Introduction to Cancer Systems Biology

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NATIONAL CANCER INSTITUTE

Integrative Cancer Biology Program

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Lawrence Berkeley National Laboratory, Berkeley, CA; Joe W. Gray, Ph.D.

University Hospital of Cleveland, Cleveland, OH
Timothy Kinsella, M.D.
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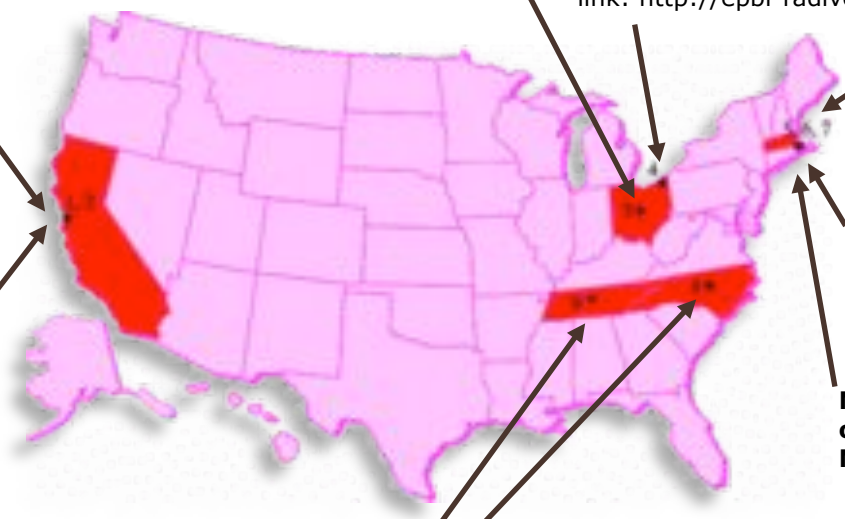


Massachusetts General Hospital, Boston, MA, Thomas Deisboeck, M.D.
link: http://www.cvit.org

Dana Farber Cancer Institute, Boston, MA
Todd Golub, M.D.

Massachusetts Institute of Technology, Boston, MA; Richard Hynes, Ph.D.

Stanford University School of Medicine, Stanford, CA; Sylvia Plevritis, Ph.D.

Duke University, Durham, NC
Joseph Nevins, Ph.D.
link: http://icbp.genome.duke.edu

Vanderbilt University Medical Center, Nashville, TN
Vito Quaranta, M.D.
link: http://www.vanderbilt.edu/VICBC

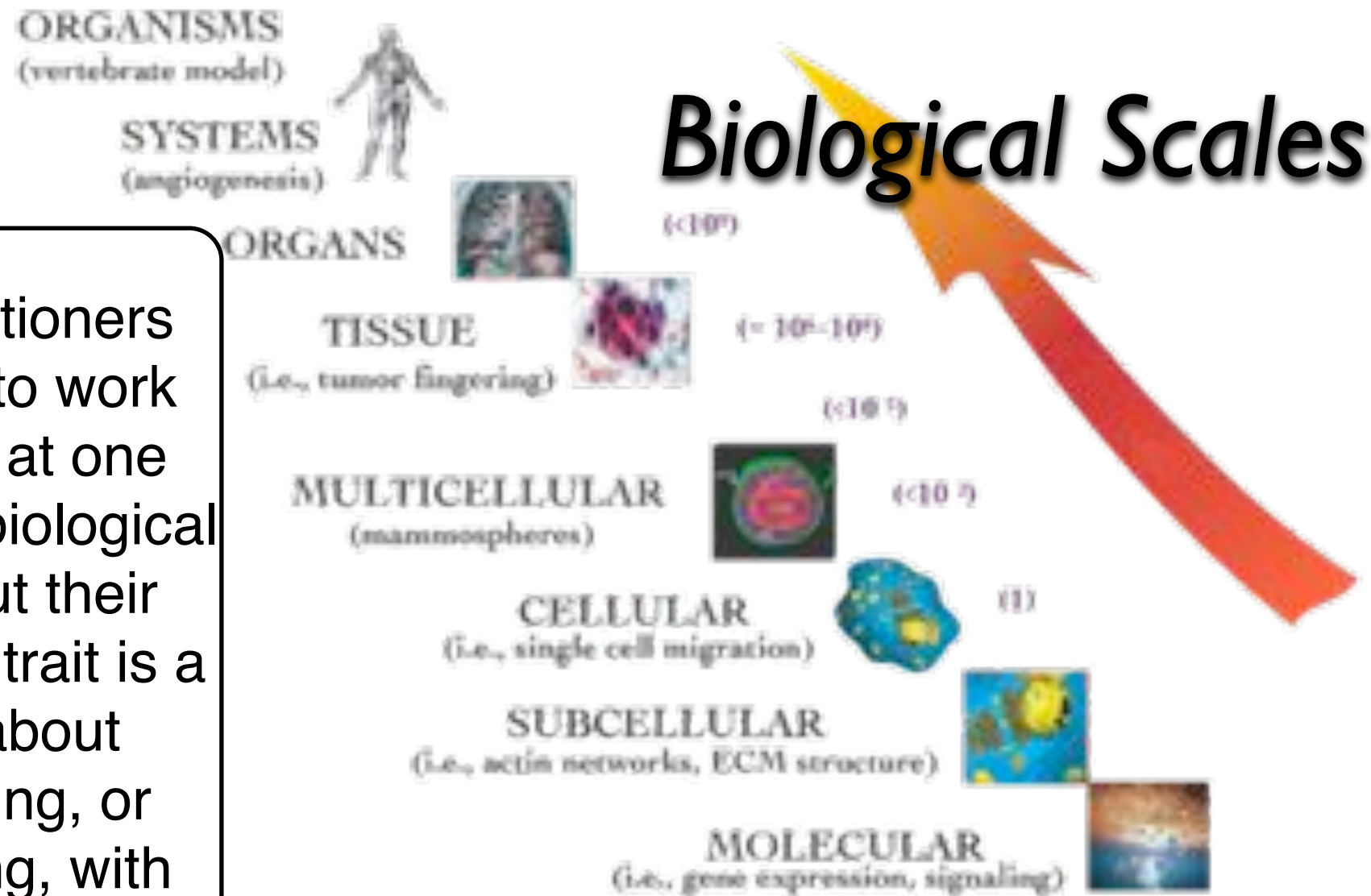
What is Integrative Cancer Biology?

- It is the same as Cancer Systems Biology, or Systems Biology of Cancer

What is Systems Biology? *(Personal Definition, VQ)*

- A system of linked coordinates that slide along Biological Scales.
- SB practitioners still tend to work primarily at one particular biological scale, but their distinctive trait is a worry about connecting, or integrating, with scale levels above and below.

Biological Scales



SB practitioners still tend to work primarily at one particular biological scale, but their distinctive trait is a worry about connecting, or integrating, with scale levels above and below.

Misconceptions about Systems Biology

- Mindless accumulation of data by some high-throughput means
- No hypothesis necessary prior to experimentation
- Large amounts of data automatically provide answers
- Can be comfortably ignored by “Conventional Biology”

Cancer Systems Biology: Why Bother?

"Enormous progress has been made in understanding ....the critical cellular processes, such as cell cycle, DNA repair, apoptosis, transcription, cell migration, and matrix structure, [that are] so critical to our understanding and treatment of cancer.

However, cancer is not a disease only of cells. It is a disease of various systems and components that interact at both a molecular and cellular level to lead to initiation and progression of the disease."

Cancer Systems Biology: Why Bother?

"These interacting systems include interactions between:

- genes in the cancer cells;
- signal transduction pathways within a cancer cell;
- cells in the tumor;
- tumor and its microenvironment;
- the individual and the macro-environment."

Cancer Systems Biology: Why Bother?

"Furthermore, the changing interactions of these ... systems in a ... dynamic environment underscore the inherent complexity of the disease.

Until recently, it has been necessary to apply a reductionist approach to cancer research, focusing on a specific mutation, signaling pathway, or cell.

While there has been remarkable progress in understanding each of these component parts, further integration across components or scales has been limited primarily by the lack of technology and tools needed to interrogate at any higher level."

Cancer Systems Biology: Why Bother?

"Within the past 10 years, new technologies have been developed that have generated extensive genomic, proteomic and other genome-wide datasets.

Other novel technologies have made possible vital imaging, isolation of rare cells, and organotypic culturing.

Together, these developments have afforded the possibility to expand the cancer research effort to include an integrative systems approach."

Cancer Systems Biology: Why Bother?

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH) (http://www.nih.gov/)

Components of Participating Organizations
National Cancer Institute (NCI) (http://www.cancer.gov)

Title: **Collaborative Research in Integrative Cancer Biology and the Tumor Microenvironment (U01)**

Announcement Type:

New

Program Announcement (PA) Number: **PAR-09-026**

Key Dates
Release/Posted Date: November 13, 2008
Opening Date: January 19, 2009 (Earliest date an application may be submitted to Grants.gov).

Why Bother with Computational and Mathematical Modeling of Cancer?

Is this equivalent to saying that we need Theory in Cancer Biology? Yes.

Impact of theory in science (+)

"There is nothing more practical than a good theory"
James Clerk Maxwell

Music theory
JS Bach

Ok, theory in CB is good, but why now, why me?

Science 20 December 1996:
Vol. 274. no. 5295, pp. 2039 – 2040
DOI: 10.1126/science.274.5295.2039

PERSPECTIVES

Biologists Put on Mathematical Glasses

Torbjörn Fagerström, Peter Jagers, Peter Schuster, Eörs Szathmary

"No new principle will declare itself from below a heap of facts"
Sir Peter Medawar

Assuming we must, how do we build a Theory of Cancer?

Short Answer: *Nobody knows. However, we can try.*

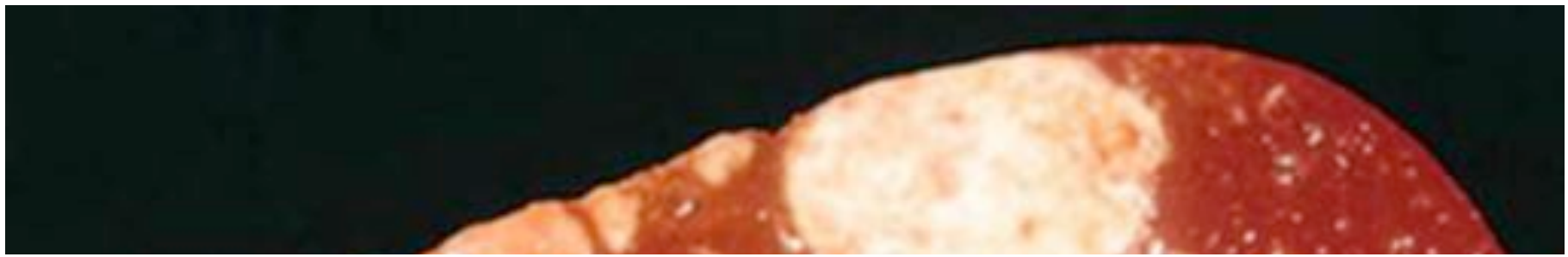
OPTIONS:

- *Armchair*
- *Take a page from other sciences: Physics and Engineering are recent and excellent examples of the power of computational/mathematical modeling*

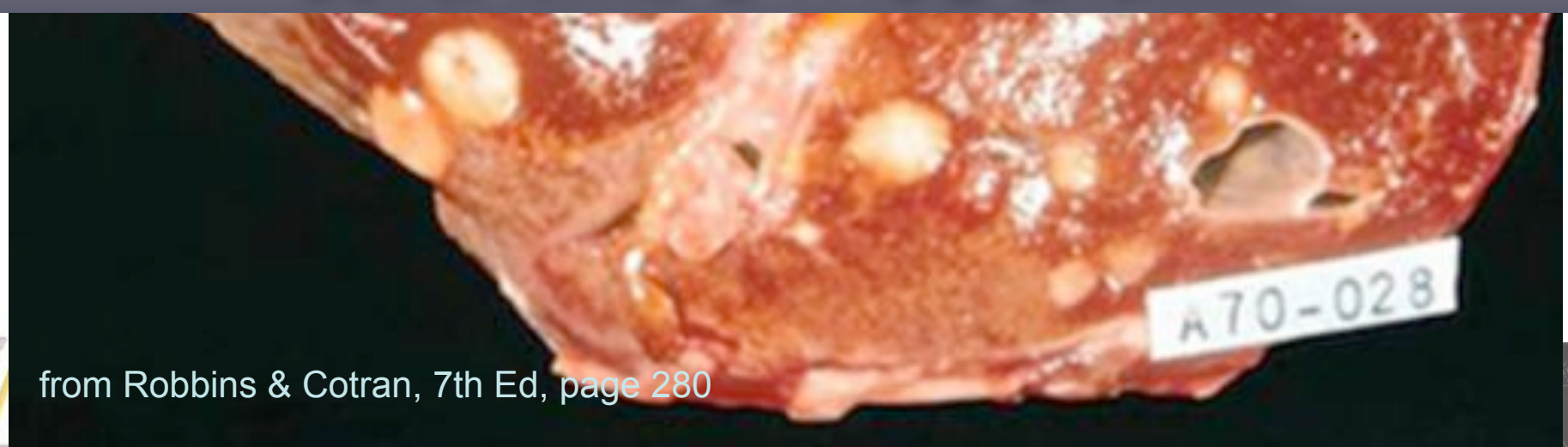
Outline

- A 4 minute course on Cancer: all you need to know to follow the remainder of this talk
- The interface between Oncology and Cancer Systems Biology
- How to practice Cancer Systems Biology
- Tangible examples of Cancer Systems Biology, including the experience in our own group (+AW)

Macroscopic Appearance of Cancer Tissue



How we evaluate cancer disease in a patient (Diagnosis and Prognosis): Pathologists determine STAGE and.....

