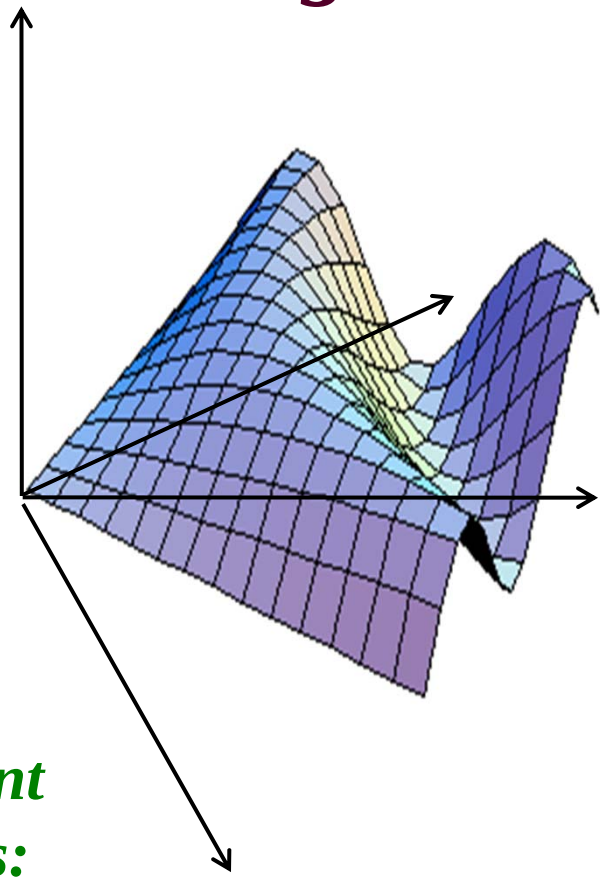
NCI ICBP
Integrative Cancer Biology Program --
MIT Grant, R Hynes PI

- **DNA damage signaling network (Michael Yaffe [Biol/BE], Leona Samson [BE/Biol], DL [BE/Biol/ChE])**
- **ErbB signaling network (Tyler Jacks [Biol], Peter Sorger [Biol/BE], Forest White [BE], DL [BE/Biol/ChE])**
- **Cell migration and invasion processes (Richard Hynes [Biol], Frank Gertler [Biol], DL [BE/Biol/ChE])**
- **Computational modeling (Bruce Tidor [BE/EECS], Jacob White [EECS])**
- **RNAi manipulation (Phil Sharp [Biol], Jianzhu Chen [Biol])**

Integrative Systems Modeling

System Operation ('phenotype'):

cell,
tissue,
organism,
...



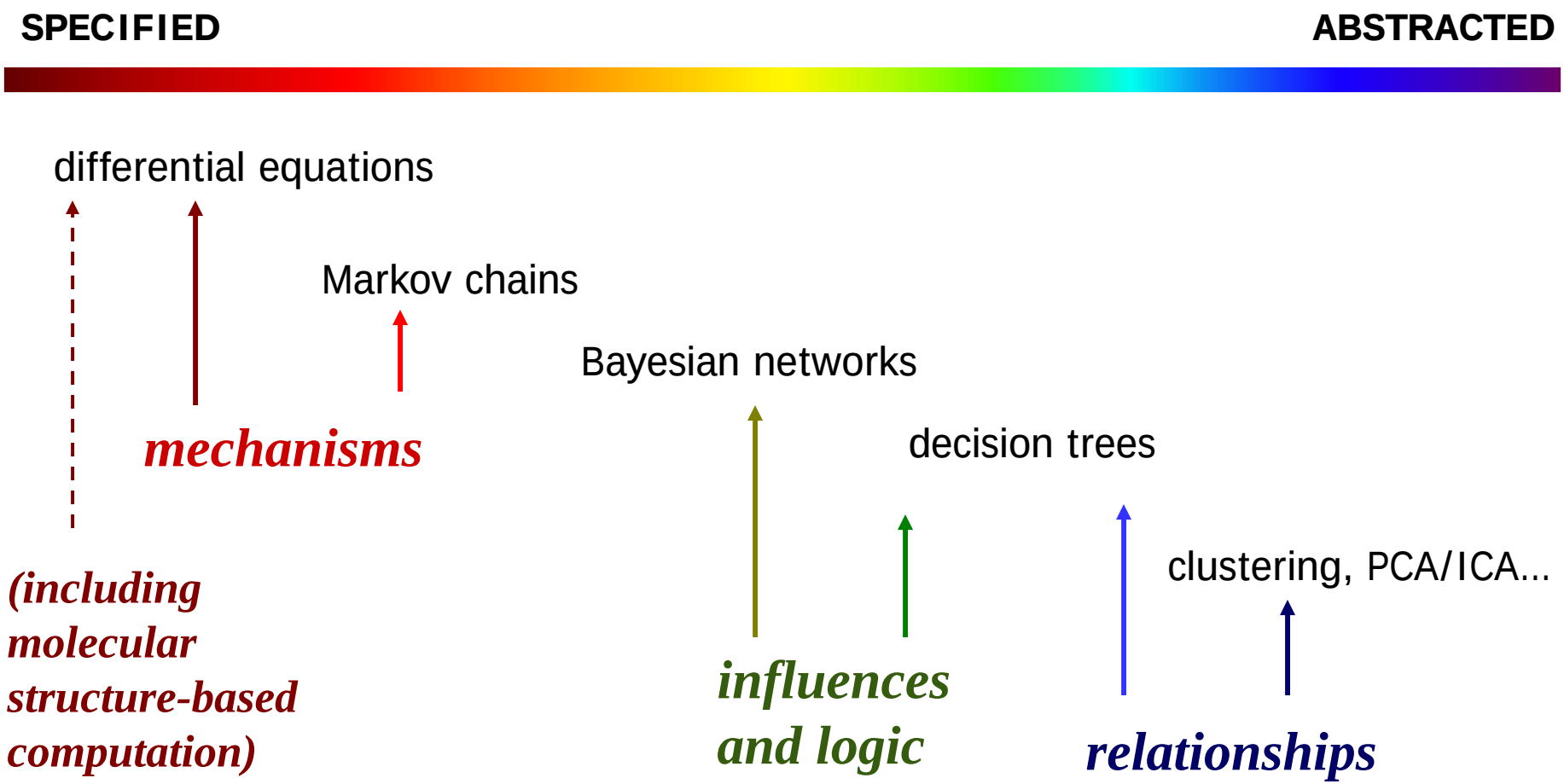
Component Properties:

molecular levels / states / locations / interactions / activities... (arising from sequence & structure)

Objective:

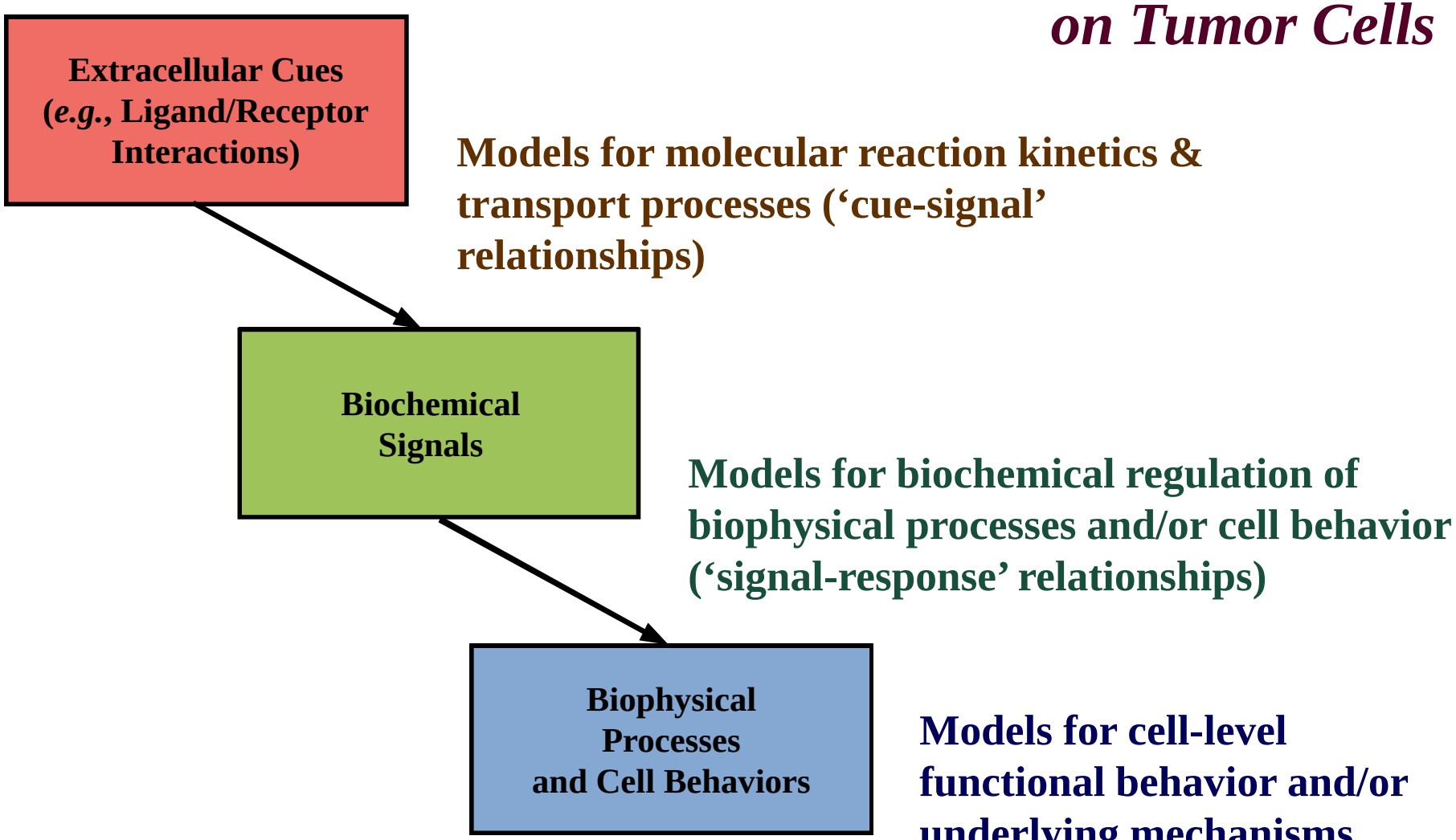
Predictive understanding for effect of component properties -- in quantitative, dynamic, multi-variate manner

