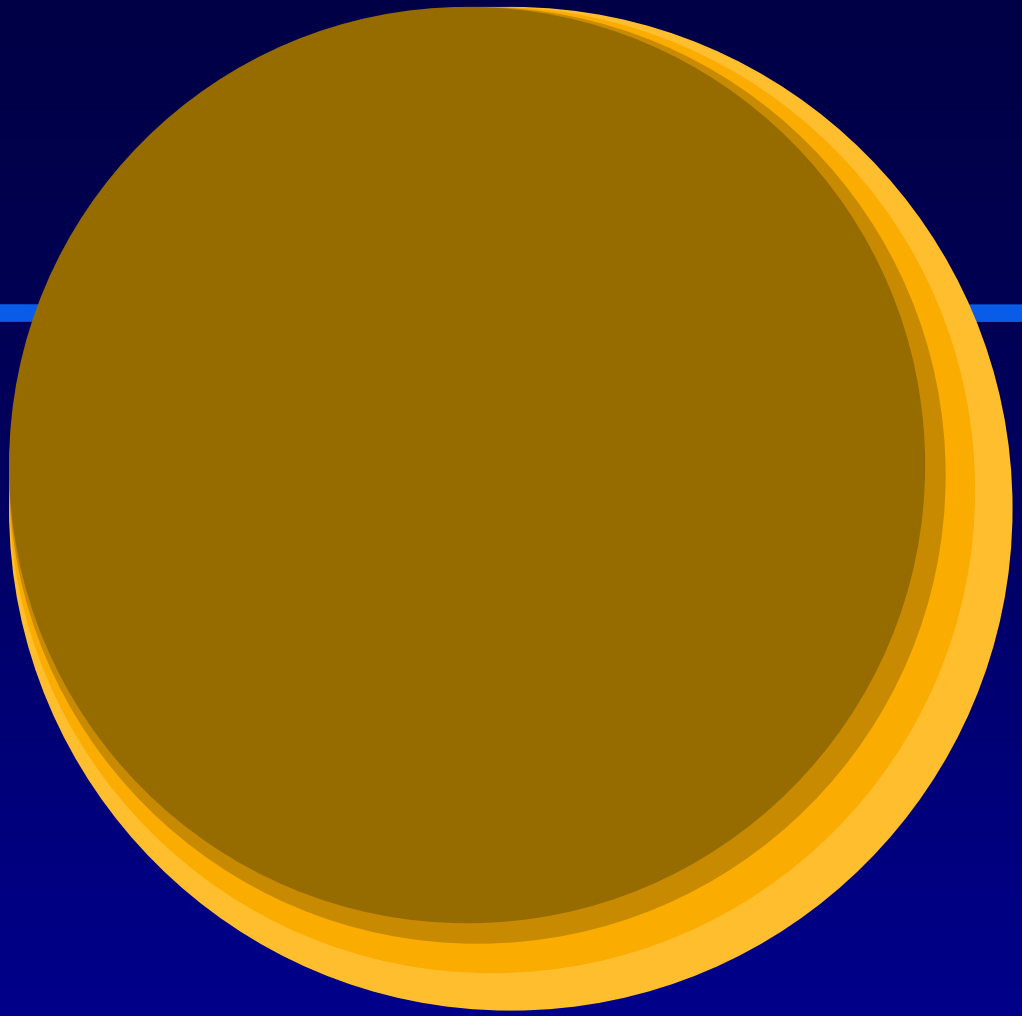

Lecture 1: Cancer Biology for Modellers

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Motivation

- To be effective biomathematicians, we need to "speak biology" as well mathematics and programming.
  - Helps in communicating with team members
  - Biological understanding helps inform:
    - Model formulation and analysis
    - Evaluation of modelling predictions
    - Parameter estimation
    - Calibration
      - relates to image processing
      - Need to understand what you're seeing (histopathology)

Lecture Outline

- Cell organisation
- Tissue organisation
- Maintaining tissue structure
- Cell birth and death
- Cell signalling
- Cell motility
- Oncogenes and tumour suppressor genes
- Abusing the system: cancer progression
- Coming next
- References and resources

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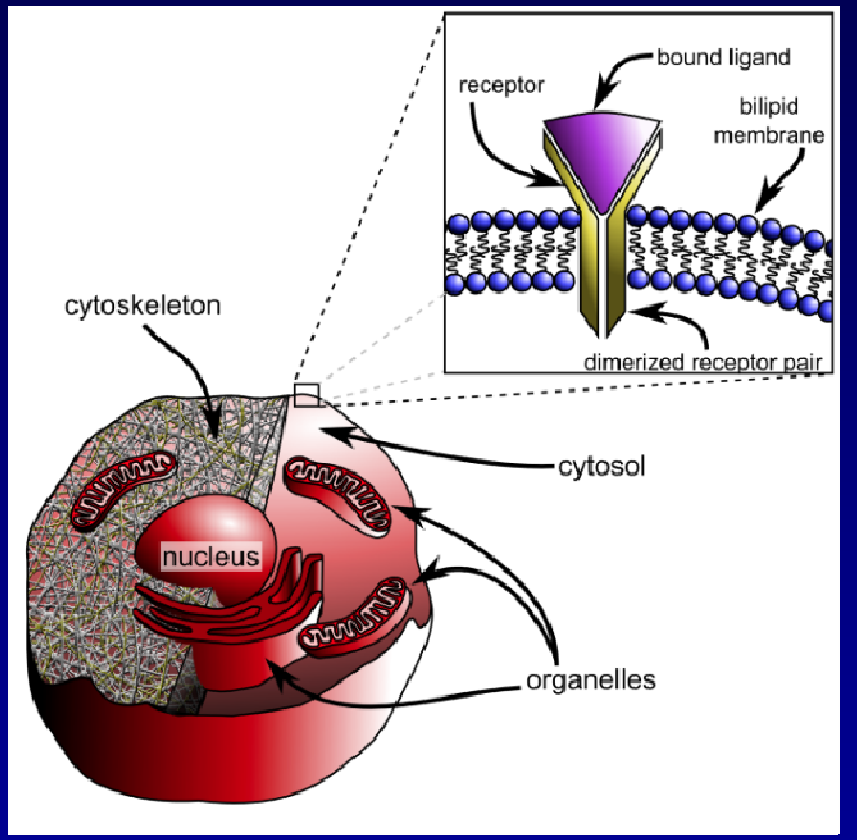
Cell Organisation

