Mathematical models for brain lactate kinetics

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Brain : organ with high energy needs ; 2% of body weight, 20% of energy needs

Energy is necessary to support neural activity ; comes from many sources : glutamate, glucose, oxygen, ..., lactate

Glioma : tumor which starts in the glial cells ; around 30% of brain cancers and 80% of malignant brain tumors

Leads to alterations of cell's energy management

Lactate creation, consumption, import and export play a key role in the cancer development

Lactate (=ionized form of lactic acid) : considered for a long time as a waste product resulting from anaerobic exercise

Actually : gluconeogenic precursor ; 30% of cell glucose used during exercise is derived from lactate

Lactate formation occurs in aerobic conditions ; lactate production is the result of glucose used by muscle cells under aerobic conditions

Lactate is crucial for the brain : main fuel used by neurons ; essential for long-term memory and may be involved in Alzheimer's disease

1990's : it was postulated that a well orchestrated collaboration between atrocytes and neurons is the basis of brain energy metabolism

$\rightarrow$Astrocytes produce lactate, which flows to neurons

Entry and exit of lactate : concentration dependent ; mediated by MCT's

Gliomas : MCT's are more active ; essential for the tumor survival

Tumor cells favor lactate creation and consumption

Neuroimaging techniques : allow an indirect and noninvasive measure of cerebral activities ; allow measurement of various metabolic concentrations (lactate)

MRI : reference imaging technique for soft tissues (brain) ; allows to obtain quality data without opening the skull

Allows to follow cerebral activity in certain zones of the brain (functional MRI)

Allows to see tissue composition (diffusional MRI)

Energy management in healthy and tumoral cells and gliomas can be difficult to observe and explain experimentally

$\rightarrow$Mathematical modeling can be helpful to describe and understand cells energy changes

We consider a simplified model for lactate exchanges between a cell and blood (A. Aubert, R. Costalat, P.J. Magistretti, L. Pellerin)

Aim : follow in a simple way lactate kinetics between a cell and the capillary network in its neighborhood

Built in vivo : we need to consider loss and input terms for both intracellular and capillary lactate concentrations

We set :

u_ε : intracellular lactate concentration (in nM)
v_ε : capillary lactate concentration (in nM)
ε : volume separating the compartments (main parameter in the model)

To manage blood flow, vessels dilate and modify their volume

$\rightarrow$It is important to know how variations of their volume, correlated with variations of ε, impact the whole dynamics

Main features of the model :

• There is a lactate cotransport through the brain blood

Taken into account by a simplified version of an equation for carrier-mediated symport (the nonlinear term in the equation depends on the maximum transport rate between the blood and the cell ($T > 0$) and the Michaelis-Menton positive constants k (intracellular) and k' (extracellular))

• A cell can equally produce and consume lactate, but also export surplus lactate to neighboring cells

J : balance sheet of the whole phenomenon ; nonnegative, depends on t and u_ε (seen as a regulatory term), bounded by a constant B_J, Lipschitz continuous

A cell manages its lactate concentration by means of its amount, not of the experiment's duration

$\rightarrow J$ does not depend on t

A cell imports more lactate when its lactate concentration is low

$\rightarrow J$ is monotone decreasing

Example : $J(x) = G_J - L_J + \frac{c_J}{x+\varepsilon_J}$ (creation-consumption+import)

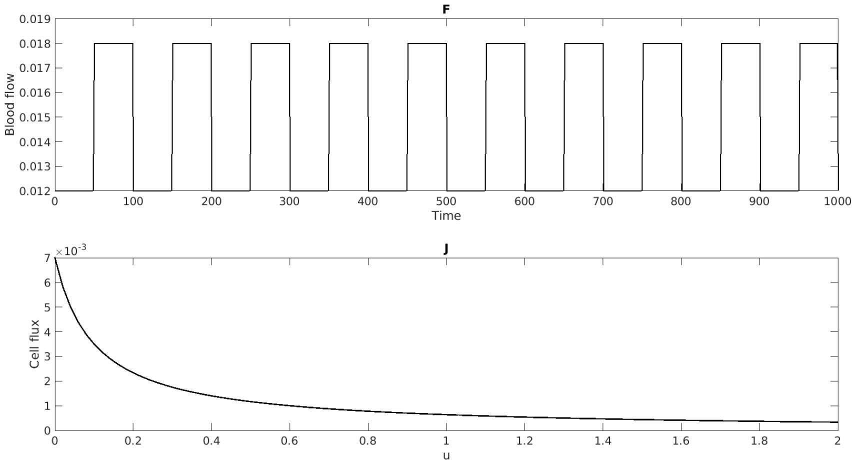
• There is a blood flow contribution to capillary lactate concentration depending on both arterial and venous lactates

