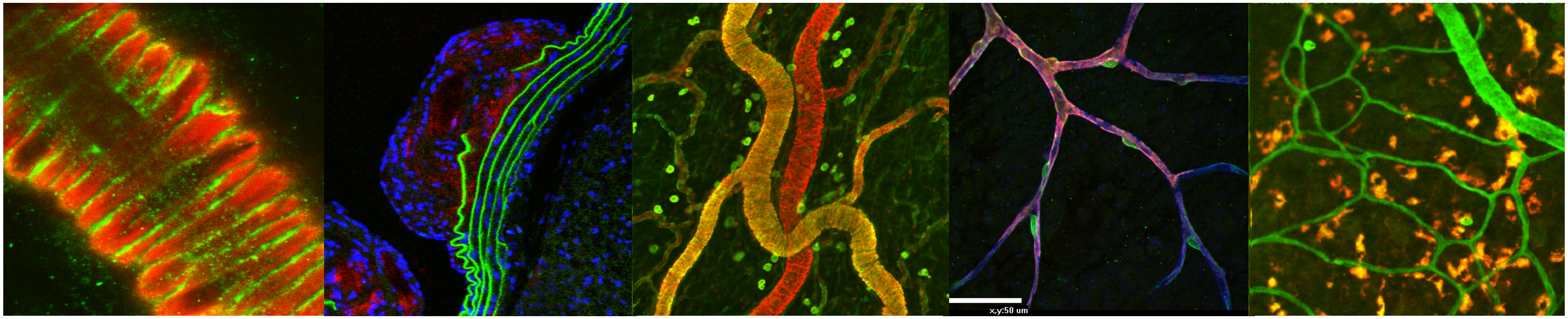


Multiscale models for understanding regulators of tissue growth and remodeling

Shayn Peirce-Cottler, Ph.D.

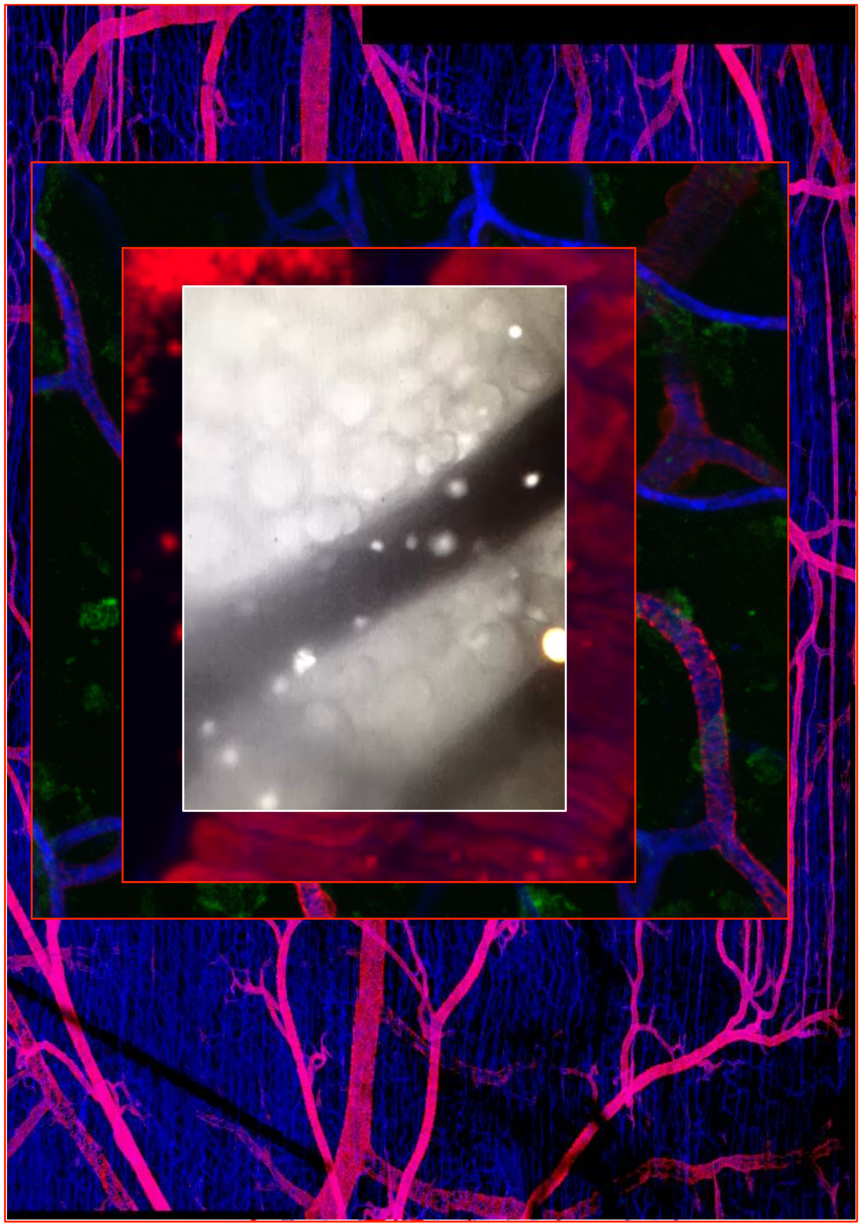
Associate Professor of Biomedical Engineering

6.13.14

The DEPARTMENT *of* BIOMEDICAL ENGINEERING

School of Engineering and Applied Science • School of Medicine

Growth & Remodeling: spans length scales and is dynamic



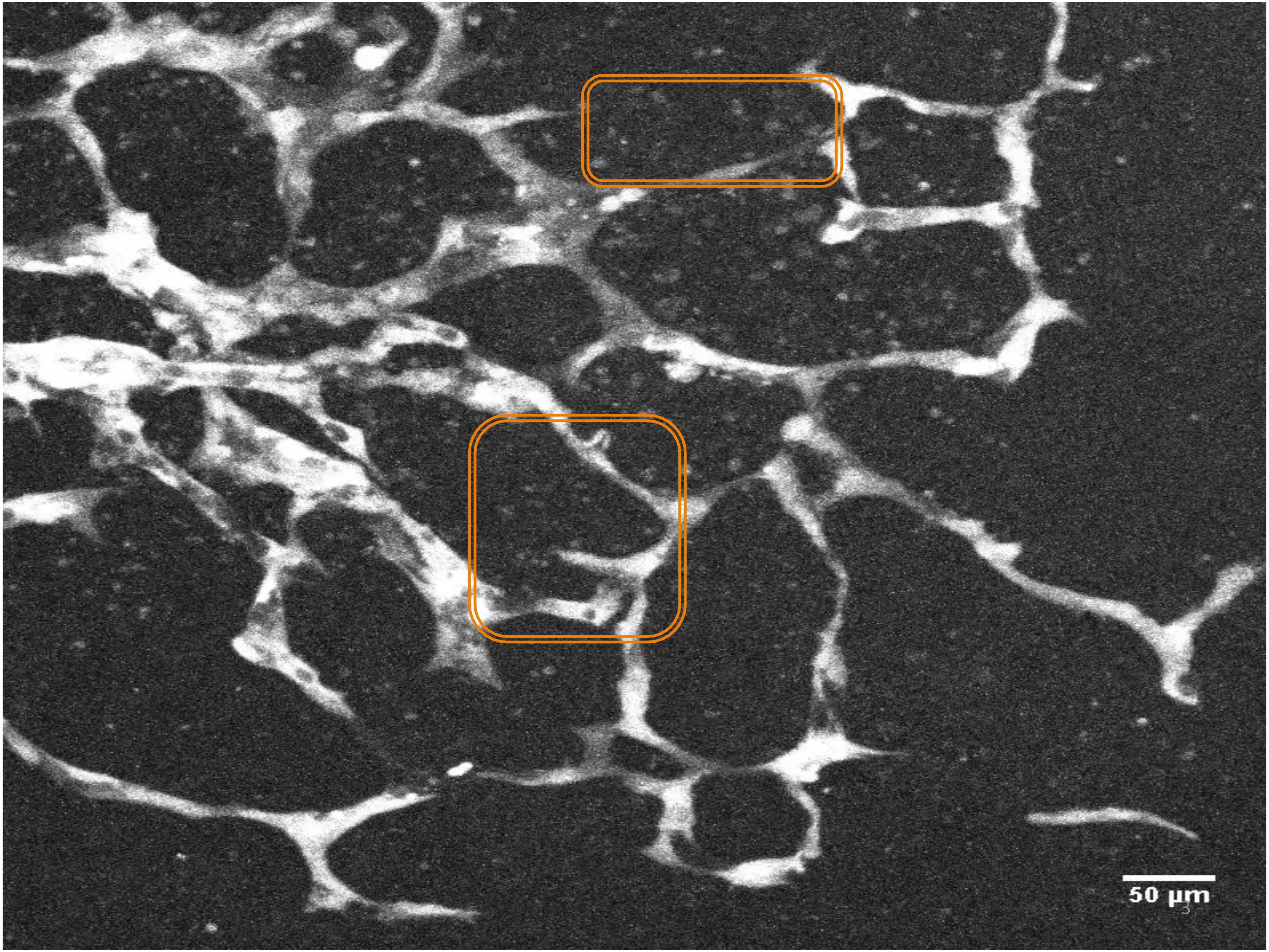
Organism

Organ & Tissue

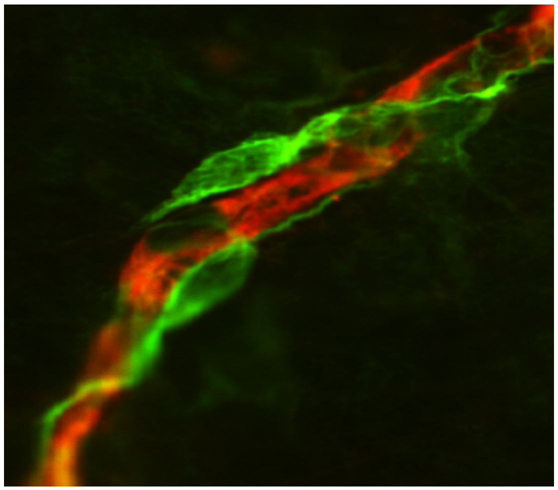
Multi-Cell

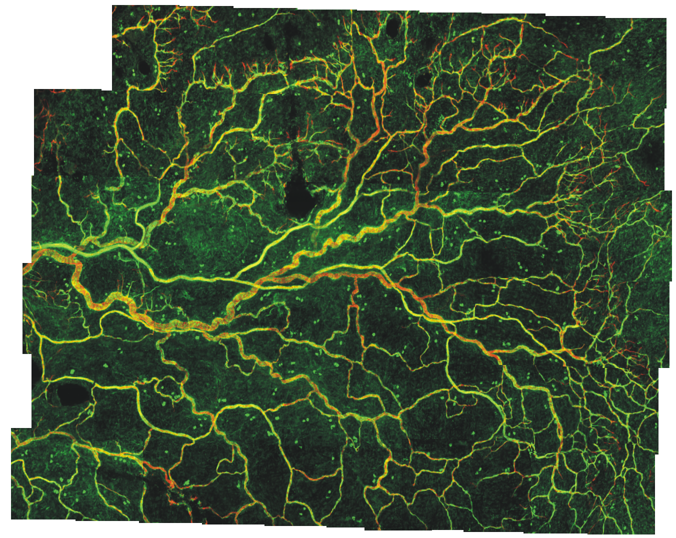
Intracellular

Gene / Protein

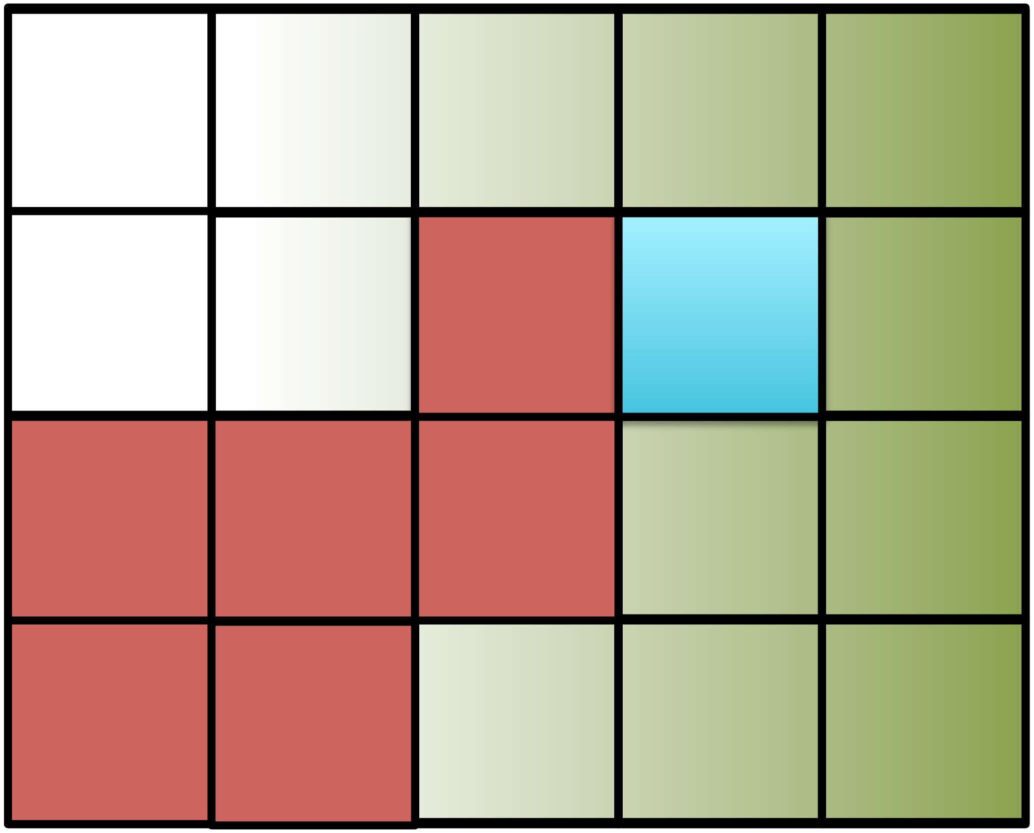

50 µm

Growth & Remodeling:
Results from emergent behavior of individual cells





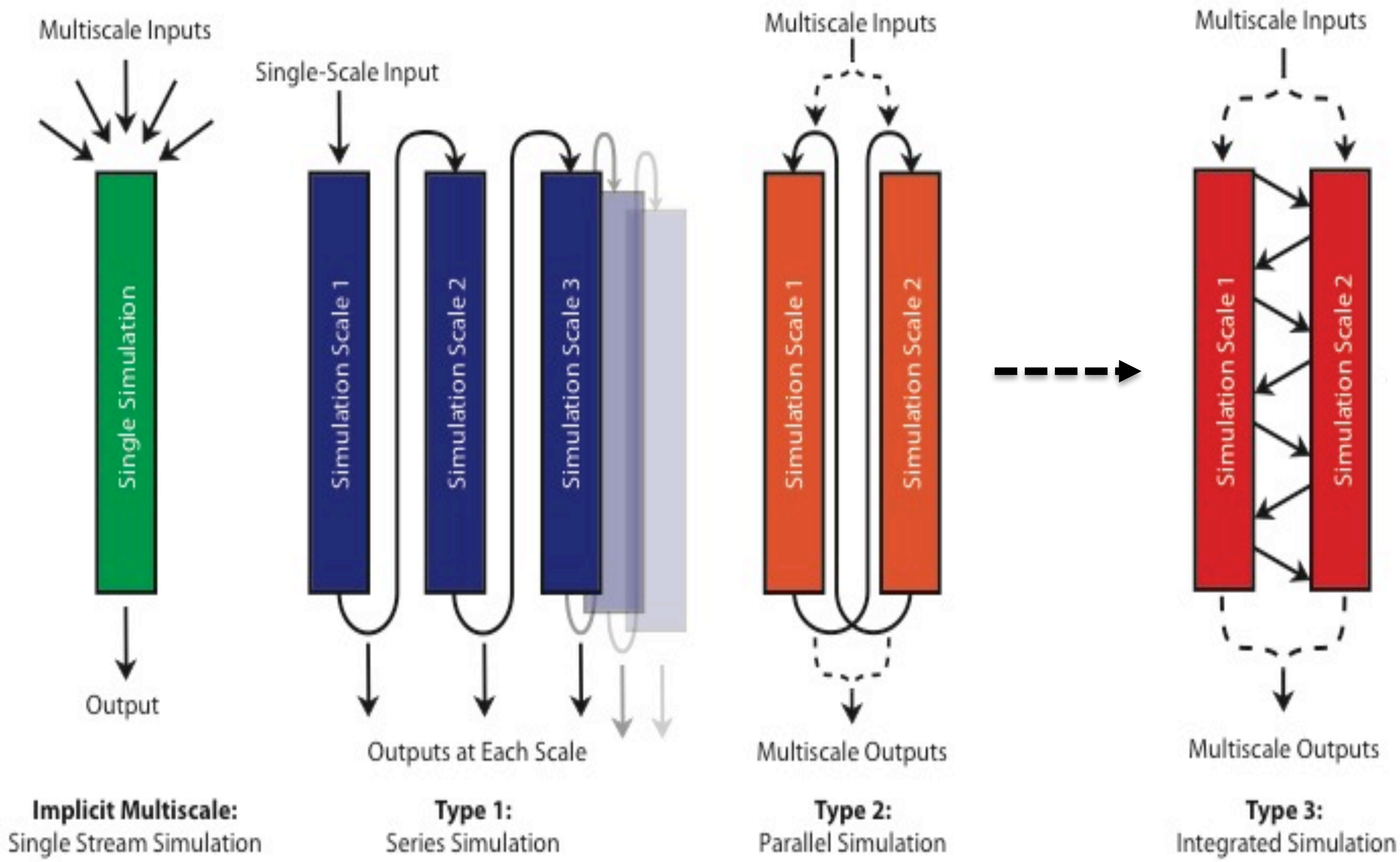
Agent-based Modeling:
Cells are agents that interact and respond to rules