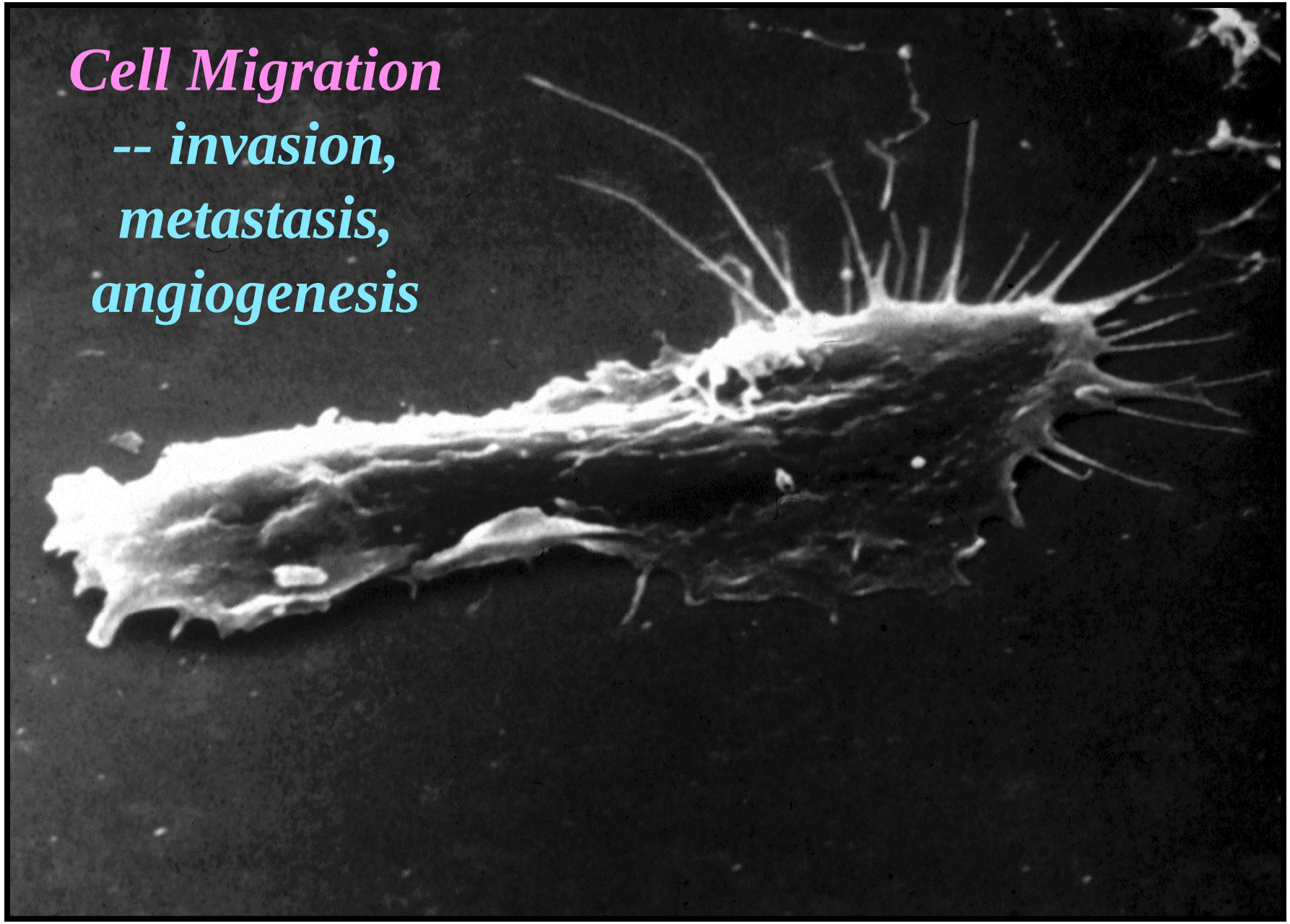
Spectrum of Computational Modeling Methods



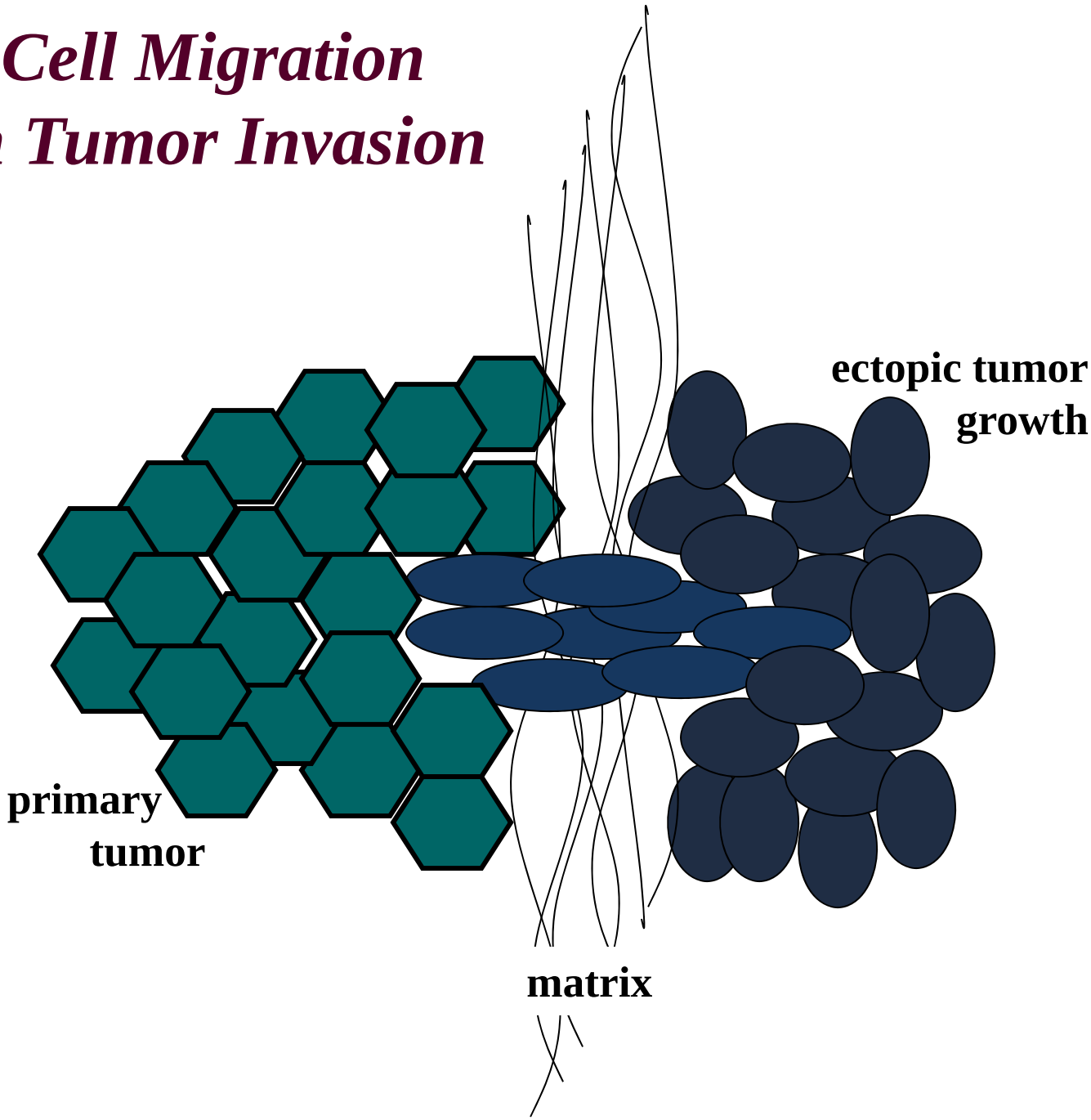
Appropriate approach depends on question and data

Modeling Chain Needed for Prediction of Effects of Gene Mutations and Drug Effects on Tumor Cells