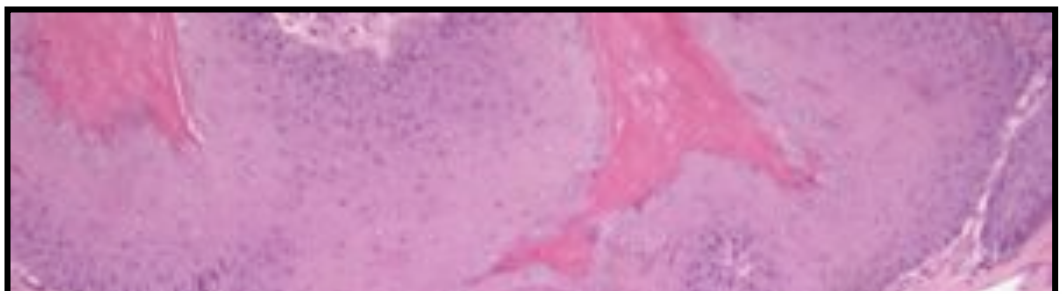


from Robbins & Cotran, 7th Ed, page 280

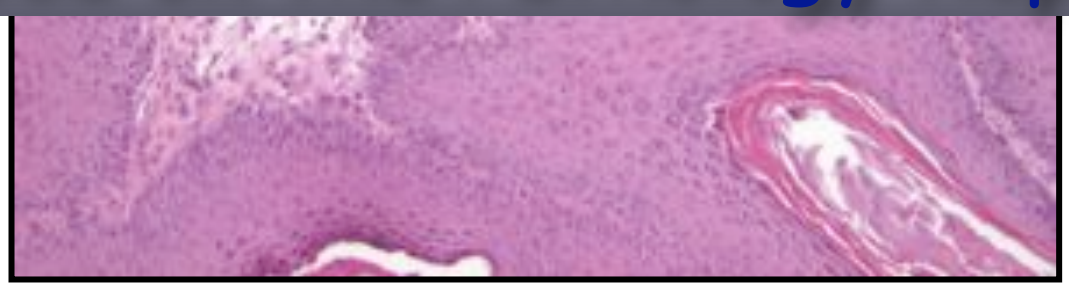
CBC

MATHEMATICS

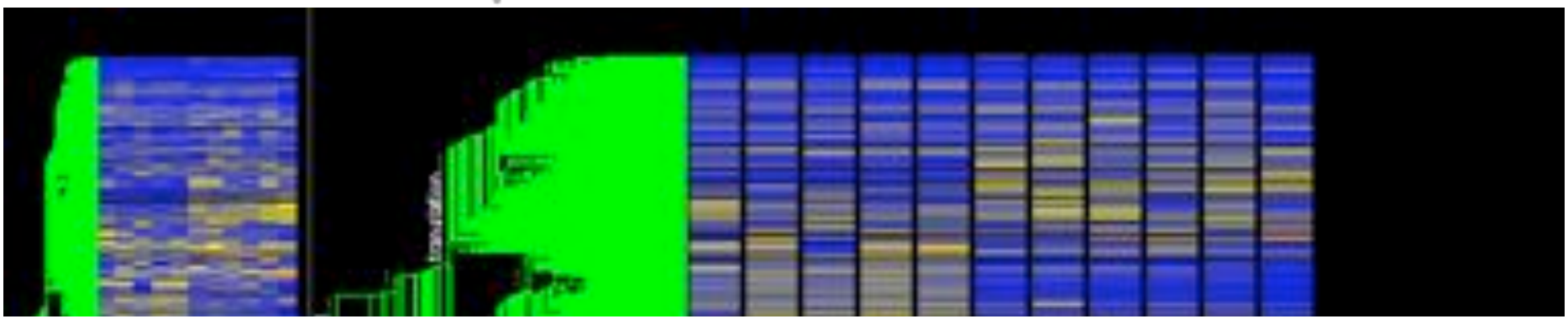
Microscopic Appearance of Cancer Tissue



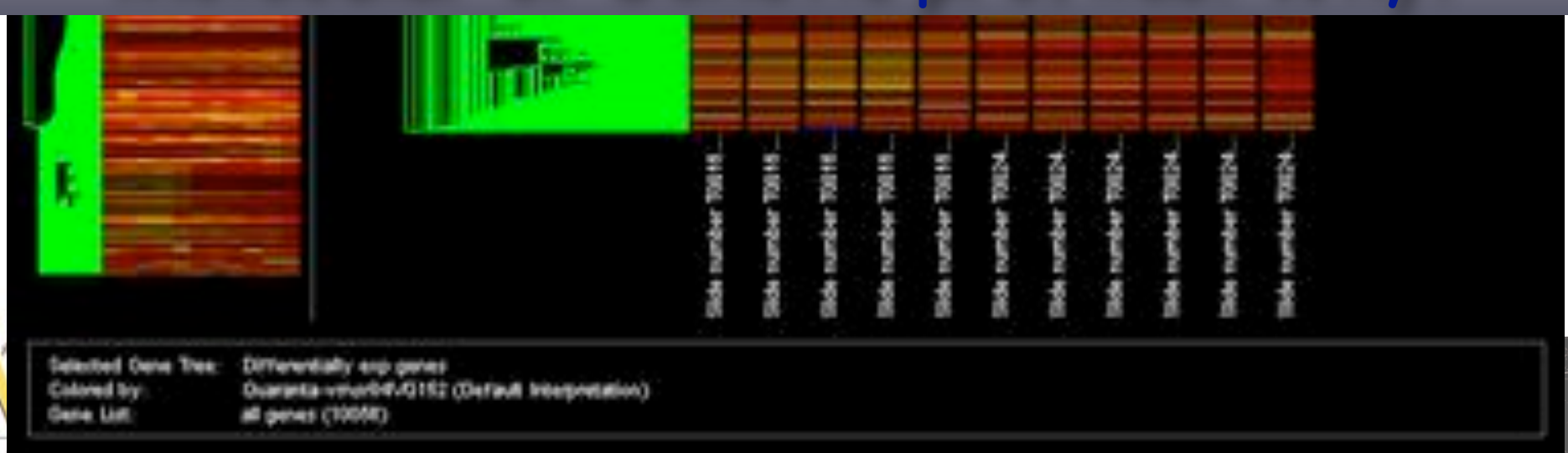
....GRADE: All subsequent clinical decision are based on the Pathology Report



Genes Expressed in Cancer Tissue



How we would like to evaluate cancer disease in a patient (Diagnosis and Prognosis): Molecular or Genetic profiles. Why?

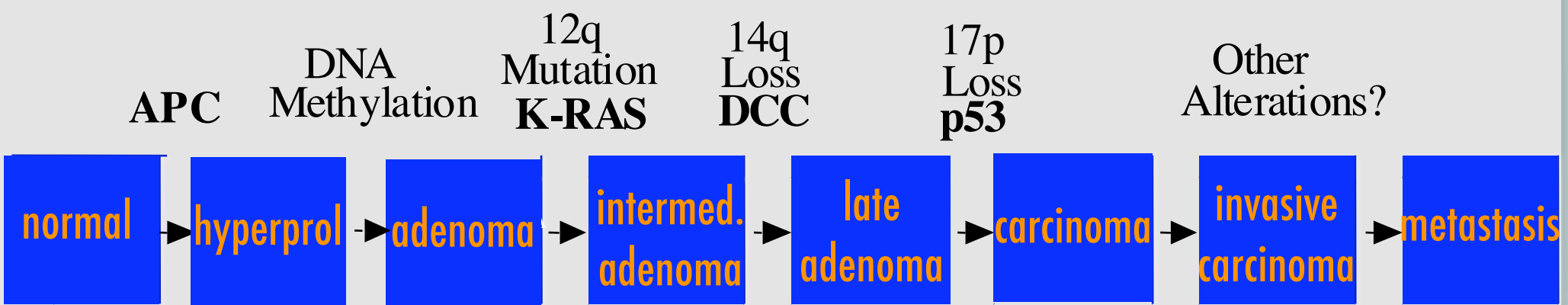


Multistage Tumor Progression: A Current Theoretical Framework

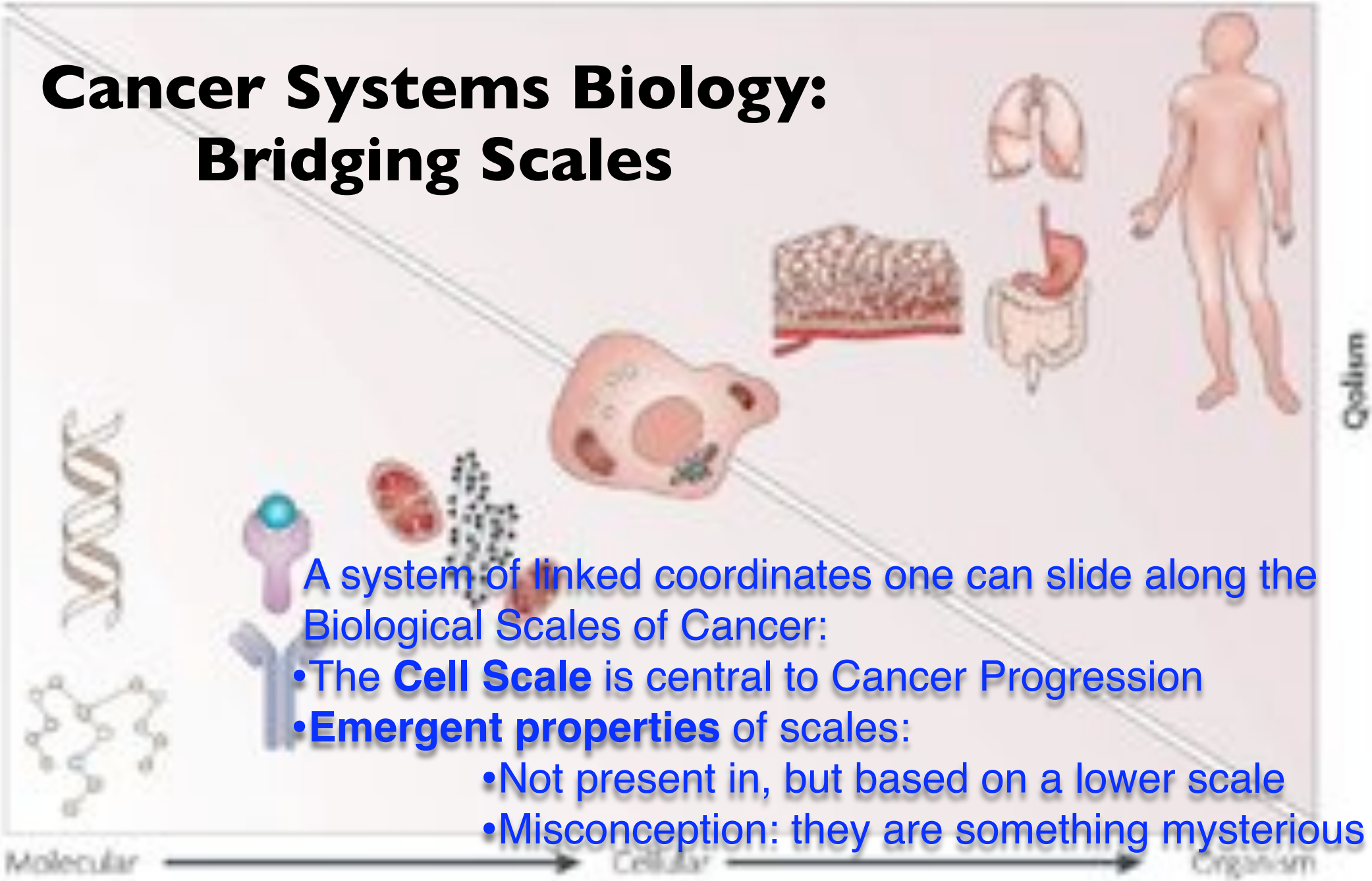
Cellular:

This is great! Molecular or Genetic Profiling is entering in the clinical practice in some instances. But, there is a complication.... Gene to Phenotype mapping is not one-to-one.