Example Behaviors:

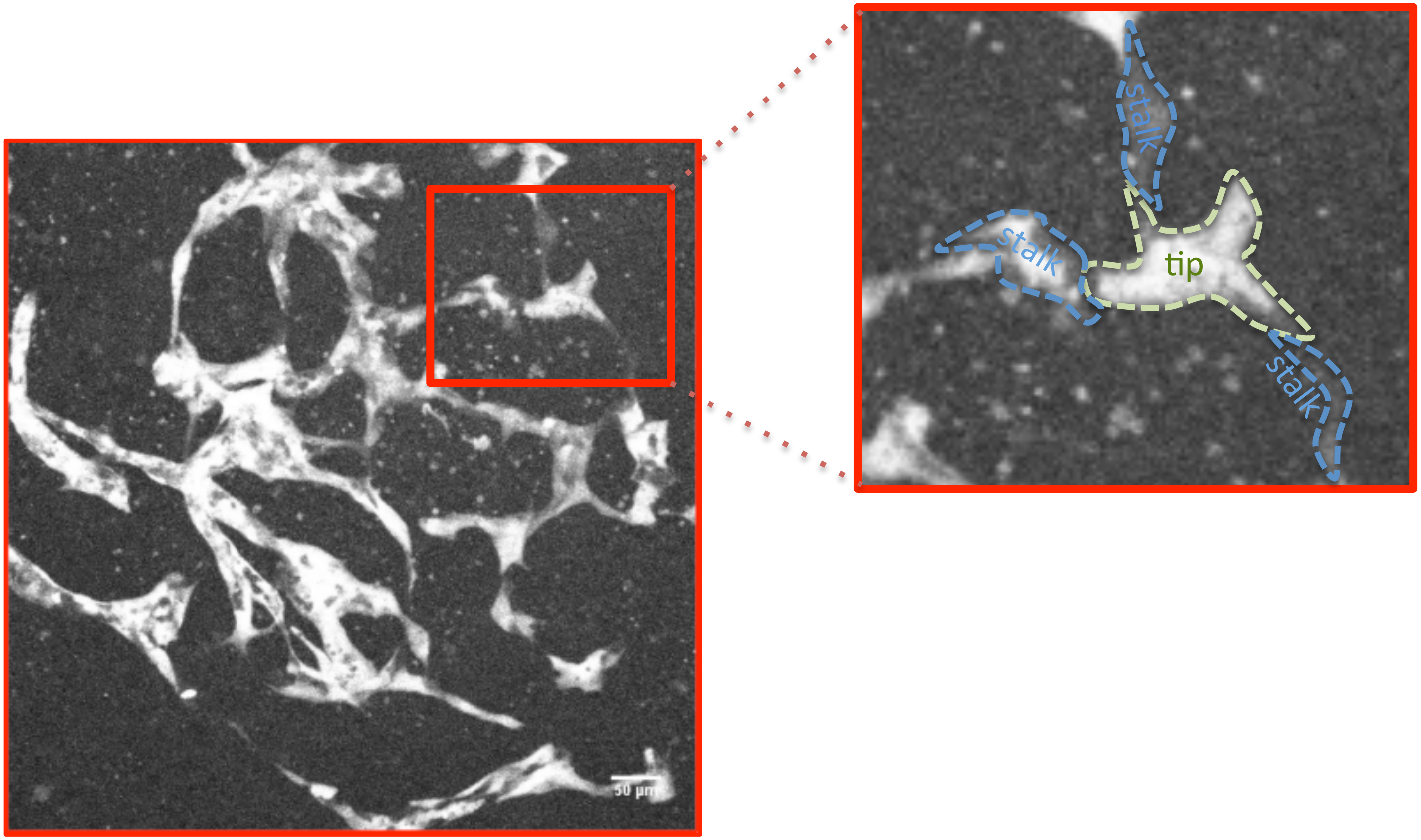
1. Growth Factor Secretion
2. Phenotype Switch
3. Chemotaxis
4. Mitosis
5. Apoptosis/Necrosis

AGENT-BASED MODELS: OFFER A FLEXIBLE PLATFORM FOR MULTISCALE MODELING



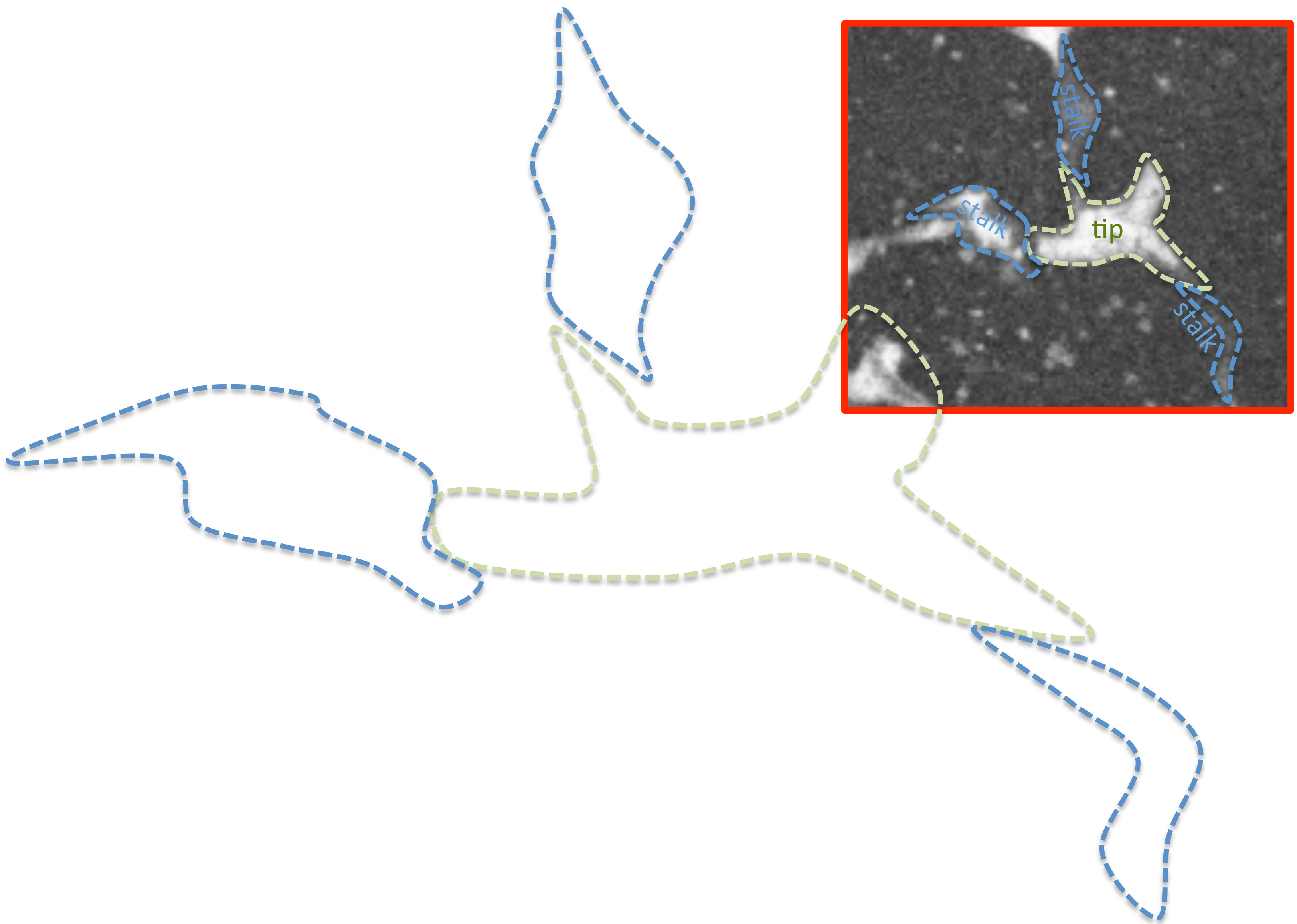
J. Walpole, J.A. Papin, S.M. Peirce (2013) Annual Reviews of Biomedical Engineering

Angiogenesis:
Tip/Stalk Cells Respond to VEGF and each other

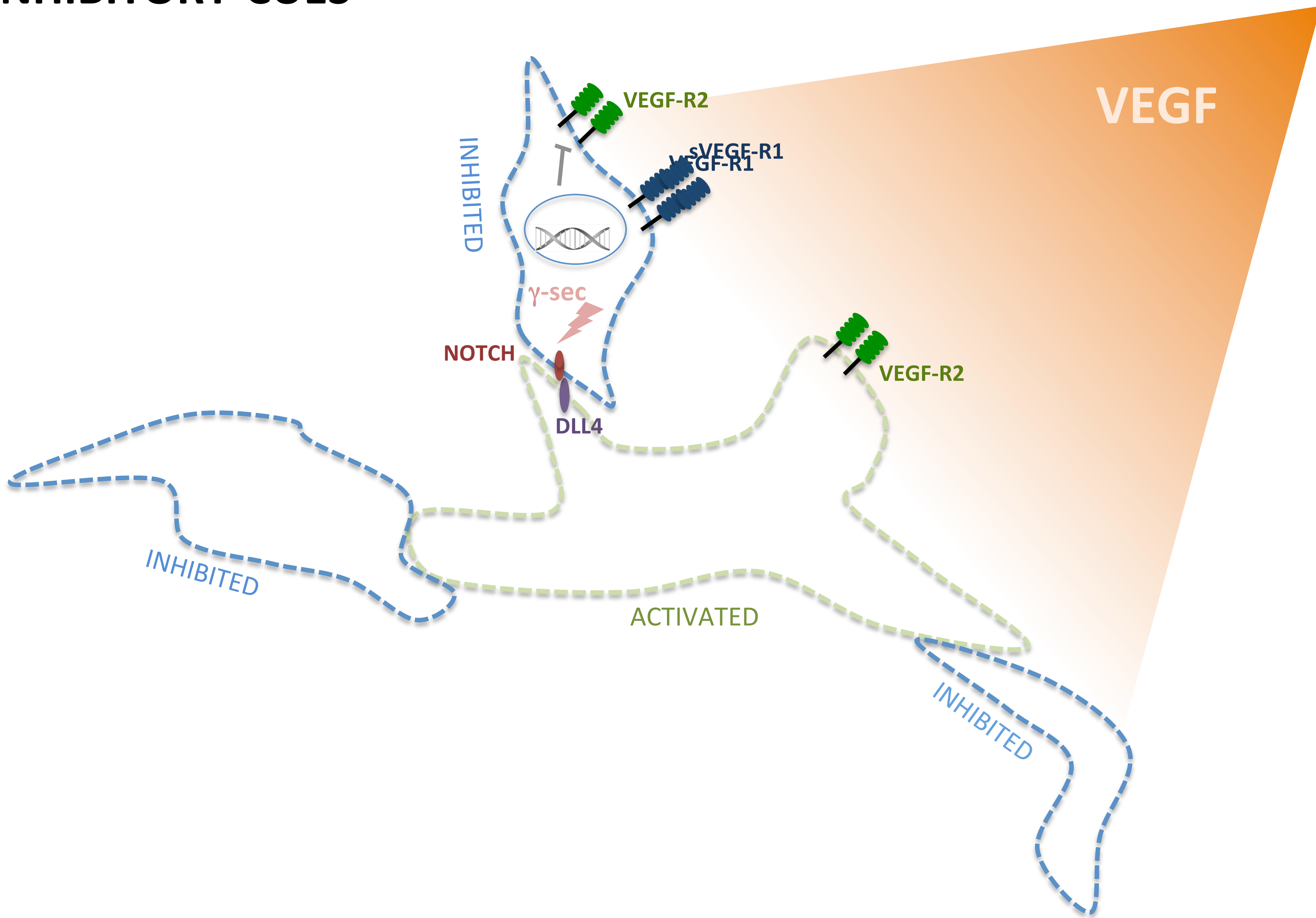


F. Mac Gabhann, S.M. Peirce, V. Bautch (2012)

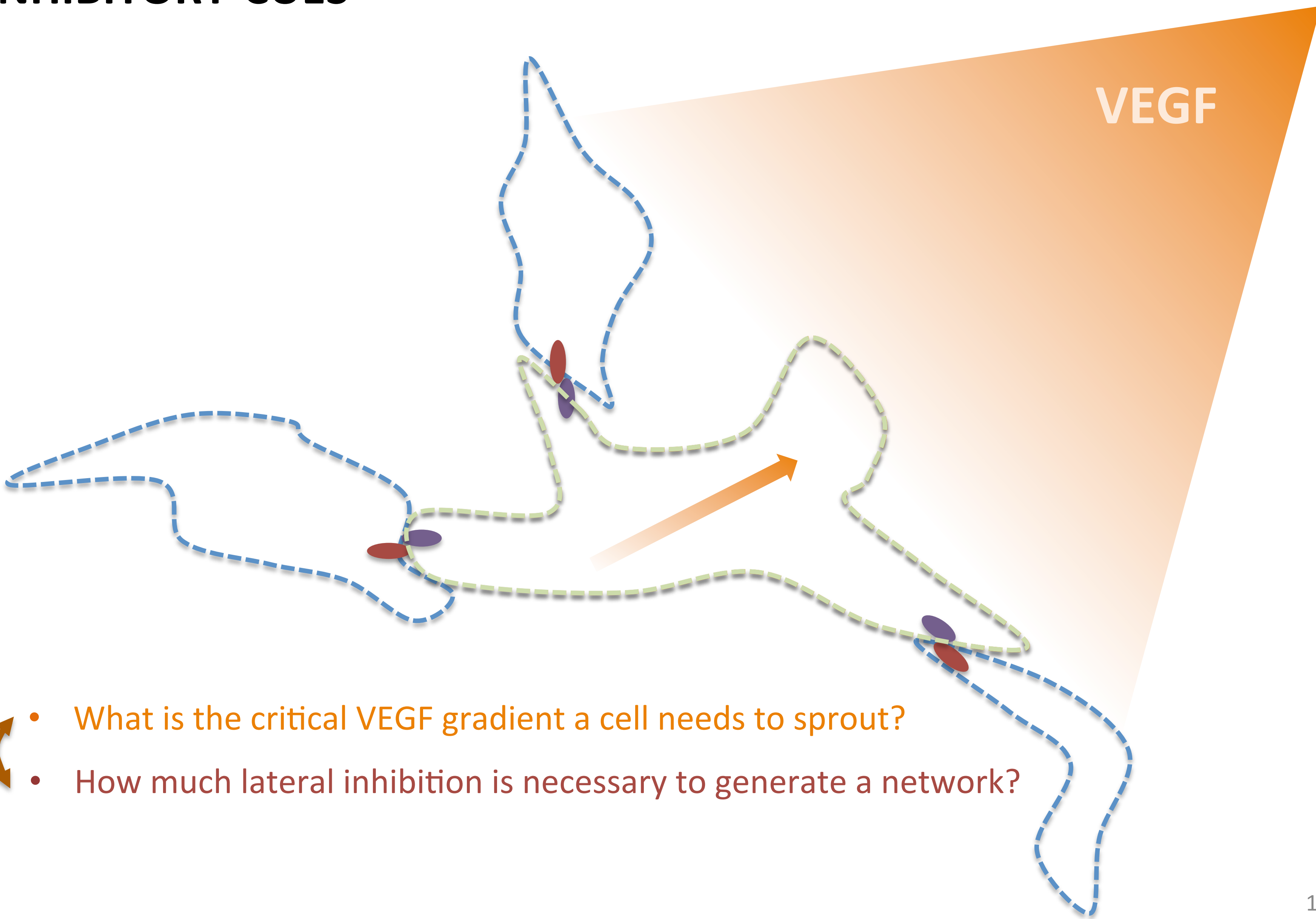
Sprout initiation: a balance between stimulatory and inhibitory cues