$L > 0$: arterial lactate concentration
F : blood flow ; positive, bounded ($0 < F_1 \leq F \leq F_2$), continuous, seen as a forcing term

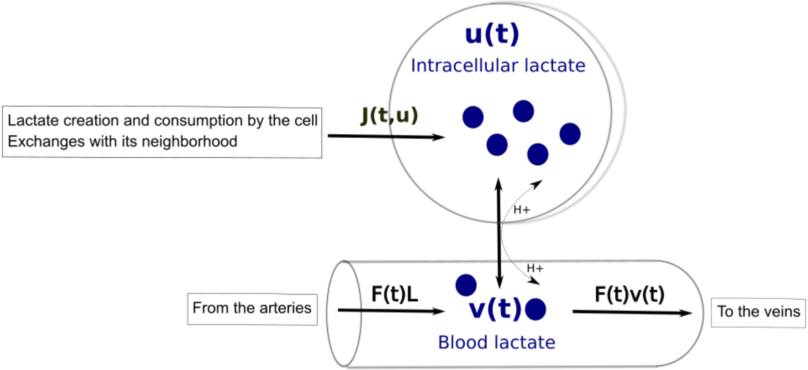
Example : periodic function (not continuous)

$$F(t) = F_0(1 + \alpha_f) \text{ if } \exists N \in \mathbb{N}/(N-1)t_f + t_i < t < Nt_f$$

$$F(t) = F_0 \text{ otherwise}$$



F
Blood flow
0.019
0.018
0.017
0.016
0.015
0.014
0.013
0.012
0
100
200
300
400
500
600
700
800
900
1000
Time
J
Cell flux
×10^-3
7
6
5
4
3
2
1
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
u


u(t)
Intracellular lactate
Lactate creation and consumption by the cell
Exchanges with its neighborhood
J(t,u)
H+
H+
From the arteries
F(t)L
v(t)
Blood lactate
F(t)v(t)
To the veins

Play/Pause

Simplified model :

$$\overbrace{u'_\varepsilon(t)}^{\substack{\text{lactate variation}\\ \text{cell}}} = \overbrace{J(t, u_\varepsilon(t))}^{\substack{\text{cell consumption,}\\ \text{exchanges with neighborhood}}} - \overbrace{T\left(\frac{u_\varepsilon(t)}{k + u_\varepsilon(t)} - \frac{v_\varepsilon(t)}{k' + v_\varepsilon(t)}\right)}^{\text{Exchange cell/blood by symport}}$$

$$\underbrace{\varepsilon}_{\substack{\text{volume}\\ \text{difference}}} \times \underbrace{v'_\varepsilon(t)}_{\substack{\text{lactate variation}\\ \text{capillary}}} = \underbrace{F(t)(L - v_\varepsilon(t))}_{\text{blood flux}} + \underbrace{T\left(\frac{u_\varepsilon(t)}{k + u_\varepsilon(t)} - \frac{v_\varepsilon(t)}{k' + v_\varepsilon(t)}\right)}_{\text{exchange cell/blood by symport}}$$

$t = 0 : u_\varepsilon(0) = \bar{u} \geq 0$ and $v_\varepsilon(0) = \bar{v} \geq 0$

Remark : more complete model

$$\frac{du}{dt} + T_1\left(\frac{u}{k+u} - \frac{p}{k_n+p}\right) + T_2\left(\frac{u}{k+u} - \frac{q}{k_a+q}\right) + T\left(\frac{u}{k+u} - \frac{v}{k'+v}\right) = J_0$$

$$\frac{dp}{dt} + T_1\left(\frac{p}{k_n+p} - \frac{u}{k+u}\right) = J_1$$

$$\frac{dq}{dt} + T_2\left(\frac{q}{k_a+q} - \frac{u}{k+u}\right) + T_a\left(\frac{q}{k_a+q} - \frac{v}{k'+v}\right) = J_2$$

$$\varepsilon\frac{dv}{dt} + Fv + T\left(\frac{v}{k'+v} - \frac{u}{k+u}\right) + T_a\left(\frac{v}{k'+v} - \frac{q}{k_a+q}\right) = FL$$

Intracellular compartment split into 2 parts : neurons (p) and astrocytes (q)