Molecular:



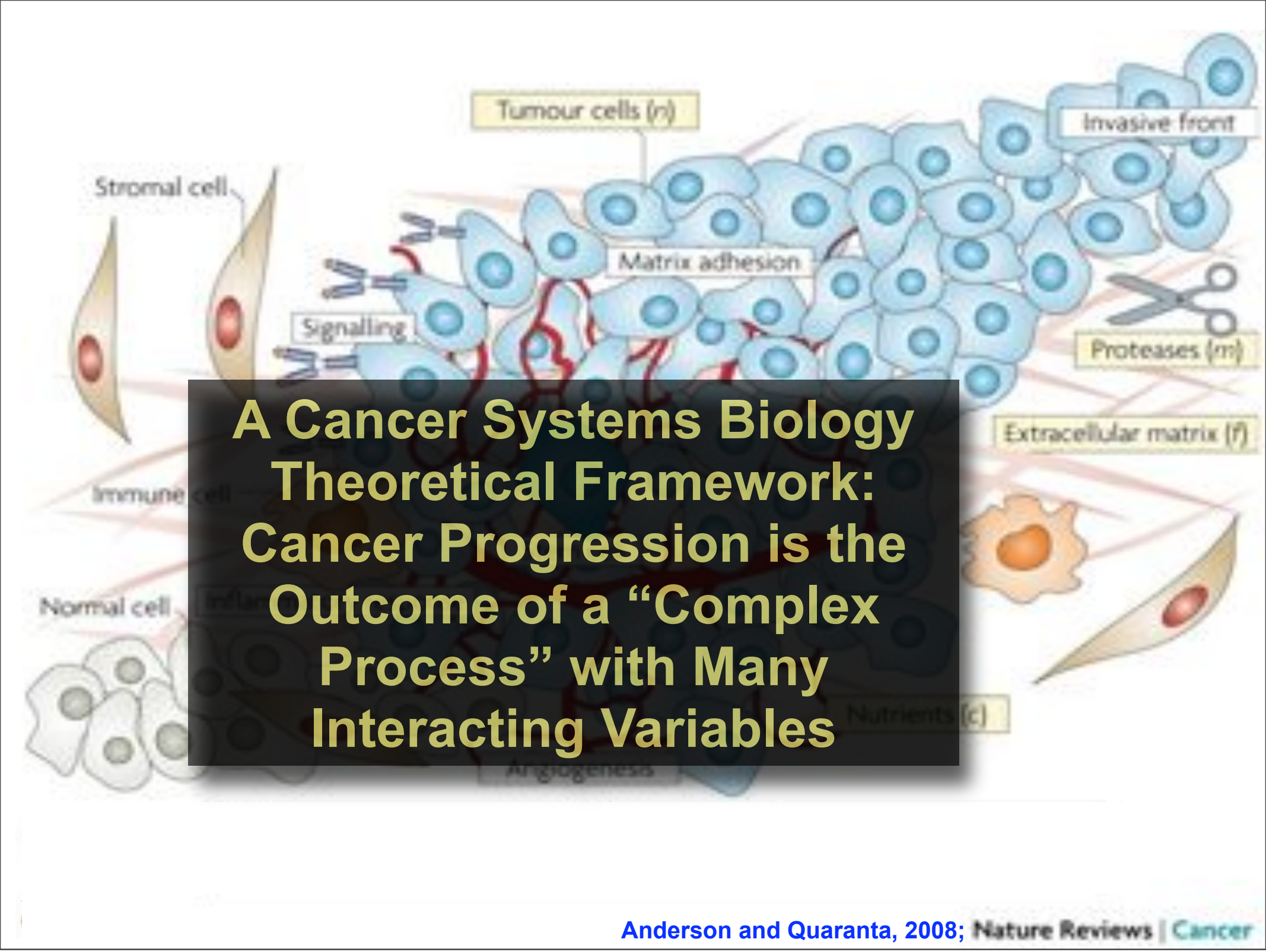
Cancer Systems Biology: Bridging Scales



A system of linked coordinates one can slide along the Biological Scales of Cancer:

- The **Cell Scale** is central to Cancer Progression
- **Emergent properties** of scales:
  - Not present in, but based on a lower scale
  - Misconception: they are something mysterious

Anderson and Quaranta, Nature Cancer Reviews, 2008



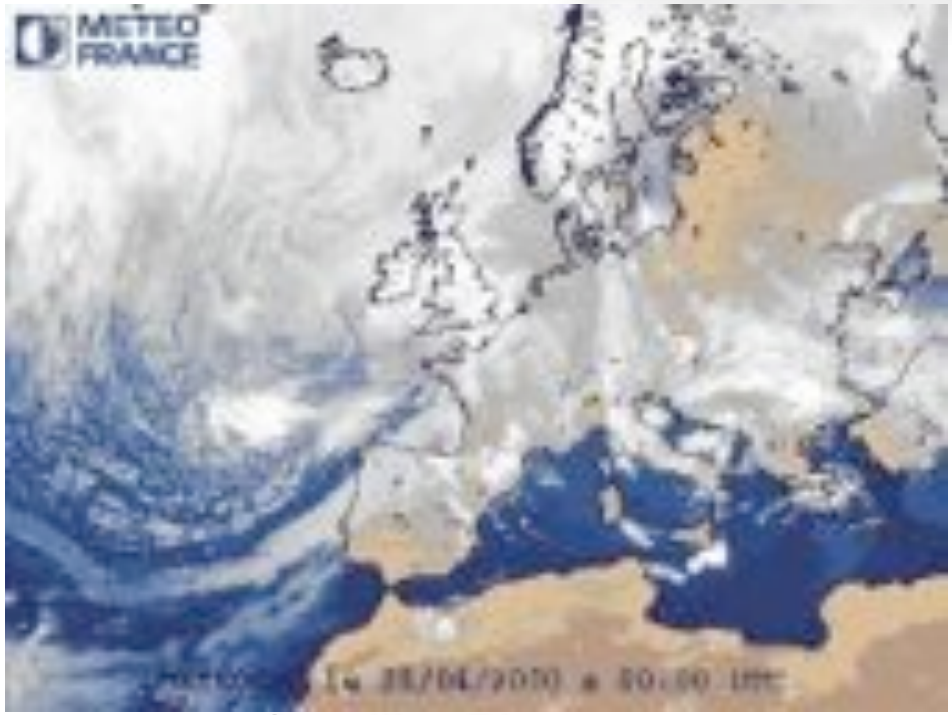
A Cancer Systems Biology Theoretical Framework: Cancer Progression is the Outcome of a "Complex Process" with Many Interacting Variables

Anderson and Quaranta, 2008; Nature Reviews | Cancer

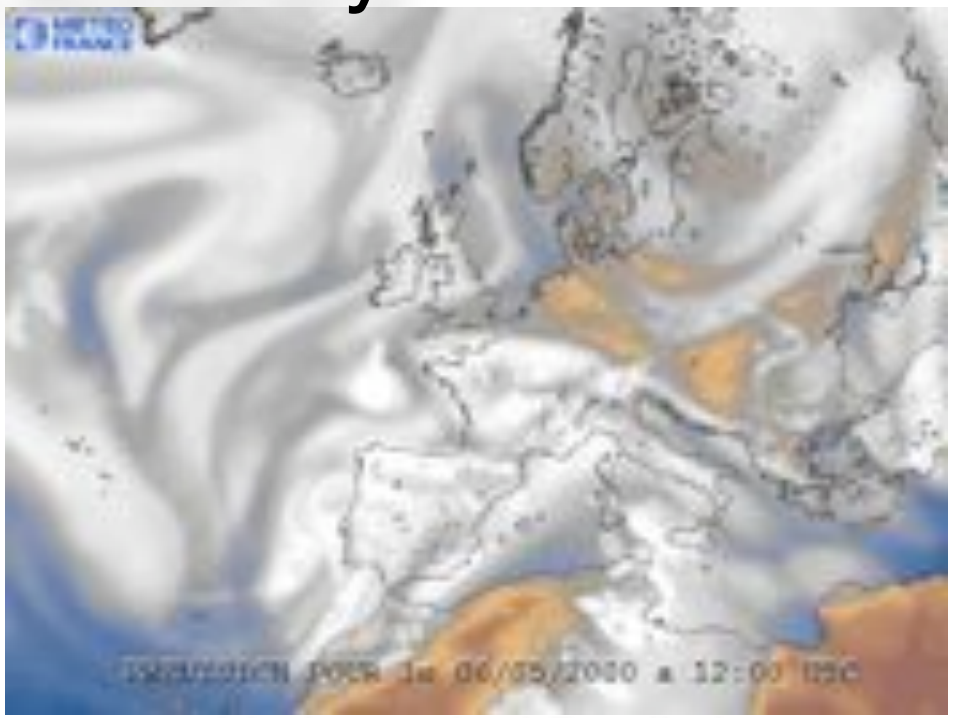
How does one do CSB?

- Collect large datasets
- Interpret them with mathematical models, from statistical to mathematical to computational.
- Validate the models

Modeling with Large Datasets Improves Prediction Accuracy



Satellite Pictures



Mathematical Prediction

- Input current weather information e.g. wind speed, pressure, temperature, humidity etc.
- Mathematical models are then solved numerically to predict how this information will change in time

