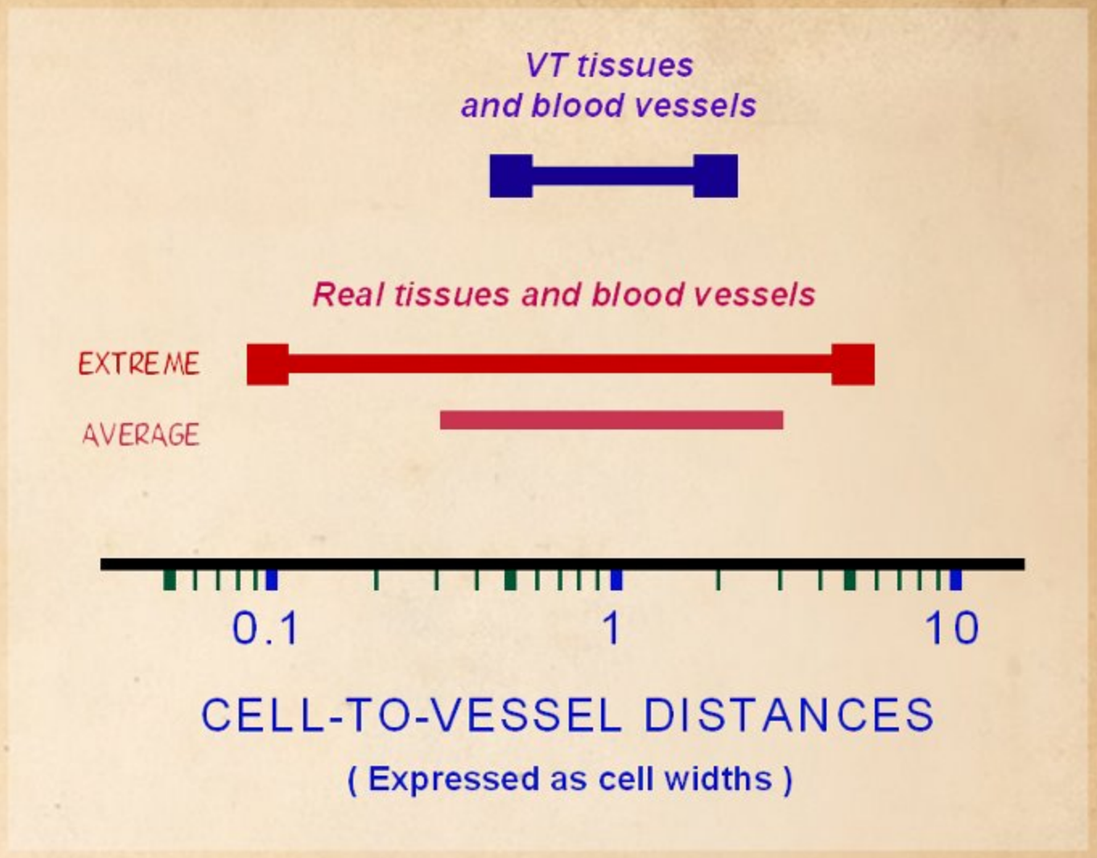
Arteries and veins

Capillaries

Vessel diameters

2D versus 3D



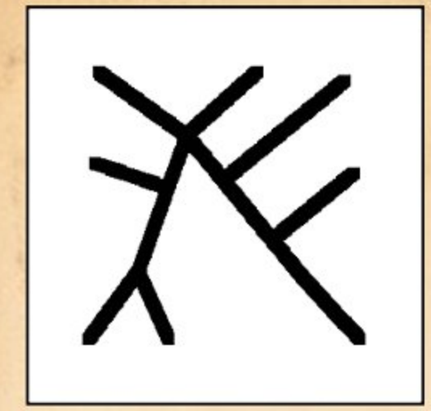


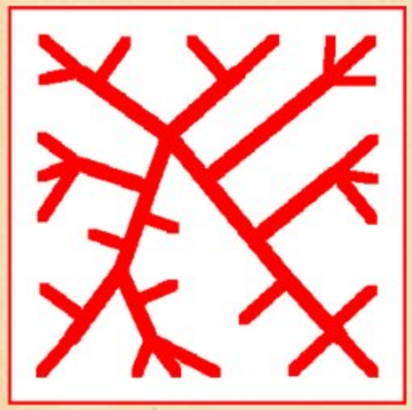
Realistic parameter choices

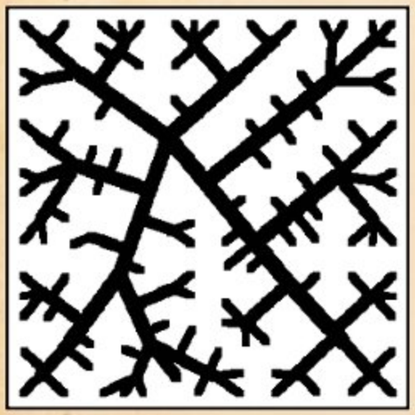
closely match real

cell-to-vessel distances.

