Modeling cancer (and mechanics)

Lecture 7 of Introduction to Biological Modeling
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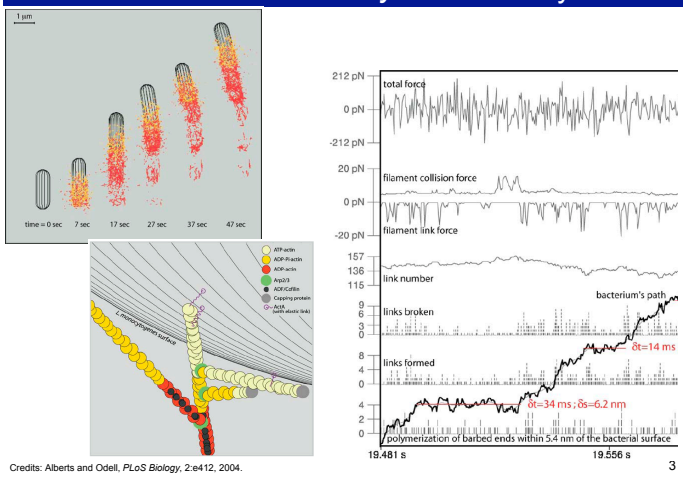
Modeling mechanics
Cancer introduction
Cancer incidence models
Tumor growth models
Summary

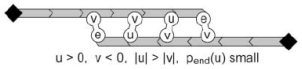
Alberts and Odell: *Lysteria* motility

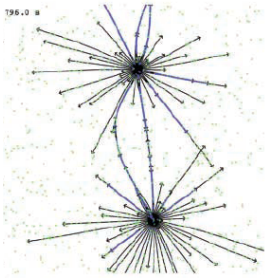


Credits: Alberts and Odell, *PLoS Biology*, 2:e412, 2004.

Nédélec: microtubule asters

Q: What stabilizes the microtubule asters?
A: double-headed motors that push and pull.

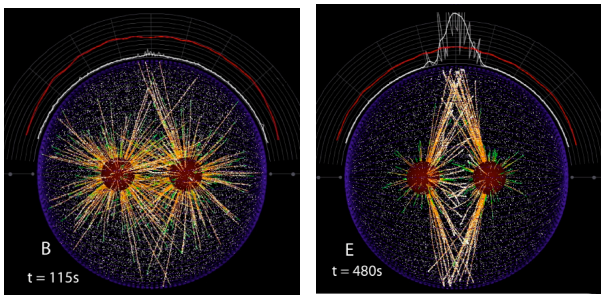




movies: http://www.embl.de/~nedelec/reprints/asters/figure2/index.html

Credits: http://dms.dartmouth.edu/compton/photos/photos/#; Nédélec, *J. Cell Biol.* 158:1005, 2002.

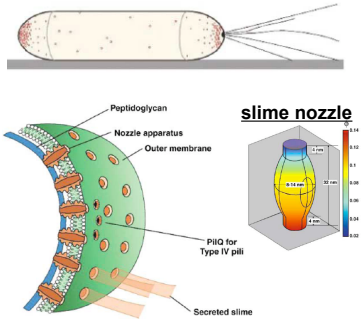
Odell and Foe: eukaryotic cell division furrow

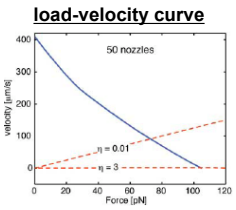


After DNA segregation, dynamic microtubules extend in all directions, and stable ones extend towards equator. MKLP1 motors carry centralspindlin to cortex at equator, which activates Rho, which activates actin and myosin, which contracts the cell.

Credit: Odell and Foe, *J. Cell Biol.* 183:471, 2008.

Wolgemuth: myxobacteria gliding with slime

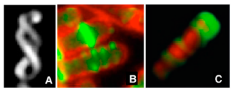




Slime expands when it leaves the cell because it hydrates. Expansion creates a force that pushes the bacterium forwards.