How one does CSB

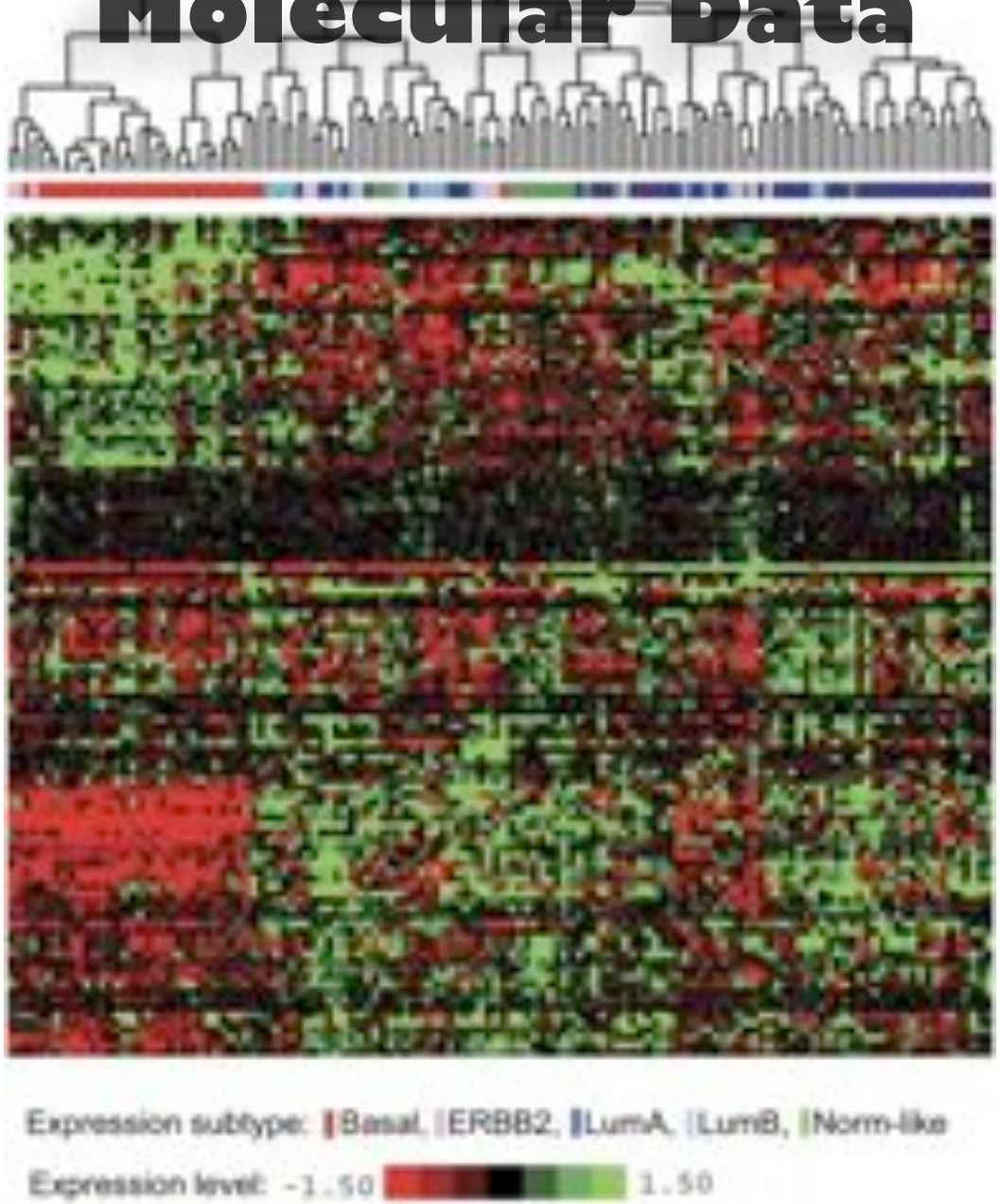
- Does one need to collect large datasets?
  - Not to get going, but eventually yes, because accuracy of modeling improves with more data
  - Example from other sciences
  - Biological variability
- Why does one need models?
  - Large datasets cannot be easily grasped by human mind
  - Outcomes are often counterintuitive

CSB Examples: Data Collection, Production, Modeling

- The genetic scale
  - Microarrays
  - microRNAs
- The molecular scale
  - Proteomics
  - Signaling networks
- The cellular scale
  - Response to mE and drugs
    - Altschuler
    - Sorger
    - Our group
- The tissue scale
- The organism scale
- The population scale

- Examples of modeling techniques
  - Statistical
  - Mathematical

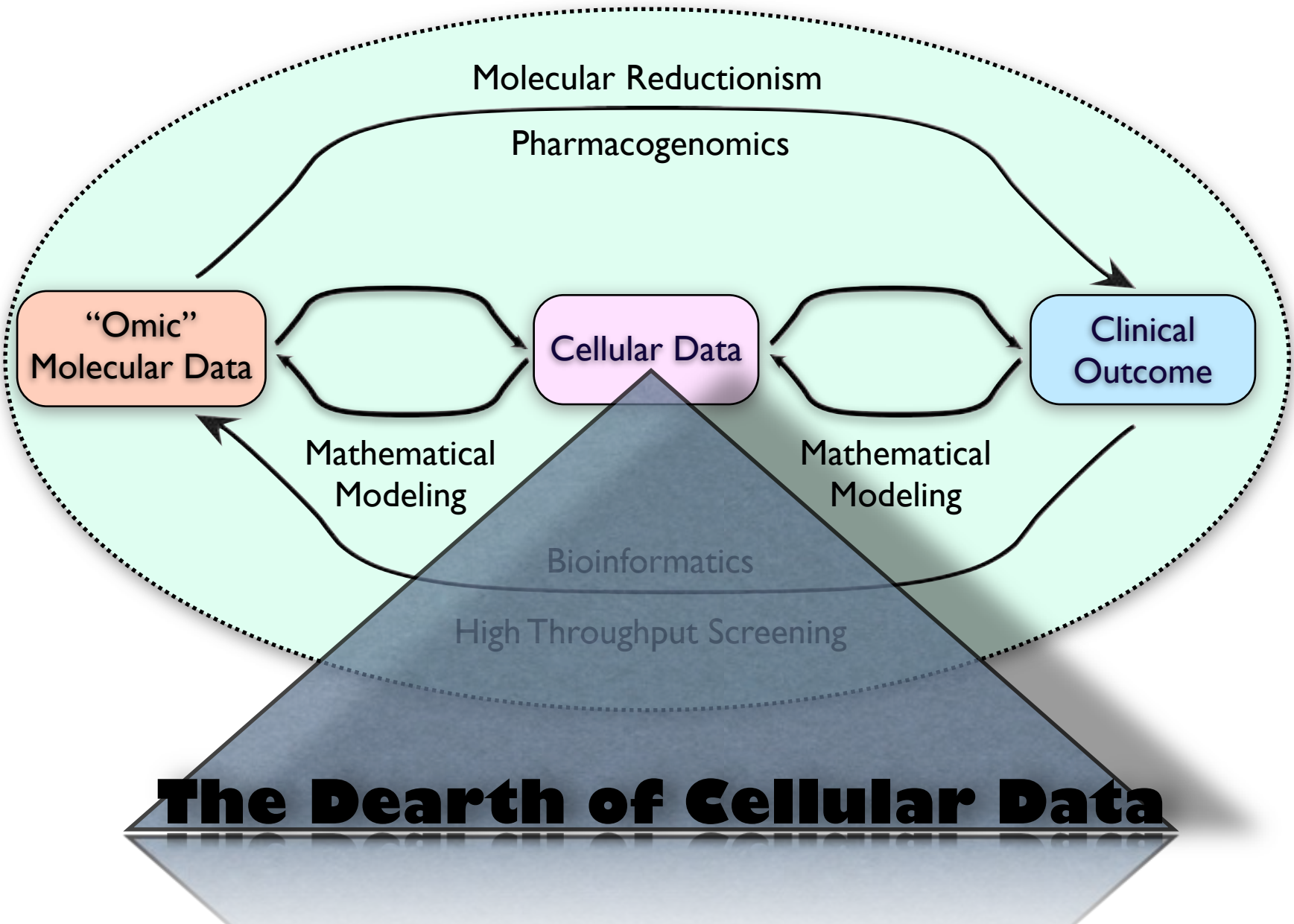
The Deluge of Genetic and Molecular Data



Chin et al. Cancer Cell. 10:529, 2006

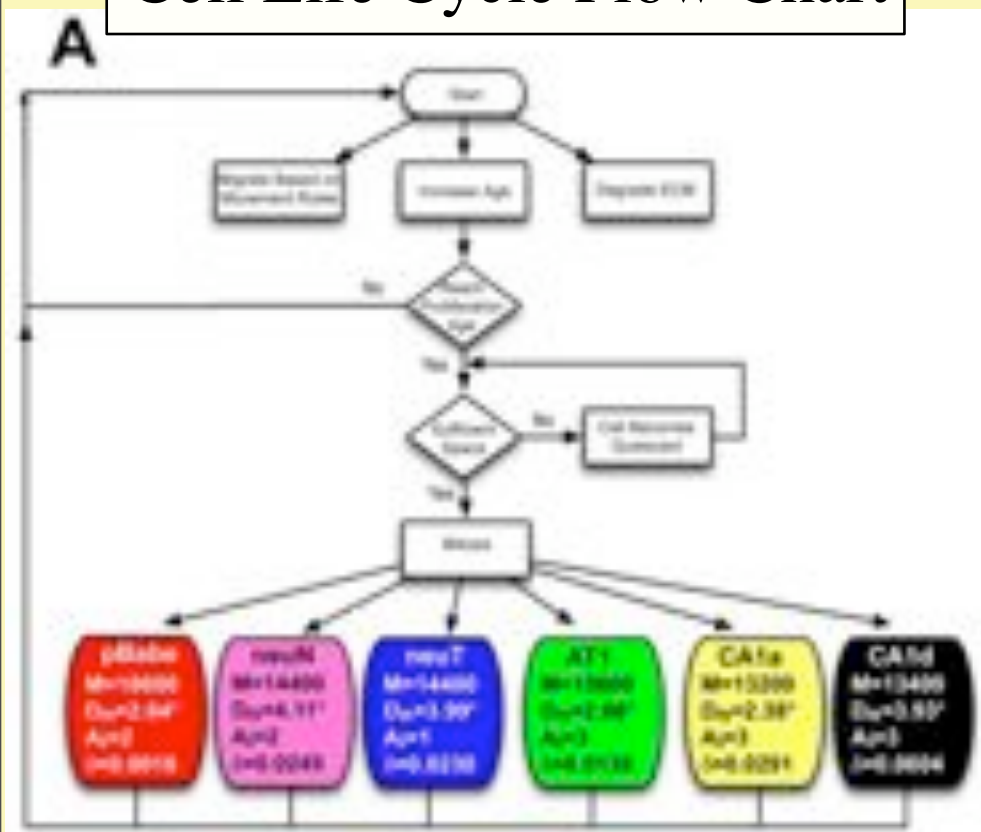
Figure 4. Results of unsupervised hierarchical clustering of 130 breast tumors using intrinsically variable gene expression but excluding any transcripts whose levels were significantly associated with genome copy numberRed indicates increased expression, and green indicates reduced expression. An annotated version is provided as Figure S3.

Cancer Systems Biology

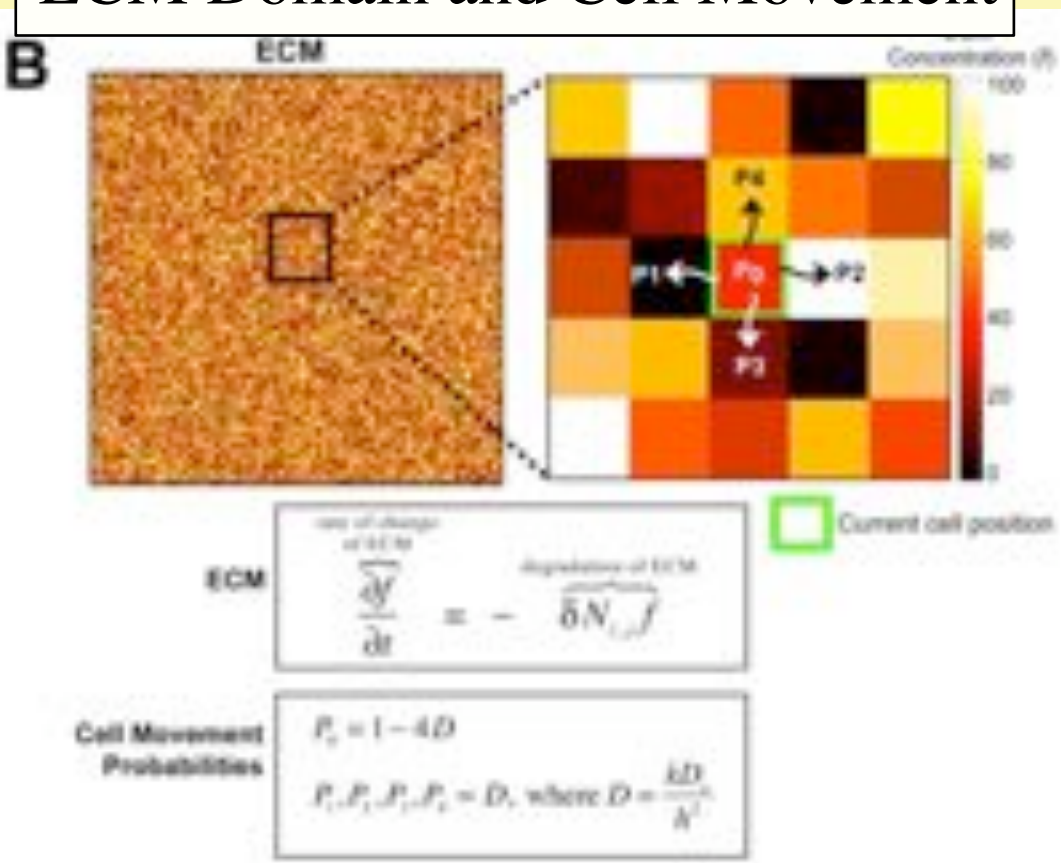


Insufficient Cell Data is Particularly Acute in the Case of Cellular Automata Models

