Mathematical Oncology

A Differential Equation approach to Cancer Growth and Metastasis

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3MC Project
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Section 1

Introduction

Definition — Cancer

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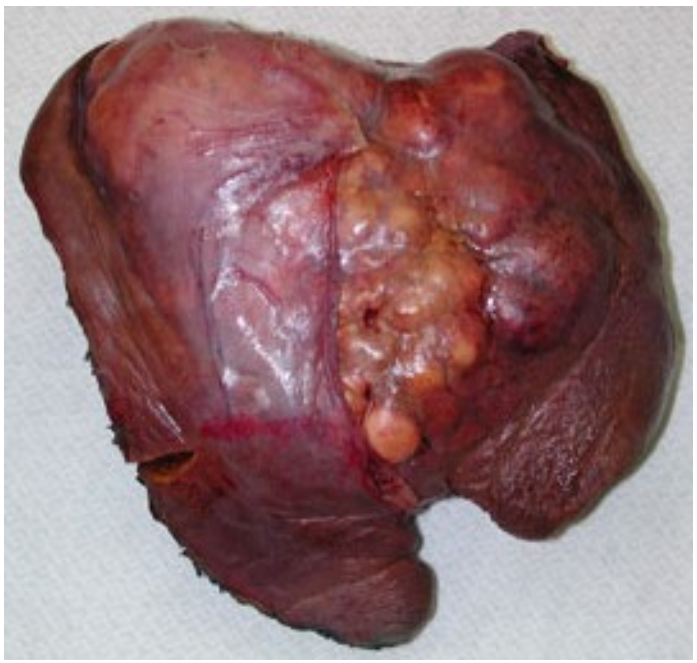

Figure: *Hepatocellular* carcinoma, the most common liver cancer. (Source: Science Photo Library)

Section 1: Introduction

Some numbers

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- By 2030, cancer will develop in 20% of the global population before they reach the age of 75.

Sources: Cancer Research UK, World Health Organization (WHO) 2018 and Eurostat 2013

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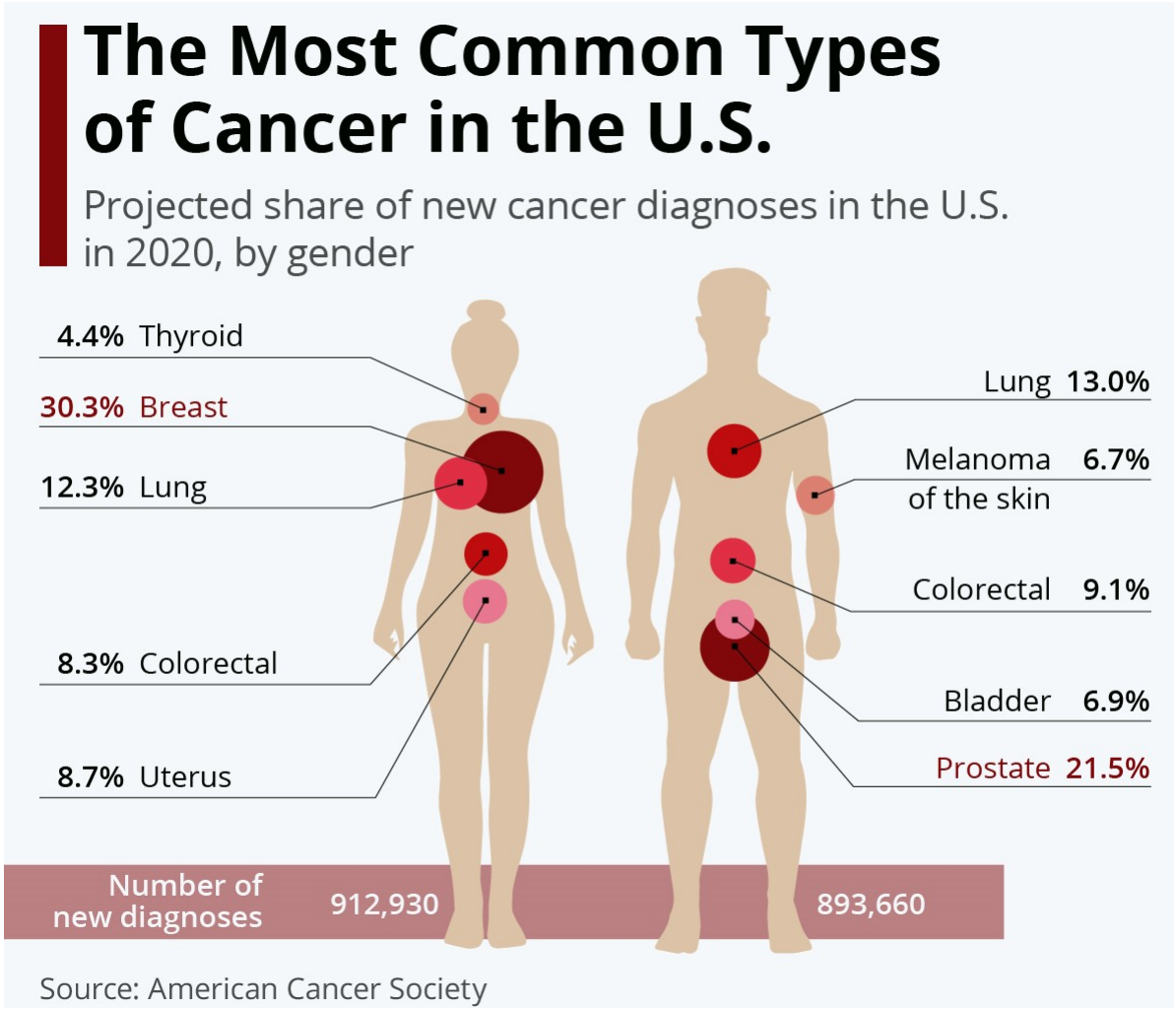
- *Central nervous system cancers*: appear in the tissues of the brain and spinal cord.

Source: National Institute of Health (NIH), US



In South Africa (2019):

Women:

- Breast
- Cervix
- Colorectal
- Uterus
- Non-Hodgkin's Lymphoma

Men:

- Prostate
- Colorectal
- Lung
- Non-Hodgkin's Lymphoma
- Melanoma

National Cancer Registry (NCR), ZA

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The treatment depends primarily on the type of cancer; most patients receive a combination of treatments.

(Source: NIH)

Definition — Oncology

Oncology is a branch of medicine that deals with the prevention, diagnosis, and treatment of cancer.

(Source: National Institues of Health (NIH), USA)

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Definition — Mathematical Oncology

Mathematical Oncology scientific discipline that studies processes in oncology using mathematical tools and methods.

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An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer), or malignant (cancer).

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Definition — Solid Tumour

An abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancer), or malignant (cancer). Examples of solid tumors are carcinomas, sarcomas, and lymphomas. Leukemias (blood cancers) generally do not form solid tumors.

(Source: NIH)

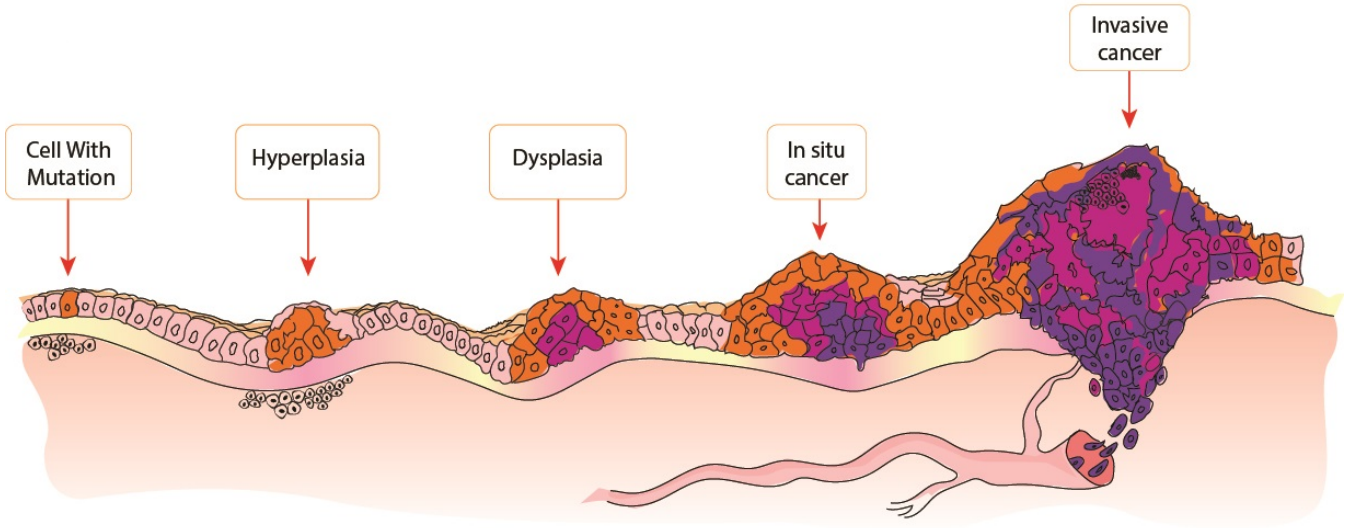
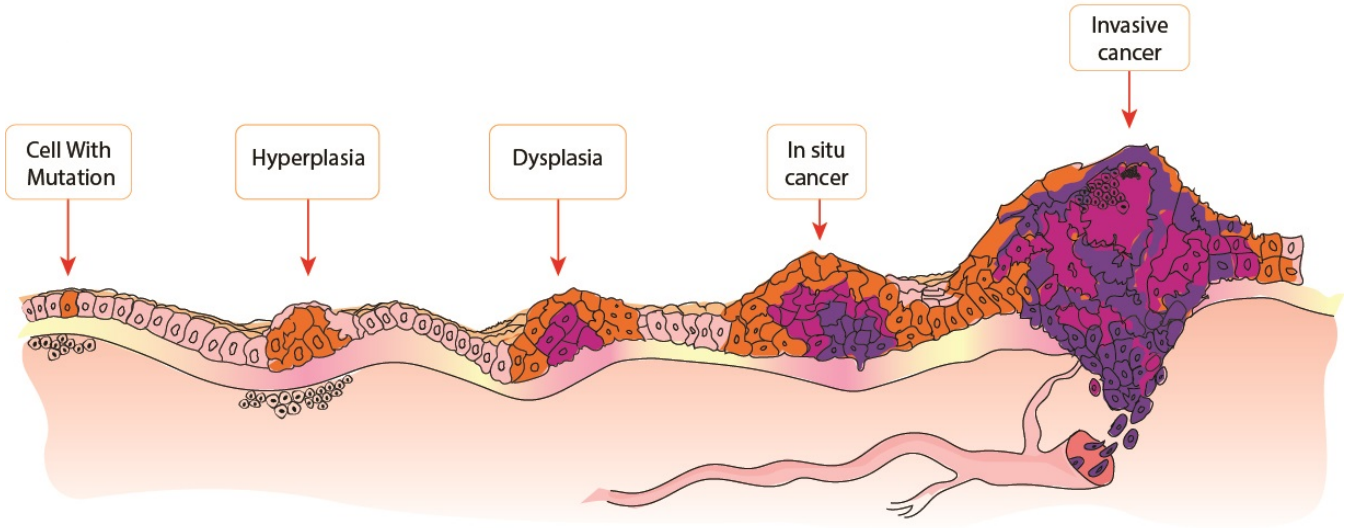


Figure: Schematic depiction of a possible tumour progression path that includes 4 stages of mutation (Source: National Institute of Health (NIH), US)



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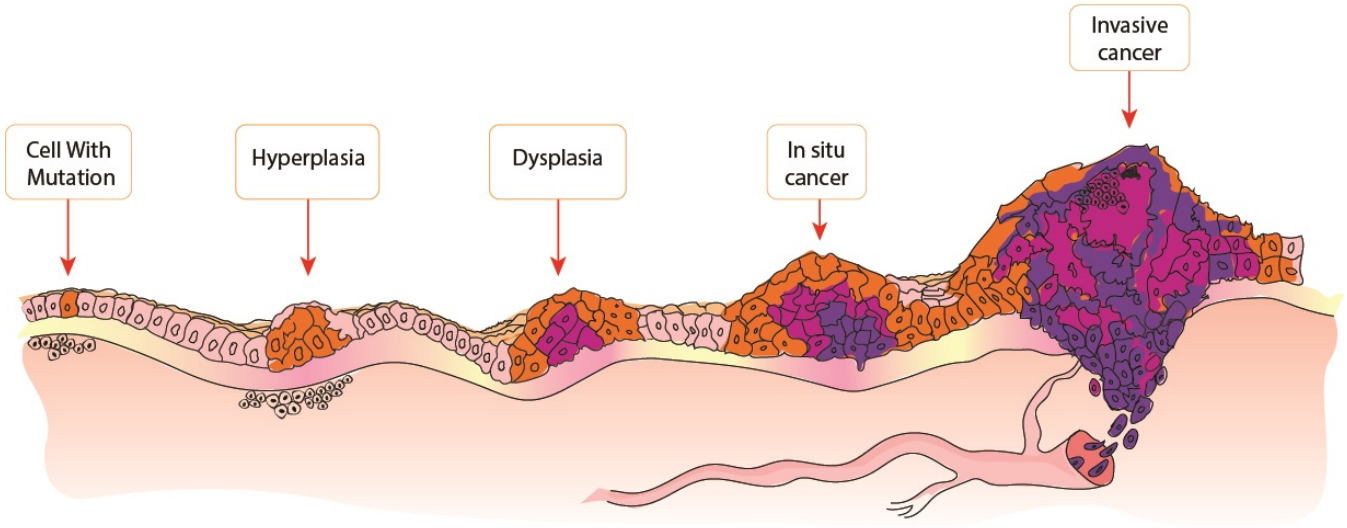

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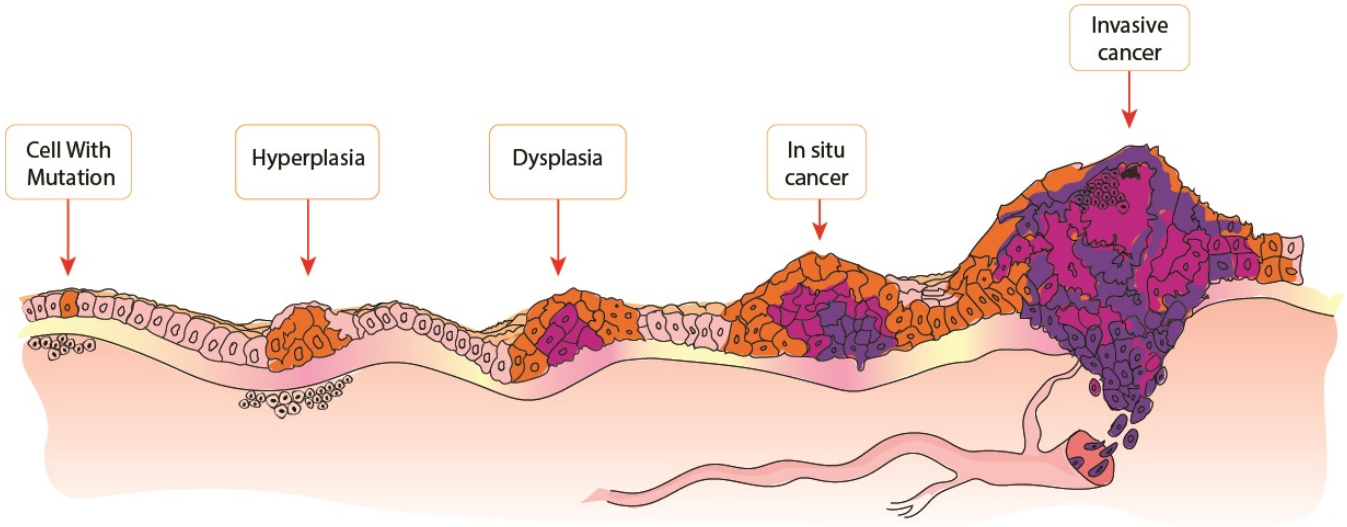

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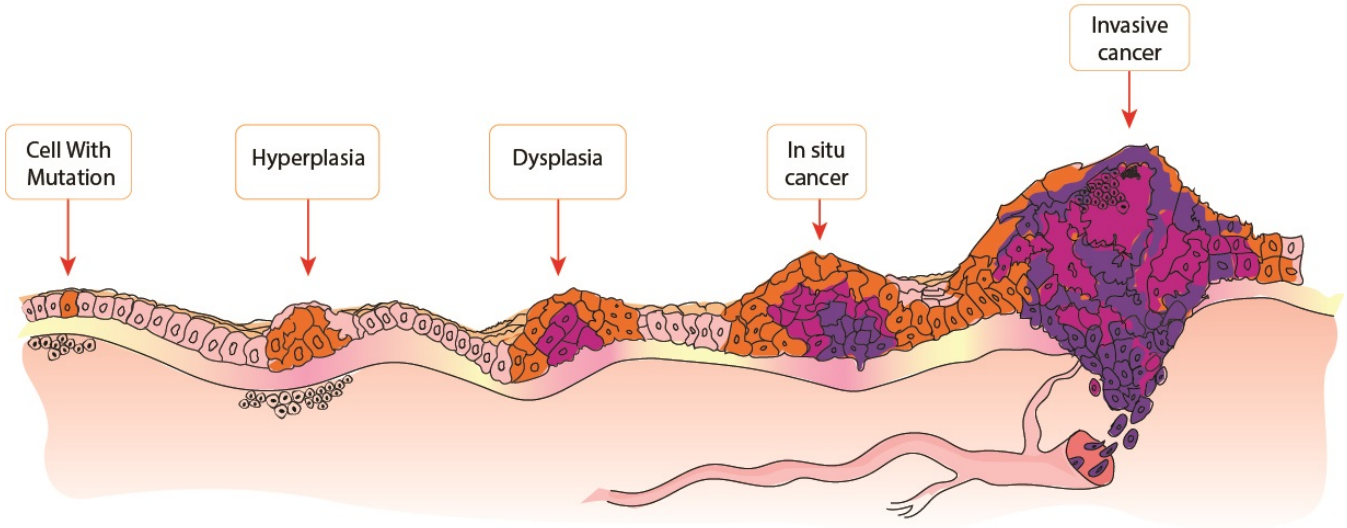

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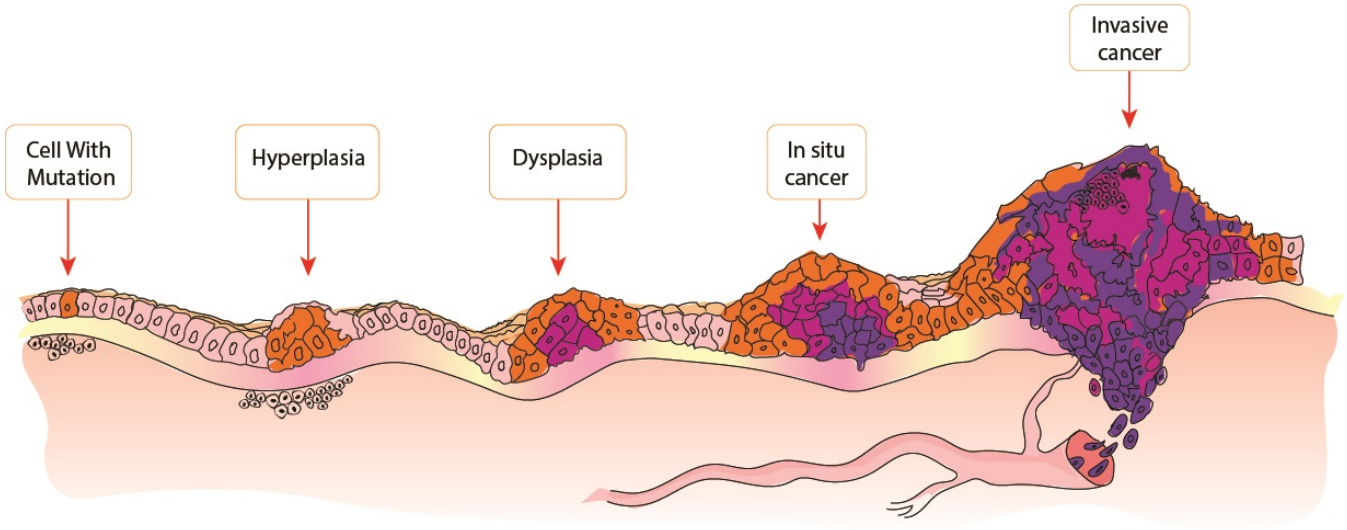

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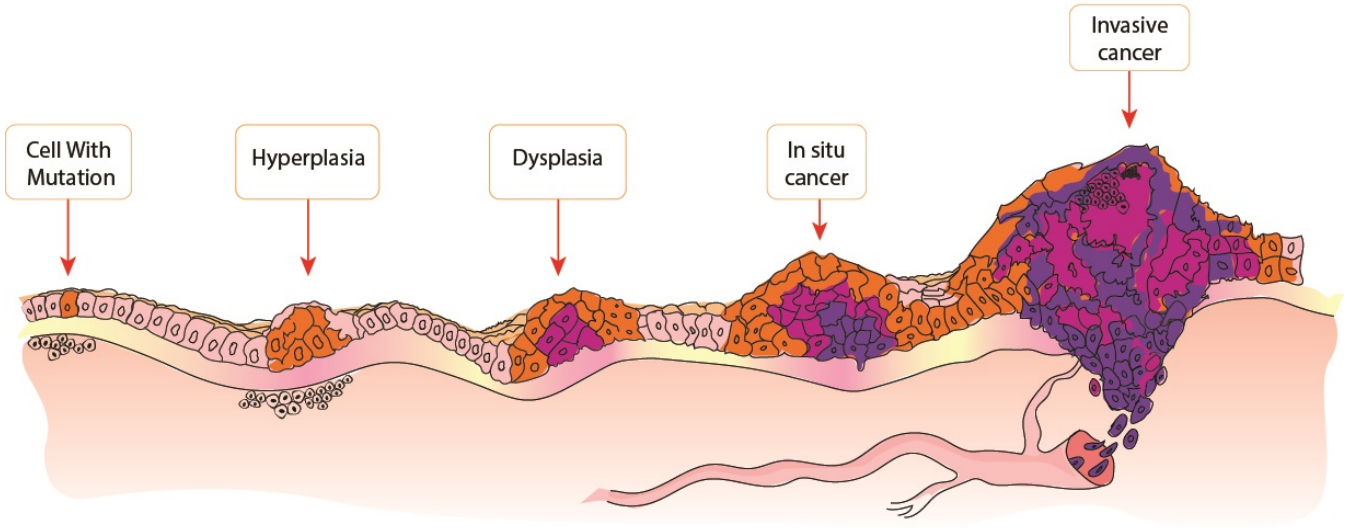

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5. **Metastasis:** Some malignant cells spread through the circulatory or lymphatic systems. They can establish new tumours in secondary locations, known as metastases.

Source: NIH US

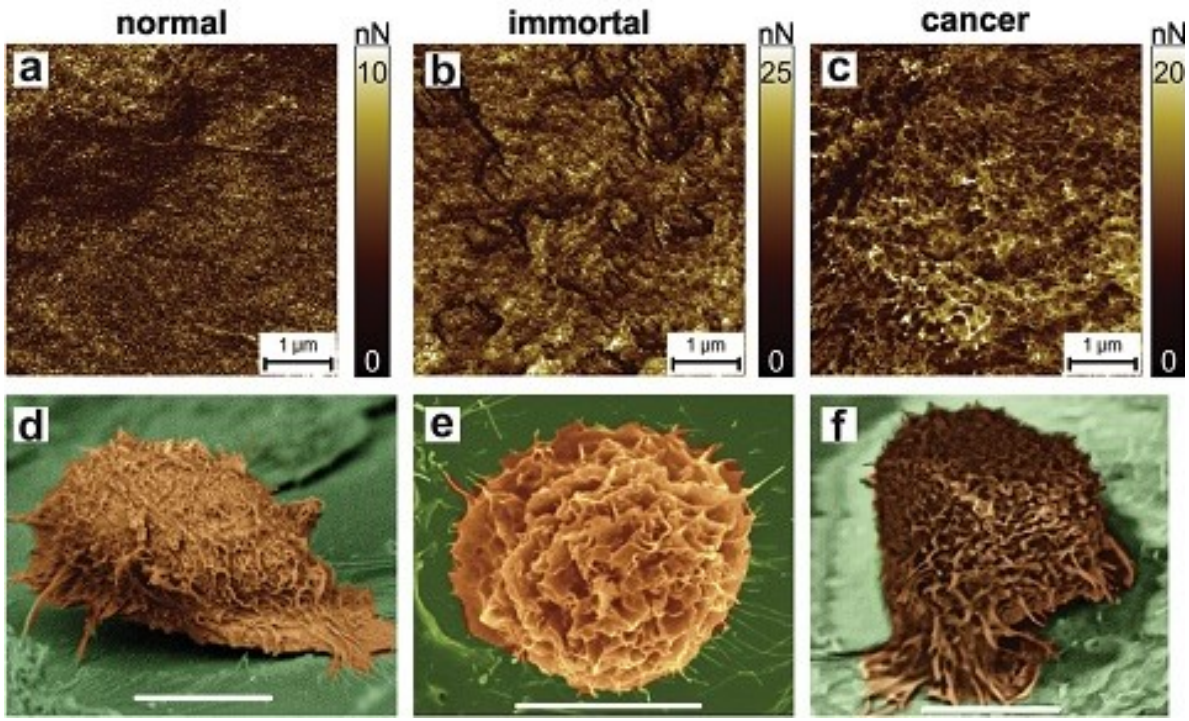
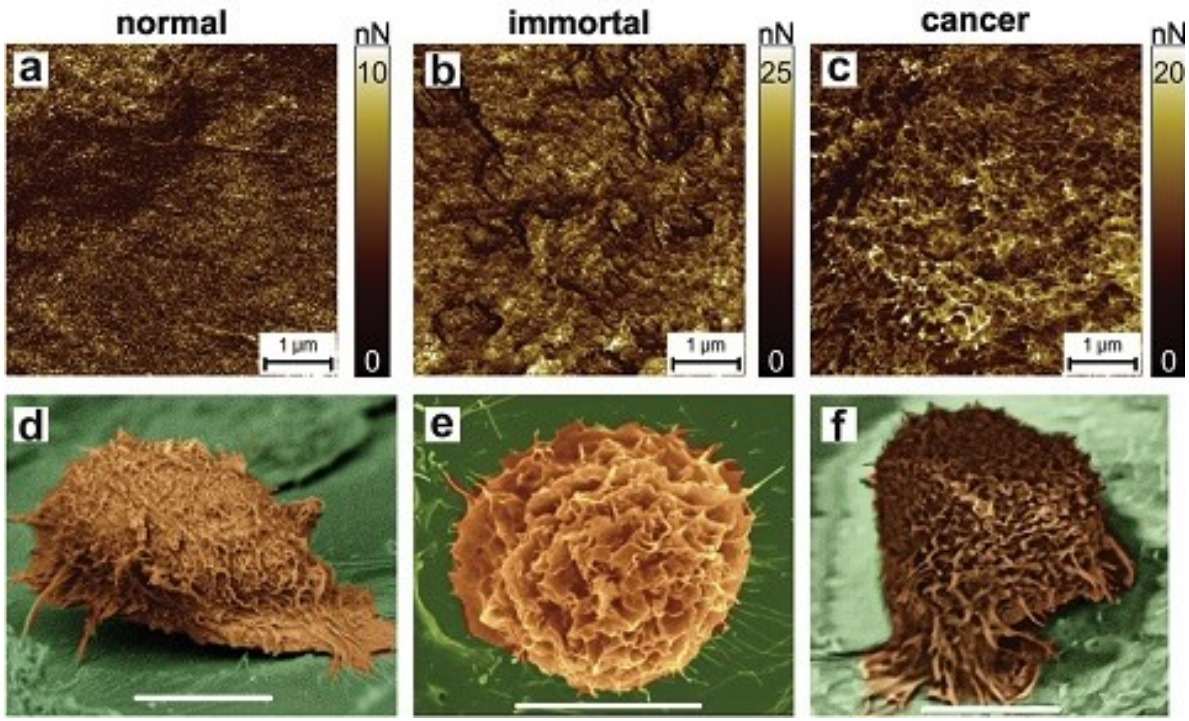


Figure: Normal, premalignant immortal, and cancer cells (second line) and tissue (first line) (Source: Sokolov et al, New Journal of Physics)



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1. **Uncontrolled Proliferation:** Cancer cells proliferate uncontrollably and form tumours, lacking the normal cells' ability to stop dividing at optimal density.
2. **Lack of Self-Repair Ability:** Cancer cells exhibit genomic instability and altered DNA repair mechanisms, contributing to their unregulated growth, rather than a complete lack of self-repair.
3. **Evasion of Apoptosis:** Cancer cells evade programmed cell death (apoptosis), allowing them to survive and proliferate beyond their typical lifespan, which aids in tumor progression and treatment resistance.

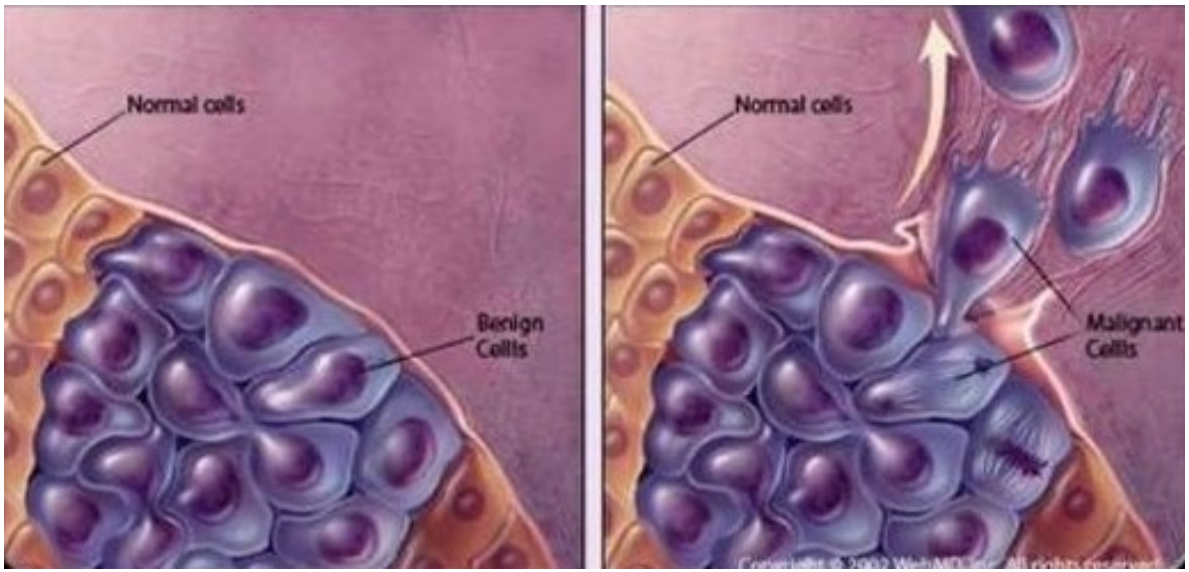
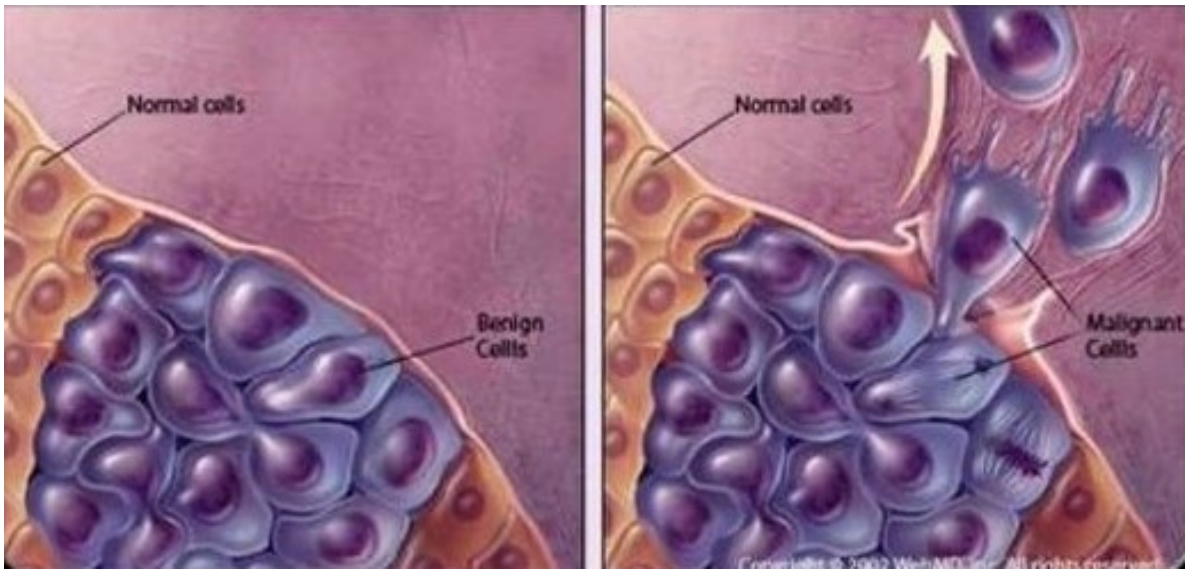


Figure: Differences between *benign* and *malignant* cancer cells (Source: Raj&Kumar 2016)



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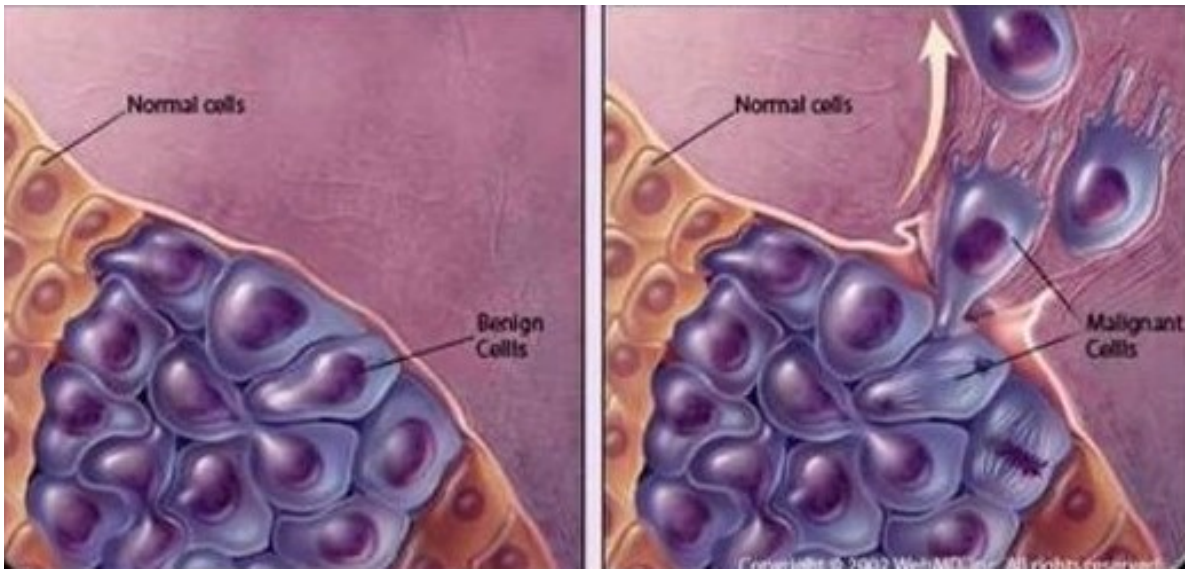

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- *Benign tumours*:
  - do not invade their surrounding tissue or spread around the body;
  - grow slowly and generally respond better to treatment.
- *Malignant tumours*:
  - invade the surrounding tissue and potentially spread around the body through the circulatory or lymphatic system;
  - grow quickly (time scale of weeks) and are (generally) more resilient to treatments.

