CViT
Center for the Development of a Virtual Tumor

Multiscale Lung Cancer Modeling

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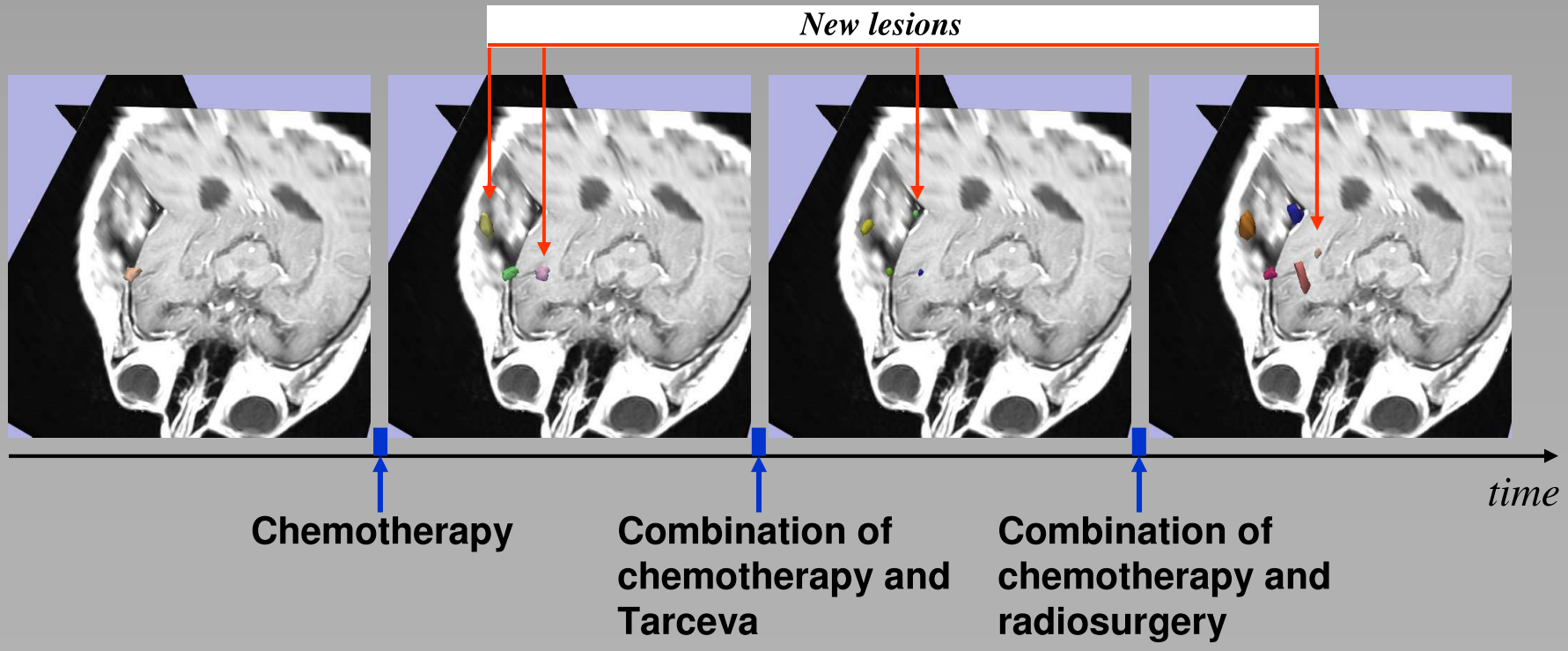
Background – clinical statistics

- More than 160,000 people die every year of lung cancer in the United States.
- Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases; advanced NSCLC is the leading cause of cancer-related deaths.
- Up until now, the outcome of current clinical treatment for NSCLC has been discouraging.
- Only a small fraction of patients with NSCLC, who failed to respond to conventional chemotherapy, respond clinically to molecular targeted drugs including e.g., gefitinib (Iressa) and erlotinib (Tarceva).

Background – NSCLC, a metastatic disease

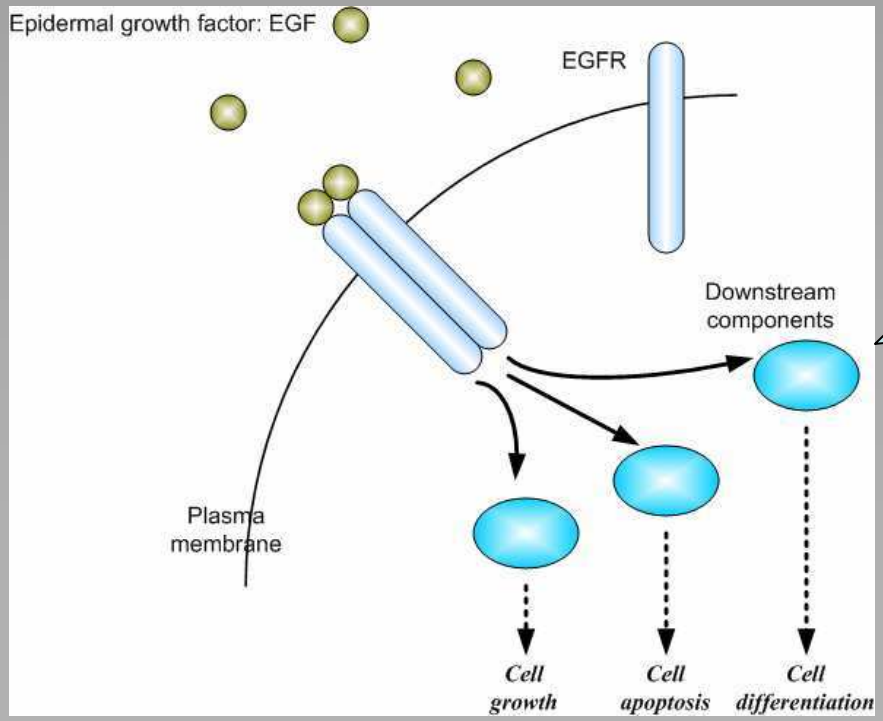
- NSCLC originates in lung epithelial cells and most patients with advanced NSCLC present with metastatic disease.

Example: data from a patient with metastatic NSCLC to the brain



Background – cell signaling & computational model

Overexpression and mutations of epidermal growth factor receptor (EGFR), a member of the ErbB family of cell-surface receptors, are frequently reported in most NSCLC cases.