Cell Life Cycle Flow Chart



ECM Domain and Cell Movement



[CANCER RESEARCH 38, 2651-2660, September 1978]

Tumor Heterogeneity and the Biology of Cancer Invasion and Metastasis[1]

Isaiah J. Fidler

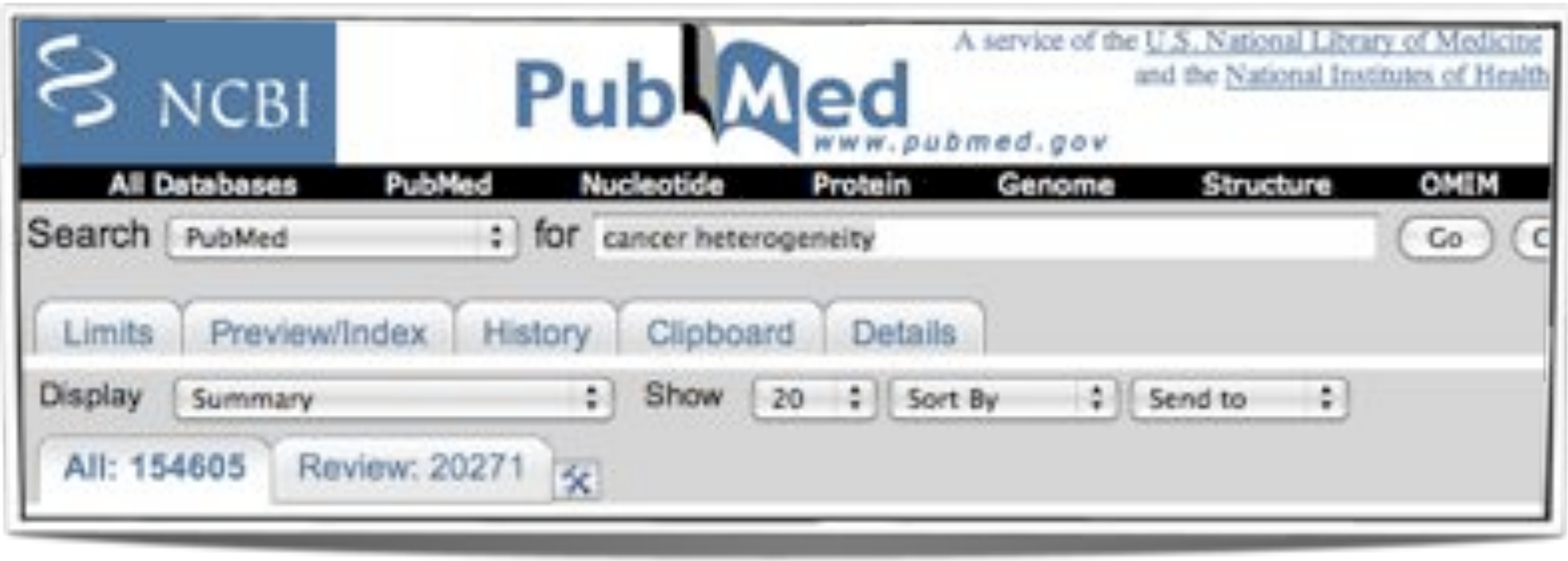
Cancer Biology Program, National Cancer Institute Frederick Cancer Research Center, Frederick, Maryland 21701

Abstract

The development of a metastasis is dependent on an interplay between host factors and intrinsic characteristics of malignant tumor cells. The process of metastasis is highly selective, and the metastatic lesion represents the end point of many destructive events that only a few cells can survive. Neoplasms, which are predominantly heterogeneous, contain a variety of subpopulations of cells with differing metastatic potential. Furthermore, metastatic cell variants have been shown to preexist in murine neoplasms of old and recent origin. The possible existence of highly metastatic variant cells within a primary tumor suggests that we no longer should consider a neoplasm to be a uniform entity. Efforts to design effective therapeutic agents and procedures against malignant tumors should be directed toward the few but fatal metastatic subpopulations of cells.

of the biology of the phenomenon and, therefore, allow the development of new approaches to the therapy of disseminated disease.

We have recently developed one such animal model for qualitative studies of metastasis. Mice are given i.d. injections, in the external ear, of 0.05 ml of tumor cell suspension. Three to 4 weeks later, when the tumors are established, the ear is amputated at its base and the mice are allowed to survive. Six to 8 weeks later, the mice are killed and examined for the presence of lymph node or visceral metastases. In the model shown in Fig. 1a, 25,000 viable cells of the B16 melanoma, syngeneic to the C57BL/6 mouse, were injected into the medial surface of the external ear. The ear and growing tumor were amputated 3 weeks after s.c. injection. If the tumor mass contained no metastatic cells, the amputation of the ear would be curative. Alternatively, if the growing tumor contained some metastatic cells, which invaded blood vessels and lymphatics


NCBI
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A service of the U.S. National Library of Medicine
and the National Institutes of Health
All Databases
PubMed
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Protein
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Structure
OMIM
Search
PubMed
for
cancer heterogeneity
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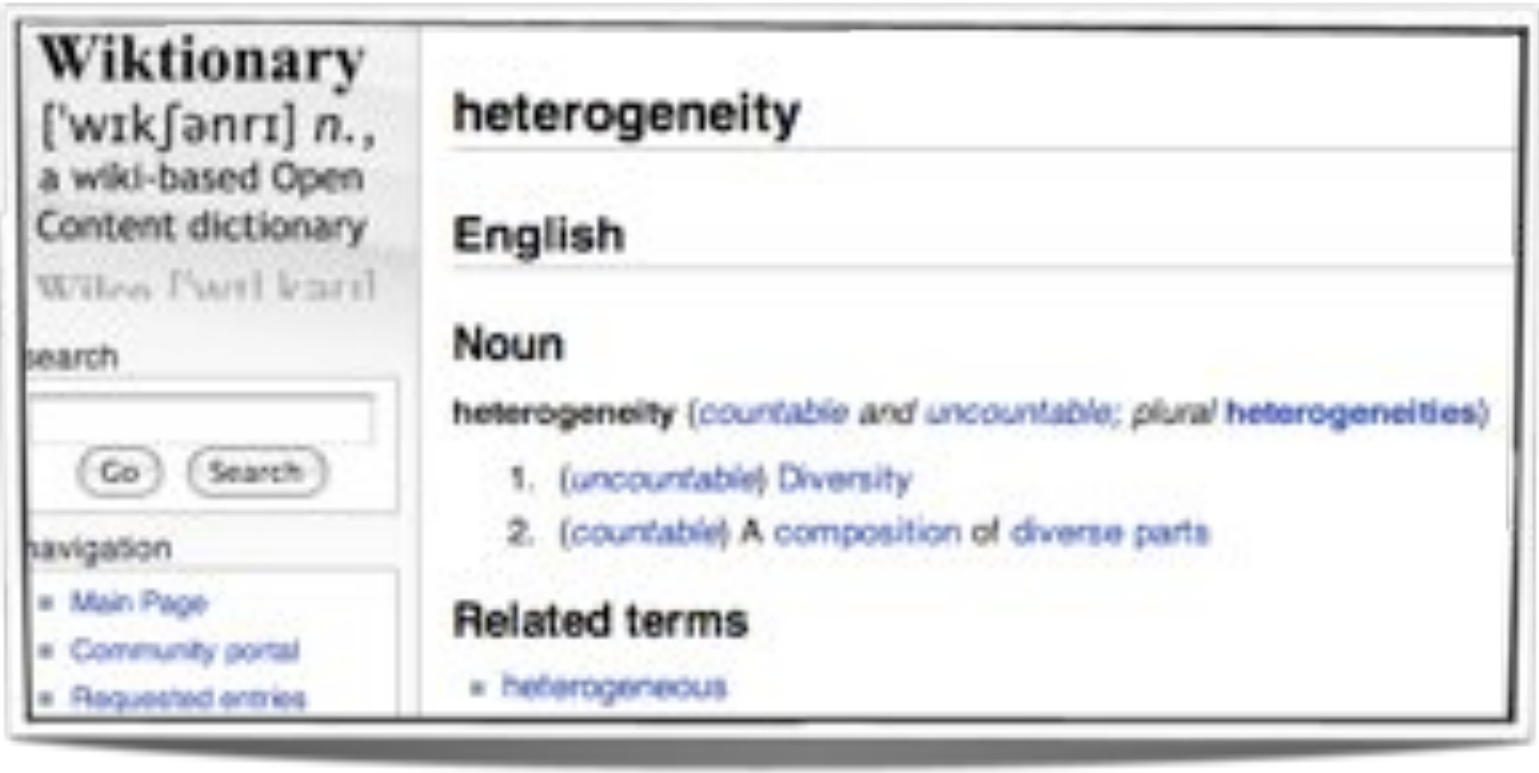
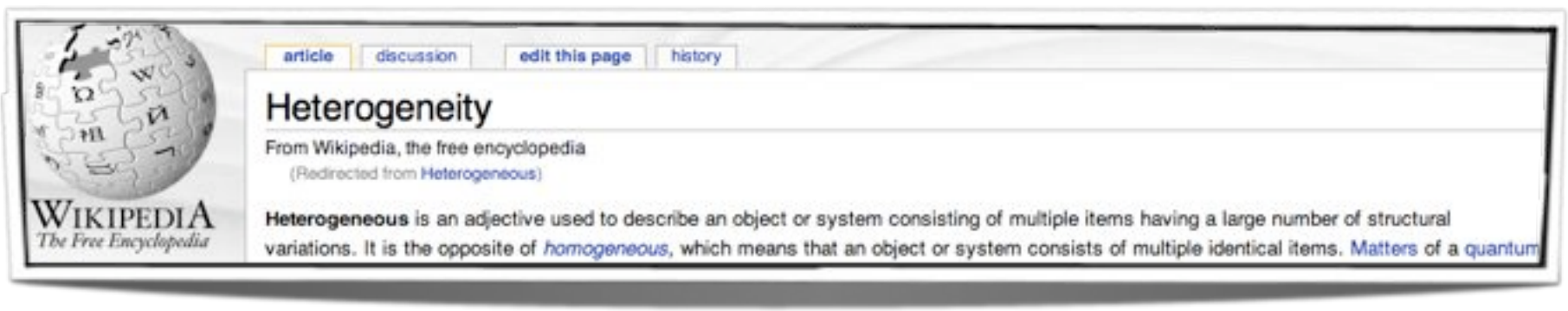
Limits
Preview/Index
History
Clipboard
Details
Display
Summary
Show
20
Sort By
Send to
All: 154605
Review: 20271


Google
cancer heterogeneity
Search
Advanced Search
Preferences
Web
Results 1 - 10 of about 1,320,000 for cancer heterogeneity. (0.22 seconds)

Heterogeneity

- What is it?
- How do we quantify it?