Section 1: Introduction

Epithelial-to-Mesenchymal Transition (EMT)

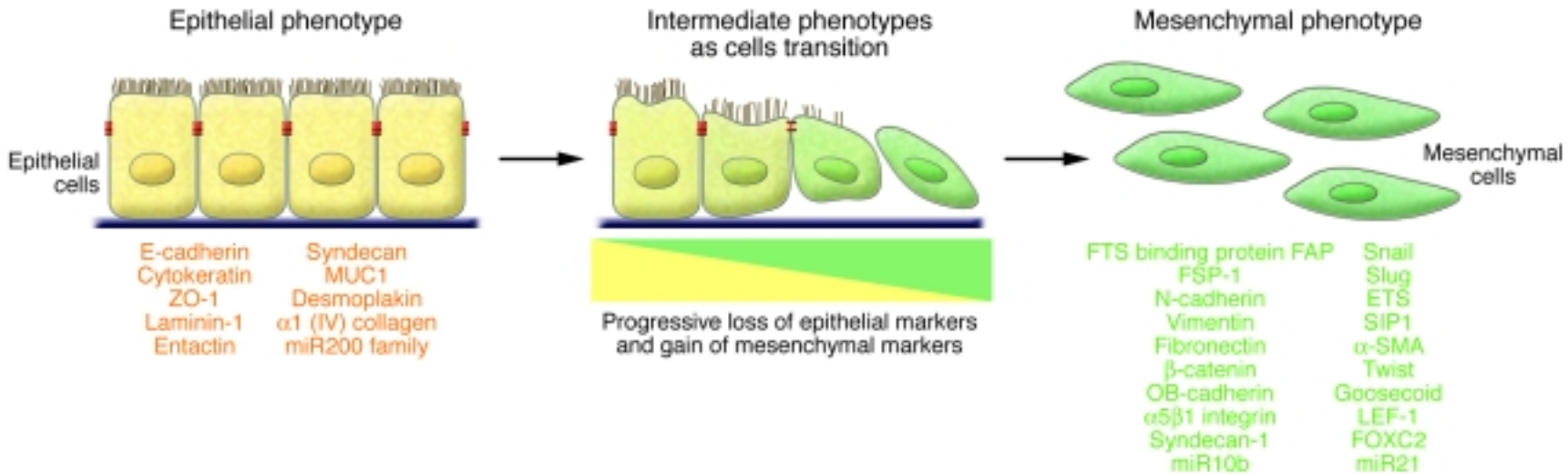

Figure: Schematic representation of the transition from epithelial to mesenchymal phenotype (Source: Kalluri&Weinberg 2009)

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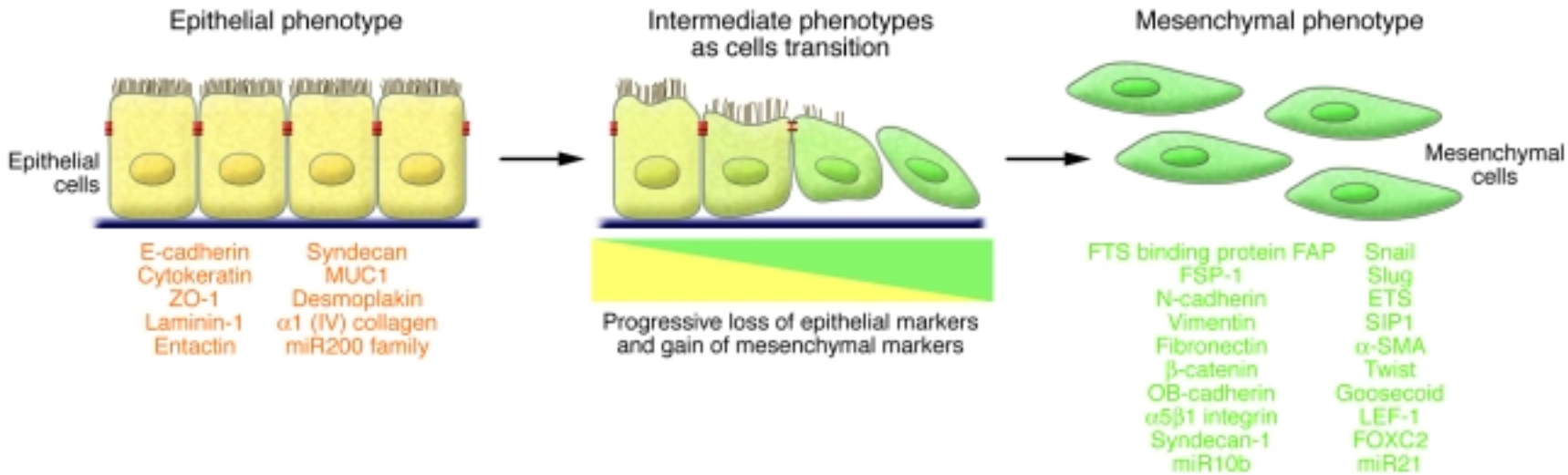

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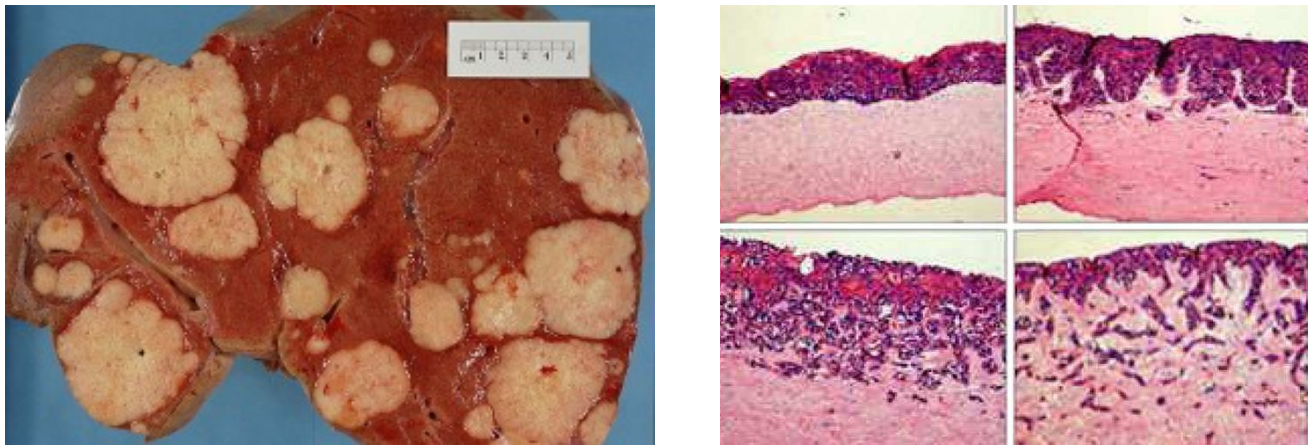
Epithelial-to-Mesenchymal Transition (EMT)

A cell programming process by which *epithelial cells* lose their cell polarity and cell-cell adhesion to gain *mesenchymal traits*, including enhanced migratory and invasive properties. EMT endows the cells with the ability to move more freely and invade other tissues.

EMT in Cancer: Progression to Malignancy

EMT enables cancer cells to detach from the primary tumor, invade surrounding tissues, and contribute to the formation of metastases at distant sites. EMT is associated with increased resistance to chemotherapy and the development of a more aggressive tumor phenotype.



(a) (b)

Figure: (a): Human liver adenocarcinoma; emergence and growth of various tumour "islands" (Source: Haymanj/Wikimedia Commons). (b): *In vitro* invasion of healthy tissue (pink) by cancer cells (dark red) (Source: Andasari et al. 2014)

After EMT, cancer cells:

- **Break Cell-Cell Adhesions:** The process disrupts tight cell junctions, allowing cancer cells to detach from the primary tumor mass. This detachment is crucial for subsequent migration and invasion.
- **Increase Motility and Invasion:** By acquiring mesenchymal traits, cancer cells enhance their ability to move and invade. They can degrade and remodel the extracellular matrix (ECM).
- **Interact with the Tumor Microenvironment:** EMT is influenced by the tumor microenvironment. Growth factors, cytokines, and ECM components promote EMT in cancer cells, indicating a complex interplay that supports their invasive capabilities.

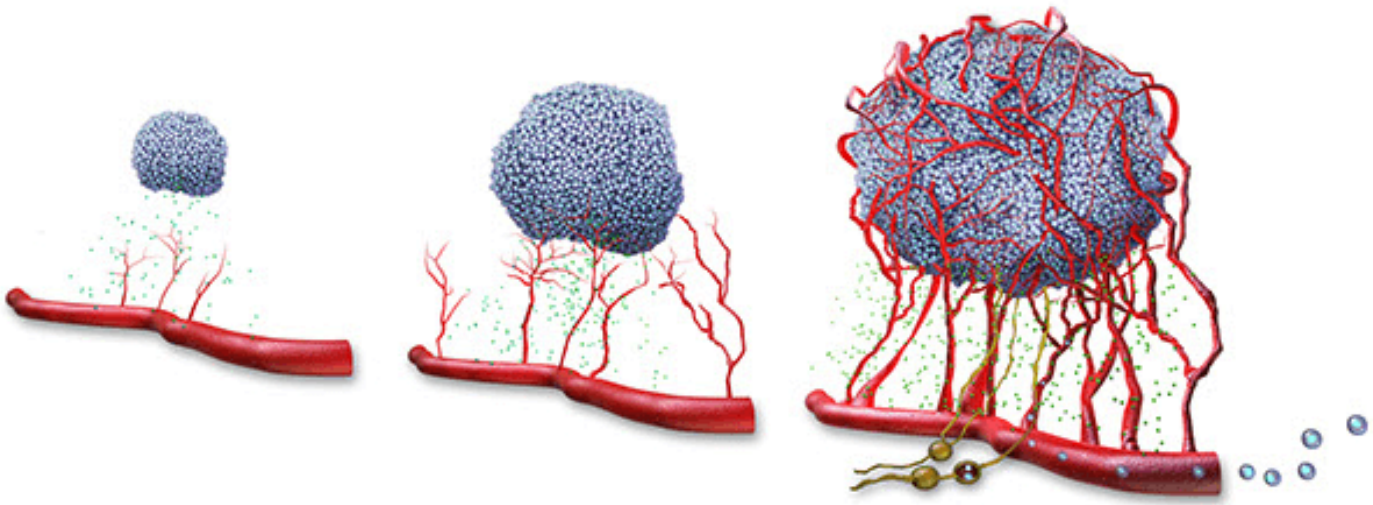


Figure: Graphical depiction of the gradual formation of blood vessels in the vicinity of a tumour as a response to the growth factors (small green dots) secreted by the cancer cells (Source: Creative BioArray)

- Tumours promote the formation of new blood vessels (*angiogenesis*) in their vicinity by secreting specialized proteins, known as *tumor angiogenic factors* (TAFs). These new blood vessels supply the tumor with essential oxygen and nutrients and facilitate the migration of cancer cells from the primary tumor site. Cancer cells utilize these vessels to enter the bloodstream and metastasize to new locations within the organism.

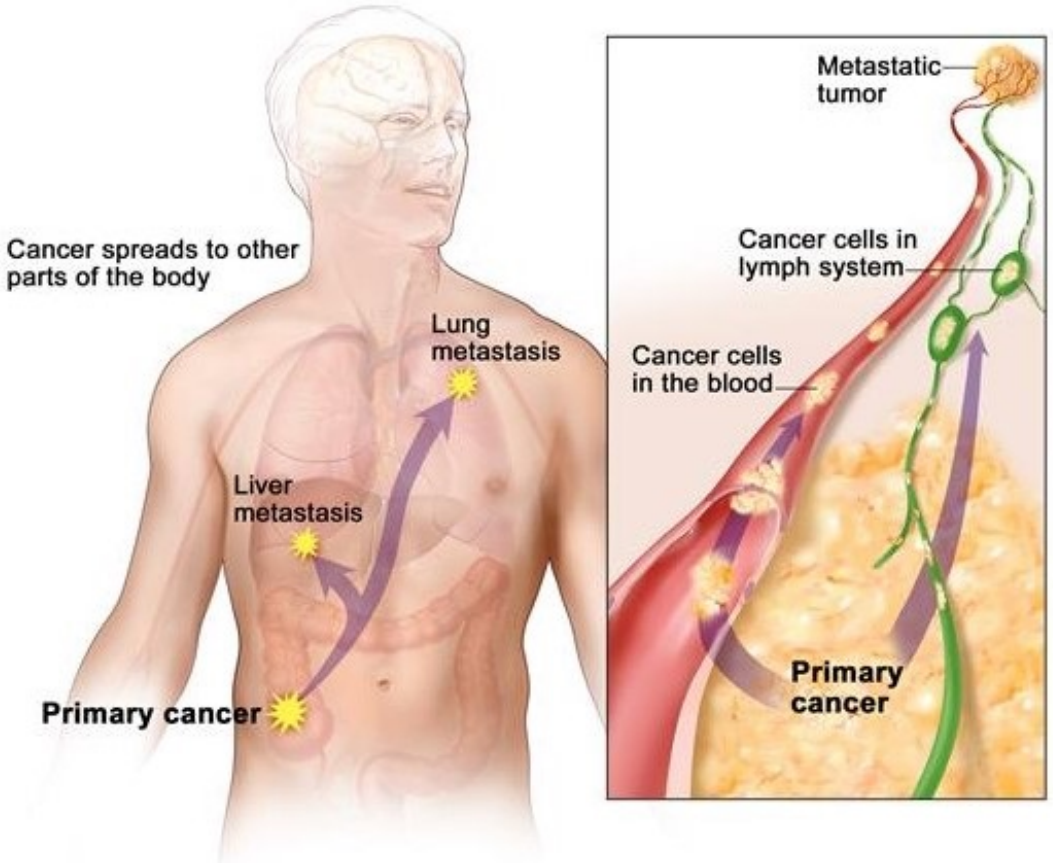


Figure: Large scale schematic description. (Source: Terese Winslow LLC)

- After *intravasation*, the cancer cells must survive the hostile environment of the bloodstream. If they manage to do so, they can *extravasate* at a new site within the organism. Here, they may potentially establish new cancer cell colonies, completing the process of *metastatic spread* by forming secondary tumors through complex interactions with the new tissue microenvironment.

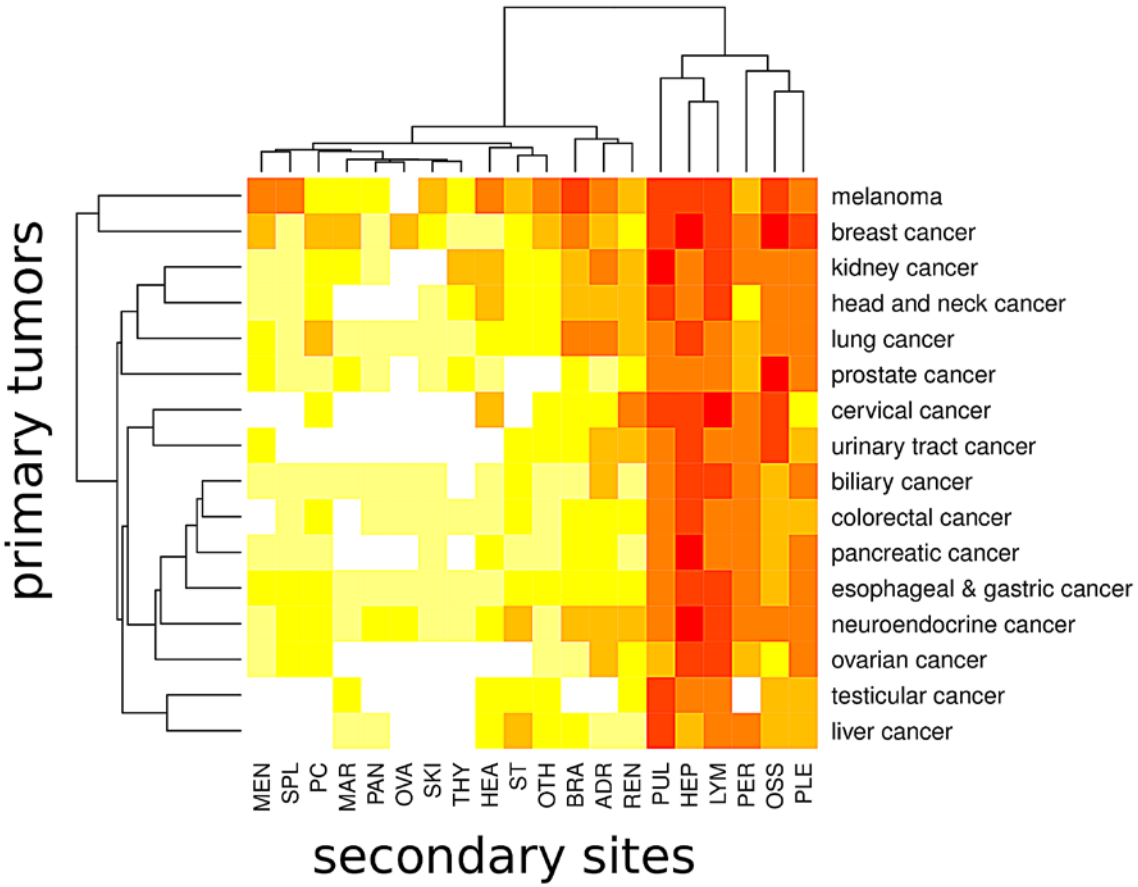


Figure: Metastatic pattern of 16 major cancer types on 1008 patients. (Source: Budczies et al, Oncotarget 2015)

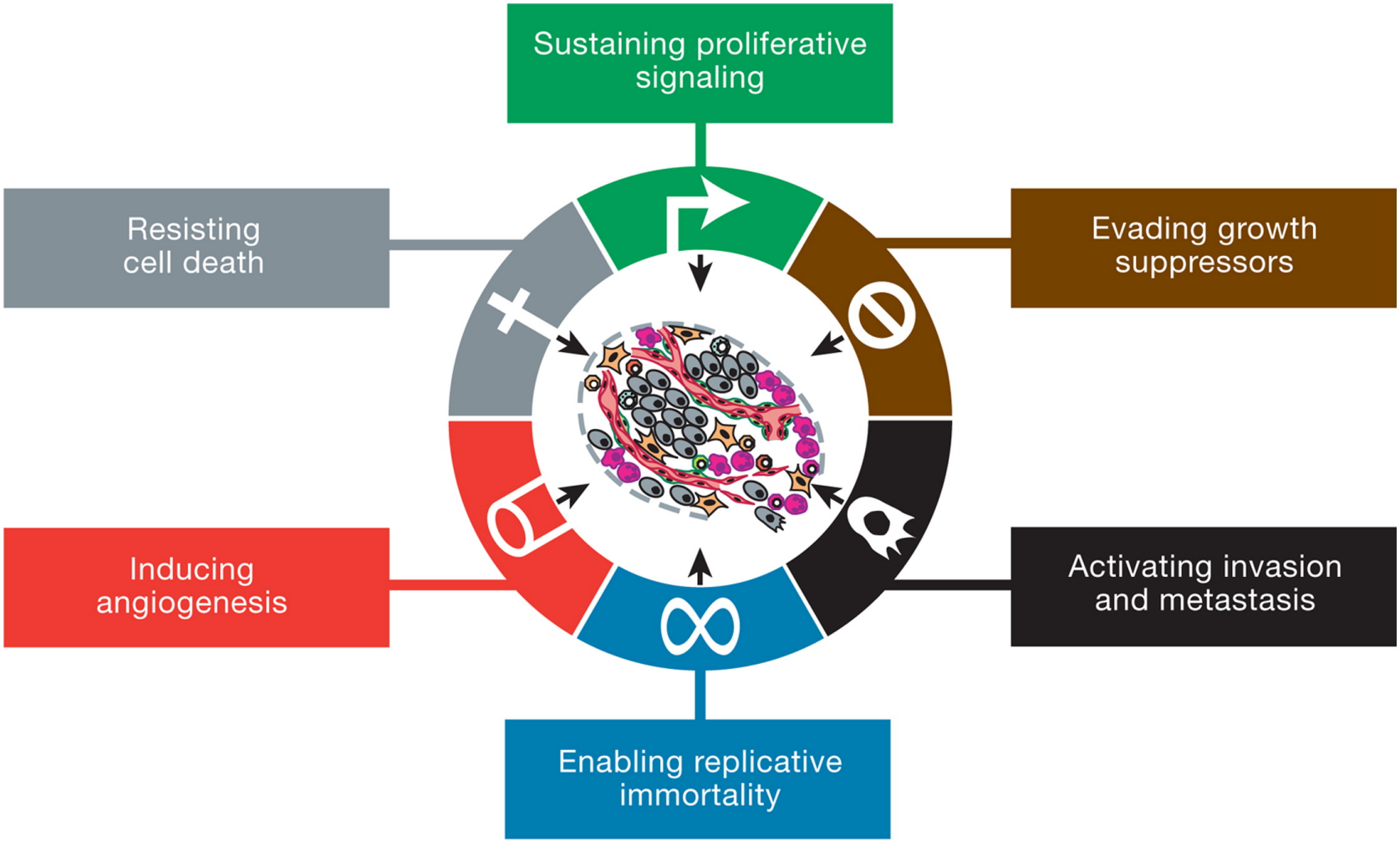


Figure: Capabilities acquired by most, if not all, tumours. (Source: Hanahan&Weinberg 2000)

Section 2

Tumour Spheroid Models, Growth Curves, & Necrotic cores

Section 2.1: Tumour Spheroid models

Sigmoid growth curves

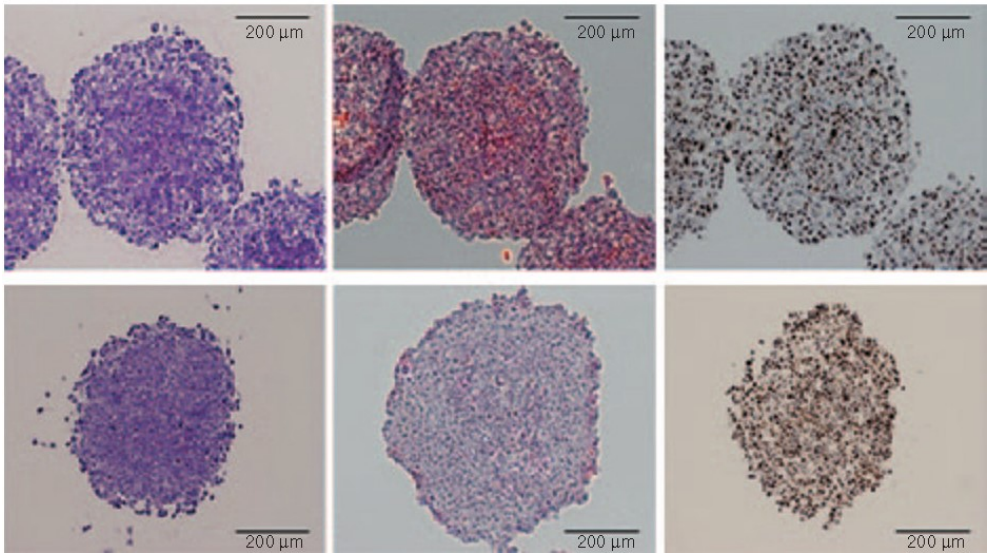


Figure: Examples of various multicellular tumour spheroids. (Source: Carver et al 2014)

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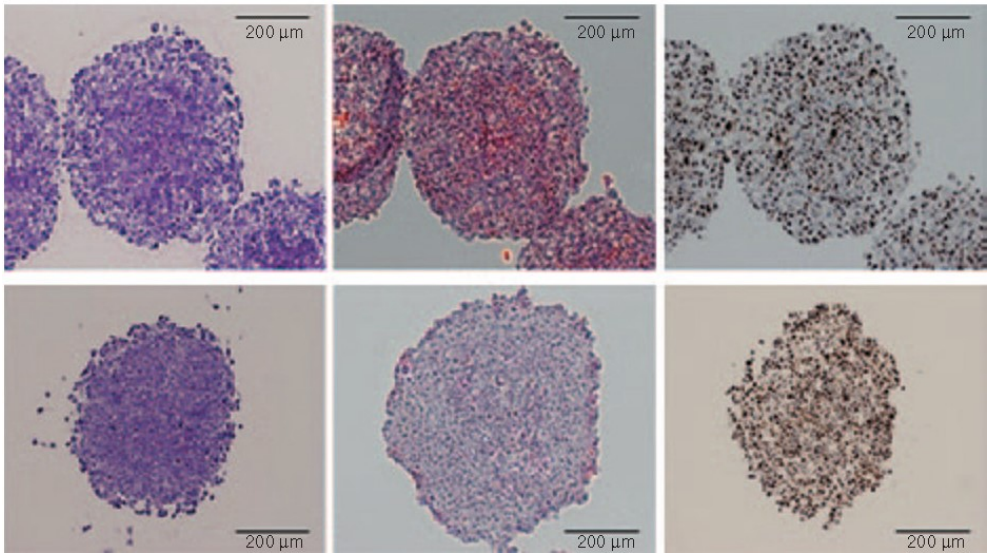

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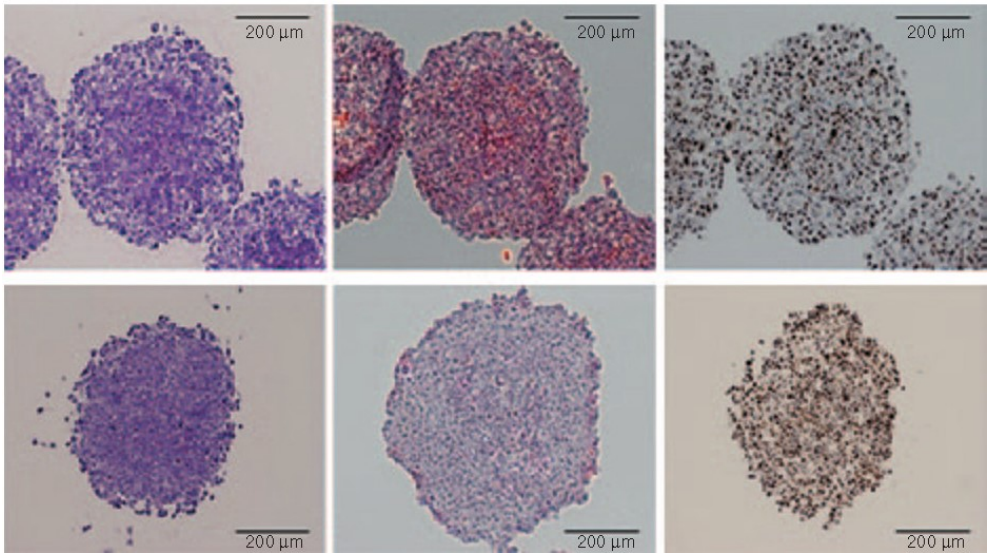

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Spheroids? Really?

In early *avascular* stages, the tumour grows as a *spheroid*, and its growth curve is a *sigmoid* (A.K. Laird 1964).

Section 2.1: Tumour Spheroid models

Sigmoid growth curves

(generalised) *von Bertalanffy* equation

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Let $N(t)$ be the size/volume/mass of the tumour:

$$\frac{dN}{dt} = \alpha N^{\lambda} - \beta N^{\mu}, \tag{1}$$

for $\alpha, \beta, \lambda,\ \mu > 0$, and $\mu > \lambda$.
Here N^{λ} represents "cell proliferation" and N^{μ} represents "cell death". For $N(0) > 0$, it holds $N(t) \overset{t\to\infty}{\longrightarrow} K = \left(\frac{\alpha}{\beta}\right)^{\frac{1}{\mu-\lambda}}$ (why?)

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Logistic equation

The von Bertalanffy (1) reads for $\lambda = 1$, $\mu = 2$, $\alpha = r$, $\beta = \frac{r}{K}$ as

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right), \tag{2}$$

for $r,\ K > 0$.
Q: What processes does this model describe?
Note: If $0 < N(0) < K$ then $N(t) \overset{t\to\infty}{\longrightarrow} K$ (why?).

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Of course, it also holds $N(t) \overset{t\to\infty}{\longrightarrow} K$ when $N(0) > K$.

Section 2.1: Tumour Spheroid models

Sigmoid growth curves

Surface-to-Volume ratio

Some biological structures “tend” to decrease the ratio

$$\text{SA:V} = \frac{\text{Surface Area}}{\text{Volume}}$$

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Surface-to-Volume ratio for spheres

A 3D sphere of radious $r > 0$ has volume $V = \frac{4}{3}\pi r^3$ and surface area $A = 4\pi r^2$, i.e.

$$A \propto V^{2/3}$$

A: The uptake of nutrients/resources/energy, modelled by $N^{2/3}$ is through the surface and their consumption through the bulk of the tumour, represented by N.

Gompertz equation

The von Bertalanffy equation (1) $\left(\frac{dN}{dt} = \alpha N^{\lambda} - \beta N^{\mu}\right)$ reads for $\mu = 1$ (decay proportional to volume/mass), as

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Remark: We have yet to understand why this "entropy"-like model has been so successful, i.e. we do not understand the biological "analogue" behind the $\lambda \to 1^{-}$ limit.