- Bilipid layer surrounding cytoplasm
  - Permeable to small molecules
  - Requires active transport of others
    - Ion pumps control cell volume, pH, etc.
  - Impermeable to larger proteins
- Cytoskeleton provides structure
- Organelles embedded in the cytoplasm to perform specialised functions
- Relatively rigid nucleus in the centre
- Receptors on cell surface:
  - Mediate cell-microenvironment communication by binding to ligands
  - Mechanically link cell cytoskeleton to membrane and microenvironment



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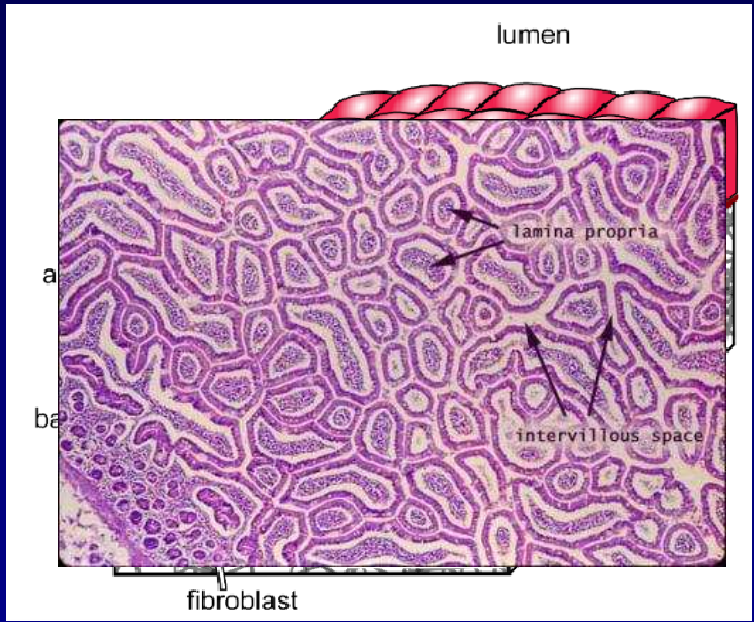
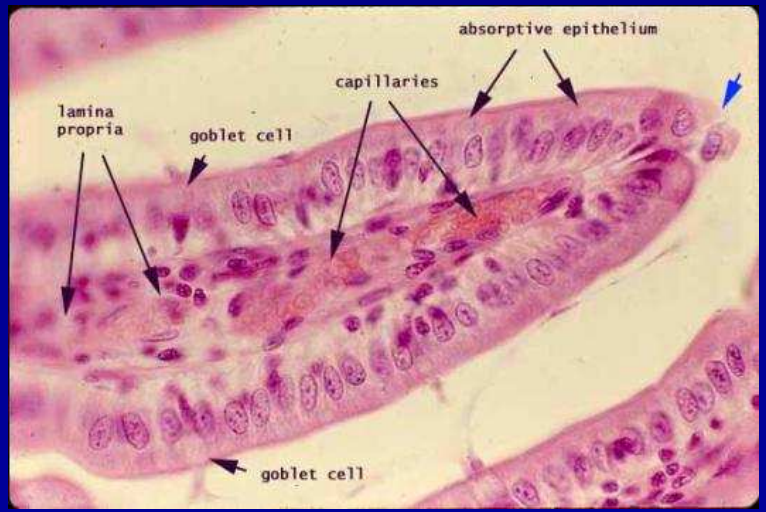
Tissue Organisation

- Typical tissue microstructure in an organ:
  - Epithelial tissue (epithelium)
    - Sheets of specialised cells that perform the work of the organ (secretory products, filtration, etc.)
  - Loose connective tissue (stroma)
    - Extracellular matrix (ECM) supports the organ
    - Contains blood vessels, lymphatics, nerves
  - Tissues separated by basement membrane (BM)
  - Often a *lumen* (fluid- or air-filled cavity)
    - Transports secretory products from/to epithelium
    - stroma-BM-epithelium microstructure: designed to maximise surface area of epithelium-lumen interface





- Notable biophysics and transport:
  - BM is a physical barrier to cell motion between tissues
  - Oxygen, glucose, and growth factors can only reach epithelium by diffusion

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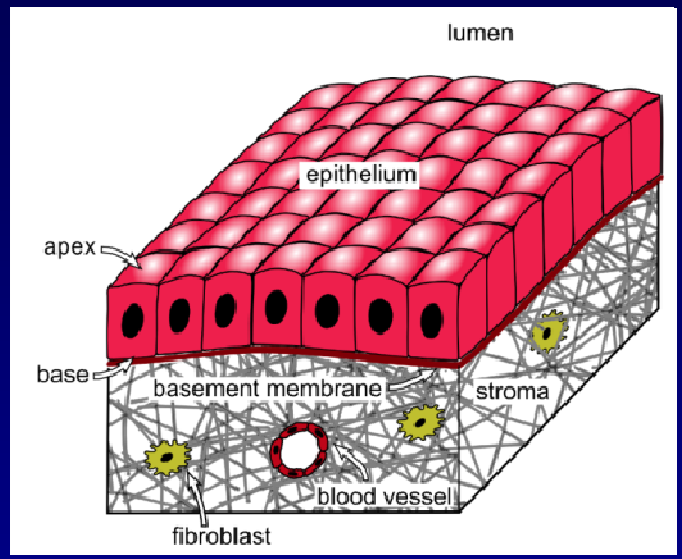
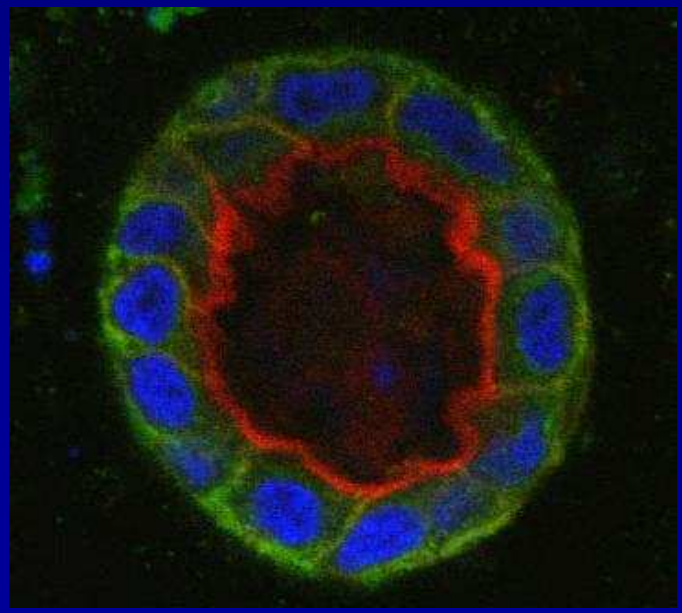
Maintaining Tissue Structure: Mechanics

- Mesenchymal cells (e.g., fibroblasts) can move freely in the stroma, secrete and degrade ECM

- Epithelial cells are polarised:
  - Anisotropic adhesion receptor distribution
  - Integrins on base for cell-BM adhesion
    - Heterophilic adhesion
  - No adhesion receptors on apex
  - E-cadherins on basolateral sides for cell-cell adhesion
    - Homophilic adhesion

- Mechanics determine tissue geometry:
  - Balance of cell-cell and cell-BM strength
  - Distribution of cell receptors likely help in determine curvature
  - Mechanics of cell-BM adhesion, stresses, BM-to-ECM coupling likely determines BM curvature.