Wiktionary
['wɪkʃənrɪ] n.,
a wiki-based Open Content dictionary
search
Go
Search
navigation
Main Page
Community portal
Requested entries
heterogeneity
English
Noun
heterogeneity (countable and uncountable; plural heterogeneities)
1. (uncountable) Diversity
2. (countable) A composition of diverse parts
Related terms
heterogeneous


WIKIPEDIA
The Free Encyclopedia
article
discussion
edit this page
history
Heterogeneity
From Wikipedia, the free encyclopedia
(Redirected from Heterogeneous)
Heterogeneous is an adjective used to describe an object or system consisting of multiple items having a large number of structural variations. It is the opposite of homogeneous, which means that an object or system consists of multiple identical items. Matters of a quantum

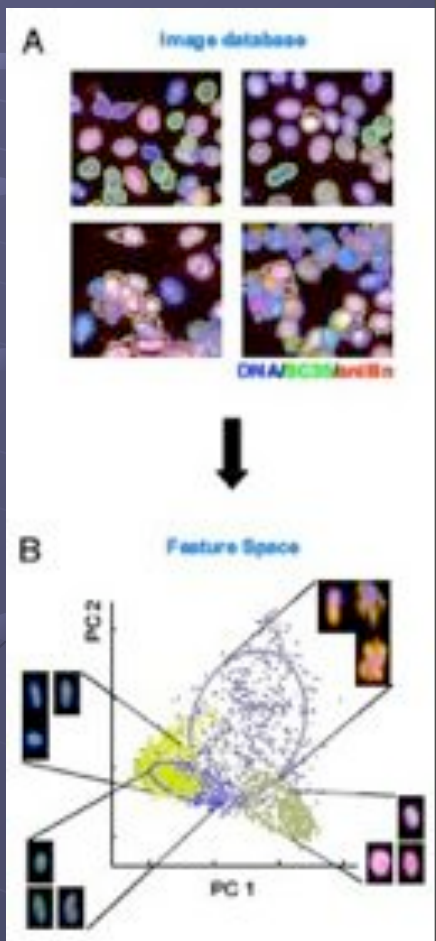
Cell Heterogeneity

- Genetic Heterogeneity
- Even genetically identical cells behave in different ways

- Non-Genetic Heterogeneity, sources:
  - **protein expression**
  - **mRNA expression**
  - **Chromosomal abnormalities**
  - **Phenotypic response to stimuli**

"the variation in cell behavior is far greater than previously recognized."
(Gascoigne and Taylor, 2008)

"***biology at the single-cell level sharply diverges from expectations***"
(Levsky and Singer, 2003)

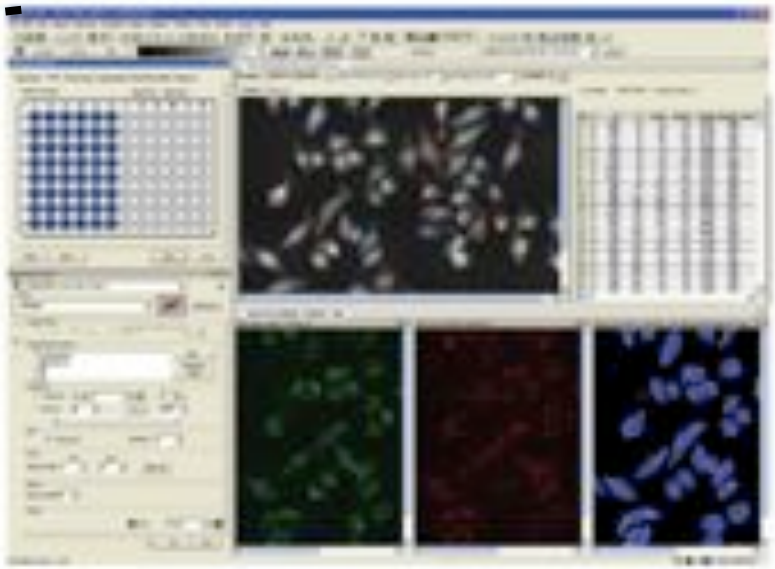


Slack, et al., 2008

High-throughput Automated Microscopy Platform

Quantify cell population Adaptability from single-cell sampling

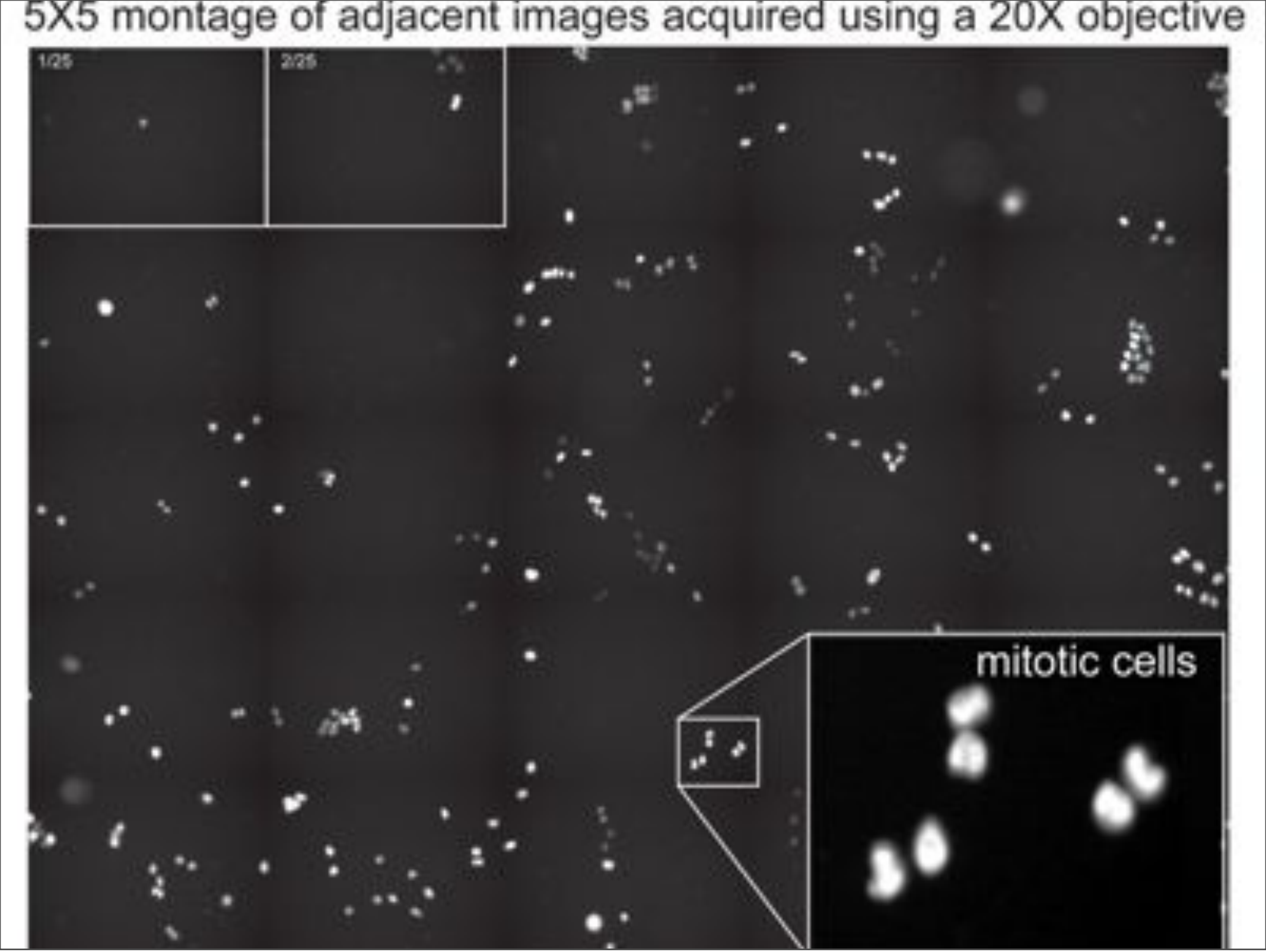
BD Pathway 855 Bioimager



Cells - Breast Cancer Cell Panel (ICBP45)

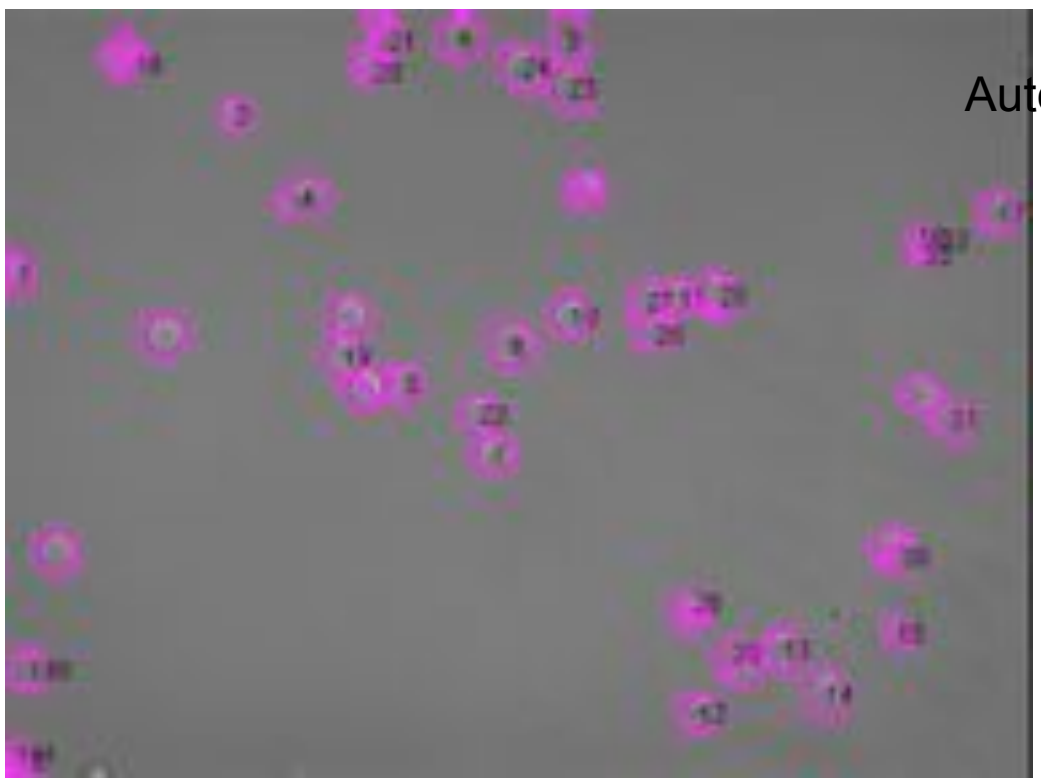
mEs stimulus
Mitogens (growth factors)
Nutrients (glucose, amino acids)
Other (insulin, oxygen)
Drug treatment

Phenotype traits
single cell distributions/spatial information
Proliferation (time to cell division)
Death (apoptosis)
Metabolism (glucose uptake)
Motility (velocity, angle distribution)


5X5 montage of adjacent images acquired using a 20X objective
1/25
2/25
mitotic cells