Sprout initiation: a balance between stimulatory and inhibitory cues

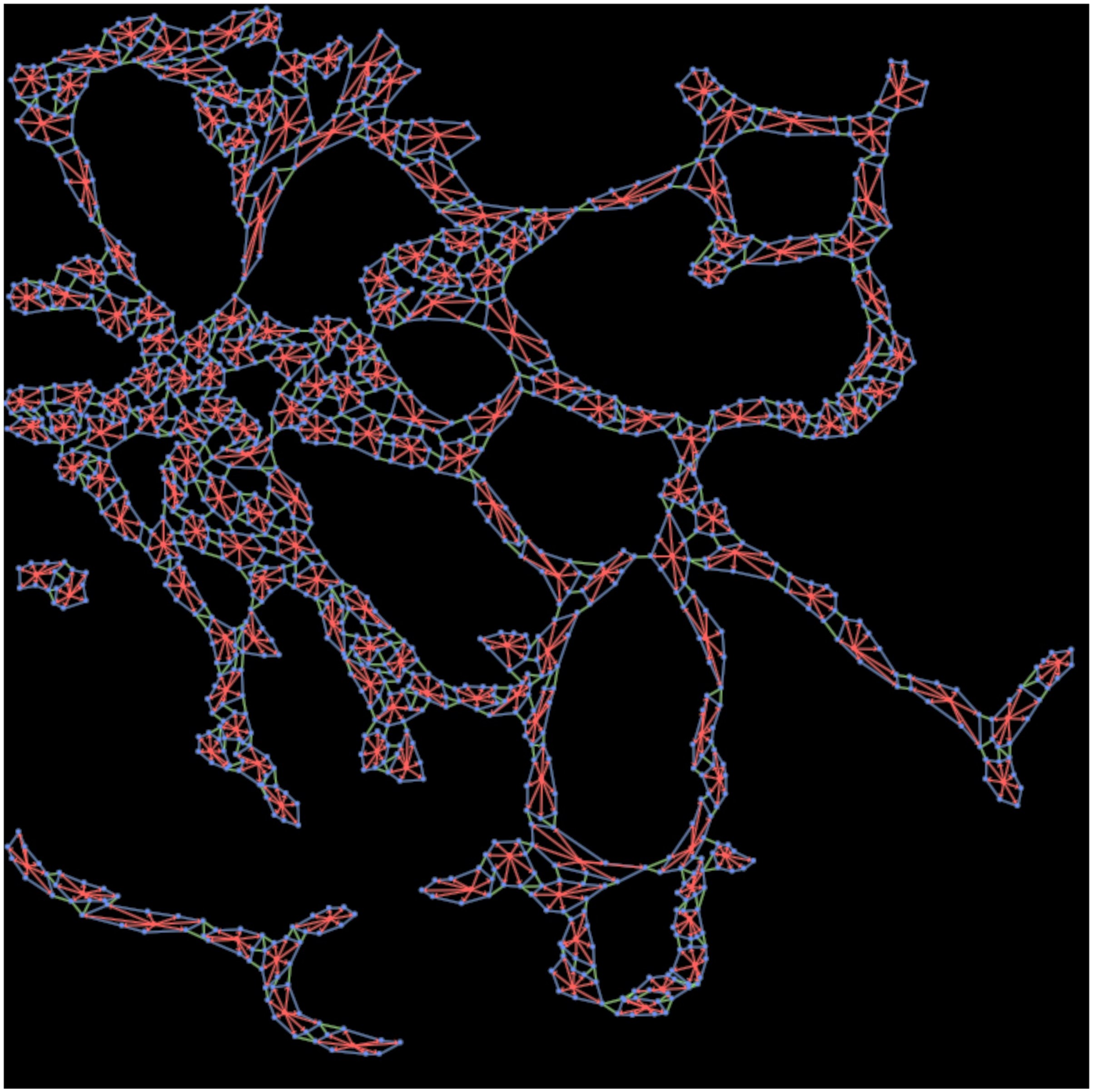


Sprout initiation: a balance between stimulatory and inhibitory cues

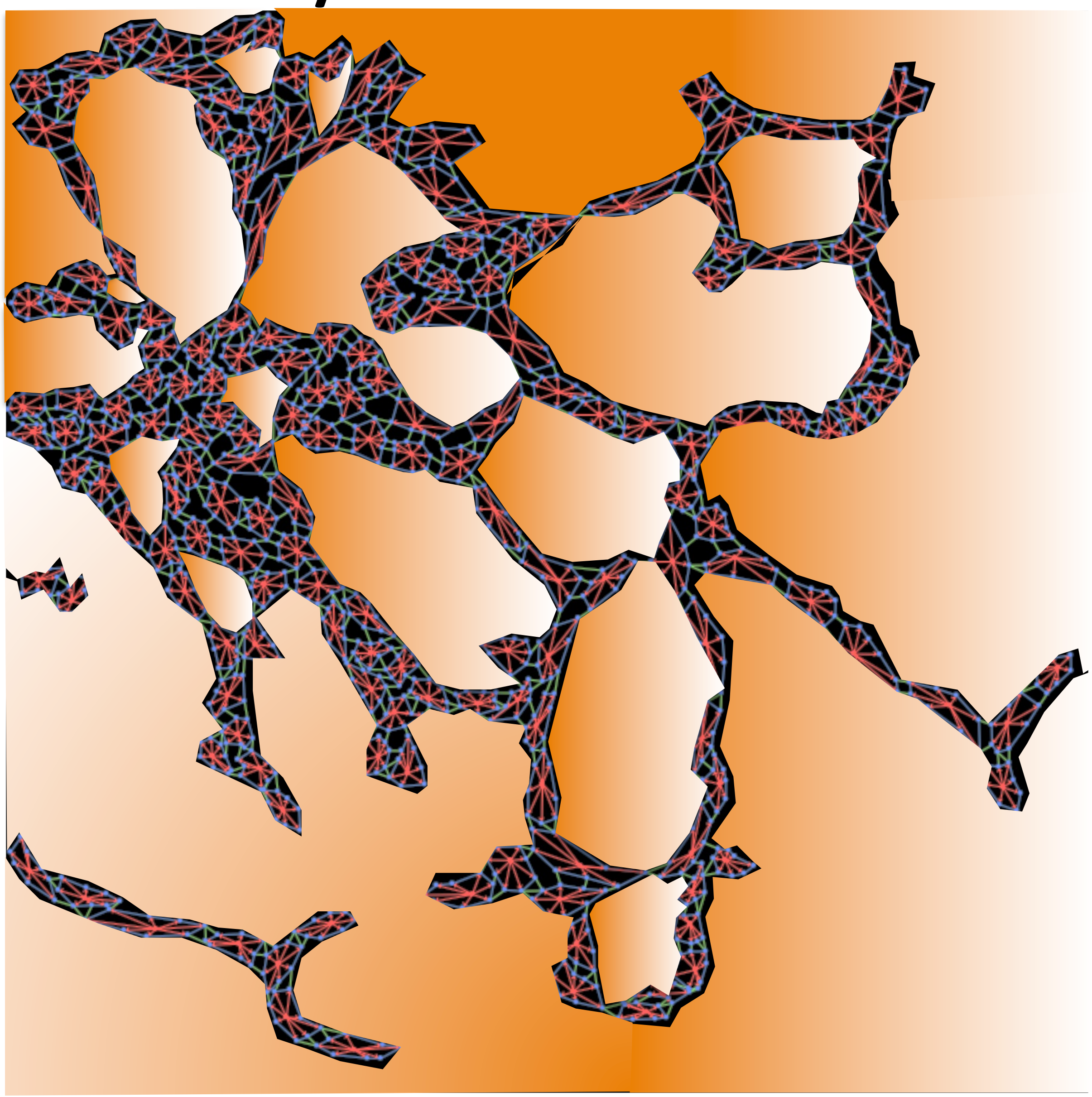


- What is the critical VEGF gradient a cell needs to sprout?
- How much lateral inhibition is necessary to generate a network?

Initial conditions for ABM are based on actual network

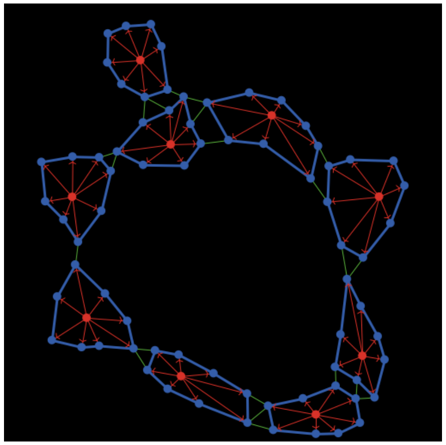


Growth factor diffusion and ligand-receptor binding are predicted by ODE/PDE diffusion and kinetics model



RULES AND PARAMETERS ARE LITERATURE DERIVED AND CROSS-VERIFIED

ABM



Rate of VEGFR2 production depends on NOTCH:

$$qVEGFR2 = qVEGFR2_{min} + (qVEGFR2_{max} - qVEGFR2_{min})e^{-k*Active\_NOTCH}$$

scaling coefficient fit to PDE

literature derived

amount of activated NOTCH in same cell

Activated NOTCH is a function of DLL4:

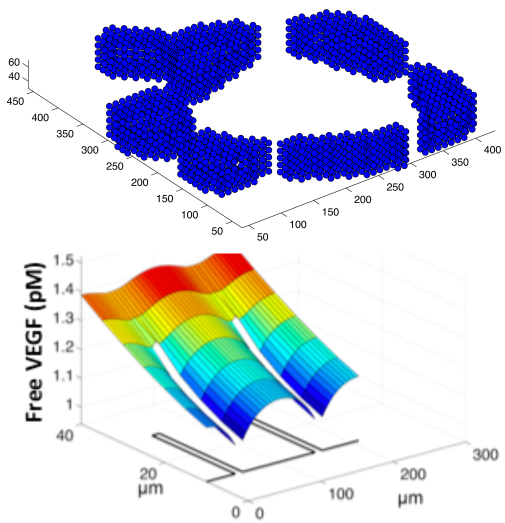
$$\frac{dActive\_NOTCH}{dt} = k_{Activation} * Inactive\_NOTCH * \sum_{cells} \alpha DLL4 - k_{deg} * Active\_NOTCH$$

rate constant for NOTCH activation

DLL4-to-NOTCH conversion

degradation rate of active NOTCH

PDE/ODE



Protein transport is governed by a coupled system of PDEs:

$$\frac{\partial[V]}{\partial t} = q_V + D_V\nabla^2[V] - \sum_i\left(k_{on}[V][M_i] - k_{off}[V\cdot M_i]\right) - \sum_j\left(k_{on}[V][R_j] - k_{off}[V\cdot R_j]\right) - k_{deg}[V]$$

diffusion through interstitial space

production rate (determined by ABM)

reversible binding to ECM & soluble receptors

and membrane receptors

degradation

Cell surface density of receptors is governed by ODEs:

$$\frac{dR}{dt} = s_R - k_{int\,R} - \sum_i\left(k_{on}[V_i][R] - k_{off}[V_i\cdot R]\right) - \sum_i\left(k_{dim}[V_i\cdot R][R] - k_{off}[R\cdot V_i\cdot R]\right)$$

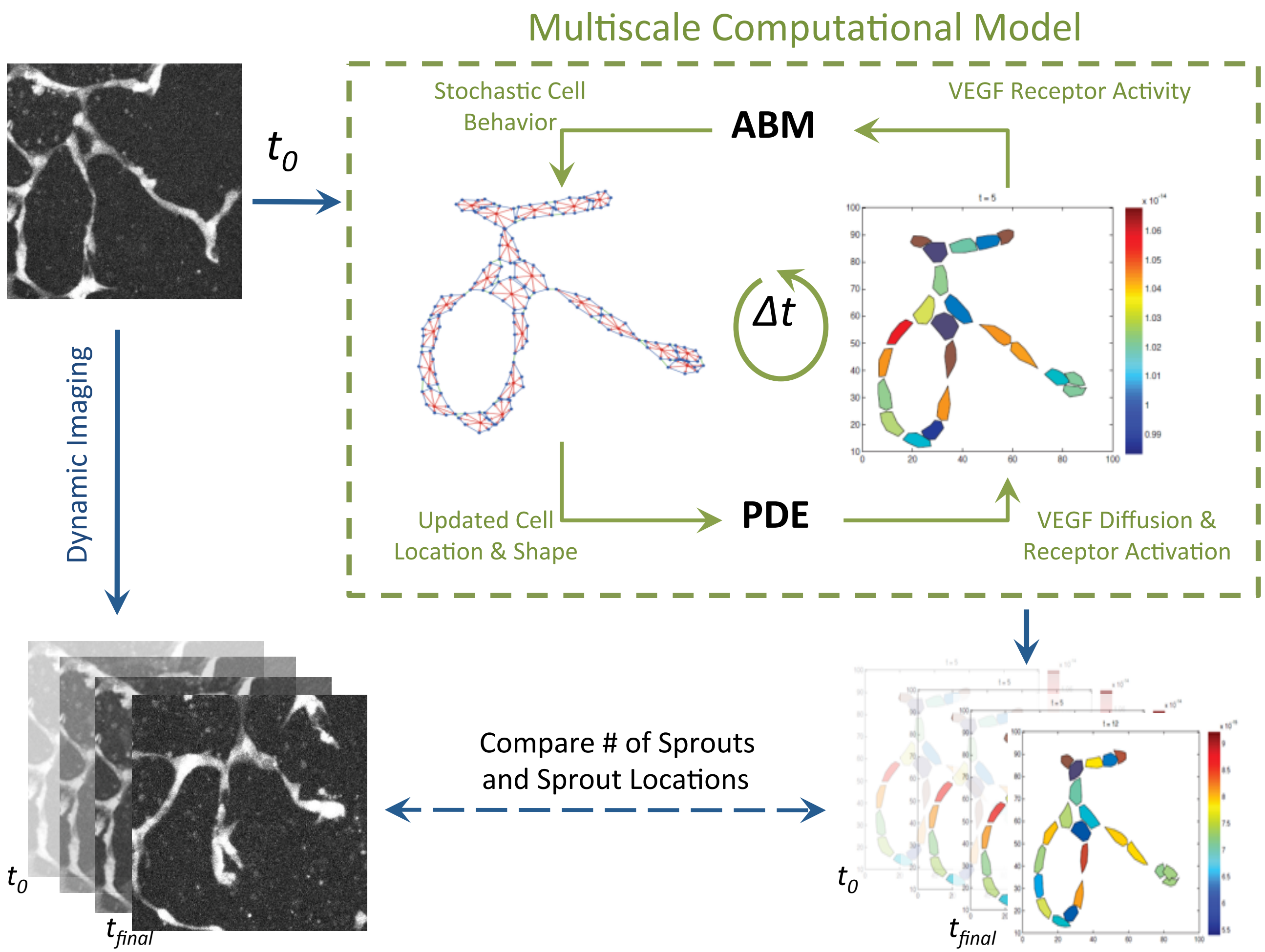
insertion in the membrane (calculated by ABM)