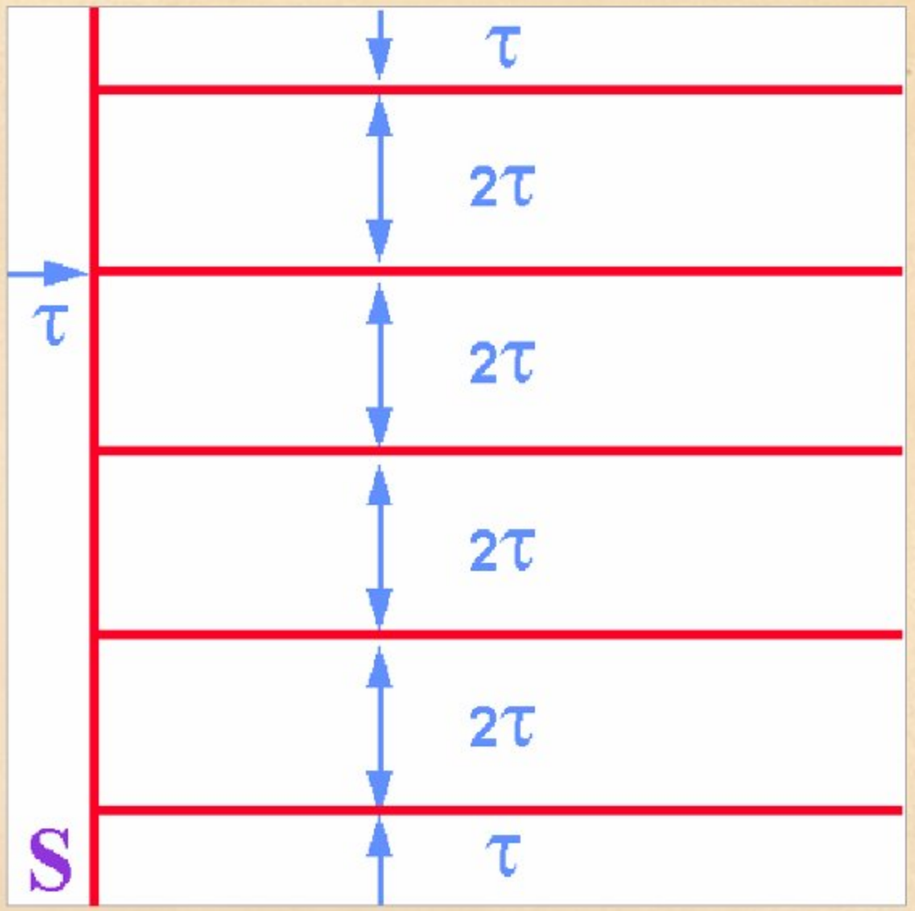
VT = "Vascular neT" model

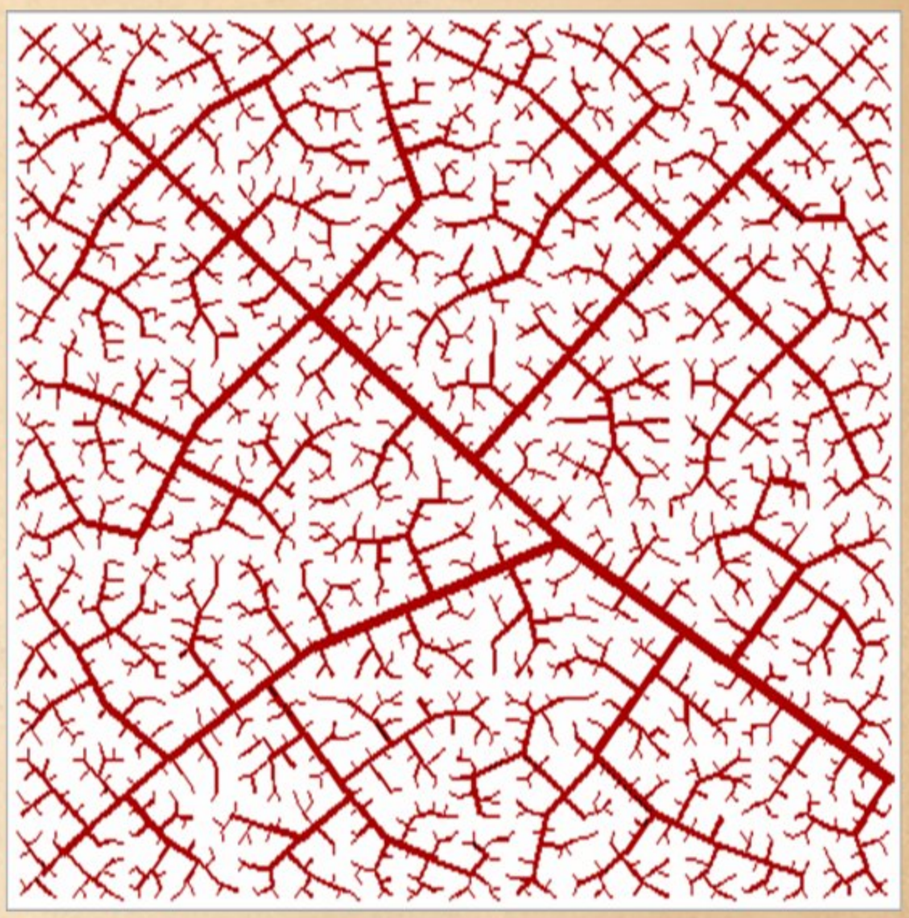




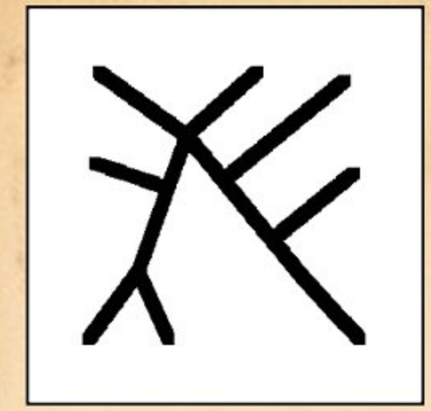


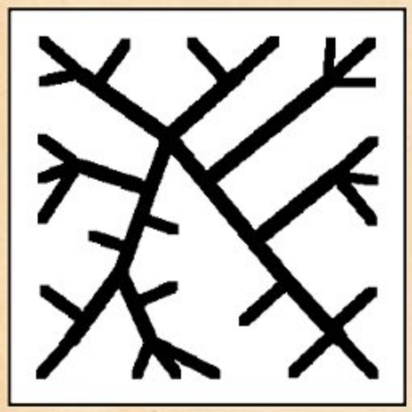
How little information is needed to engineer vascular networks, and how efficient is the process?