Computational Systems Biology

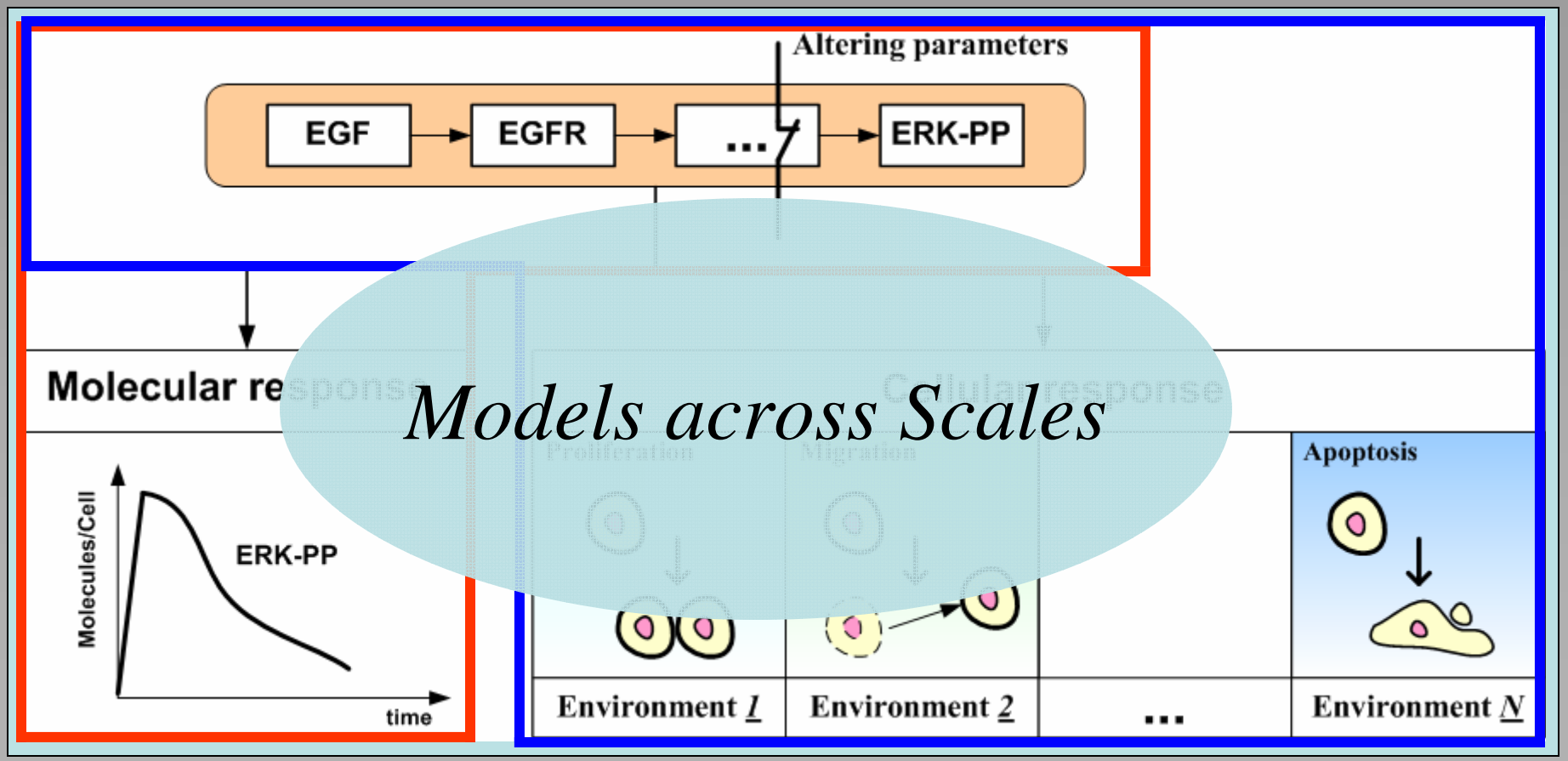
Computational Models

- to understand …
- to test …
- to drive …
- to predict …

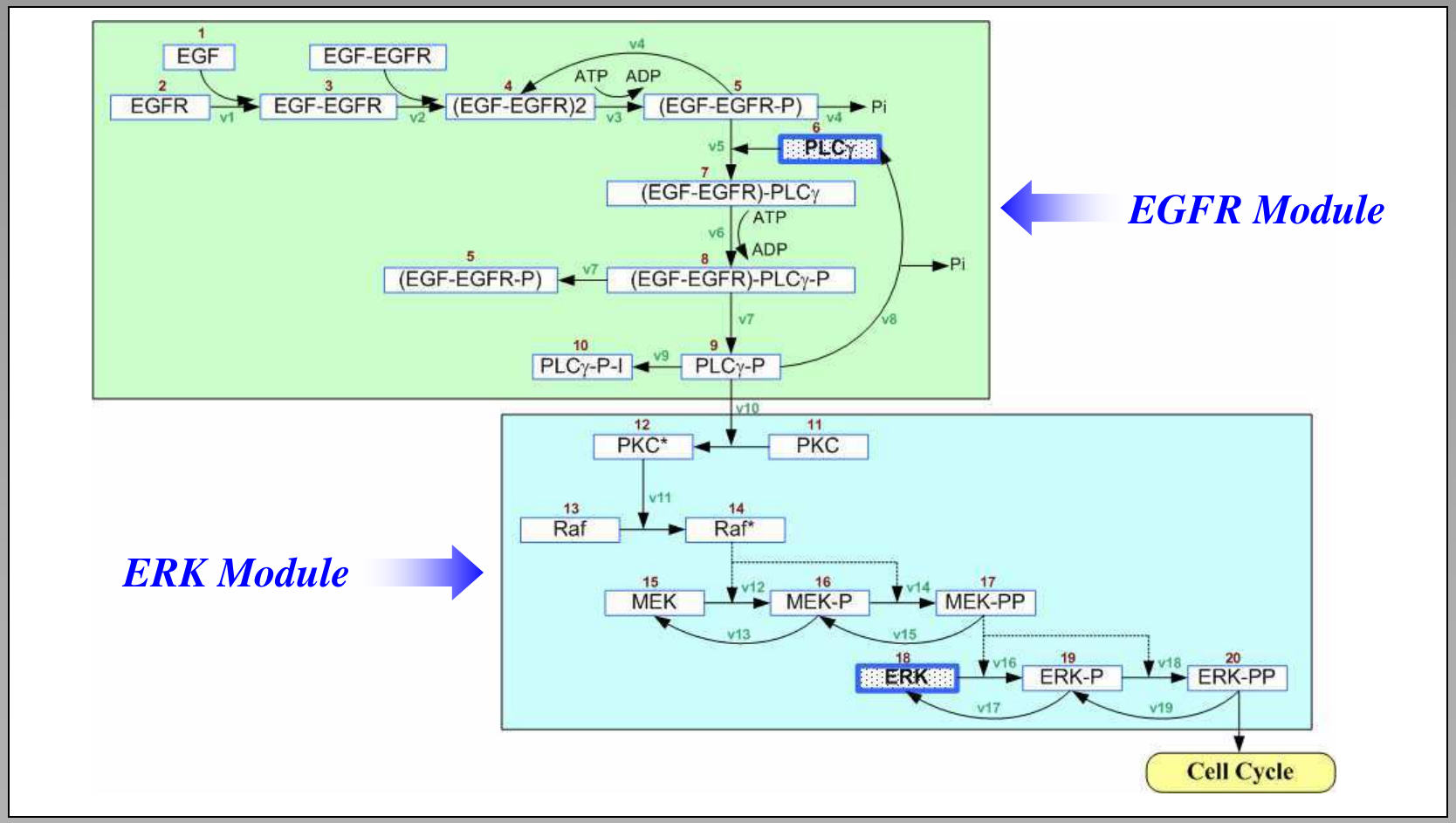
Complex Cancer Systems

Necessity of Multiscale for Cancer Models

Complex cancer systems are context-dependent.



Molecular Network



Wang et al., Theor Biol Med Model 2007, 4:50.

Equation

$$[A]+[B]\underset{k_r}{\overset{k_f}{\rightleftharpoons}}[A\cdot B]$$

***For example*:**

$$[EGF]+[EGFR]\underset{k_{1r}}{\overset{k_{1f}}{\rightleftharpoons}}[EGF\cdot EGFR] \qquad [EGF\cdot EGFR]+[EGF\cdot EGFR]\underset{k_{2r}}{\overset{k_{2f}}{\rightleftharpoons}}[EGF\cdot EGFR]2$$

$$\begin{cases} v_1 = k_{1f}[EGF][EGFR]-k_{1r}[EGF\cdot EGFR] \\ v_2 = k_{2f}[EGF\cdot EGFR]-k_{2r}[EGF\cdot EGFR]2 \end{cases}$$

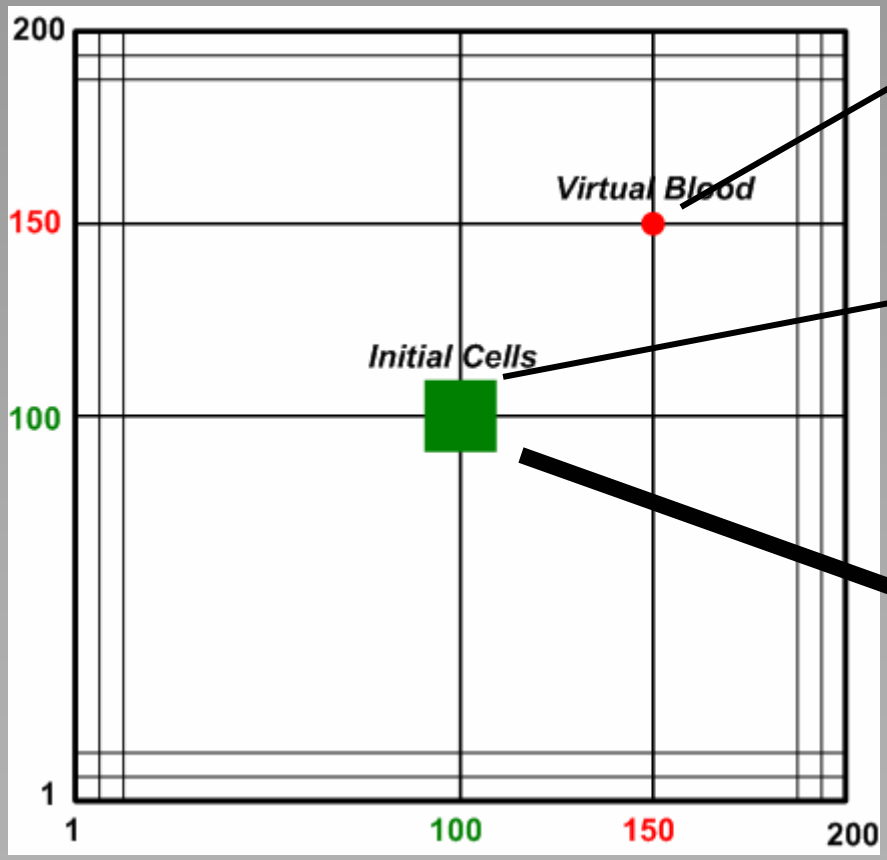
To determine the change in concentration of a certain reaction component $[X_i]$ over time

$$\frac{d[X_i]}{dt} = \sum v_{\text{Production}} - \sum v_{\text{Consumption}}$$

Reaction rates producing $[X_i]$ **Reaction rates consuming $[X_i]$**

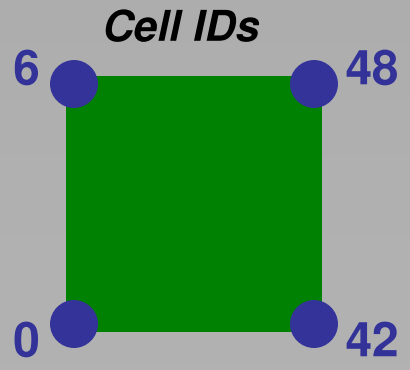
$$\Rightarrow \begin{cases} \dfrac{d[EGF]}{dt} = -v_1 & \dfrac{d[EGFR]}{dt} = -v_1 & \dfrac{d[EGF\cdot EGFR]}{dt} = v_1 - 2v_2 \end{cases}$$