Section 2.2: Tumour Spheroid models

Necrotic core & the diffusion-limited nutrient stage

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Necrotic core & the diffusion-limited nutrient stage

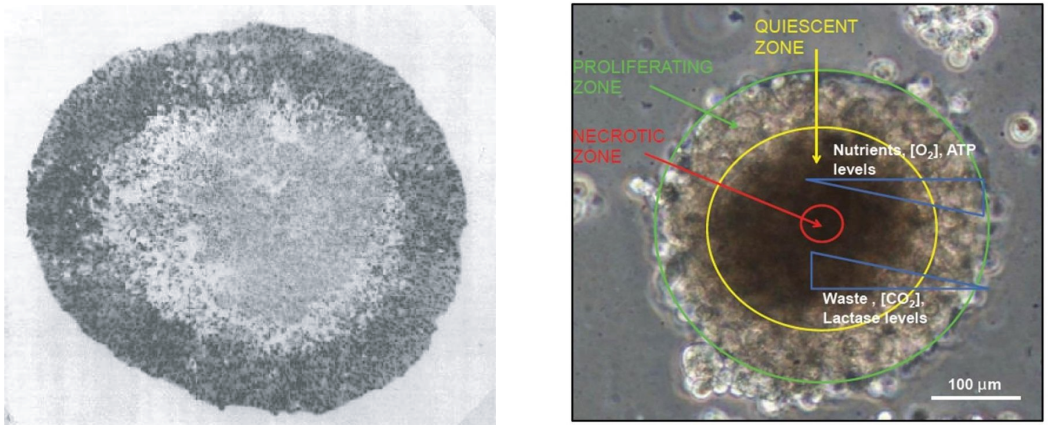

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Figure: (a) Typical tumour spheroid; the grey interior is comprised of dead cancer cells the necrotic core while the dark outer region are the living cancer cells (Source: Sutherland et al 1986). (b) A more "realistic" identification of tumour spheroid zones: necrotic, quiescent, proliferating (Source: Chandrasekaran & King 2017)

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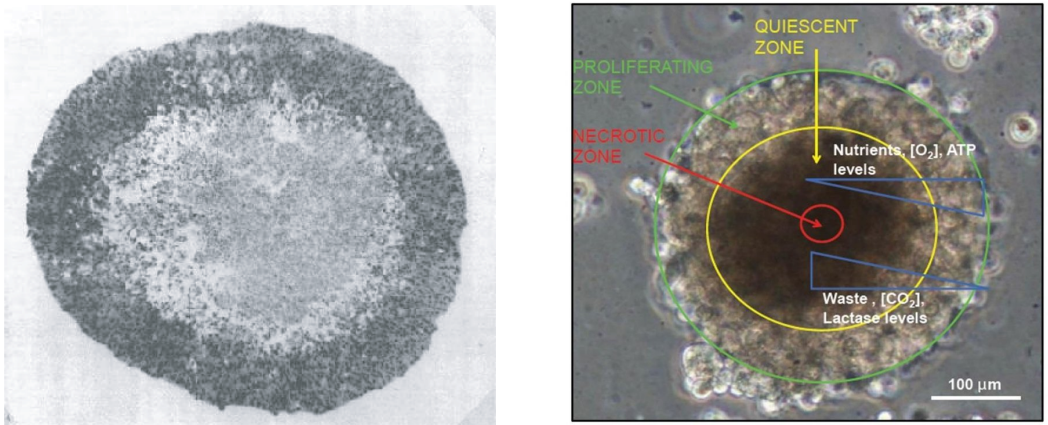

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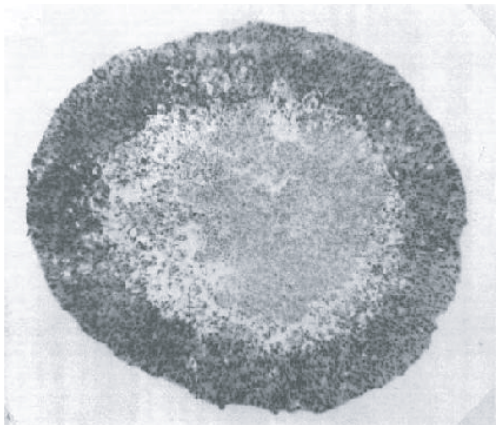

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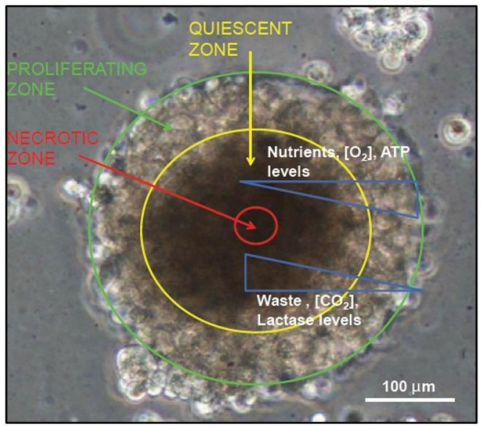

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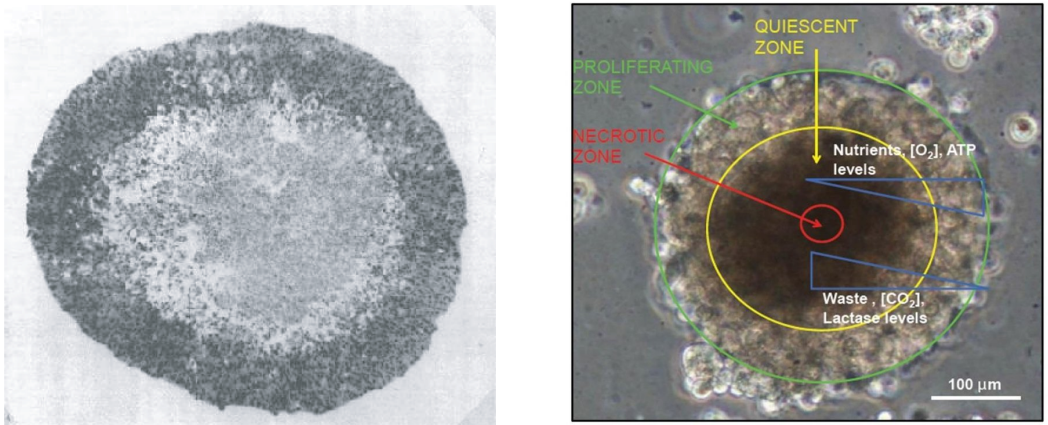

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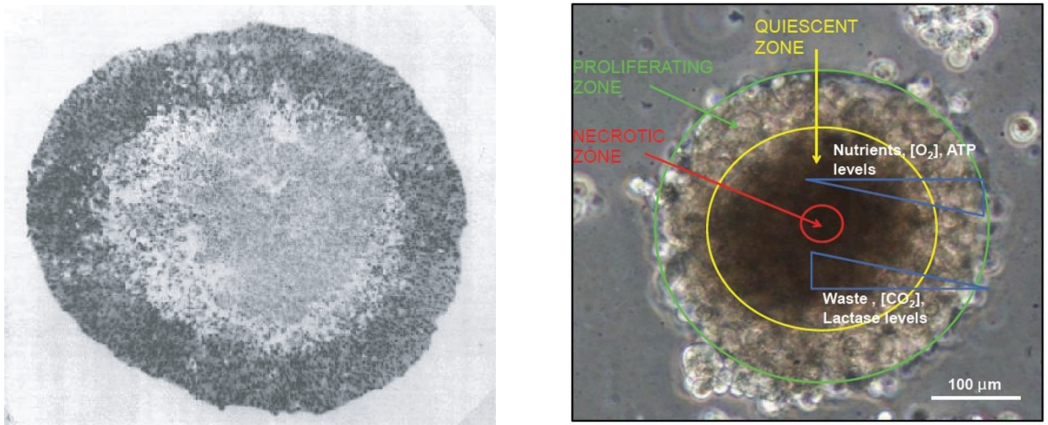

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- As the tumour grows, the nutrients can no longer reach the innermost cancer cells, which die resulting in a *necrotic core*.
- The tumour might grow larger still, **the thickness of the living-cancer-cells layer remains the same**. The tumour reaches a *diffusion-limited state*.

Section 2.2: Tumour Spheroid models

Necrotic core model & Free Boundary Problems

From a mathematical modelling point of view

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- $c(r)$: concentration of the resource (e.g. oxygen) at distance r, D its diffusion, and k the (constant) uptake of the nutrient by the live cancer tissue (not the necrotic).

From a mathematical modelling point of view

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since, in spherical coordinates $(x, y, z) = (r\cos\theta\sin\phi, r\sin\theta\sin\phi, r\cos\phi) \in \mathbb{R}^3$, it holds

$$\Delta = \partial_r^2 + \frac{2}{r}\partial_r + \frac{1}{r^2}\left(\partial_\phi^2 + \cot\phi\partial_\phi\right) + \frac{1}{r^2\sin^2\phi}\partial_\theta^2$$

and since the spherical symmetry enforces $\partial_\phi c = \partial_\theta c = 0$.

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The interface $r = r_{\text{nec}}$ (between the necrotic core and proliferative layer) is *unknown*; it is given by the density $c = c_{\text{thr}}$ of the nutrient below which cells die.

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Mathematical objective:

Identify r_{nec}, i.e. solve the *Free Boundary Problem* (5).

Section 2.2: Tumour Spheroid models

Necrotic core model; a first look into *Free Boundary Problems*

Case 1: No necrotic core: $r_{\text{nec}} = 0$

Solve the Free Boundary Problem without necrotic core: (i.e. say something about r_{nec} and r_{tum})

$$0 = \begin{cases} \cancel{D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right)}, & 0 \le r < \cancel{r_{\text{nec}}} \, 0 \\ D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) - k, & \cancel{r_{\text{nec}}} \, 0 \le r \le r_{\text{tum}} \end{cases}$$

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The BCs over $[0, r_{\text{tum}}]$ read

$$\left.\frac{dc}{dr}\right|_{r=0} = 0, \quad c(r_{\text{tum}}) = c_{\text{env}}.$$

Note that $J = -D\frac{dc}{dr}$ represents the flux.

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Note that $J = -D\frac{dc}{dr}$ represents the flux. The above (one branch) equation reads after some manipulation (multiply by r^2, integrate, divide by r^2, integrate, employ BCs) as

$$c(r) = -\frac{1}{6}\frac{k}{D}\left(r_{\text{tum}}^2 - r^2\right) + c_{\text{env}}, \qquad r \in [0, r_{\text{tum}}] \tag{6}$$

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Q: What does the naturally imposed constraint $c(0) \ge 0$ implies?

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i.e. *a non-necrotic core living tumour has a finite maximum size*

Case 2: The necrotic core "solution": $r_{\text{nec}} > 0$

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The BCs over the living part of the tumour $[r_{\text{nec}}, r_{\text{tum}}]$ are

$$c(r_{\text{nec}}) = c_{\text{thr}},\ J(r_{\text{nec}}) = 0,\ c(r_{\text{tum}}) = c_{\text{env}}$$

where J is the flux of the nutrient

$$J = -D\frac{dc}{dr}.$$

By integration of the second branch $D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) - k$ we obtain (do the calculation)

$$c(r) = \frac{1}{6}\frac{k}{D}r^2 + \frac{A}{r} + B;$$

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employing the BCs $\left(c(r_{\text{nec}}) = c_{\text{thr}},\ J(r_{\text{nec}}) = 0,\ c(r_{\text{tum}}) = c_{\text{env}}\right)$ we further get

$$c_{\text{env}} = \frac{1}{6}\frac{k}{D}r_{\text{tum}}^2 + \frac{A}{r_{\text{tum}}} + B, \quad c_{\text{thr}} = \frac{1}{6}\frac{k}{D}r_{\text{nec}}^2 + \frac{A}{r_{\text{nec}}} + B, \quad 0 = \frac{1}{3}\frac{k}{D}r_{\text{nec}} - \frac{A}{r_{\text{nec}}^2}$$

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which yield (do it!)

$$c_{\text{env}} - c_{\text{thr}} = \frac{1}{6}\frac{k}{D}\left(1 + 2\frac{r_{\text{nec}}}{r_{\text{tum}}}\right)(r_{\text{tum}} - r_{\text{nec}})^2$$

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What did we learn from that ?

By integration of the second branch $D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) - k$ we obtain (do the calculation)

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As the tumour grows large, e.g. $r_{\text{tum}} \to \infty$, it holds:

- $\frac{r_{\text{nec}}}{r_{\text{tum}}} \overset{r_{\text{tum}}\to\infty}{\longrightarrow} 1$ (divide by r_{tum}^2 and calculate the limit)

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- $\dfrac{r_{\text{nec}}}{r_{\text{tum}}} \overset{r_{\text{tum}}\to\infty}{\longrightarrow} 1$ (divide by r_{tum}^2 and calculate the limit)
- Moreover, $r_{\text{tum}} - r_{\text{nec}} \overset{r_{\text{tum}}\to\infty}{\longrightarrow} \sqrt{2\dfrac{D}{k}(c_{\text{env}} - c_{\text{thr}})}$ (calculate the limit!)

By integration of the second branch $D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) - k$ we obtain (do the calculation)

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employing the BCs $\left(c(r_{\text{nec}}) = c_{\text{thr}},\ J(r_{\text{nec}}) = 0,\ c(r_{\text{tum}}) = c_{\text{env}}\right)$ we further get

$$c_{\text{env}} = \frac{1}{6}\frac{k}{D}r_{\text{tum}}^2 + \frac{A}{r_{\text{tum}}} + B, \quad c_{\text{thr}} = \frac{1}{6}\frac{k}{D}r_{\text{nec}}^2 + \frac{A}{r_{\text{nec}}} + B, \quad 0 = \frac{1}{3}\frac{k}{D}r_{\text{nec}} - \frac{A}{r_{\text{nec}}^2}$$

which yield (do it!)

$$c_{\text{env}} - c_{\text{thr}} = \frac{1}{6}\frac{k}{D}\left(1 + 2\frac{r_{\text{nec}}}{r_{\text{tum}}}\right)(r_{\text{tum}} - r_{\text{nec}})^2$$

What did we learn from that ?

As the tumour grows large, e.g. $r_{\text{tum}} \to \infty$, it holds:

- $\dfrac{r_{\text{nec}}}{r_{\text{tum}}} \overset{r_{\text{tum}}\to\infty}{\longrightarrow} 1$ (divide by r_{tum}^2 and calculate the limit)
- Moreover, $r_{\text{tum}} - r_{\text{nec}} \overset{r_{\text{tum}}\to\infty}{\longrightarrow} \sqrt{2\dfrac{D}{k}(c_{\text{env}} - c_{\text{thr}})}$ (calculate the limit!)
  i.e. **the thickness of the proliferating cancer cells ring remains constant.**

Section 2.3: Tumour Spheroid models

Angiogenesis and Angiogenesis Inhibition model

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Angiogenesis and Angiogenesis Inhibition model

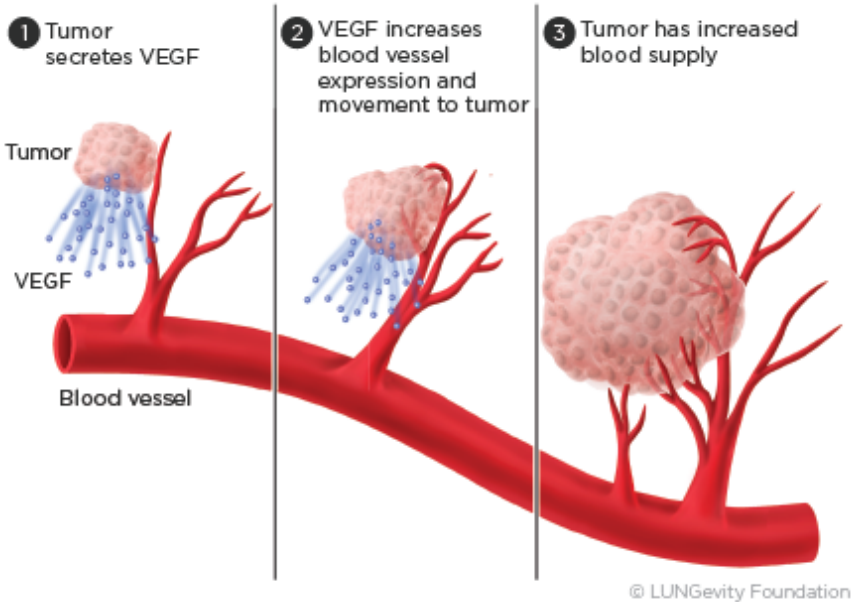

Figure: Graphical depiction of tumour induced angiogenesis. Vascular Endothelial Growth Factors (VEGF) are secreted by the cancer cells and, in turn, assit /provoke the formation of new blood vessel branches. (Source: LUNGevity Foundation)

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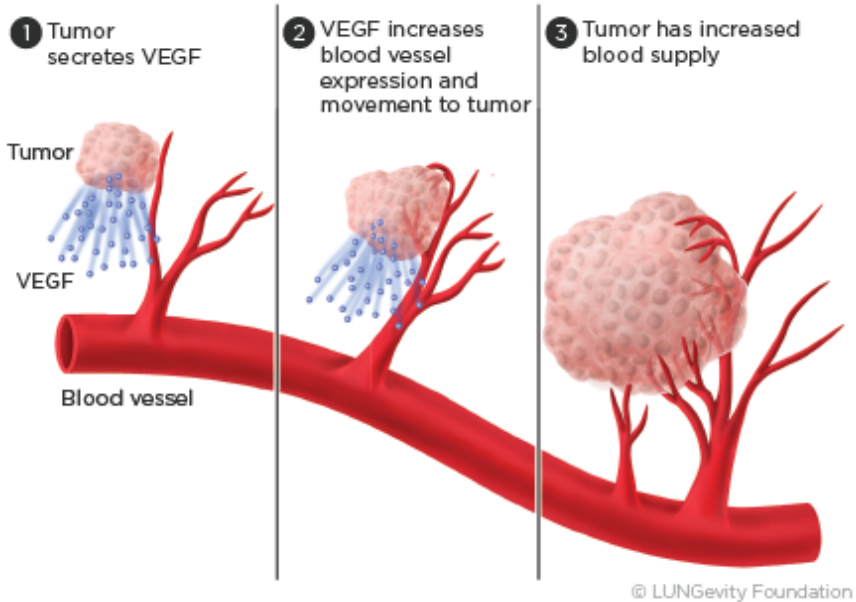

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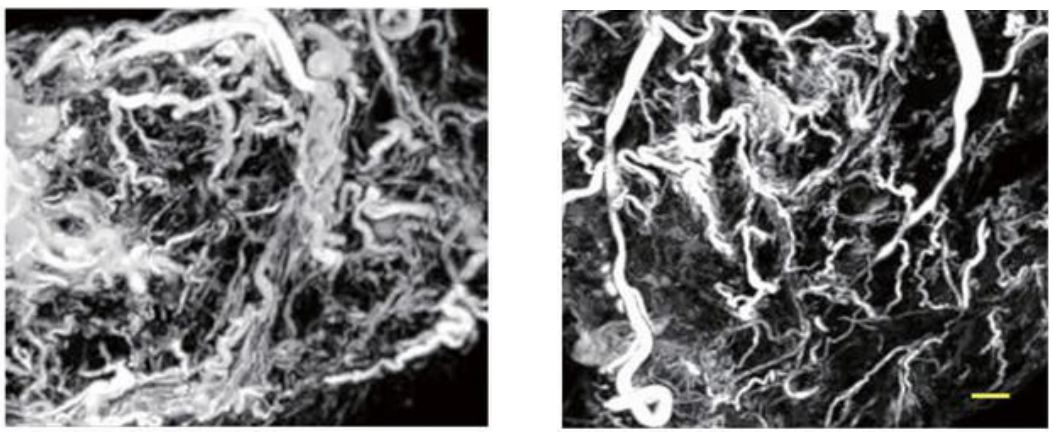
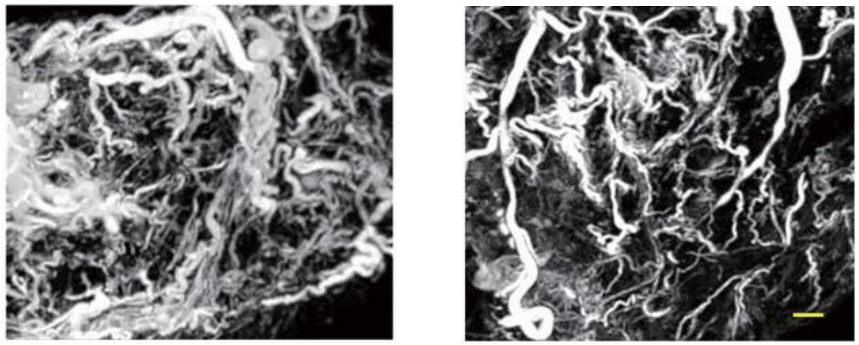


Figure: Tumour microvessels *in vitro*; (left) untreated/control group; (right): anti-angiogenics (drugs that block vascular growth factors) treated group



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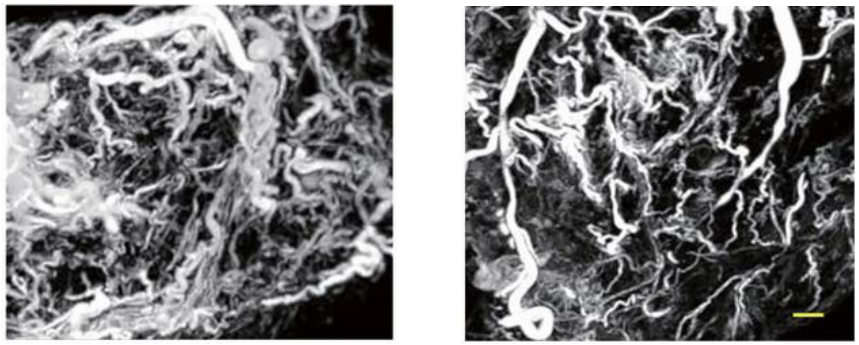

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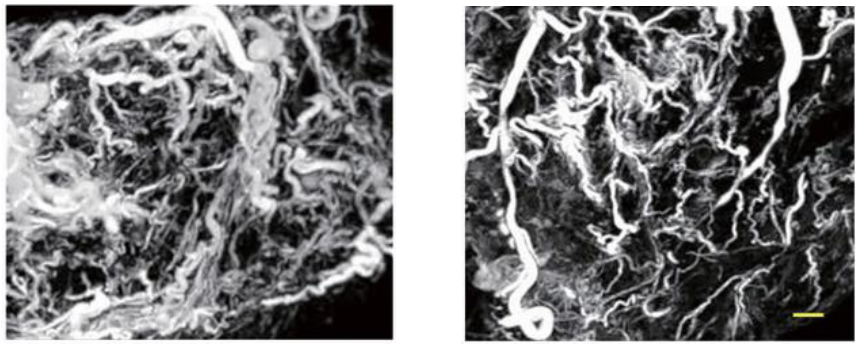
$$\begin{cases} \dfrac{dN}{dt} = aN\left(1 - \dfrac{N}{K}\right) \\ \\ \end{cases}$$

$N(t)$: mass/volume cancer cell population $K(t)$: carrying capacity
(resources provided by vasculature)



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$$\begin{cases} \dfrac{dN}{dt} = aN\left(1 - \dfrac{N}{K}\right) \\ \dfrac{dK}{dt} = \omega N - \gamma N^{2/3} K \end{cases}$$

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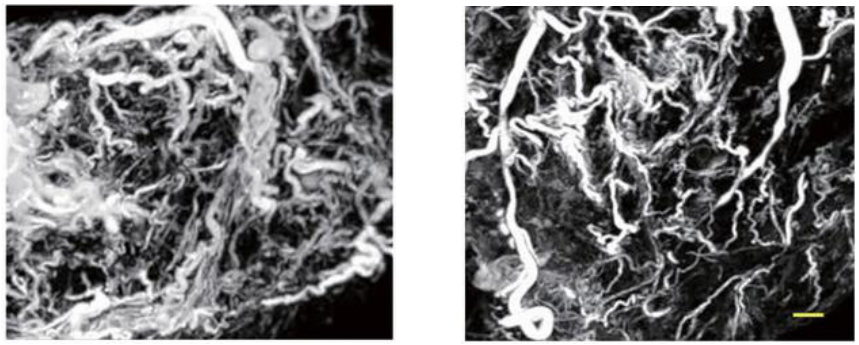
ωN: stimulation of angiogenesis

$\gamma N^{2/3} K$: tumour uptake of resources



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$$\begin{cases} \dfrac{dN}{dt} = aN\left(1 - \dfrac{N}{K}\right) \\ \dfrac{dK}{dt} = \omega N - \gamma N^{2/3} K - \alpha c(t) K \end{cases}$$

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$\alpha K c(t)$: vasculature decay due to treatment $c(t)$

- Without treatment, $c \equiv 0$, we obtain one non-trivial steady state (SS) calculated from $\frac{dN}{dt} = \frac{dK}{dt} = 0$:

$$\left(\tilde{N}, \tilde{K}\right) = \left(\left(\frac{\omega}{\gamma}\right)^{3/2}, \left(\frac{\omega}{\gamma}\right)^{3/2}\right)$$

To characterise the steady state, we study the corresponding Jacobian matrix (cf. Appendix Linear Stability Analysis)

$$\tilde{J} = J\left(\tilde{N}, \tilde{K}\right) = \begin{pmatrix} -\alpha & \alpha \\ \frac{1}{3}\omega & -\omega \end{pmatrix},$$

for which we see that

$$\det \tilde{J} = \frac{2}{3}\alpha\,\omega > 0, \qquad tr\,\tilde{J} = -\alpha - \omega < 0,$$

This means that the SS $\left(\tilde{N}, \tilde{K}\right)$ is asymptotically stable—either in an oscillatory fashion or not depending on the sign of the discriminant $\Delta = \left(tr\,\tilde{J}\right)^2 - 4\det J$.

- With treatment, $c \not\equiv 0$, the non trivial steady state satisfies from

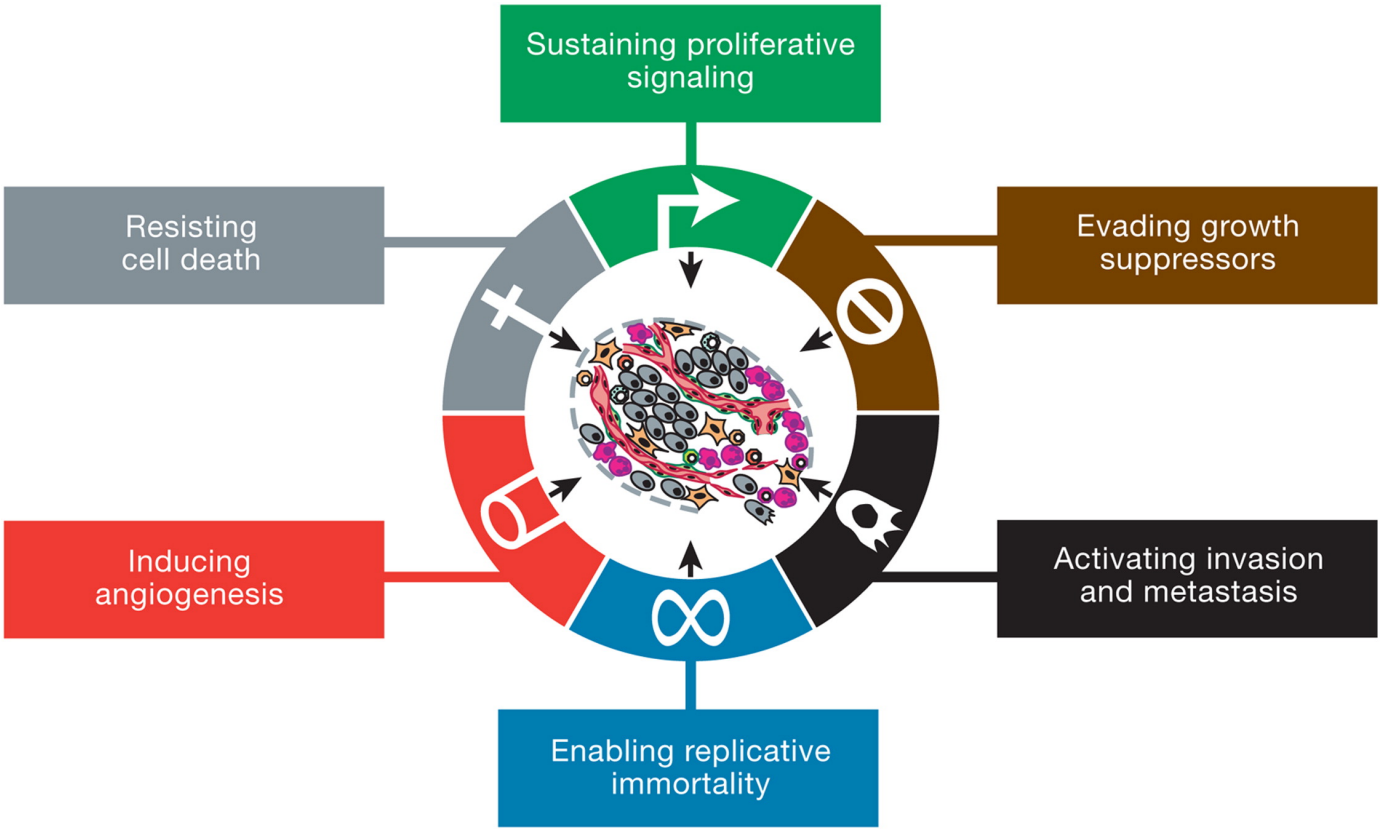
$$\begin{cases} \tilde{N} = \tilde{K} \\ \omega \tilde{K} - \gamma \tilde{K}^{5/3} - \alpha c(t) \tilde{K} = 0 \end{cases}$$

Assuming that $K \neq 0$ we see that

$$\tilde{K}^{2/3} = \frac{\omega - \alpha c(t)}{\gamma}$$

which clearly indicates that the (asymptotic) size of the tumour $\tilde{N}$ decreases with the administration of the drug (cf. with the previous no-treatment case)

Section 3: Immune Response & Cancer



Hallmarks of Cancer by Hanahan and Weinberg

Section 3.1: Immune response

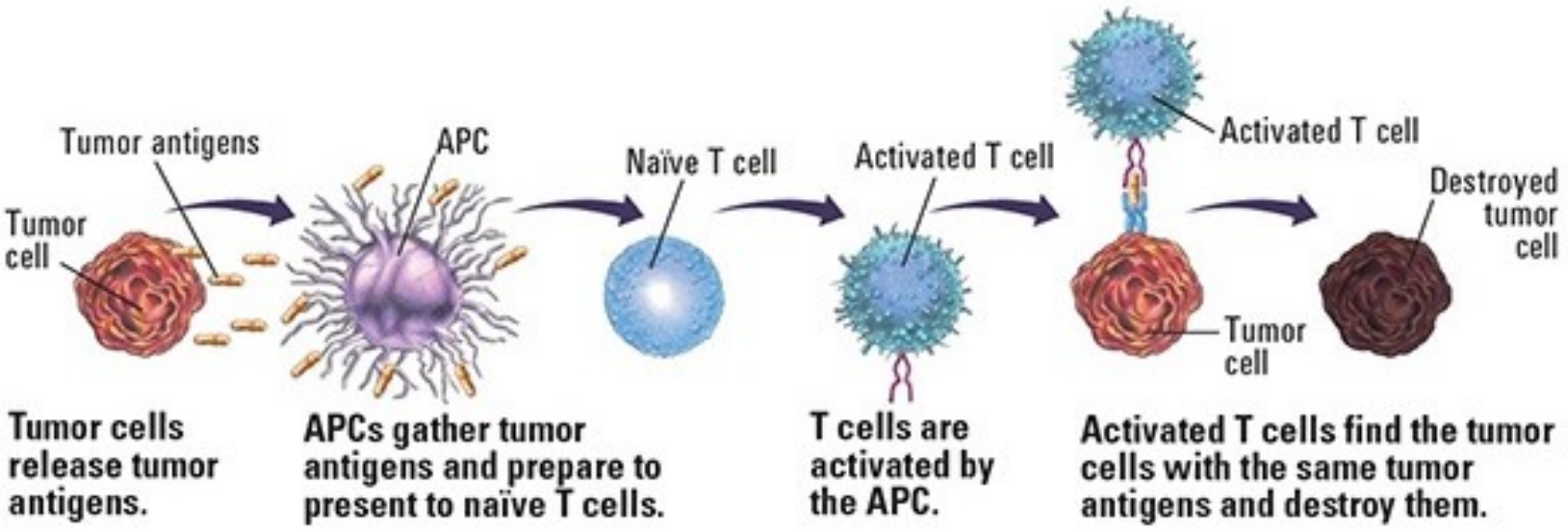


Figure: Cancer immune system cascade (Source: Patient Resource LLC)

- *Antigens*: proteins produced by the (cancer) cells.
- *Antigen-presenting cells* (APCs): cells that digest antigens, process them, and *present* them to T-cells so they know who to attack.
- *T-cells*: (named after the thymus gland where they mature) immune system cells, activated by APCs, that attack the antigen producer (cancer) cells.
- Destroyed cancer cells undergo *lysis*.
- *Lysis*: Cell disintegration via membrane breakdown.