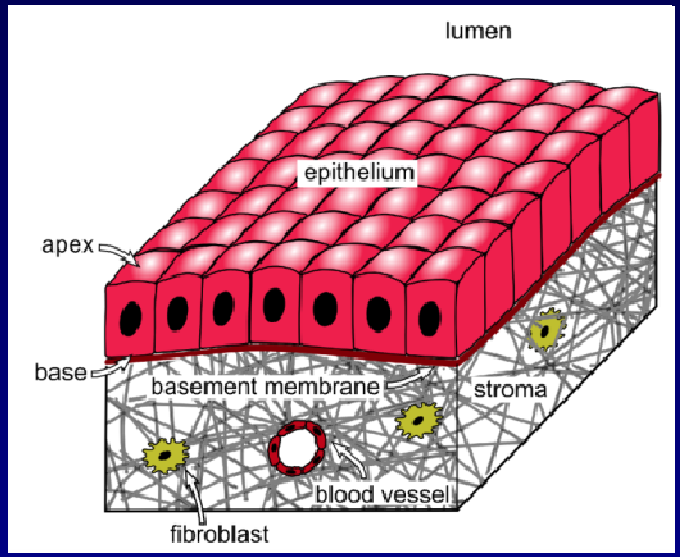


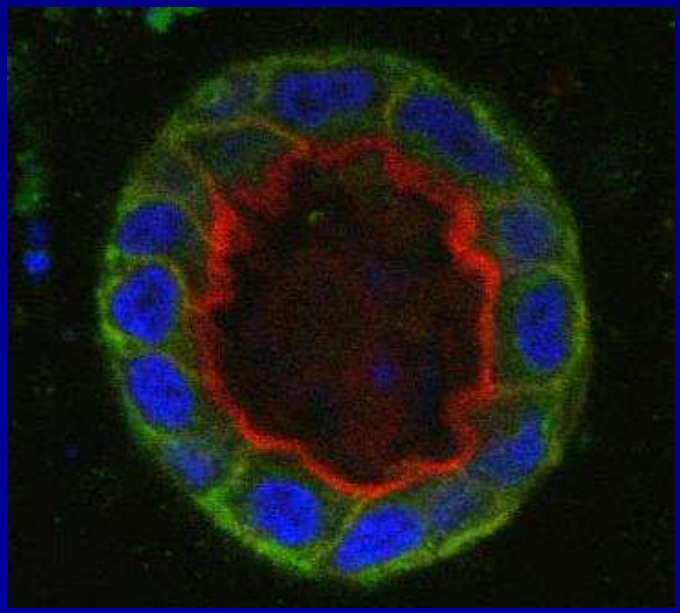


Maintaining Tissue Structure: Population Dynamics

- **Cell populations must be maintained in homeostasis**
  - **Proliferation to replace aged cells**
  - **Apoptosis to remove damaged cells, or those out of place**

- **Adhesion receptors are not merely mechanical:**
  - **E-cadherin helps detect presence/absence of neighbours**
    - **Trigger proliferation when missing a neighbour (E-cadherin/β-catenin)**
    - **Suppress cell cycle when attached to neighbours (block Cyclin D1, etc.)**
  - **Integrins detect detachment from BM**
    - **Trigger apoptosis (anoikis)**
  - **(This is why they're *receptors*. ☺)**





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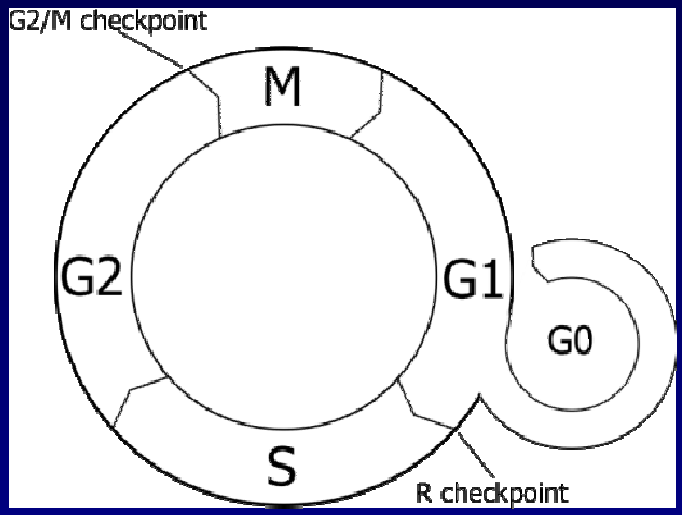
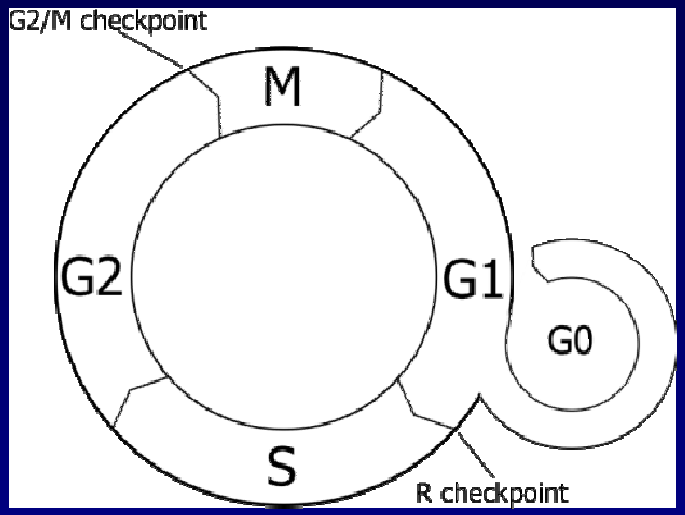
Cell Birth and Death: Proliferation