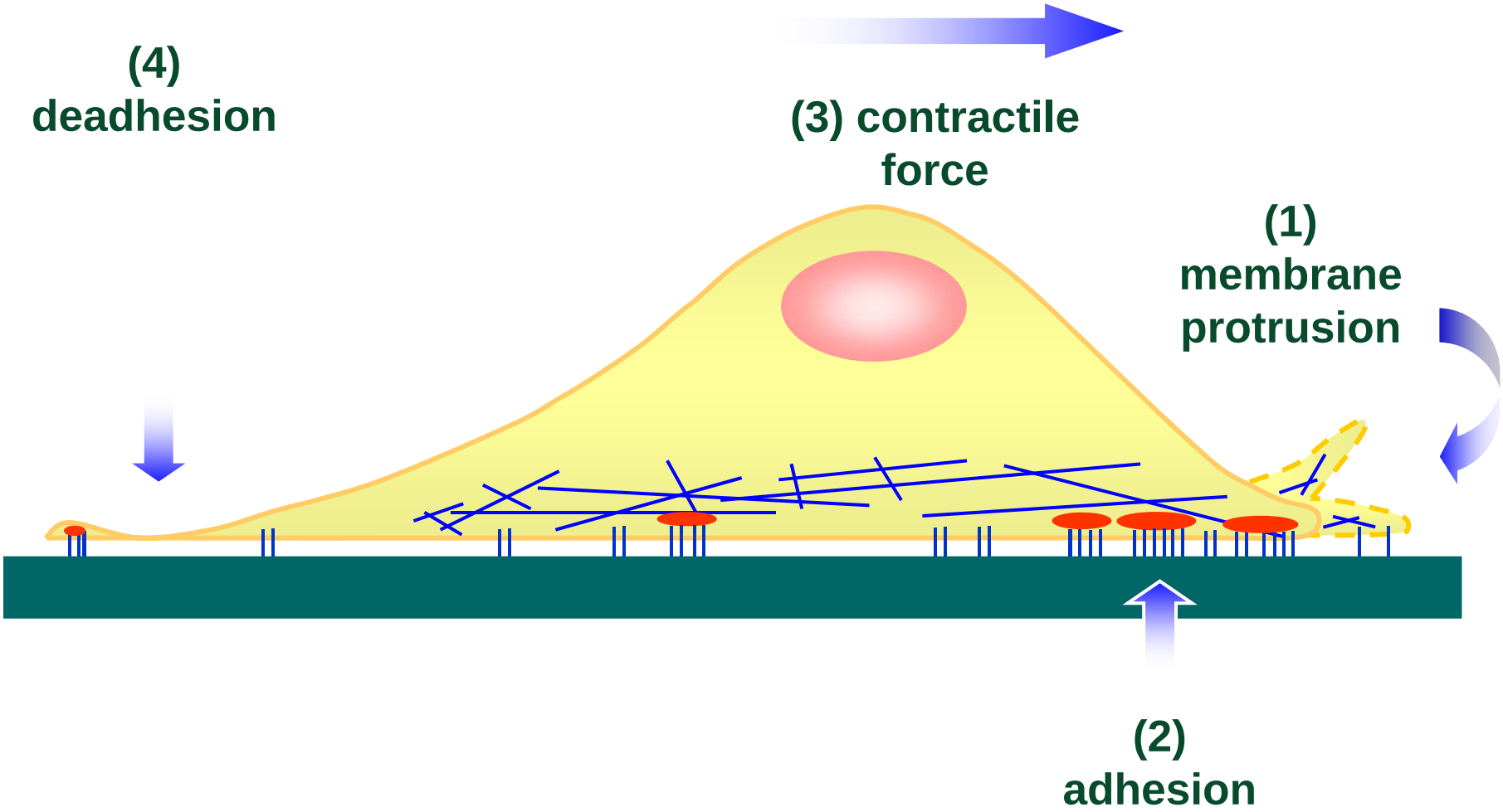



Cell Migration
-- invasion,
metastasis,
angiogenesis

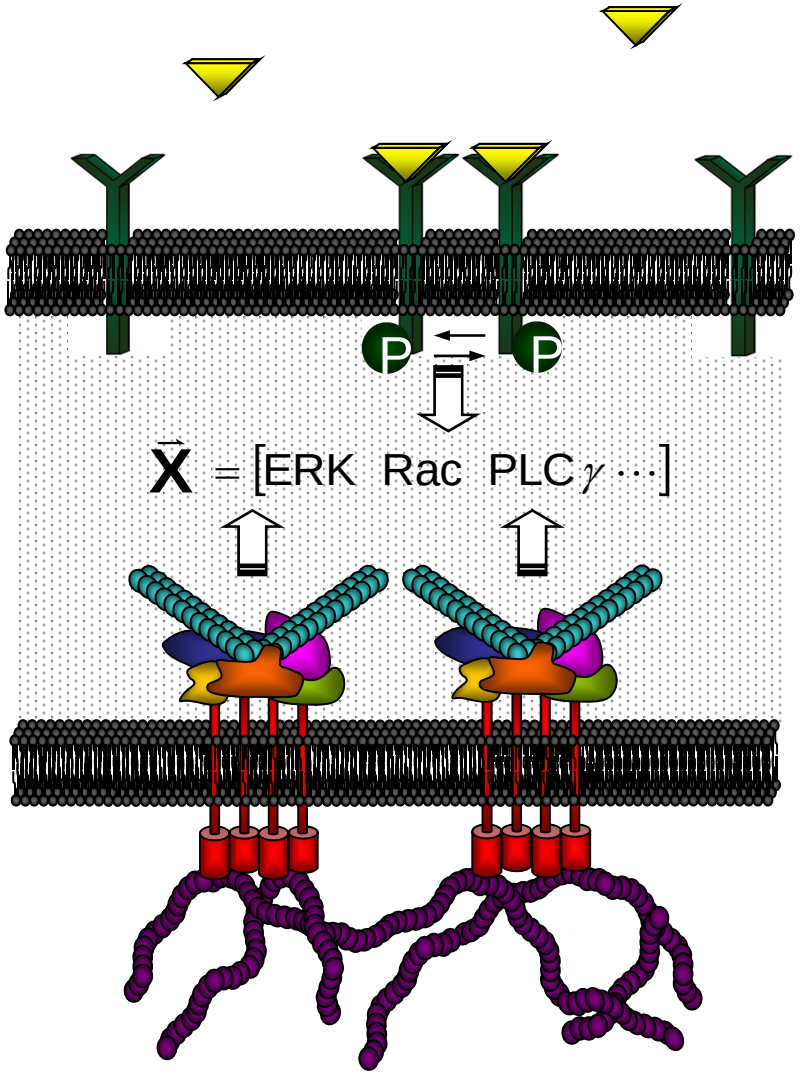
Cell Migration In Tumor Invasion



Cell Migration "Cycle" of Biophysical Processes



Regulation of Biophysical Processes by Biochemical Signals



soluble ligands (*e.g.*, EGF)

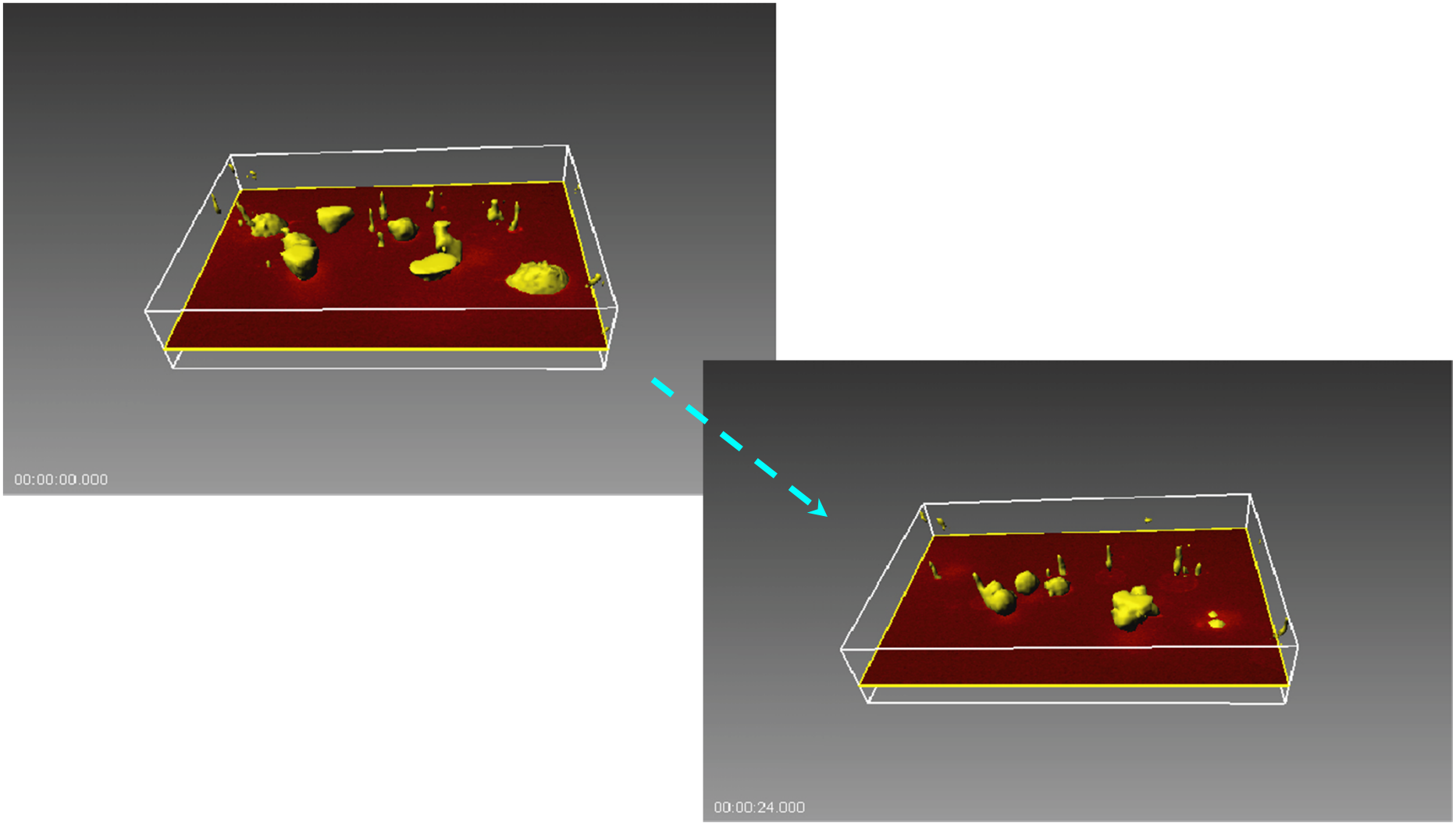
$f(\vec{X})$

Migration (speed, persistence, orientation)

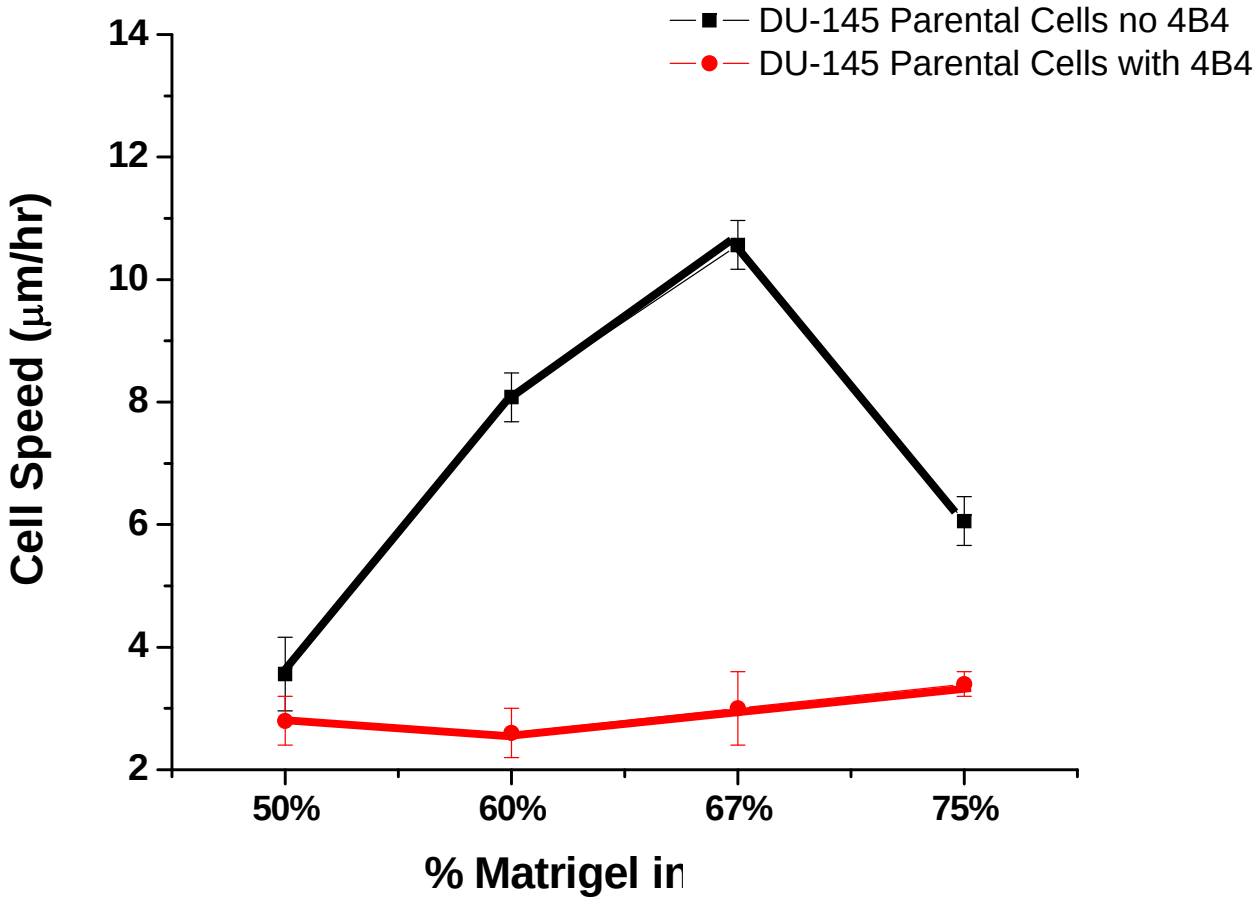
matrix ligands (*e.g.*, Fibronectin)