Includes transport from capillary to intracellular astrocytes

The case $\varepsilon > 0$

Well-posedness

We write the system in the form

$$x' = f(t,x),\ x = (u_\varepsilon, v_\varepsilon),\, f = (f_1, f_2)$$

The system is quasipositive : $x \geq 0, x_i = 0 \implies f_i(t,x) \geq 0$

$\rightarrow$Solutions with nonnegative initial data remain nonnegative

f is globally Lipschitz continuous

$\rightarrow$Existence and uniqueness of the global in time solution

Bounds on the solutions

Viability domain

Upper bound on the capillary lactate concentration :

$$v_\varepsilon'(t) \leqslant -\frac{F_1 v_\varepsilon(t)}{\varepsilon} + \frac{F_2}{\varepsilon} + \frac{T}{\varepsilon}$$

Gronwall's lemma implies

$$v_\varepsilon(t) \leqslant exp(\frac{-F_1 t}{\varepsilon})\bar{v} + \frac{T + F_2 L}{F_1}(1 - exp(\frac{-F_1 t}{\varepsilon}))$$

and

$$v_\varepsilon(t) \leqslant \max(\bar{v}, \frac{T + F_2 L}{F_1}) := B_v$$

We do not have an upper bound on the intracellular lactate u_ε in general

We can find a sufficient condition ensuring and upper bound

We assume that

$$J(t,x) \leqslant B_J$$

We have

$$u'_\varepsilon(t) \leqslant B_J + T\frac{B_v}{B_v + k'} - T\frac{u_\varepsilon(t)}{k + u_\varepsilon(t)}$$

Assume that

$$B_J < T(1 - \frac{B_v}{k' + B_v}) \Leftrightarrow B_J(k' + B_v) < Tk'$$

Related to the equation $f(x) = 0$ for $f(x) = B_J - \frac{Tx}{k+x} + \frac{TB_v}{k'+B_v}$ and for which a positive solution exists if and only if $B_J < T(1 - \frac{B_v}{k'+B_v})$

Biological interpretation : at each time, the lactate uptake by a cell cannot be larger than the lactate it can purge through the blood (otherwise, the cell lactate increase may not be limited)

Set $z = \frac{B_v}{k'+B_v} + \frac{B_J}{T}$: we have $1 - z > 0$

If $u_\varepsilon(t) > \frac{kz}{1-z}$:

$$B_J + T\frac{B_v}{B_v + k'} - T\frac{u_\varepsilon(t)}{k + u_\varepsilon(t)} < 0$$

and

$$u'_\varepsilon(t) < 0$$

$\rightarrow u_\varepsilon(t) \leqslant \max(\frac{kz}{1-z}, \bar{u}) := B_u$

Remark : The sufficient condition can be slightly relaxed. Take

$$J(x) = G_J - L_J + \frac{c_J}{x + \varepsilon_J}$$

Does not satisfy the sufficient condition

If $G_J > L_J$ (creation is larger than consumption) and $G_J < L_J + \frac{Tk'}{k'+B_v}$ (lactate creation of the cell is smaller than its consumption and purge through the blood ; able to manage lactate excess), the sufficient condition is only satisfied for

$$x \geqslant \frac{C_j}{\frac{Tk'}{k'+B_v} - G_J + L_J} = N$$

Sufficient to conclude that

$$u_\varepsilon(t) \leqslant \max(N, \frac{kz}{1-z}, \bar{u})$$

Lower bounds : we already know that u_ε and v_ε are nonnegative

Note that

$$v_\varepsilon'(t) \geqslant -\frac{F_2 v_\varepsilon(t)}{\varepsilon} + \frac{F_1}{\varepsilon} - \frac{T}{\varepsilon}\frac{B_v}{k' + B_v}$$

If $\frac{F_1 L - T\frac{B_v}{k'+B_v}}{F_2} \geqslant 0$ and $v_\varepsilon(t) \leqslant \frac{F_1 L - T\frac{B_v}{k'+B_v}}{F_2}$, then $v_\varepsilon'(t) \geqslant 0$:

$$v_\varepsilon(t) \geqslant \min(\bar{v}, \frac{F_1 L - T\frac{B_v}{k'+B_v}}{F_2})$$

If $\frac{F_1 L - T\frac{B_v}{k'+B_v}}{F_2} < 0$: no positive lower bound

$$v_\varepsilon(t) \geqslant \min(\bar{v}, \max(\frac{F_1 L - T\frac{B_v}{k'+B_v}}{F_2}, 0)) := M_v$$

We have

$$u'_\varepsilon(t) \geqslant T\left(\frac{M_v}{k' + M_v} - \frac{u_\varepsilon}{k + u_\varepsilon}\right)$$