- **Tightly-controlled cell-cycle:**
  - **G0: quiescent "resting state"**
  - **S: Synthesis of new DNA**
  - **G2: "gap" phase – final prep for division**
  - **M: mitosis phase**
    - **DNA divided into two daughter nuclei (mitosis)**
    - **Cytoplasm and organelles divided into daughter cells (cytokinesis)**
  - **G1: "gap" or "growth" phase – daughter cells grow in volume, then exit cycle**
  - ***Note 1*: Some biologists treat G0+G1 as long, variable-length G1 phase (often seen in flow cytometry)**
  - ***Note 2*: Others treat G1 as relatively fixed length, with G0 of variable length (useful for Ki-67 matching)**



Cell Birth and Death: Proliferation

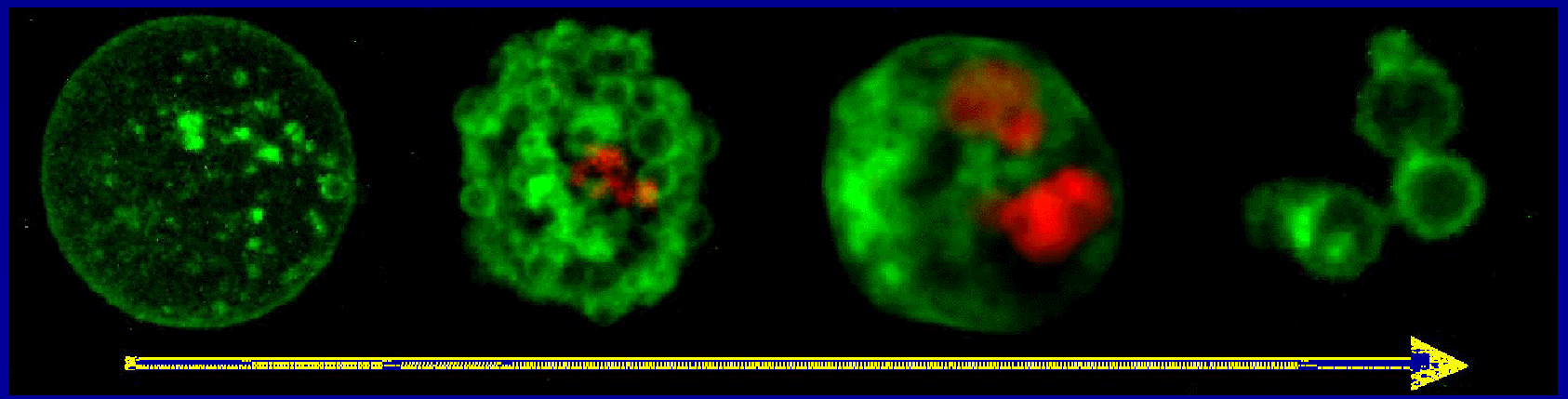
- **Checkpoints provide opportunities for:**
  - **Cycle arrest: Restriction checkpoint R at G1/S**
  - **DNA error checking and repair**
  - **Apoptosis for irreparable damage**



- **Cycle progression controlled by intracellular signalling**
  - **Cyclins and cyclin-dependent kinases (CDKs)**
  - **Connected to other signalling networks**

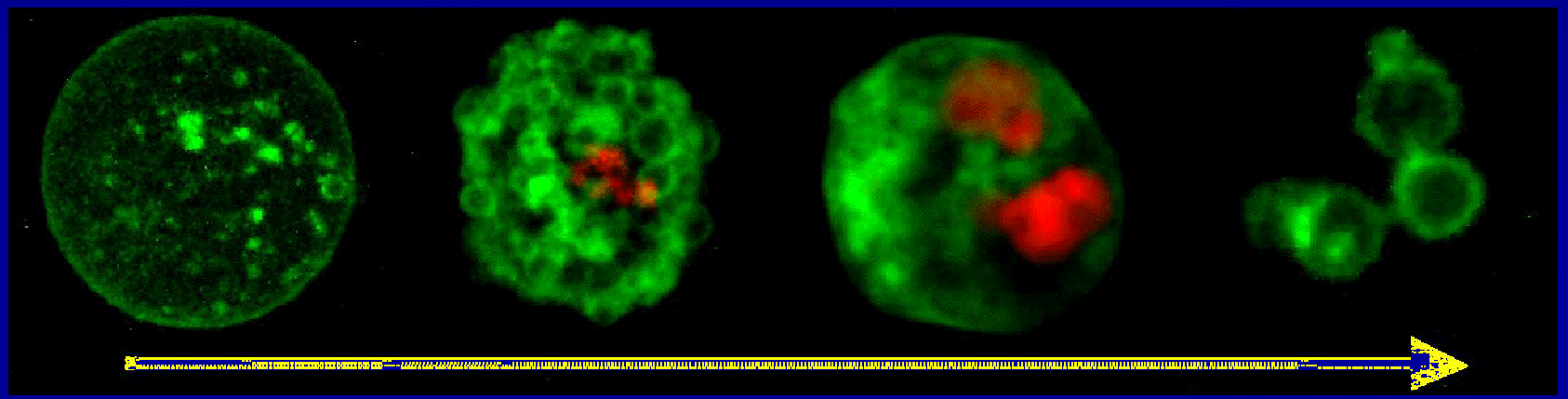
Cell Birth and Death: Apoptosis

- **Apoptosis: orderly cell death**
  - **Self-regulated, in response to signalling events**
  - **Early processes:**
    - **Mitochondria lose membrane potential, integrity**
    - **Pre-positioned caspases are activated (cleaved), begin degrading cell**
  - **Orderly cell volume shrinking**
    - **requires active N+, Ka+ pumps!**