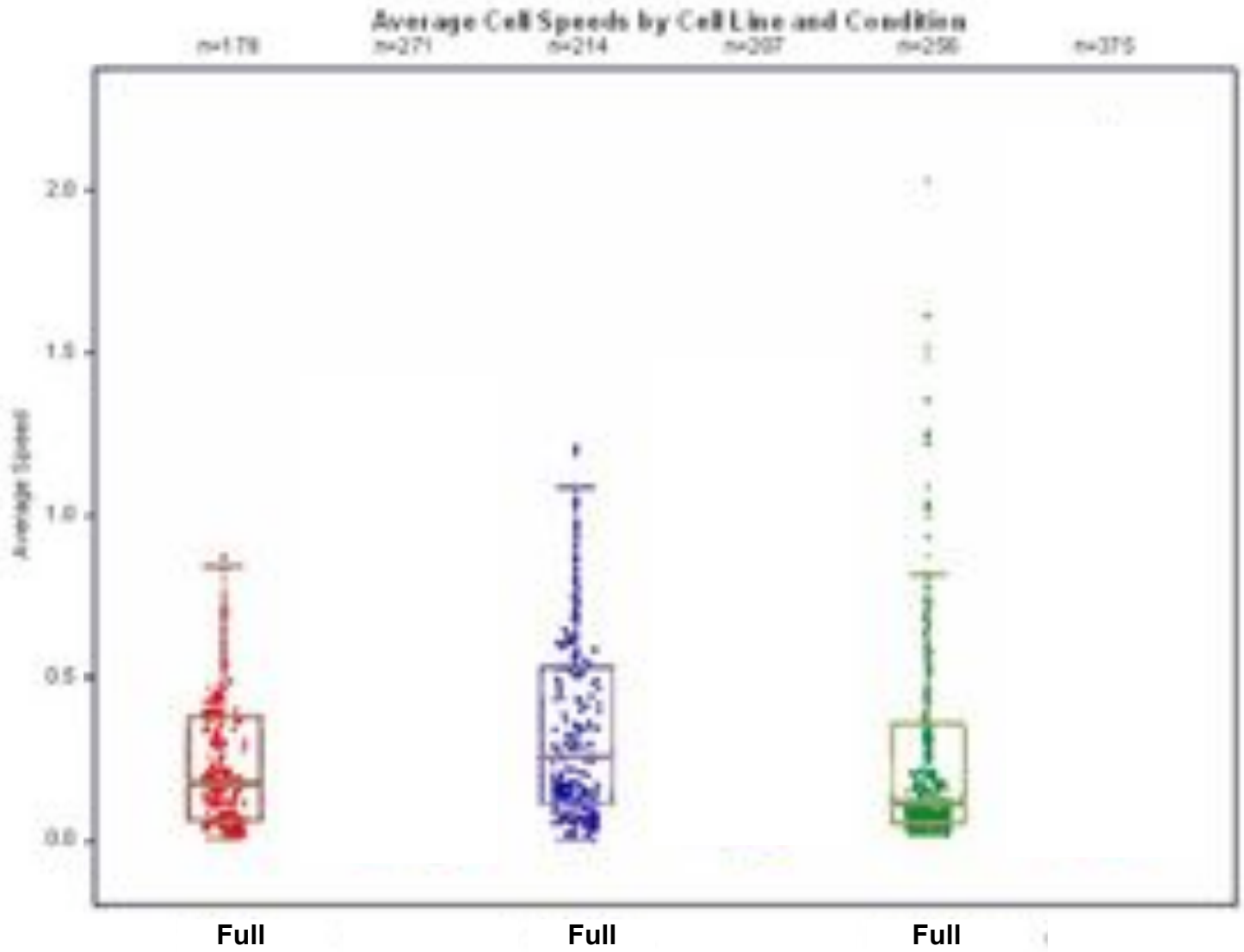
Automated Single Cell Tracking

Cell Lines	**6**	MCF, AT1, CA1d, HT-1080, A431, CAFTD
ECM	**6**	Ln-332, FN, Col, bLG4, LG3, Matrigel
Conditions	**4**	+/- serum, +/- Matrigel
# Movies	**800**	4,000 hrs
# Pictures	**75,000**	
Space Required	**668 Gb**	Raw images + stacks + tracks
# Cells tracked	**7,300**	
# x,y coordinates	**454,000**	



Automated Tracks

Evidence of Heterogeneity with Respect to Motility from Single-Cell Measurements

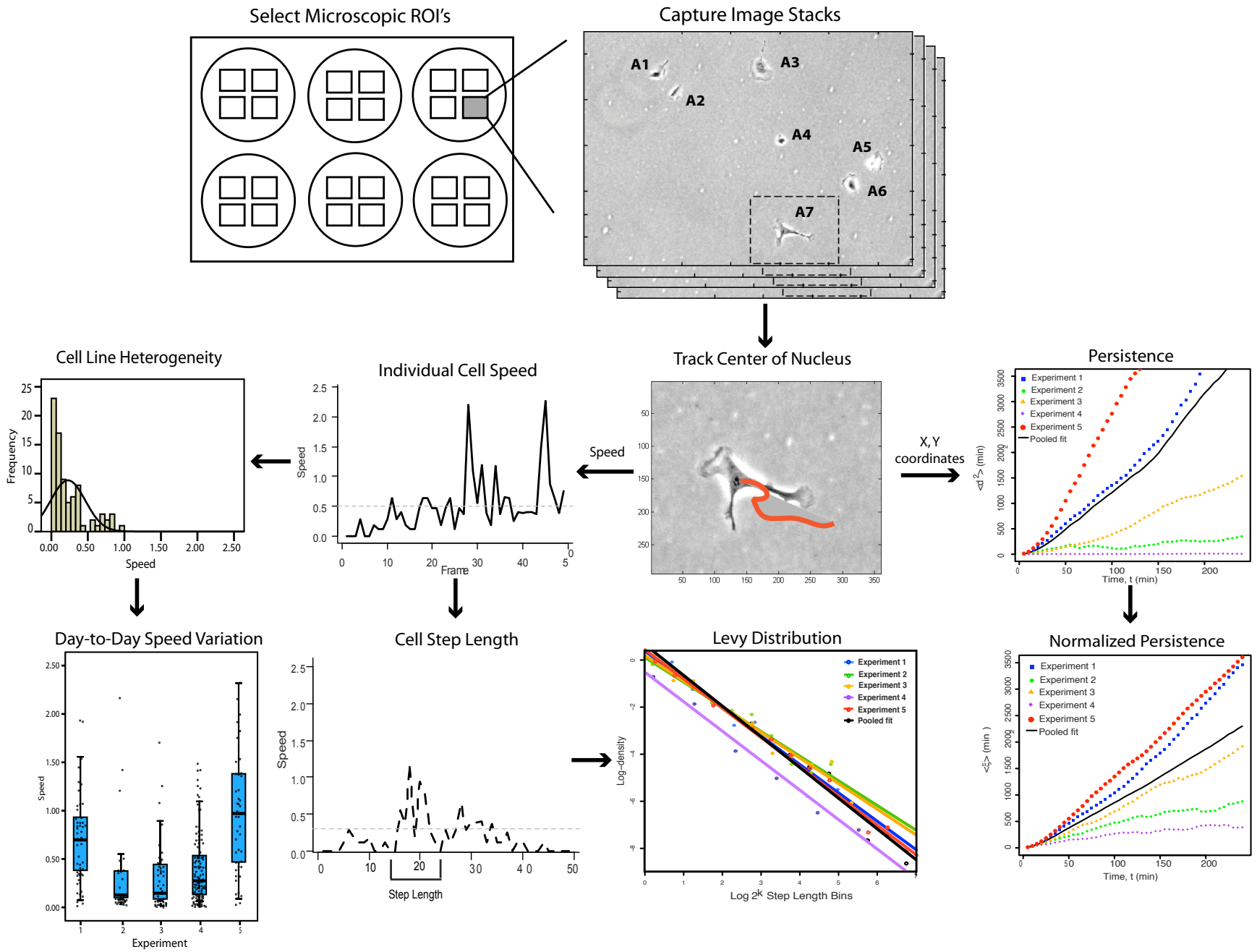


AT1
tumorigenic

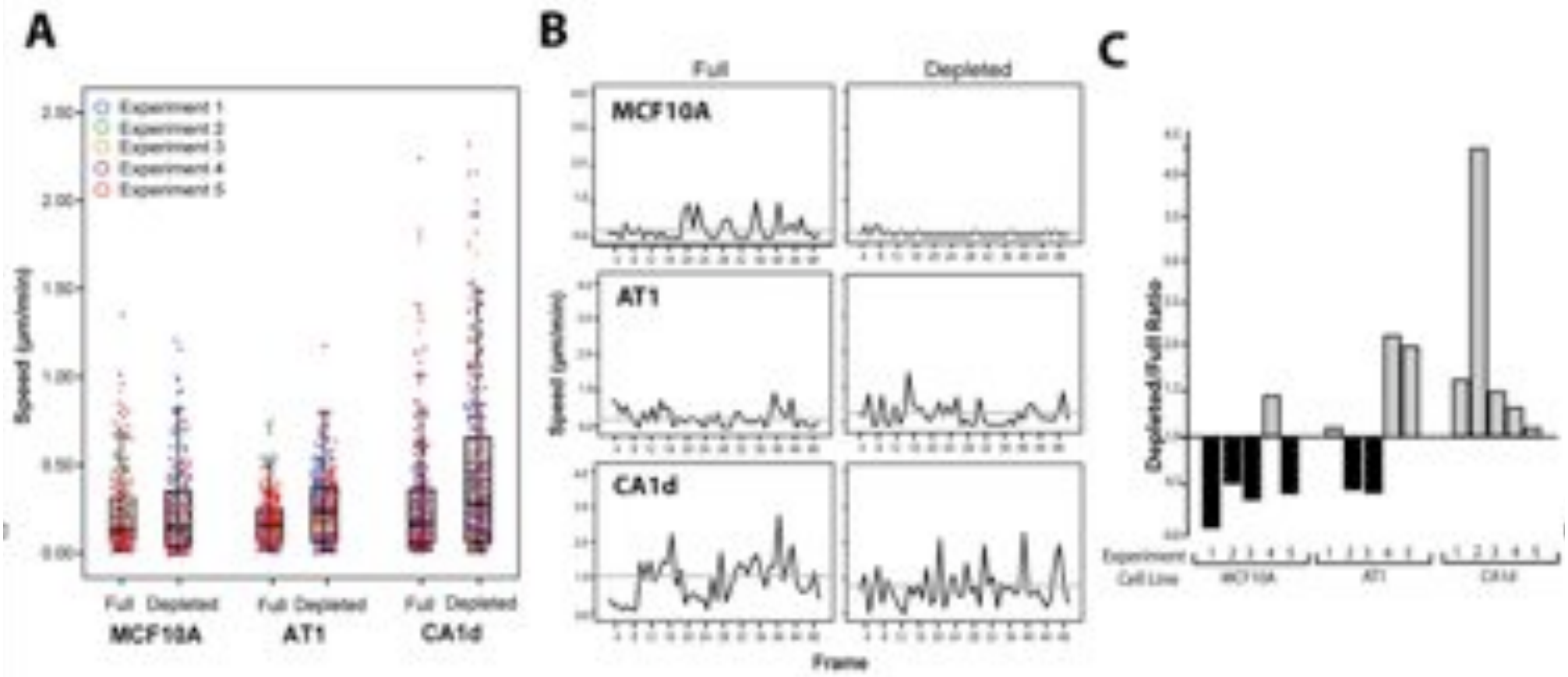
MCF
"normal"

CA1d
invasive

Quantifying Cell Heterogeneity with Respect to Motility



Heterogeneity of Motility within Cell Lines: Impact of mE Perturbations

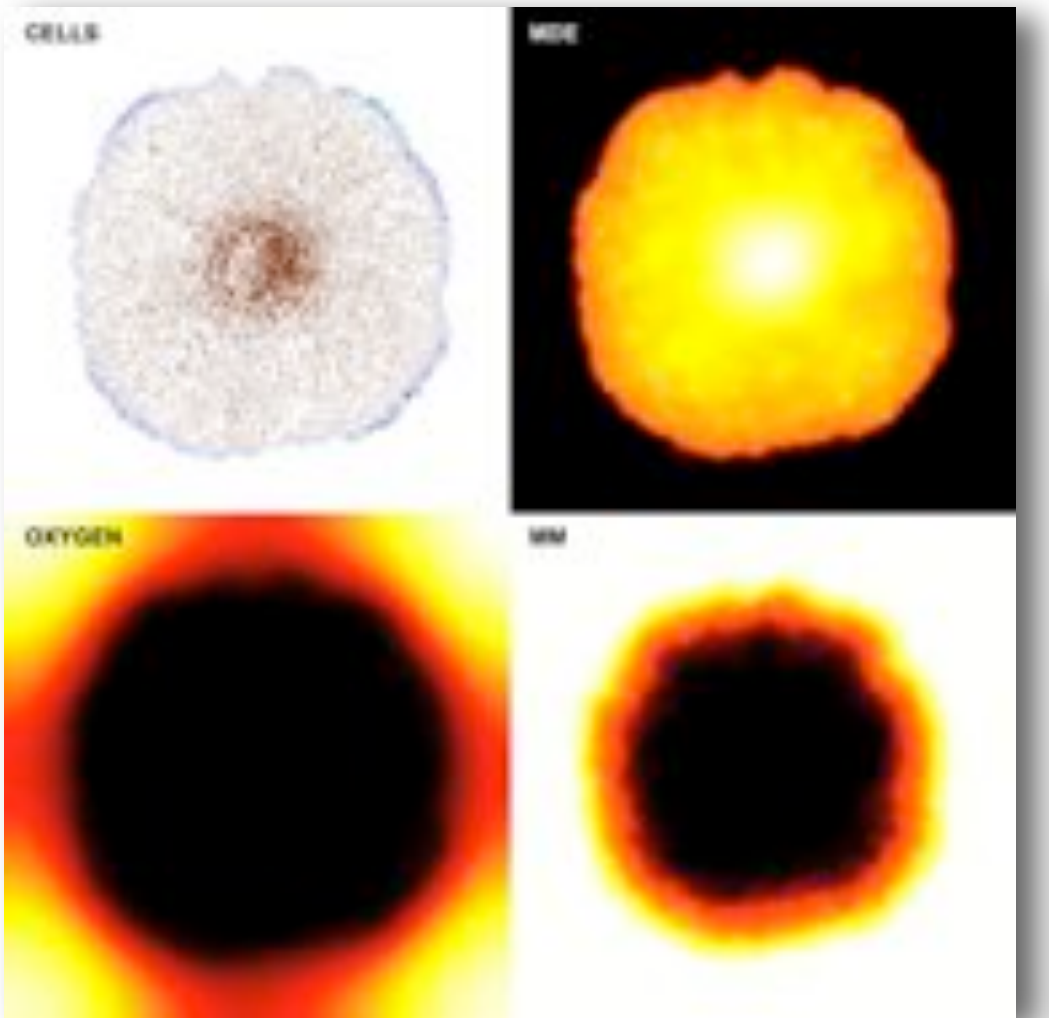


Trait Variability of Cancer Cells Quantified by High-Content Automated Microscopy of Single Cells