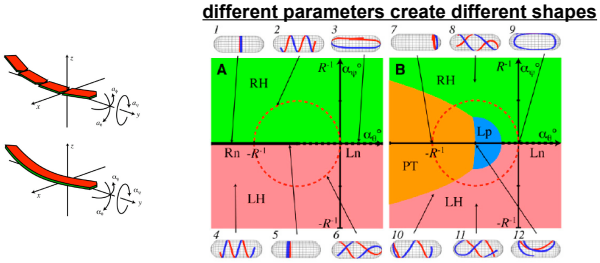
Credits: Wolgemuth *et al. Current Biology* 12:369, 2002.

Andrews and Arkin: shapes of bacterial polymers



Many bacteria have helical or ring-shaped membrane-bound polymers. These shapes can arise from simple mechanics.

different parameters create different shapes



Credit: Andrews and Arkin, *Biophys. J.* 93:1872, 2007.

Overview of cellular mechanics modeling

Lots of research on polymers
- actin, microtubules (and motors)
- bacterial cytoskeletal polymers
- DNA, RNA, nuclear pore polymers, etc.

Other mechanics research
- cell motility with slime
- membrane shape
- development, growth, gastrulation, wound healing

Methods
- physics: mechanics, polymer & membrane physics, rheology
- custom software (MatLab, C, C++, Java, etc.)
- many "agent-based" models

Good book
Jonathon Howard, *Mechanics of Motor Proteins and the Cytoskeleton*, 2001.

Modeling mechanics
Cancer introduction
Cancer incidence models
Tumor growth models
Summary

Cancer

Cancer is important
- kills 1/5 of Americans
- somewhat preventable (e.g. smoking, obesity, UV radiation, screening)
- somewhat curable (e.g. surgery, chemotherapy, radiation)
- 4.8 billion $/year NCI funding
- mission of the Hutch, and other cancer centers

Cancer is complex
- can arise in any organ or tissue
- causes include: mutations, epigenetic mutations, viruses
- oncogenes and tumor-suppresor genes
- cell systems: signaling, cell cycle, DNA repair, apoptosis
- stages: DNA damage, proliferation, vascularization, metastatis

Cancer modeling

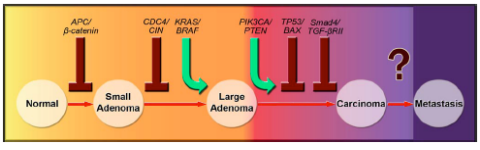
Lots of statistical modeling
- identifying cancer causes
- finding tumor suppresor genes and oncogenes
- analysis of cancer incidence rates

Some tumor development modeling
Surprisingly little biochemical modeling

Some cancer modeling resources

Center for the Development of a Virtual Tumor	https://www.cvit.org
Cancer Intervention and Surveillance Network	http://cisnet.cancer.gov

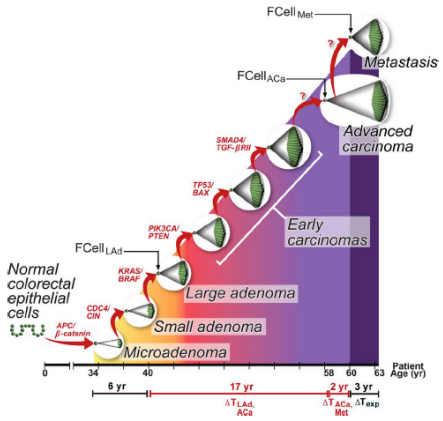
Colorectal cancer



Typical steps
1. mutation that inactivates APC/β-catenin pathway
2. mutation in CDC4 and other cell cycle genes, causing chromosomal instability
3. mutations in KRAS/BRAF oncogenes (EGF signaling pathway)
4. additional mutations
5. invasion of tumor into underlying tissues (a carcinoma)
6. metastasis to other parts of the body

Credit: Jones *et al. Proc. Natl. Acad. Sci. USA* 105:4283, 2008.