If $u_\varepsilon(t) \leqslant M_v \frac{k}{k'}$, then $u'_\varepsilon(t) \geqslant 0$:

$$u_\varepsilon(t) \geqslant \min(\bar{u}, M_v \frac{k}{k'}) := M_u$$

Stability of the equilibrium

We take F and J constant

Solve

$$0 = J - T\left(\frac{u}{k + u_\varepsilon} - \frac{v}{k' + v}\right)$$

$$0 = F(L - v) + T\left(\frac{u}{k + u} - \frac{v}{k' + v}\right)$$

Unique equilibrium :

$$u_l = \frac{k(\frac{J}{T} + \frac{v_l}{k'+v_l})}{1 - (\frac{J}{T} + \frac{v_l}{k'+v_l})}$$

$$v_l = L + \frac{J}{F}$$

Exists provided that

$$\frac{J}{T} + \frac{LF+J}{F(k'+L)+J} < 1 \Leftrightarrow J^2 + JF(L+k') - TFk' < 0$$

Remarks :
(i) We know that $v_\varepsilon(t) \leqslant L + \frac{T}{F} = B_v$. Then $v_l \leqslant B_v$ (as $J \leqslant T$)

(ii) We fix all parameters, except for J. Solving $J^2 + JF(L+k') - TFk' = 0$, there is an equilibrium only when $J \in]J_b, J_h[$

$$J_b := \frac{1}{2}(-F(L+k') - \sqrt{\Delta_J})(< 0)$$

$$J_h := \frac{1}{2}(-F(L+k') + \sqrt{\Delta_J})(> 0)$$

$$\Delta_J = F^2(L+k')^2 + 4TFk' > 0$$

If $0 < J < J_h$: one equilibrium, asymptotically stable (node)

If $J > J_h$: no equilibrium

(iii) Therapeutic hint : have the equilibrium outside the vialability domain, where cell necrosis occurs

$\rightarrow$Explore playing on cell lactate intake : large J involves unbounded cell lactate concentration leading to exit of cell viability domain and glioma cell death

The case $\varepsilon = 0$

Relevant to study the limit $\varepsilon \to 0$

We take F and J constant

Limit system :

$$u_0'(t) = J - T(\frac{u_0(t)}{k + u_0(t)} - \frac{v_0(t)}{k' + v_0(t)})$$

$$0 = F(L - v_0(t)) + T(\frac{u_0(t)}{k + u_0(t)} - \frac{v_0(t)}{k' + v_0(t)})$$

$$u_0(0) = \bar{u}_0 \in \mathbb{R}^+$$

Set

$$\varphi_c :]-c,+\infty[\to]-\infty, T[, \ s \mapsto \frac{Ts}{c+s}$$

$$\psi_c :]-c,+\infty[\to \mathbb{R}, \ s \mapsto Fs + \varphi_c(s)$$

ψ_c is a bijection from $]-c,+\infty[$ onto $\mathbb{R}$ and from $\mathbb{R}^+$ onto itself

Equivalent system :

$$v_0(t) = \psi_{k'}^{-1}(FL + \varphi_k(u_0(t))) := \Psi(u_0(t))$$

$$u_0'(t) = J - T(\frac{u_0(t)}{k+u_0(t)} - \frac{\Psi(u_0(t))}{k' + \Psi(u_0(t))}) := G(u_0(t))$$

Well-posedness, nonnegativity

Upper bound on v_0 :

$$v_0(t) \leqslant L + \frac{T}{F} := B_{v,0}$$

Conditional upper bound on u_0 : $B_{u,0}$

Unique equilibrium, locally stable (when it exists)

Set $u = u_\varepsilon - u_0$ and $v = v_\varepsilon - v_0$, $u_\varepsilon(0) = u_0(0) = \bar{u}_0$

Then

$$u'(t) = T\left(\frac{k'v(t)}{(v_\varepsilon(t)+k')(v_0(t)+k')} - \frac{ku(t)}{(u_\varepsilon(t)+k)(u_0(t)+k)}\right)$$

$$\varepsilon v'(t) = -Fv(t) + T\left(\frac{ku(t)}{(u_\varepsilon(t)+k)(u_0(t)+k)} - \frac{k'v(t)}{(v_\varepsilon(t)+k')(v_0(t)+k')}\right) - \varepsilon v_0'(t)$$

$$u(0) = 0$$

We have

$$v_0(t) \leqslant B_{v,0}$$

$$|v_0'(t)| \leqslant \frac{kT(J+T)}{\left(F + \frac{k'T}{(k'+B_{v,0})^2}\right)} := \gamma$$

