Modeling liquid and cells flow in tumor growth

2. Glucose metabolism and ATP production

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Adenosine-triphosphate is obtained by the phosphorylation of ADP or AMP or by direct synthesis. It is converted back to its precursors by metabolic processes transferring chemical energy to the cells.

ATP production rate can be considered as a viability index of cells.


Some experimental papers


**Cell Energy Metabolism**

- **Glycolysis**
  - Glucose $\xrightarrow{\text{ATP}}$ Pyruvate $\xrightarrow{\text{Lactate}}$
  - Pyruvate $+\text{NADH}+\text{H}^+ \rightleftharpoons \text{Lactate}+\text{NAD}^+$

- **Anaerobic**
  - Pyruvate $\rightarrow$ Ac-CoA $\rightarrow$ NADH $\rightarrow$ Krebs cycle $\rightarrow$ GTP

- **Mitochondrion**
  - Ac-CoA $\rightarrow$ NADH $\rightarrow$ ETS $\rightarrow$ ATP
  - Krebs cycle $\rightarrow$ CO$_2$, O$_2$, H$_2$O

- **Aerobic**
  - Pyruvate $+\text{NAD}^+ + \text{FAD} + 3\text{H}_2\text{O} + \text{P}_i + \text{GDP} \rightarrow 3\text{CO}_2 + 4(\text{NADH} + \text{H}^+) + \text{FADH}_2 + \text{GTP}$

  - $10(\text{NADH} + \text{H}^+) + 2\text{FADH}_2 + 6\text{O}_2 \rightarrow 10\text{NAD}^+ + 2\text{FAD} + 12\text{H}_2\text{O}$
The transformation of 1 NADH molecule in NAD+ provides energy for the formation, in average, of about 2.5 ATP molecules, 1 FADH2 molecule generates about 1.5 ATP molecules.
Conclusions:

1. anaerobic metabolism is far less efficient in ATP production
2. it leads to the production of LACTATE and eventually to lactic acid (H$^+$ ions)

It is typical of quiescence
Otto Heinrich Warburg (Nobel laureate, 1924) postulated (1966) that cancer cells choose anaerobic pathway (Warburg hypothesis)

Warburg effect was later attributed simply to hypoxia. Today Warburg hypothesis is being reconsidered because the shift to glicolytic pathway interferes with the mechanism of apoptosis
ATP PRODUCTION MODEL

Concentrations are denoted by $\sigma$, with subscript $G$, $O$, $L$, $P$ for glucose, oxygen, lactate and pyruvate. $f$ denotes consumption rate.

Overbar denotes intracellular concentration, and $V$ is the cell volume.

Pyruvate and lactate

$$
\frac{vd\bar{\sigma}_P}{dt} = 2f_G(\sigma_G) - \psi(\bar{\sigma}_P, \bar{\sigma}_L) - \phi_P(\bar{\sigma}_P, \sigma_O),
$$

$$
\frac{vd\bar{\sigma}_L}{dt} = \psi(\bar{\sigma}_P, \bar{\sigma}_L) + F_L \frac{\sigma_L}{K_L + \sigma_L} + \bar{h}v(\sigma_L - \bar{\sigma}_L),
$$

with

$$
f_G(\sigma_G) = F_G \frac{\sigma_G}{K_G + \sigma_G},
$$

glucose uptake (mol/cell·sec)
(no Pasteur effect = uptake increase in hypoxic state, for the moment)

$$
\psi(\bar{\sigma}_P, \bar{\sigma}_L) = (k_+ \bar{\sigma}_P - k_- \bar{\sigma}_L)v,
$$

pyruvate→lactate flux

$$
\phi_P(\bar{\sigma}_P, \sigma_O) = F_P \frac{\bar{\sigma}_P}{K_P + \bar{\sigma}_P} \frac{\sigma_O}{K_O + \sigma_O}.
$$

pyruvate flux to Krebs cycle

Glycolytic phenotype: high $k_+$ and/or low $F_P$
At the **steady state**, the **intracellular** concentrations of pyruvate and lactate can be derived in terms of the **extracellular** concentrations. The **consumption rates** \( f_O \) and \( f_L \) can be computed simply on the basis of **stoichiometry**:

\[
    f_O = 6f_G + 3f_L,
    \quad f_O = 3\phi_P.
\]