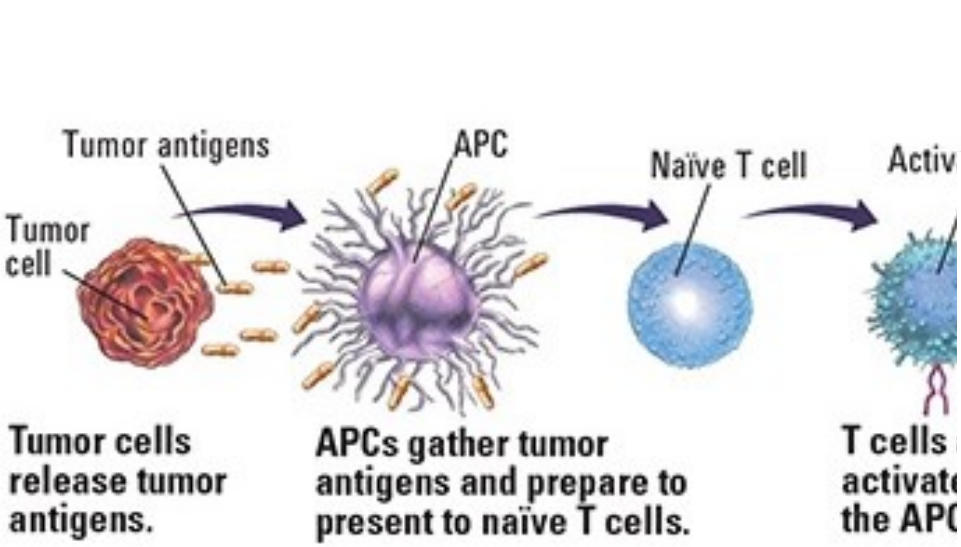
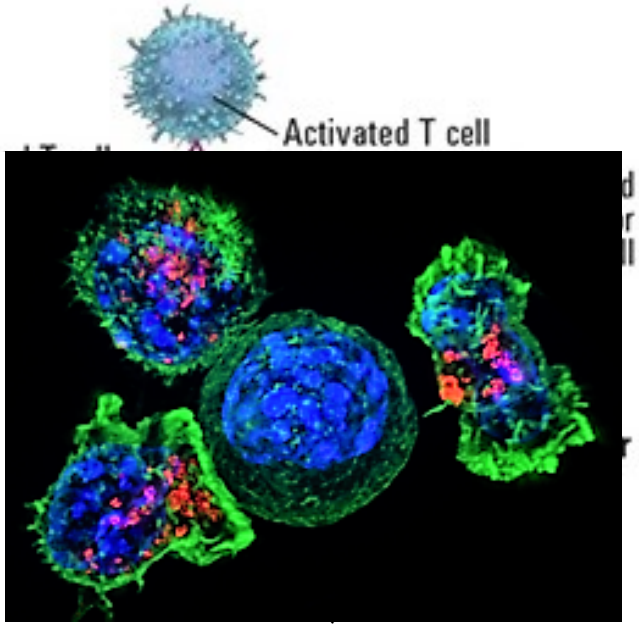


Figure: Cancer immune system cascade (Sour



3 T-cells attack a cancer cell (middle)

(NIH A. Ritter, J. Schwarz, G. Griffiths)

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Section 3.2: A first immune response model

Let N be the cancer cells and T the T-cells respectively, and for $g, k, \phi, \mu > 0$

$$\begin{cases} \dfrac{dN}{dt} = gN - kNT \\ \dfrac{dT}{dt} = \phi NT - \mu T \end{cases}$$

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$$(N^*, T^*) = (0, 0) \text{ and } \left(\frac{\mu}{\phi}, \frac{g}{k}\right)$$

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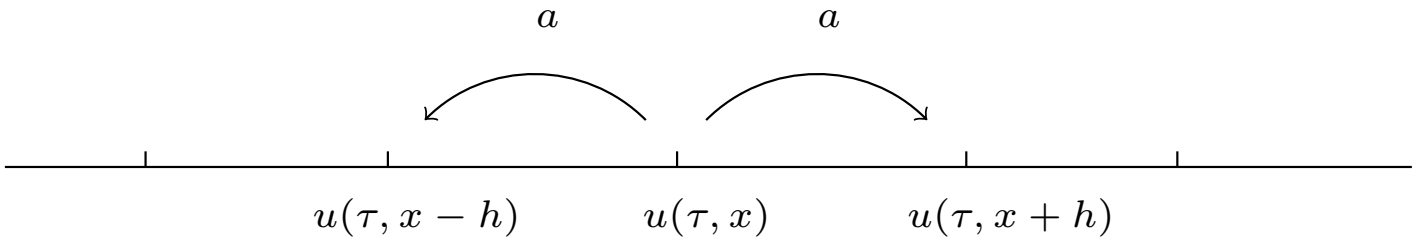
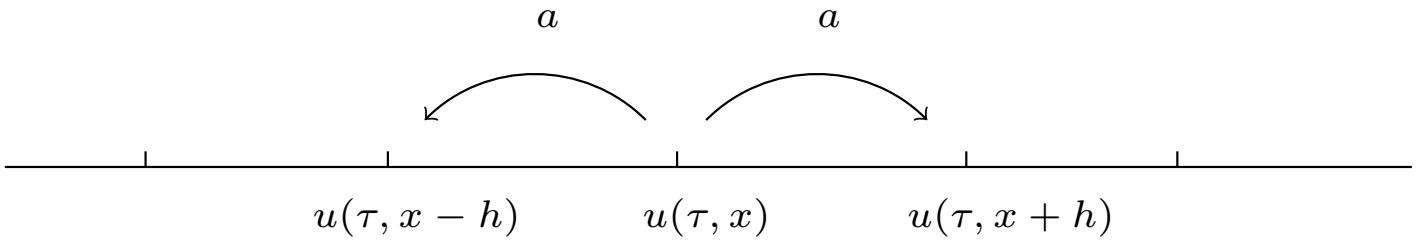
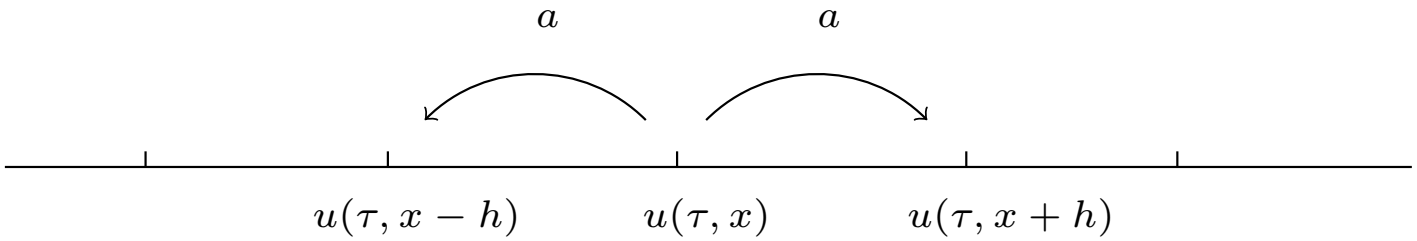
- Steady state $(N^*, T^*) = (0, 0)$: $\operatorname{tr}(J^*) = g - \mu$, $\det(J^*) = -g\mu < 0$, and $\Delta = (g + \mu)^2 > 0$; hence the steady state $(0, 0)$ is a saddle.


a
a
$u(\tau, x-h)$
$u(\tau, x)$
$u(\tau, x+h)$



$$u_\tau(\tau, x) = \underbrace{au(\tau, x-h)}_{\text{gains from the left}} + \underbrace{au(\tau, x+h)}_{\text{gains from the right}} - \underbrace{au(\tau, x)}_{\text{losses to the left}} - \underbrace{au(\tau, x)}_{\text{losses to the right}}$$

for $0 < h << 1$,



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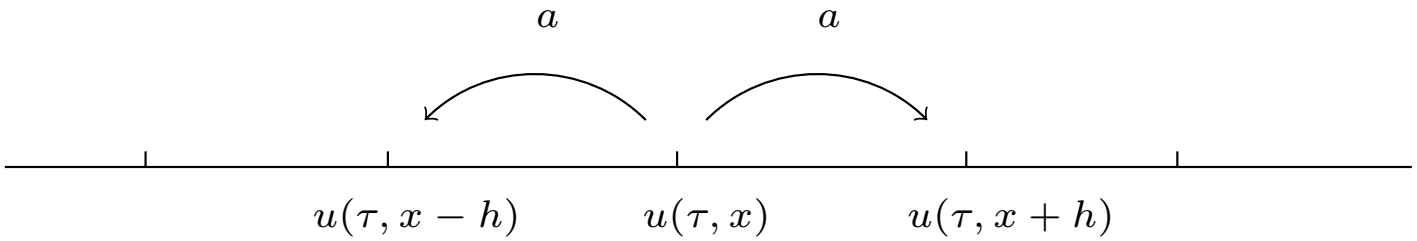

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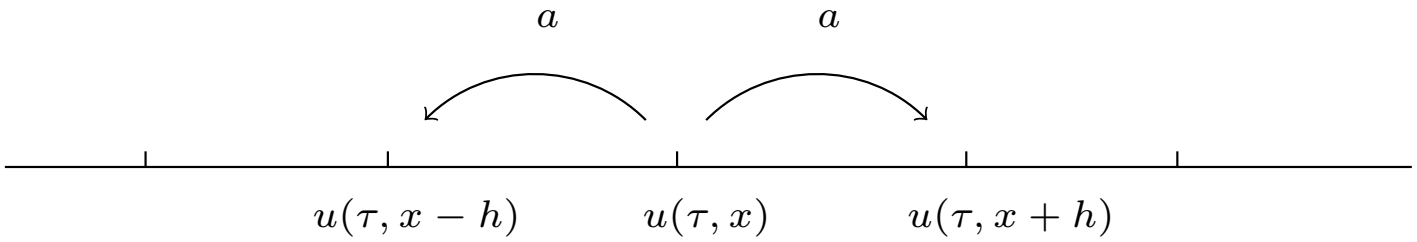

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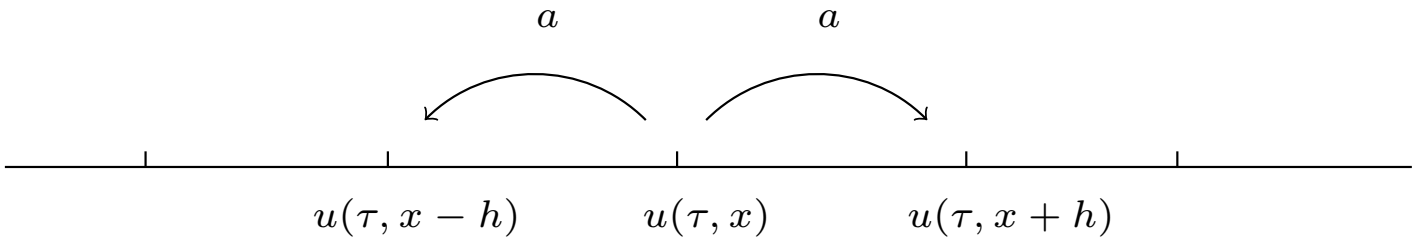
Rescaling time as $\tau = \lambda t$, for which we obtain $u_\tau(\tau,x) = \frac{1}{\lambda}u_t(t,x)$ (why?) which, when combined with the above, yields

$$u_t(t,x) = a\lambda h^2u_{xx}(\tau,x) + \mathcal{O}(\lambda h^3).$$



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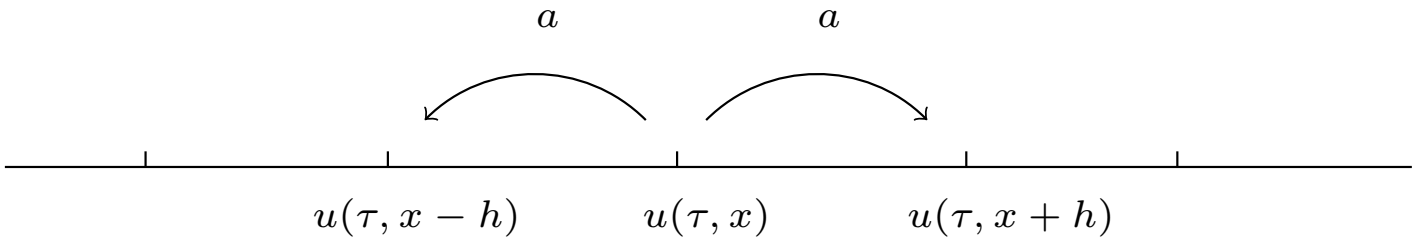
The final modelling assumption, is the so called *parabolic space-time scaling*, i.e.

$$\text{we demand } \frac{1}{\lambda} \to 0,\ h \to 0 \text{ in such way that } \lambda h^2 \to \text{const.};$$

hence

$$a\lambda h^2 \to D;$$



$$u_\tau(\tau,x) = \underbrace{au(\tau,x-h)}_{\text{gains from the left}} + \underbrace{au(\tau,x+h)}_{\text{gains from the right}} - \underbrace{au(\tau,x)}_{\text{losses to the left}} - \underbrace{au(\tau,x)}_{\text{losses to the right}}$$

for $0 < h << 1$, or, after expanding $u(\tau, x \pm h)$ in Taylor series about (τ, x) as:

$$\begin{aligned} u_\tau(\tau,x) &= -2au(\tau,x) + a\left(u(\tau,x) - hu_x(\tau,x) + \frac{1}{2}h^2u_{xx}(\tau,x) + \mathcal{O}(h^3)\right) \\ &\quad + a\left(u(\tau,x) + hu_x(\tau,x) + \frac{1}{2}h^2u_{xx}(\tau,x) + \mathcal{O}(h^3)\right) \\ &= ah^2u_{xx}(\tau,x) + \mathcal{O}(h^3) \end{aligned}$$

Rescaling time as $\tau = \lambda t$, for which we obtain $u_\tau(\tau,x) = \frac{1}{\lambda}u_t(t,x)$ (why?) which, when combined with the above, yields

$$u_t(t,x) = a\lambda h^2 u_{xx}(\tau,x) + \mathcal{O}(\lambda h^3).$$

The final modelling assumption, is the so called *parabolic space-time scaling*, i.e.

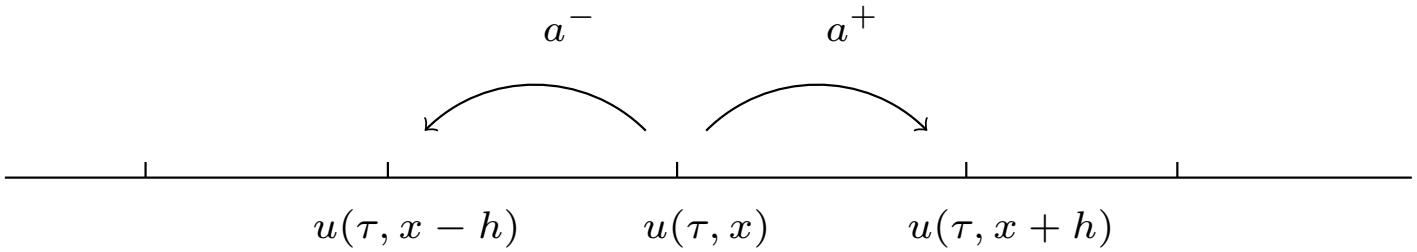
$$\text{we demand } \frac{1}{\lambda} \to 0,\ h \to 0 \text{ in such way that } \lambda h^2 \to \text{const.};$$

hence

$$a\lambda h^2 \to D;$$

which, when employed in the above gives rise to the Diffusion eq.

$$\boxed{u_t = Du_{xx}}$$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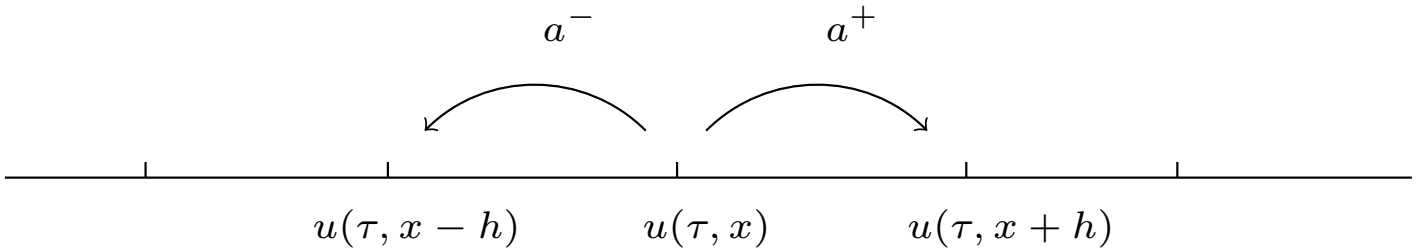

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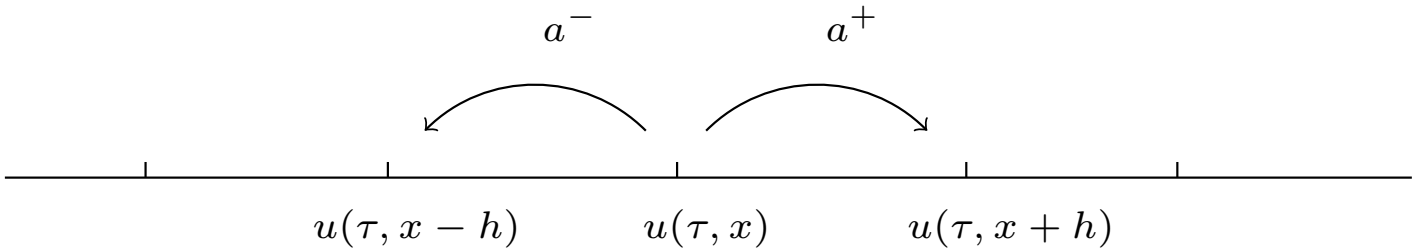
Section 3.3: Main modelling tool

from Biased Random Walk to Advection-Diffusion



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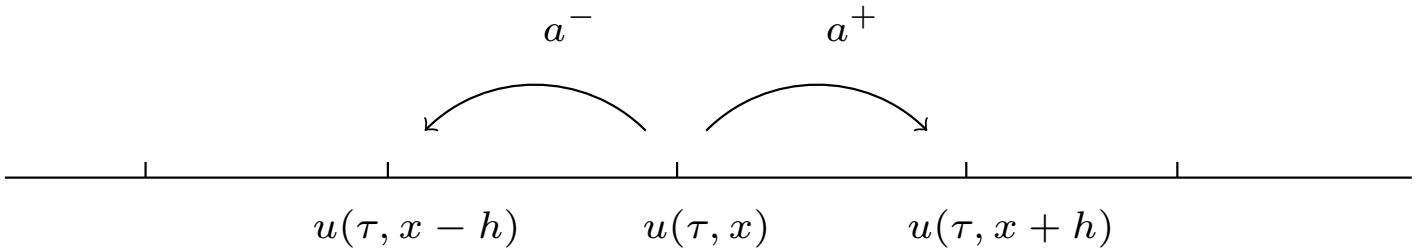
$$\begin{aligned} u_\tau(\tau,x) =& (\alpha+\beta h)\left(u(\tau,x) - hu_x(\tau,x) + \frac{h^2}{2}u_{xx}(\tau,x) + \mathcal{O}(h^3)\right) \\ &+ (\alpha-\beta h)\left(u(\tau,x) + hu_x(\tau,x) + \frac{h^2}{2}u_{xx}(\tau,x) + \mathcal{O}(h^3)\right) \\ &- (\alpha+\beta h+\alpha-\beta h)\,u(\tau,x) \\ =& \alpha h^2 u_{xx}(\tau,x) - 2\beta h^2 u_x(\tau,x) + \mathcal{O}(h^3) \end{aligned}$$



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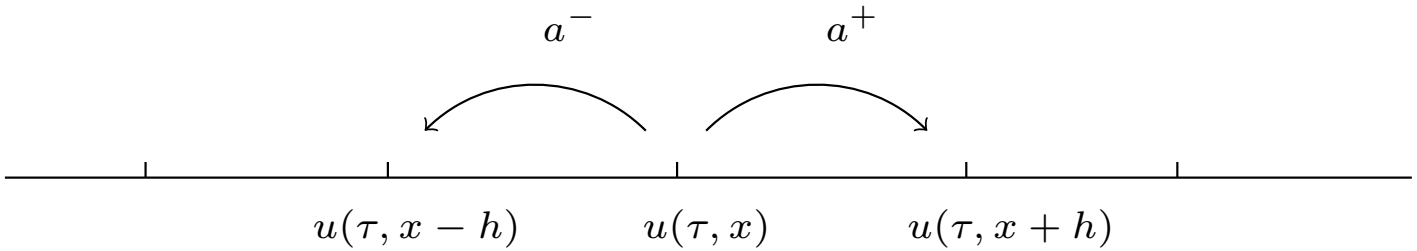

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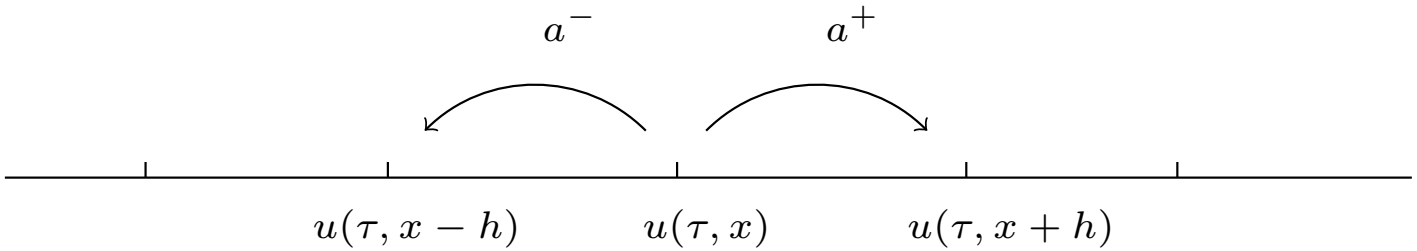
Section 3.3: Main modelling tool

from Biased Random Walk to Advection-Diffusion



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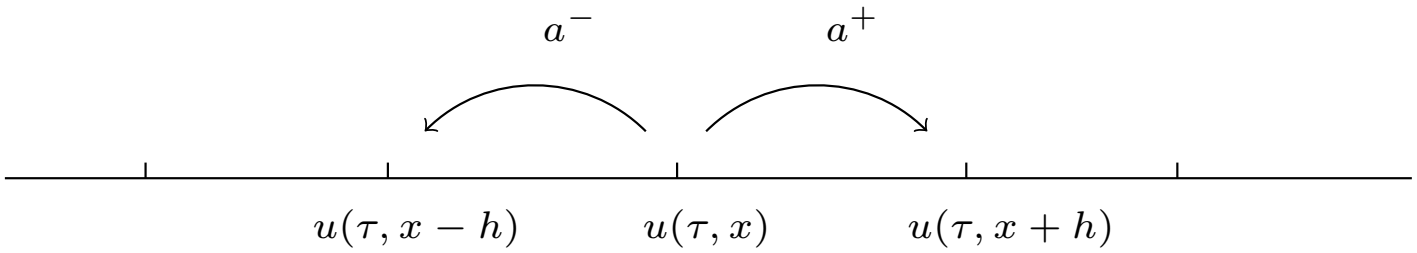
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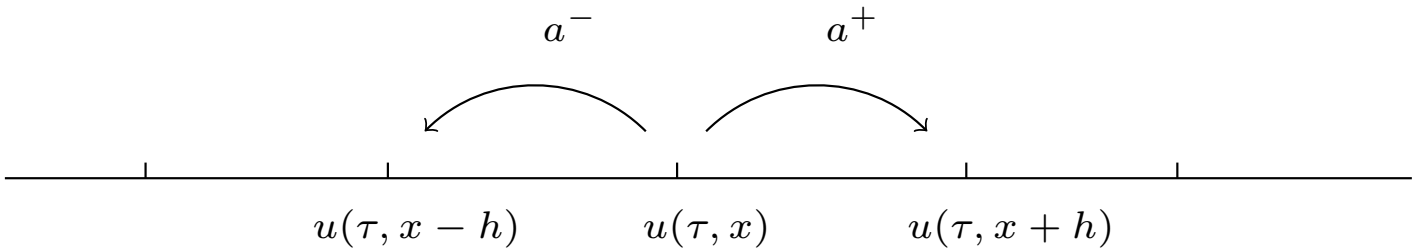
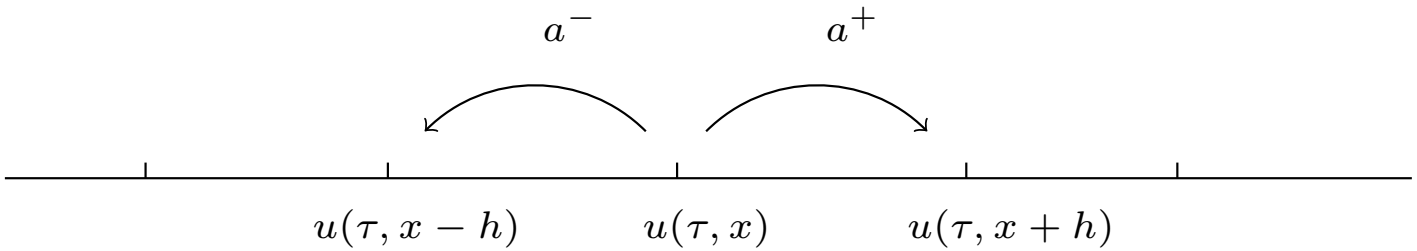


- space dependent jumping rate, e.g. the existence of a chemoattractant: $a^{\pm} = a^{\pm}(x)$



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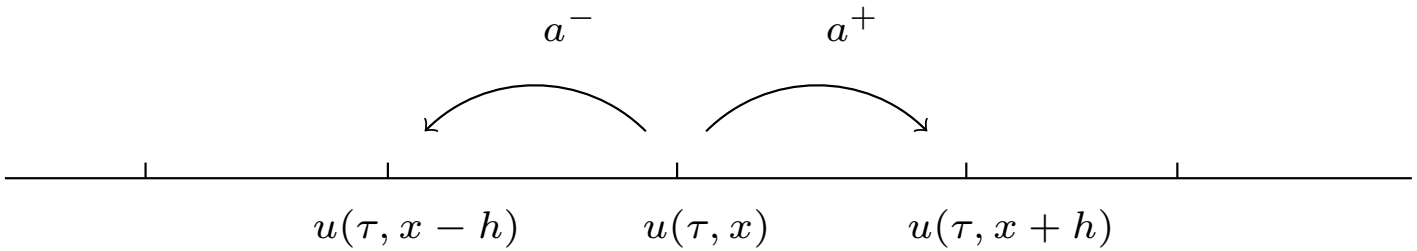

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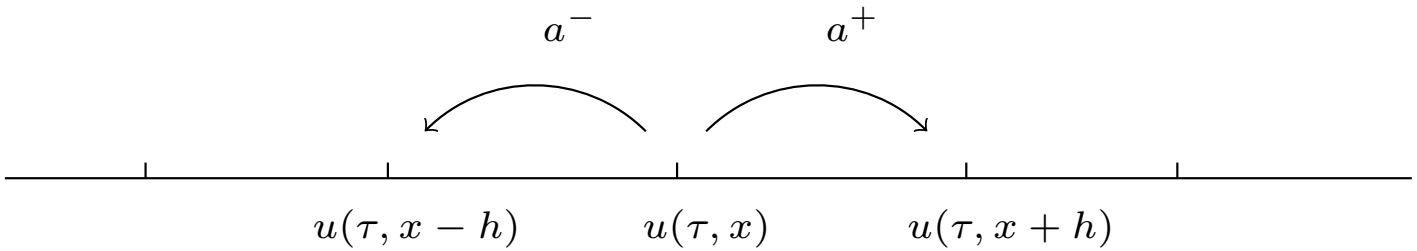

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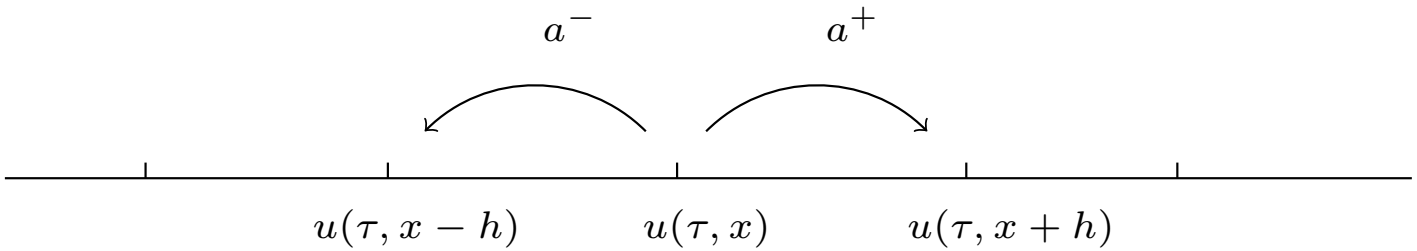

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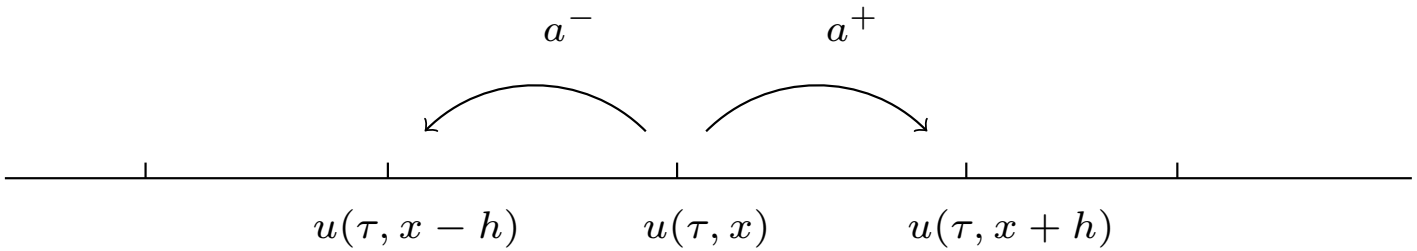

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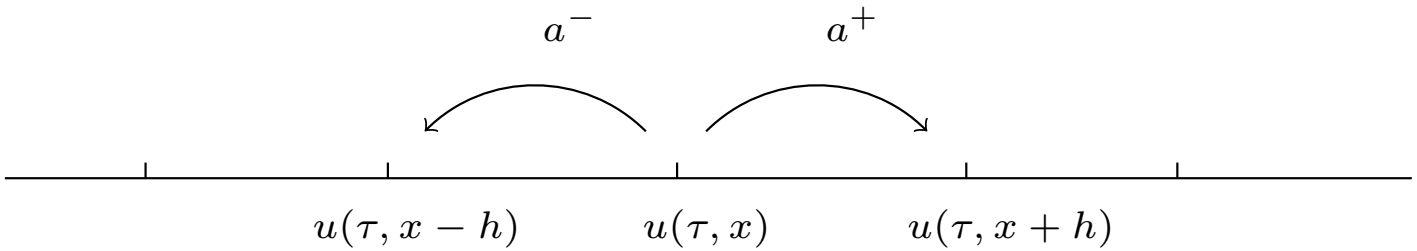

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Note/Disclaimer/Limitations:

The *agents* are assumed massless, volume-less particles that jump left-or-right; cells don't jump. The approach implies large number of *agents*; this might not be the case.

Section 3.4: (another) Immune response model

Tumour growth model without immune response

$$\frac{\partial X}{\partial t} = D\Delta X + rX\left(1 - \frac{X}{K}\right) \tag{7}$$

$X(\mathbf{r}, t)$: concentration of cancer cells ($\mathbf{r} = (x, y, z) \in \mathbb{R}^3$ or similar)
$E(\mathbf{r}, t)$: activated T-cell concentration
r: proliferation rate

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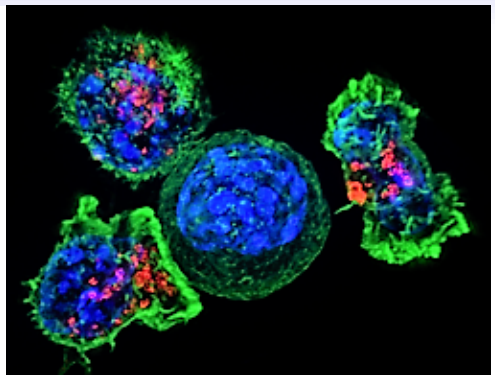

3 T-cells attack a cancer cell (middle)
(NIH A. Ritter, J. Schwarz, G. Griffiths)

Cancer-cell *lysis* reaction sub-model

$$\underbrace{X}_{\text{cancer cell}} + \underbrace{E}_{\text{T-cell}} \xrightarrow{k_1} \underbrace{C = E : X}_{\text{complex}} \xrightarrow{k_2} E + \underbrace{P}_{\text{lysate}}$$

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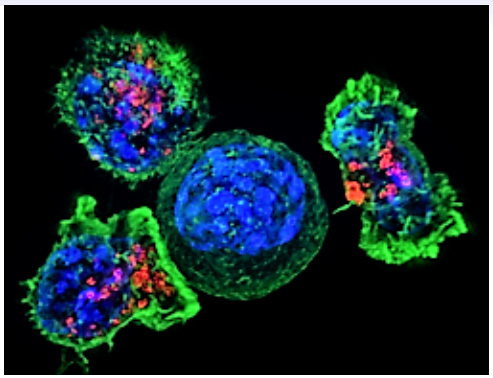

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In mathematical terms (cf. Appendix Chemical 2 Mathematical Reactions):

$$\begin{cases} \dfrac{\partial E}{\partial \tau} = -k_1 EX + k_2 C \\ \dfrac{\partial C}{\partial \tau} = k_1 EX - k_2 C \end{cases} \tag{8}$$

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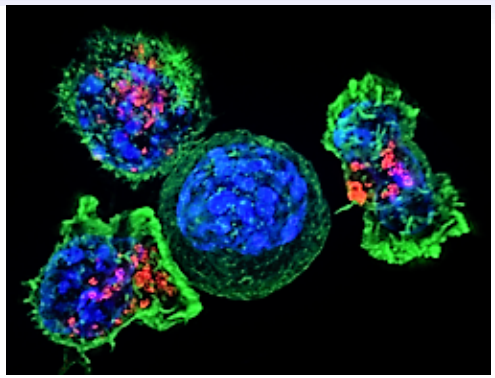

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$$\frac{d}{d\tau}(E + C) = 0 \to E + C = E_0 \quad \text{constant} \tag{9}$$

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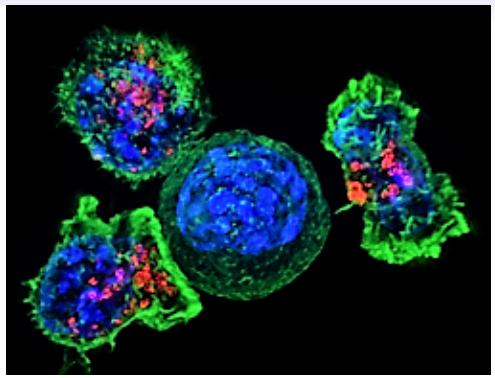

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We expect the *lysis* to be very fast in w.r.t the other processes. We hence assume that the system is in a QSSS (cf. Appendix QSSS)

$$\frac{\partial C}{\partial \tau} = 0$$

The QSSS assumption $\frac{\partial C}{\partial \tau} = 0$ leads to

$$k_1 EX - k_2 C = 0$$

The QSSS assumption $\frac{\partial C}{\partial \tau} = 0$ leads to

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Which, together with the conservation of T-cells (9): $E + C = E_0$, yields:

$$E = \frac{k_2 E_0}{k_2 + k_1 X}$$

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So, the rate at which cancer cells are destroyed is

$$-k_1 EX = -\frac{k_2 k_1 E_0 X}{k_2 + k_1 X} \tag{10}$$

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$$-k_1 E X = -\frac{k_2 k_1 E_0 X}{k_2 + k_1 X} \tag{10}$$

Including the immune response (10) in the tumour growth model (7) we obtain:

$$\frac{\partial X}{\partial \tau} = D\Delta X + \underbrace{rX\left(1 - \frac{X}{K}\right)}_{\text{cancer cell proliferation}} - \underbrace{\frac{k_2 k_1 E_0 X}{k_2 + k_1 X}}_{\text{immune response}} \tag{11}$$

$$\frac{\partial X}{\partial \tau} = D\Delta X + \underbrace{rX\left(1-\frac{X}{K}\right) - \frac{k_2 k_1 E_0 X}{k_2 + k_1 X}}_{f(X)}$$

$$\frac{\partial X}{\partial \tau} = D\Delta X + \underbrace{rX\left(1-\frac{X}{K}\right) - \frac{k_2 k_1 E_0 X}{k_2 + k_1 X}}_{f(X)}$$

$$f(X) = X\underbrace{\left(r\left(1-\frac{X}{K}\right) - \frac{k_1 k_2 E_0}{k_2 + k_1 X}\right)}_{g(X)}$$

$$= \frac{X}{k_2 + k_1 X}\underbrace{\left(-\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right)\right)}_{h(X)}$$

$$\frac{\partial X}{\partial \tau} = D\Delta X + \underbrace{rX\left(1-\frac{X}{K}\right) - \frac{k_2 k_1 E_0 X}{k_2 + k_1 X}}_{f(X)}$$

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It holds that

$$f(0) = 0 \text{ and } h(0) = k_2\left(r - k_1 E_0\right)$$

$$\frac{\partial X}{\partial \tau} = D\Delta X + \underbrace{rX\left(1-\frac{X}{K}\right) - \frac{k_2 k_1 E_0 X}{k_2 + k_1 X}}_{f(X)}$$

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$$= \frac{X}{k_2 + k_1 X}\underbrace{\left(-\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right)\right)}_{h(X)}$$

It holds that

$$f(0) = 0 \text{ and } h(0) = k_2\left(r - k_1 E_0\right)$$

and that h exhibits a maximum at

$$\tilde{X} = \frac{Kk_1 - k_2}{2k_1} \text{ with } h(\tilde{X}) = \frac{r(Kk_1 + k_2)^2}{4Kk_1} - k_1 k_2 E_0.$$

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1E_0\right)$$

$$h_{\max} = h(\tilde{X}) = \frac{r(Kk_1 + k_2)^2}{4Kk_1} - k_1k_2E_0$$

$$f'(X) = \frac{\left(h(X) + Xh'(X)\right)\left(k_2 + k_1X\right) - k_1Xh(X)}{\left(k_2 + k_1X\right)^2}$$

$$f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1X}$$

$$g(X) = r\left(1 - \frac{X}{k}\right) - \frac{k_1k_2E_0}{k_2 + k_1X}$$

$$f'(X) = g(X) + Xg'(X)$$

- Case $r < k_1E_0$:

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1E_0\right)$$

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$$f'(X) = g(X) + Xg'(X)$$

- Case $r < k_1E_0$:
  It holds that $f'(0) = g(0) = r - k_1E_0 < 0$, i.e. the steady-state $X = 0$ is asymptotically stable; small perturbations are (self-)corrected, i.e. new (and hence small) tumours are eradicated.