Colorectal cancer



Credit: Jones *et al. Proc. Natl. Acad. Sci. USA* 105:4283, 2008.

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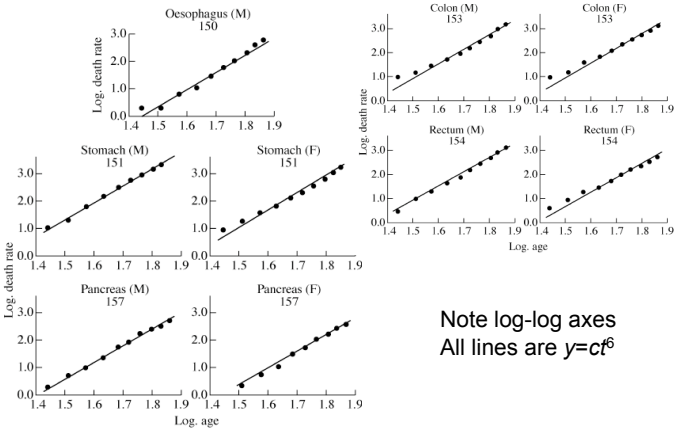
Cancer incidence questions

Why study cancer incidence?

- improve understanding of cancer
  - How long does each step take?
  - How many mutations are required?
- find best time(s) for cancer screening tests
- predict outcomes for individuals
- risk assessment
- predict benefit of an intervention

Raw data, from 1950s



Note log-log axes
All lines are $y=ct^6$

Credit: Armitage and Doll, *Int. J. Epidemiology*, 33:1174, 2004, which is reprint of Armitage and Doll, *Br. J. Cancer* 8:1, 1954.

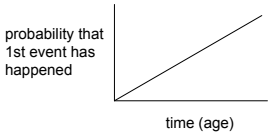
Armitage and Doll's theory

incidence ~ t^6 could arise from

- 7 rare events
- in a specific sequence
- each event has a constant liklihood over time

Armitage and Doll math

Suppose probability of occurance of r^{th} event is p_r per unit time
So, probability that 1st event has happened is about $p_1 t$



Ignoring the sequence of events,
the probability of event #1, and event #2, and ..., and event #6
is $(p_1 t)(p_2 t)(p_3 t)(p_4 t)(p_5 t)(p_6 t) = p_1 p_2 p_3 p_4 p_5 p_6 t^6$

There are 6! possible sequences of 6 events. Only one of them is the "correct" one. So, the probability that 6 events have happened, in the correct sequence, is $\frac{p_1 p_2 p_3 p_4 p_5 p_6}{6!}$

Armitage and Doll math

The probability of the 7th event occuring during time interval Δt is $p_7 \Delta t$.

The probability that 6 events happened by time t, and then the 7th event during the next Δt is

$$\frac{p_1 p_2 p_3 p_4 p_5 p_6 p_7}{6!} t^6$$

For r events:

$$\text{cancer death rate} = \frac{p_1 p_2 \cdots p_r}{(r-1)!} t^{r-1}$$

Why a specific sequence?

(death rate is still ~t^6 if the sequence is ignored)

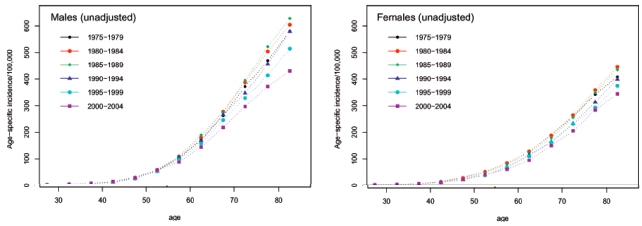
- data show that cancer probability is directly proportional to carcinogen concentration
- data show a long lag time between carcinogen exposure and cancer
- These makes sense if the carcinogen only affects event #1.

