Introduction to *Agent-Based Modeling* for Studying Biological Tissue Patterning Processes

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Agent-Based Systems Approach

. Dynamic, complex system of many interacting, discrete agents

. Agents interact in the environment, giving rise to ***emergent phenomena***

NC Wildlife Resources Commission

Examples:
. ecology
. financial markets
. sociology

Agent-based Modeling (ABM)

. "Bottom up" approach: simple rules for agent interaction generate complex systems-level outcomes

. Emergent phenomena can have (non-intuitive) properties that are different than the properties of individual agents.

. Accommodates spatially & temporally heterogeneous information

Agents, Behaviors, Rules

. Any autonomous individual

  . individual organisms
  . individual cells
  . individual proteins within a cell

. Maintain their own identity, but interact ('behave') with other agents

. Based on the prescribed rule set, agents make their own "decisions" to exhibit a particular behavior

ABM Algorithm

t = 0
Perturbation in environment
(cell dies)

↓

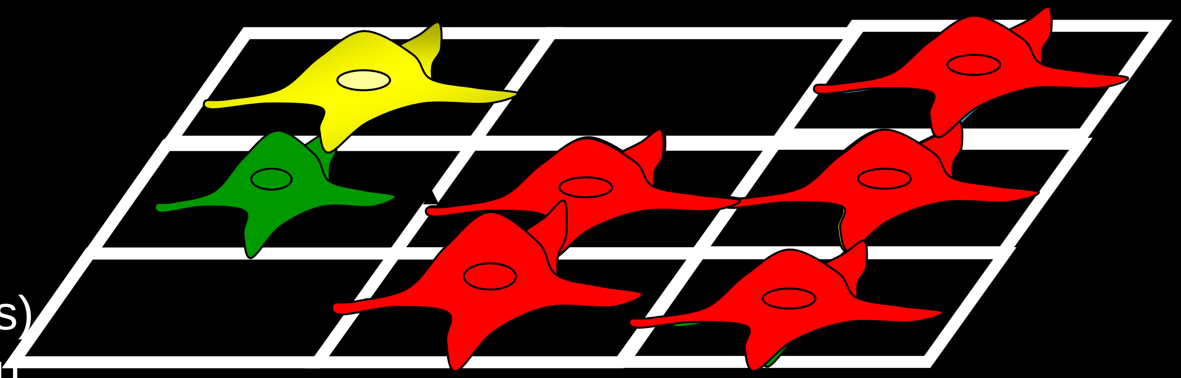
Neighboring cells "sense" this environmental perturbation and make a decision based on a rule(s)
(Rule: if neighboring cell dies, you die, too!)

↓

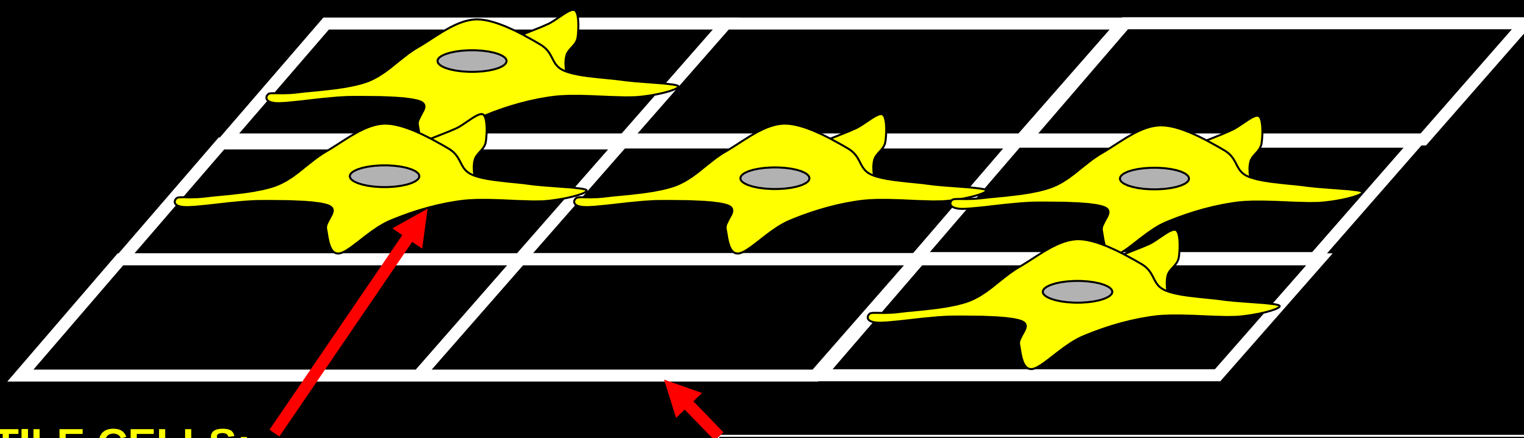
Neighboring cells change their states
(die)