Microenvironment

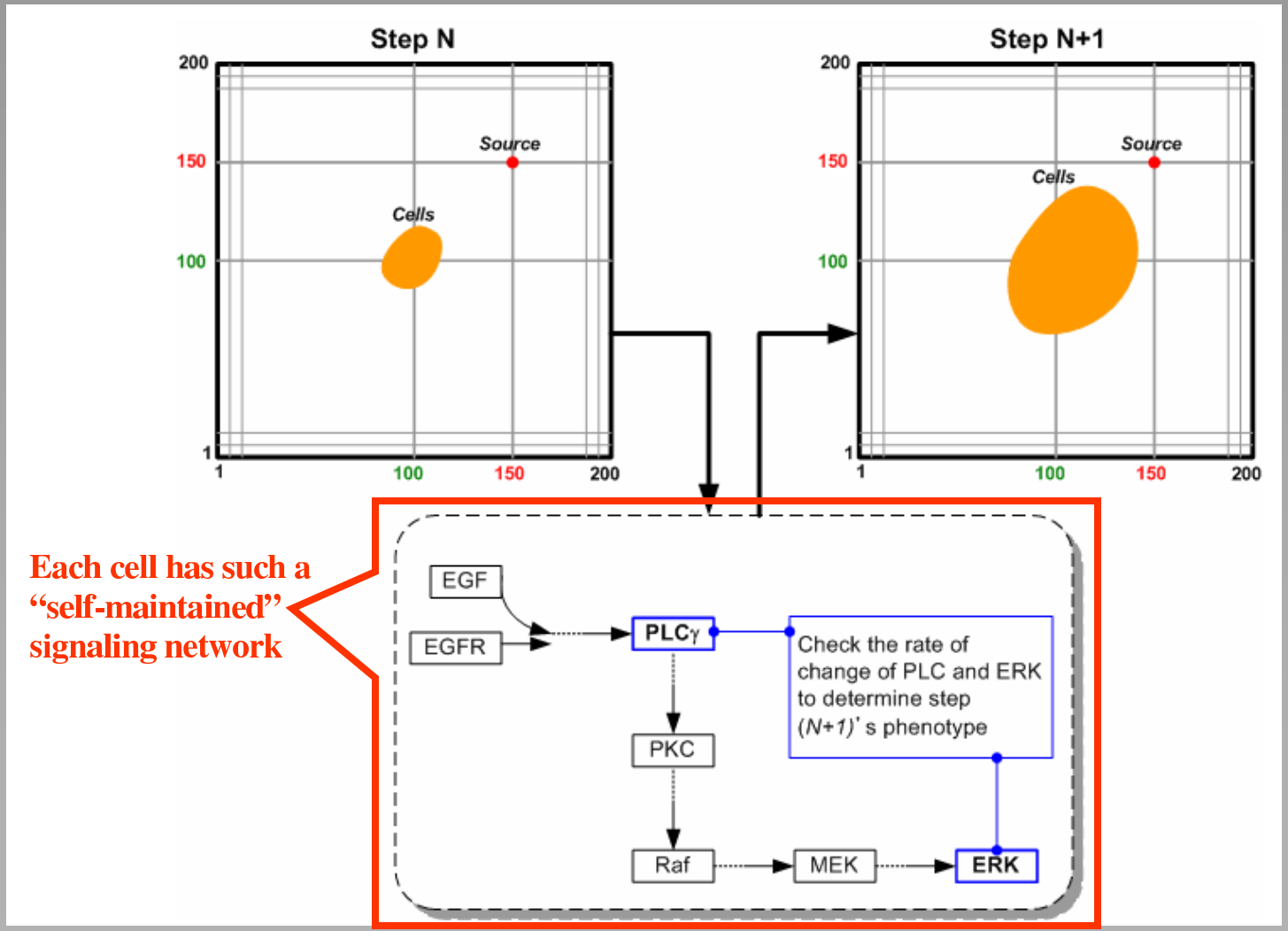


With the highest glucose, *EGF* concentration, and oxygen tension value.

In our simulations, there are a total of *(7x7=)49* cells initially set up at the center of the square lattice.



Linking Molecular Signals to Cellular Behavior

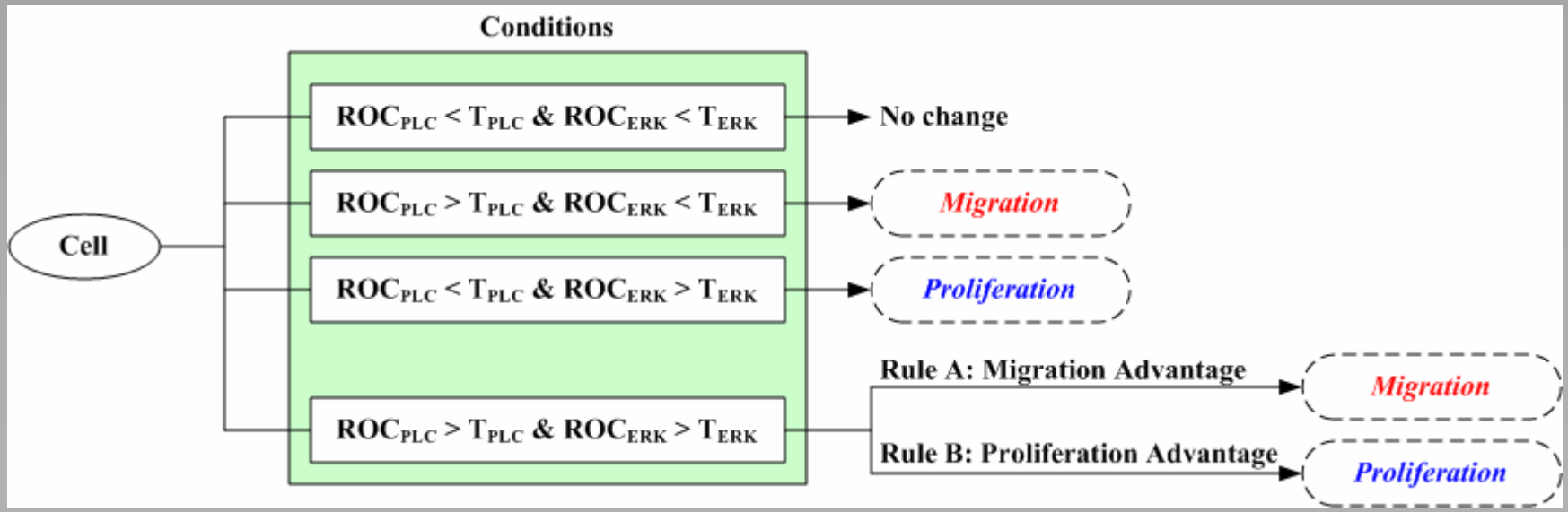


Cellular Phenotype Decision Algorithm

The Rate of Change of **PLCγ** ($ROC_{PLC\gamma}$) **to decide** → **Cell Migration**

The Rate of Change of **ERK** (ROC_{ERK}) **to decide** → **Cell Proliferation**

Four situations exist at any time step, t_i:

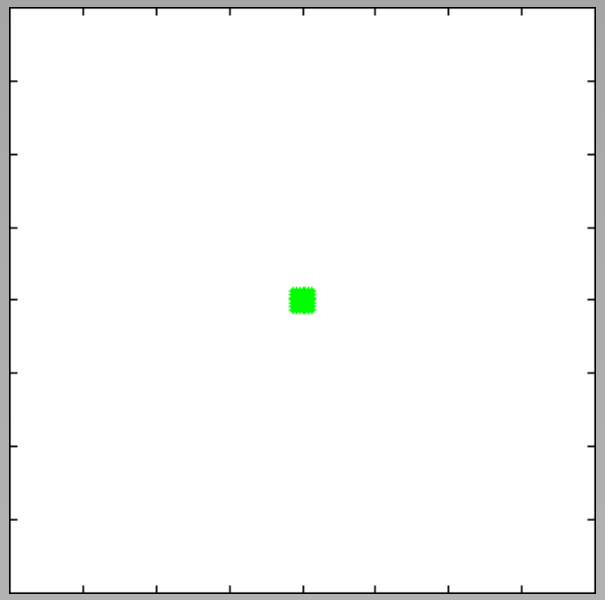


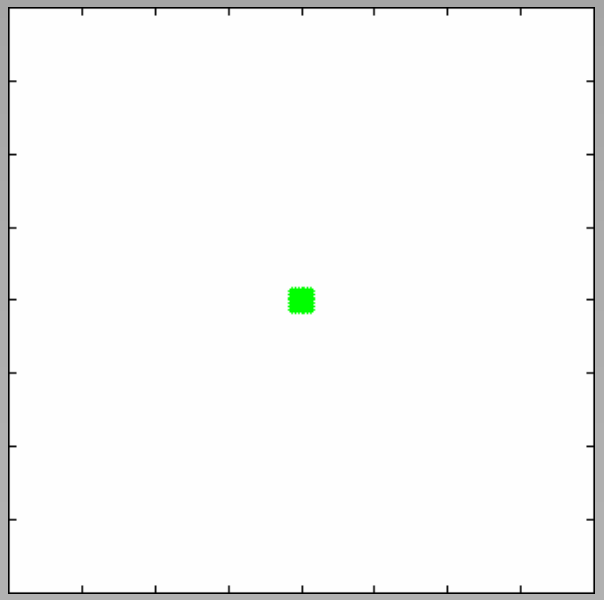
Typical Simulations

$ROC_{PLC\gamma} > \sigma_{PLC\gamma}$ & $ROC_{ERK} > \sigma_{ERK}$

Rule A: **migration advantage**

Rule B: **proliferation advantage**

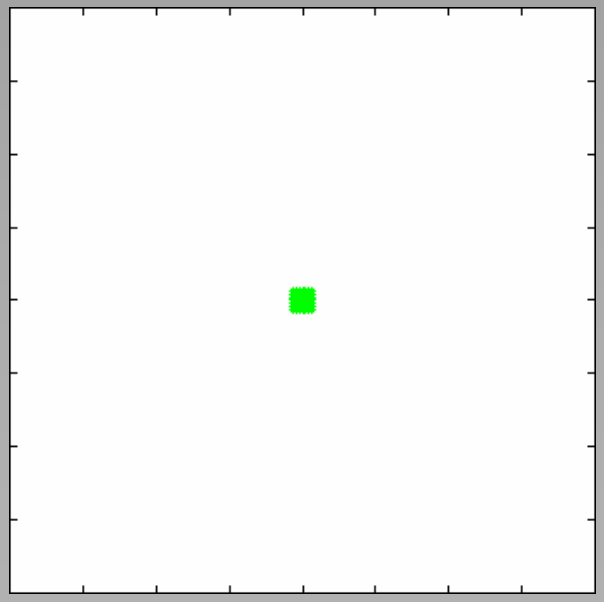




Change of EGF on Multi-Cellular Dynamics

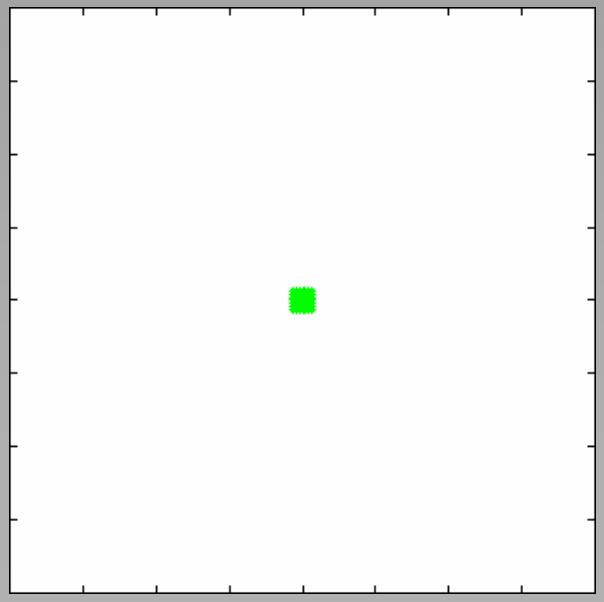
Rule A (Migration Advantage)

EGF concentration: 2.65 (nM)



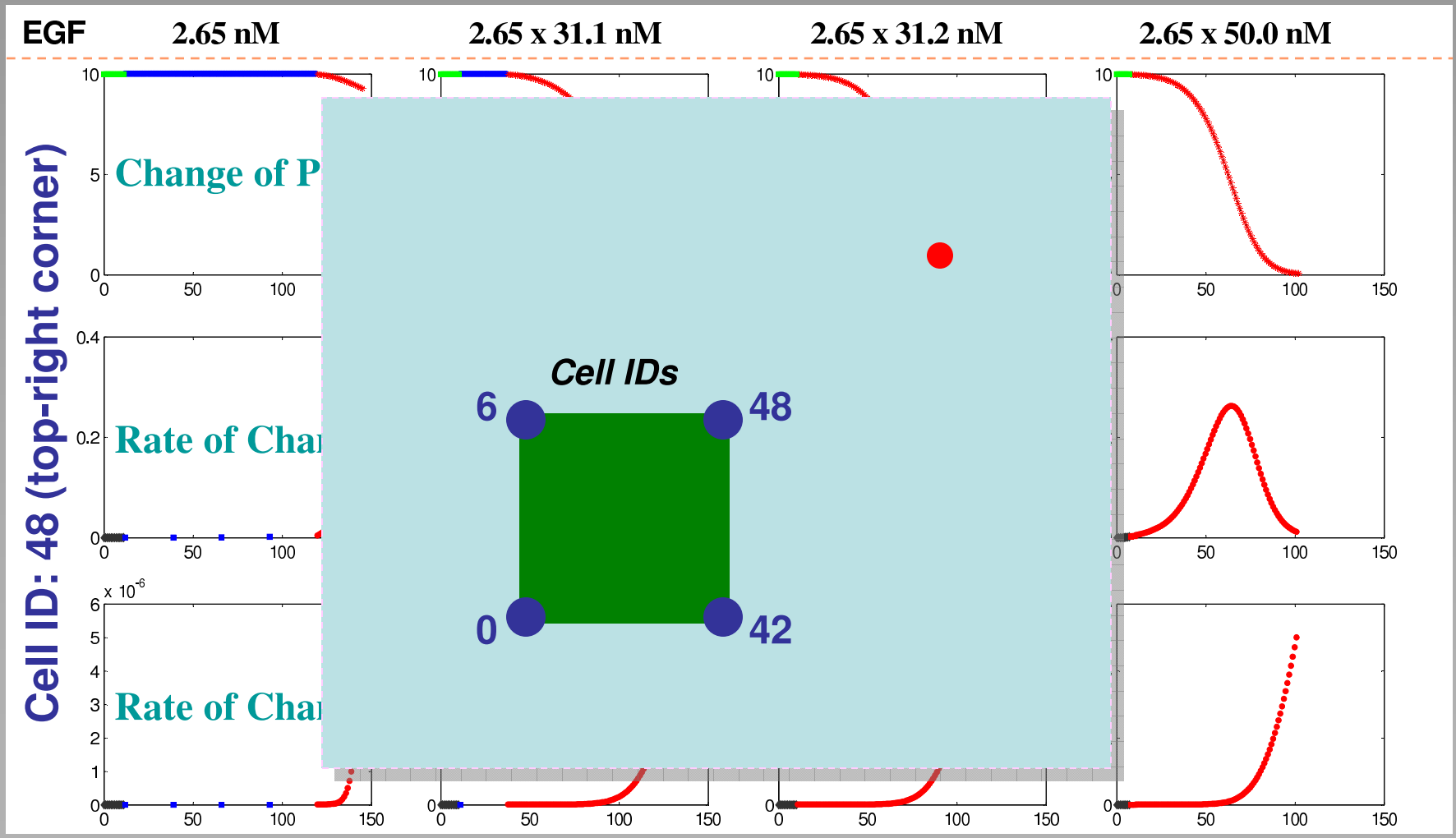
145 time steps

EGF concentration: 2.65 x 50 (nM)



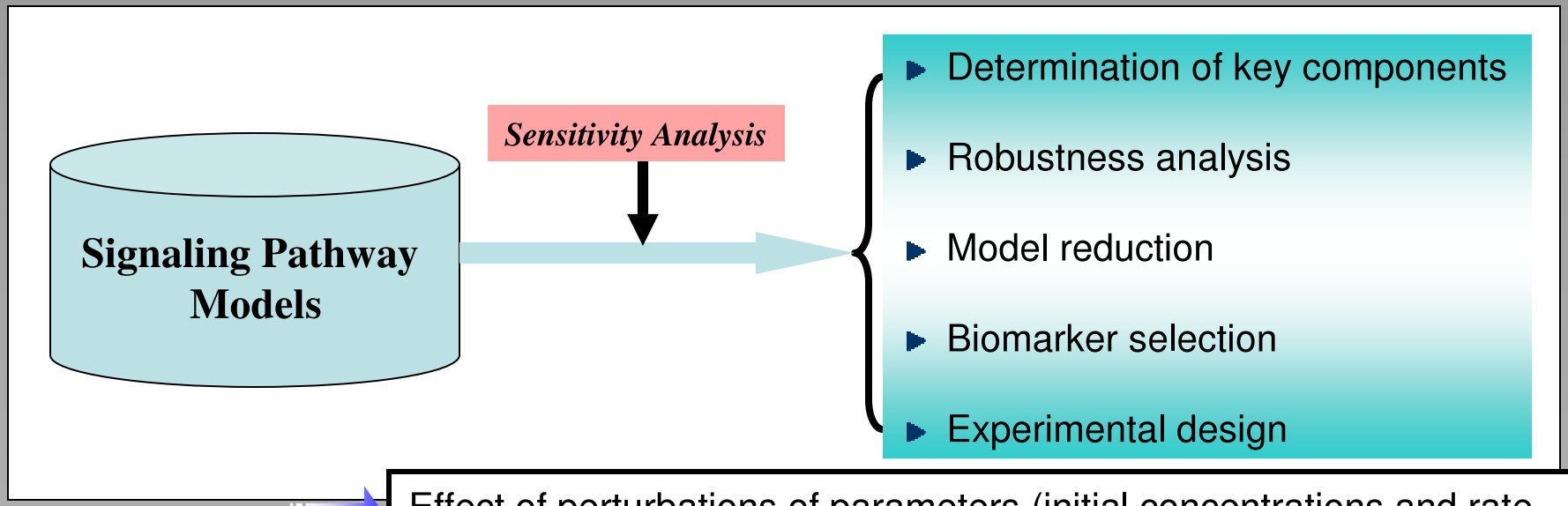
102 time steps

Molecular Changes with Increasing EGF



Sensitivity Analysis

Current Condition:



In Cancer Systems:

Cancer cells react and respond to heterogeneous biochemical environments.