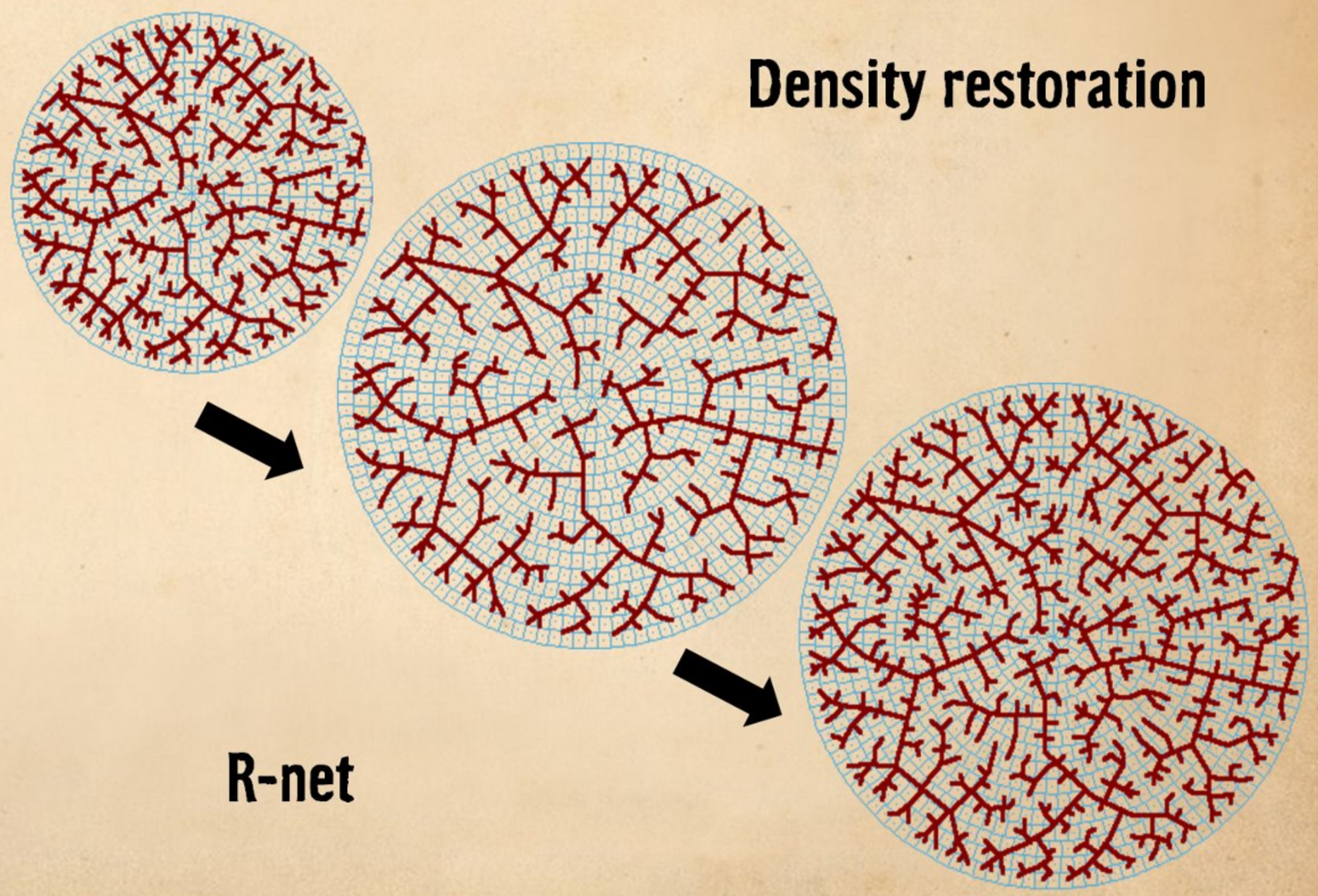


Length ratios $\approx$ 1

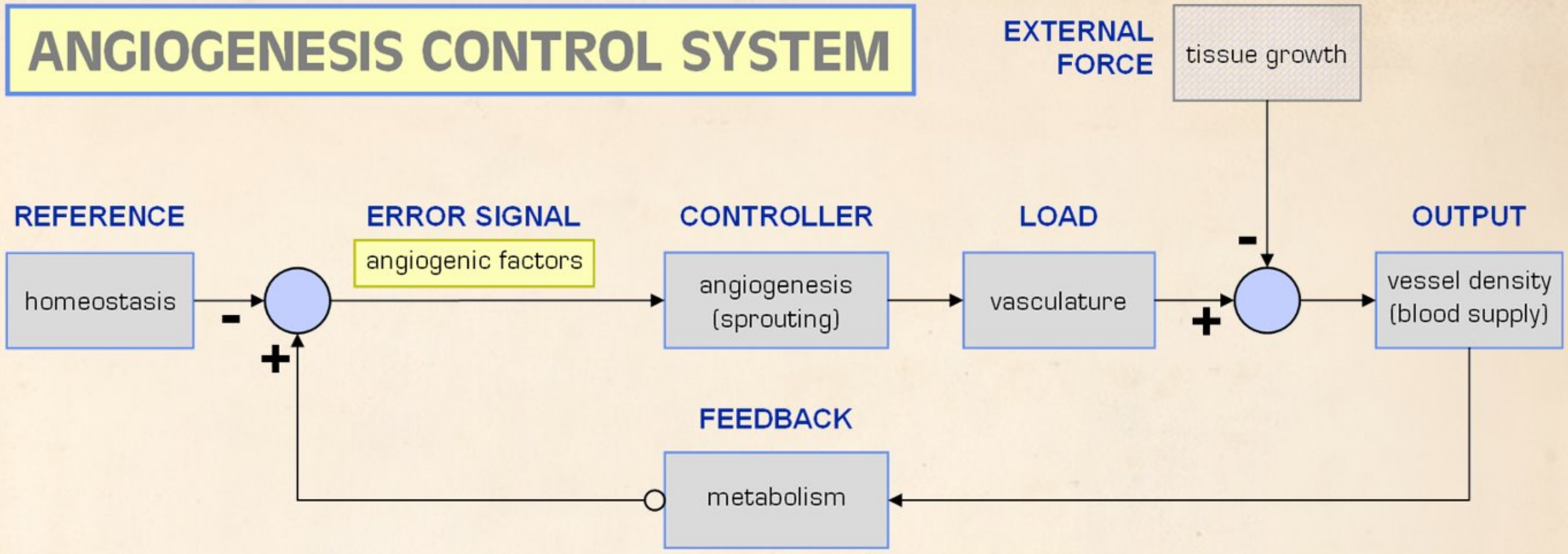




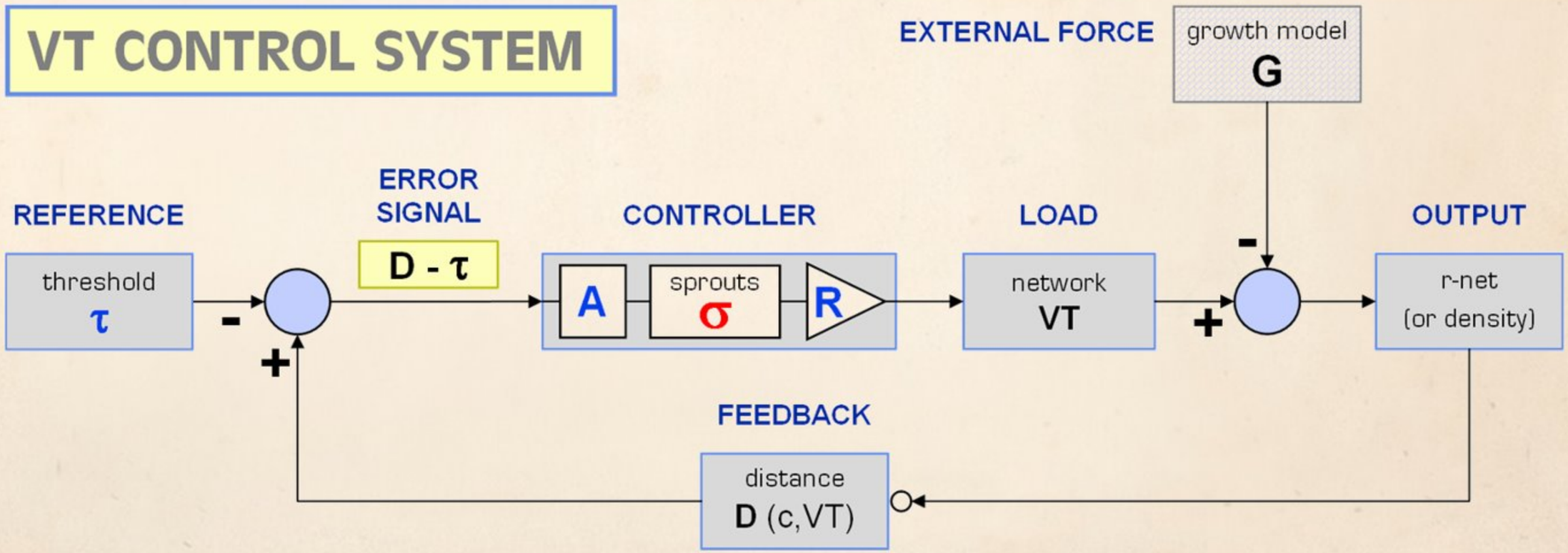
How does the system ensure that the life-and-death accuracy of the process is conserved?

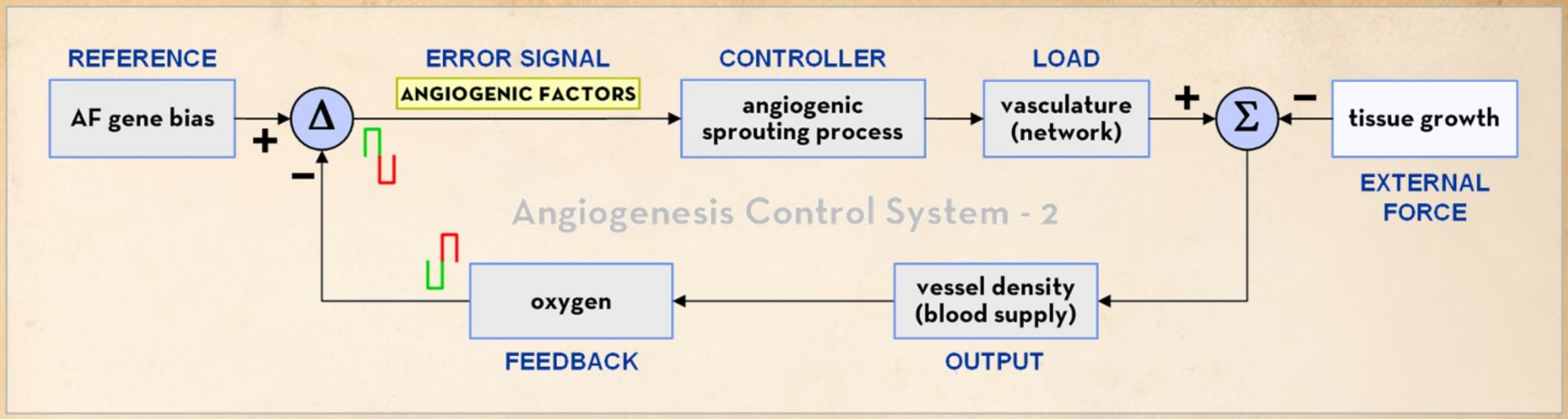


ANGIOGENESIS CONTROL SYSTEM



VT CONTROL SYSTEM





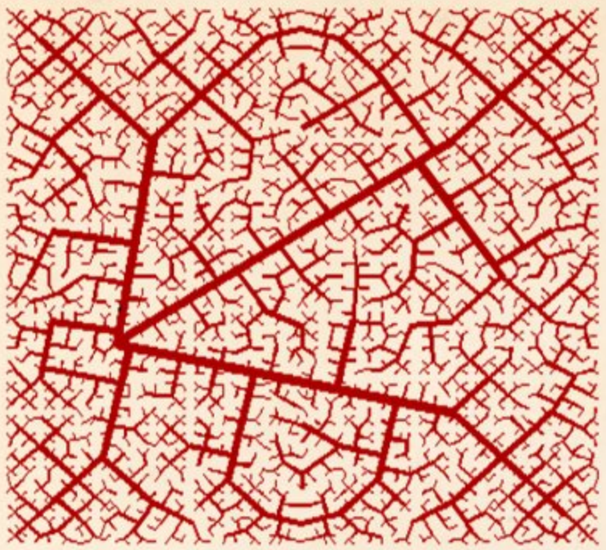
promoter = vegf

inhibitor = oxygen

Elements of the Control Systems

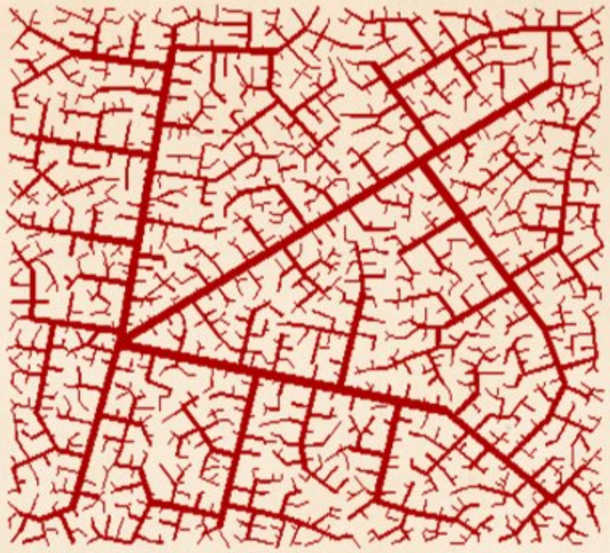
ANGIOGENESIS	GENERAL	VT
oxygen	feedback	distance D(c,VT)
correct oxygen (vegf gene bias)	system reference	threshold τ
angiogenic factors	error signal	D - τ
sprouting process	controller	sprouting, A, R
vascular network	load	VT network
r-net, blood supply	output	r-net, vessel density
tissue growth	external perturbation	growth model