receptor internalization

ligand binding

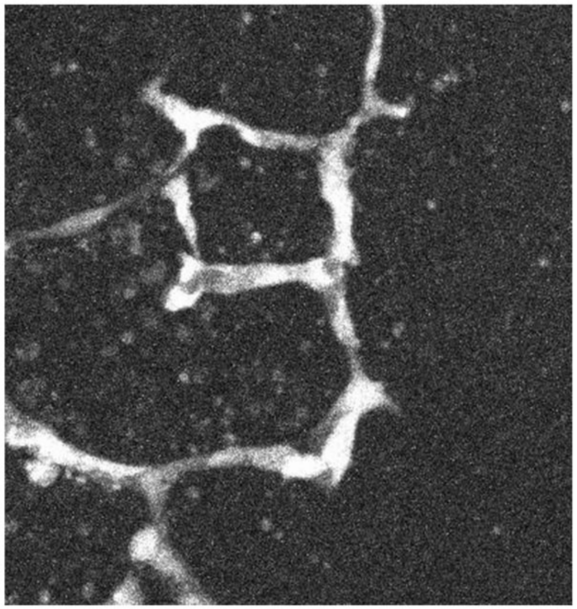
receptor dimerization

MULTISCALE MODEL: ABM MODEL OF CELL BEHAVIOR COUPLED TO PDE/ODE MODEL OF PROTEIN DIFFUSION/RECEPTOR BINDING

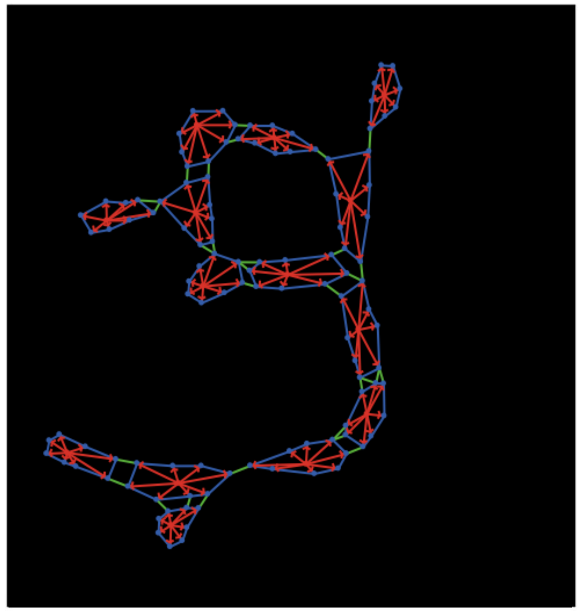


Multiscale Model Predictions: Sprout frequency and location (true/false positives)

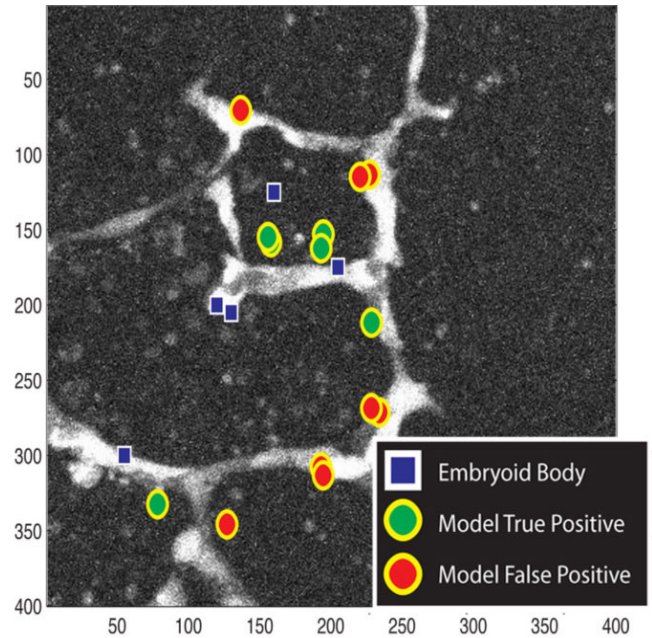
Embryoid Body



Multiscale Model



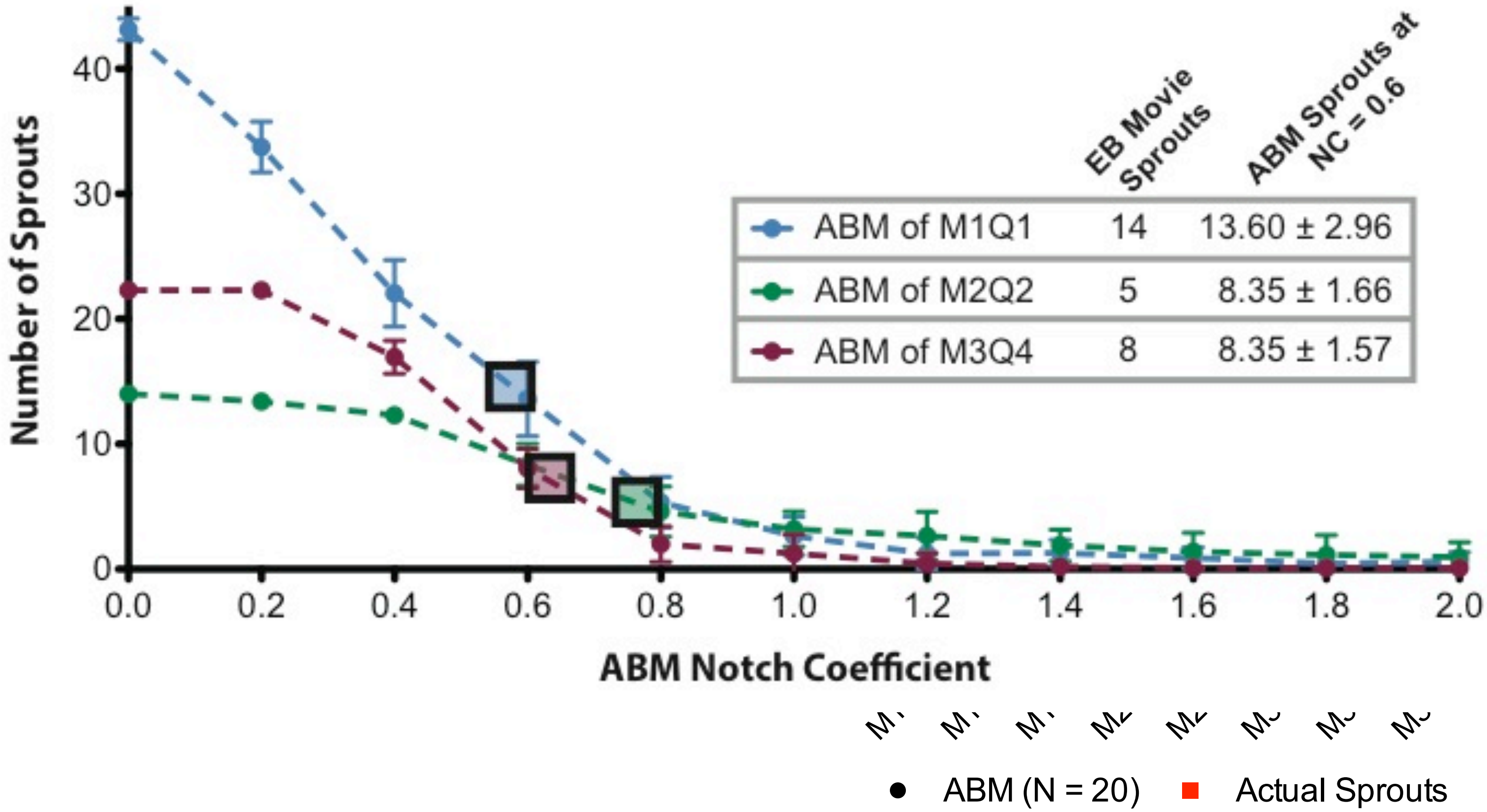
Sprout Frequency and Location



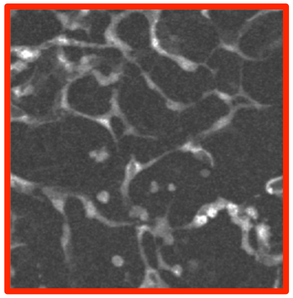
True Positive – Model prediction within 1 cell length of actual sprout

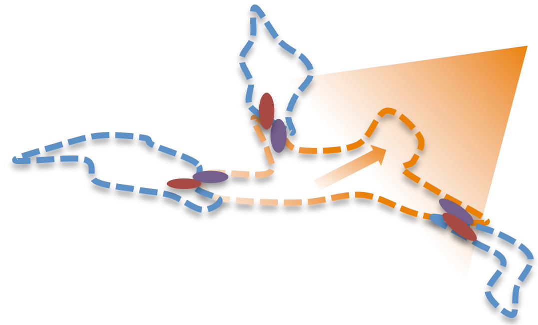
False Positive – Model prediction outside range of actual sprout

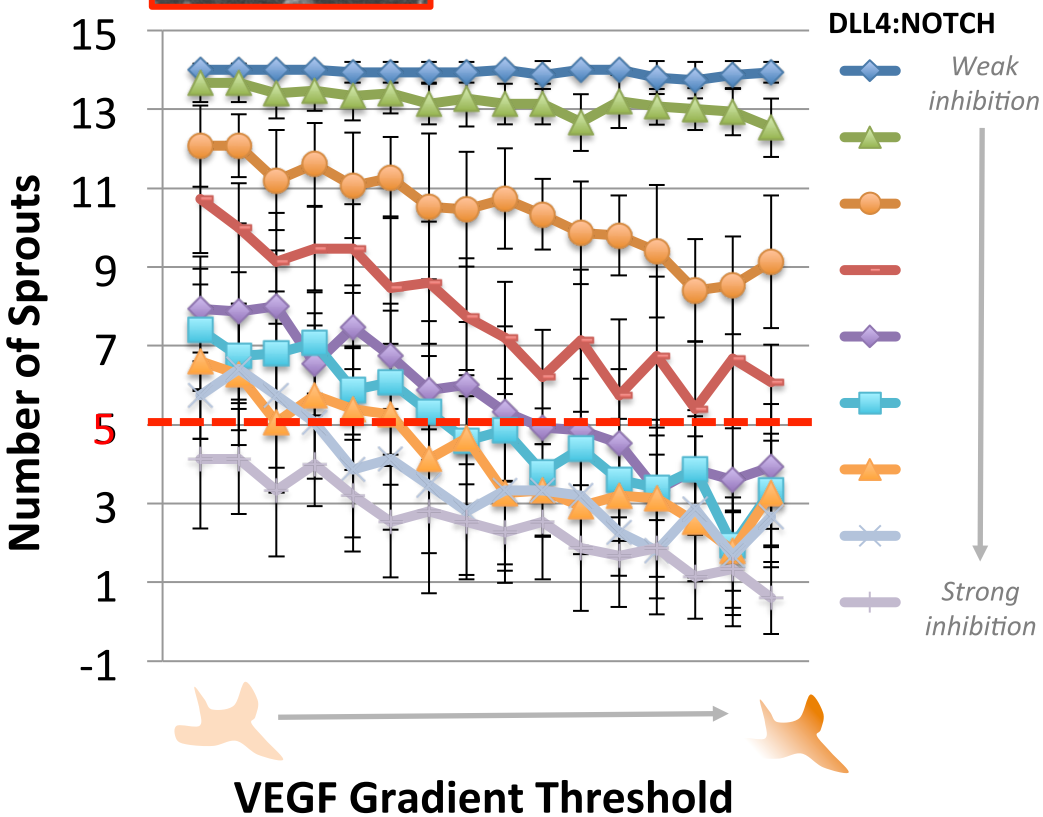
MODEL IS PARAMETERIZED USING TRAINING DATA FOR SPROUT FREQUENCY AND VALIDATED AGAINST INDEPENDENT TEST DATA

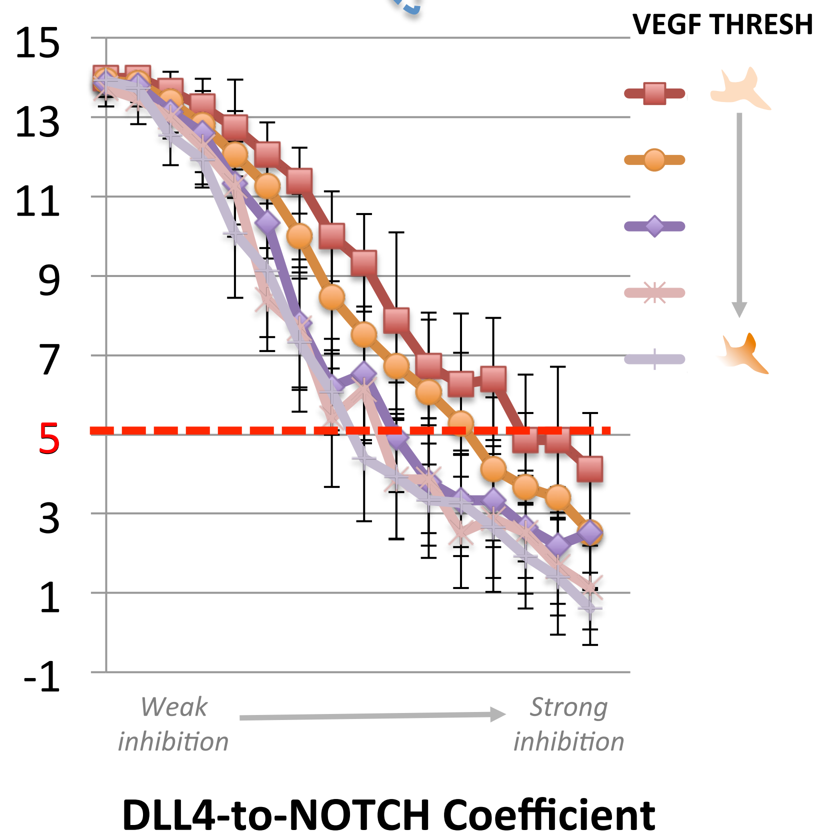


Bivariate sensitivity analysis suggests sensivity to inhibition supersedes sensitivity to stimulation