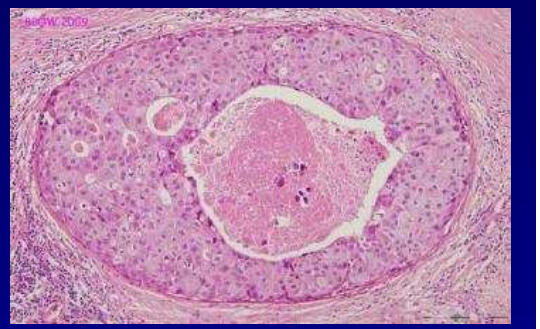
Cell Birth and Death: Apoptosis

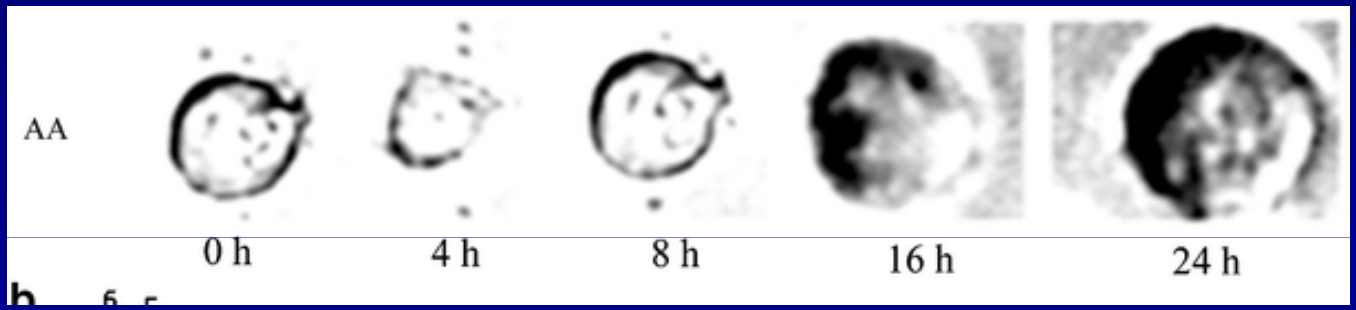
- **Apoptosis: orderly cell death (continued)**
  - **DNA is chopped into pieces**
  - **Organelles disassembled**
  - **Cell contents encapsulated into apoptotic bodies**
    - **Protects surrounding cells from otherwise damaging reactions**
  - **Cell lyses to release apoptotic bodies**
  - **Apoptotic bodies phagocytosed**
  - **Entire process requires energy!**

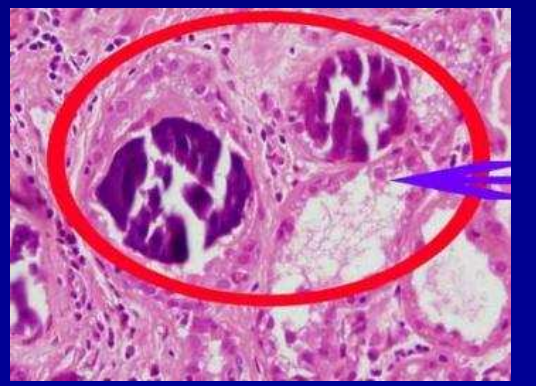


Cell Birth and Death: Necrosis and Calcification

- **Necrosis: uncontrolled cell death**
  - Can occur due to energy depletion (hypoxia or hypoglycemia), mechanical injury, chemical stressors, failure during apoptosis, etc.
  - Uncontrolled cell volume
    - No energy for N+, Ka+ pumps
    - Cell swells, then bursts
    - Cell contents released into microenvironment







  - No orderly disassembly of nucleus, organelles, etc.
  - Generally no phagocytosis
  - Calcification:
    - Ca+ pumps not active
    - Solid cell fraction replaced by calcium phosphate and oxolate cyrstals
    - Hard microcalcifications results

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Cell Signalling

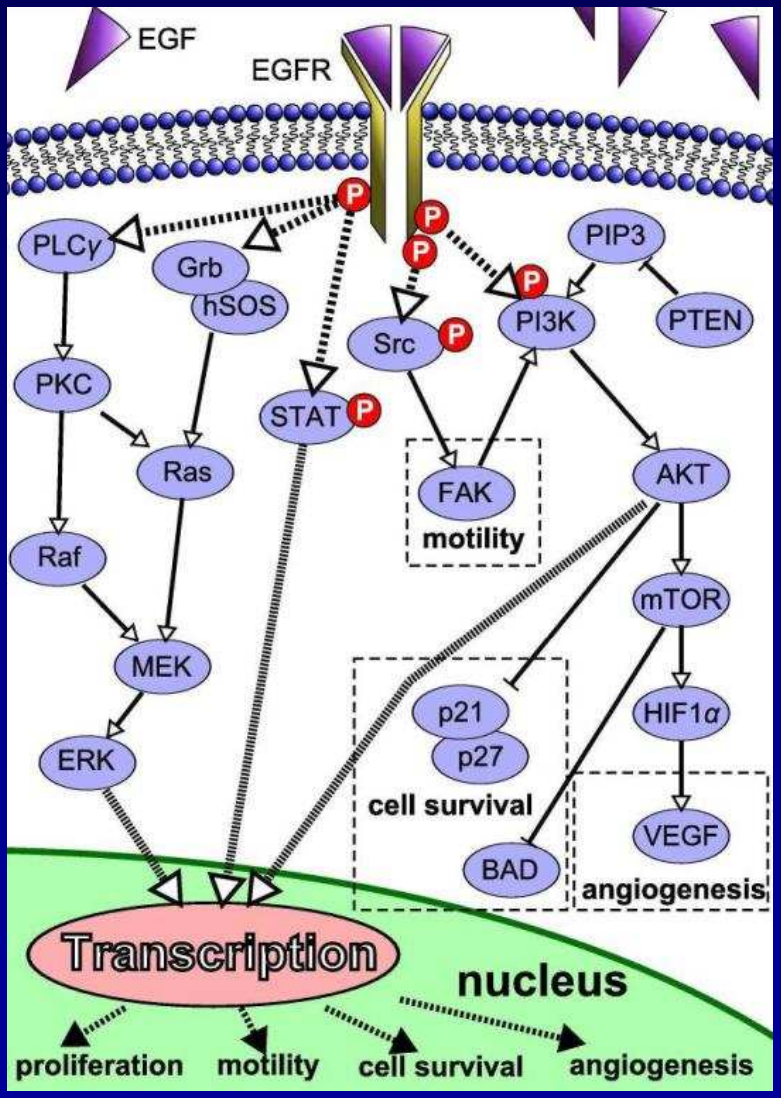
- Cells are regulated by internal signalling networks
  - DNA transcribes RNA
  - RNA encodes proteins
  - Proteins:
    - Assemble into structures
    - Perform “duties”
    - Transmit information through reactions
  - Network:
    - Redundancies
    - Feedback loops
    - Signal amplification

Cell Signalling: Two examples

- HIF signalling:
  - Cells create hypoxia-inducible factors (HIFs)
    - Big example: HIF-1α
  - Ordinarily, O_2 tags these for degradation
  - During hypoxia, HIFs accumulate → HIFs as O_2 sensors
  - Trigger downstream transcription
    - Decreased cell adhesion
    - Increased motility
    - Glycolysis
    - Temporary resistance to apoptosis
    - VEGF secretion