Improved cancer incidence model

Problems with Armitage-Doll model

- the exact A-D model suggests ~10 sequential rare events, not 7
- biology work suggests only about 2 or 3 necessary rare events (APC/β-catenin mutations)
- newer and better data don't fit t^6 incidence curve

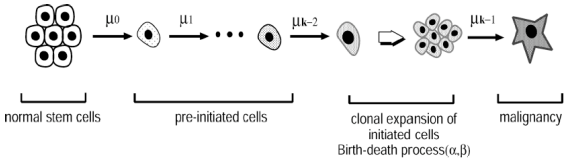
Incidence of colorectal cancer, 1975 - 2004



Note linear scales, not log-log scales

Credit: Meza *et al. Proc. Natl. Acad. Sci. USA* 105:16284, 2008.

Multi-stage clonal expansion (MSCE) model



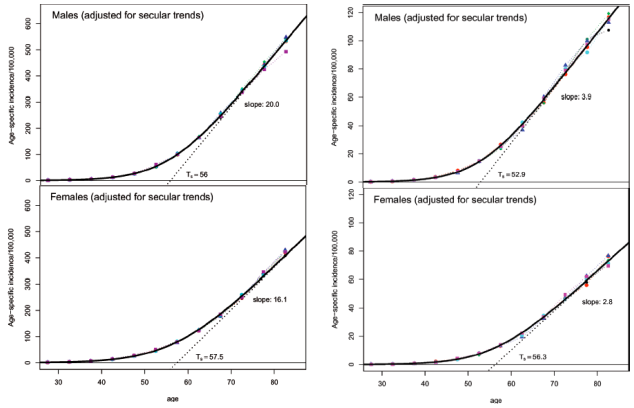
3 stage model (Luebeck's group)

- Initiation requires 2 rare events
  mutation of both copies of APC tumor suppresor,
  rates are μ_0 and μ_1
- Clonal expansion of initiated cells
  cell division rate α, cell death or differentiation rate β
  net cell growth rate $\alpha-\beta$
- One of the new cells transforms to metastatic
  malignant transformation rate μ_2

Credit: Meza *et al. Proc. Natl. Acad. Sci. USA* 105:16284, 2008.

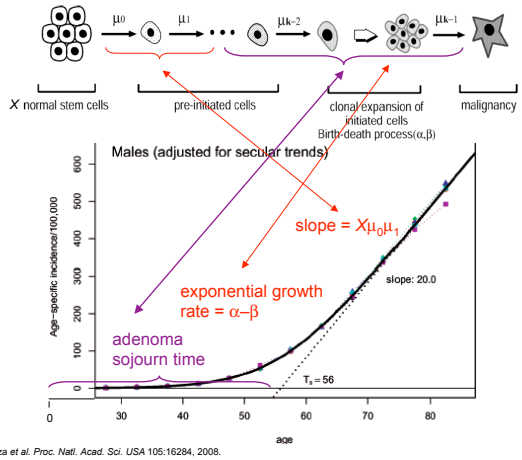
MSCE model results

Colorectal cancer **Pancreatic cancer**



Credit: Meza *et al. Proc. Natl. Acad. Sci. USA* 105:16284, 2008.

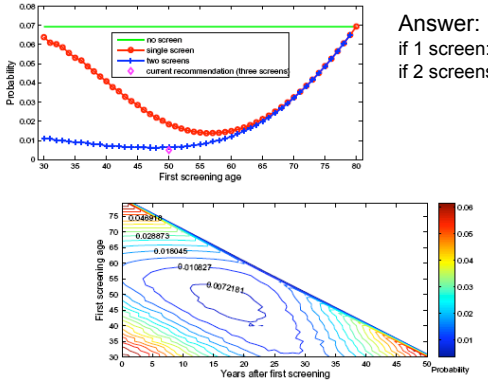
MSCE model interpretation



Credit: Meza *et al. Proc. Natl. Acad. Sci. USA* 105:16284, 2008.