a



threshold τ = 0.7
reach R = 1.0
sprout P = 1.0

c

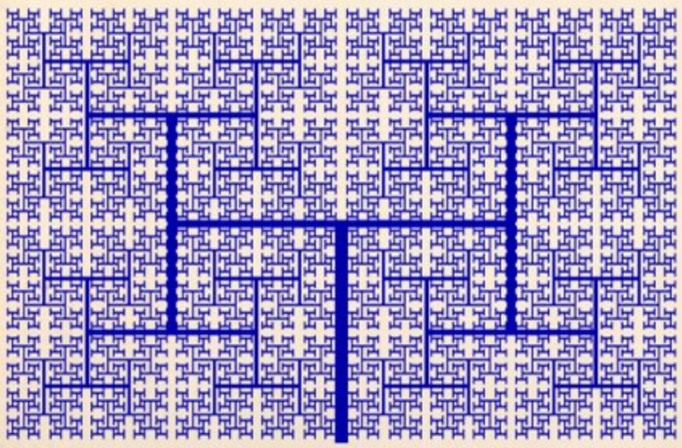


reach R = 1 ± 0.5 (efd)
sprout P = 0.5

e

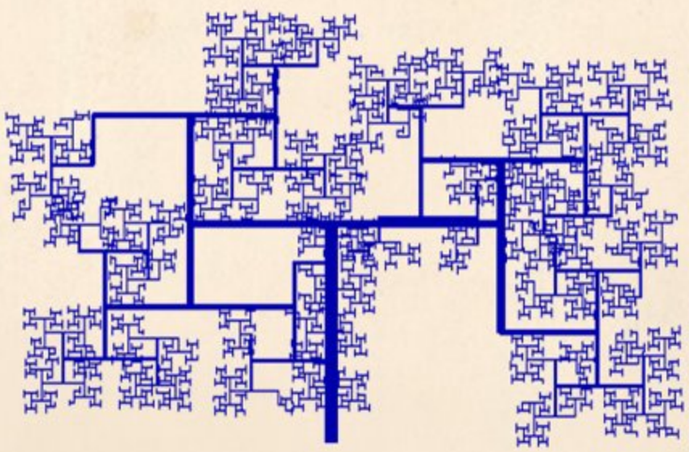
threshold τ = 0.14 to 2.10 (efd)
reach R = 1 ± 1.0 (efd)
sprout P = 0.25

b



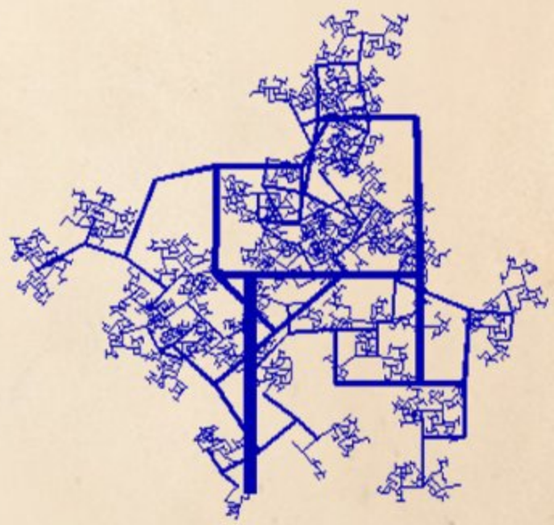
angles: left = right = π/2
scaling: left = right = 1/√2
sprout P = 1.0

d

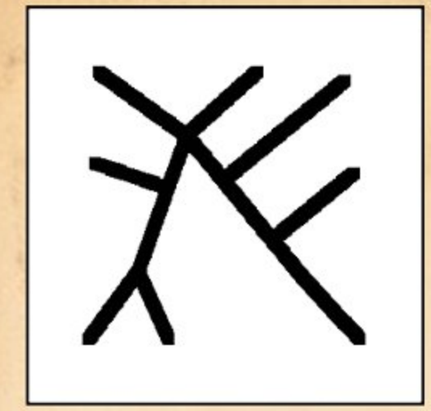


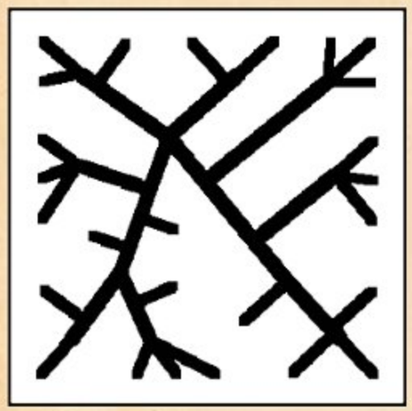
scaling: left = (1 ± 0.5) x 1/√2 (ngd)
sprout P = 0.95

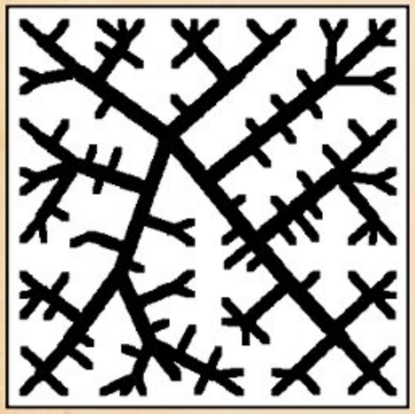
f



angles: left = π/2 ± arctan(√2) (ngd)
scaling: left = 1/√2 ± 1/√2 (ngd)
sprout P = 0.90







What are the geometries and topologies of vascular networks, and why do other structures share them?