Vito Quaranta[1,2,#], Darren R. Tyson[1,2], Shawn P. Garbett[2], Brandy Weidow[1,2], Mark P. Harris[1], Walter Georgescu[2,3]

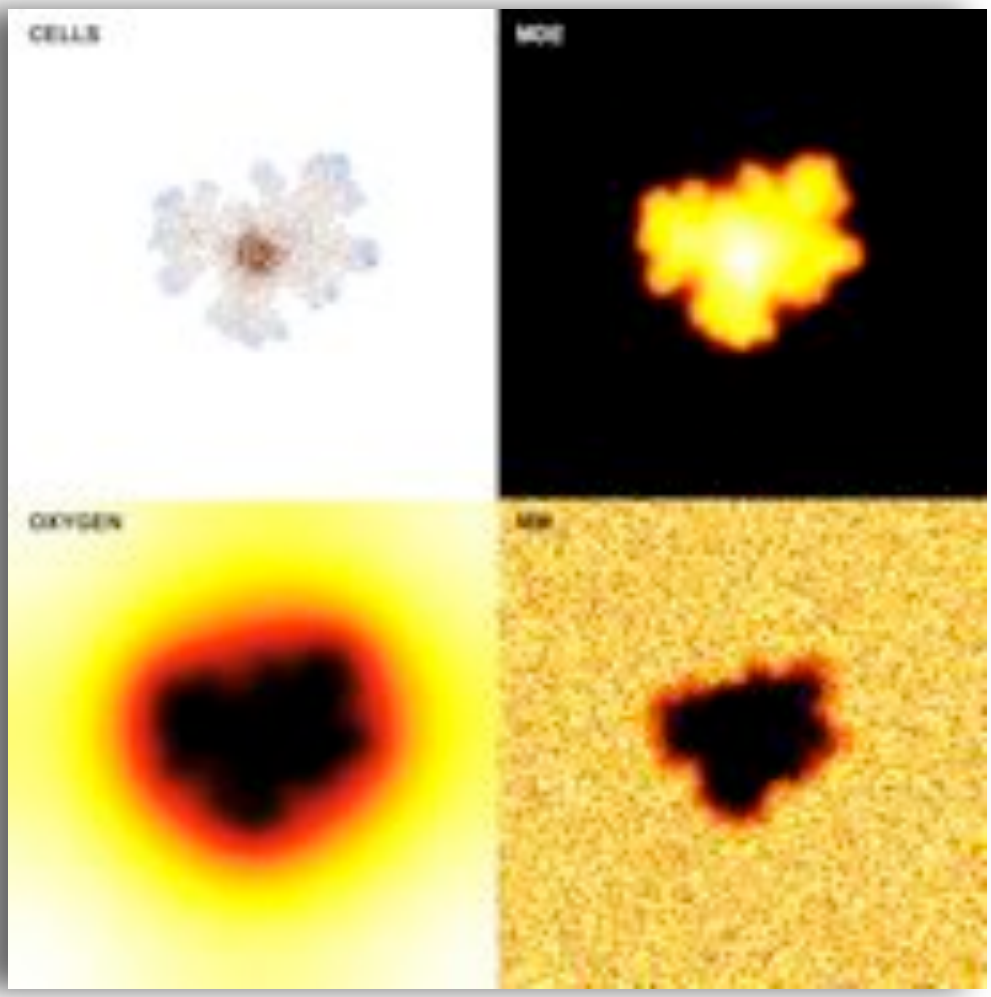
Methods in Enzymology, vol.4xx, Computer Methods B, 2009 (or 2010)

Theoretical Simulations of Tumor Progression: Impact of Matrix Composition on Morphology and Clonal Selection



Concentration

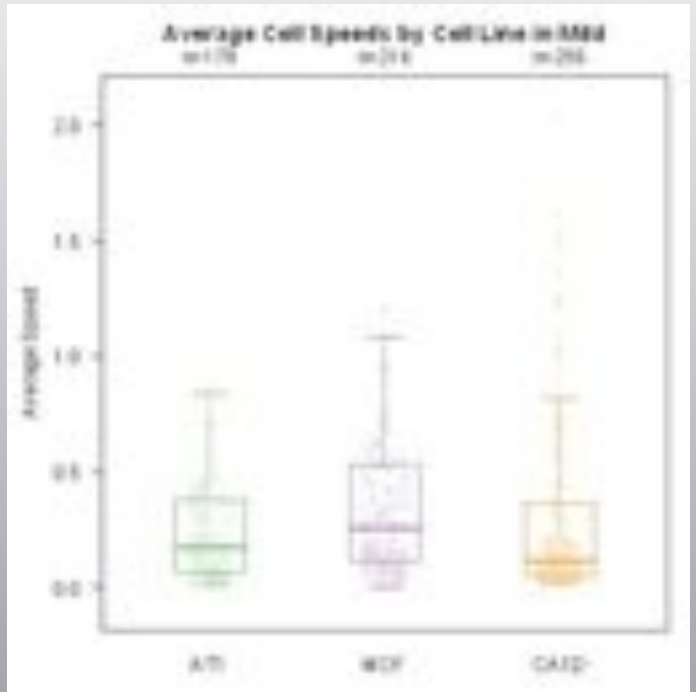
Low High

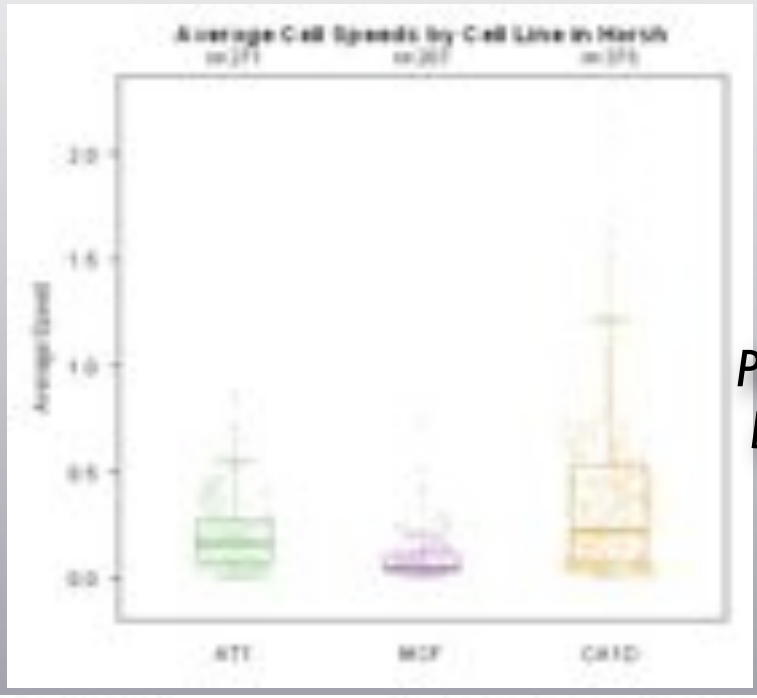


Clone Aggressiveness

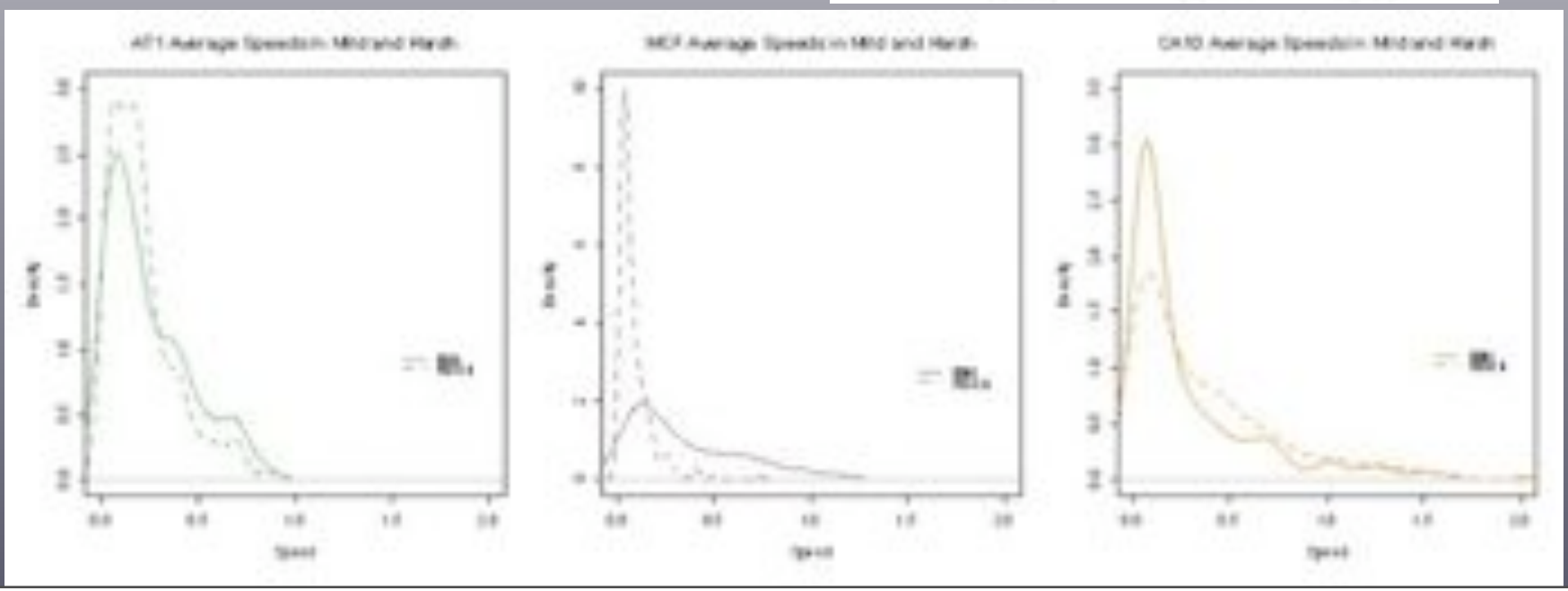
Dead

Cell Motility Distribution Data





Response to Harsh mE Preliminary Data by Mark Harris



Integration of Cancer Progression Variables in the Hybrid Discrete-Continuous Model

- Continuous equations

$$\overbrace{\frac{\partial m}{\partial t}}^{\text{rate of change of matrix degrading enzyme}} = \overbrace{D_m \nabla^2 m}^{\text{diffusion of MDE}} - \overbrace{\lambda m}^{\text{decay of MDE}} + \overbrace{\mu N_{i,j}}^{\text{production of MDE by Cells}}$$

Matrix Degrading Enzymes

$$\overbrace{\frac{\partial f}{\partial t}}^{\text{rate of change of Matrix Macromolecule}} = - \overbrace{\delta m f}^{\text{degredation of MM by MDE}}$$

Matrix Macro-molecules

$$\overbrace{\frac{\partial c}{\partial t}}^{\text{rate of change of oxygen}} = \overbrace{D_c \nabla^2 c}^{\text{diffusion of oxygen}} - \overbrace{\gamma N_{i,j} c}^{\text{Conumsption of oxygen by tumour cells}} + \overbrace{\beta f}^{\text{production of oxygen by MM}}$$

Oxygen

- Discrete tumour cell equation

$$n_{i,j}^{q+1} = n_{i,j}^{q} P_0 + n_{i+1,j}^{q} P_1 + n_{i-1,j}^{q} P_2 + n_{i,j+1}^{q} P_3 + n_{i,j-1}^{q} P_4,$$

with $x=ih$, $y=jh$ and $t=qk$