Cross-Scale Sensitivity Analysis

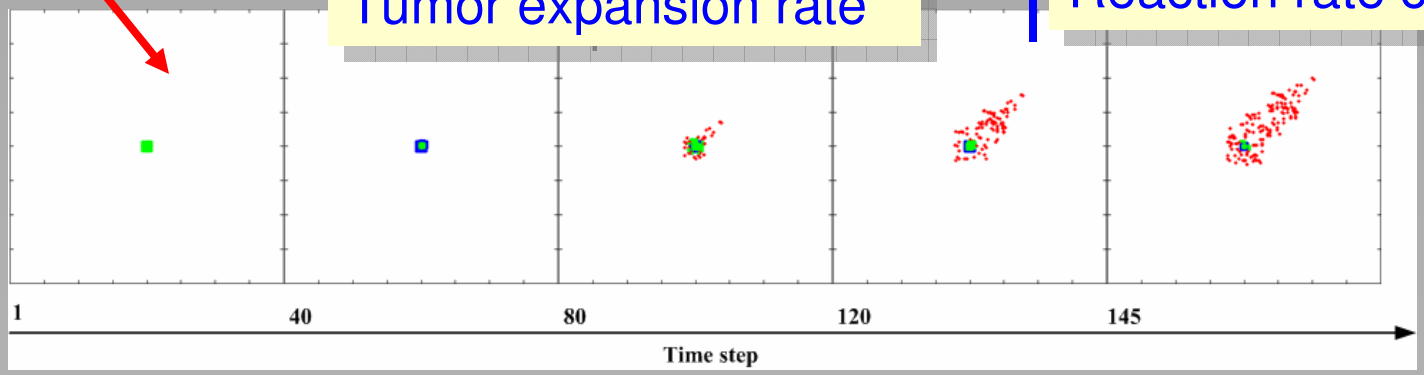
Sensitivity Coefficient: $$S_p^M = \frac{\delta M / M}{\delta p / p}$$

where p represents the parameter that is varied in a simulation and M the response of the system; δM is the change in M due to δp, the change in p.

Pathway components

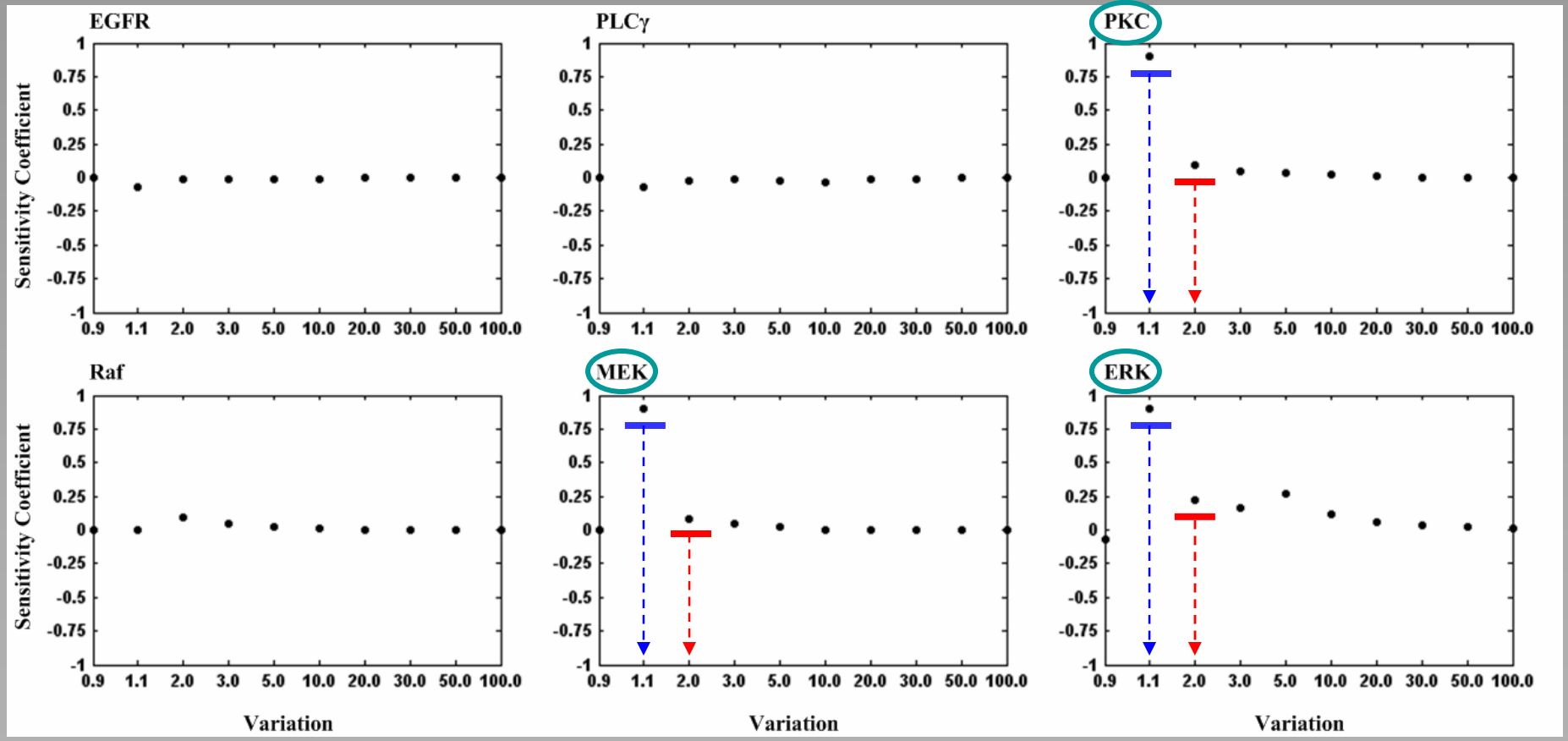
Reaction rate constants

Tumor expansion rate



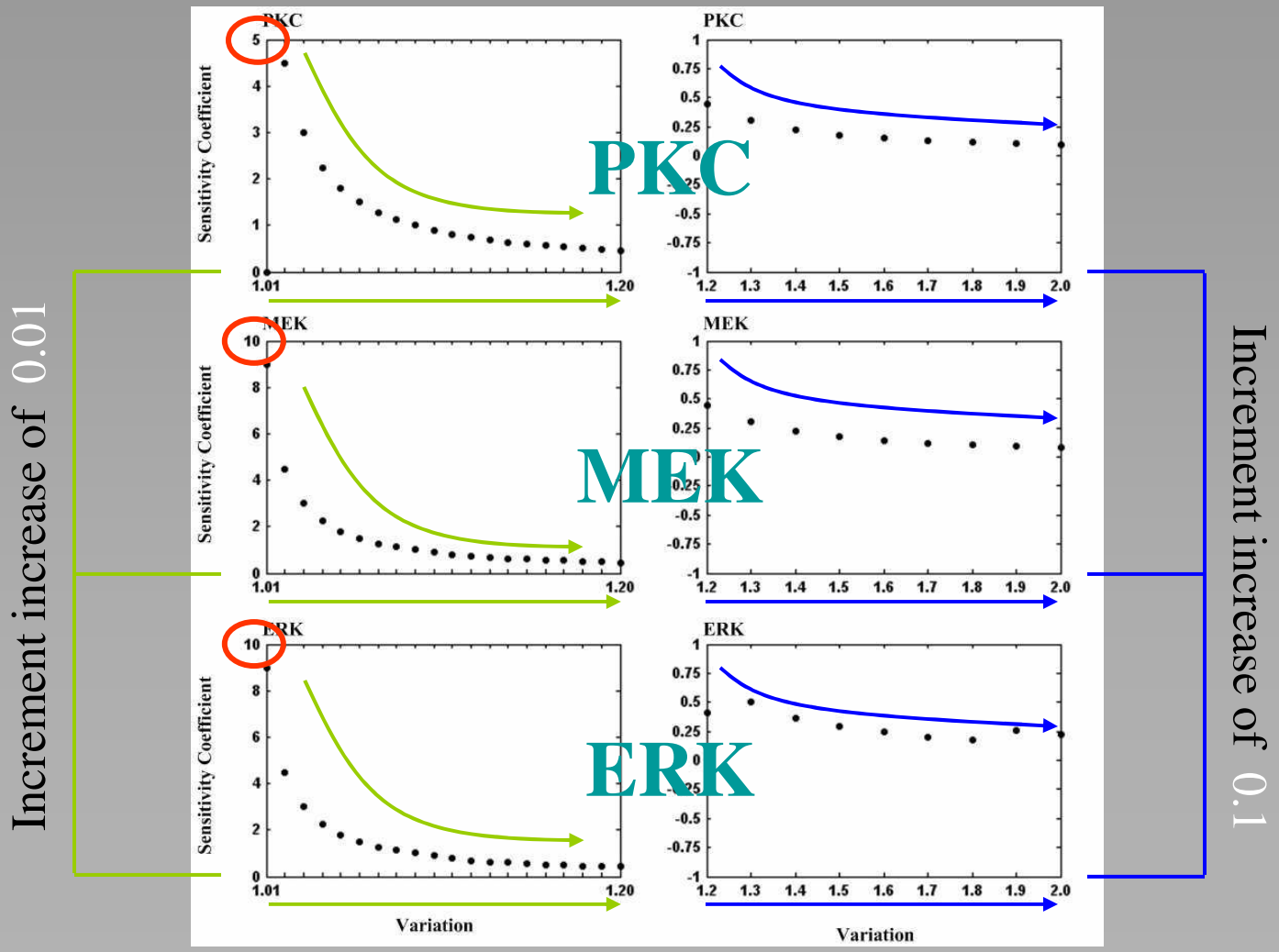
Wang et al., Biosystems 2008, 92(3):249-258.