Vascular networks are fractal r-nets

Isauxetic growth of old vessels

Established structure enlarges with the growth process

creating room for new structure

Rescaling

Host growth — *Active* — *Reactive* — *Control loop*

Self-similarity

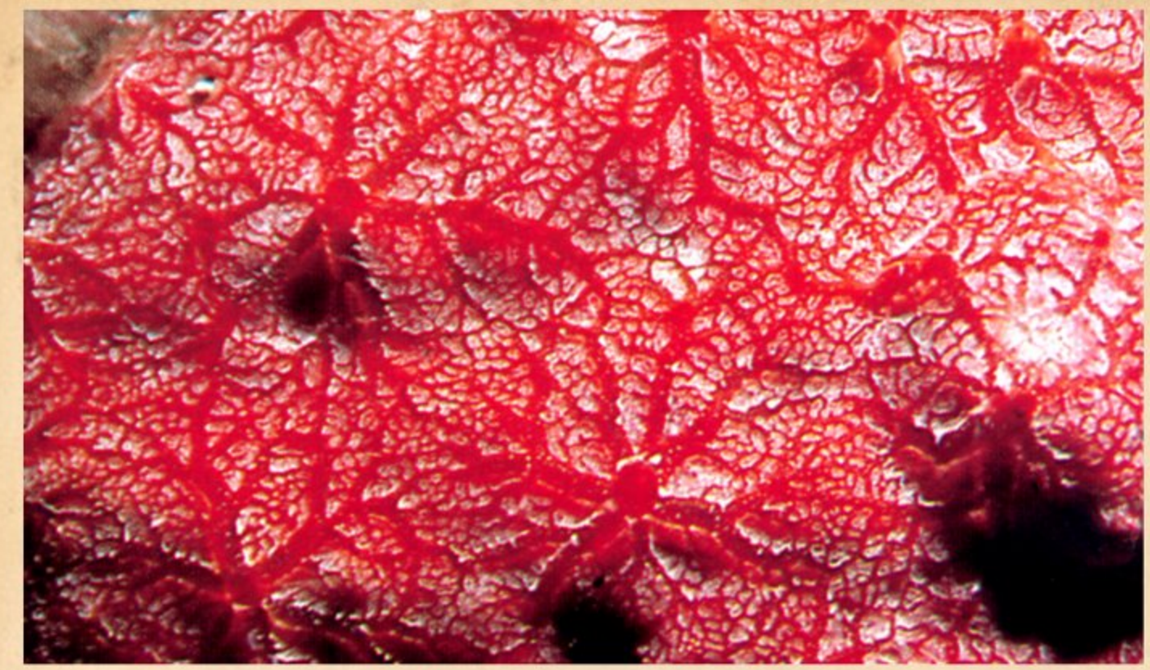
Fractal growth of new sprouts

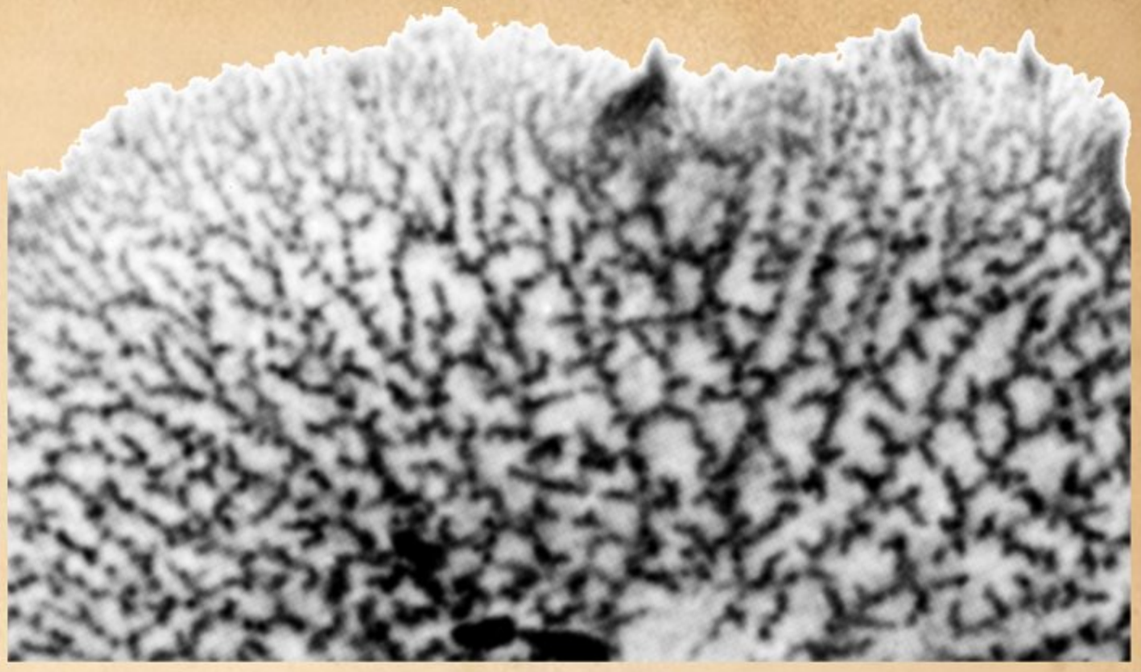
Fixed rules create new structure at a fixed scale

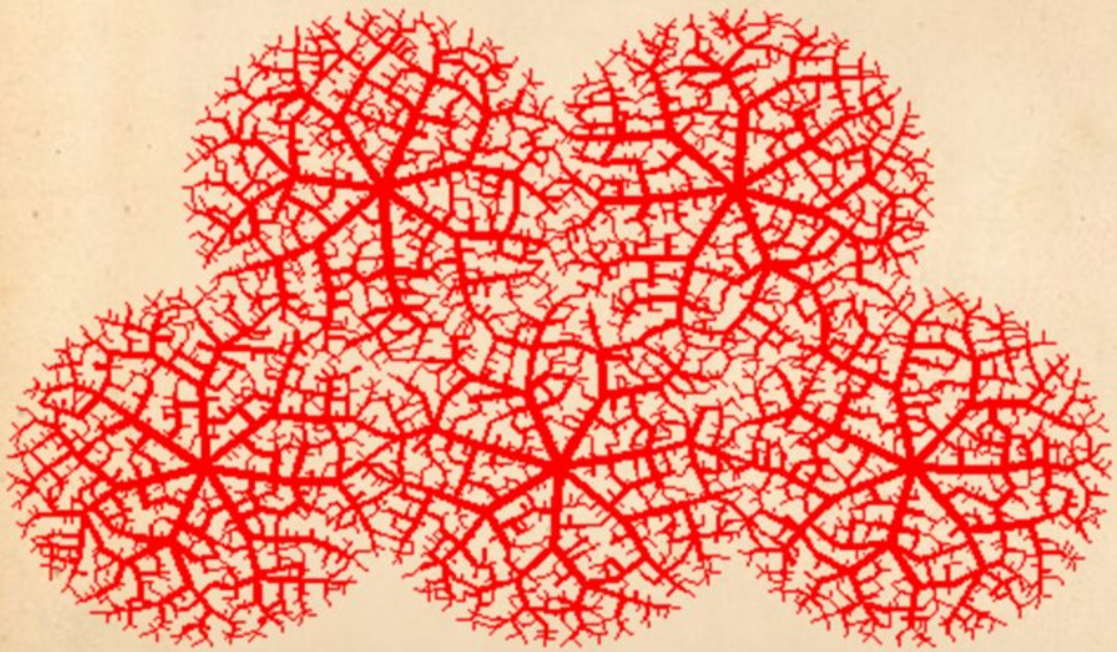
with characteristic patterns

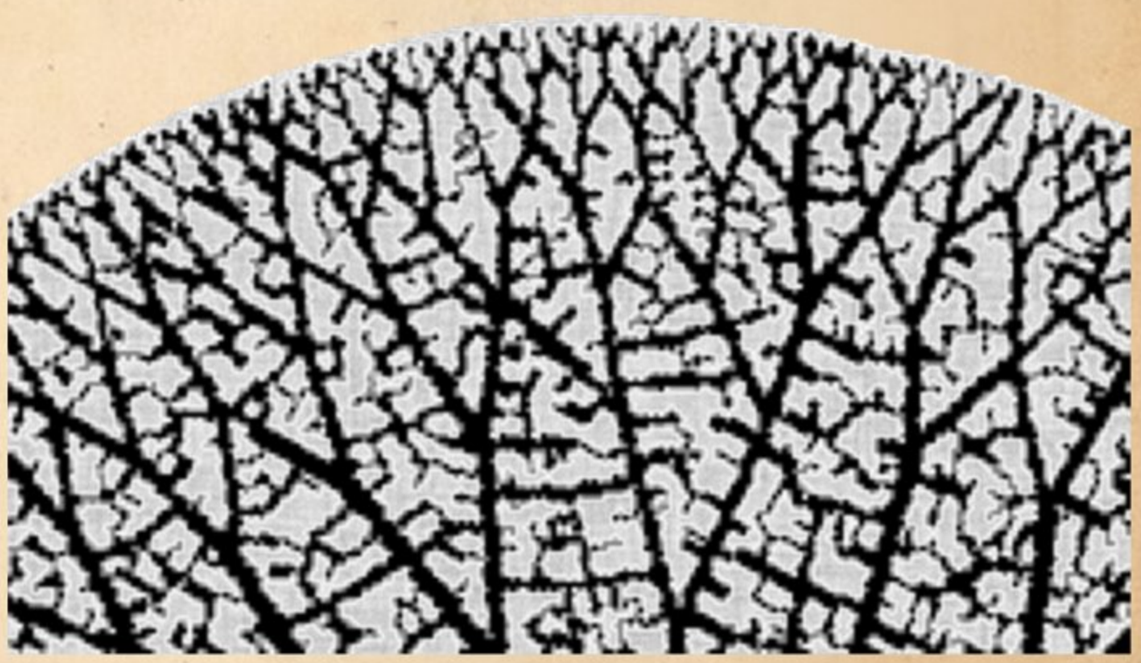
$$V_i \leftarrow g_i(V_{i-1}) \bigcup \{\sigma\}_i$$

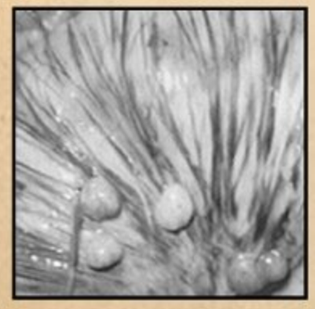
$$V_i = \{\Psi_{1,\ldots,N(i)}\} = \bigcup_{k=0}^{i} g^{(i-k)}(\{\sigma\}_k)$$