↓

t = t+1



2-D ABM Framework



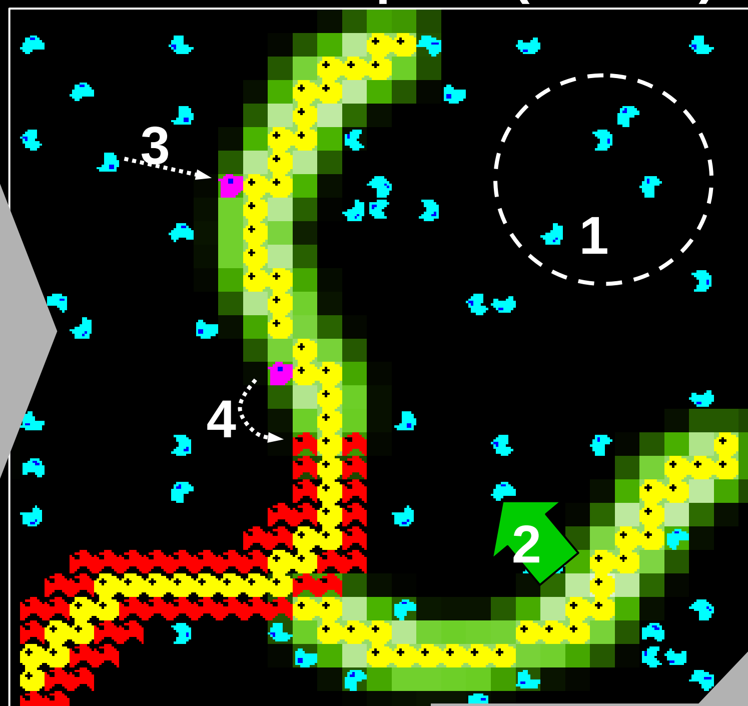
MOTILE CELLS:
Size
Age
Location
Phenotype
Cell-cell contact status
GF Receptor expression
Integrin expression
Cadherin expression
Metabolic properties
Cytoskeletal properties
Mechanical loading state
...

STATIONARY PIXELS
Growth Factor Concentrations
Concentrations of ECM Proteins
...

Emergent Tissue Patterning

Boundary Conditions
- Initial concentrations
- Cell numbers
- Tissue architecture

Simulation Space (Tissue)