Critical Components

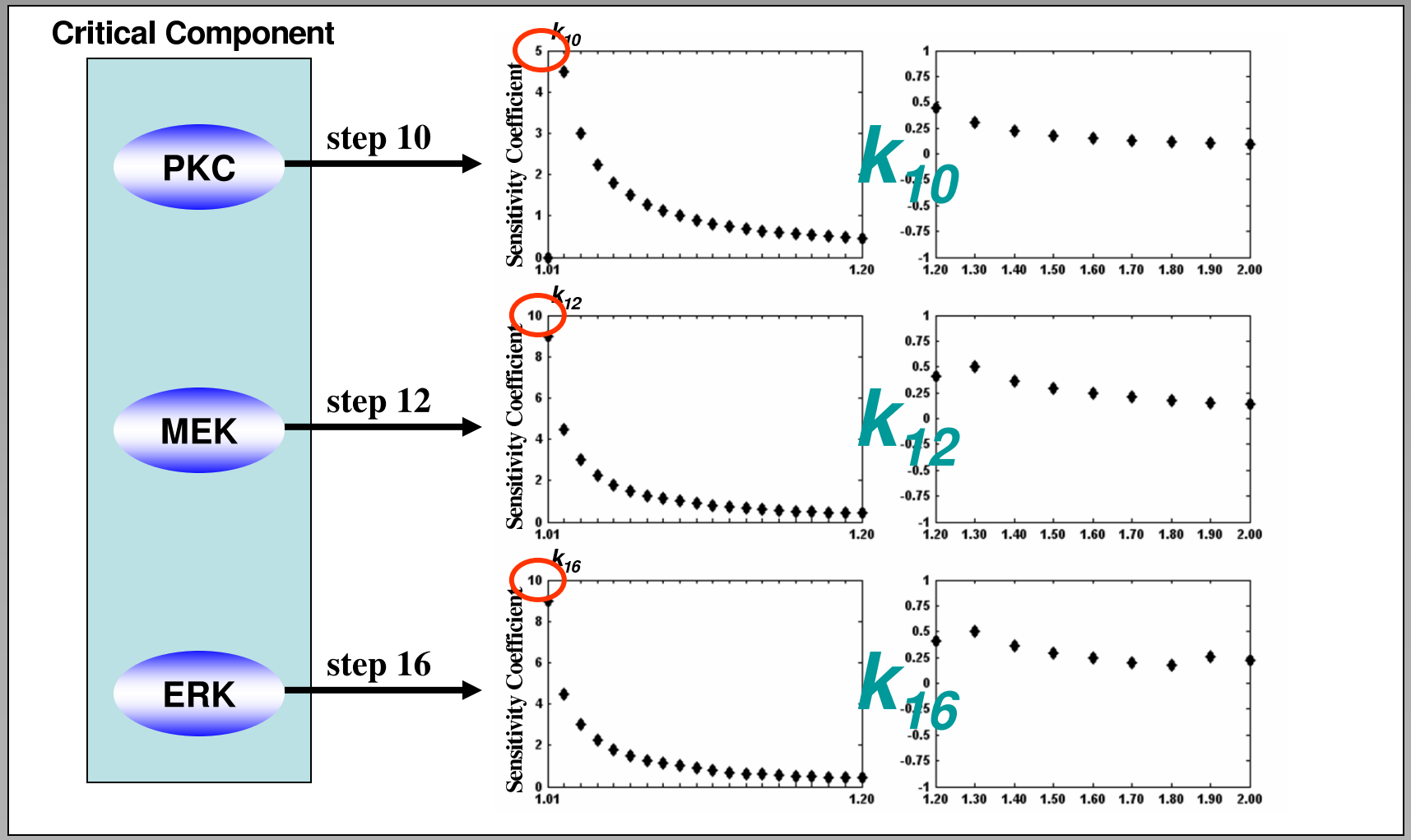


PKC, *MEK* & *ERK* are considered to be critical.