Section 3.4: (another) Immune response model

Model predictions II

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1 X}$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right)$$

$$g(X) = r\left(1 - \frac{X}{k}\right) - \frac{k_1 k_2 E_0}{k_2 + k_1 X}$$

$$h_{\max} = h(\tilde{X}) = \frac{r(Kk_1 + k_2)^2}{4Kk_1} - k_1 k_2 E_0$$

$$f'(X) = g(X) + Xg'(X)$$

$$f'(X) = \frac{\left(h(X) + Xh'(X)\right)(k_2 + k_1 X) - k_1 X h(X)}{(k_2 + k_1 X)^2}$$

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1E_0\right)$$

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- Case $r > k_1E_0$:

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X) \qquad f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1 X}$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right) \qquad g(X) = r\left(1 - \frac{X}{k}\right) - \frac{k_1 k_2 E_0}{k_2 + k_1 X}$$

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- Case $r > k_1 E_0$:
  - For $X = 0$: $f'(0) = g(0) = r - k_1 E_0 > 0$ i.e. the steady-state $X = 0$ is unstable; i.e. new (and hence small) tumours will not be eradicated.

It holds $h(\tilde{X}) = \frac{r(Kk_1+k_2)^2}{4Kk_1} - k_1 k_2 E_0 \geq 0$ (since $\frac{4Kk_1k_2}{(Kk_1+k_2)^2} \leq 1$),

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1E_0\right)$$

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$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X) \qquad f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1 X}$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right) \qquad g(X) = r\left(1 - \frac{X}{k}\right) - \frac{k_1 k_2 E_0}{k_2 + k_1 X}$$

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$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

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So $\exists$ two spatially uniform steady-states $X = 0$ and $X = X^*$.

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X) \qquad f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1 X}$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right) \qquad g(X) = r\left(1 - \frac{X}{k}\right) - \frac{k_1 k_2 E_0}{k_2 + k_1 X}$$

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So $\exists$ two spatially uniform steady-states $X = 0$ and $X = X^*$.

- For $X = X^*$: since $h(X^*) = 0$ and $h'(X^*) < 0$ we obtain $f'(X^*) < 0$, i.e. the steady-state X^* is asymptotically stable.

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X) \qquad f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1 X}$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right) \qquad g(X) = r\left(1 - \frac{X}{k}\right) - \frac{k_1 k_2 E_0}{k_2 + k_1 X}$$

$$h_{\max} = h(\tilde{X}) = \frac{r(Kk_1 + k_2)^2}{4Kk_1} - k_1 k_2 E_0 \qquad f'(X) = g(X) + Xg'(X)$$

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- Case $r > k_1 E_0$:
  - For $X = 0$: $f'(0) = g(0) = r - k_1 E_0 > 0$ i.e. the steady-state $X = 0$ is unstable; i.e. new (and hence small) tumours will not be eradicated.

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So $\exists$ two spatially uniform steady-states $X = 0$ and $X = X^*$.

- For $X = X^*$: since $h(X^*) = 0$ and $h'(X^*) < 0$ we obtain $f'(X^*) < 0$, i.e. the steady-state X^* is asymptotically stable.

The above, basic phase-field analysis reveals that there exist a solution connecting the unstable SS $X = 0$ to the stable one $X = X^*$.

Section 3.4: (another) Immune response model

Model predictions II

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1 X}$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right)$$

$$g(X) = r\left(1 - \frac{X}{k}\right) - \frac{k_1 k_2 E_0}{k_2 + k_1 X}$$

$$h_{\max} = h(\tilde{X}) = \frac{r(Kk_1 + k_2)^2}{4Kk_1} - k_1 k_2 E_0$$

$$f'(X) = g(X) + Xg'(X)$$

$$f'(X) = \frac{\left(h(X) + Xh'(X)\right)(k_2 + k_1 X) - k_1 X h(X)}{(k_2 + k_1 X)^2}$$

Conslusions:

Section 3.4: (another) Immune response model

Model predictions II

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1E_0\right)$$

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$$f'(X) = g(X) + Xg'(X)$$

Conslusions:

- Case $r < k_1E_0$ (Strong Immune System):

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1E_0\right)$$

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- Case $r < k_1E_0$ (Strong Immune System): the immune system is strong enough to eradicate small tumours.

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$$f'(X) = g(X) + Xg'(X)$$

Conslusions:

- Case $r < k_1E_0$ (Strong Immune System): the immune system is strong enough to eradicate small tumours.
- Case $r > k_1E_0$ (Weak Immune System):

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

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$$h(X) = -\frac{rk_1}{K}X^2 + r\left(k_1 - \frac{k_2}{K}\right)X + k_2\left(r - k_1 E_0\right)$$

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$$f'(X) = \frac{\left(h(X) + Xh'(X)\right)(k_2 + k_1 X) - k_1 X h(X)}{(k_2 + k_1 X)^2}$$

Conslusions:

- Case $r < k_1 E_0$ (Strong Immune System): the immune system is strong enough to eradicate small tumours.
- Case $r > k_1 E_0$ (Weak Immune System): the immune system cannot eradicate the tumour; it rather contributes (along with the limited resources accounted for in the carrying capacity K) in confining it in a finite size.

$$\frac{\partial X}{\partial \tau} = D\Delta X + f(X)$$

$$f(X) = Xg(X) = \frac{Xh(X)}{k_2 + k_1 X}$$

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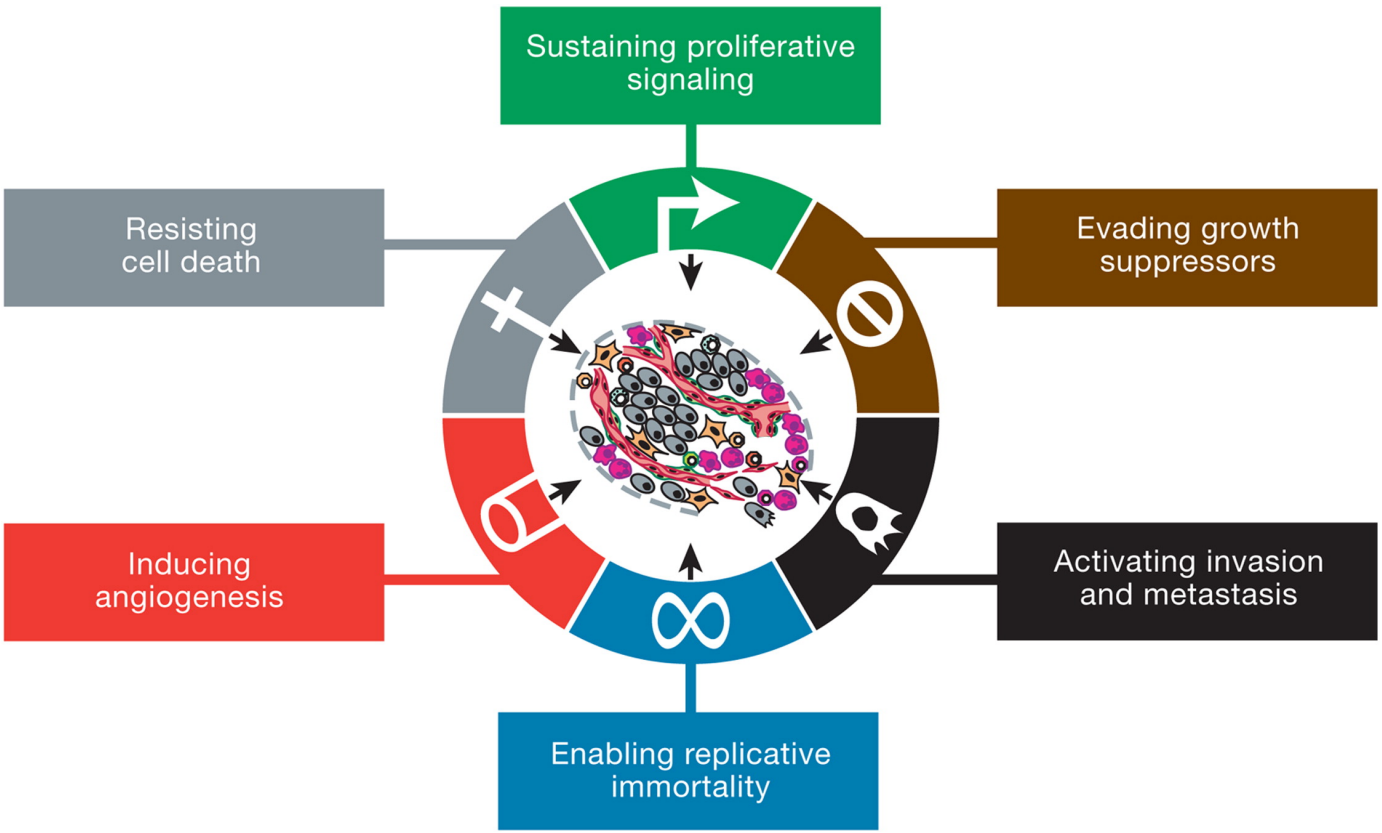
Conslusions:

- Case $r < k_1 E_0$ (Strong Immune System): the immune system is strong enough to eradicate small tumours.
- Case $r > k_1 E_0$ (Weak Immune System): the immune system cannot eradicate the tumour; it rather contributes (along with the limited resources accounted for in the carrying capacity K) in confining it in a finite size.
- In any Case: you'll need something more (cf. Appendix Travelling Wave Analysis)

Section 4

Tumour induced Angiogenesis

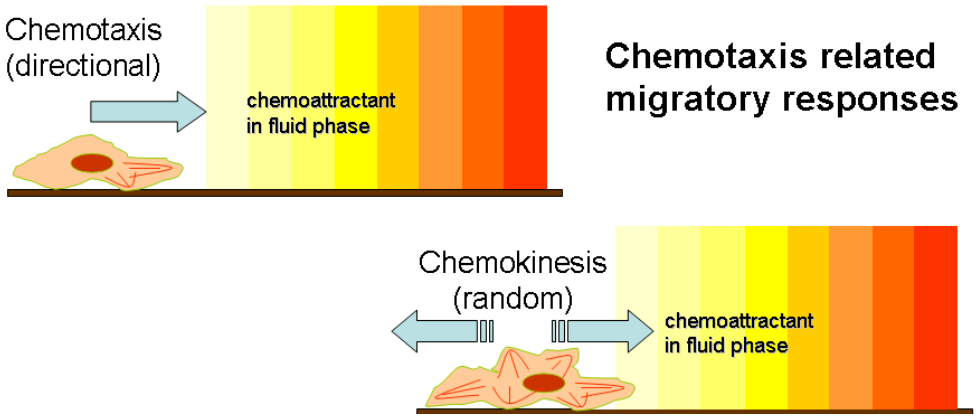


Hallmarks of Cancer by Hanahan and Weinberg

Section 4.1: Chemotaxis

Section 4.1: Chemotaxis

... of *eukariotic* cells

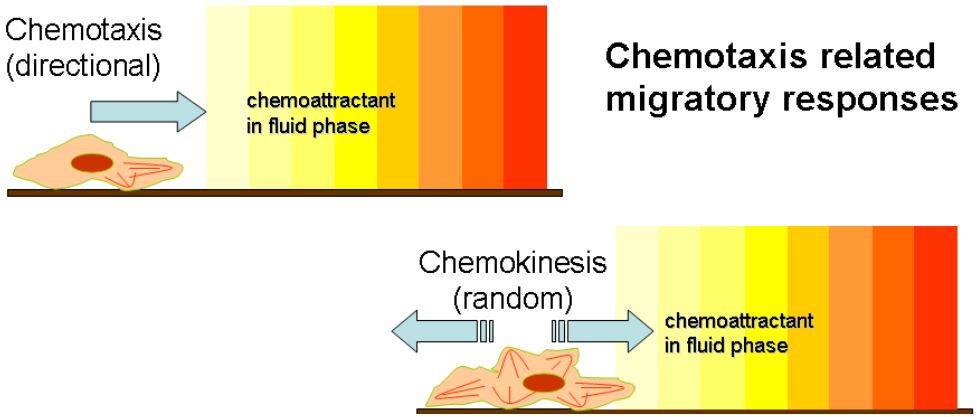


Source: L. Kohidai 2008

Examples: white blood cells chase bacteria collective leukocytes

Section 4.1: Chemotaxis

... of *eukariotic* cells



Source: L. Kohidai 2008

Examples: white blood cells chase bacteria collective leukocytes

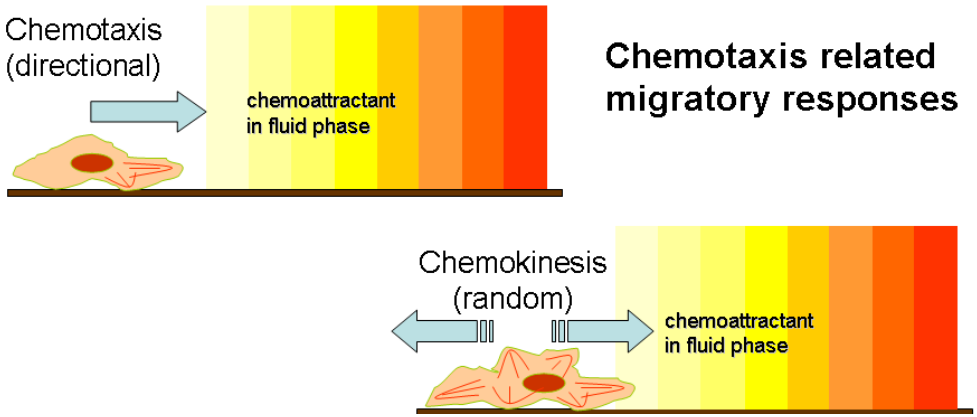
Chemokinesis

Chemically prompted, but not directional, *kinesis*/motile response to chemical stimuli.

Source: E.L. Becker 1977

Section 4.1: Chemotaxis

... of *eukariotic* cells



Source: L. Kohidai 2008

Examples: white blood cells chase bacteria collective leukocytes

Chemokinesis

Chemically prompted, but not directional, *kinesis*/motile response to chemical stimuli.

Source: E.L. Becker 1977

Chemotaxis

Directional locomotion of cells towards a source of a chemical gradient.

Source: Encyclopedia of Immunology

Section 4.1: Chemotaxis

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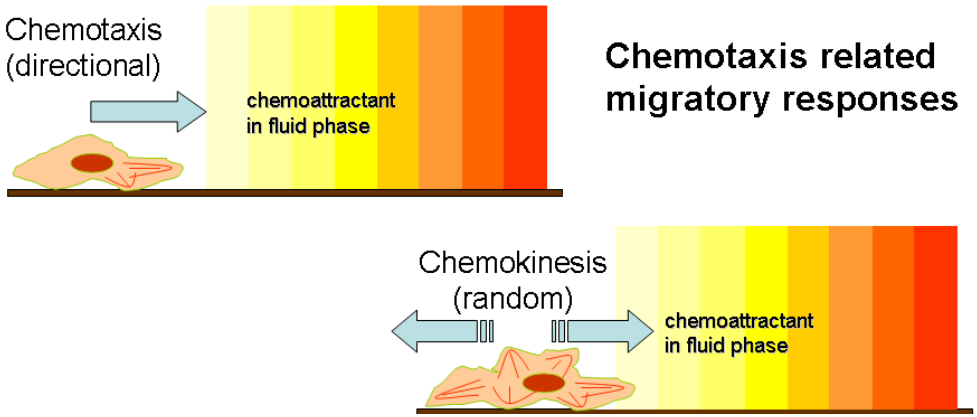

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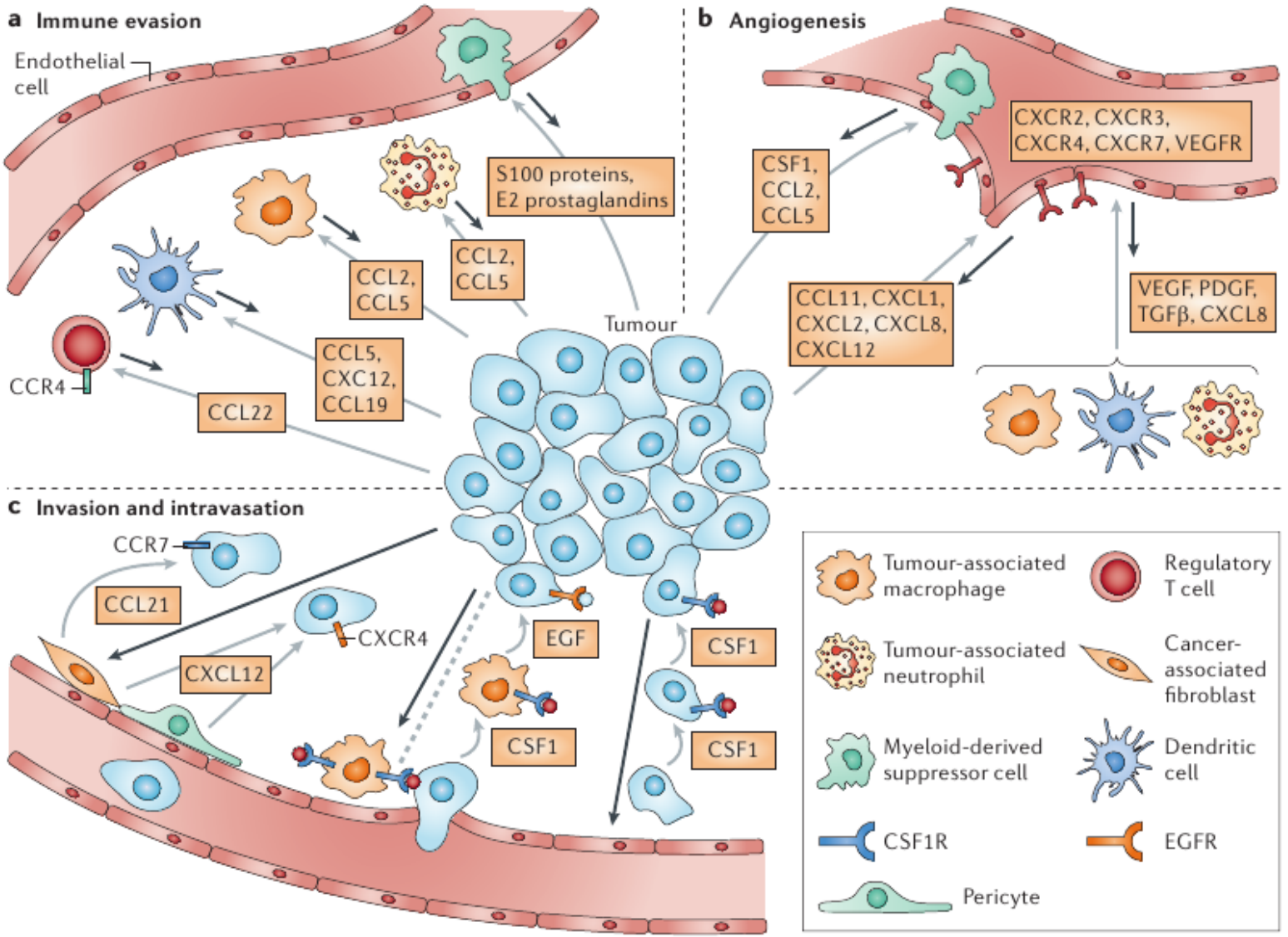
Directional locomotion of cells towards a source of a chemical gradient.

Source: Encyclopedia of Immunology

- First observed in 1884 by Pfeffer in *spermatozoa*; shortly after, 1888, by Leber in mamalian *leukocytes*. Since then, *chemotaxis* is accepted as an important mechanism in a wide range of biological processes/phenomena; cancer included.

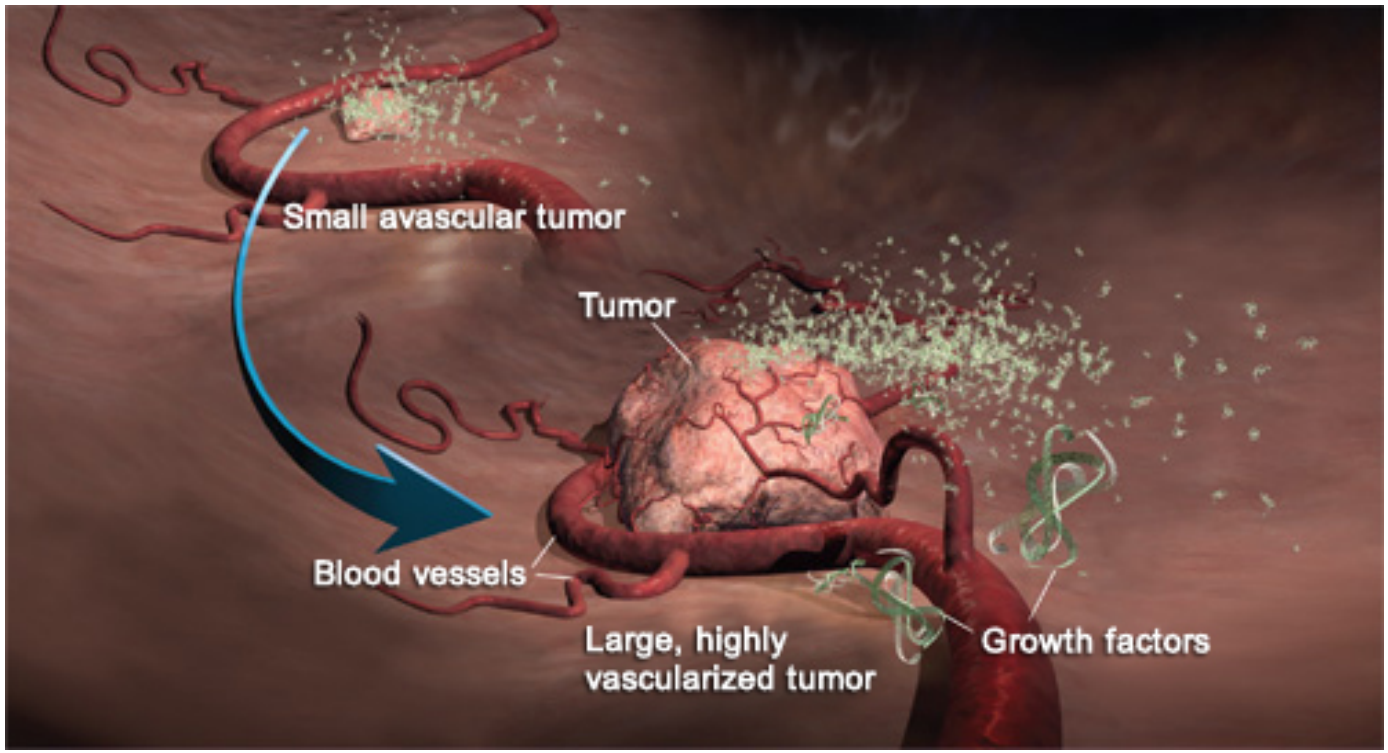
Section 4.1: Chemotaxis

Chemotaxis and Cancer by Rousos et al., Nature, 2011



Section 4.1: Tumour induced Angiogenesis

Tumour Angiogenesis Factors (TAFs)



A host of TAFs

- *Vascular Endothelial Growth Factors* (VEGF)
- *Epidermal growth factors* (EGF)
- *Transforming Growth Factor beta* (TGF-β)
- …

Reminder: Angiogenesis model I

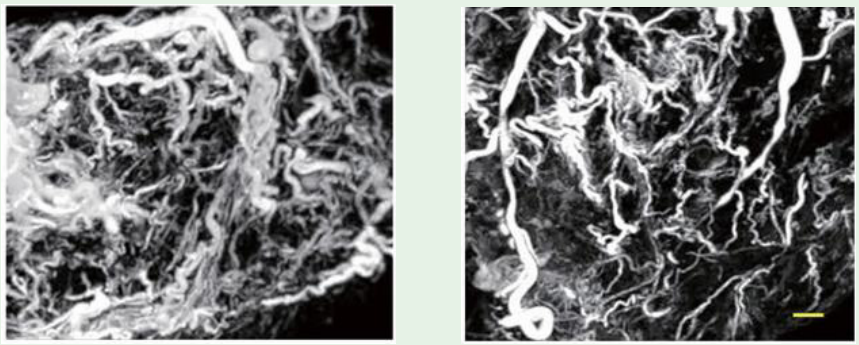


Figure: tumour microvessels *in vitro*; (left) untreated control group; (right): antiangiogenics treated group

$$\begin{cases} \dfrac{dN}{dt} = aN\left(1-\dfrac{N}{K}\right) \\ \dfrac{dK}{dt} = \omega N - \gamma N^{2/3}K - \alpha K c(t) \end{cases}$$

$N(t)$: cancer cell population

$K(t)$: carrying capacity (resources due to vasculature)

ωN: stimulation of angiogenesis

$\gamma N^{2/3}K$: tumour uptake of resources

$\alpha K c(t)$: vasculature decay due to treatment $c(t)$

TAF submodel

$$\frac{\partial e}{\partial t} = \underbrace{D\Delta e}_{\text{diffusion}} - \underbrace{f(e)g(n)}_{\text{uptake by } n} - \underbrace{h(e)}_{\text{decay}} \tag{12}$$

e : concentration of TAFs
n : concentration of endothelial cells (representing blood vessels)

TAF submodel

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e : concentration of TAFs
n : concentration of endothelial cells (representing blood vessels)

Blood vessel submodel

$$\frac{\partial n}{\partial t} = G(e)F(n) - H(n) - \nabla \cdot \mathbf{J} \tag{13}$$

$H(n)$: loss of blood vessels in the absence of TAFs
$G(e)F(n)$: production of blood vessels when stimulated by the TAFs
$\mathbf{J}(e, n)$: blood vessel kinesis-taxis flux

TAF submodel

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$$\mathbf{J} = \mathbf{J}_{\text{diff}} + \mathbf{J}_{\text{chemo}} = -D\nabla n + n\chi(e)\nabla e, \tag{14}$$

corresponding to/modelling the random and biased part of the growth of blood vessels; i.e.

TAF submodel

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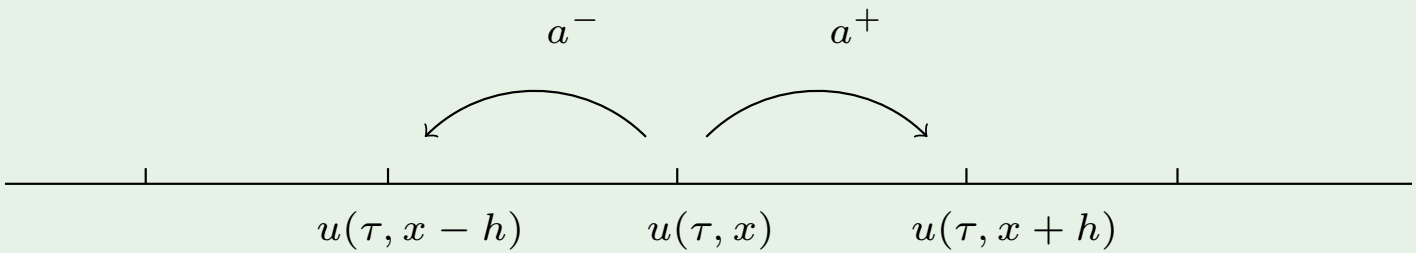
$$\frac{\partial n}{\partial t} = G(e)F(n) - H(n) + D\Delta n - \nabla \cdot (n\chi(e)\nabla e) \tag{15}$$

But, where does the flux J comes from?

Reminder:
from biased random walk to advection-diffusion



$$u_\tau(\tau,x) = \underbrace{a^+ u(\tau,x-h)}_{\text{gains from the left}} + \underbrace{a^- u(\tau,x+h)}_{\text{gains from the right}} - \underbrace{a^- u(\tau,x)}_{\text{losses to the left}} - \underbrace{a^+ u(\tau,x)}_{\text{losses to the right}}$$

We set $a^\pm = \alpha \pm \beta h$ and the above reads, after Taylor expansions, as

$$\begin{aligned} u_\tau(\tau,x) =& (\alpha+\beta h)\left(u(\tau,x) - h u_x(\tau,x) + \frac{h^2}{2} u_{xx}(\tau,x) + \mathcal{O}(h^3)\right) \\ &+ (\alpha-\beta h)\left(u(\tau,x) + h u_x(\tau,x) + \frac{h^2}{2} u_{xx}(\tau,x) + \mathcal{O}(h^3)\right) \\ &- (\alpha+\beta h+\alpha-\beta h)\, u(\tau,x) \\ =& \alpha h^2 u_{xx}(\tau,x) - 2\beta h^2 u_x(\tau,x) + \mathcal{O}(h^3) \end{aligned}$$

Rescale time $\tau = \lambda t$ to obtain $u_\tau(\tau,x) = \frac{1}{\lambda} u_t(t,x)$ and the above yields

$$u_t(t,x) = \alpha\lambda h^2 u_{xx}(t,x) - 2\beta\lambda h^2 u_x(t,x) + \mathcal{O}(\lambda h^3)$$

Parabolic space-time scaling:

$$h \to 0 \text{ and } \frac{1}{\lambda} \to 0 \text{ such that } \alpha\lambda h^2 \to D \text{ and } 2\beta\lambda h^2 \to \chi$$

leads to

$$u_t(t,x) + \chi u_x(t,x) = D u_{xx}(t,x)$$

Angiogenesis model II

Based on (12) and (15) we summarise

$$\begin{cases} \dfrac{\partial e}{\partial t} = D_e \Delta e - f(e)g(n) - h(e) \\ \dfrac{\partial n}{\partial t} = D_n \Delta n - \nabla \cdot (n\chi(e)\nabla e) + G(e)F(n) - H(n) \end{cases} \tag{16}$$

e : concentration of TAFs
n : concentration of endothelial cells (representing blood vessels)

(usual) Control functions

$$h(e) = de, \qquad f(e) = \frac{V_m e}{K_m + e}$$

$$g(n) = \frac{n}{n_0}, \qquad \chi(e) = \frac{\chi_0}{1 + ae}$$

$$F(n) = rn\left(1 - \frac{n}{n_0}\right) \qquad H(n) = k_p n,$$

$$G(e) = \begin{cases} 0, & e \le e^* \\ \dfrac{e - e^*}{e_b} & e > e^* \end{cases}, \quad e^* \le e_b$$

Angiogenesis model II

e : concentration of TAFs

n : concentration of endothelial cells (representing blood vessels)

$$\begin{cases} \dfrac{\partial e}{\partial t} = \underbrace{D_e \Delta e}_{\text{mol. diffusion}} - \underbrace{\dfrac{V_m e}{K_m + e}\, n_0}_{\text{angio-uptake}} \dfrac{n}{} - \underbrace{de}_{\text{mol. decay}} \\ \dfrac{\partial n}{\partial t} = \underbrace{D_n \Delta n}_{\text{cel. diffusion}} - \underbrace{\nabla\left(n \dfrac{\chi_0}{1+ae} \nabla e\right)}_{\text{chemotaxis}} + \underbrace{rG(e)n\left(1 - \dfrac{n}{n_0}\right)}_{\text{angio-formation}} - \underbrace{k_p n}_{\text{angio-decay}} \end{cases}$$

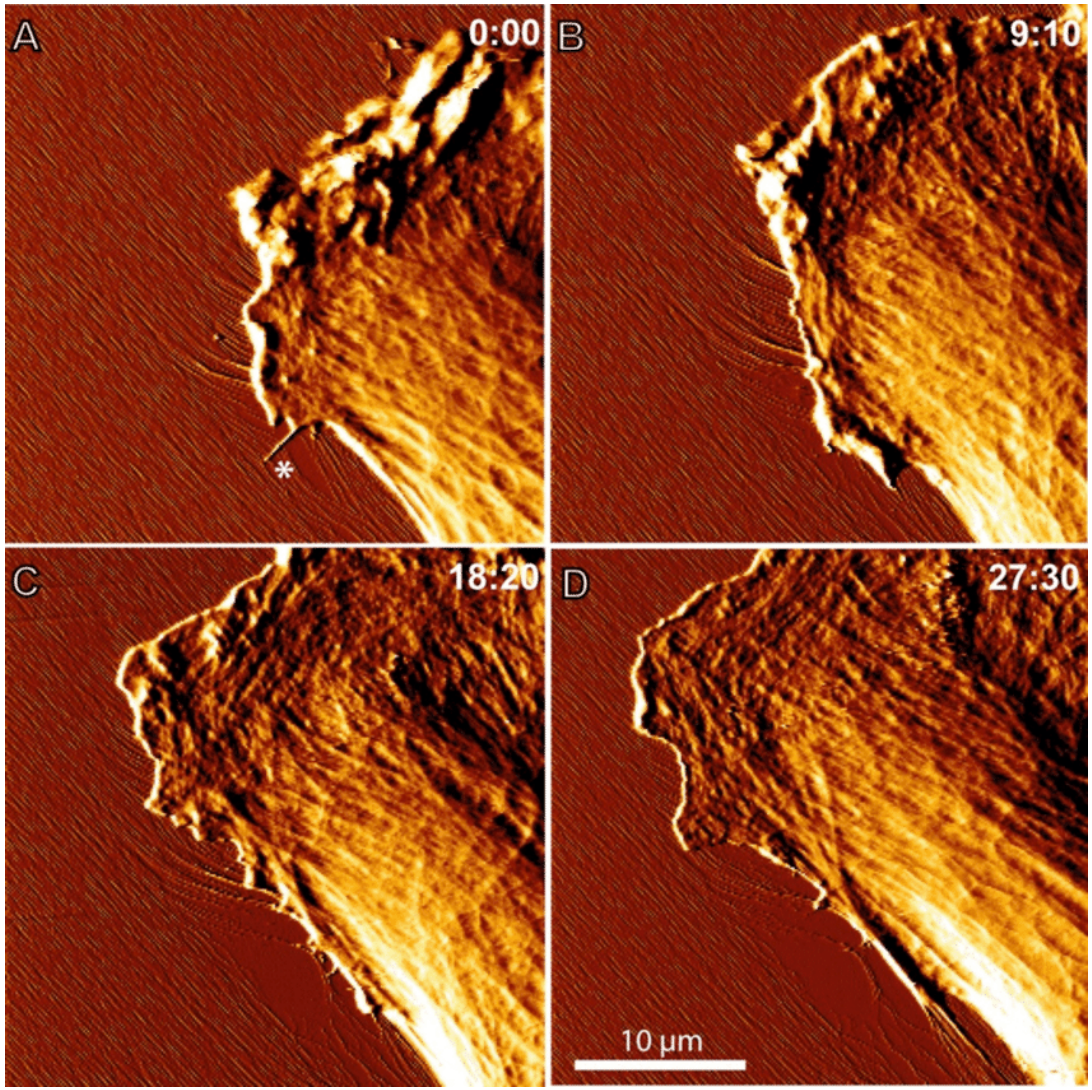
where the angiogenesis is controlled by the biochemical switch mechanism:

$$G(e) = \begin{cases} 0, & e \le e^* \\ \dfrac{e - e^*}{e_b}, & e > e^* \end{cases}, \quad e^* \le e_b$$

Section 4.3: Haptotaxis

Eukariotic cells

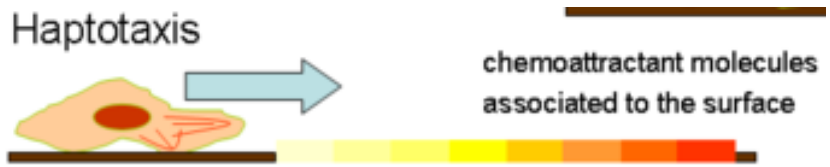
... adhere on the matrix



Matrix deformation due to cell adhesion. Source: Han et al. 2013

Haptotaxis...