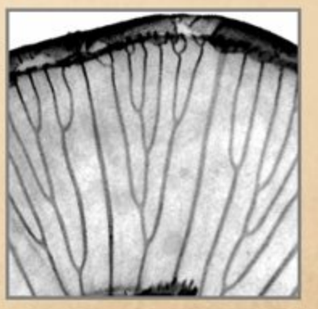


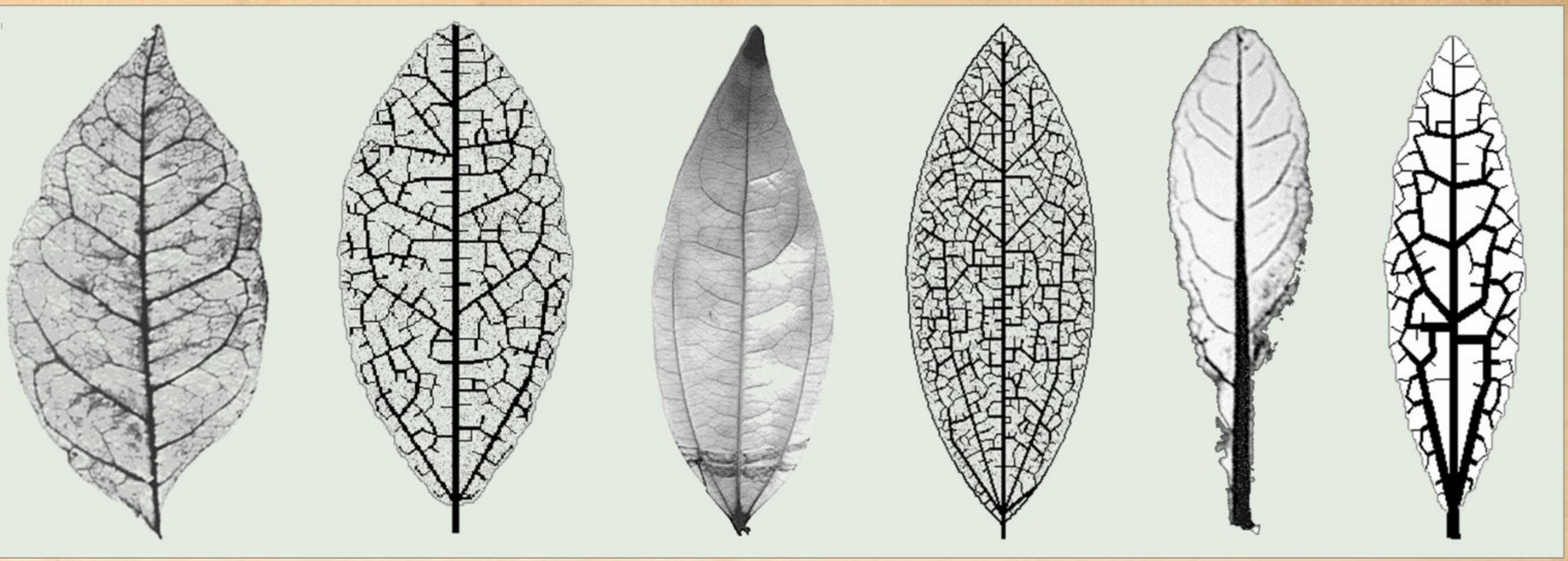


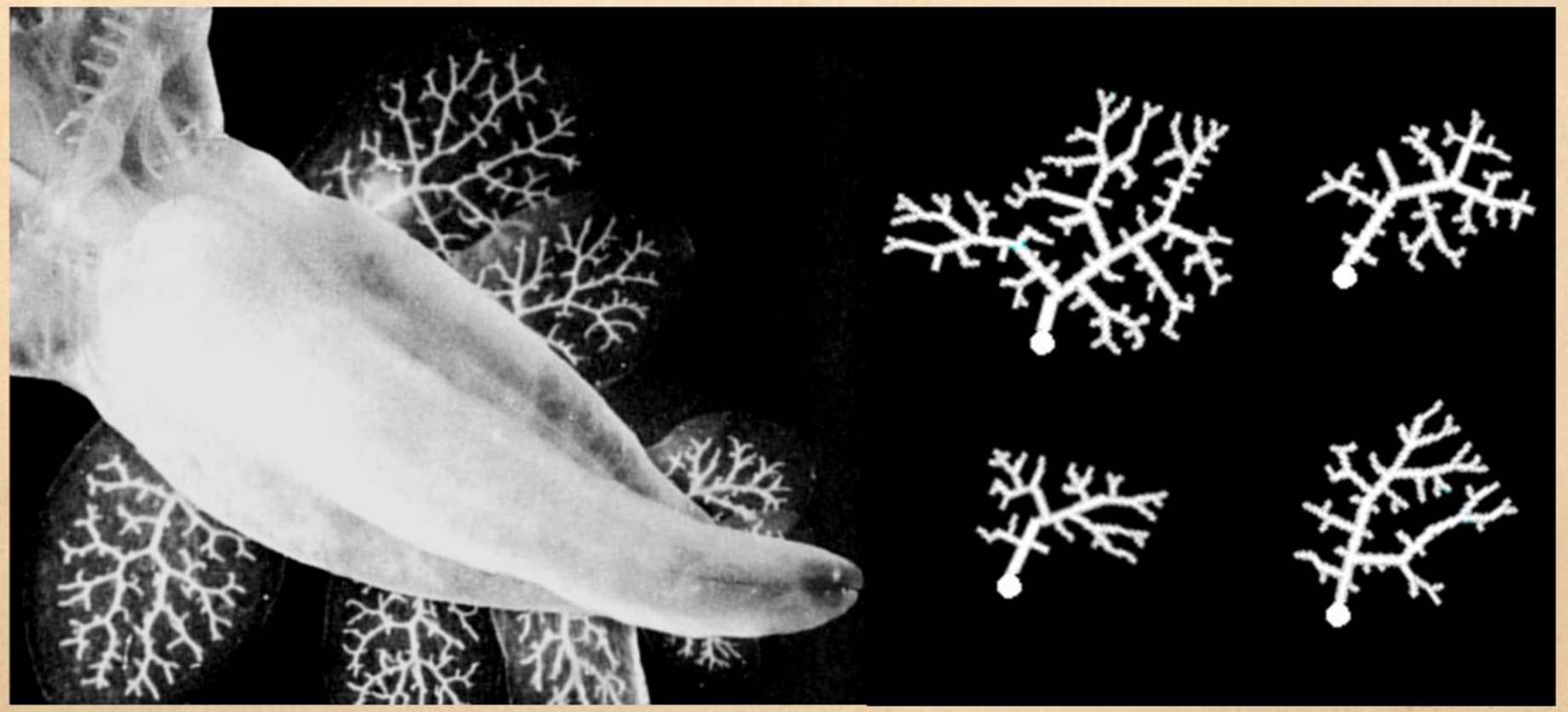


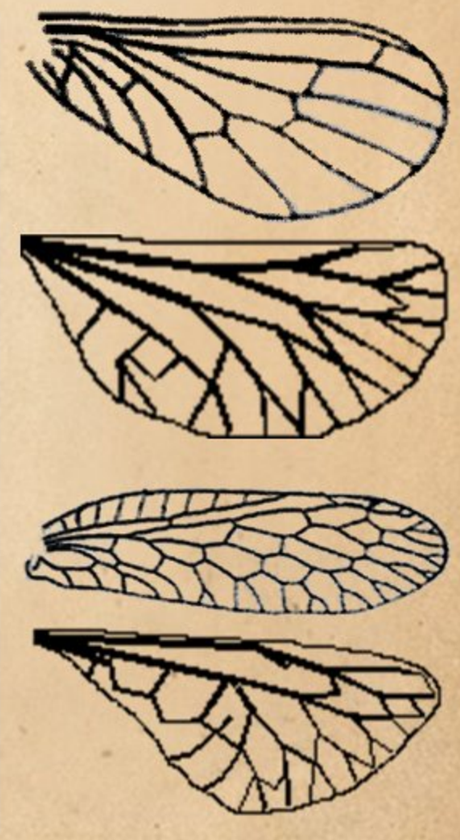








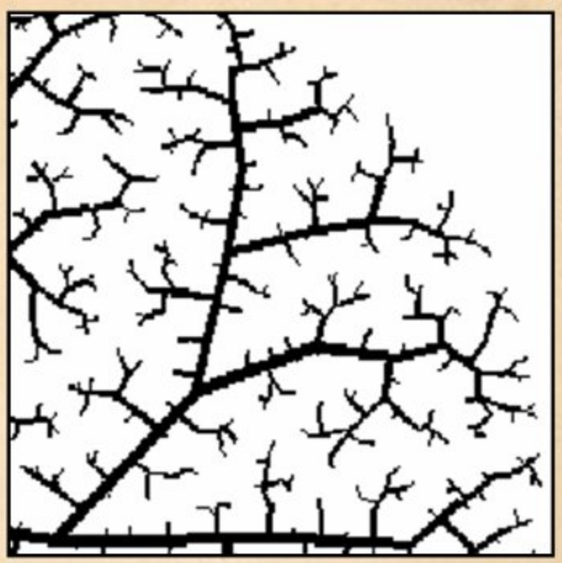
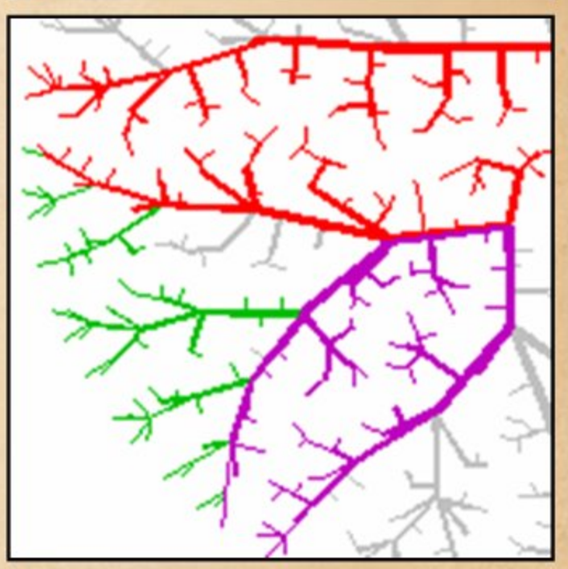