MSCE model application

When is the best age for a colonoscopy screening?



Answer:
if 1 screen: age 57
if 2 screens: ages 50 and 68

Credit: Jeon *et al. Mathematical Biosciences* 213:56, 2008.

MSCE model conclusions

Model fits incidence data

Model agrees with biology
- 2 rate-limiting mutations
- then, chromosomal instability, so more mutations follow
- time for growth of adenoma
- rate-limiting transformation to metastatic
- fast cancer after metastatic

Model enables screening recomendations

Modeling mechanics
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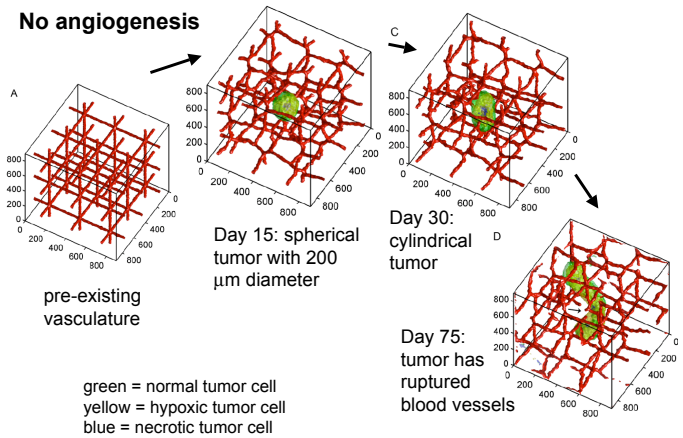
Tumor growth models
Summary

Glazier's tumor growth model

No angiogenesis

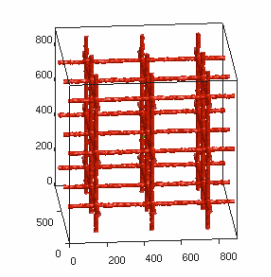


pre-existing vasculature

green = normal tumor cell
yellow = hypoxic tumor cell
blue = necrotic tumor cell

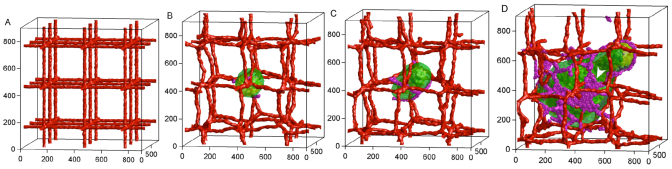
Credits: Shirinifard et al. *PLoS ONE* 4:e7190, 2009.

Movie, no angiogenesis



Credits: Shirinifard et al. *PLoS ONE* 4:e7190, 2009.

Glazier's results, with angiogenesis



pre-existing vasculature

Day 15: spherical tumor with 300 µm diameter

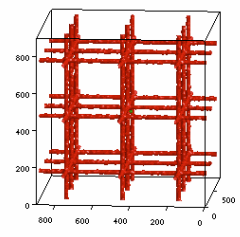
Day 30: cylindrical tumor

Day 75: developed vascularized tumor

green = normal tumor cell
yellow = hypoxic tumor cell
blue = necrotic tumor cell
purple = new vasculature

Credits: Shirinifard et al. *PLoS ONE* 4:e7190, 2009.

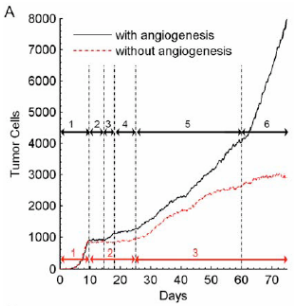
Glazier's results, with angiogenesis



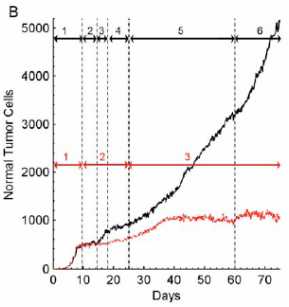
Credits: Shirinifard et al. *PLoS ONE* 4:e7190, 2009.