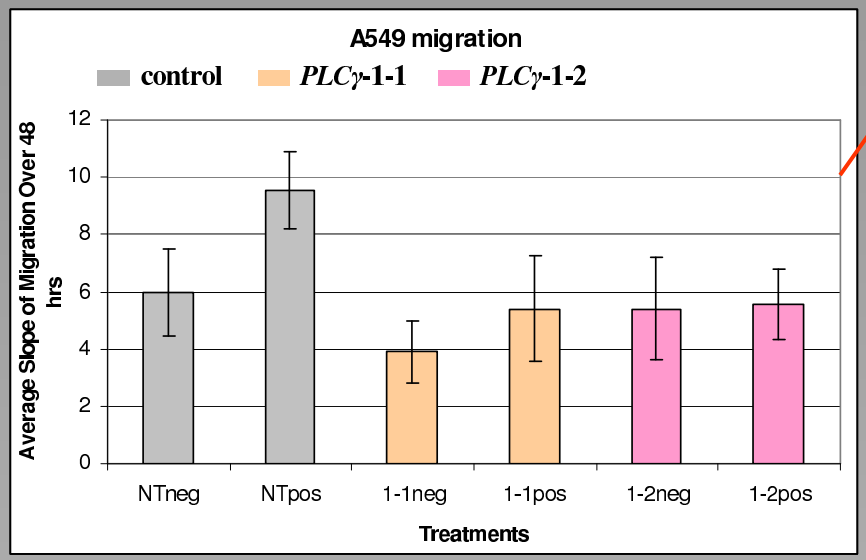
Smaller Changes in Critical Components



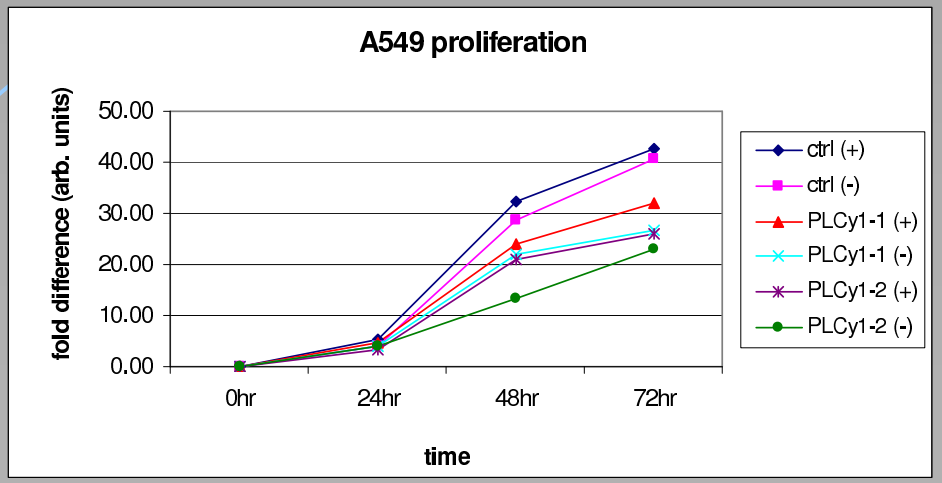
Critical Reaction Steps



Model Validation – on microscopic level

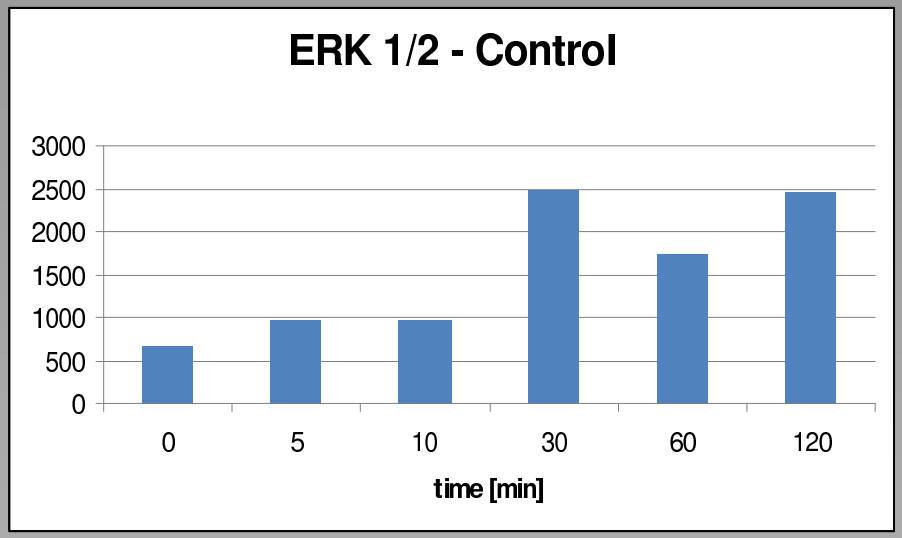


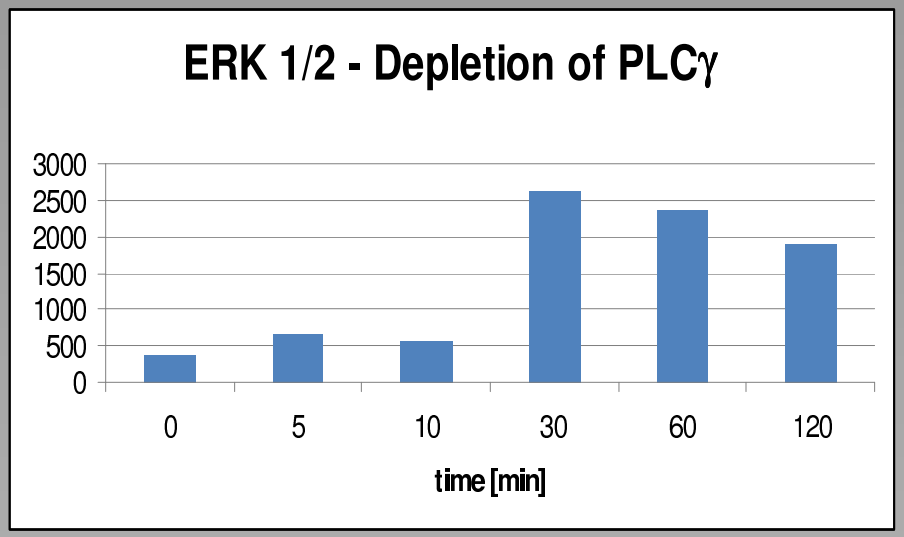
- The maximal change in cell migration occurs in the control group with EGF stimuli.
- *PLC*γ, as a key downstream signaling component of classic MAPK pathway, plays a role in regulating cell migration.
- Inhibition of *PLC*γ reduces the activity of tumor cells in migration.



- The maximal change in cell proliferation occurs in the control group with EGF stimuli.
- *PLC*γ plays a role in regulating cell proliferation.
- Inhibition of PLCγ reduces the activity of tumor cells in proliferation.

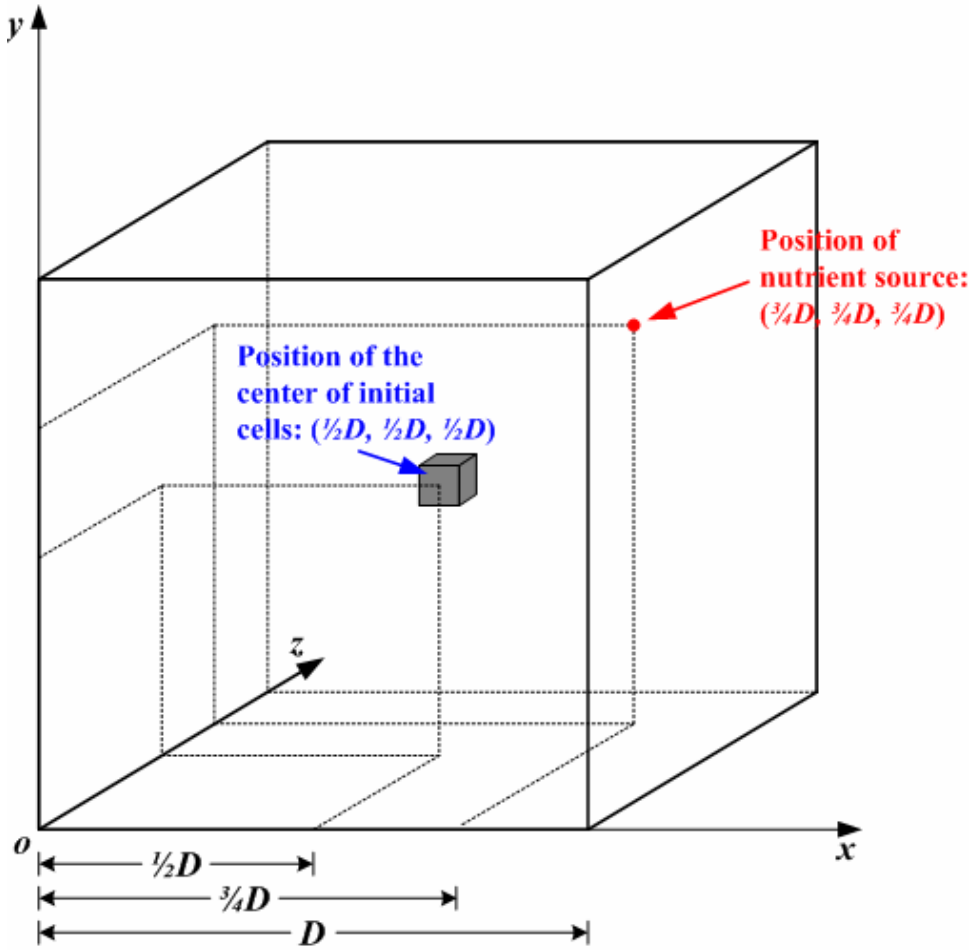
Model Validation – on molecular level





- Inhibition of PLCg effectively suppresses the activation of ERK to some level at the early stage.
- The activation of ERK gets recovered at the later stage, part of which is probably due to compensation of other pathways in activating ERK via a cross-talk manner.

Model Extension – on microscopic level

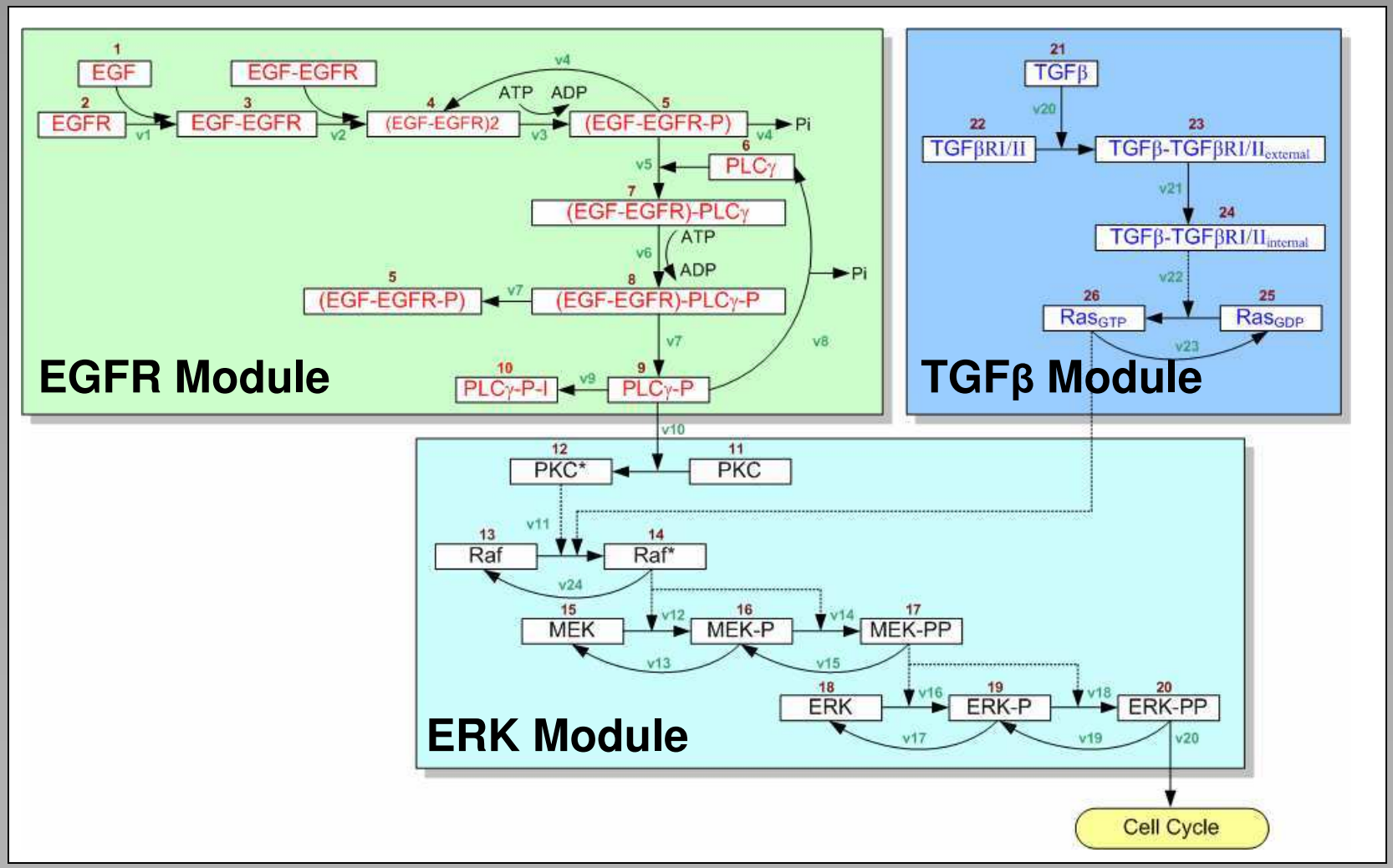


Why Three-Dimensional (3D)?

1) A 3D environment is a more accurate representation of a real tumor, thus supports translation to clinical application.