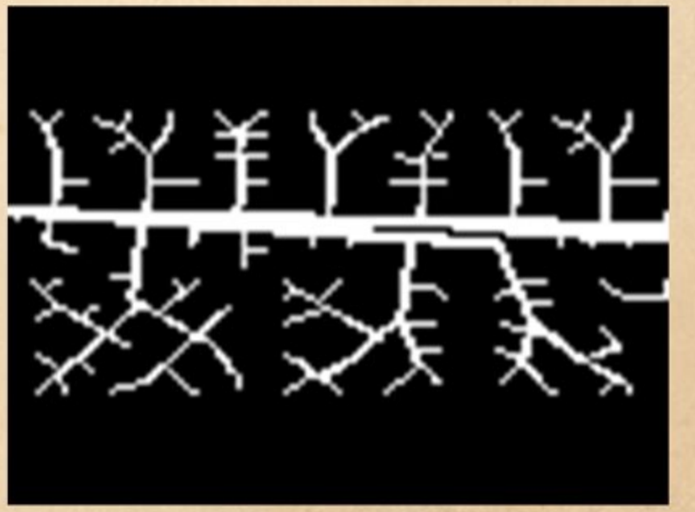


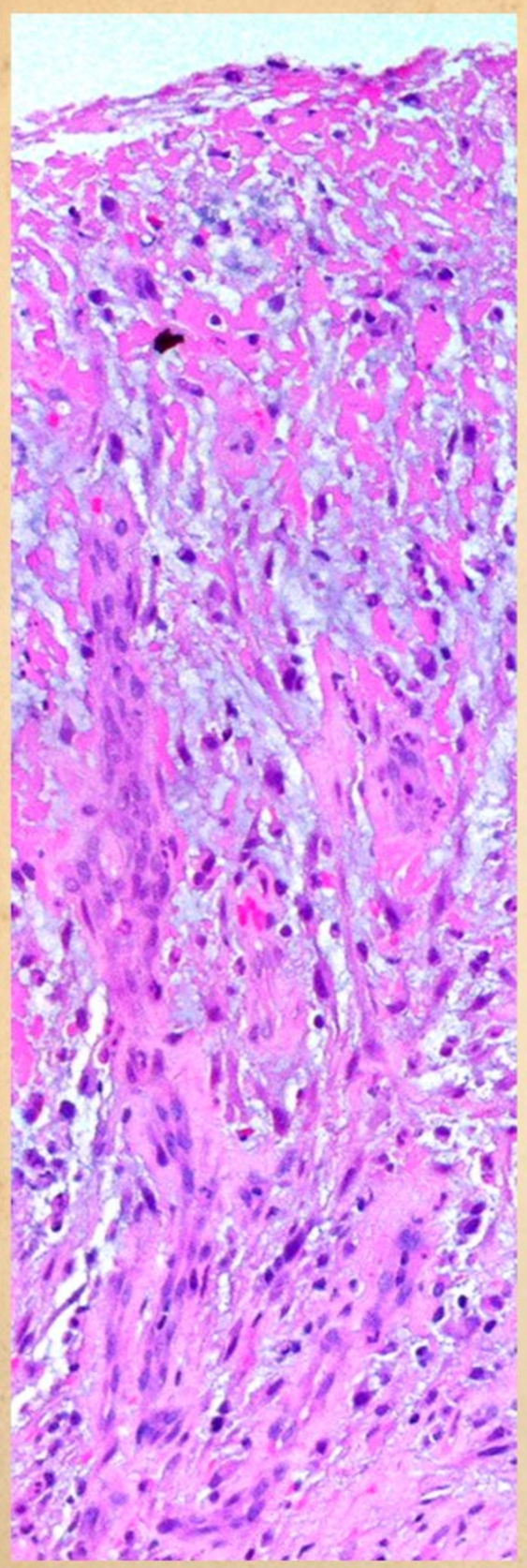


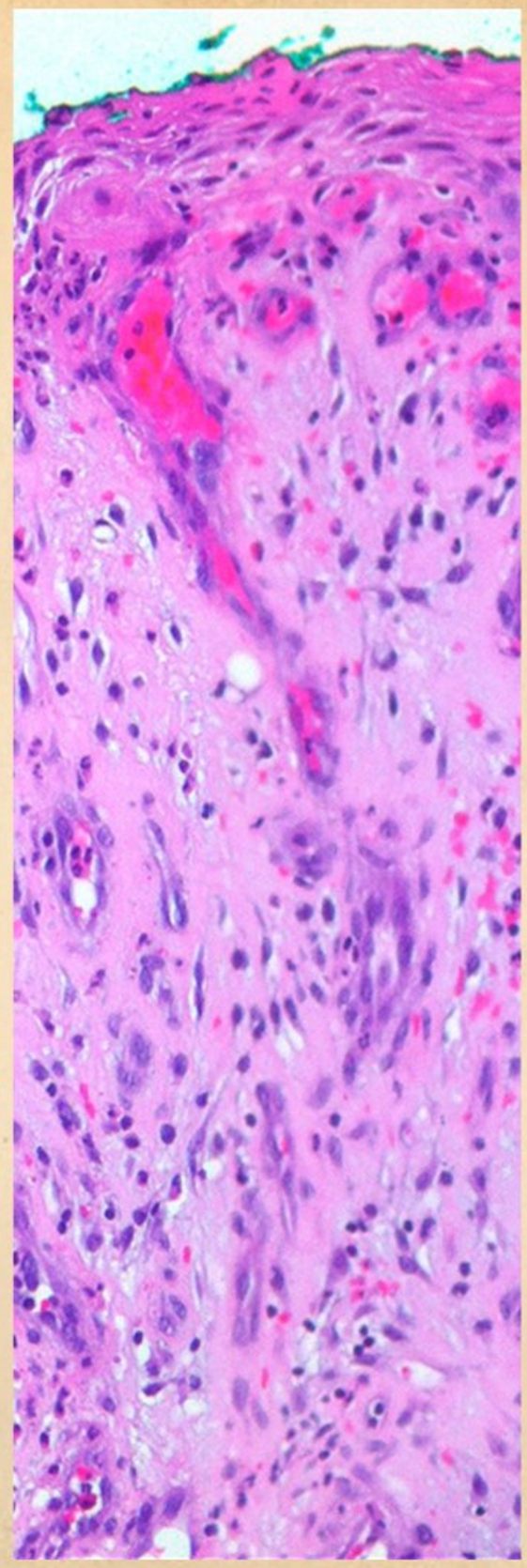


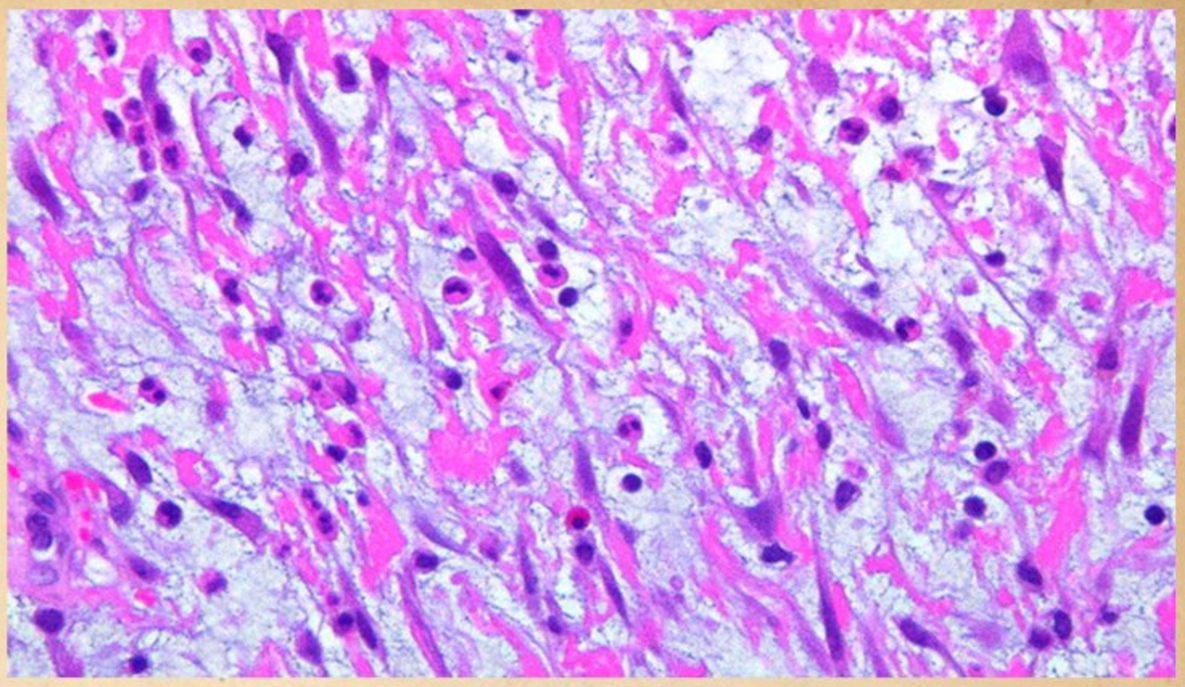


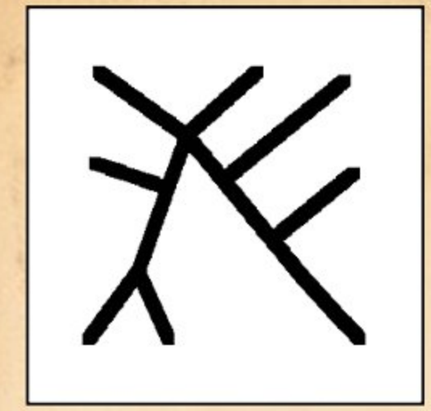


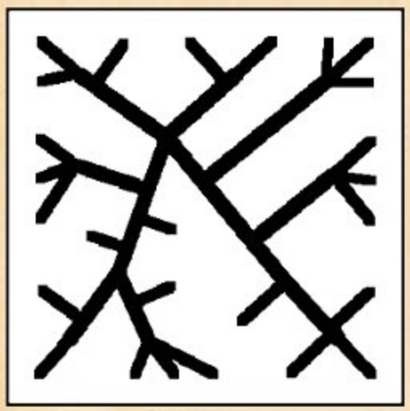


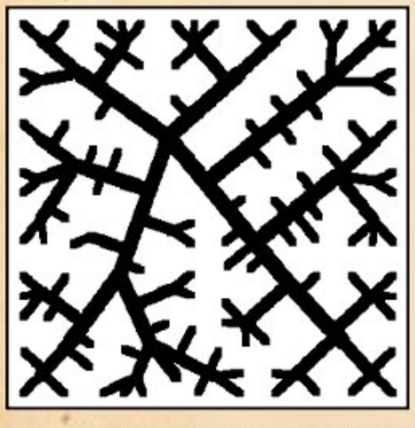




Field angiogenesis	Target angiogenesis
developmental	**incidental**
embryonic, growth & maturation	*wound, tumor, follicles, implants*
closed loop	**open loop**
controlled	**unregulated**
vessel restoration inhibits the controller	*vessel restoration does NOT inhibit the controller*
dispersed	**vector**







How do VEGF and angiogenesis operate to create a vascular network?

Simple physical system contingent on promoter-inhibitor diffusion.

How little information is needed; how efficient is the process?