Cells respond independently

Coordinated tissue patterning

Rules

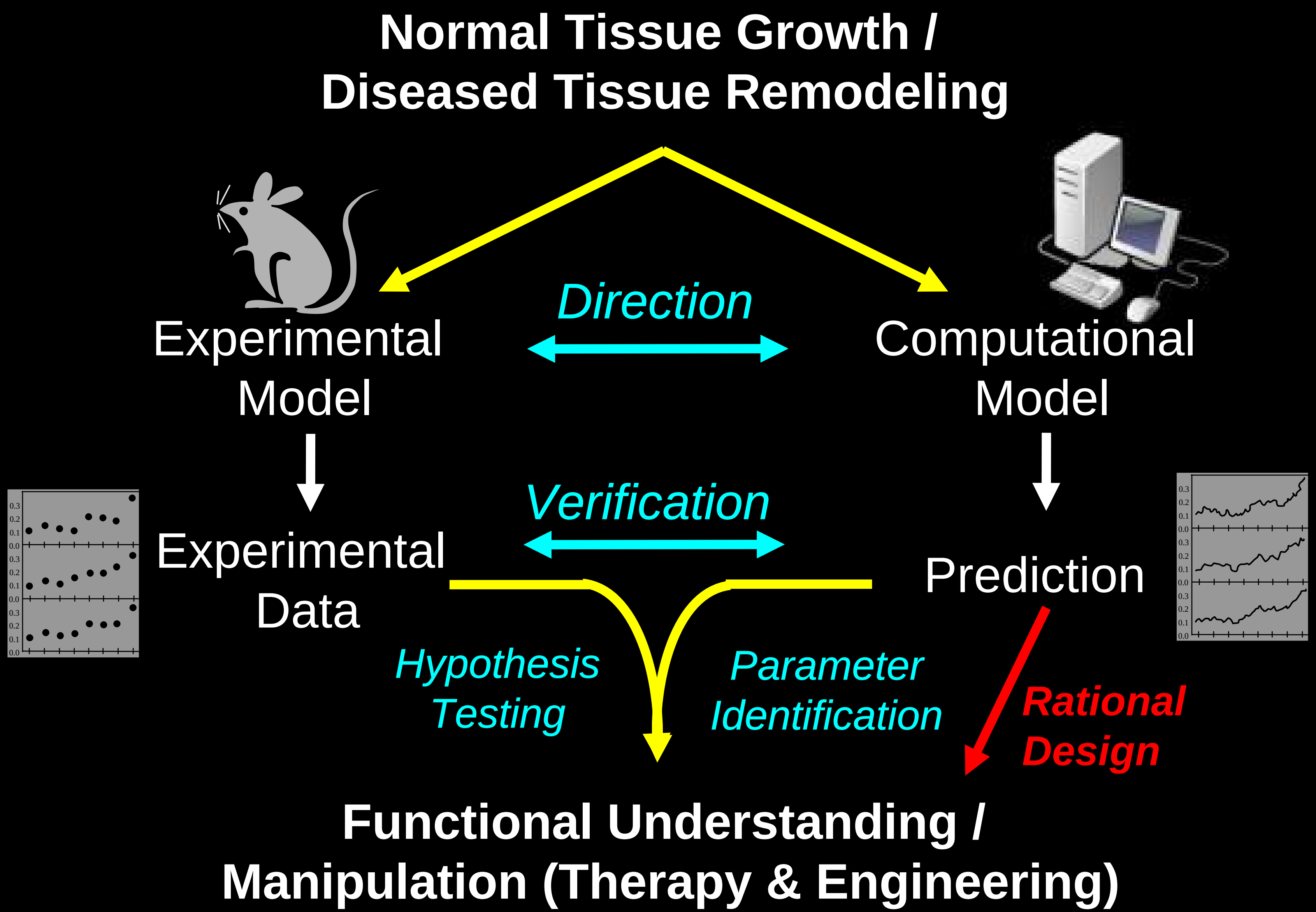
SMC Doubling Time=
$40+82.8*(e^{-3.2[PDGFBB]}) -0.15[PDGFBB]$