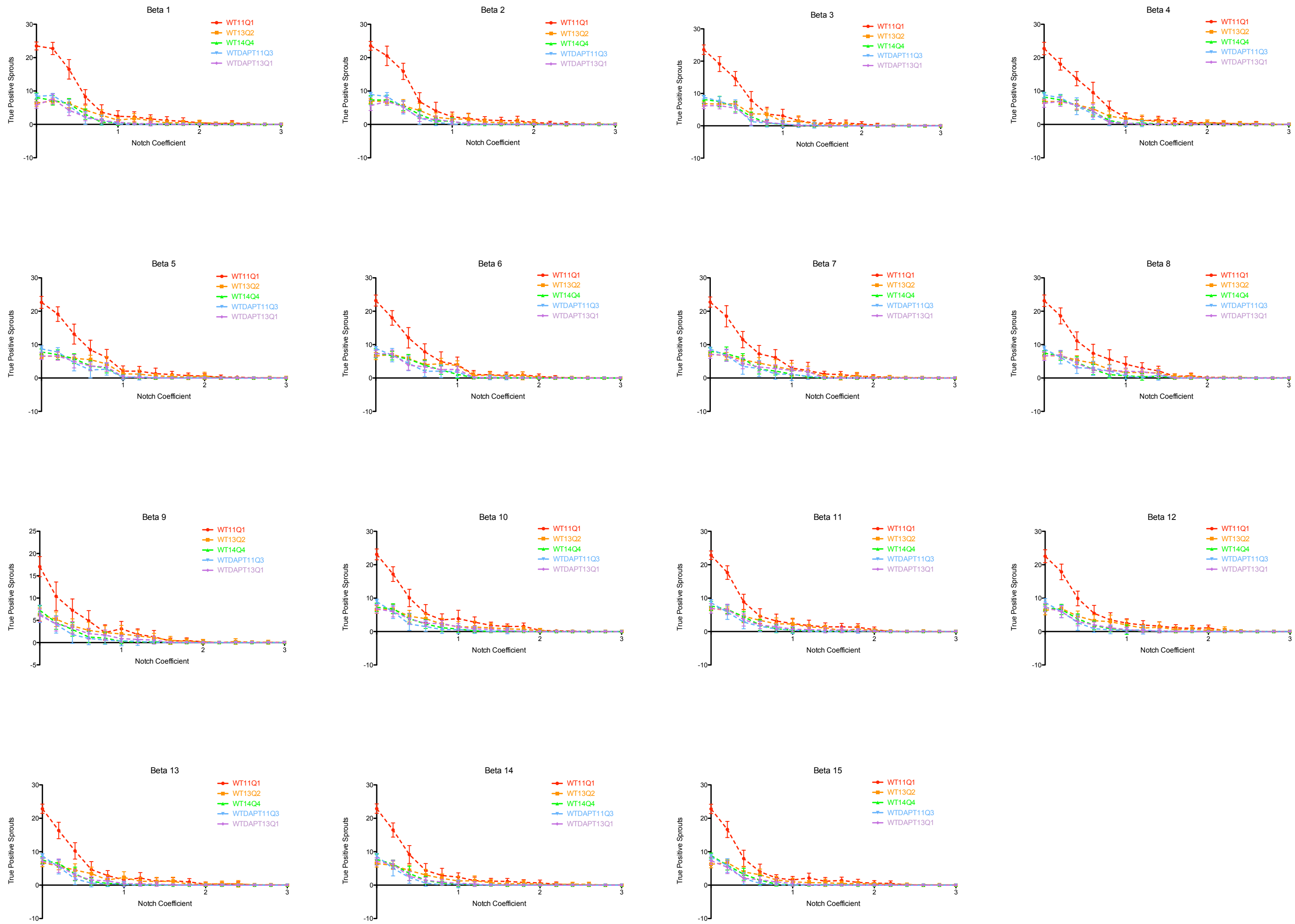




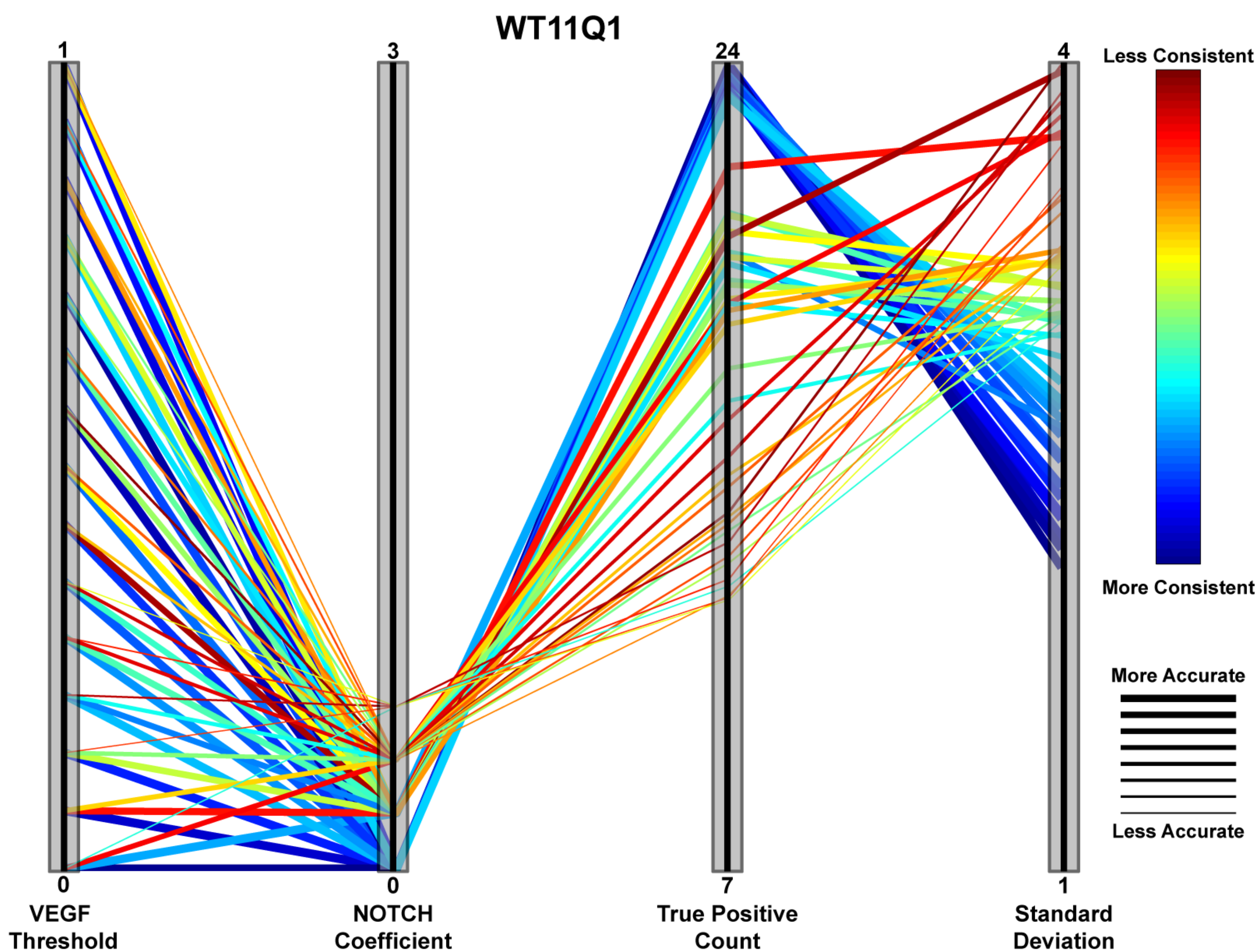




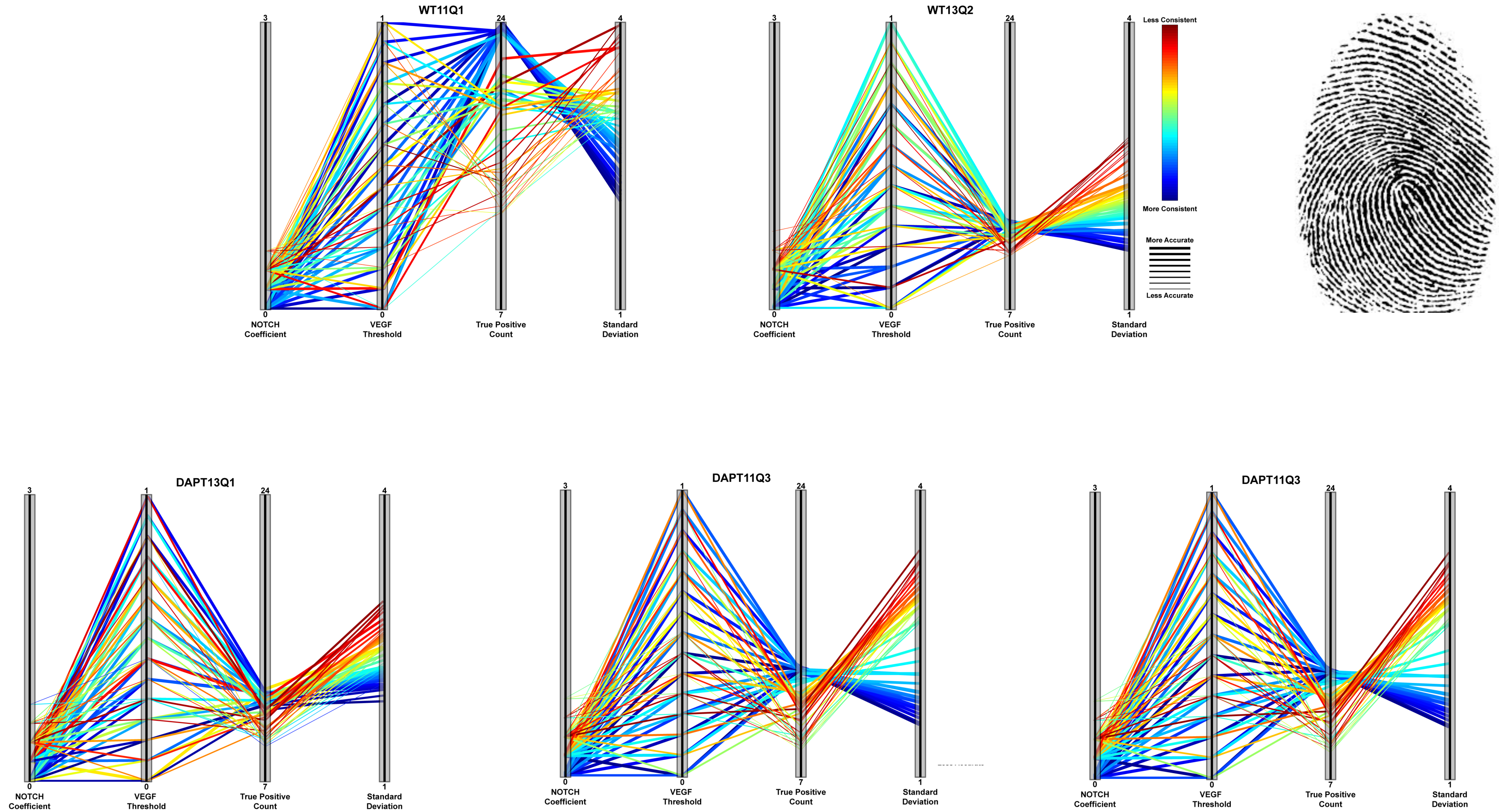
MULTIPARAMETRIC DATA POSES A CHALLENGE FOR DATA VISUALIZATION



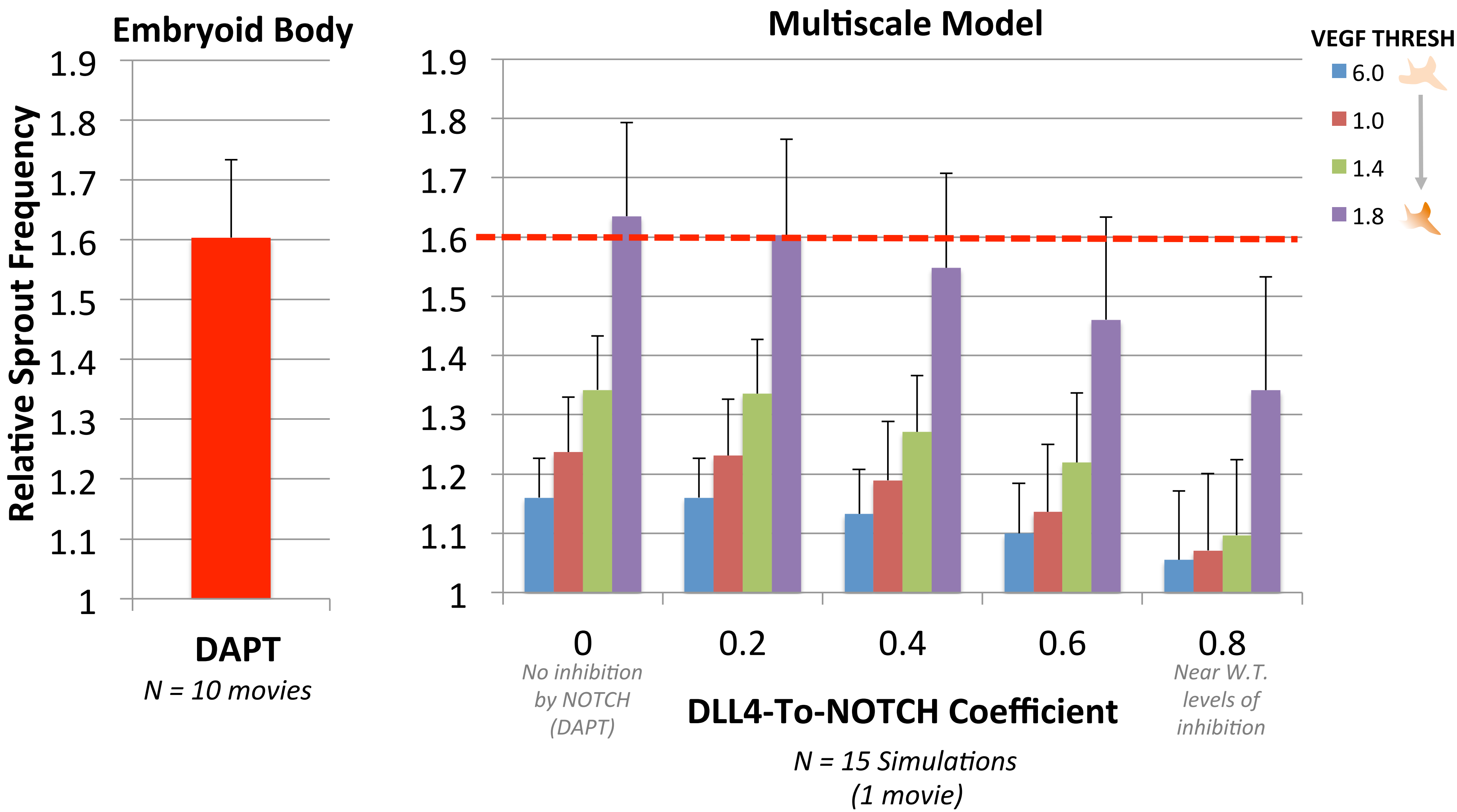
Multivariate sensitivity analyses pose a challenge for data visualization: Help from Parallel Coordinates