Tumor Cell Migration in 3D Environments

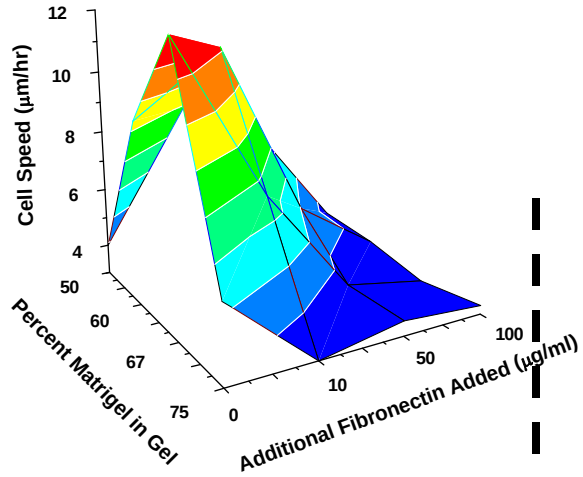
-- DU145 prostate tumor cells (single-cell tracking); Matrigel / Collagen-I / Fibronectin

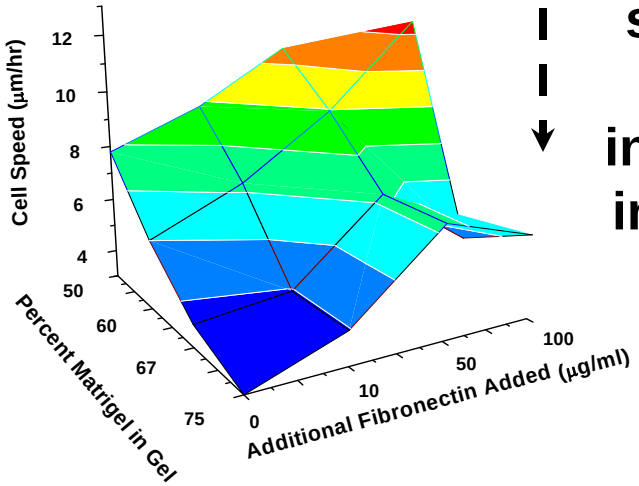


Biphasic Relationship is Found for 3D Tumor Cell Migration Speed vs Matrix Density -- Integrin-mediated adhesion? Matrix sterics and mechanics?

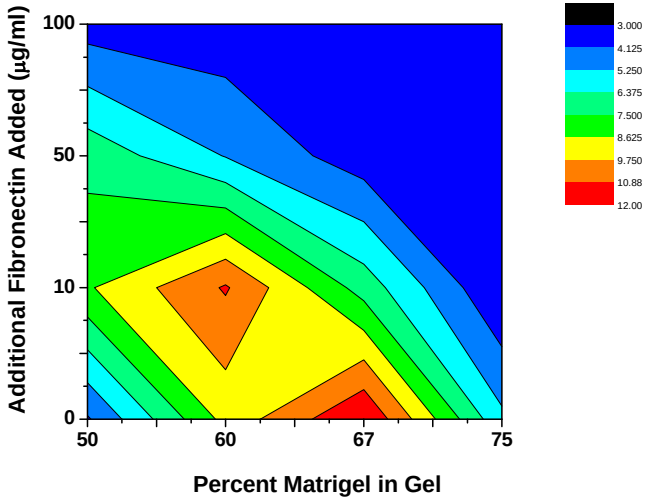


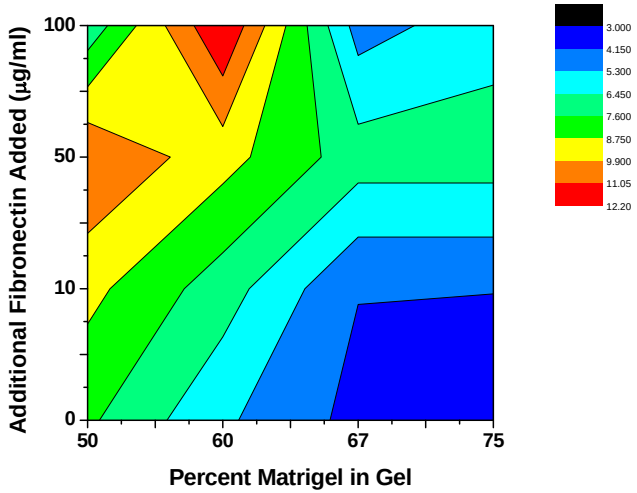
"All of the Above" -- Complex Landscape of Cell/Matrix Adhesion and Matrix Steric & Mechanical Properties Governs 3D Migration



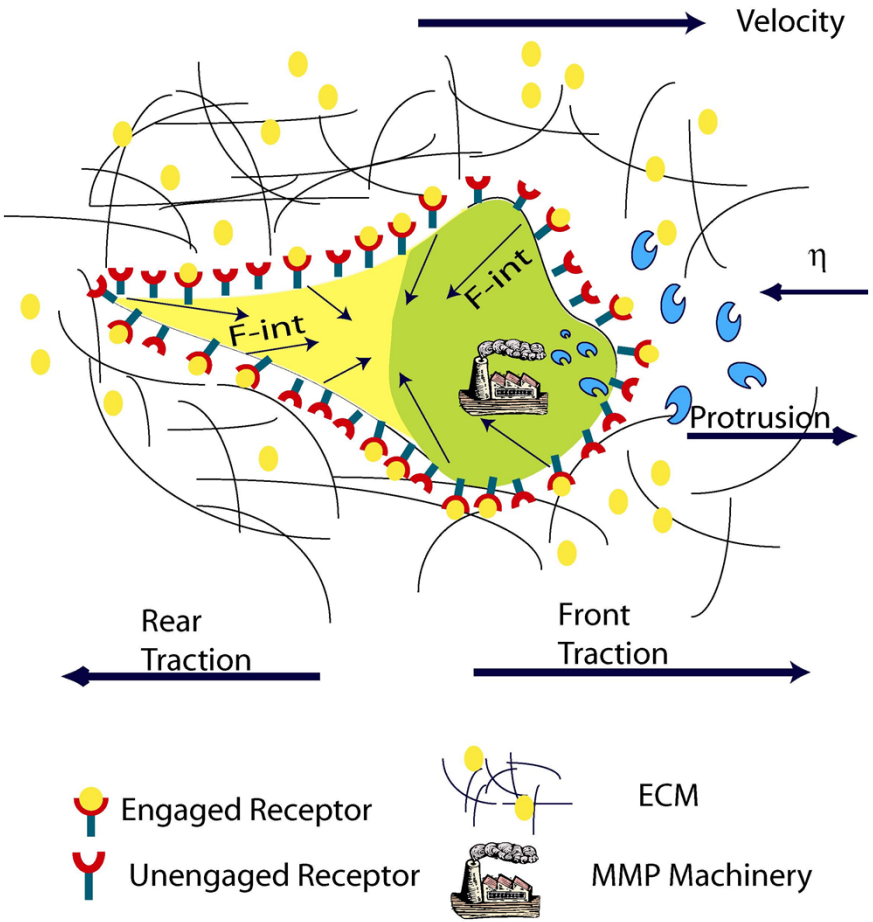


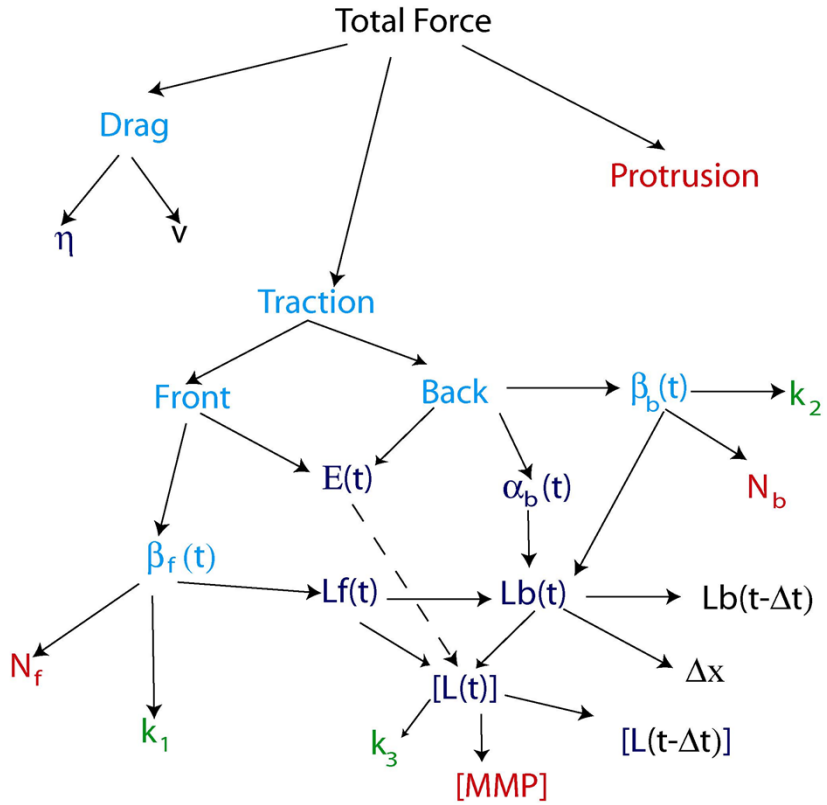
Adhesion-inhibitory antibody decreases migration in some situations but increases it in others…