- \( f_O \) and \( f_L \) are functions of \( \sigma_G \), \( \sigma_O \) and \( \sigma_L \)
- \( f_O \) increases and eventually saturates with \( \sigma_O \), \( \sigma_G \) and \( \sigma_L \) (**no Crabtree effect** = increase of \( f_O \) when \( \sigma_G \) decreases)
- \( f_L \) **can be negative**, meaning lactate production.
- \( f_G \), \( f_O \) and \( f_L \) depend on eight parameters or parameter combinations.
CELL CONSUMPTION RATES

\[ f_L = 0 \]

\[ \sigma_G = 0 \]

\[ \sigma_G = 2 \mu M \]

\[ \sigma_L = 0 \]

\[ \sigma_L = 10 \text{mM} \]
Denoting by $\eta_1$ and $\eta_2$ the efficiency of ADP phosphorylation into ATP, driven by the oxidation of NADH and FADH$_2$, the ATP production rate $f_{ATP}$ can be expressed as:

$$f_{ATP} = 2f_G + \frac{(5\eta_1 + \eta_2 + 1)f_O}{3}.$$

$\eta_1 \approx 2.5, \eta_2 \approx 1.5$
We assume that cells die when $f_{ATP}$ reaches the threshold $f_N$, viable rim: $\rho_N < r < R$ defined by the inequality $f_{ATP} > f_N$.

Nutrients diffusion can be considered quasi-steady

The extracellular concentrations $\sigma_G$, $\sigma_O$ and $\sigma_L$ are prescribed at $r = R$:

$$
\sigma_i(R) = \sigma_i^* > 0, \quad i = G, O, \quad \sigma_L(R) = \sigma_L^* \geq 0.
$$

(*) denotes concentrations on the boundary of the spheroid
In the viable region the concentrations $\sigma_G, \sigma_L, \sigma_O$ obey the equations:

\[
\begin{align*}
D_{eG} \Delta \sigma_G &= \frac{\nu^*}{\nu} f_G(\sigma_G) \\
D_{eL} \Delta \sigma_L &= \frac{\nu^*}{\nu} f_L(\sigma_G, \sigma_L, \sigma_O) \\
D_{eO} \Delta \sigma_O &= \frac{\nu^*}{\nu} f_O(\sigma_G, \sigma_L, \sigma_O)
\end{align*}
\]

$\nu^*$ = cellular volume fraction, supposed constant

$D_{ei}$ = effective diffusivities.

When a necrotic core is present, i.e. $\rho_N > 0$, the necrotic boundary bears the conditions:

**Threshold** → $f_{ATP}(\rho_N) = f_N$

**No flux** → $\sigma'_i(\rho_N) = 0$, $i = G, L, O$.

In the absence of necrosis, the no-flux conditions on $\sigma_i$’s hold at $r = 0$. 
Typical profiles

The lactate level could be the cause of necrosis
RESULTS

For $R$ sufficiently large, the inequality $f_{ATP}(r) > f_N$ cannot hold in the whole interval $(0, R)$.

For $R$ sufficiently large, there exists one and only one solution $\sigma_G$, $\sigma_O$, $\sigma_L$, $\rho_N$ of the free boundary problem.

$\rho_N$ is an increasing function of $R$. 
existence and uniqueness of $(\rho_N, R)$

The proof goes through a complicated shooting-type argument, which is also the basis of the numerical method
COMPARISON WITH EXPERIMENTS

(First attempt: not so good !!)
A single set of parameters (including the threshold $f_N$) for all the six cases.