Cell Signalling: Two examples

- EGFR signalling
  - Epidermal growth factor (EGF) binds to EGFR receptor
  - Ligated EGFR receptors dimerise
  - Dimerised EGFR receptors phorphorylate intracellular proteins
  - Downstream actions:
    - Transcription
    - Increased motility
    - Increased proliferation
    - Cell survival



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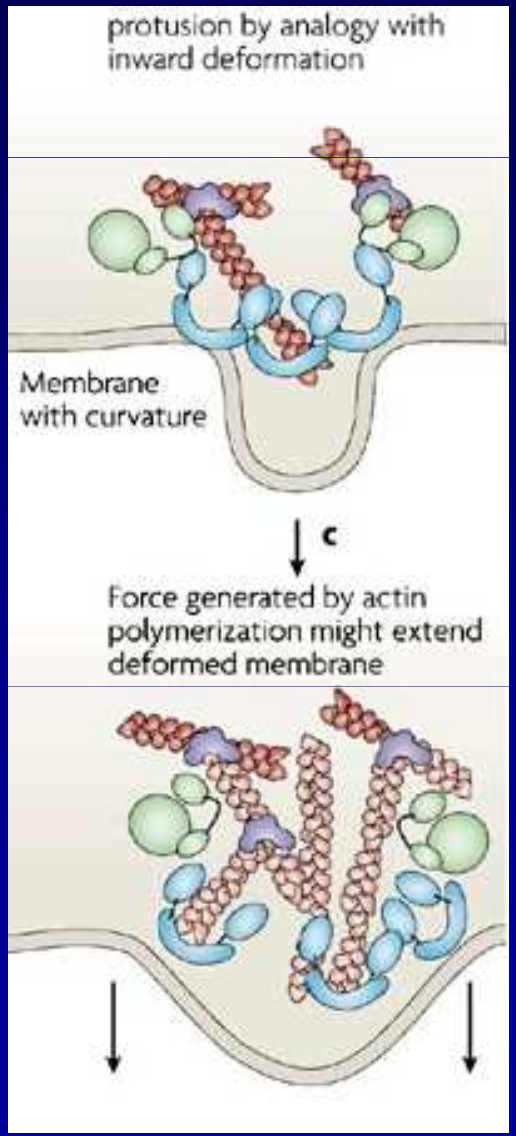
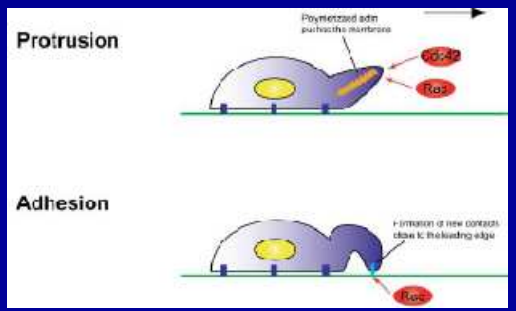
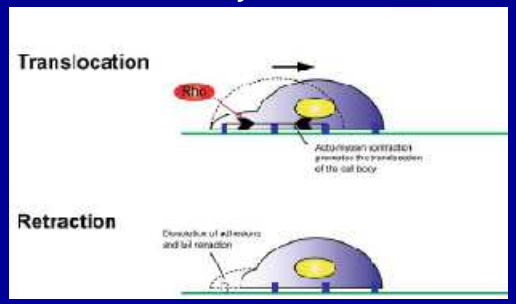
Cell Motility

- Actin polymerisation and depolymerisation:
  - Actin monomers join or leave chains to grow or shrink the cytoskeleton
- Cell signalling can nucleate biased polymerisation (e.g., in response to a gradient)
  - EGFR → Src → N-Wasp → Arp2/3 nucleation → …
- Actin fibres deform and extend cell membrane, forming a pseudopod ("false foot")
  - Filopodium: finger-like projection
  - Lamellipodium: sheet-like projection
- Cells focally secrete MMPs from invadopodia:
  - Degrade ECM
  - Break integrin bonds
  - Create space for motion
- Cell forms new focal adhesion on leading edge
- Actin polymers broken down in trailing edge (depolymerisation)
- Cell contracts to pull towards leading edge
- Protrusion – Adhesion – Contraction – Retraction cycles







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Oncogenes and Tumour Suppressor Genes

- Oncogenes:
  - Proliferation-promoting genes : “gas pedal”
  - Examples:
    - Growth factor secretion (including autocrine): EGF, PDGF, VEGF
    - Internal promotion of cell cycle: β-catenin promotes transcription of Cyclin D1
    - Counter-act TSGs: MDM2 degerades p53
    - Growth factor receptors: EGFR / ErbB
    - Downstream regulators of receptor pathways: Ras, Raf, Src
- Tumour suppressor genes (TSGs):
  - Impede proliferation : “brake pedal”
  - Examples:
    - Block oncogenic signals: VHL helps degrade HIF-1α
    - Regulate cell cycle / create inhibitory signals: Rb impedes cell cycle, promotes arrest at G1/S
    - Repair DNA damage: TP53 impedes cell cycle to allow DNA repair at G1/S
    - Promote apoptosis: p53 can trigger apoptosis
  - Knudson 2-hit hypothesis:
    - You have 2 copies of each TSG, so need to eliminate both copies to lose function
      - Discovered in studying Rb (retinoblastoma) TSG
      - Mitigating factor: loss of heterozygosity
      - Mitigating factor: partial loss of function