... of *eukariotic* cells



Source: L. Kohidai 2008

Extracellular Matrix (ECM)

A network of *macromolecules* such as *collagen* and *glycoproteins* that provide structural and biochemical support to surrounding cells.

Haptotaxis

(similar to chemokinesis and chemotaxis) the biased random motion up the gradient of ECM-bound chemoattractants.

Haptotaxis...

... of *eukariotic* cells

ECM submodel I

Assuming just degradation (by the endothelial cells) of the matrix

$$\frac{\partial v}{\partial t} = -\mu n v \tag{17}$$

v : concentration of collagen, fibronectin

n : concentration of blood vessels (represented by endothelial cells)

ECM submodel I

Assuming just degradation (by the endothelial cells) of the matrix

$$\frac{\partial v}{\partial t} = -\mu n v \tag{17}$$

v : concentration of collagen, fibronectin
n : concentration of blood vessels (represented by endothelial cells)

Blood vessel submodel II

$$\frac{\partial n}{\partial t} = D\Delta n - \underbrace{\chi_0 \nabla \cdot (n \nabla e)}_{\text{chemotaxis}} - \underbrace{\rho_0 \nabla \cdot (n \nabla v)}_{\text{haptotaxis}} \tag{18}$$

e : concentration of TAFs

Section 4.4: Chemo- & haptotaxis together

ECM submodel II

Assuming just degradation (by the endothelial cells) of the matrix

$$\frac{\partial v}{\partial t} = \beta n - \mu n v \tag{19}$$

v : concentration of collagen, fibronectin

n : concentration of blood vessels (represented by endothelial cells)

ECM submodel II

Assuming just degradation (by the endothelial cells) of the matrix

$$\frac{\partial v}{\partial t} = \beta n - \mu n v \tag{19}$$

v : concentration of collagen, fibronectin

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The Chaplain-Anderson model (1998)

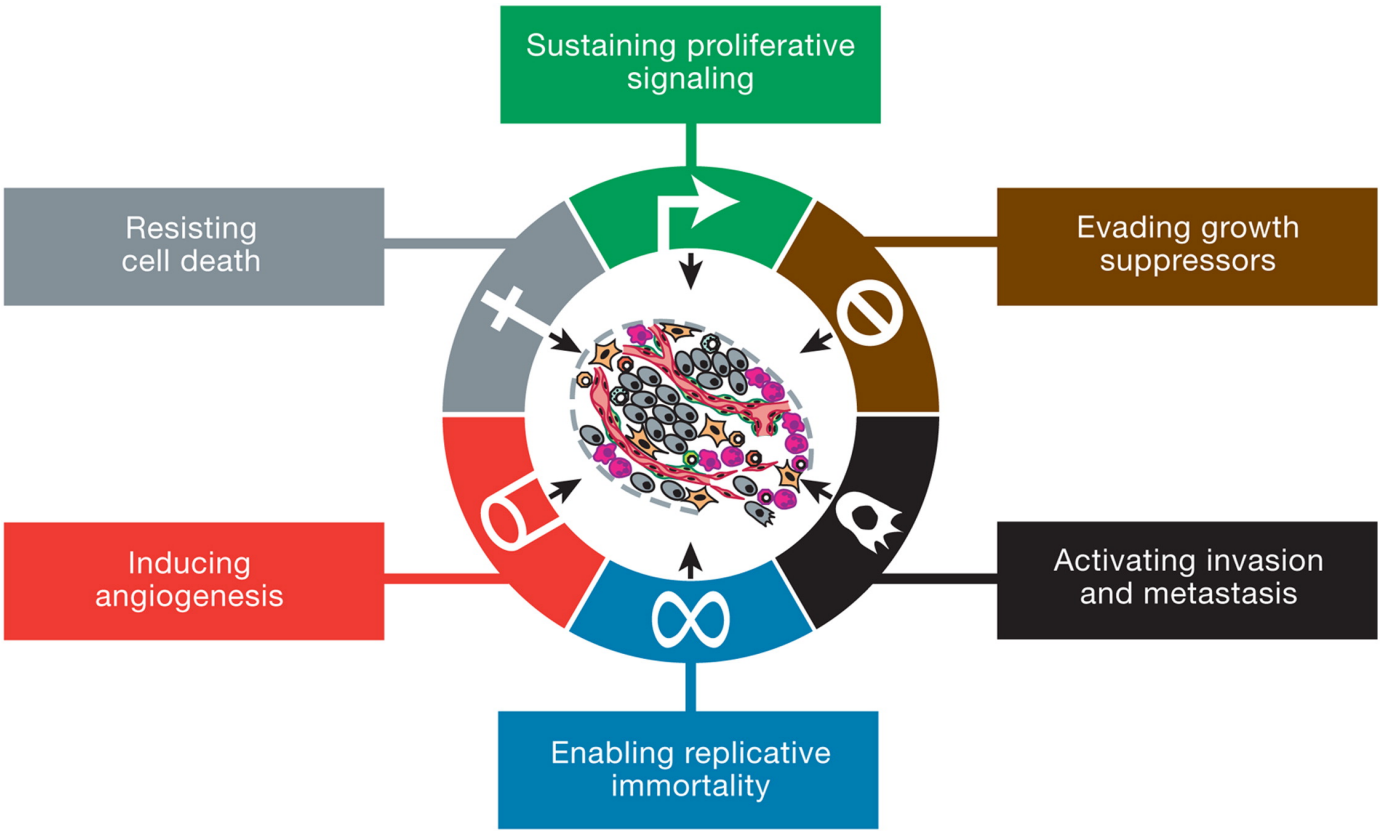
$$\begin{cases} \dfrac{\partial n}{\partial t} = D_n \Delta n - \nabla \cdot \left(\dfrac{\chi_0}{1+ac} n \nabla e \right) - \nabla \cdot (\rho n \nabla v) \\ \dfrac{\partial e}{\partial t} = D_e \Delta e - \eta n e \\ \dfrac{\partial v}{\partial t} = \beta n - \mu n v \end{cases} \tag{20}$$

n : endothelial cell density (representing blood vessels)

v : ECM (represented by collagens)

e : tumour angiogenesis factors (secreted by the cancer cells)

Invasion of the ECM and metastasis



Hallmarks of Cancer by Hanahan and Weinberg

Section 5.1: The Gatenby model(-s)

Cancer invasion models

the Gatenby-Gawlinski 1996 model

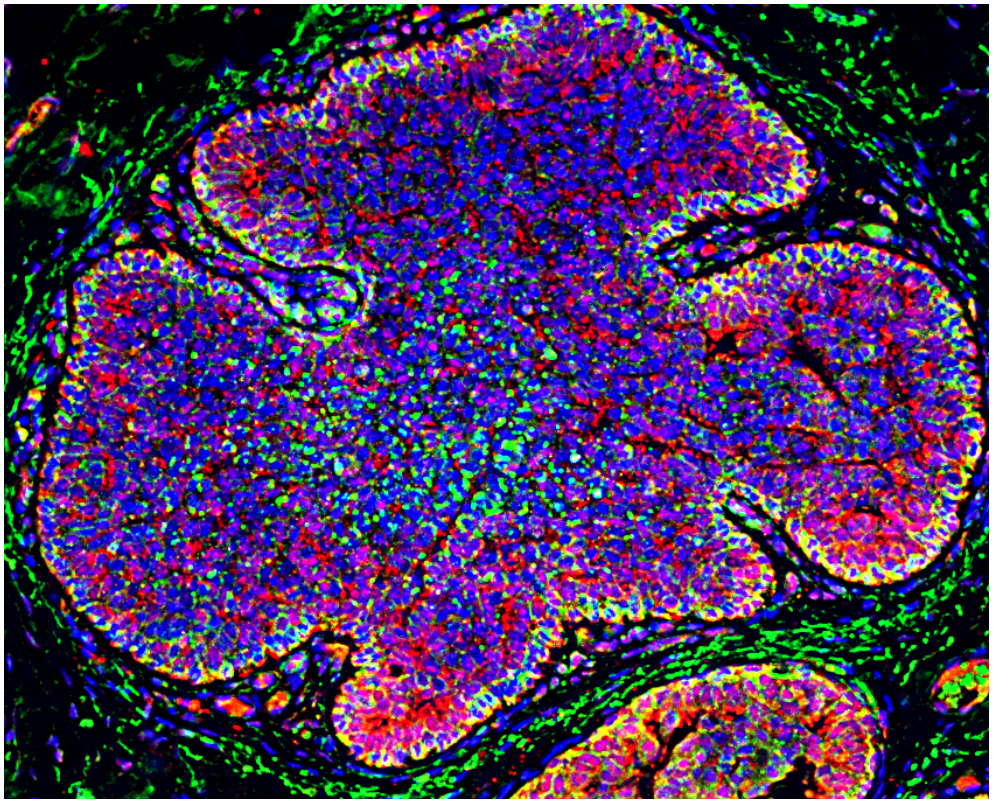


Figure: Low pH promotes aggressive tumour growth. A cross-section of a human breast tumour showing that low pH regions (red) coincide with regions of rapid retraction of the healthy tissue (green). (Source: Nazanin Rohani & PNAS)

Cancer invasion models
the Gatenby-Gawlinski 1996 model

We follow the authors

> *"...we hypothesize that transformation-induced reversion of neoplastic tissue to primitive glycolytic metabolic pathways, with resultant increased acid production and the diffusion of that acid into surrounding healthy tissue, creates a peritoumoral microenvironment in which tumour cells survive and proliferate, whereas normal cells are unable to remain viable."*

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More specifically, the main assumptions behind the model are:

> *"(a) high H^+ ion concentrations in tumours will extend, by chemical diffusion, as a gradient into adjacent normal tissue, exposing these normal cells to tumour-like interstitial pH;*

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> *"(a) high H^+ ion concentrations in tumours will extend, by chemical diffusion, as a gradient into adjacent normal tissue, exposing these normal cells to tumour-like interstitial pH;*
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> *(b) normal cells immediately adjacent to the tumour edge are unable to survive in this chronically acidic environment; and*
> *(c) the progressive loss of layers of normal cells at the tumour-host interface facilitates tumour invasion."*

Cancer invasion models

the Gatenby-Gawlinski 1996 model

Initial model version:

$$\begin{cases} \dfrac{\partial N}{\partial t} = \nabla \cdot (D_N T \nabla N) + r_N N \left(1 - \dfrac{N}{K_N} - b_{NT} \dfrac{T}{K_T}\right) - d_N L N \\ \dfrac{\partial T}{\partial t} = \nabla \cdot (D_T N \nabla T) + r_T T \left(1 - \dfrac{T}{K_T} - b_{TN} \dfrac{N}{K_N}\right) \\ \dfrac{\partial L}{\partial t} = D_L \Delta L + r_L T - d_L L \end{cases}$$

N: (healthy) tissue cell population T: tumour cell population L: H^+ concentration

Cancer invasion models

the Gatenby-Gawlinski 1996 model

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N: (healthy) tissue cell population T: tumour cell population L: H^+ concentration

Further modelling assumptions:

$$\begin{cases} D_N T = 0, & \text{immovable tissue} \\ D_T N = D_T \left(1 - \dfrac{N}{K_N}\right), & D_T \text{ constant} \\ b_{NT} = b_{TN} = 0, & \text{no cross-competition for resources} \end{cases}$$

Cancer invasion models

the Gatenby-Gawlinski 1996 model

To obtain:

$$\begin{cases} \dfrac{\partial N}{\partial t} = r_N N \left(1 - \dfrac{N}{K_N}\right) - d_N L N \\ \dfrac{\partial T}{\partial t} = D_T \nabla \cdot \left(\left(1 - \dfrac{N}{K_N}\right) \nabla T\right) + r_T T \left(1 - \dfrac{T}{K_T}\right) \\ \dfrac{\partial L}{\partial t} = D_L \Delta L + r_L T - d_L L \end{cases} \tag{21}$$

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N: (healthy) tissue cell population T: tumour cell population L: H^+ concentration

Non-dimensionalisation:

$$v = \frac{N}{K_N},\ c = \frac{T}{K_T},\ L = \frac{L}{L_0}, \tau = r_N t,\ \chi = \sqrt{\frac{r_N}{D_L}} x,\ L_0 = r_L \frac{K_T}{d_L}$$

Cancer invasion models

the Gatenby-Gawlinski 1996 model

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the above model recasts into:

$$\begin{cases} \dfrac{\partial v}{\partial \tau} = v\,(1 - v) - \sigma \Lambda v \\ \dfrac{\partial c}{\partial \tau} = \nabla \cdot (D\,(1 - v)\,\nabla c) + r c\,(1 - c) \\ \dfrac{\partial L}{\partial \tau} = \Delta L + \omega\,(c - L) \end{cases} \tag{22}$$

for $\sigma = \dfrac{d_N}{d_L} \dfrac{r_L}{r_N} K_T, \omega = \dfrac{d_L}{r_N}, D = \dfrac{D_T}{D_L}, r = \dfrac{r_T}{r_N}$

Cancer invasion models

the Gatenby-Gawlinski 1996 model

To obtain:

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What can we do with that?

Cancer invasion models

the Gatenby-Gawlinski 1996 model

To obtain:

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for $\sigma = \dfrac{d_N}{d_L} \dfrac{r_L}{r_N} K_T, \omega = \dfrac{d_L}{r_N}, D = \dfrac{D_T}{D_L}, r = \dfrac{r_T}{r_N}$

What can we do with that? Well, not much...

Cancer invasion models
the Gatenby-Gawlinski 1996 model

Spatially Uniform Steady States (SSs):

We solve the algebraic system

$$\begin{cases} v^* \left(1 - v^* - \sigma L^*\right) = 0 \\ r c^* \left(1 - c^*\right) = 0 \\ \omega \left(c^* - L^*\right) = 0 \end{cases}$$

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$$(v^*, c^*, L^*) = (0,0,0)\,,\ (1,0,0)\,,\ (1-\sigma,1,1)\,,\ (0,1,1)$$

Stability of the SSs:

For the quality of the SS we further need the Jacobian

$$J(v^*, c^*, L^*) = \begin{pmatrix} 1 - 2v^* - \sigma L^* & 0 & -\sigma v^* \\ 0 & r - 2rc^* & 0 \\ 0 & \omega & -\omega \end{pmatrix}$$

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and calculate the corresponding eigenvalues:

$$(v^*, c^*, L^*) = \begin{cases} (0,0,0) & \text{eigen: } (\lambda_1, \lambda_2, \lambda_3) = (1, r, -\omega) :: \text{unstable SS} \\ (1,0,0) & \text{eigen: } (\lambda_1, \lambda_2, \lambda_3) = (-1, r, -\omega) :: \text{unstable SS} \\ (1-\sigma,1,1) & \text{eigen: } (\lambda_1, \lambda_2, \lambda_3) = (-1+\sigma, -r, -\omega) :: \text{stable if } \sigma < 1 \\ (0,1,1) & \text{eigen: } (\lambda_1, \lambda_2, \lambda_3) = (1-\sigma, -r, -\omega) :: \text{stable if } \sigma > 1 \end{cases}$$

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Meaning of the SSs:

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SS-1: complete degradation of the tissue and tumour eradication;

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Meaning of the SSs:

SS-1: complete degradation of the tissue and tumour eradication; SS-2: complete tumour eradication and survival of the tissue to optimal density;

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Comment/Outcome:

The stability of SS-3 and SS-4 is driven by the constant

$$\sigma = \frac{d_N}{d_L}\frac{r_L}{r_N}K_T, \quad (N: \text{ healthy tissue}, T: \text{ cancer cells}, L: \text{ acid}).$$

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$$\sigma = \frac{d_N}{d_L}\frac{r_L}{r_N}K_T, \quad (N: \text{ healthy tissue}, T: \text{ cancer cells}, L: \text{ acid}).$$

It is conceivable that σ can change with time, e.g. if the resources that cancer cells consume (e.g. oxygen or nutrients) increase, so will K_T. It could then happen that σ switches from $\sigma < 1$ to $\sigma > 1$ and the dynamics shift from the SS-3 (stable when $\sigma < 1$) to the SS-4 (stable when $\sigma > 1$). This clearly implies that a tumour that previously coexisted with the healthy tissue will now become aggressive and consume/replace the healthy tissue altogether.

Cancer invasion models

the Gatenby-Gawlinski 1996 model

For $(\chi, \tau) \in \mathbb{R} \times [0, \infty)$

$$\begin{cases} \dfrac{\partial v}{\partial \tau} = v\,(1 - v) - \sigma L v \\ \dfrac{\partial c}{\partial \tau} = \nabla \cdot (D\,(1 - v)\,\nabla c) + r c\,(1 - c) \\ \dfrac{\partial L}{\partial \tau} = \Delta L + \omega\,(c - L) \end{cases}$$

Not much we can do here....

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Travelling wave solutions:

$$\text{for } z = \chi - \xi\tau, \text{ (wave speed) } \xi > 0, \text{ it holds } \frac{\partial}{\partial \tau} = -\xi \frac{d}{dz}, \quad \frac{\partial}{\partial \chi} = \frac{d}{dz}$$

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$$\begin{cases} -\xi v' = v\,(1 - v) - \sigma L v \\ -\xi c' = D\left((1 - v)\,c'' - v' c'\right) + r c\,(1 - c) \\ -\xi L' = L'' + \omega\,(c - L) \end{cases}$$

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There exist a travelling wave $c(\cdot)$ (one variable) s.t. for $z = \chi - \xi\tau$ holds

$$c(\chi, \tau) = c(z)$$

For fixed $\chi \in \mathbb{R}$, the solution $c(\chi, \cdot)$ (two variables) at the initial time $\tau = 0$ is found at $z = \chi$ of the travelling wave, i.e.

$$c(\chi, 0) = c(\chi).$$

For fixed $\chi \in \mathbb{R}$, the solution $c(\chi, \cdot)$ (two variables) at really future times $\tau \to \infty$, is found at $z \to -\infty$ of the travelling wave, i.e.

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The following are assumptions placed on the travelling wave solutions for $c(\cdot)$ and $L(\cdot)$

$$\lim_{z \to -\infty} c(z) = 1, \quad \lim_{z \to \infty} c(z) = 0$$

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Still, how are these states at $\pm\infty$ connected? i.e. what do the travelling waves $c(\cdot)$ and $L(\cdot)$ look like? i.e. how does the invading fronts (for c and L) look like?

Returning to the travelling wave ODE-system

$$\begin{cases} -\xi v' = v\,(1-v) - \sigma L v \\ -\xi c' = D\left((1-v)\,c'' - v'c'\right) + rc\,(1-c) \\ -\xi L' = L'' + \omega\,(c-L) \end{cases}$$

we see that there is not much we can do....

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Still, we can adjust it slightly to account for a) the differences in the diffusion rates:

$$D = \frac{D_T}{D_L}\left(= \frac{\text{cancer cell diffusion}}{\text{acid diffusion}}\right) \approx 0,$$

and

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Still, we can adjust it slightly to account for a) the differences in the diffusion rates:

$$D = \frac{D_T}{D_L}\left(= \frac{\text{cancer cell diffusion}}{\text{acid diffusion}}\right) \approx 0,$$

and b) the slow cancer propagation/invasion speed ξ vs the diffusion of the acid.
Accordingly we obtain:

$$\begin{cases} -\xi v' = v\,(1-v) - \sigma L v \\ -\xi c' = rc\,(1-c) \\ 0 = L'' + \omega\,(c-L) \end{cases}$$

Here we could solve for c, and then L, and v ...

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the Gatenby-Gawlinski 1996 model

$$\begin{cases} -\xi v' = v\,(1-v) - \sigma L v \\ -\xi c' = r c\,(1-c) \\ 0 = L'' + \omega\,(c-L) \end{cases}$$

$$\lim_{z \to -\infty} c(z) = 1, \quad \lim_{z \to \infty} c(z) = 0$$

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Clearly(!) from the c-ODE we can deduce

$$c(z) = \frac{1}{1 + \mathcal{A} e^{r/\xi z}}, \quad \mathcal{A} > 0$$

and verify that the asymptotic assumptions are satisfied $\lim_{z \to -\infty} c(z) = 1$, $\lim_{z \to \infty} c(z) = 0$.

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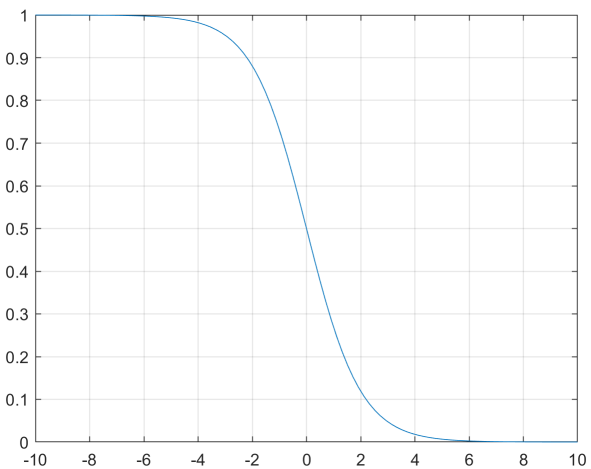

Figure: Graph of $2/(1 + e^x)$

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What remains is to solve a v, L-ODE system

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We will not pursue that any further because it becomes quite technical to solve, still the idea is to solve the L-ODE first and then substitute in and solve the v-ODE.

Cancer invasion models

the Gatenby et al 2002 model

$$\begin{cases} \dfrac{\partial N}{\partial t} = D_N \dfrac{\partial^2 N}{\partial x^2} + r_N N \left(1 - \dfrac{N}{K_N} - \dfrac{T}{K_T}\right) \\ \dfrac{\partial T}{\partial t} = D_T \dfrac{\partial^2 T}{\partial x^2} + r_T T \left(1 - \dfrac{T}{K_T} - \dfrac{N}{K_N}\right) \end{cases} \tag{23}$$

N: (healthy) tissue cell population
T: tumour cell population
r_N, r_T: growth rates
K_N, K_T: maximal cell densities
b_{NT}, b_{TN}: lumped competition terms
D_N, D_T: cellular diffusion coeffs.

Non-dimensionalisation:

$$v = \frac{N}{K_N},\ c = \frac{T}{K_T},\ \tau = r_N t,\ \bar{x} = \sqrt{\frac{r_N}{D_N}}x,$$

Cancer invasion models

the Gatenby et al 2002 model

$$\begin{cases} \dfrac{\partial N}{\partial t} = D_N \dfrac{\partial^2 N}{\partial x^2} + r_N N \left(1 - \dfrac{N}{K_N} - \dfrac{T}{K_T}\right) \\ \dfrac{\partial T}{\partial t} = D_T \dfrac{\partial^2 T}{\partial x^2} + r_T T \left(1 - \dfrac{T}{K_T} - \dfrac{N}{K_N}\right) \end{cases} \tag{23}$$

N: (healthy) tissue cell population
T: tumour cell population
r_N, r_T: growth rates
K_N, K_T: maximal cell densities
b_{NT}, b_{TN}: lumped competition terms
D_N, D_T: cellular diffusion coeffs.

Non-dimensionalisation:

$$v = \frac{N}{K_N},\ c = \frac{T}{K_T},\ \tau = r_N t,\ \bar{x} = \sqrt{\frac{r_N}{D_N}} x,$$

the above model recasts into:

$$\begin{cases} \dfrac{\partial v}{\partial \tau} = \Delta v + v\,(1 - v - c) \\ \dfrac{\partial c}{\partial \tau} = D\Delta c + rc\,(1 - c - v) \end{cases} \tag{24}$$

for $D = \frac{D_T}{D_N}, r = \frac{r_T}{r_N}$

Cancer invasion models

the Gatenby et al 2002 model

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Cancer invasion models

the Gatenby et al 2002 model

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Setting the reaction terms $F = v\,(1 - v - c)$ and $G = rc\,(1 - c - v)$, we identify the steady states by solving the (algebraic) system‘

$$\begin{cases} F(v^*, c^*) = 0 \\ G(v^*, c^*) = 0 \end{cases}$$

which yields

$$(v^*, c^*) = (0, 0)\,,\ (1, 0)\,,\ (0, 1)\,,\ (v^*, 1 - v^*)\,,\ \text{as long as } v^* < 1$$

Cancer invasion models

the Gatenby et al 2002 model

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The characterisation of the steady states follows from the Jacobian:

$$J(v, c) = \begin{pmatrix} \partial_v F & \partial_c F \\ \partial_v G & \partial_c G \end{pmatrix} = \begin{pmatrix} 1 - c - 2v & -v \\ -rc & r(1 - v - 2c) \end{pmatrix}$$

Cancer invasion models

the Gatenby et al 2002

- The SS $(v^*, c^*) = (0, 0)$ corresponds to complete loss of healthy tissue and complete eradication of the tumour;

Cancer invasion models

the Gatenby et al 2002

- The SS $(v^*, c^*) = (0, 0)$ corresponds to complete loss of healthy tissue and complete eradication of the tumour; it is unstable since:

$$\det\left(J(0,0)\right) = r > 0 \text{ and } \operatorname{tr}\left(J(0,0)\right) = 1 + r > 0.$$

Cancer invasion models

the Gatenby et al 2002

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Cancer invasion models

the Gatenby et al 2002

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- The SS $(v^*, c^*) = (1, 0)$ corresponds to complete cancer eradication and survival of the healthy tissue; it is a stable centre since:

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Cancer invasion models

the Gatenby et al 2002

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Cancer invasion models

the Gatenby et al 2002

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Cancer invasion models

the Gatenby et al 2002

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$$\det\left(J(v^*, 1-v^*)\right) = 0 \text{ and } \operatorname{tr}\left(J(v^*, 1-v^*)\right) = -v^* - r(1-v^*) < 0.$$

Section 5.2: The Chaplain-Lolas *urokinase* model

Cancer invasion models

The multifacted role of *urokinase*

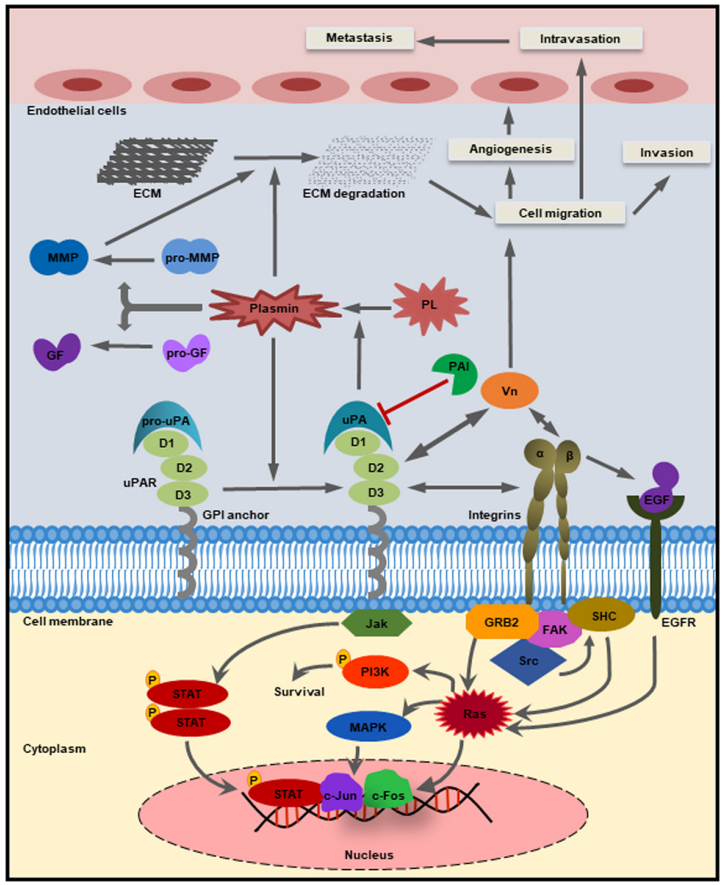


Figure: Schematic diagram of the uPA–*urokinase-type plasminogen activator receptor* (uPAR)-mediated pathways.“The *glysocylphosphatidylinositol* (GPI)-anchored receptor uPAR consisting of three domains (D1, D2, and D3) has the ability to bind the *zymogen* pro-uPA as well as the active uPA through the growth factor domain. The catalytically active form of uPA then converts inactive plasminogen into plasmin, which in turn can cleave and activate GFs, matrix metalloproteases (MMPs), as well as the extracellular matrix (ECM). The activated MMPs can directly cause the degradation of ECM and thereby release various growth factors. *Plasminogen activator inhibitor-1* (PAI-1) can inhibit the catalytic activity of both uPA and plasmin. Apart from uPA, uPAR also binds to integrins and other cell surface receptors to activate different intracellular signaling pathways, e.g. focal adhesion kinase (FAK), and Rac, and regulates cellular processes such as cell proliferation, survival, migration, invasion, angiogenesis, and metastasis.”