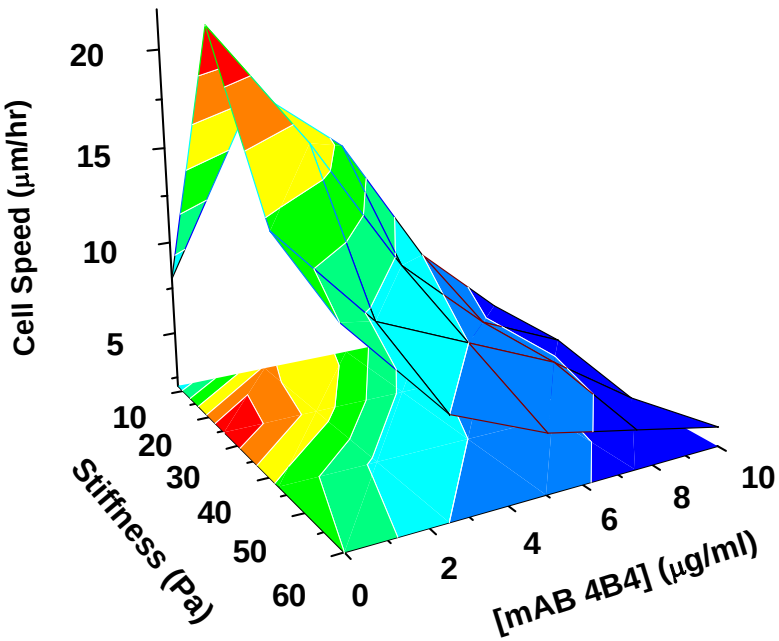


3D Cell Migration Computational Model, Single-Cell Biophysical Simulation (Biophys. J. [2005])