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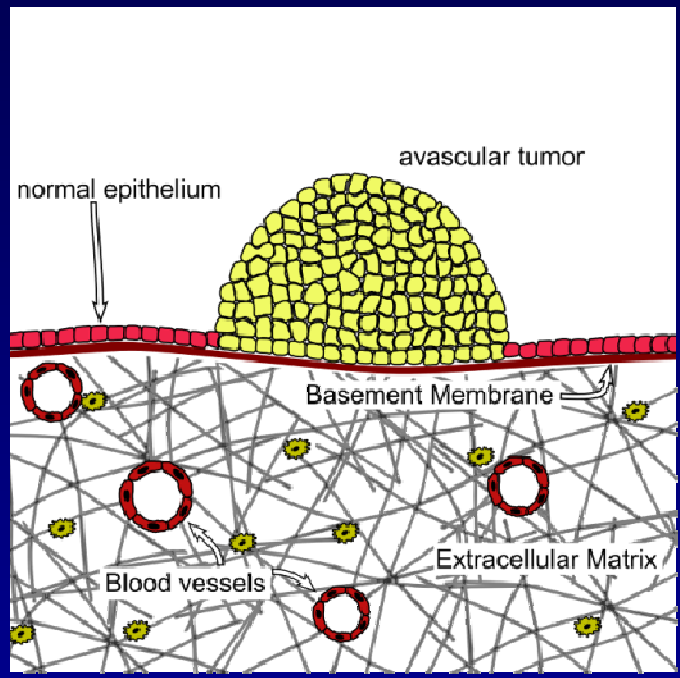
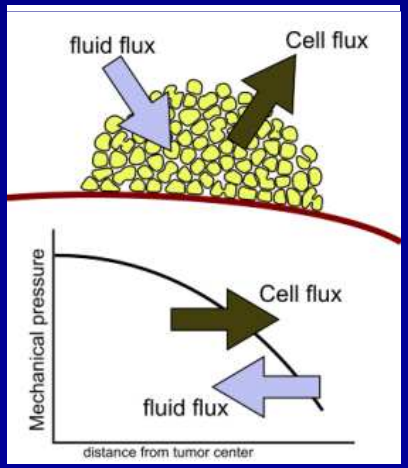
Abusing the system: Carcinogenesis

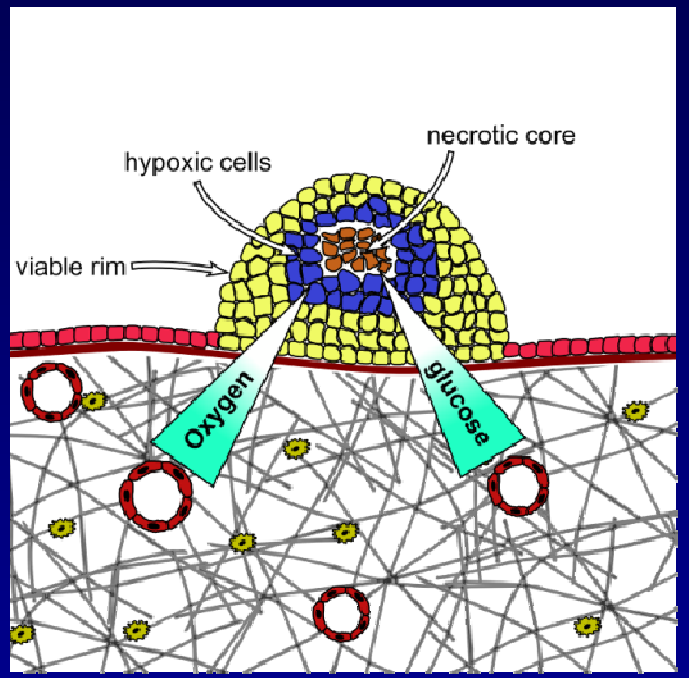
- **Mutations and/or epigenetic events:**
  - **Down-regulate apoptosis (lose TSGs)**
    - **No anoikis – cells can survive in the lumen**
    - **p53 mutation – cells can ignore apoptosis signals**
  - **Up-regulate proliferation (oncogenes)**
    - **Decreased contact inhibition – proliferate even in the presence of neighbours**
    - **Increased secretion of growth signals → self-signalling**
    - **"stuck switches"**
      - **HER2 – can dimerise without binding ligand**
        - » **increases signalling activity**
      - **K-ras mutation – constitutive active, allowing EGFR signalling with EGF**
- **Consequences:**
  - **Increased survival fitness versus normal cells**
  - **Forms a colony of hyperproliferative cells**
- **Mechanics:**
  - **Mechanical pressure, stresses created by proliferating cells**
  - **Net outward flux of cells as mass grows – Darcy's law**
  - **Net inward fluid flux**

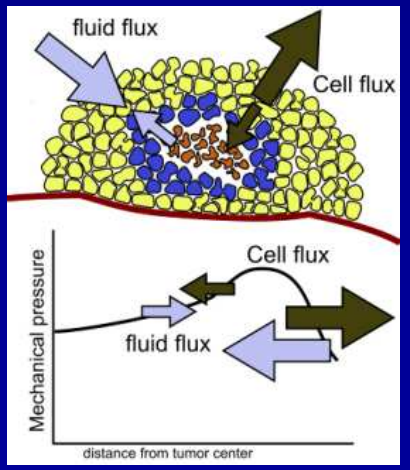


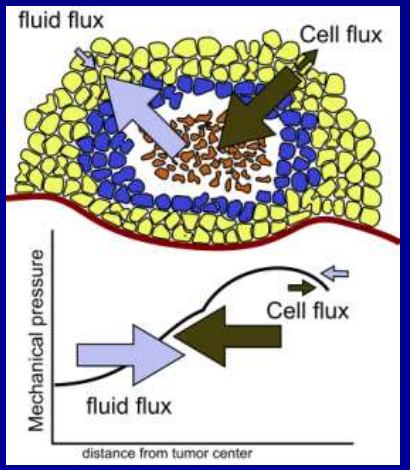


Abusing the system: Avascular Growth

- Can only receive substrates by diffusion from the stroma
  - Substrate gradients
  - Hypoxia
  - Hyperglycemia
- Consequences:
  - Viable rim thickness related to diffusion length scale
  - Heterogeneous growth rates – relationship with oxygen and glucose (cell energetics)
  - Inner band of hypoxic cells
    - HIF signalling
  - Interior necrotic core
- Mechanics:
  - Outward fluid flux from necrotic core due to lysis
  - Inward cell flux due to reduced interior strain
  - Steady tumour volume:
    - Cell flux out of viable rim ≈ fluid flux from necrotic core