Fold change in SM-MHC expression =
$0.73*\ln([TGF\beta])+1.1$

$[VEGF]_{r,t}=([VEGF]_{source}/4\pi Dt)*\exp(-r^2/4Dt)$

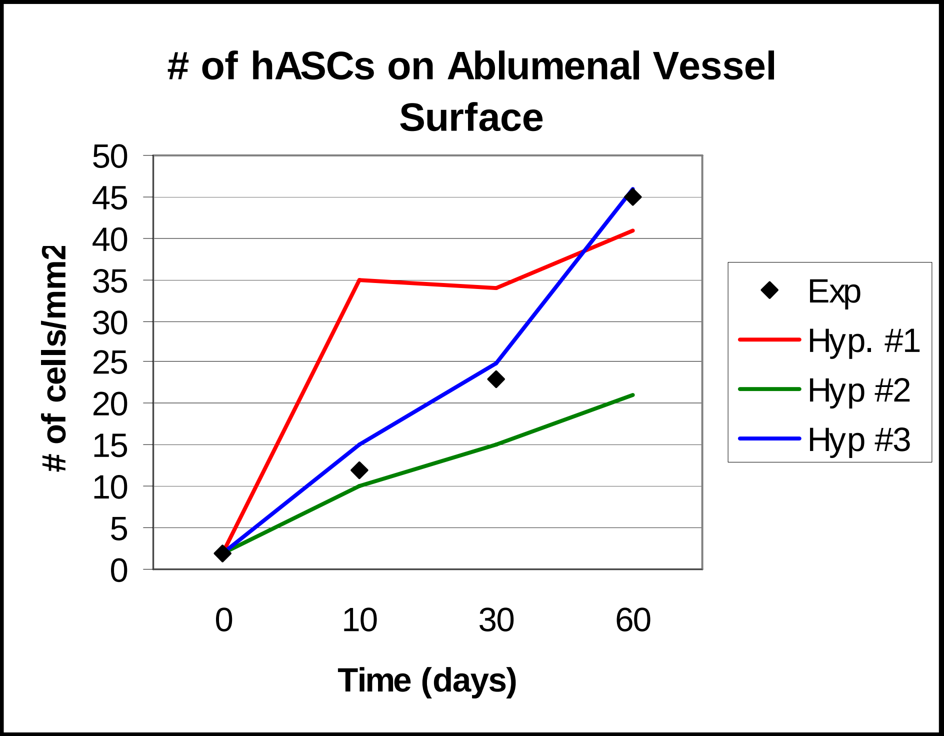
Patterning Metrics

Parallel Approach



Utility of ABM in Biology

. Useful for testing and contrasting (alternative) hypotheses



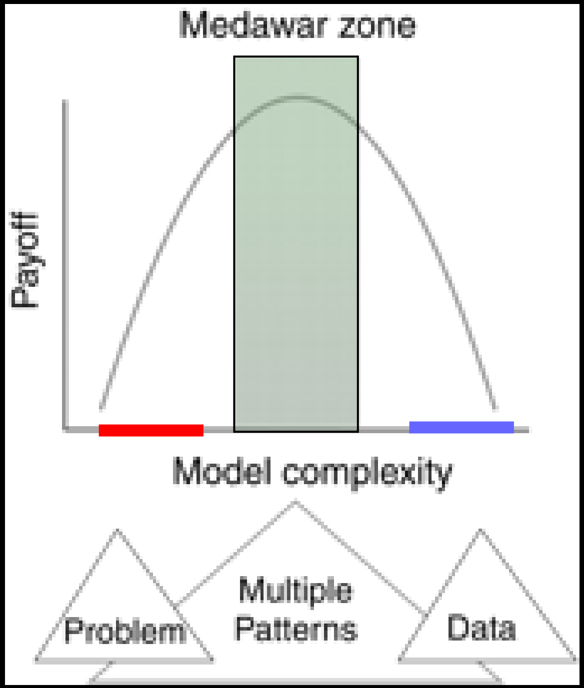
. Useful for generating new hypotheses

Limitations of Current ABM Modeling

- Only as good as the rules you input
- How do you know when to stop adding rules?
- Spatial and temporal scaling can be challenging
- Defining the “agent” unit can limit the range of conclusions one can draw
- Biological tissues are 3-D

Tactics for ABM in Biology

. Use observed patterns to your advantage: when designed to produce multiple patterns, ABM are more likely to be "structurally realistic" ***(V. Grimm)***



Grimm et al., *Science* 2005

If a model is too simple, it neglects essential mechanisms of the real system, limiting its potential to provide new understanding and testable predictions

If a model is too complex, its analysis will be cumbersome and get bogged down in detail

Need to shoot for Medawar zone.

Tools for ABM

Railsback, SF, SL Lytinen, and SK Jackson. (In preparation). Agent-based simulation platforms: review and development recommendations. Article submitted to *Simulation*.

NetLogo is the highest-level platform, providing a simple yet powerful programming language, built-in graphical interfaces, and comprehensive documentation. It is designed primarily for ABMs of mobile individuals in a grid space with local interactions, but not necessarily clumsy for others. NetLogo is highly recommended, even for prototyping complex models. *(intermediate speed) www.ccl.northwestern.edu/netlogo/*

MASON is least mature and designed with execution speed a high priority. *(fastest) www.cs.gmu.edu/~eclab/projects/mason*

The Objective-C version of Swarm: most mature library platform, stable, and well-organized. Objective-C seems more natural for ABMs than Java, but weak error-handling and the lack of developer tools are drawbacks. *(sometimes fastest; sometimes slowest) www.swarm.org*

Java Swarm allows Swarm's Objective-C libraries to be called from Java; it does not seem to combine the advantages of the two languages well. *(sometimes fastest; sometimes slowest) www.swarm.org*

Repast provides Swarm-like functions in a Java library and is a good choice for many, but parts of its organization and design could be improved. *(fastest) www.repast.sourceforg.net*