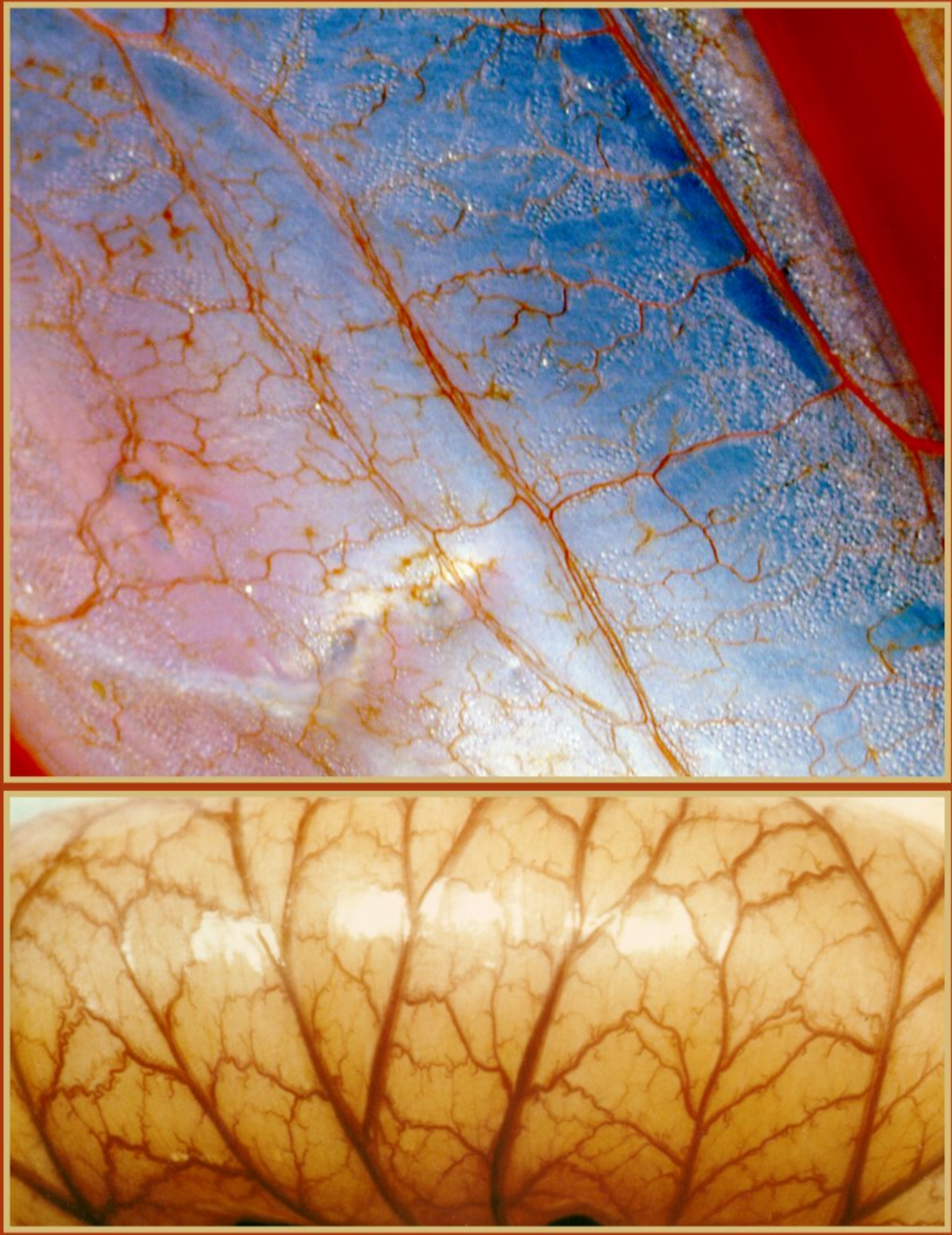
Very little. Very efficient. Parsimonious self-organization.

How is the life-and-death accuracy of the process conserved?

Process is a reactive, space-driven, density-restoring error-correcting closed-loop feedback control system.

What are the geometries and topologies; why in other structures?

Vascular networks are fractal r-nets, life-and-death crucial, highly conserved through evolution.



THE CENTURY OF THE SYSTEM

DEVELOPMENTAL ANGIOGENESIS

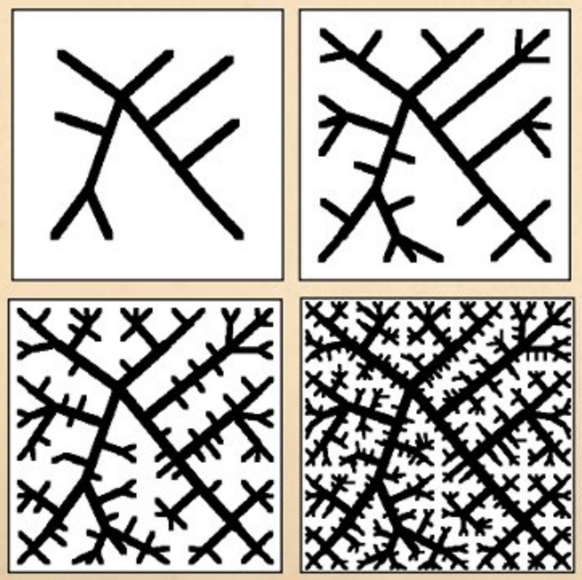
=

CLOSED LOOP CONTROL SYSTEM

The control loop ensures the correct development of the life-and-death critical vascular network. Multicellular life cannot exist without it.

THE VT MODEL OF ANGIOGENESIS

The Vascular neT Model of the Formation of Blood Vessels and Vascular Networks



ARIMEDICA

www.arimedica.com