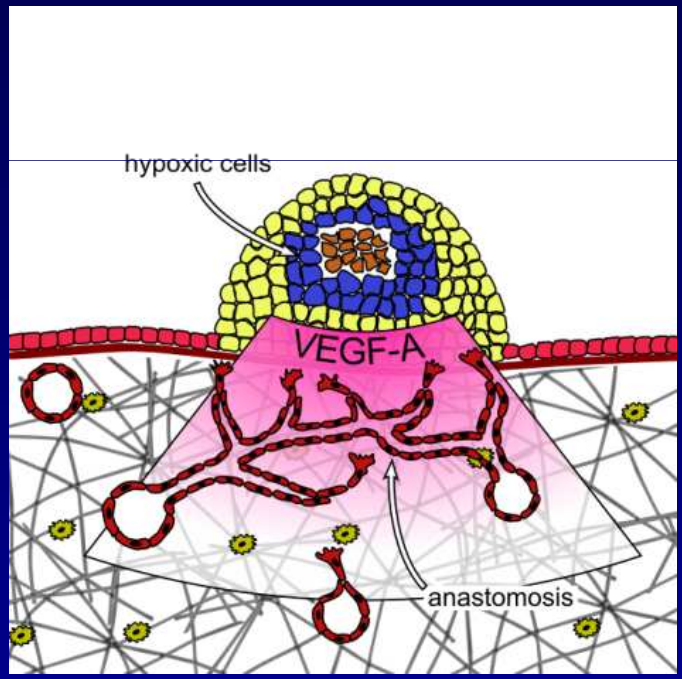






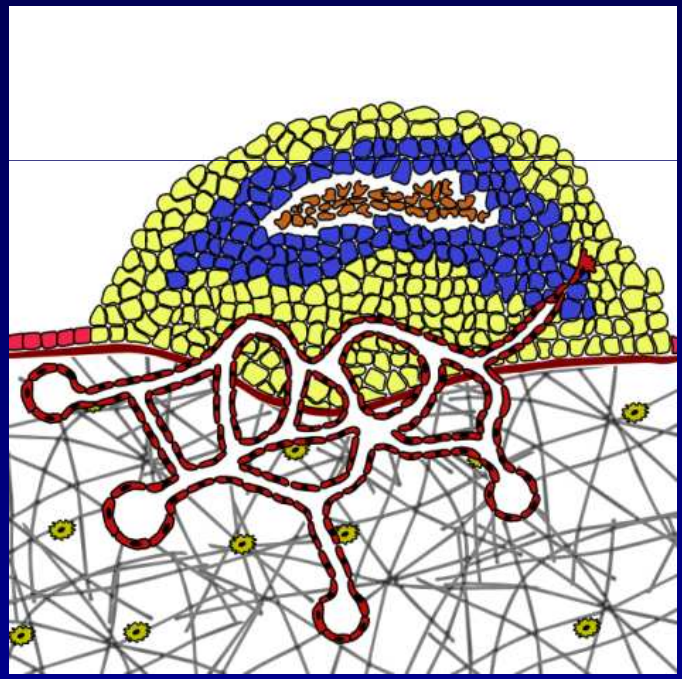
Abusing the system: Angiogenesis

- Hypoxic cells release angiogenic factors
- VEGF diffuses into stroma
- Endothelial cells respond to VEGF
  - Degrade vessel walls
  - Chemotaxis (up ∇VEGF), haptotaxis (up ∇ECM)
  - Increased proliferation
  - Temporary suspension of anoikis (to facilitate survival until new basal lamina surrounds mature vessels)
- New vessels grow towards tumour, generally towards the VEGF gradient
- New vessels cross-link (anastomose)
- New blood flow in the vessels – new substrate transport to fuel further tumour growth
- Vessels mature: pericytes recruited, deposit basal lamina around vessels



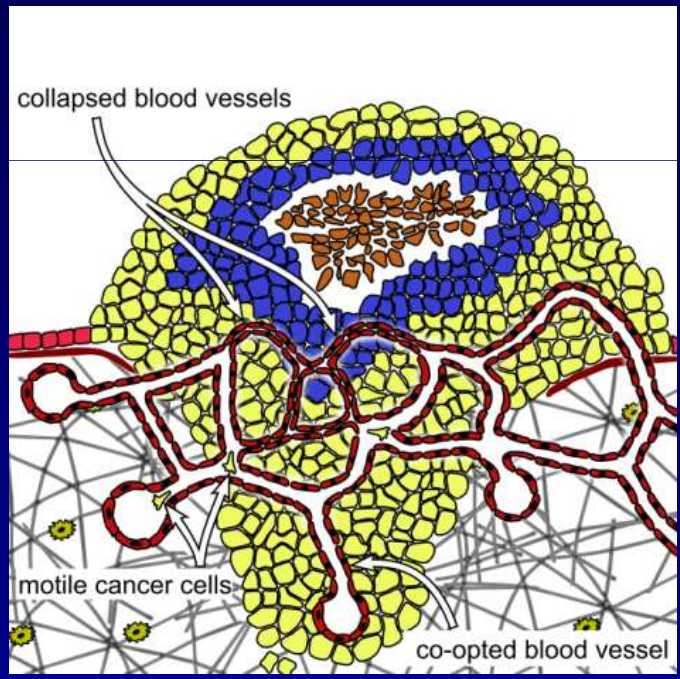
Abusing the system: Vascular Growth & Invasion

- **New vessels fuel rapid tumour growth**
- **BM deformation and stress**
- **Hypoxic stress remains**
  - **Glycolysis**
  - **Acidosis**
  - ***Selection pressures***



Abusing the system: Vascular Growth & Invasion

- **Mutations**
  - Acid-resistant
  - BM and ECM degradation (by MMPs)
  - Motility
- **Invasion into stroma**
  - By growth and by motility
  - Co-option of blood vessels
- **Sustained tissue stress**
  - Collapsed blood vessels
  - New rounds of angiogenesis
- **Metastasis**
  - Travel through blood vessels and lymphatics
  - Extravasation, growth of new tumour
  - Possible role of metastatic niche



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Coming Next:

- **Lecture 1:**
  - **Cancer biology for modellers**
- **Lecture 2:**
  - **An agent-based cell model; application to DCIS**
- **Lecture 3:**
  - **Parameter estimation, patient-specific calibration**
- **Lecture 4:**
  - **Numerical method, simulation results**

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Some References

- Some biology texts:
  - P. Macklin. Biological background. In: V. Cristini and J. Lowengrub. *Multiscale Modeling of Cancer*. Cambridge University Press, Cambridge, UK, 2010. Chapter 2, pages 8-24. ISBN 978-0521884426. (in press)
  - B. Alberts et al. *Molecular Biology of the Cell*. Garland Science, New York, NY USA, 5th edition, 2007. ISBN 978-0815341116.
  - M. Knowles and P. Selby, eds., *Introduction to the Cellular and Molecular Biology of Cancer*. Oxford Univ. Press, Oxford, UK, 4th edition, 2005. ISBN 0-19-852563-X.
- Also see some great modelling texts by Wodarz & Komarova, Anderson et al.
- Some great websites:
  - Cell biology and animations: http://www.johnkyrk.com/
  - SIU histology: http://www.siumed.edu/~dking2/
  - Zoomified histology: http://www.meddean.luc.edu/lumen/MedEd/Histo/virtualhistology.htm

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    - (new but under construction)
  - http://biomathematics.shis.uth.tmc.edu
    - (old but already built)