(Source: Frontiers in Oncology, Mahmood et al (2018))

Cancer invasion models

The multifacted role of *urokinase*

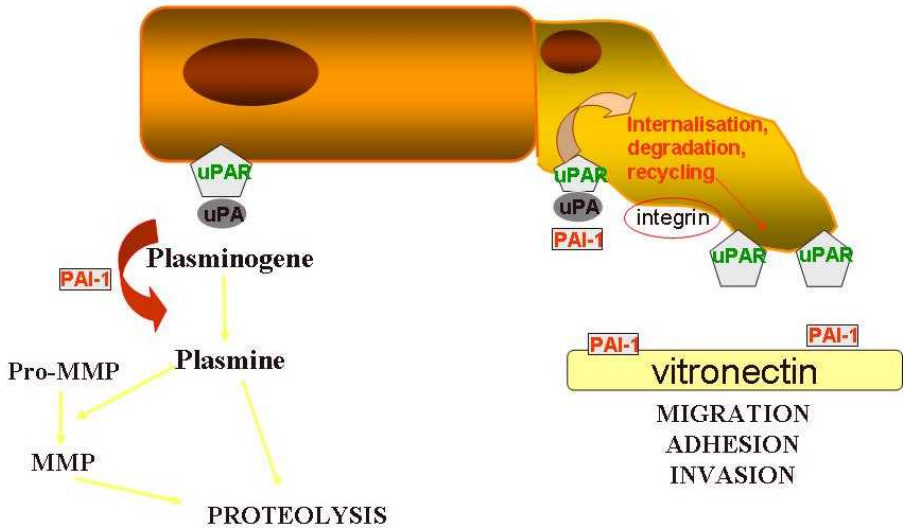


Figure: The role of uPA (Source: Laboratoire de Biologie des Tumeurs et du Dèveloppement, Liége)

- *plasmin*: ECM degradation protein
- MMP: *matrix metaloproteinases*
- uPA (*urokinase plasminogen activator*: proteolytic enzyme, over expressed by cancer cells) binds to VN (*vitronectin*) and weakens migration
- uPA bounds to uPAR (uPA Receptors: anchored on the cells); activates plasmin (weakens ECM/cell-contact); stimulates proliferation
- PAI-1: (*Plasminogen Activator Inhibitor*) inhibits/blocks uPA/uPAR activity; weakens migration
- PAI-1 binds to VN; weakens ECM/cell-contact; strengthens migration

Cancer invasion models

The multifaceted role of *urokinase* – Chaplain - Lolas (2006)

$$\frac{\partial c}{\partial t} = D_c \underbrace{\frac{\partial^2 c}{\partial x^2}}_{\text{diffusion}} \underbrace{- \frac{\partial}{\partial x}\left(\chi_c c \frac{\partial u}{\partial x} + \zeta_c c \frac{\partial p}{\partial x} + \xi_c c \frac{\partial v}{\partial x}\right)}_{\text{hapto-, chemotaxis}} + \underbrace{\phi_{13} c u}_{\text{uPA/uPAR}} + \mu_1 c(1-c)$$

$$\frac{\partial v}{\partial t} = \underbrace{\phi_{21} p u}_{\text{PAI-1/uPA}} - \underbrace{\phi_{22} p v}_{\text{PAI-1/VN}} + \mu_2 v(1-v) - \delta v m$$

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} - \underbrace{\phi_{31} p u}_{\text{PAI-1/uPA}} - \underbrace{\phi_{33} c u}_{\text{uPA/uPAR}} + \alpha_{31} c$$

$$\frac{\partial p}{\partial t} = D_p \frac{\partial^2 p}{\partial x^2} - \underbrace{\phi_{41} p u}_{\text{PAI-1/uPA}} - \underbrace{\phi_{42} p v}_{\text{PAI-1/VN}} + \alpha_{41} m$$

$$\frac{\partial m}{\partial t} = D_m \frac{\partial^2 m}{\partial x^2} - \underbrace{\phi_{51} p u}_{\text{PAI-1/uPA}} + \underbrace{\phi_{52} p v}_{\text{PAI-1/VN}} + \underbrace{\phi_{53} c u}_{\text{uPA/uPAR}}$$

c :	cancer cells	uPA/uPAR :	yields plasmin, increases cell proliferation
v :	extracellular matrix	PAI-1/VN :	increases plasmin production
u :	uPA	PAI-1/uPA :	decreases plasmin, increases vitronectin
p :	PAI-1 inhibitors		
m :	plasmin		

Cancer invasion models

The multifaceted role of *urokinase* – Chaplain - Lolas (2006)

- Special setting: consider the following set of parameters

$$
\begin{array}{llll}
D_c = 3.5 \times 10^{-4} & D_u = 2.5 \times 10^{-3} & D_p = 3.5 \times 10^{-3} & D_m = 4.91 \times 10^{-3} \\
\chi_u = 3.05 \times 10^{-2} & \chi_p = 3.75 \times 10^{-2} & \chi_u = 2.85 \times 10^{-2} & \mu_1 = 0.25 \\
\delta = 8.15 & \phi_{21} = 0.75 & \phi_{22} = 0.55 & \mu_2 = 0.15 \\
\phi_{31} = 0.75 & \phi_{33} = 0.3 & \alpha_{31} = 0.215 & \\
\phi_{41} = 0.75 & \phi_{42} = 0.55 & \alpha_{41} = 0.5 & \\
\phi_{52} = 0.11 & \phi_{53} = 0.75 & \phi_{54} = 0.5 &
\end{array}
$$

- Special setting: Initial conditions

$$c(0,\mathbf{x}) = e^{-|x|^2/\varepsilon},\ v(0,\mathbf{x}) = 1 - 0.5e^{-|x|^2/\varepsilon},\ u(0,\mathbf{x}) = 0.5e^{-|x|^2/\varepsilon}$$

$$p(0,\mathbf{x}) = 1/20e^{-|x|^2/\varepsilon},\ m(0,\mathbf{x}) = 0$$

Analytical treatment

- Special setting: spatially uniform steady states. The authors calculated (we don't need to do that here) that the system possesses the, following steady state

$$(c, v, u, p, m) = (1, 0.047, 0.222, 0.889, 0.343)$$

- Special setting: the Jacobian (verify and correct if needed)

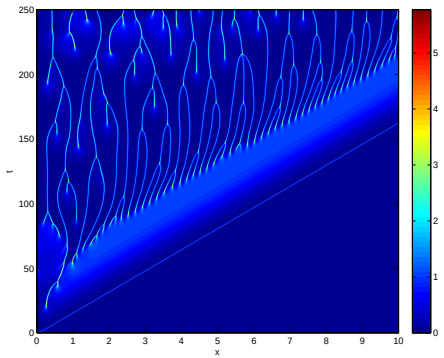
$$J = \begin{pmatrix} \mu_1(1-2c) & 0 & 0 & 0 & 0 \\ 0 & -\delta m - \phi_{22}p + \mu_2(1-2v) & \phi_{21}p & \phi_{21}u - \phi_{22}v & -\delta v \\ -\phi_{33}u + a_{31} & 0 & -\phi_{31}p - \phi_{33}c & -\phi_{31}u & 0 \\ 0 & -\phi_{42}p & -\phi_{41}p & -\phi_{41}u - \phi_{42}v & a_{41} \\ \phi_{53}u & \phi_{52}p & \phi_{53}c & \phi_{52}v & -\phi_{54} \end{pmatrix}$$

which has all its eigenvalues with negative real part

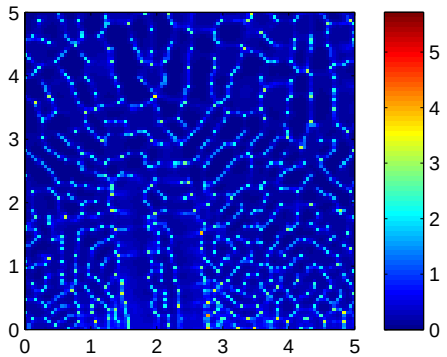
Cancer invasion models

The multifaceted role of *urokinase* – Numerical treatment – Sfakianakis et al (2016)

- Dynamical solutions:



1D

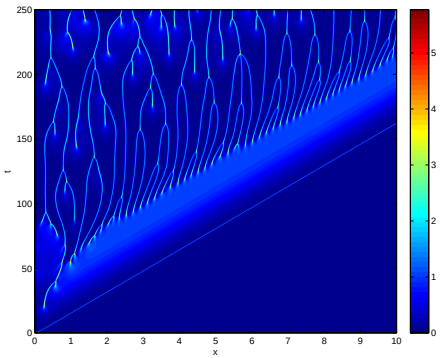


2D

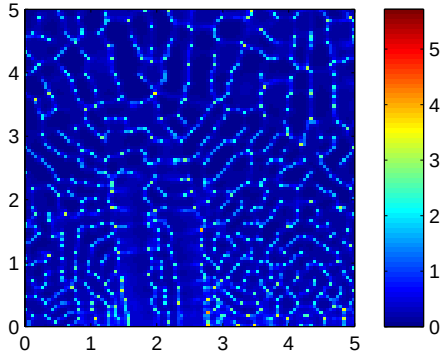
Cancer invasion models

The multifaceted role of *urokinase* – Numerical treatment – Sfakianakis et al (2016)

- Dynamical solutions:

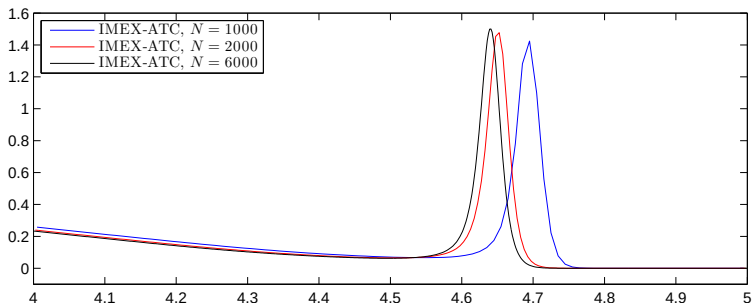


1D

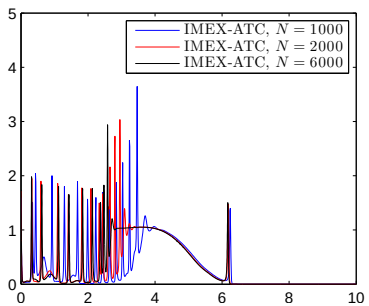


2D

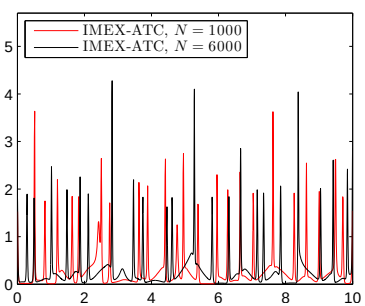
- (very) Strong dependence on grid:



(a) early time



(b) later time



(c) even later time

Section 5.3: Two-scale modelling

Cancer invasion models

EMT and metastasis

Cancer invasion models

EMT and metastasis

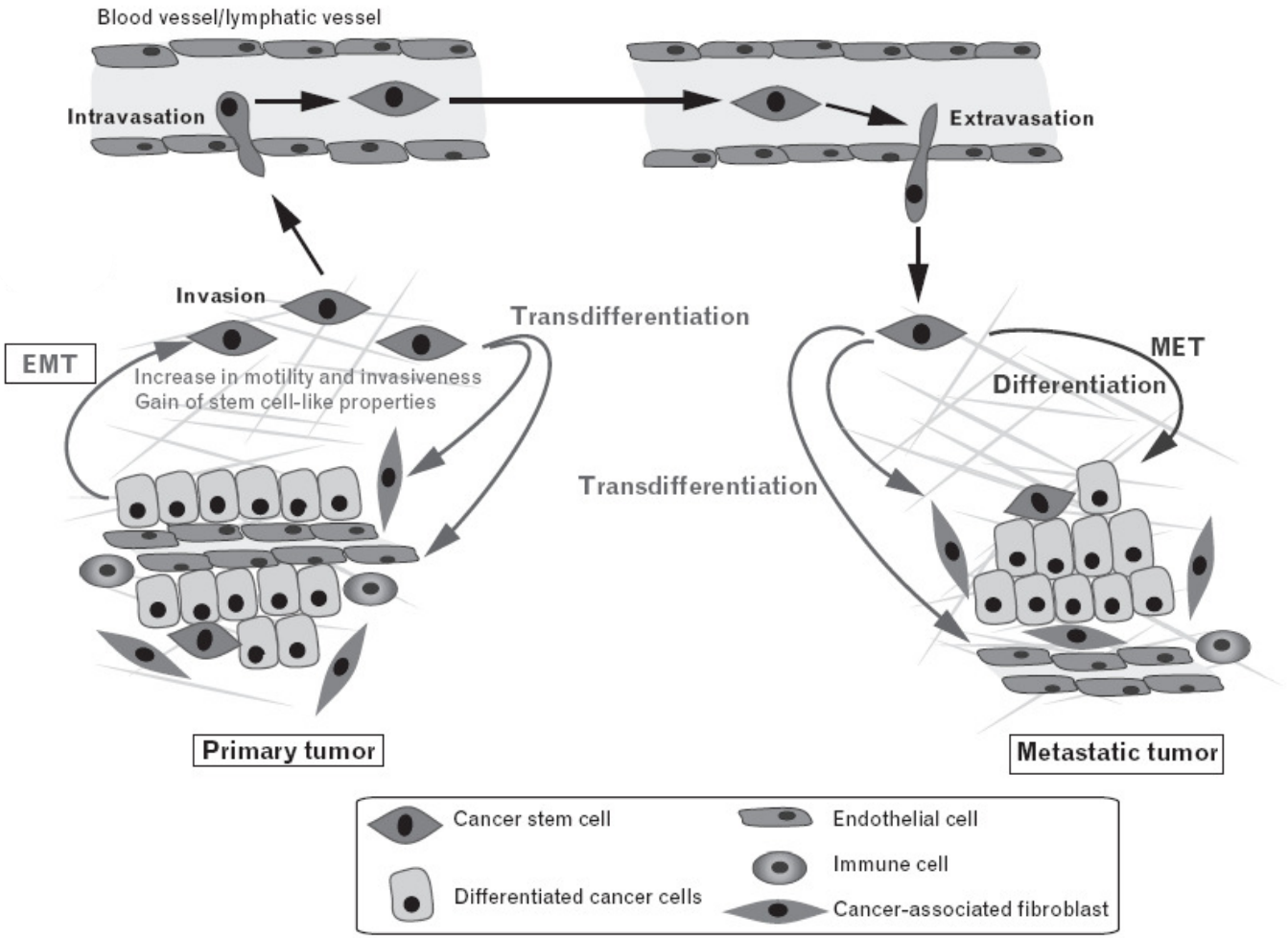


Figure: (Soufce: Katsumo et al., Curr. Opin. Oncol., 2013)

Cancer invasion models

The Sfakianakis-Kolbe model (2018)

$$
\begin{aligned}
\frac{\partial c_d}{\partial t} &= \underbrace{D_d \Delta c_d}_{\text{diffusion}} - \underbrace{\chi_d \nabla \cdot (c_d \nabla v)}_{\text{haptotaxis}} && - \mu_{\text{EMT}}\, c_d && + \underbrace{\mu_d\, c_d\, V_{\text{free}}}_{\text{proliferation}} \\
\frac{\partial c_s}{\partial t} &= D_s \Delta c_s - \chi_s \nabla \cdot (c_s \nabla v) && -\mu_{\text{TRA}}\, c_s + \mu_{\text{EMT}}\, c_d && + \mu_s\, c_s\, V_{\text{free}} \\
\frac{\partial c_f}{\partial t} &= D_f \Delta c_f + \chi_F \nabla \cdot (c_f \nabla v) && +\mu_{\text{TRA}}\, c_s && -\beta_f\, c_f + \mu_f\, c_f\, V_{\text{free}} \\
\frac{\partial v}{\partial t} &= && && -\delta_v\, m v + \mu_v\, c_f\, V_{\text{free}} \\
\frac{\partial m}{\partial t} &= D_m \Delta m && +\alpha_d\, c_d + \alpha_s\, c_s && -\beta_m\, m \\
& && && V_{\text{free}} = (1 - c_d - c_s - c_f - v)^+
\end{aligned}
$$

c_d:	differentiated cancer cells (*non-metastatic*)	v:	extracellular matrix
c_s:	de-differentiated cancer cells		
c_f:	cancer associated fibroblast cells	m:	matrix degen. proteine
EMT:	epithlial-mesenchymal transition	TRA:	transdifferentiation

Cancer invasion models

The Sfakianakis-Kolbe model (2018)

Michaelis-Menten type kinetics:

$$\mu_{\text{EMT}} = \mu_0 \frac{g_d^b}{\mu_{1/2} + g_d^b} \, ,$$

with

$$\begin{cases} \partial_\tau g^b = & k_+ g^f r^f - k_- g^b \\ \partial_\tau g^f = D_f \Delta g^f - & k_+ g^f r^f + k_- g^b \end{cases}$$

bound EGF :: $g^b = g_c^b + g_d^b$,
free EGFR :: r^f.

Cancer invasion models

The Sfakianakis-Kolbe model (2018)

Michaelis-Menten type kinetics:

$$\mu_{\text{EMT}} = \mu_0 \frac{g_d^b}{\mu_{1/2} + g_d^b} \,,$$

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bound EGF :: $g^b = g_c^b + g_d^b$,
free EGFR :: r^f.

and time (re-)scaling

$$\tau = \frac{t}{\varepsilon}, \quad 0 < \varepsilon << 1 \,.$$

gives

$$g^b = \frac{g^f}{k_D + g^f} \left(\lambda_s c_s + \lambda_d c_d \right)$$

total EGFR :: λ_s, λ_d

Cancer invasion models

The Sfakianakis-Kolbe model (2018)

Michaelis-Menten type kinetics:

$$\mu_{\text{EMT}} = \mu_0 \frac{g_d^b}{\mu_{1/2} + g_d^b} \,,$$

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bound EGF :: $g^b = g_c^b + g_d^b$,
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$$\tau = \frac{t}{\varepsilon}, \quad 0 < \varepsilon << 1 \,.$$

gives

$$g^b = \frac{g^f}{k_D + g^f} \left(\lambda_s c_s + \lambda_d c_d\right)$$

total EGFR :: λ_s, λ_d

So

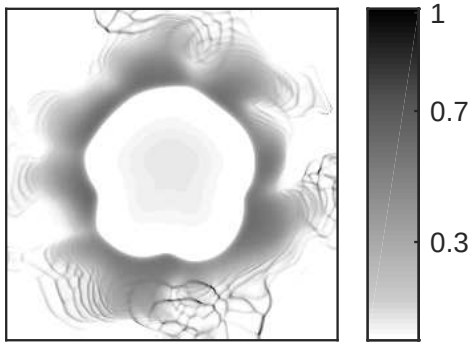
$$\mu_{\text{EMT}} = \mu_0 \frac{g^f \lambda_d c_d}{\mu_{1/2} k_D + \mu_{1/2} g^f + g^f \lambda_d c_d}$$

Cancer invasion models

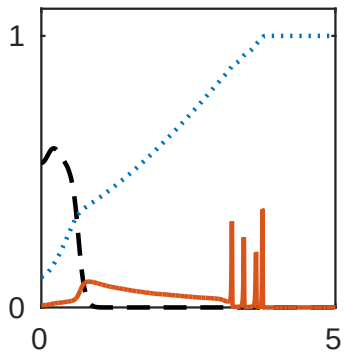
The Sfakianakis-Kolbe model (2018)

Highly dynamic metastatic cells

Invasion 2D: ▷ ▷



Invasion 1D: ▷



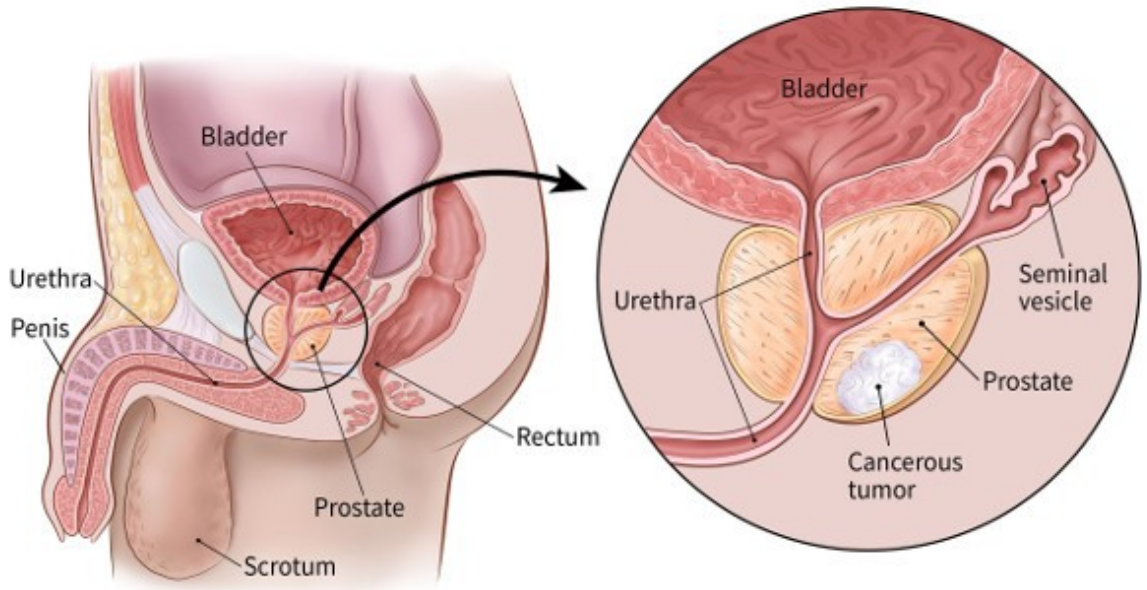
Section 5.4: Prostate cancer modelling

Cancer invasion models

Prostate cancer modelling

Cancer invasion models

Prostate cancer modelling

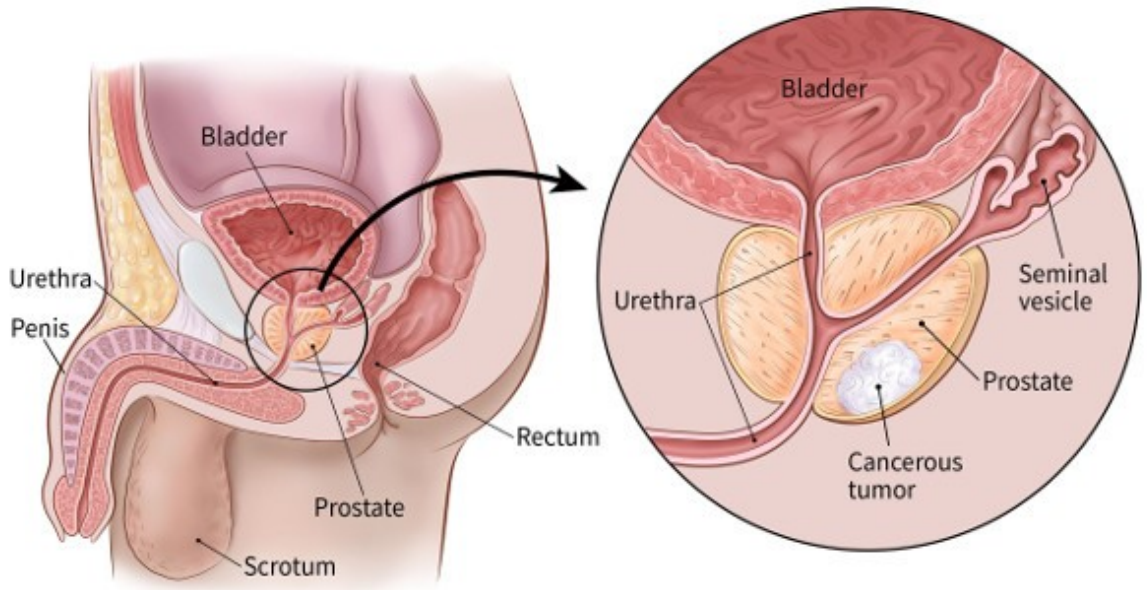


Source: American Cancer Society

- Most common form of cancer amongst men in the UK; almost 0.2% of the overall men population.
- Elevated levels of the *prostate specific antigen* (PSA) in blood are correlated with *prostatic tissue hyperplasia*.
- PSA is related to *androgenic hormones*, (*testosterone* or *dihydrotestosterone*) which bind to the *androgen receptor* (AR)
- AR function as *transcription factors* with many biological actions in the reproductive, musculoskeletal, cardiovascular, immune, neural and haemopoietic systems.
- When overexpressed, AR might lead to a local prostatic tissue hyperplasia.

Cancer invasion models

Prostate cancer modelling



Source: American Cancer Society

- Most common form of cancer amongst men in the UK; almost 0.2% of the overall men population.
- Elevated levels of the *prostate specific antigen* (PSA) in blood are correlated with *prostatic tissue hyperplasia*.
- PSA is related to *androgenic hormones*, (*testosterone* or *dihydrotestosterone*) which bind to the *androgen receptor* (AR)
- AR function as *transcription factors* with many biological actions in the reproductive, musculoskeletal, cardiovascular, immune, neural and haemopoietic systems.
- When overexpressed, AR might lead to a local prostatic tissue hyperplasia.

Still it is more complex than that...

Cancer invasion models

Prostate cancer modelling - the Jackson model (2004)

Assumptions

Cancer invasion models

Prostate cancer modelling - the Jackson model (2004)

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- The tumour is comprised of two populations of cancer cells: AR dependent (ARd) and AR independent (ARi)

Cancer invasion models

Prostate cancer modelling - the Jackson model (2004)

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- The increase of the *androgen* levels ...
  - increases in the proliferation of the ARds;
  - does not affect the proliferation of the ARis ;
  - decreases the *apoptosis* of the ARds ;
  - increases the *apoptosis* of the ARis.

Cancer invasion models

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Tumour-wide Jackson-model

For p: ARd, q: ARi, and for a: AR (androgen)

$$\begin{cases} \dfrac{dp(t)}{dt} = a_p \theta_p(a) p - \delta_p \omega_p(a) p \\ \dfrac{dq(t)}{dt} = a_q \theta_q(a) q - \delta_q \omega_q(a) p \end{cases} \tag{25}$$

where $a_p, a_q > 0$, δ_p, δ_q are the *maximum* cell proliferation and death rates, and where

Cancer invasion models

Prostate cancer modelling - the Jackson model (2004)

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$$\begin{cases} \theta_p = \theta_1 + (1-\theta_1)\dfrac{a}{a+K}, \quad 0 \le \theta_1 \le 1, \\ \theta_q = 1, \\ \omega_p = \omega_1 + (1-\omega_1)\dfrac{a}{a+K}, \quad \omega_1 > 1 \\ \omega_q = \omega_2 + (1-\omega_2)\dfrac{a}{a+K}, \quad 0 \le \omega_2 \le 1 \end{cases} \tag{26}$$

Continuum version Jackson model

Assuming radial symmetry (with r being the radious) of the tumour and $p(r,t)$, $q(r,t)$: cancer cell type *volume fraction*, i.e. $p(r,t)+q(r,t)=k$, constant

$$\begin{cases} \dfrac{\partial p}{\partial t} + \nabla \cdot (up) = D_p \Delta p + a_p \theta_p(a) p - \delta_p \omega_p(a) p \\ \dfrac{\partial q}{\partial t} + \nabla \cdot (uq) = D_q \Delta q + a_q \theta_q(a) q - \delta_q \omega_q(a) p \end{cases} \tag{27}$$

where u is the vector of collective cell migration.

Cancer invasion models

Prostate cancer modelling - the Jackson model (2004) cont'd

Continuum version Jackson model

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Single cancer cell type equation

Adding the above two equations one obtains:

$$k \nabla \cdot u = (D_p - D_q)\, \Delta p + a_p \theta_p(a) p + a_q \theta_q(a)(k-p) - \delta_p \omega_p(a) p - \delta_q \omega_q(a)(k-p)$$

which, based on the radial symmetry, can be used to solve for u.

Cancer invasion models

Prostate cancer modelling - the Jackson model (2004) cont'd

Continuum version Jackson model

Assuming radial symmetry (with r being the radious) of the tumour and $p(r,t)$, $q(r,t)$: cancer cell type *volume fraction*, i.e. $p(r,t)+q(r,t)=k$, constant

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which, based on the radial symmetry, can be used to solve for u.

Adding AR specific treatment

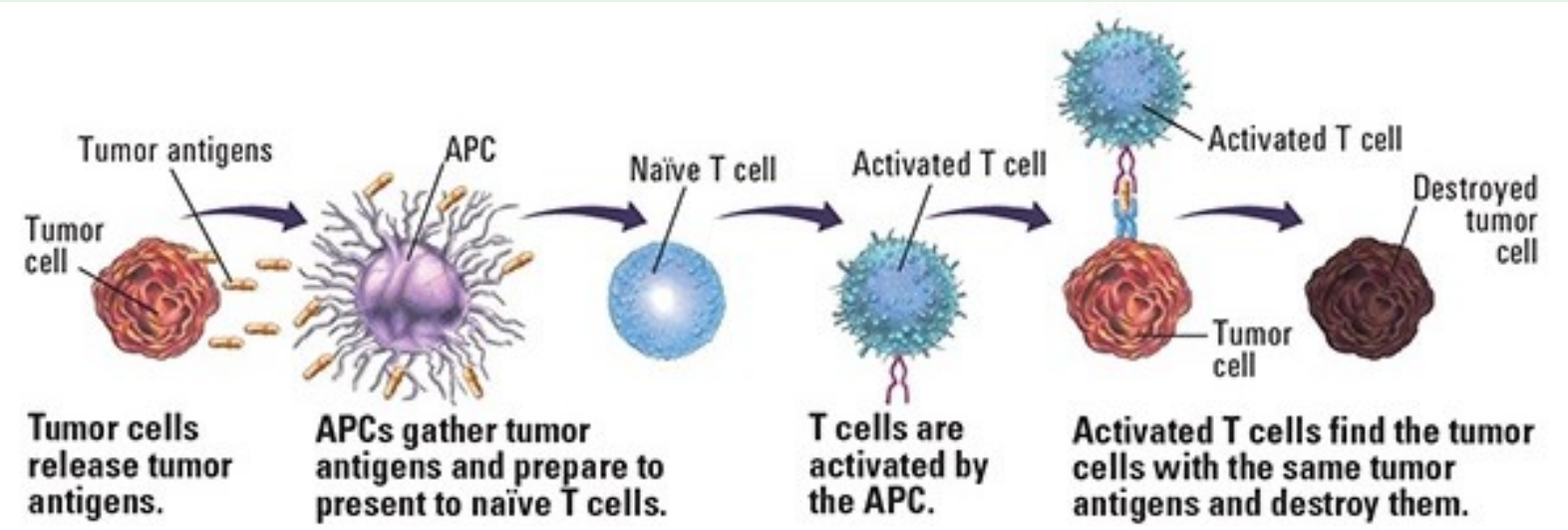
Assuming that AR levels $a(r,t)$ is at a steady state a_0 before treatment (surgical or chemical) is introduced

$$a(r,t) = \begin{cases} a_0, & t \le T \\ (a_0 - a_m) e^{-b(t-T)} + a_m, & t \ge T \end{cases}$$

where $0 \le a_m \le a_0$ is the minimum AR levels that can be achieved by the therapy.

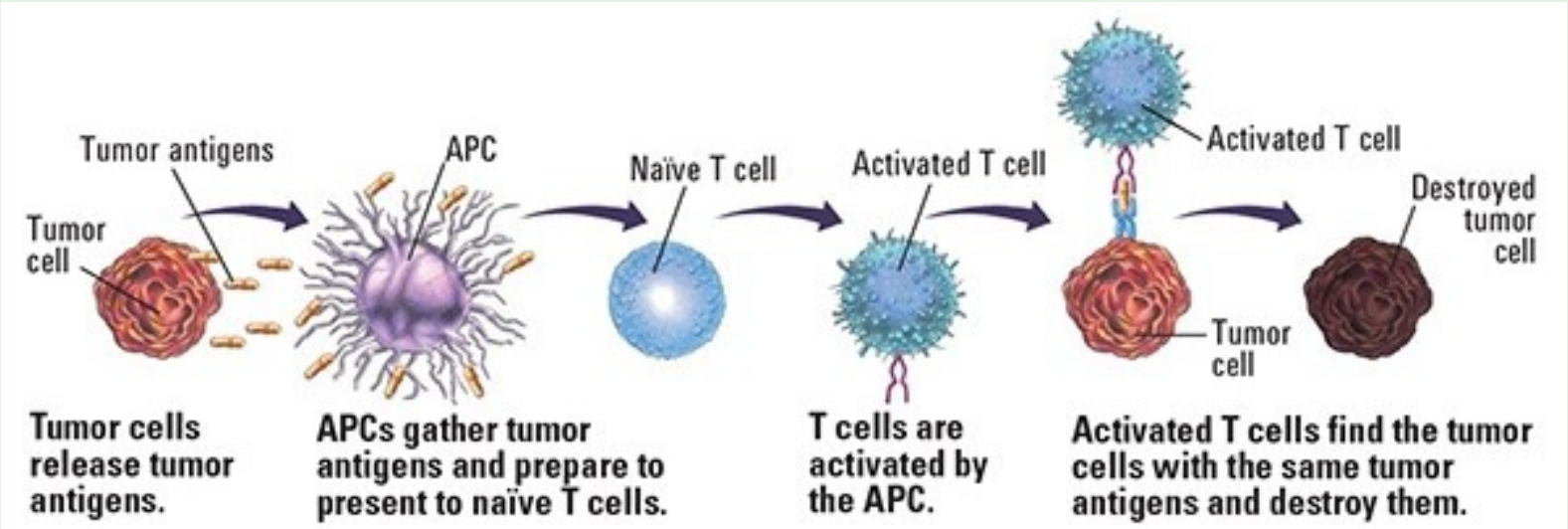
Cancer invasion models

Prostate cancer modelling - the Portz-Kuang-Nagy model (2012)



Cancer invasion models

Prostate cancer modelling - the Portz-Kuang-Nagy model (2012)



Some definition

- *Dendritic cells* (DC) are a class of *Antigen Presenting Cells*.
- *Cytokines* is a large group of proteins secreted, for communication, by cells of the immune system.
- *Homeostasis* is a self-regulating process of recovering physical and chemical stability in the organism.

Cancer invasion models

Prostate cancer modelling - the Portz-Kuang-Nagy model (2012) cont'd

$$
\begin{cases}
\text{ARds}: & \dfrac{dX_1}{dt} = r_1(A)X_1 - \underbrace{m(A)X_1}_{\text{mutation to } X_2} - \underbrace{\dfrac{e_1 X_1 T}{g_1 + X_1}}_{\text{killed by T cells}} \\
\text{ARis}: & \dfrac{dX_2}{dt} = r_2 X_2 + \underbrace{m(A)X_1}_{\text{mutation from } X_1} - \underbrace{\dfrac{e_1 X_2 T}{g_1 + X_2}}_{\text{killed by T cells}} \\
\text{T-cells}: & \dfrac{dT}{dt} = \underbrace{\dfrac{e_2 D}{g_2 + D}}_{\text{activation by DCs}} - \mu T + \underbrace{\dfrac{e_3 T I_L}{g_3 + I_L}}_{\text{clonal expansion}} \\
\text{cytokines}: & \dfrac{dI_L}{dt} = \underbrace{\dfrac{e_4 T(X_1 + X_2)}{g_4 + X_1 + X_2}}_{\text{production by T-cells}} - \omega I_L \\
AR: & \dfrac{dA}{dt} = \underbrace{\gamma\,(a_0 - A)}_{\text{homeostasis}} - \underbrace{\gamma a_0 u(t)}_{\text{therapy}} \\
\text{DCs}: & \dfrac{dD}{dt} = -cD
\end{cases}
\tag{28}
$$

Cancer invasion models

Prostate cancer modelling - the Salim et al model (2021)

Link to the paper

Section 5.5: Glioblastoma modelling

Cancer invasion models

Glioblastoma modelling

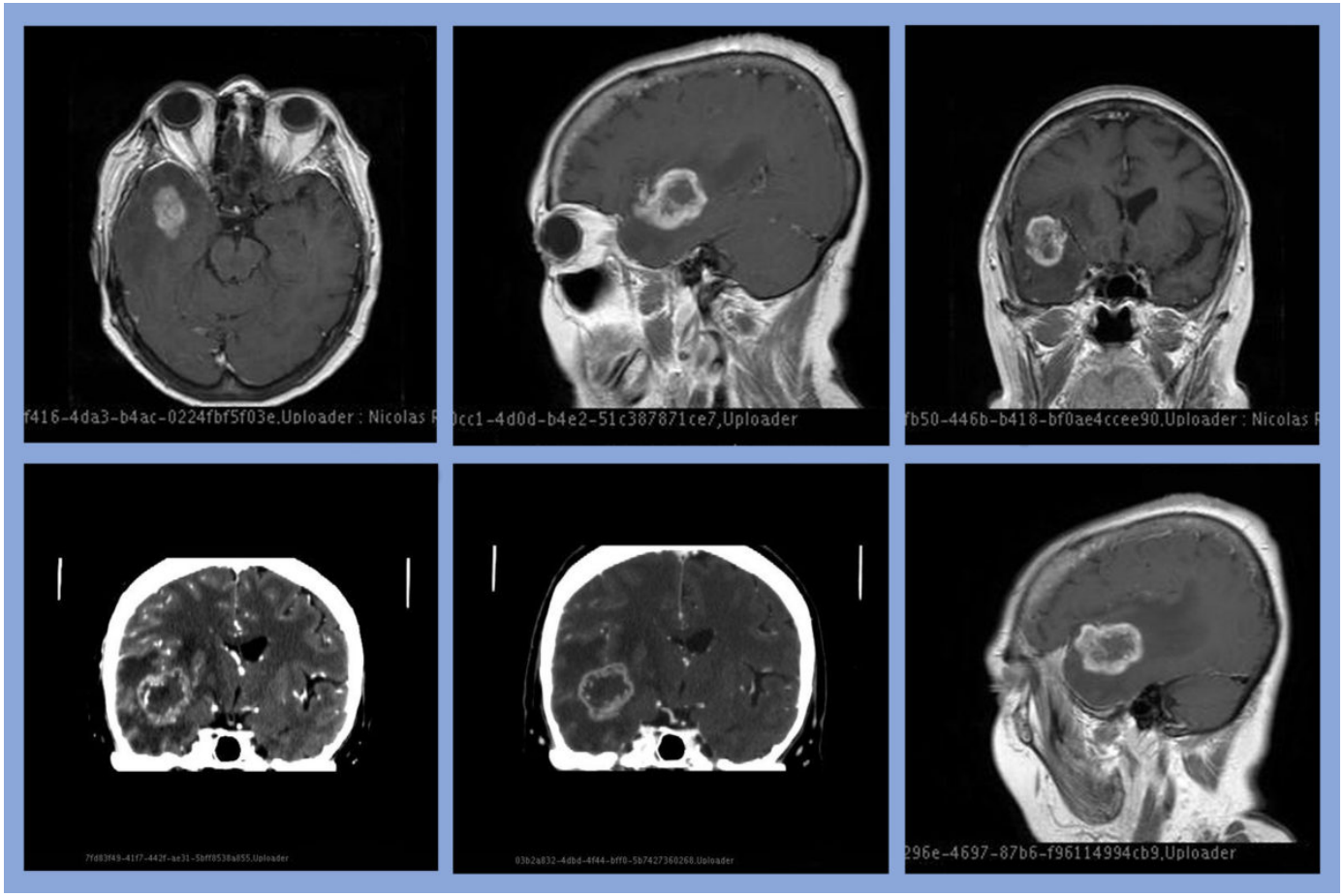


Figure: Brain scan of an 11 year old boy with a large size glioblastoma tumour (Source: NIH)

Glioblastoma (GBM)

A fast-growing type of central nervous system tumor that forms from *glial* (supportive) tissue of the brain and spinal cord and has cells that look very different from normal cells.