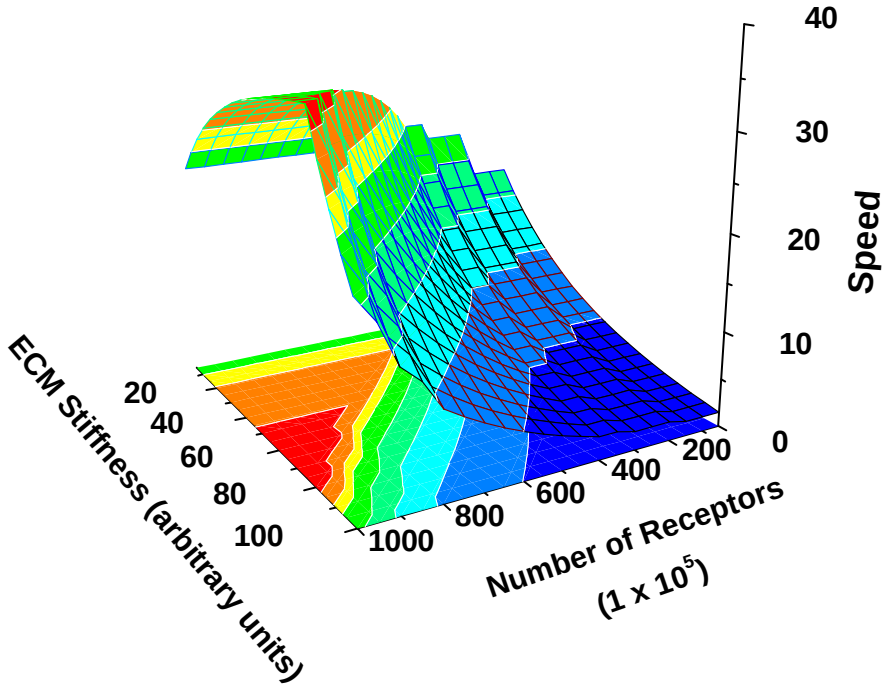




Model - Experiment Comparison



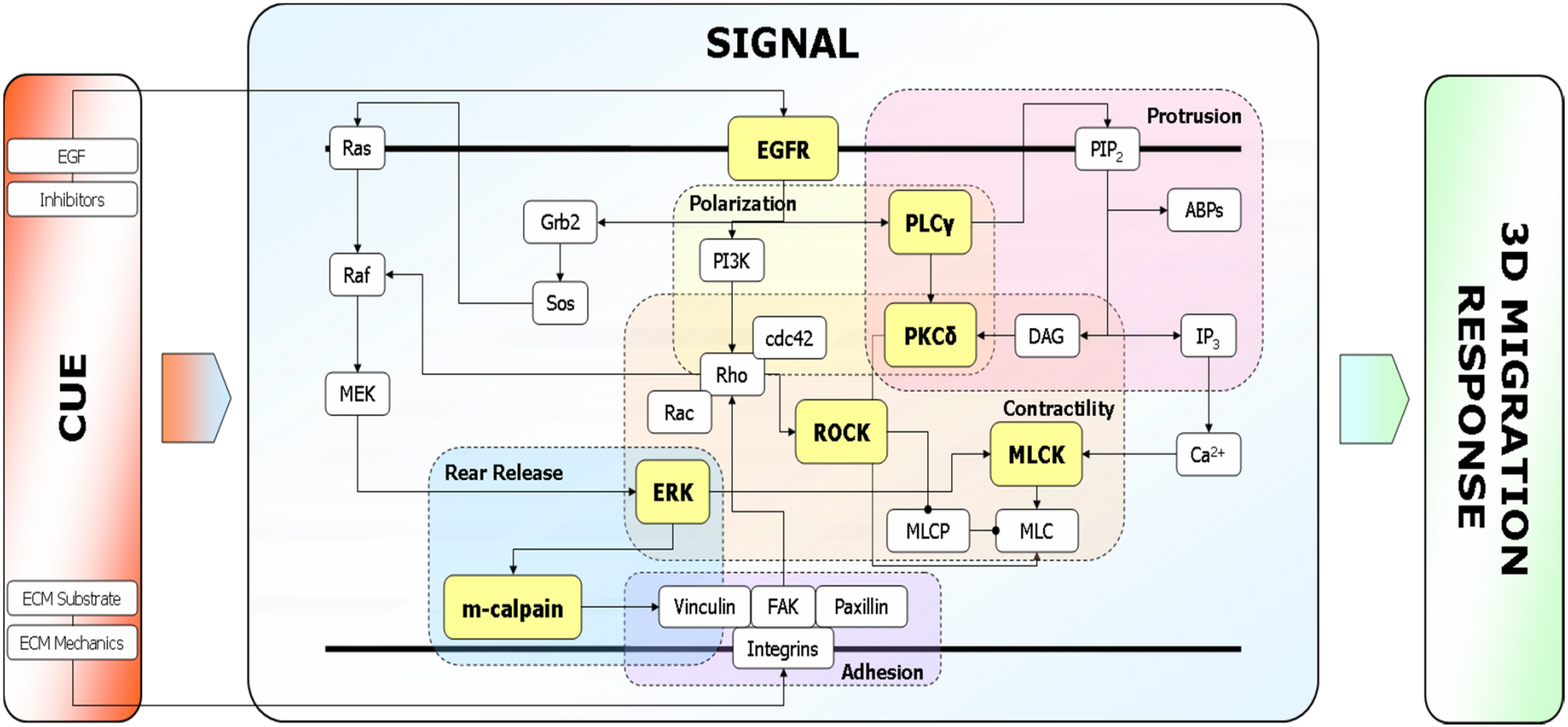
Experimental Data



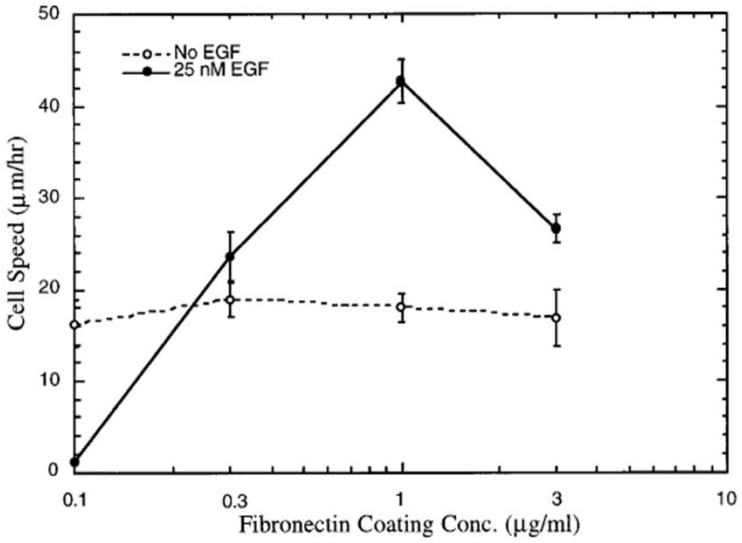
Model Predictions

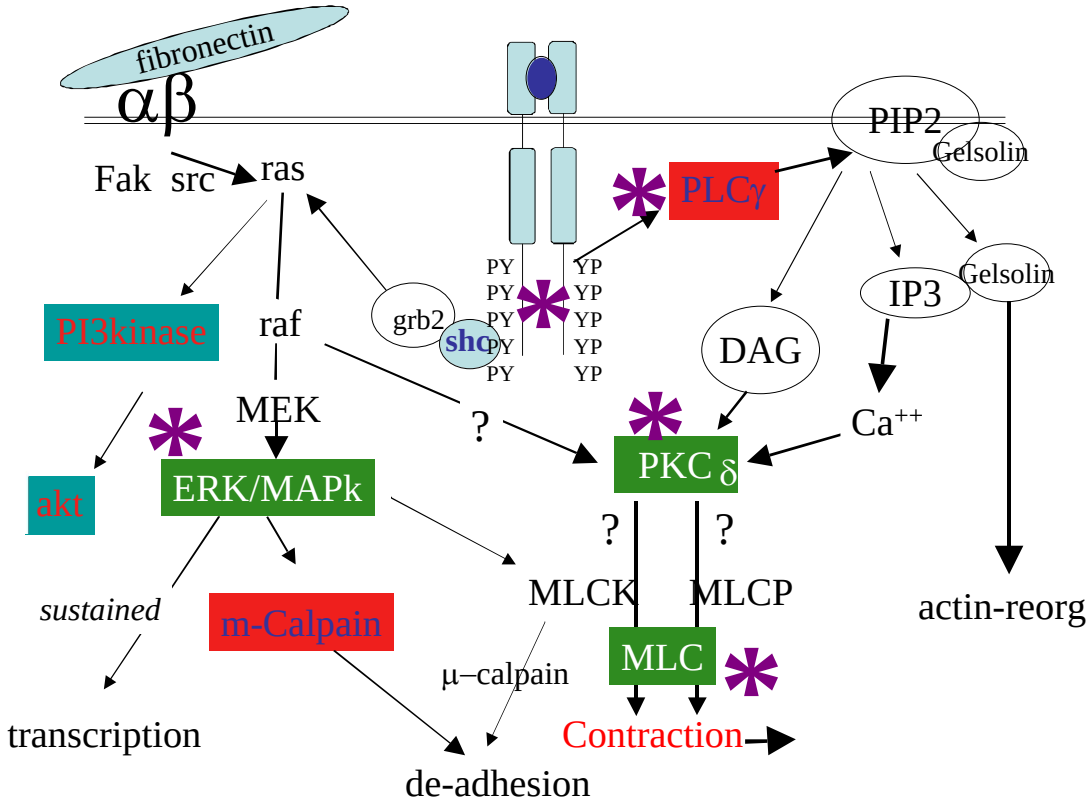
Then, how are these biophysical motility processes and resulting migration controlled by biochemical signals?

-- for prospective drug effects

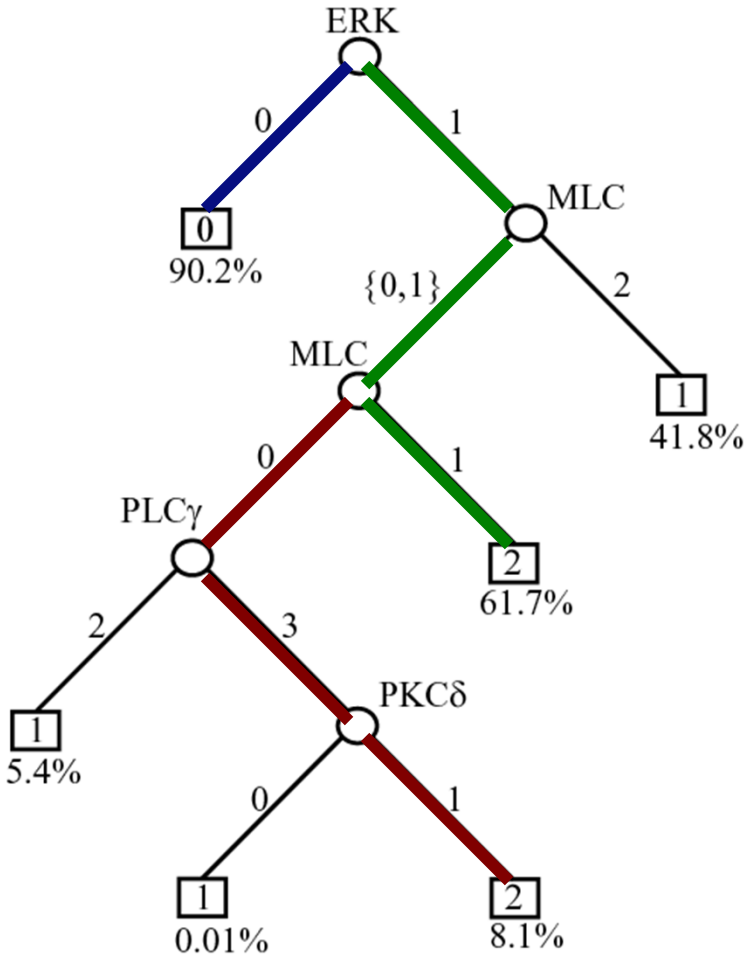


Example:
How do signals downstream of EGF and Fibronectin integrate to influence cell migration speed?





Decision Tree Model for 5-Minute Signaling Data



(70% overall accuracy)

IF p-ERK is low: cell migration is slow; ~90% of the slowly-migrating cohort observations can be explained with this rule.

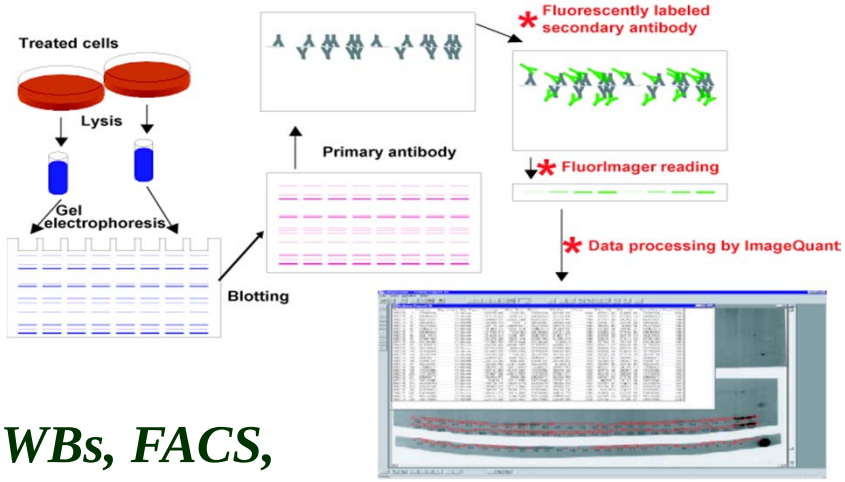
IF p-ERK is high AND p-MLC is intermediate: cell migration is fast; ~60% of the swiftly-moving cohort observations can be explained with this rule.

Another ~10% of the swiftly-moving cohort observations can be explained with the rule IF p-ERK is high AND p-MLC is low AND p-PLCγ is high AND p-PKCδ is high.

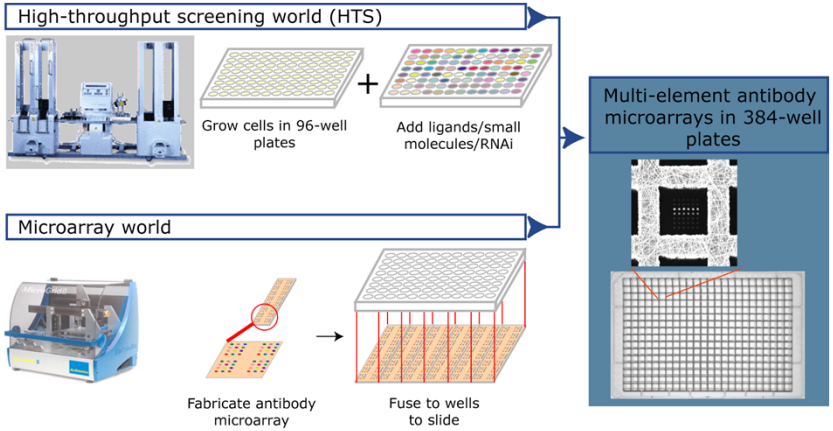
"Network Logic" indicates predominant combined roles of MLC and ERK in regulating the critical balance between cell contractile force and cell/substratum adhesion for governing migration speed.

(Bioinformatics [2005])

Moving Forward -- "High-Throughput" Protein-Centric Quantitative Measurement -- Protein Levels, States, Activities, Locations, Interactions…