MULTIVARIATE SENSITIVITY ANALYSES POSE A CHALLENGE FOR DATA VISUALIZATION: HELP FROM PARALLEL COORDINATES

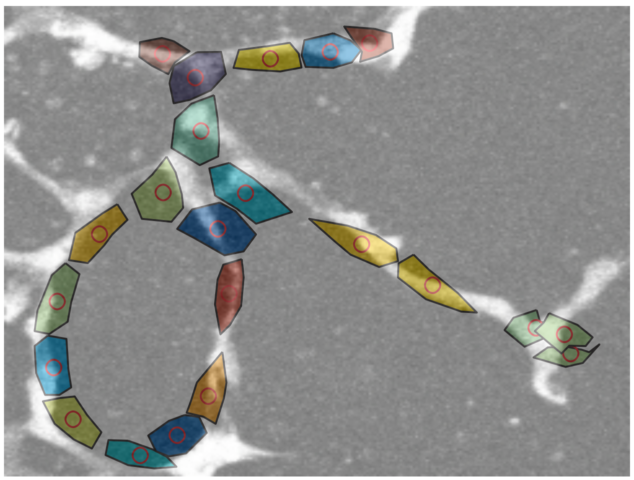


SIMULATING REDUCED INHIBITION RECAPITULATES DAPT (GAMMA-SECRETASE INHIBITOR) EXPERIMENTS

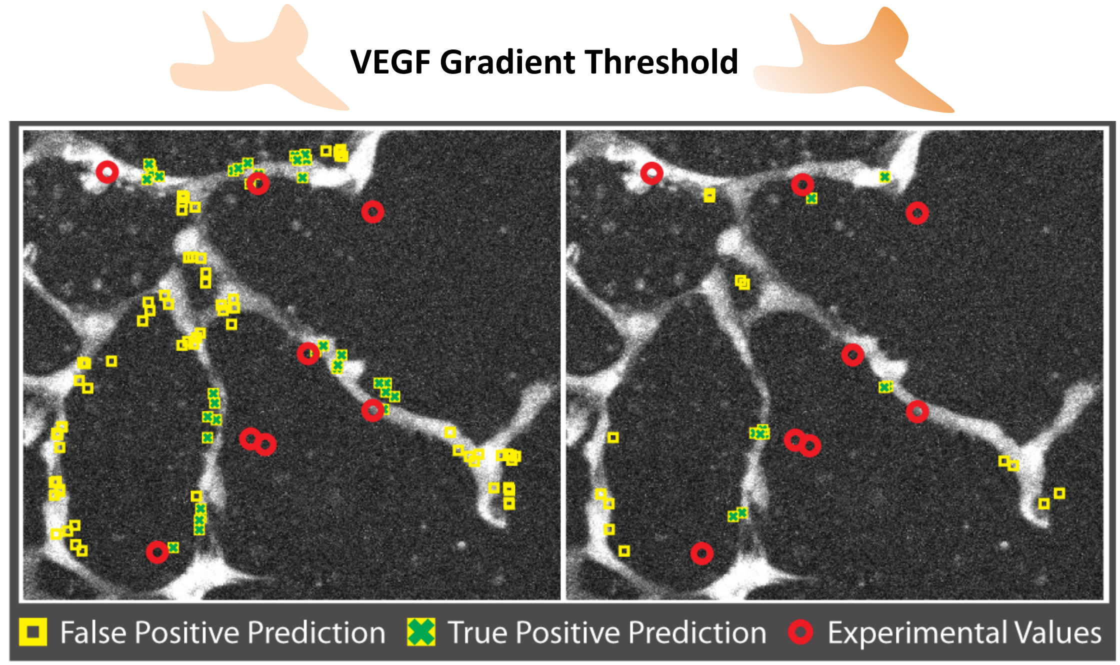


ABM PREDICTS VEGF-R ACTIVATION (HARD TO MEASURE), AS WELL AS SPROUT LOCATION

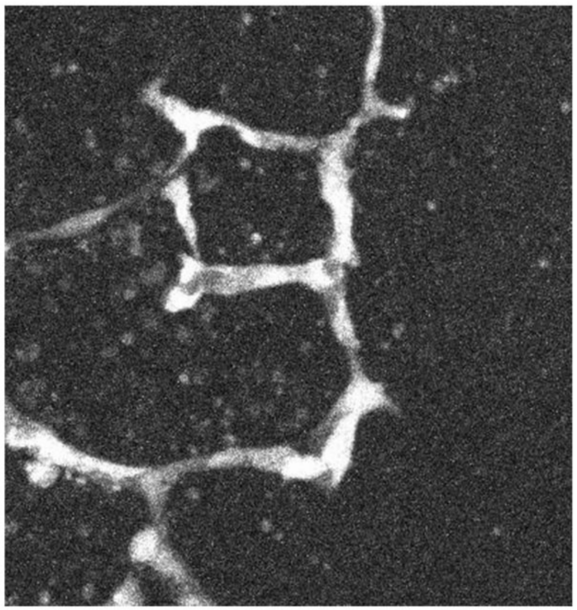
VEGF-R2 Activation

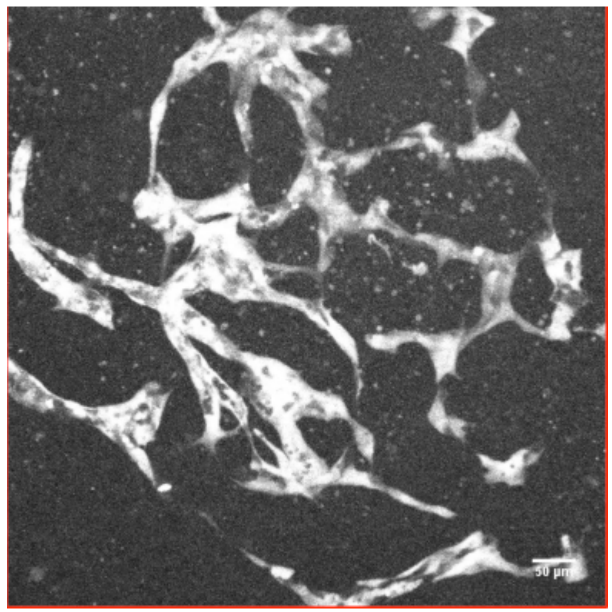


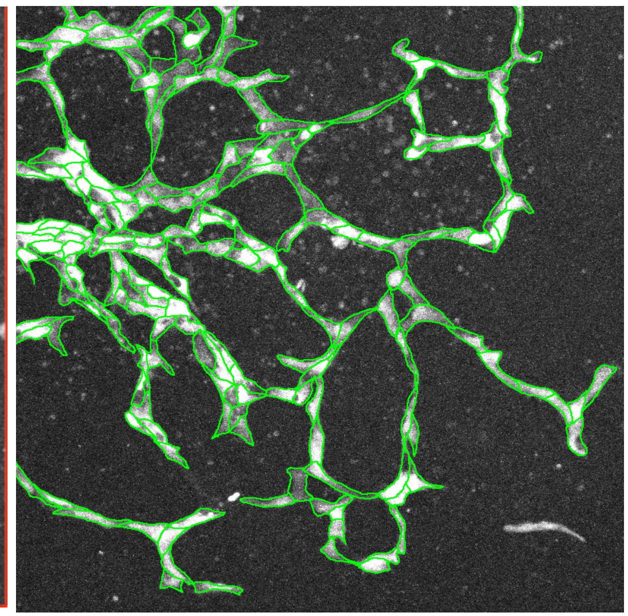
VEGF Gradient Threshold



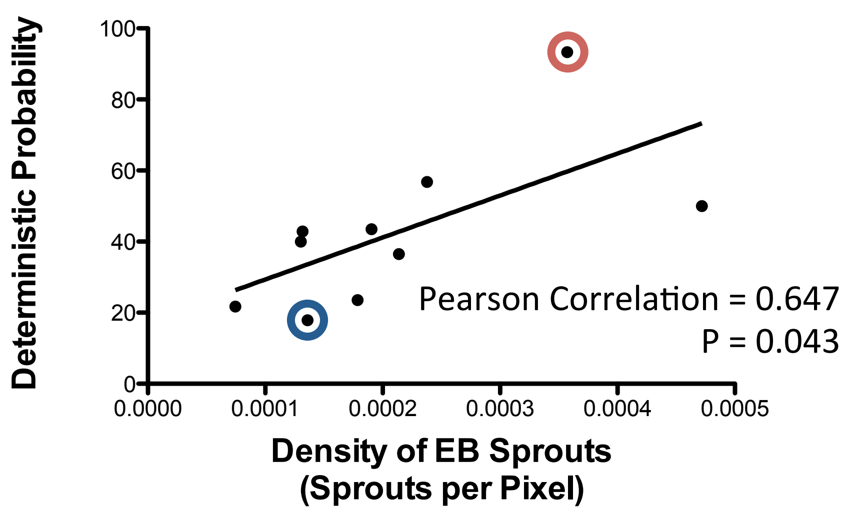
DOES SPROUT DENSITY AFFECT THE MODEL'S ABILITY TO CORRECTLY PREDICT SPROUT LOCATIONS?

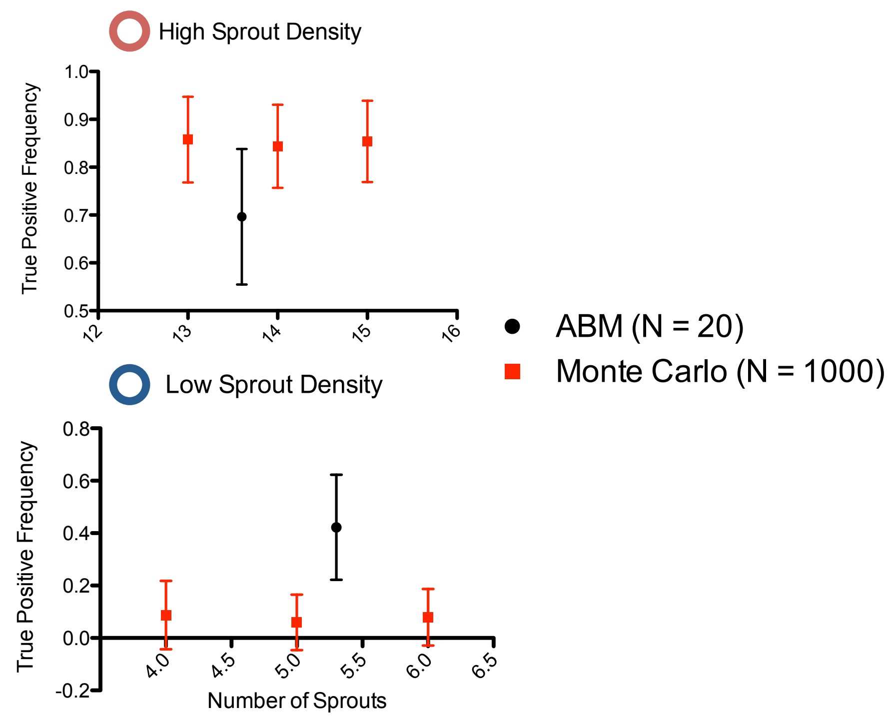




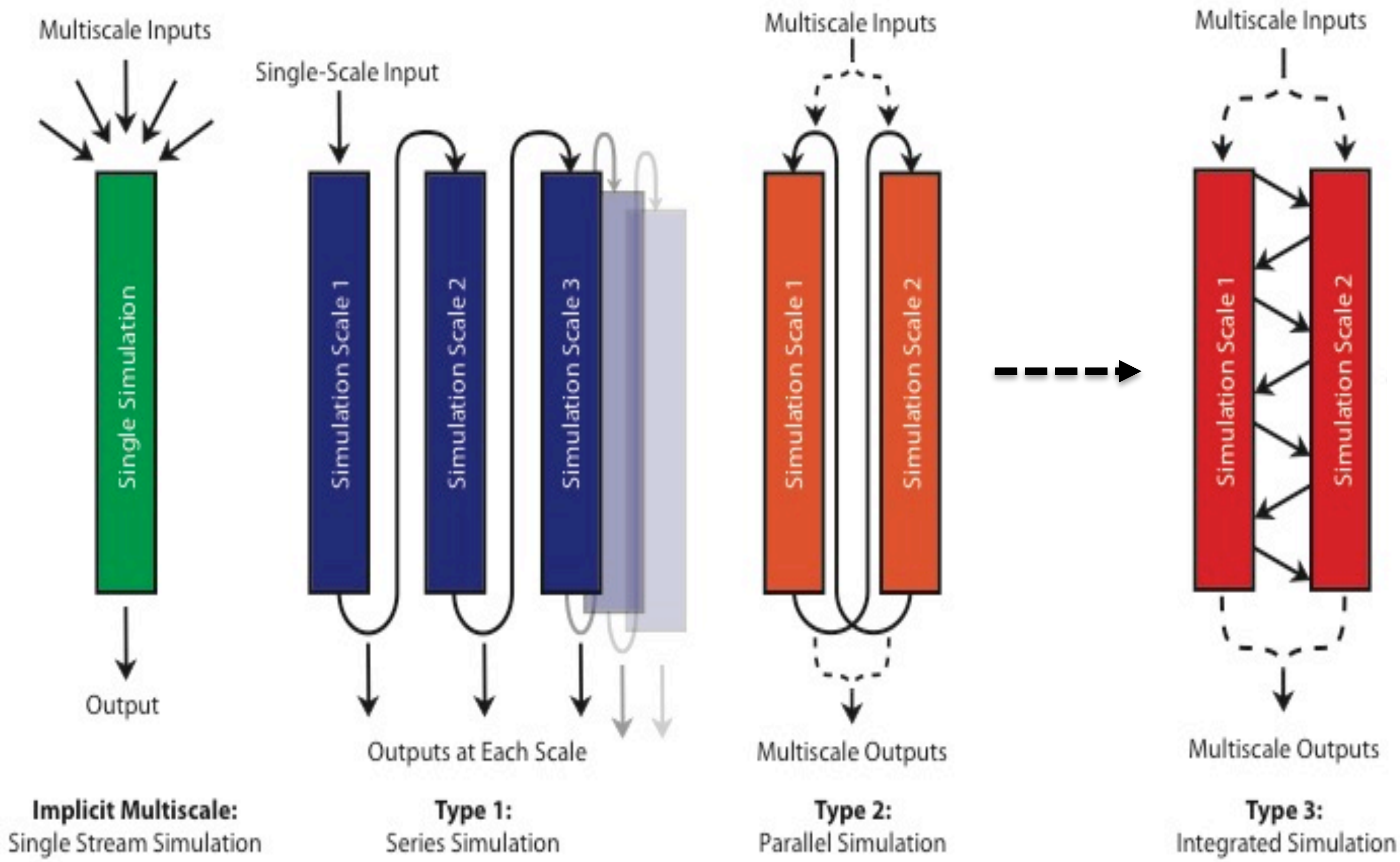


Probability of randomly selecting correct sprout locations is proportional to sprout density