Source: NIH

Cancer invasion models

Glioblastoma modelling - The Stepien et al model

A single equation model by Stepien et al, (2015)

$$\frac{\partial u}{\partial t} = \nabla \cdot \left(D \left(\frac{u}{u_{\text{max}}} \right) \nabla u \right) + gu \left(1 - \frac{u}{u_{\text{max}}} \right) - \text{sgn}(\mathbf{x}) v \nabla \cdot u$$

for the non-constant diffusion coefficient $D(u) = D_1 - \frac{D_2 \, u^n}{a^n + u^n}$

$u(r,t)$: invasive tumour cells at radius r at time t

v: invasion "speed" (in the sense of advection)

u_{max}: carrying capacity

$g > 0$

Cancer invasion models

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1-D analogue

The 1-D analogue reads, after expanding the diffusion derivatives,

$$\frac{\partial u}{\partial t} = D\left(\frac{u}{u_{\text{max}}}\right) \frac{\partial^2 u}{\partial x^2} + \frac{1}{u_{\text{max}}} D'\left(\frac{u}{u_{\text{max}}}\right) \left(\frac{\partial u}{\partial x}\right)^2 + gu\left(1 - \frac{u}{u_{\text{max}}}\right) - v\frac{\partial u}{\partial x}$$

Cancer invasion models

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Non-dimensionalisation

We rescale using the change of variables

$$t^* = gt,\ x^* = x\sqrt{g},\ u^* = \frac{u}{u_{\text{max}}},\ v = \frac{v}{\sqrt{g}},$$

Cancer invasion models

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Non-dimensionalisation

We rescale using the change of variables

$$t^* = gt,\ x^* = x\sqrt{g},\ u^* = \frac{u}{u_{\text{max}}},\ v = \frac{v}{\sqrt{g}},$$

divide by gu_{max}, and drop the asterisk, the previous PDE recasts into

$$\frac{\partial u}{\partial t} = D(u) \frac{\partial^2 u}{\partial x^2} + D'(u) \left(\frac{\partial u}{\partial x}\right)^2 - v\frac{\partial u}{\partial x} + u(1-u)$$

Cancer invasion models

Glioblastoma modelling - The Stepien et al model cont'd

$$\frac{\partial u}{\partial t} = D\left(u\right)\frac{\partial^2 u}{\partial x^2} + D'\left(u\right)\left(\frac{\partial u}{\partial x}\right)^2 - v\frac{\partial u}{\partial x} + u\left(1-u\right)$$

Invasion-like travelling wave solution

Wave speed k: $w(z) = w(x-kt)$ if $\lim_{z\to-\infty} w = 1$ and $\lim_{z\to+\infty} w = 0$ (where does these come from?), and such that $u(x,t) = w(x-kt)$ for every x and t.

$$\frac{\partial u}{\partial t} = D\left(u\right)\frac{\partial^2 u}{\partial x^2} + D'\left(u\right)\left(\frac{\partial u}{\partial x}\right)^2 - v\frac{\partial u}{\partial x} + u\left(1-u\right)$$

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$$w''(z) + \frac{1}{D(w(z))}\left((k-v)w'(z) + D'(w(z))(w'(z))^2 + w(z)(1-w(z))\right) = 0$$

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which after the change of variable $w' = y$ reads as

$$\begin{cases} w' = y \\ y' = -\dfrac{1}{D(w)}\left(D'(w)y^2 + (k-v)y + w(1-w)\right) \end{cases} \tag{29}$$

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This system possesses two steady states:: $(w^*, y^*) = (0,0)$ and $(1,0)$.

- The Jacobian reads at $(1,0)$

$$J(1,0) = \begin{pmatrix} 0 & 1 \\ \frac{1}{D(1)} & \frac{-(k-v)}{D(1)} \end{pmatrix}$$

which has negative determinant $J(1,0) = \frac{-1}{D(1)} < 0$; hence the steady state $(w^*, y^*) = (1,0)$ is a saddle point.

- Similarly, the Jacobian at $(0,0)$ reads

$$J(0,0) = \begin{pmatrix} 0 & 1 \\ -\frac{1}{D(0)} & \frac{-(k-v)}{D(0)} \end{pmatrix}$$

for which $\det J(0,0) = \frac{1}{D(0)} = \frac{1}{D_1} > 0$ and, by assuming that $k > v$, $\mathrm{tr}(0,0) = \frac{-(k-v)}{D_1} < 0$; hence the steady state $(w^*, y^*) = (0,0)$ is stable.

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(You now know how it goes...)

Cancer invasion models

Glioblastoma modelling - The (simplified) Dietrich et al (2021) model

Cancer invasion models

Glioblastoma modelling - The (simplified) Dietrich et al (2021) model

M: *glioma cell density*, Q: *brain tissue density*, h: *ion (acid) concentration*, and e: *endothelial cell density*

$$\begin{cases} \partial_t M + \nabla_x \cdot (g(y^*)M) = \dfrac{1}{1+h} M(1-M), \\ \partial_t Q = c_1 Q(1-Q-M) - c_2 \dfrac{h}{1+h} Q, \\ \partial_t h = D_h \Delta h + \gamma(1-h)\dfrac{M}{1+M} - \delta h e, \\ \partial_t e = D_e \Delta e - \varsigma_e \nabla \cdot (e(1-e)\nabla h) + \nu_e e(1-e), \end{cases} \tag{30}$$

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where y^* is the concentration of free membrane-bound (i.e. on the cell) adhesion receptors,

$$\begin{cases} g(y^*) = a_1(1-M)\mathbb{D}_W b(y^*), \\ b(y^*) = (1-\rho_1-\rho_2)\dfrac{-\nabla h}{\sqrt{1+|\nabla h|^2}} + \rho_1(1-y^*)\dfrac{\nabla Q}{\sqrt{1+|\nabla Q|^2}} + \rho_2 \dfrac{-\nabla M}{\sqrt{1+|\nabla M|^2}}, \end{cases} \tag{31}$$

and where $\mathbb{D}_W$ is the brain tissue tensor.

Cancer invasion models

Glioblastoma modelling - The Dietrich et al (2021) model (cont'd)

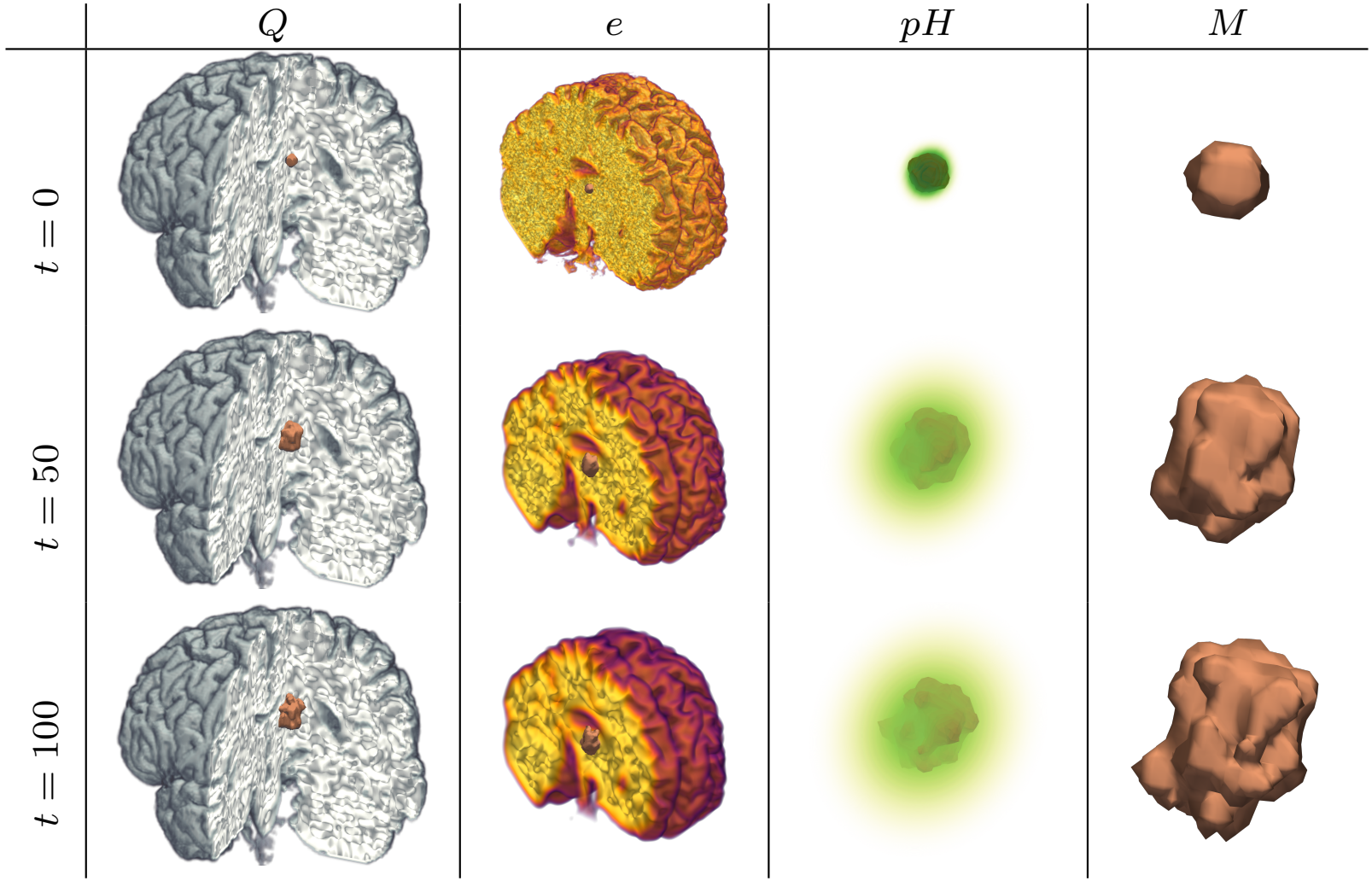


Figure: Simulation results for the brain tissue Q, the vasculature e,the pH, and of the 10^{-5} isosurface of the tumour at three different time instances.

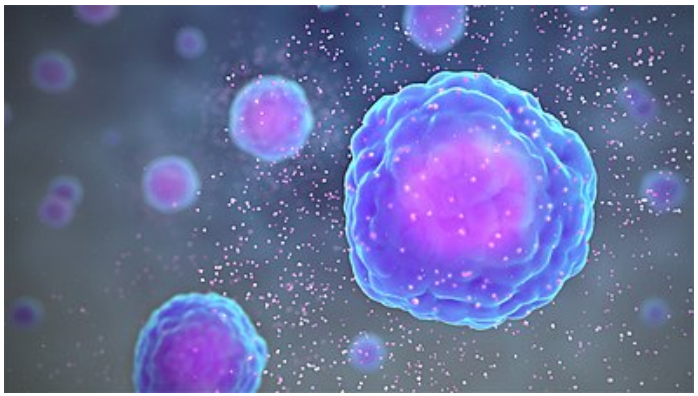
movie: ▷

Section 6

Multiscale models

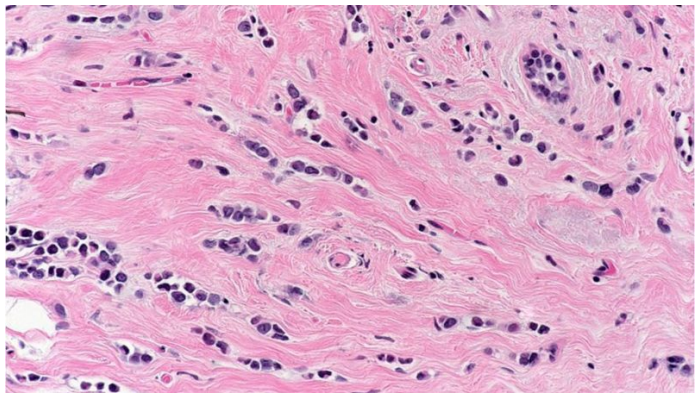
Section 6.1: Hybrid Atomistic-Macroscopic Invasion model

Hybrid atomistic-macroscopic modelling



(a) cytokine secretion

Source: Wikipedia



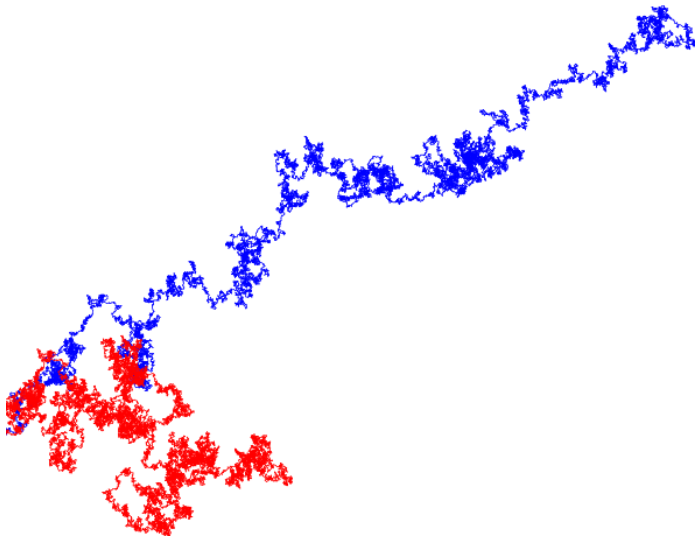
(b) breast cancer cells invading healthy tissue

Source: John Hopkins Pathology

- Many processes in biology are driven by the interactions between different scales; they take the form of e.g. *cytokines* interacting with cells, isolated cells interacting with tissues, and many-many more.
- At the same time, it is quite often the case that the main agents undergo transitions from one phase to another. An example are the dynamic cellular programming EMT and MET processes.

Both processes are combined in the modelling approach that we develop here.

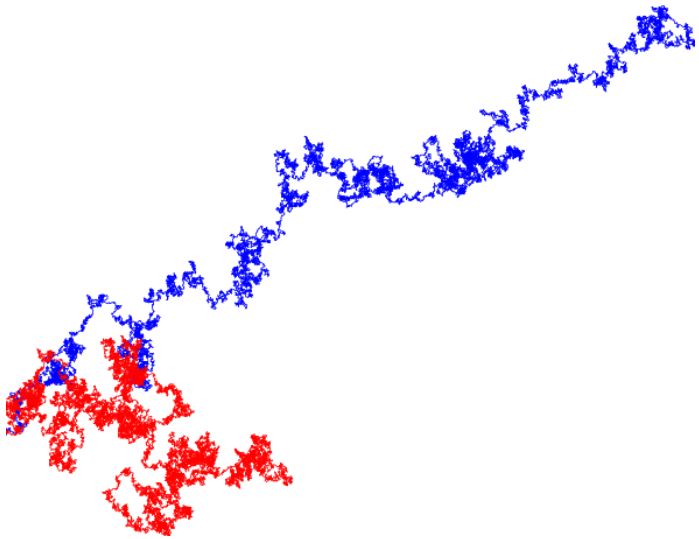
Hybrid atomistic-macroscopic modelling:
Stochastic Differential Equations



red: Brownian motion without drift (random); blue: Brownian motion with drift (biased random)

- A *stochastic process* is a family of random variables $\{\mathbf{X}_t\}$, where $t \in T$ (e.g. time) and $\mathbf{X}_t \in S$ (e.g $\mathbb{R}^2$). The family $\{\mathbf{X}_t\}$ is understood as the path of a particle moving randomly in space S.

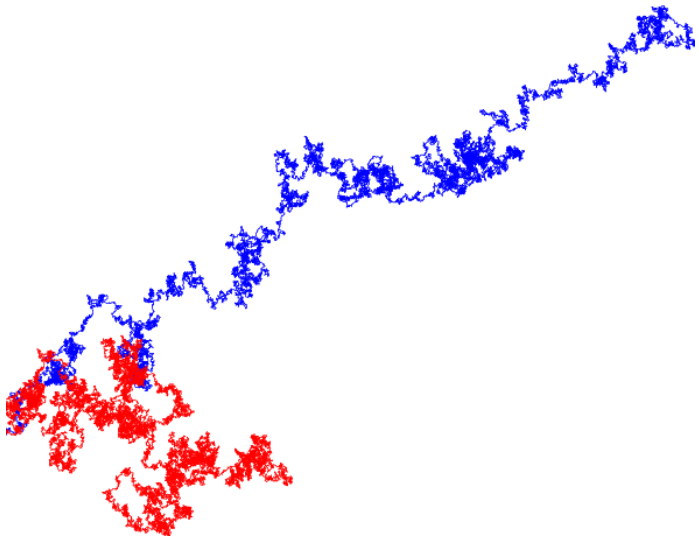
Hybrid atomistic-macroscopic modelling:
Stochastic Differential Equations



red: Brownian motion without drift (random); blue: Brownian motion with drift (biased random)

- A *stochastic process* is a family of random variables $\{\mathbf{X}_t\}$, where $t \in T$ (e.g. time) and $\mathbf{X}_t \in S$ (e.g $\mathbb{R}^2$). The family $\{\mathbf{X}_t\}$ is understood as the path of a particle moving randomly in space S.
- A *Stochastic Differential Equation* (SDE) is a differential equation where at least one of the terms is a stochastic process.

Hybrid atomistic-macroscopic modelling:
Stochastic Differential Equations



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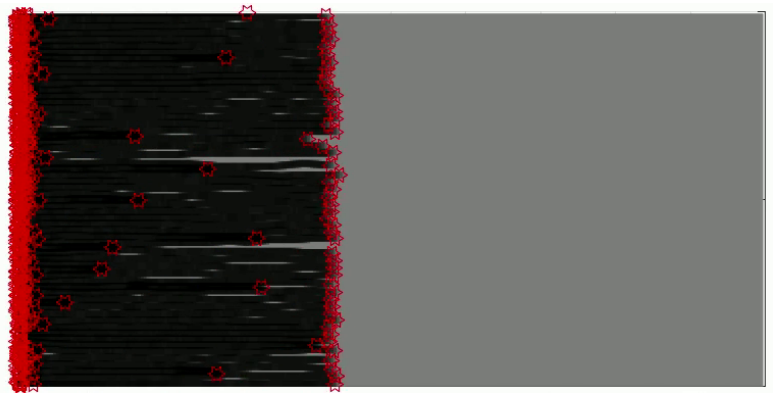
- A *Stochastic Differential Equation* (SDE) is a differential equation where at least one of the terms is a stochastic process.
- A typical SDE is of the form

$$d\mathbf{X}_t = \mu(\mathbf{X}_t, t)dt + \sigma(\mathbf{X}_t, t)dB_t$$

$\mathbf{X}_t$ :: stochastic process, μ :: drift coef. (directed part), σ :: diffusion coef. (random part)

During a small time period τ the stochastic process $\mathbf{X}_t$ (e.g. bacteria position in a petri dish) changes by an "amount" that is normally distributed with mean $\mu(\mathbf{X}_t, t)\tau$ and variance $\sigma(\mathbf{X}_t, t)^2\tau$.

Main modelling tool:
Cell migration and SDEs



A large number of particle-cells migrating with a pattern: here simulated by SDEs

Similar pattern can be seen when modelling with a density

$$d\mathbf{X}_t^p = \mu(\mathbf{X}_t^p, t)dt + \sigma(\mathbf{X}_t^p, t)d\mathbf{W}_t^p, \quad p \in P(t) = \{1 \dots N(t)\}$$

$\mathbf{X}_t^p$ :: position of cell p at time t, μ :: drift coefficient, σ :: diffusion coefficient, $\mathbf{W}_t$ :: Wiener process[1]

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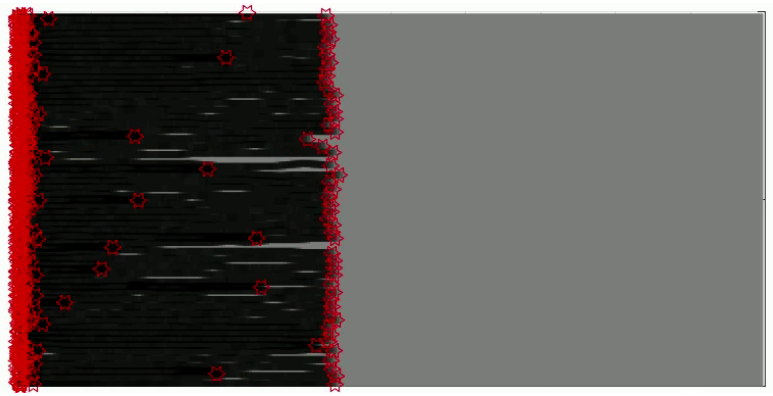

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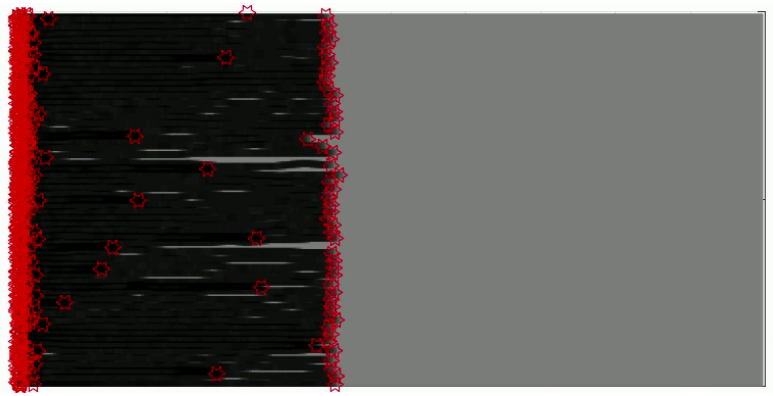

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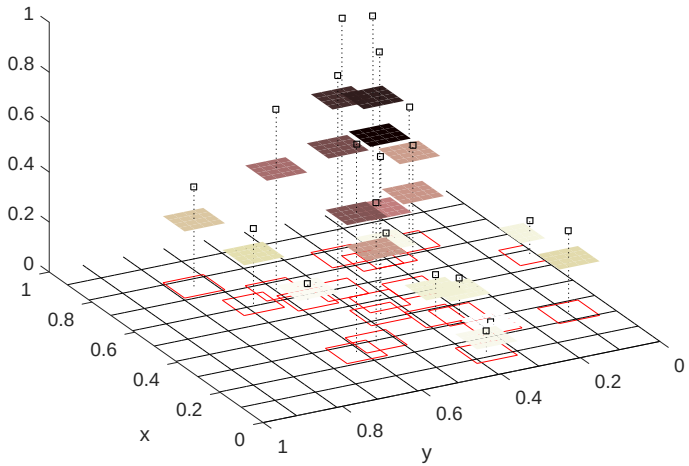
- The coefficients μ and σ encode the modelling assumptions placed on the directed and random parts of the motion of the cell-particles.
- In the large cell limit $N(t) \to \infty$ this system of SDE converges to a particular PDE. Which one? It depends on μ and σ; one needs to see in details the theory developed by Stratonovich and Itô.

Phase transition between density and cells



$$\left\{(\mathbf{x}_p(t), m_p),\ p \in P(t)\right\} \underset{\mathcal{B}}{\overset{\mathcal{F}}{\rightleftarrows}} c(\mathbf{x}, t)$$

$\mathbf{x}_p$, m_p :: position and mass of the particle p, c :: density profile

The transition between the density and (particle-)cell phases is taken care by:

$$m_p(t) = \int_{M_p} c(\mathbf{x}, t) d\mathbf{x}, \quad \mathbf{x}_p(t) \text{ :: (bary)centre of } M_p$$

M_p :: support of the cell

Hybrid atomistic-macroscopic cancer invasion model

A two-cancer-cell species, haptotaxis, EMT

Assumptions

1. Four main components: *epithelial-like cancer cells* (EC), *mesenchymal-like cancer cells* (MC), ECM, and MMPs.
2. The ECs mostly proliferate and barely migrate; the MCs migrate and barely proliferate.
3. The ECs mutate via EMT to MCs, and vice-versa through MET.
4. The ECs compete for resources with the MCs and the ECM.
5. Mechanical pushing forces are developed between the ECs.
6. The MCs perform a haptotaxis biased random motion.
7. The MMPs are produced by both ECs and MCs.
8. The MMPs diffuse freely in the environment and decay.
9. The ECM is degraded by the complexes of ECs and MCs with MMPs.

Hybrid atomistic-macroscopic cancer invasion model

A two-cancer-cell species, haptotaxis, EMT

Density description of main variables:

$$\begin{cases} \dfrac{\partial}{\partial t}c^{\alpha} = D_{\alpha}\Delta c^{\alpha} - \mu_{\alpha}^{\text{EMT}}c^{\alpha} + \mu_{\beta}^{\text{MET}}c^{\beta} + \rho_{c}^{\alpha}c^{\alpha}\left(1 - c^{\alpha} - c^{\beta} - v\right) \\ \dfrac{\partial}{\partial t}c^{\beta} = D_{\alpha}\Delta c^{\beta} - \chi_{\beta}\nabla\cdot(c^{\beta}\nabla v) + \mu_{\alpha}^{\text{EMT}}c^{\alpha} - \mu_{\beta}^{\text{MET}}c^{\beta} \\ \dfrac{\partial}{\partial t}m = D_{m}\Delta m + \rho_{m}^{\alpha}c^{\alpha} + \rho_{m}^{\beta}c^{\beta} - \lambda_{m}m \\ \dfrac{\partial}{\partial t}v = -\left(\lambda_{v}^{\alpha}c^{\alpha} + \lambda_{v}^{\beta}c^{\beta}\right)mv \end{cases} \tag{32}$$

c^{α} :: ECs | c^{β} :: MCs | m :: MMPs | v :: ECM

Note: The use of a density profile is not justified for the MCs as they are only appear in small numbers within the tumour; order 10^2 vs 10^9 epithelial-like cells in a $1\,cm^3$ tumour.

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c^{α} :: ECs | c^{β} :: MCs | m :: MMPs | v :: ECM

Note: The use of a density profile is not justified for the MCs as they only appear in small numbers inside the tumour; order 10^2 mesenchymal vs 10^9 epithelial-like cancer cells in a 1cm^3 tumour.

A system of isolated mesenchymal cells:

$$d\mathbf{X}_t^p = \mu(\mathbf{X}_t^p, t)dt + \sigma(\mathbf{X}_t^p, t)dW_t^p, \quad p \in P(t) = \{1 \dots N(t)\}$$

$\mathbf{x}_t^p$ :: position of MCs, μ :: drift coeff., σ :: diffusion coeff., $\mathbf{W}_t$ :: Wiener process

Note: How do we couple the systems of PDEs and SDEs? i.e. how do we make the *(phase) transition* from isolated cells to densities?

Splitting type approach at a discrete level

Let the discrete densities and (particle-)cells be given at time t^n

$$\mathbf{W}^n = \left\{ \mathbf{w}^n_{(i,j)} = \left(c^n_{(i,j)}, m^n_{(i,j)}, v^n_{(i,j)} \right) \right\}$$

$$\mathcal{P}^{\beta,n} = \left\{ \left(\mathbf{x}^{\beta,n}_p, m^\beta_p \right),\ p \in P^n \right\}$$

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- We perform the migration step for half time step $\Delta t/2$

$$\left(\mathbf{W}^n, \mathcal{P}^{\beta,n} \right) \xrightarrow{\mathcal{M}_{\Delta t/2}} \left(\mathbf{W}^{n+1/2}, \mathcal{P}^{\beta,n+1/2} \right)$$

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- All the particles are transformed to densities and take into account the reaction terms for a full time step Δt

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- We perform the other half of the migration step

$$\left(\tilde{\mathbf{W}}^{n+1/2}, \tilde{\mathcal{P}}^{\beta,n+1/2} \right) \xrightarrow{\mathcal{M}_{\Delta t/2}} \left(\mathbf{W}^{n+1}, \mathcal{P}^{\beta,n+1} \right)$$

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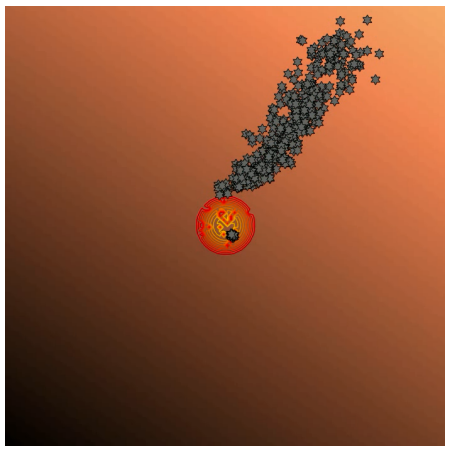
Overall:

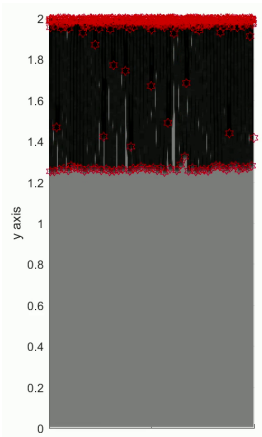
$$\boxed{\left(\mathbf{W}^{n+1}, \mathcal{P}^{\beta,n+1} \right) = \mathcal{M}_{\Delta t/2} \mathcal{R}_{\Delta t} \mathcal{M}_{\Delta t/2} \left(\mathbf{W}^n, \mathcal{P}^{\beta,n} \right)}$$

Cancer Invasion hybrid atomistic-macroscopic model

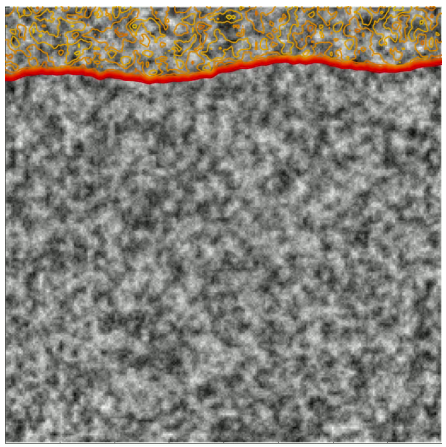
A two-cancer-cell species, haptotaxis, EMT



flow



self-generated gradient



2d-invasion

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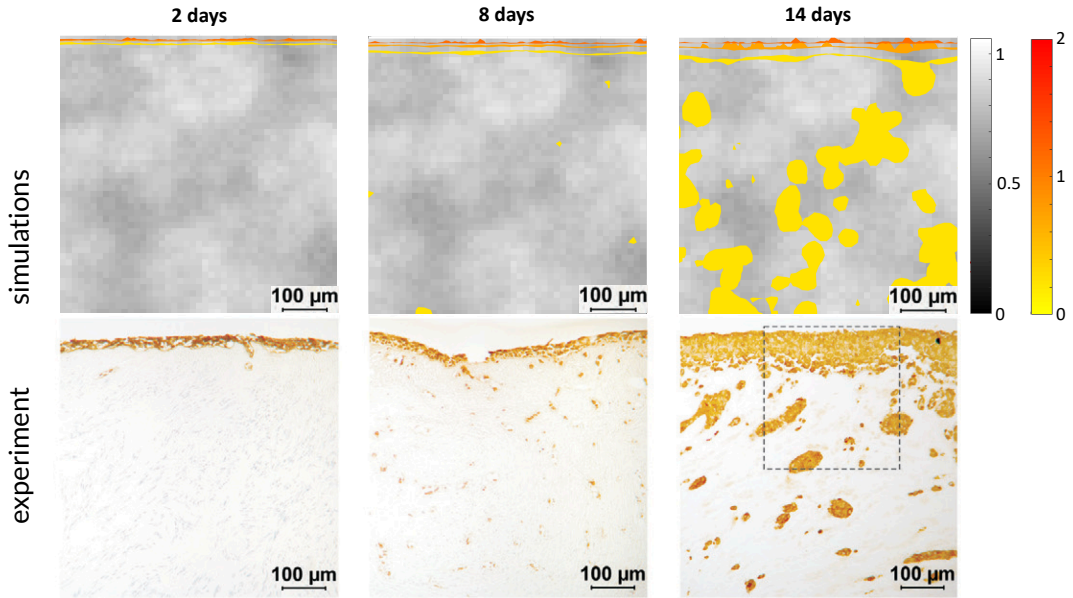
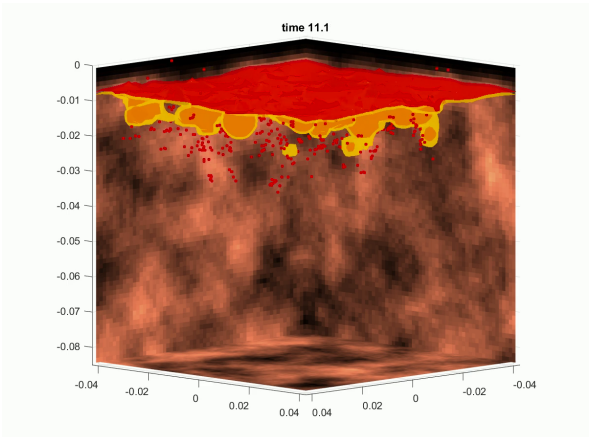
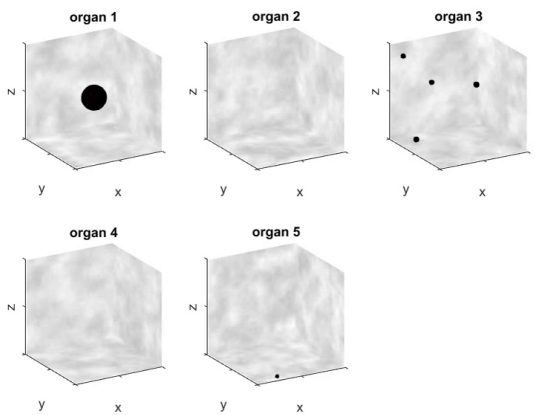


HSC-3 myoma invasion by Nurmenniemi et al. (2009)



invasion

VR insights



multi-organ