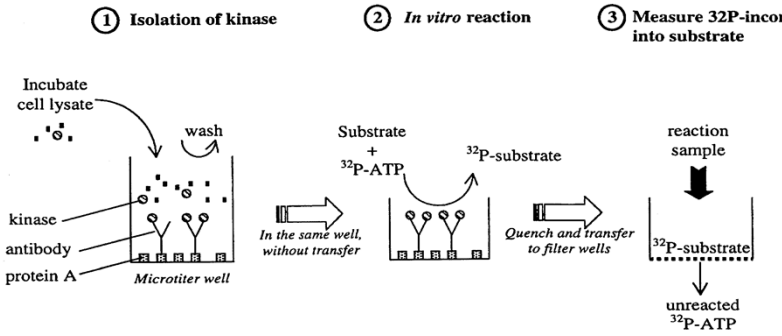


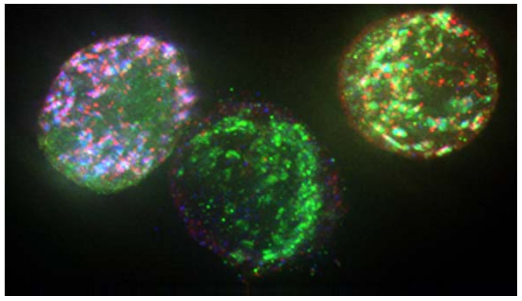
WBs, FACS, mass spectrometry



Protein microarrays

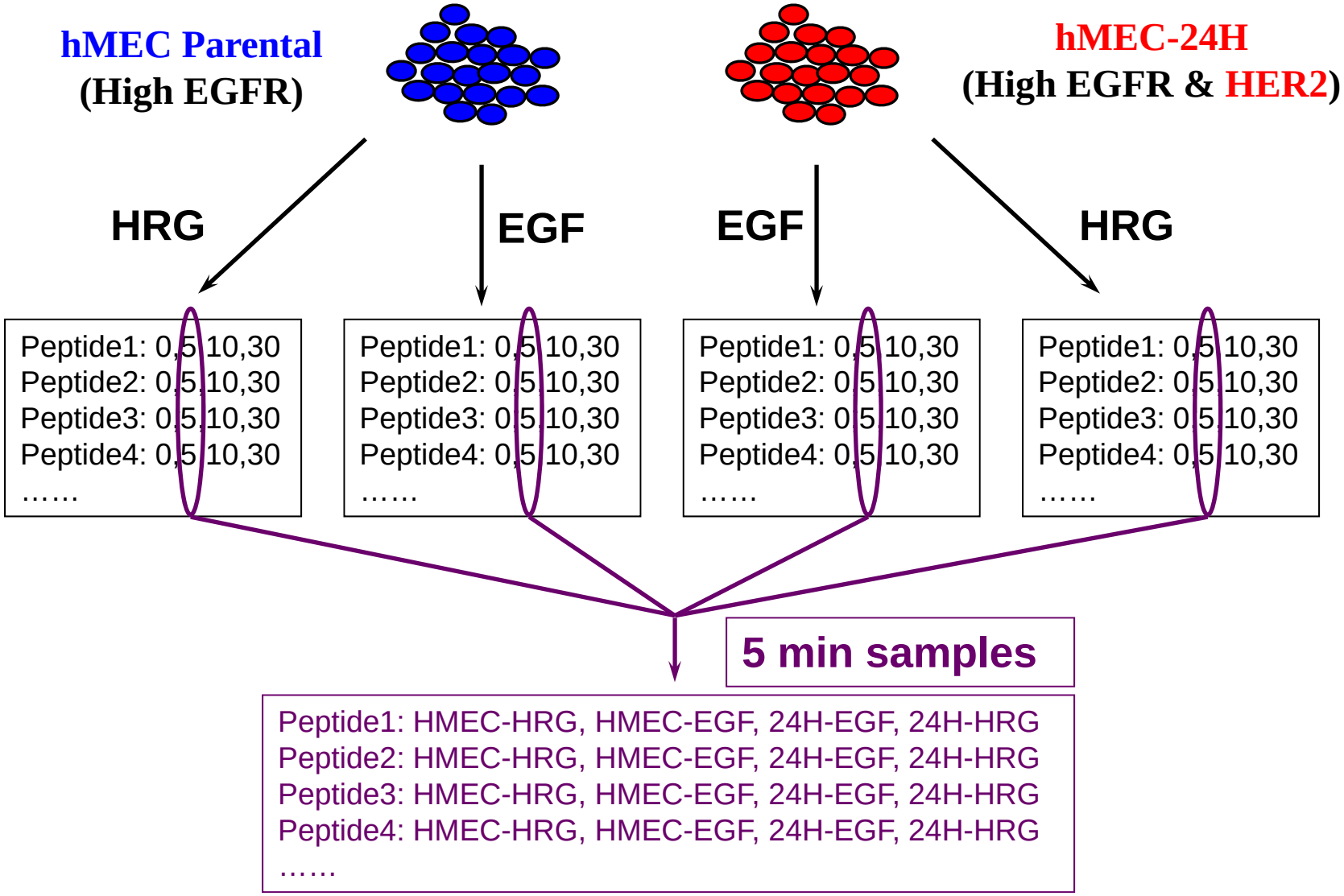
Multi-well kinase activity assays



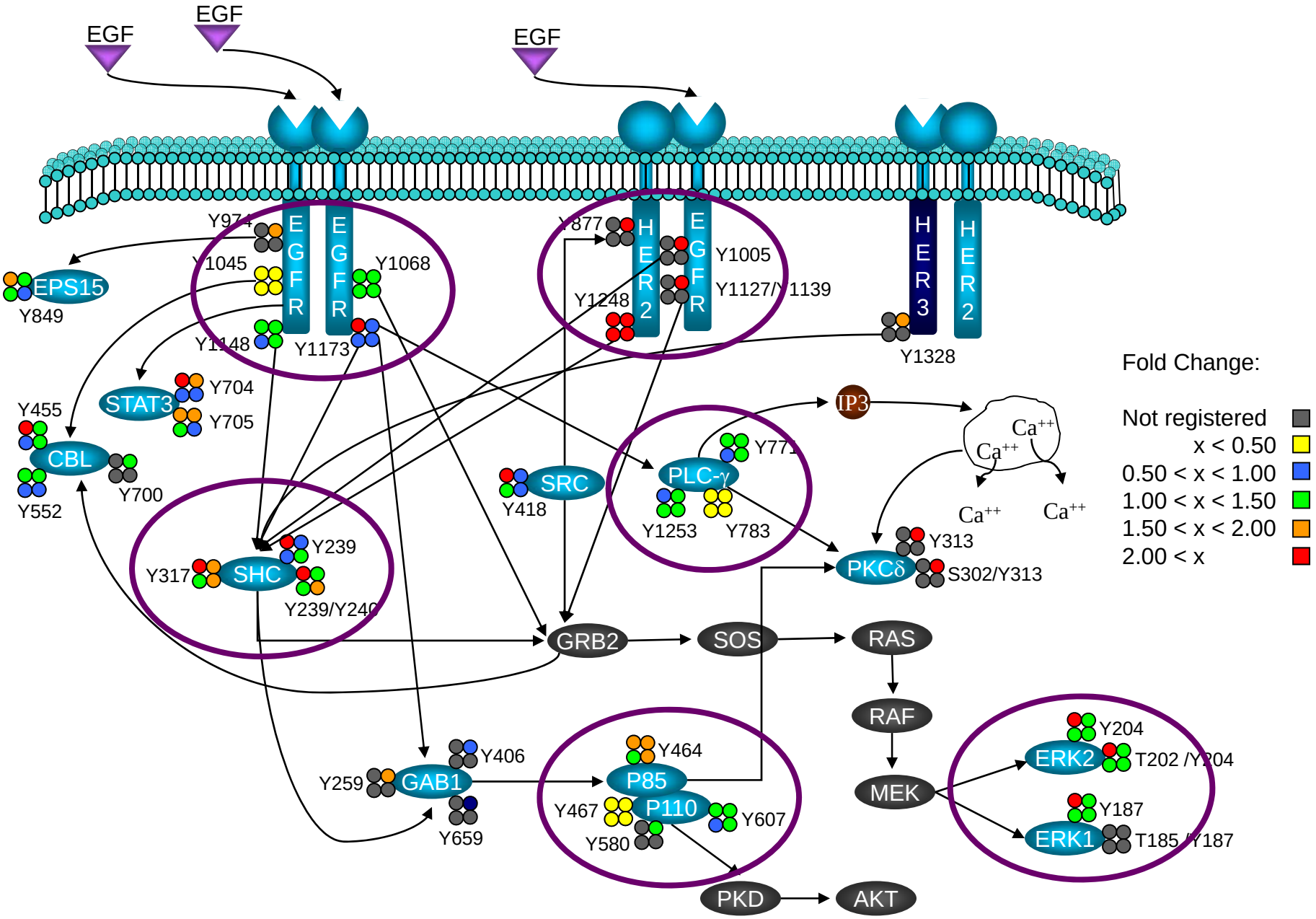


Live-cell imaging

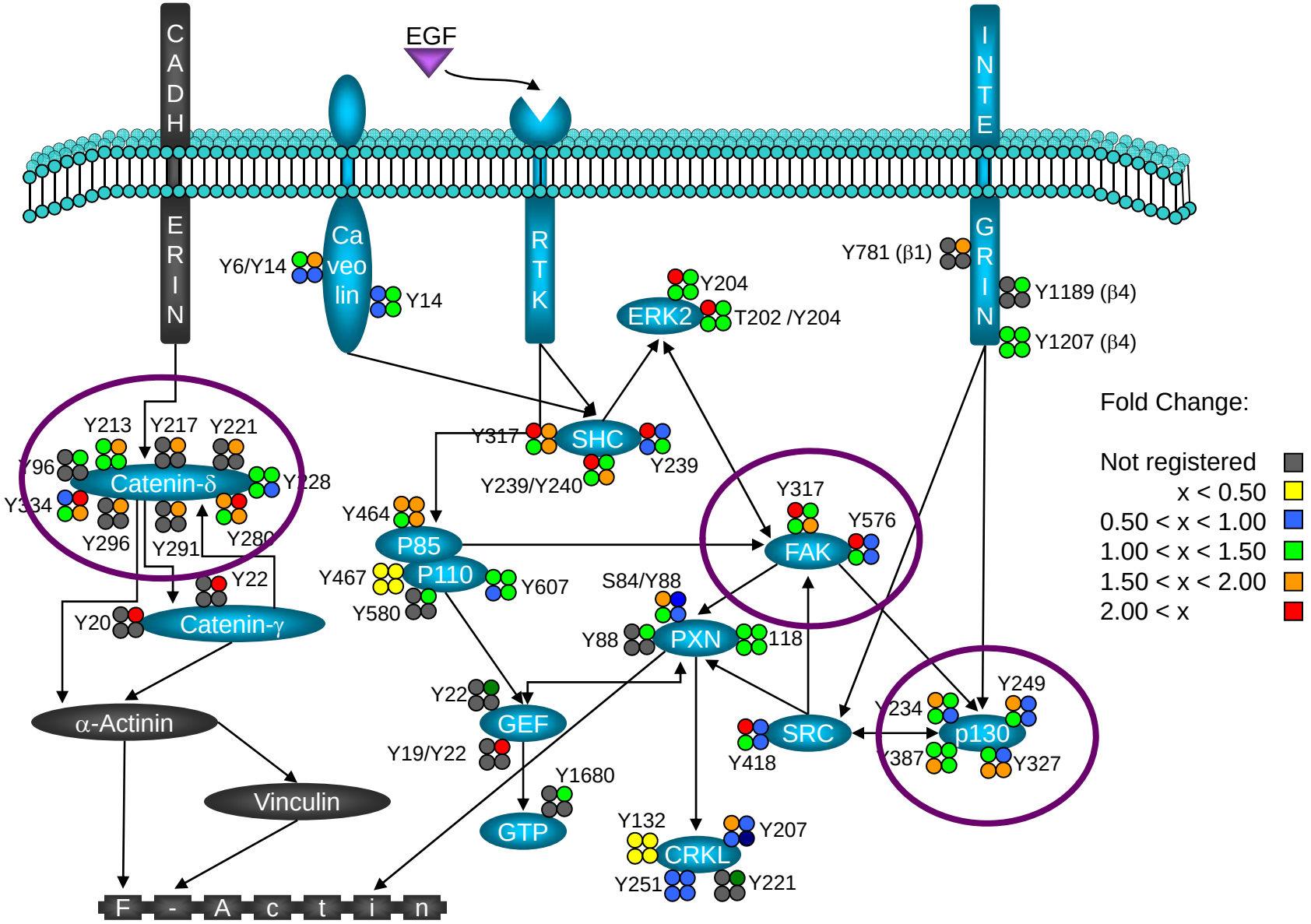
Example Problem:
HER2 Over-Expression (e.g., breast cancer)