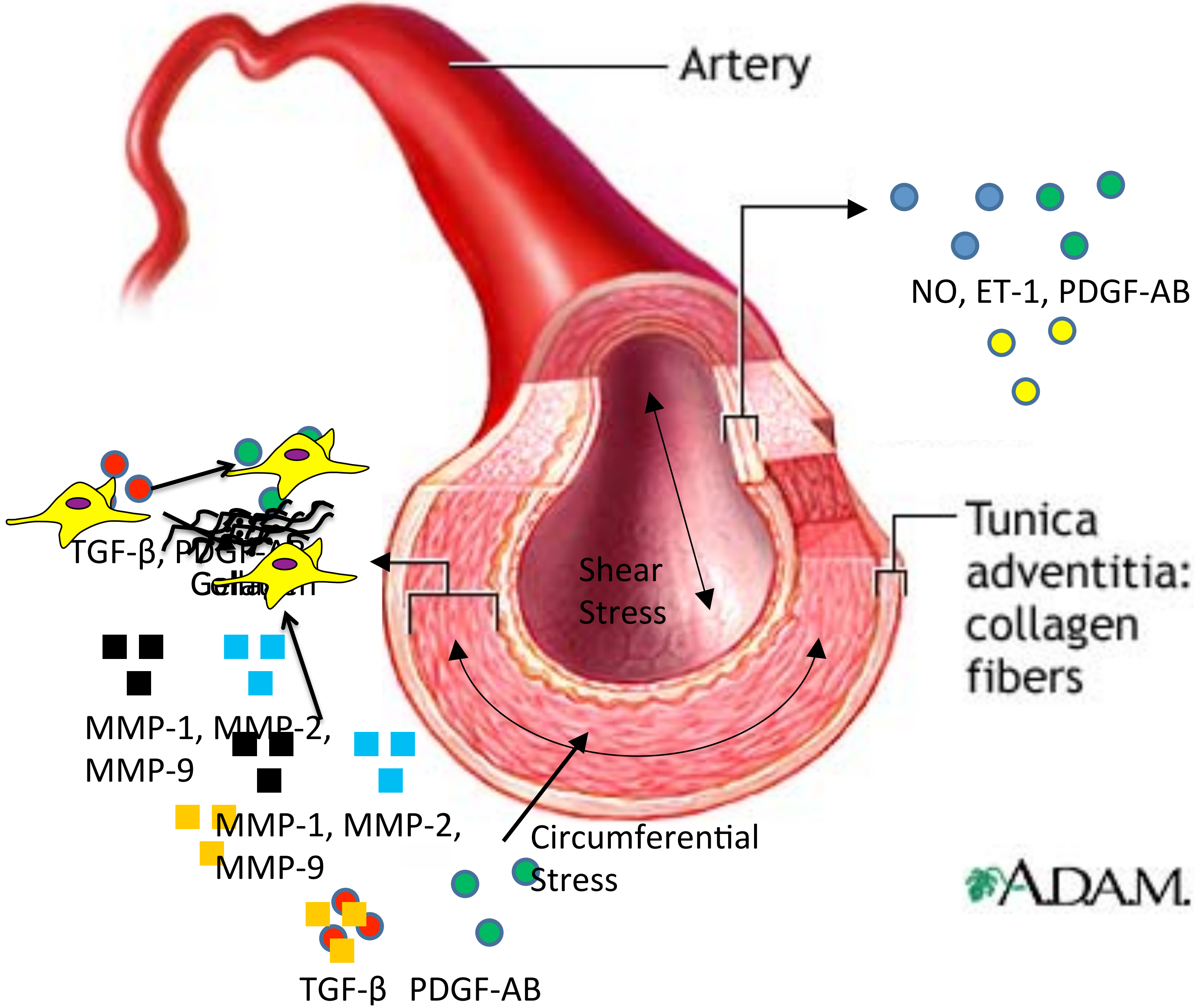


AGENT-BASED MODELS: OFFER A FLEXIBLE PLATFORM FOR MULTISCALE MODELING

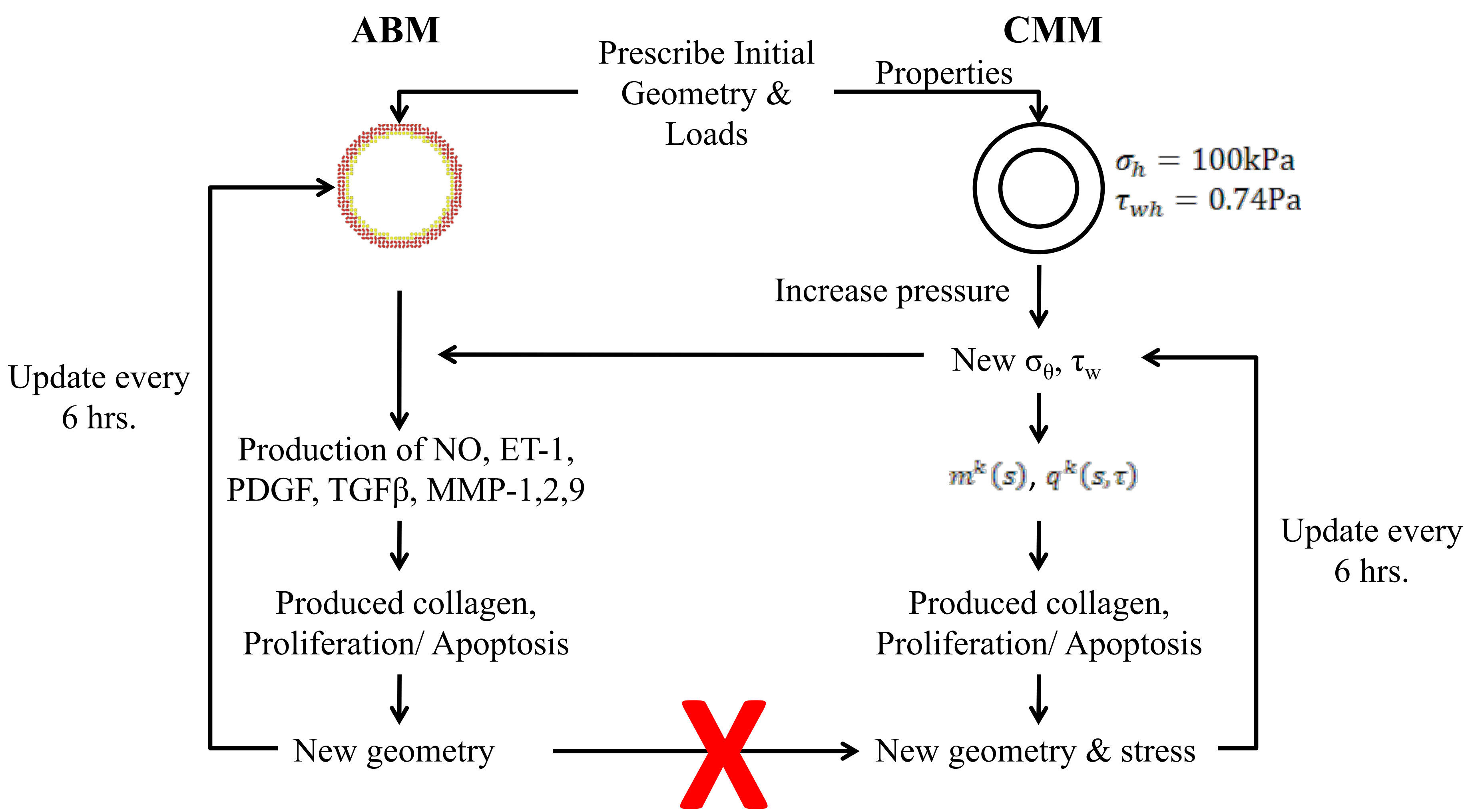


J. Walpole, J.A. Papin, S.M. Peirce (2013) Annual Reviews of Biomedical Engineering

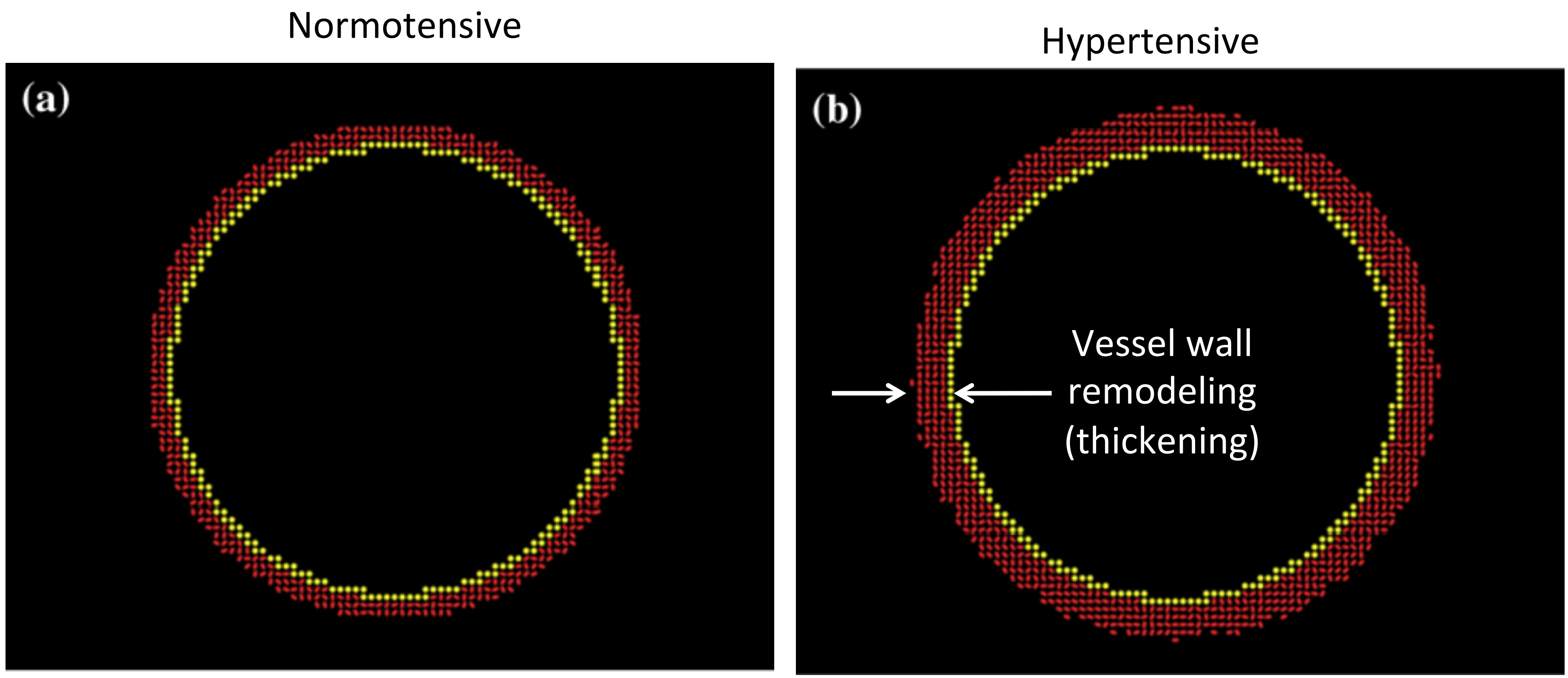
HYPERTENSION: VASCULAR WALL GROWTH AND REMODELING



MULTISCALE MODEL OF VASCULAR WALL HYPERTROPHY DURING HYPERTENSION

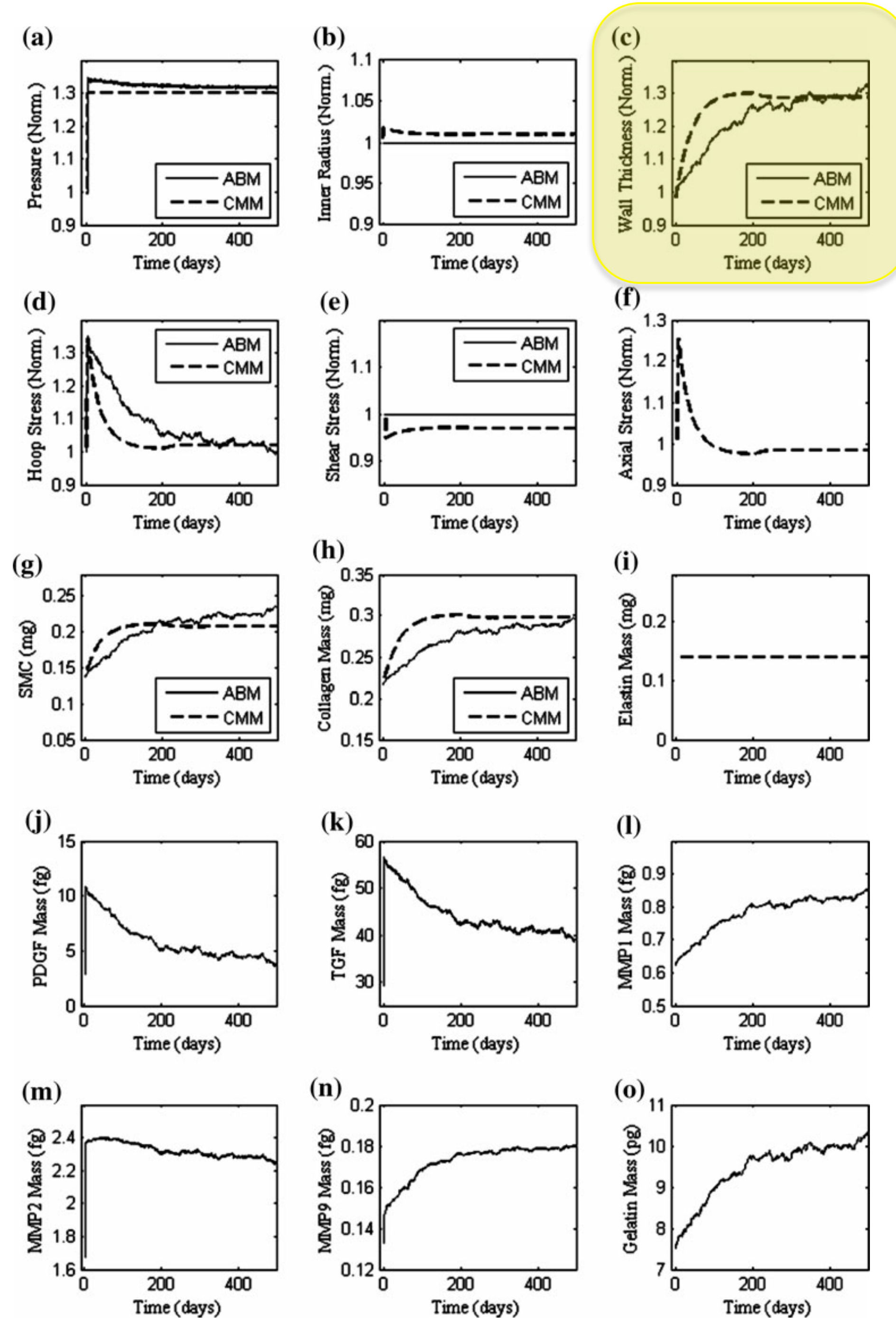


PREDICTED VESSEL REMODELING FOLLOWING 30% SYSTOLIC BLOOD PRESSURE INCREASE FOR 500 DAYS



H. Hayenga, B.C. Thorne, S.M. Peirce, J.D. Humphrey (2011)

CMM AND ABM PREDICTIONS



H. Hayenga, B.C. Thorne, S.M. Peirce, J.D. Humphrey (2011)

ENSURE CONGRUENCY BETWEEN TWO MODELS FOR COLLAGEN AND SMC MASS BY USING GENETIC ALGORITHM TO MINIMIZE OBJECTIVE FUNCTION:

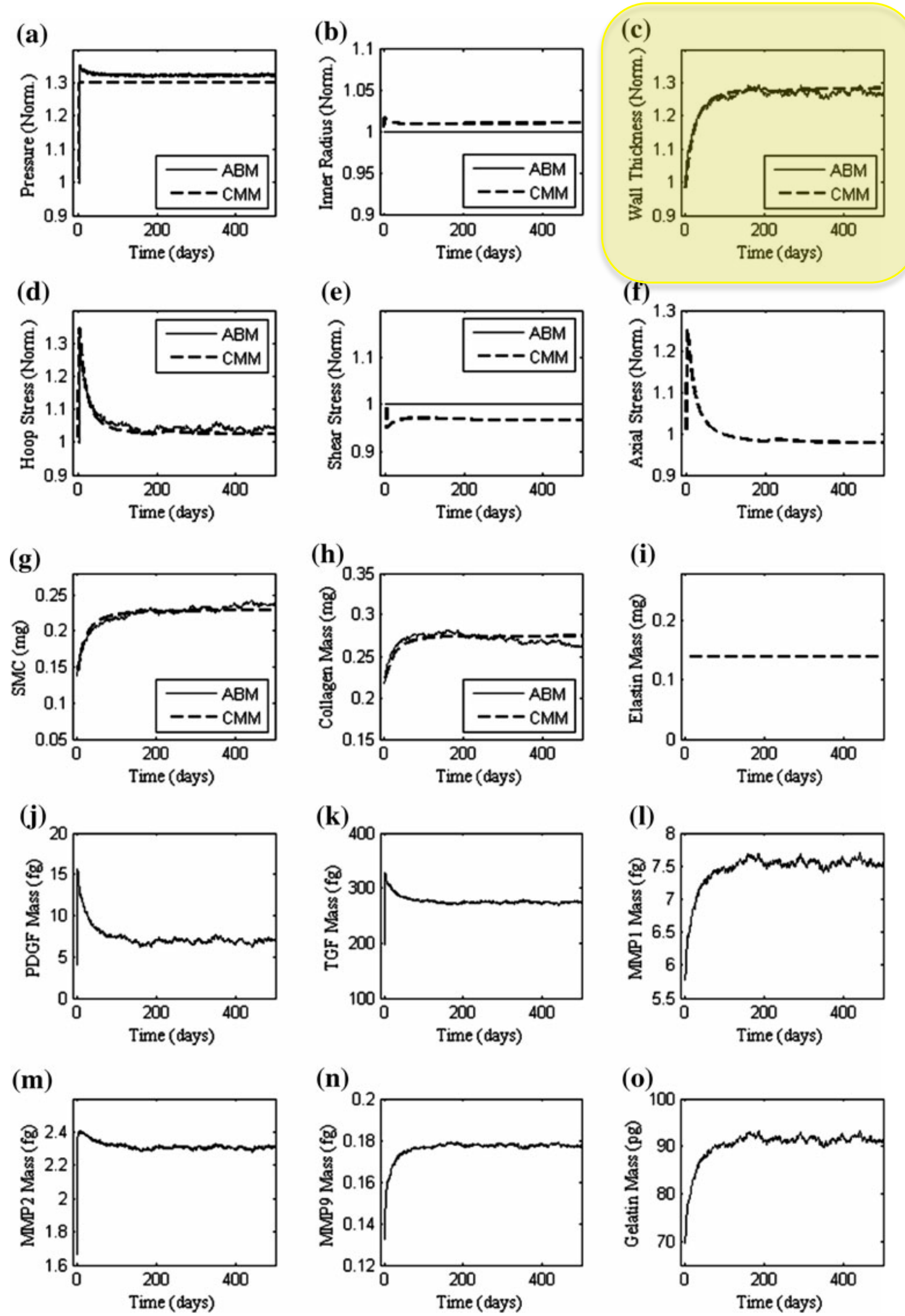
$$e = \frac{2}{N}\sum_{j}^{N}\left(\frac{\left|C_{\mathrm{NT}}^{\mathrm{ABM}} - C_{\mathrm{NT}}^{\mathrm{CMM}}\right|}{C_{\mathrm{NT}}^{\mathrm{ABM}} + C_{\mathrm{NT}}^{\mathrm{CMM}}} + \frac{\left|M_{\mathrm{NT}}^{\mathrm{ABM}} - M_{\mathrm{NT}}^{\mathrm{CMM}}\right|}{M_{\mathrm{NT}}^{\mathrm{ABM}} + M_{\mathrm{NT}}^{\mathrm{CMM}}}\right)_j + \frac{2}{S}\sum_{j}^{S}\left(\frac{\left|C_{\mathrm{HT}}^{\mathrm{ABM}} - C_{\mathrm{HT}}^{\mathrm{CMM}}\right|}{C_{\mathrm{HT}}^{\mathrm{ABM}} + C_{\mathrm{HT}}^{\mathrm{CMM}}} + \frac{\left|M_{\mathrm{HT}}^{\mathrm{ABM}} - M_{\mathrm{HT}}^{\mathrm{CMM}}\right|}{M_{\mathrm{HT}}^{\mathrm{ABM}} + M_{\mathrm{HT}}^{\mathrm{CMM}}}\right)_j$$

TABLE 2. Listed are both the initial values of the parameters and the bounds that defined the search space used in the genetic algorithm to improve congruency between ABM and CMM predictions of smooth muscle and collagen mass via Eq. (5).