Quantitative results

all tumor cells

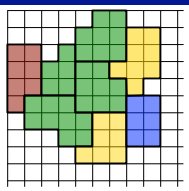


normal (not hypoxic) tumor cells



Credits: Shirinifard et al. *PLoS ONE* 4:e7190, 2009.

GGH / cellular Pott's model



Each lattice site is
- empty (i.e. extracellular medium)
- normal tumor cell (green)
- hypoxic tumor cell (yellow)
- necrotic cell (blue)
- vascular cell (red)
- neovascular cell (purple)

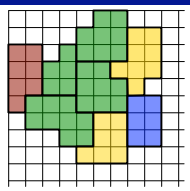
The system "energy" depends on
- contact energy at each cell-cell contact face
- pressure energy for compressed cells

$$H_{GGH} = \sum_{i,j} J\left(\tau(\sigma(\vec{i})),\tau(\sigma(\vec{j}))\right)\left[1-\delta\left(\sigma(\vec{i}),\sigma(\vec{j})\right)\right] + \sum_{\sigma} \lambda_{vol}(\tau)\left[v(\sigma)-V_t(\tau(\sigma))\right]^2$$

In each "move", the simulator
- randomly changes the contents of a random site
- accepts the move if it lowers the system energy
- accepts the move with a low probability if it raises the system energy
- otherwise, rejects the move and returns to the prior state

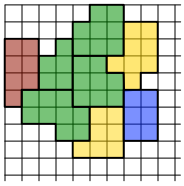
$$P = e^{-\frac{\Delta H}{T}}$$

GGH / cellular Pott's model



More rules
- cells are normal or hypoxic, depending on oxygen availability
- cells grow (target volume increases), depending on oxygen availability
- cells divide if their volume exceeds the "doubling volume"
- necrotic cells shrink (target volume decreases)
- hypoxic cells secrete VEGF-A (vascular endothelial growth factor)
- vascular cells secrete chemoattractant
- neovascular cells grow towards chemoattractant using another "energy" function

GGH / cellular Pott's model



Each lattice site has
- oxygen concentration
- VEGF-A concentration
  (vascular endothelial growth factor)
- chemoattractant for vascular growth

These are modeled with reaction-diffusion equations

VEGF equation: $\frac{\partial V}{\partial t} = -\varepsilon_V V + \delta\left(\tau(\sigma(\vec{x})), hypoxic\right)\alpha_V V + D_V \nabla^2 V$

- $-\varepsilon_V V$: decay rate of VEGF-A
- $\delta\left(\tau(\sigma(\vec{x})), hypoxic\right)\alpha_V V$: production of VEGF-A by hypoxic cells
- $D_V \nabla^2 V$: diffusion of VEGF-A

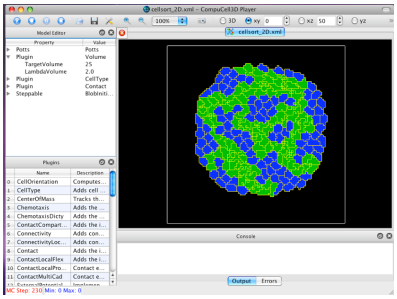
equations are similar for oxygen and chemoattractant

Software

CompuCell3D http://www.compucell3d.org

3D reaction-diffusion simulations
cellular Potts model simulations

used for simulating
- morphogenesis
- tumor growth
- cell sorting
- biofilms
- foams (?)



Summary

Mechanics
- polymer models
- slime extrusion model

Cancer incidence
- Armitage-Doll model (incidence ~ t^6)
- Luebeck model (incidence has lag, then linear)

Tumor growth
- with and without angiogenesis
- cellular Potts model
- reaction-diffusion model
- CompuCell3D software

Course summary

Introduction
Modeling dynamics
Metabolism
Gene regulatory networks
Stochasticity and robustness
Spatial modeling
Mechanics and cancer