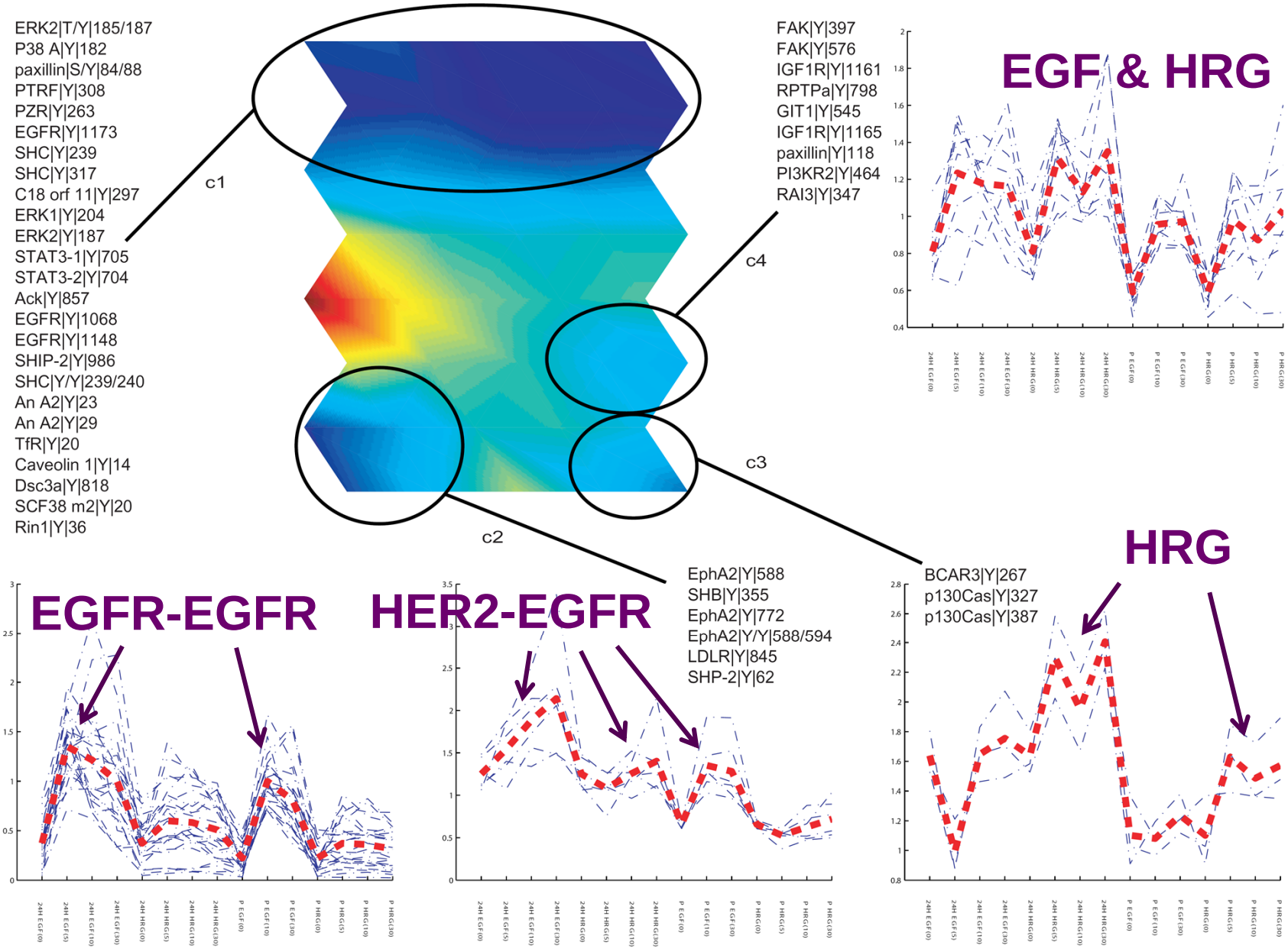
HER2 Over-Expression Effect on EGF-Induced Signaling - A



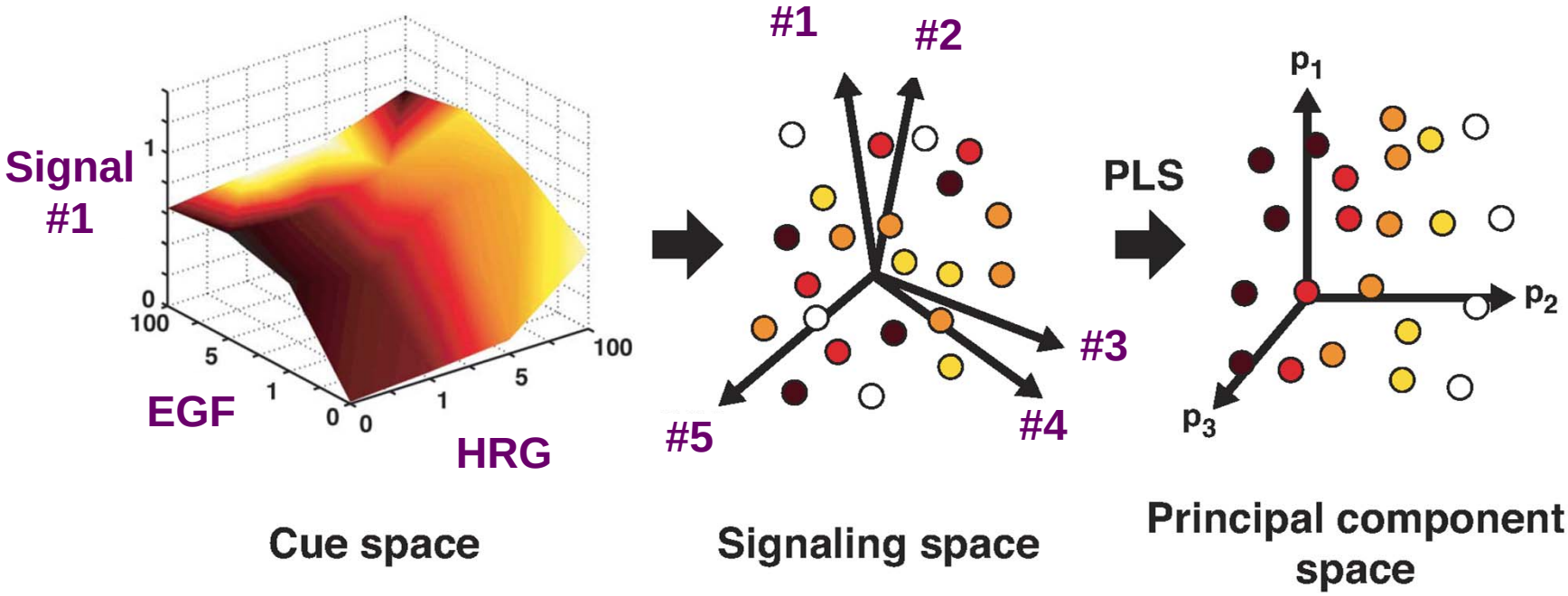
HER2 Over-Expression Effect on EGF-Induced Signaling - B



Neuronal Self-Organizing Maps (4 cell states, 4 time-points) -- elucidates consistent dynamic modules

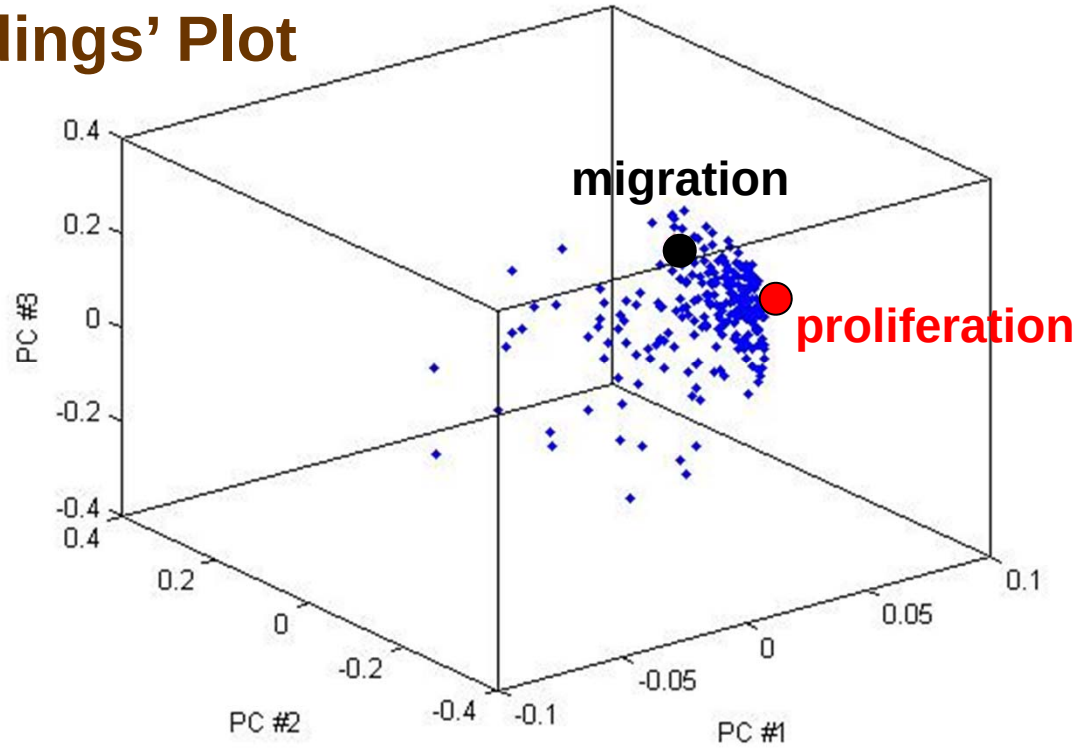


Principal Component / Partial Least-Square Regression -- elucidates key signal combinations governing responses



Determination of Key Signals Governing Enhanced Proliferation and Migration Arising from HER2 Overexpression -- Prospective Prediction of Drug Effects

PLSR 'Loadings' Plot



Modeling Chain Underway for Prediction of Effects of Gene Mutations and Drug Effects on Tumor Cells