	Parameter	Initial value	Lower bound	Upper bound	After genetic algorithm
CMM	$K^{c}_{\sigma_\theta}$	1	0.1	10	1.11
	$K^{m}_{\sigma_\theta}$	10	0.1	10	3.85
	$K^{c}_{\tau_w}$	1	0.1	10	2.85
	$K^{m}_{\tau_w}$	10	0.1	10	8.75
ABM	MMP-1_0	2.69E−04	2.69E−05	2.69E−03	9.47E−04
	$\text{MMP-1}_{\%A}$	0.39	0.039	3.93	1.04
	C_0	0.009	0.0009	0.09	0.07
	C_{TGF}	114.94	11.49	1149.42	134.57
	M_p	−1.45E+09	−1.45E+10	−9.69E+08	−1.53E+09
	M_0	80,000	53333.33	120,000	6.12E+04
	M_{a1}	71020	7102	106530	9.89E+04
	M_{a2}	100	66.66	1000	223.21
	$\mathrm{PDGF}_{\sigma_\theta}$	4.79E−07	3.19E−07	7.19E−07	7.03E−07
	PDGF_0	4.17E−05	4.17E−06	6.25E−05	6.17E−05
	$\mathrm{TGF}\beta_{\sigma_\theta}$	1.65E−06	1.65E−07	1.65E+05	7.87E−06
	$\mathrm{TGF}\beta_0$	1.03E−04	1.03E−05	1.03E−03	3.69E−04

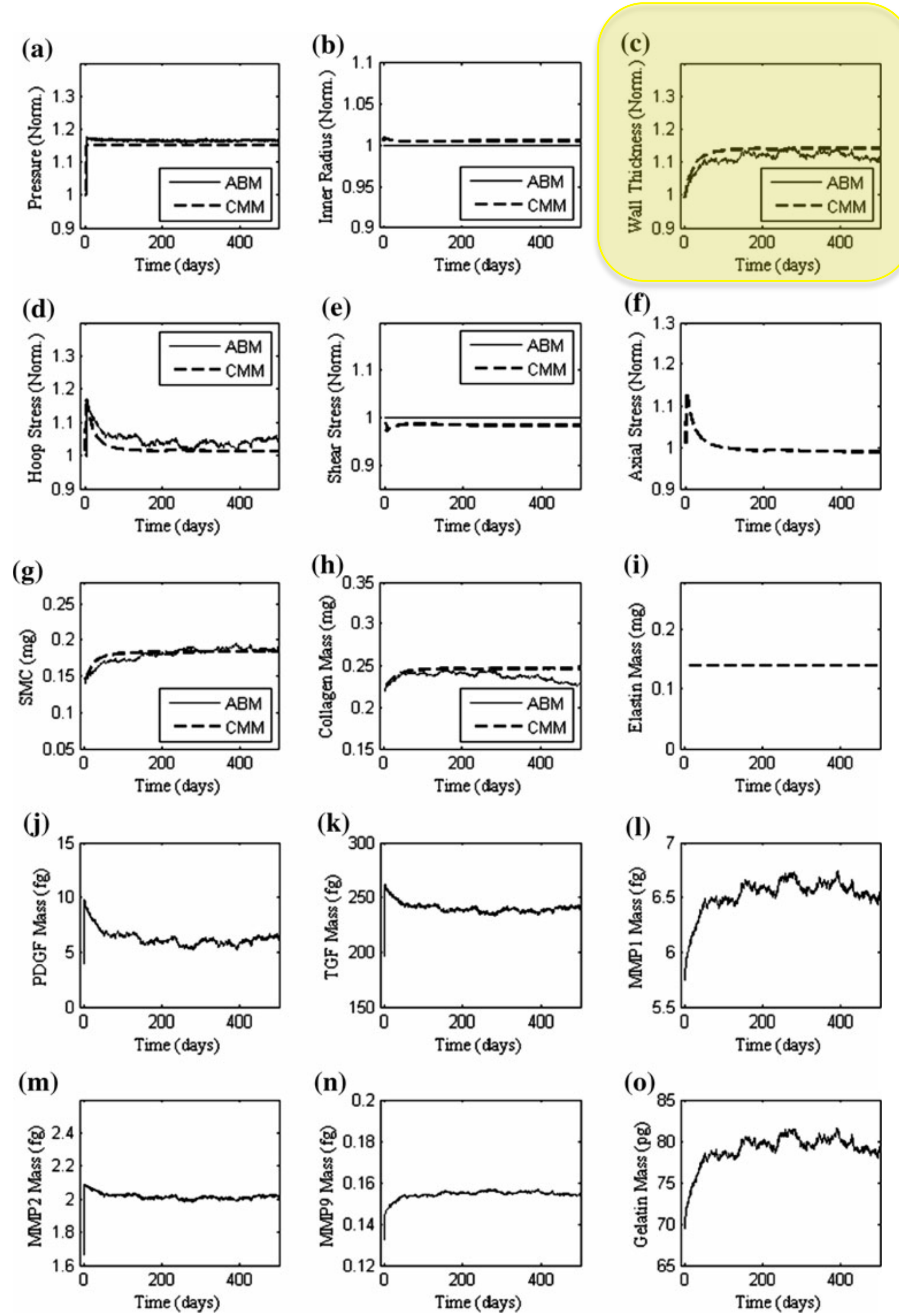
H. Hayenga, B.C. Thorne, S.M. Peirce, J.D. Humphrey (2011)

CMM and ABM Predictions After Congruency Enforcement



H. Hayenga, B.C. Thorne, S.M. Peirce, J.D. Humphrey (2011)

CMM AND ABM PREDICTIONS AFTER CONGRUENCY ENFORCEMENT (WITH 15% PRESSURE INCREASE)

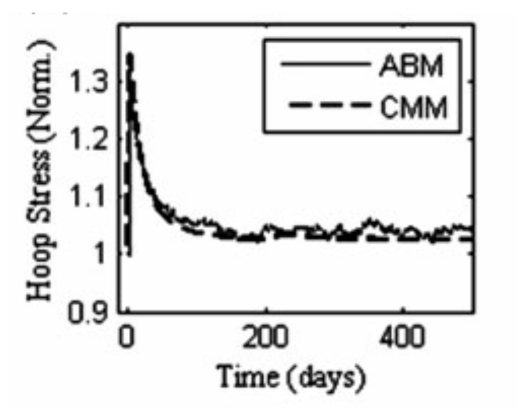


H. Hayenga, B.C. Thorne, S.M. Peirce, J.D. Humphrey (2011)

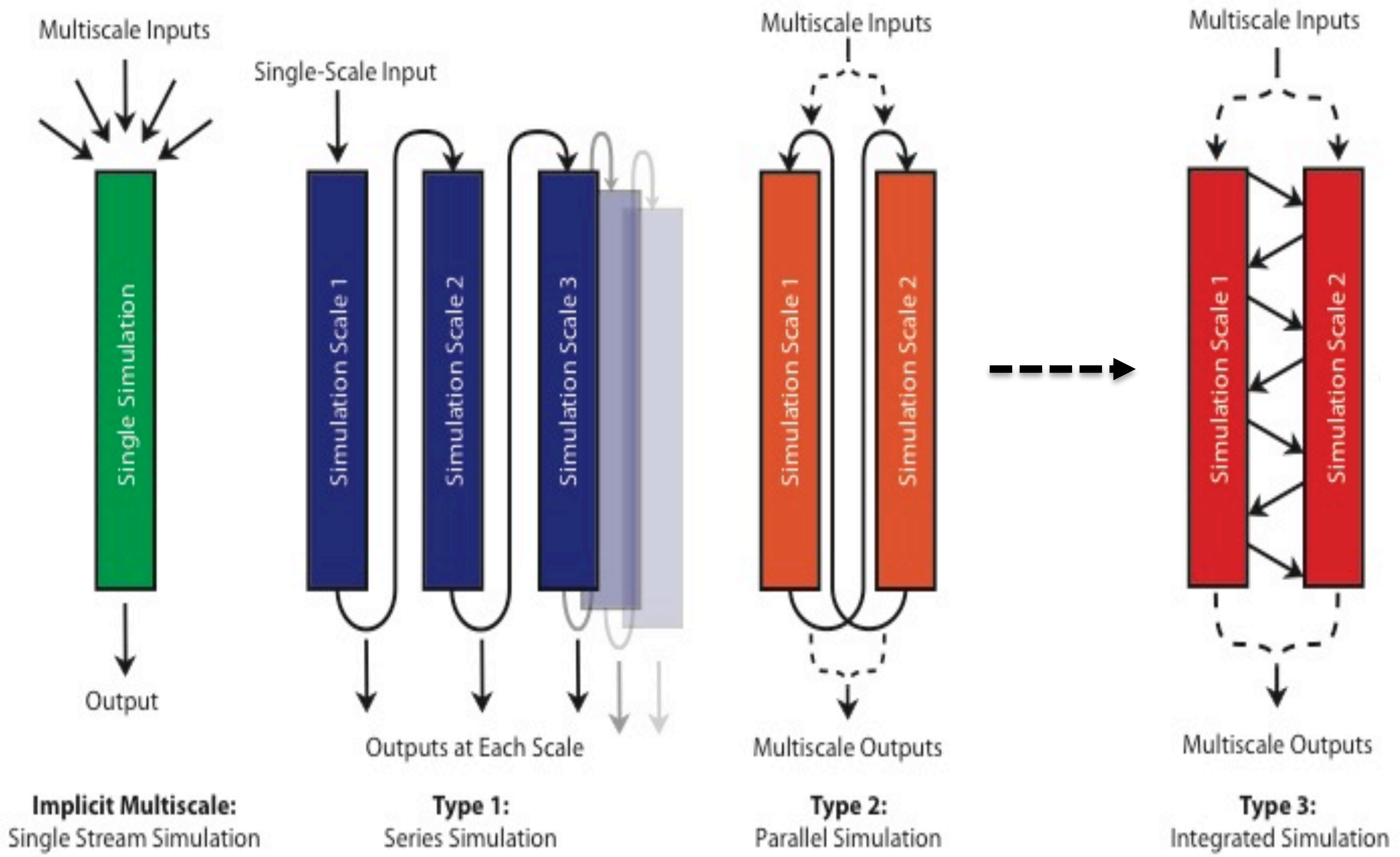
CONGRUENCY ENFORCEMENT BROUGHT MODEL PREDICTIONS CLOSER TO EXPERIMENTAL OUTCOMES

Experiment	Return to normal hoop stress	Citation
Systolic pressure increase of 24% in rats	140 days	Wolinsky (1972)
Systolic pressure increase of 30% in rats	126 day	Matsumoto & Hayashi (1994)

Model	Return to normal hoop stress
CMM Prediction	70 days
ABM Prediction	350 day
With congruency (both ABM and CMM)	125



AGENT-BASED MODELS: OFFER A FLEXIBLE PLATFORM FOR MULTISCALE MODELING



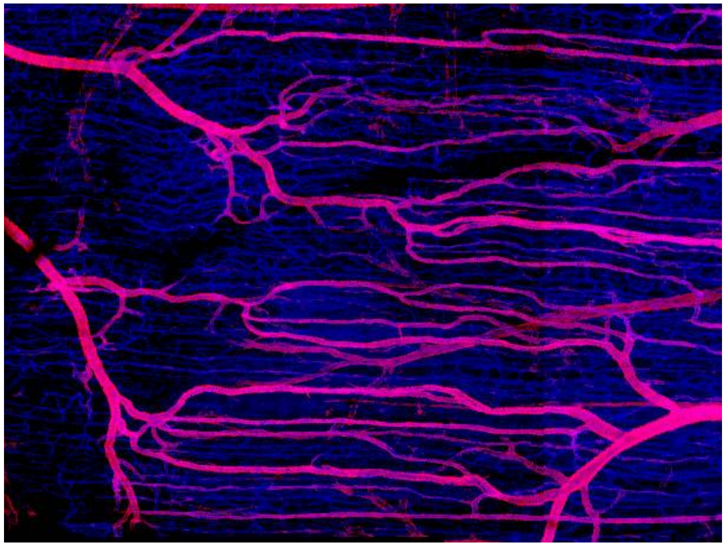
J. Walpole, J.A. Papin, S.M. Peirce (2013) Annual Reviews of Biomedical Engineering

COMPUTATIONAL MODELS ARE SANDBOXES FOR EXPLORATION

MULTISCALE MODELS ARE ENTIRE PLAYGROUNDS (AS LONG AS WE KNOW OUR LIMITS AND SYNERGIZE)

MULTISCALE MODELS ARE USEFUL TOOLS FOR BASIC RESEARCH AND DRUG DISCOVERY

- Multiscale ABM-ODE/PDE computational model predicts dynamic capillary sprouting events ***(Necessary & sufficient mechanisms)***
- Model is tunable to both VEGF stimulation and DLL/NOTCH inhibition ***(Drug dosing and potency)***
- Sensitivity to DLL/NOTCH inhibition supersedes VEGF gradient threshold ***(Combination therapies)***
- Specify conditions under which predictions fail ***(Compensatory pathways)***
- Add layers of complexity ***(Drug target identification)***



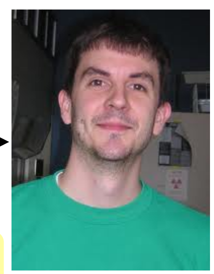
ACKNOWLEDGEMENTS

Peirce-Cottler Lab

Joseph Walpole
Anthony Bruce
Kyle Martin
Scott Seaman
Molly Kelly-Goss
Bruce Corliss
Catherine Henry
Yiqi Cao

UNC-CH

Vicki Bautch, Ph.D.
John Chappell, Ph.D. →



Johns Hopkins

Feilim Mac Gabhann, Ph.D.

Yale University

Jay Humphrey, Ph.D.
Heather Hayenga, Ph.D. (UT Dallas)

National Heart Lung and Blood Institute

National Eye Institute
NATIONAL INSTITUTES OF HEALTH

Wallace H. Coulter Foundation

The Hartwell Foundation