The parameters were estimated by LS fitting under the constraints that the maximal glucose and oxygen consumptions in a spheroid with $R=75$ µm ($\sigma_G=5.5$ mM, $\sigma_O=0.28$ mM) match the measured values (Freyer & Sutherland, 1985)
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INCLUDING PASTEUR EFFECT

Data by Freyer & Sutherland (1985) on EMT6 cells evidence a remarkable Pasteur effect (i.e., the glucose consumption increases as the oxygen concentration decreases).

We simply represented this phenomenon making the maximal glucose consumption $F_G$ dependent on the oxygen concentration.

According to the measurements, we have chosen the empirical function:

$$F_G(\sigma_O) = 15 \frac{1}{\sigma_O^{0.5} + 0.28} \text{ [mM]}$$
NECROTIC RADIUS vs. R (data from Freyer & Sutherland, 1986)

Model with Pasteur effect

Further improvement: add a necrotic threshold for acidity

**Vascularization in the gap** affected by acid, acid production controlled by the *dynamics of glucose*

Many possible cases *(with or without gap, necrotic core, etc.)*

Theoretical results *(existence and uniqueness)*
Travelling waves
The level of *lactate* determines (through a complex mechanism) the local value of $pH$:

$$\text{lactate}^- + H^+$$

Cells in the glycolitic regime may increase their *glucose uptake*, thus producing *more lactate*
The prevailing phenotype is *acid resistant* thanks to *compensation mechanisms* keeping the internal pH at normal levels.

Apoptosis threshold
for normal cells: **pH=7.1** (Casciari et al., 1992)
for tumour cells: **pH=6.8** (Dairkee et al., 1995)

*And the result is ...*

**Figure 3.** Hematoxylin and eosin stained micrographs of the tumour-host interface of a formalin-fixed specimen from human squamous cell carcinoma of the head and neck. An acellular gap between the tumour and normal tissue edges is identified (arrows), consistent with the predictions of the mathematical model (*cf.* Figure 2). Note the dying normal cells just beyond this acellular gap (arrowheads) presumably due to acid-induced apoptosis.

(from R.A. Gatenby-E.T. Gawlinski, 1996)
Defects: mass conservation? Damage on the tumour? Metabolism? Diffusion as main transport mechanism?...


\[
\frac{\partial N_1}{\partial s} = r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - d_1 LN_1,
\]

\[
\frac{\partial N_2}{\partial s} = r_2 N_2 \left(1 - \frac{N_2}{K_2}\right) + D_2 \frac{\partial}{\partial y} \left[ \left(1 - \frac{N_1}{K_1}\right) \frac{\partial N_2}{\partial y} \right],
\]

\[
\frac{\partial L}{\partial s} = r_3 N_2 - d_3 L + D_3 \frac{\partial^2 L}{\partial y^2}.
\]
Non-dimensional variables

\[ u = \frac{N_1}{K_1}, \quad v = \frac{N_2}{K_2}, \quad w = \frac{d_3}{r_3K_2}L, \quad t = r_1s, \quad x = \sqrt{\frac{r_1}{D_3}}y. \]

**carrying capacities**

**decay/production**

**prol. rate host tissue**

**ions diffusivity**

**damage rate**

\[ b > 1 \]

Basic non-dimensional parameters

\[ a = \frac{d_1r_3K_2}{d_3r_1}, \quad b = \frac{r_2}{r_1}, \quad c = \frac{d_3}{r_1}, \quad d = \frac{D_2}{D_3}. \]

Very small
The normalized G.G. model

One space dimension (space coord. $x$)

Normalized non-dimensional variables:

all concentrations vary between 0 and 1

Host tissue:

- $u_t = u(1 - u) - auw$

Tumour:

- $v_t = d[(1 - u)v_x]_x + bv(1 - v)$

H+ ions:

- $w_t = w_{xx} + c(v - w)$

$\text{d} << 1, \text{b} > 1, a > 0, c > 0$
Search for a *travelling wave*

Set

\[ u(x, t) = u(z), \quad v(x, t) = v(z), \quad w(x, t) = w(z) \]

with \[ Z = x - \theta t \]

Solutions of this form, plotted vs. \( x \), are graphs which, as time varies, *travel* with the *speed* \( \theta \) to the right (\( \theta > 0 \): our case), or to the left (\( \theta < 0 \))
The system becomes

\[ u_t = u(1 - u) - auw, \]
\[ v_t = d[(1 - u)v_x]_x + bv(1 - v), \]
\[ w_t = w_{xx} + c(v - w). \]

\[ u_t(x - \theta t) \rightarrow -\theta u'(z) \]
\[ u_x(x - \theta t) \rightarrow u'(z) \]

etc.
Asymptotic values corresponding to invasion

Normal cells: \( \max(0, 1-a) \rightarrow 1 \)

Tumour cells: \( 1 \rightarrow 0 \)

H+ ions: \( 1 \rightarrow 0 \)

For \( a < 1 \) a fraction of normal cells survives

(study of all possible travelling waves)
Two classes of waves:

- **slow waves**: \( \theta = \theta_0 d^\alpha \)  
  \((d<<1): \text{singular perturbation}!!!\)

- **fast waves**: \( \theta = O(1) \) as \( d \to 0 \)

**Slow waves:**

Technique: matching *inner* and *outer* solutions

Take \( \xi = z/d^\alpha \) as a *fast variable*: looking at the *front region* with a *magnifying lens*
Summary of the results

\[ 0 = \theta u' + u(1 - u) - auw, \]
\[ 0 = d[(1 - u)v'' - u'v'] + \theta v' + bv(1 - v), \]
\[ 0 = w'' + \theta w' + c(v - w), \]

**slow waves:** \( \theta = \theta_0 d^\alpha \quad 0 < \alpha \leq \frac{1}{2}, \)

\( \theta_0 > 0 \) for \( \alpha \in (0,1/2), \)

\( \theta_0 \geq \sqrt{b \min(a/2,1)} \) for \( \alpha = 1/2 \)

No solutions for \( \alpha > \frac{1}{2} \)

The parameter \( \alpha \) decides whether the two cellular species **overlap** or are separated by a **gap**
\(a > 2\)

\[
u(z; d) \approx \begin{cases} 
\sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha}/2 e^{[\phi_-(z) - \phi_+(z_+)]/d^{\alpha}} & \text{if } z < 0, \approx 0 \\
\sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha}/2 e^{[\phi_+(z) - \phi_+(z_+)]/d^{\alpha}} & \text{if } 0 < z < z_+, \\
1 - \frac{a}{2} e^{-\sqrt{cz}} & \text{if } z > z_+.
\end{cases}
\]

\[
\phi_+(z) = \frac{1}{\theta_0} \left[ \frac{a}{2 \sqrt{c}} (1 - e^{-\sqrt{cz}}) - z \right]
\]

\[
z_+ = \frac{1}{\sqrt{c}} \log \frac{a}{2} > 0
\]

GAP THICKNESS
Numerical simulations

\[ \alpha = \frac{1}{2}, \text{ minimal speed} \]

\[ \theta = 2\sqrt{bDd} \]

The propagating front of the tumour is very steep as a consequence of \( d \ll 1 \)

(this is the case treated by G.G.)
$a > 2$
Other invasion models are based on a combined mechanism of ECM lysis and haptotaxis (still based on the analysis of travelling waves).

A two parameter family of travelling waves with a singular barrier arising from the modelling of extracellular matrix mediated cellular invasion

Abbey J. Perumpanani\textsuperscript{a,b}, Jonathan A. Sherratt\textsuperscript{c,*,} John Norbury\textsuperscript{d}, Helen M. Byrne\textsuperscript{e}

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