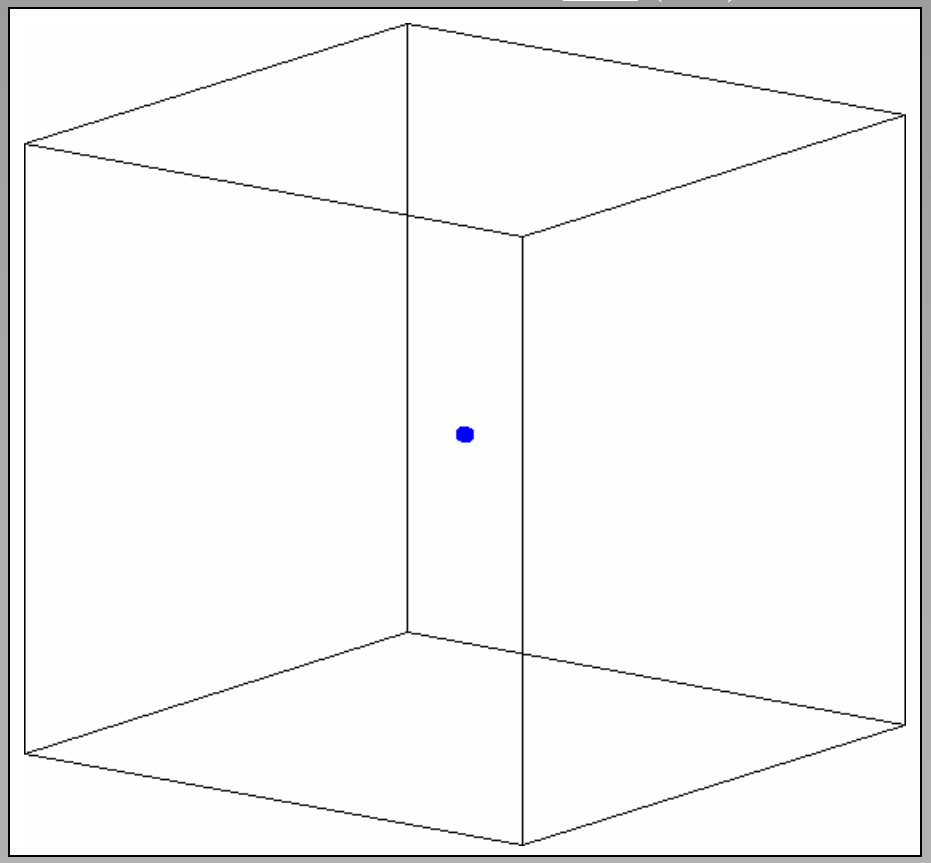
2) Tumor growth dynamics in 3D may be different from that in 2D.

Model Extension – on molecular level

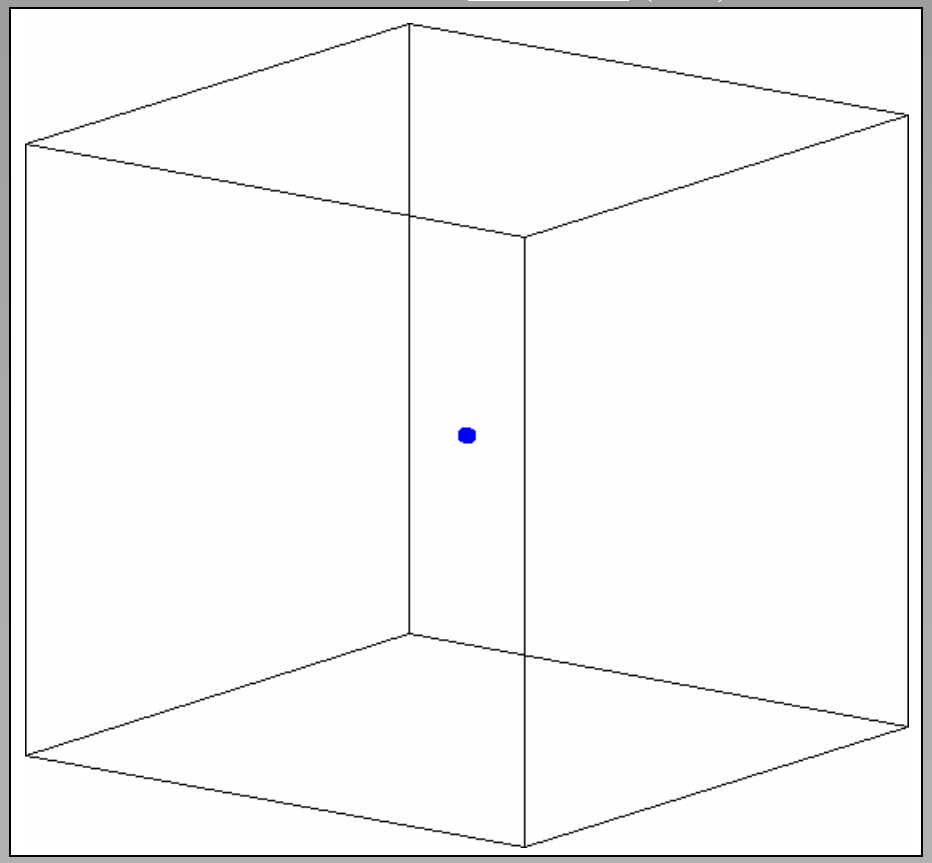


Tumor Growth in 3D

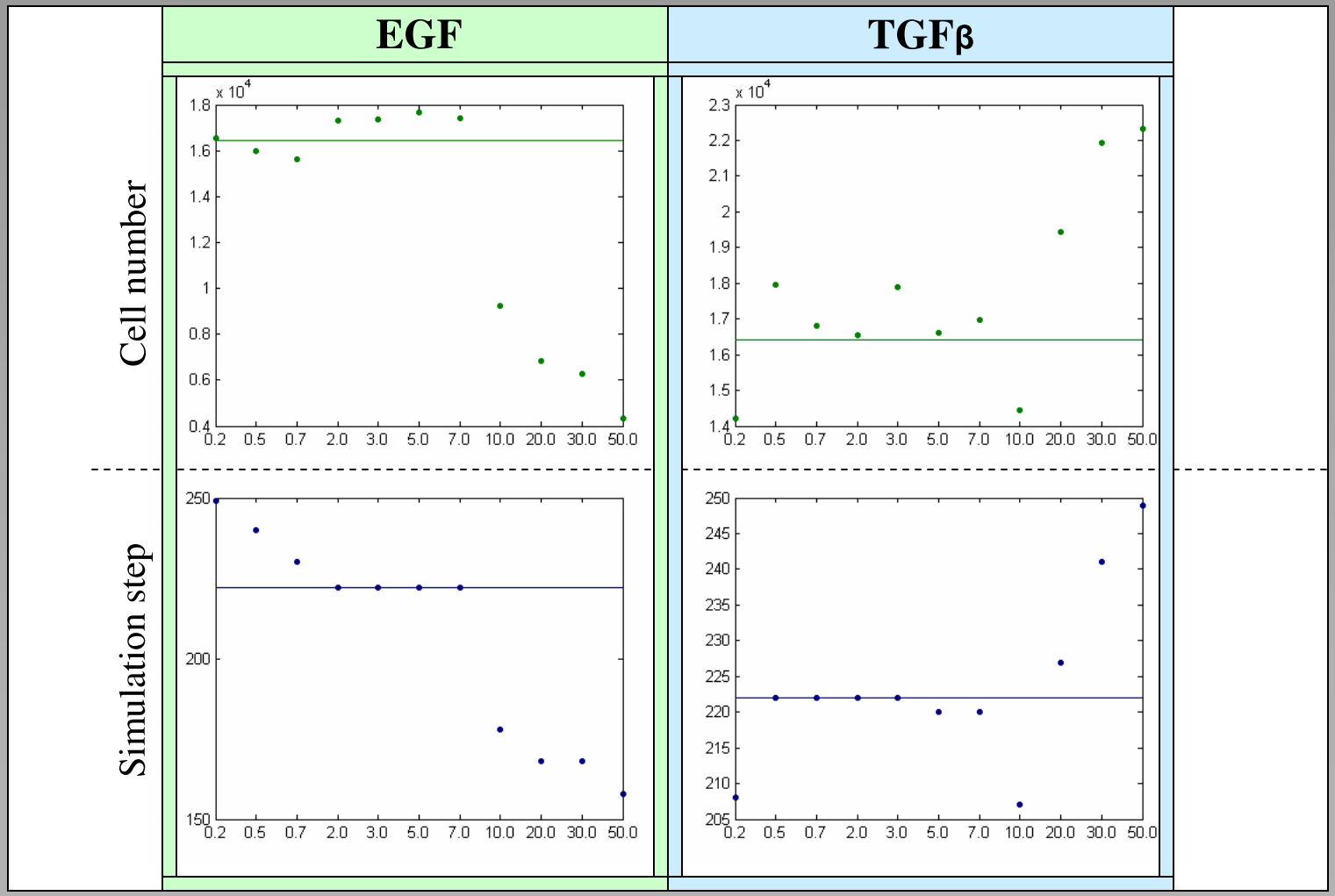
EGF concentration: 2.65 (nM)



EGF concentration: 2.65 x 10 (nM)



Impact of Change of EGF & TGF$_\beta$



Conclusion & Future Works

- Re-validating model parameters at both molecular and cellular levels with experimental data.

- With the 3D model, examining cross-talk behavior of the signaling network, in coordinating and processing different inputs (EGF and TGFβ) into biological responses at the multi-cellular level.

- Exploring the possibilities of combined effects of parameter variations simultaneously within the 3D model.

- A potential path in cancer modeling:
  Hybrid, ***Multi-scale*** and ***Multi-resolution***.

Wang and Deisboeck, Scientific Modeling and Simulation. in press.

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