Multiply the first equation by u and the second by v and sum

$$\frac{d}{dt}(u^2(t)+\varepsilon v^2(t)) \leqslant (\frac{8T^2}{Fk^2}+\frac{4T^2}{Fk'^2})(u^2(t)+\varepsilon v^2(t))+\frac{8\gamma^2}{F}\varepsilon^2$$

This gives

$$\begin{aligned} u^2(t)+\varepsilon v^2(t) \leqslant \exp\big(\frac{T^2 t}{F}(\frac{8}{k^2}+\frac{4}{k'^2})\big)(\varepsilon(\bar{v}_0-\Psi(\bar{u}_0))^2 \\ +\frac{k^2(J+T)^2}{(F+\frac{k'T}{(k'+L+\frac{T}{F})^2})^2}\frac{2\varepsilon^2}{(\frac{2}{k^2}+\frac{1}{k'^2})}) \\ -\frac{k^2(J+T)^2}{(F+\frac{k'T}{(k'+L+\frac{T}{F})^2})^2}\frac{2\varepsilon^2}{(\frac{2}{k^2}+\frac{1}{k'^2})} \end{aligned}$$

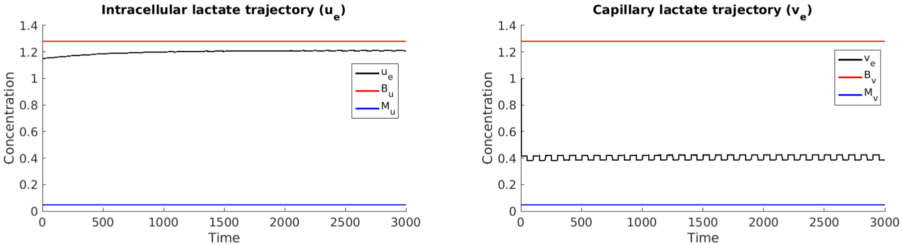
If $\bar{v}_0 = \Psi(\bar{u}_0)$:

$$u^2(t) + \varepsilon v^2(t) \leqslant (\exp\big(\frac{T^2 t}{F}(\frac{8}{k^2} + \frac{4}{k'^2})\big) - 1)\frac{2\gamma^2\varepsilon^2}{T^2(\frac{2}{k^2} + \frac{1}{k'^2})}$$

On the finite time interval $[0, t_m]$:

$$|u(t)| \leqslant C_{t_m}\varepsilon,\ |v(t)| \leqslant C_{t_m}\sqrt{\varepsilon}$$

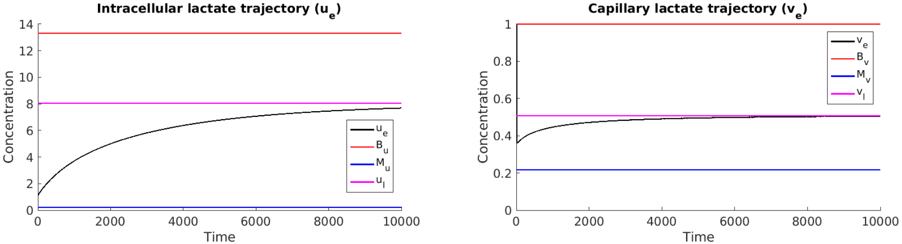
$\varepsilon > 0$: simulations of u_ε and v_ε



Lactate dynamics for varying F and J. Left : concentration of intracellular lactate. Right : capillary lactate.

Red : computed upper bound
Black : lactate trajectory
Blue : computed lower bound

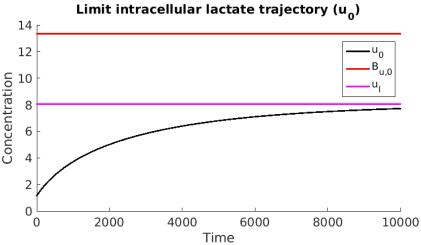
$\varepsilon > 0 : u_\varepsilon$ and v_ε

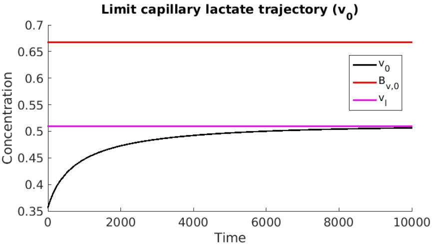


Dynamics for constant F and J. Left : intracellular. Right : capillary.

Red : Upper bound
Magenta : computed equilibrium
Black : trajectory
Blue : lower bound

$\varepsilon = 0 : u_0$ and v_0

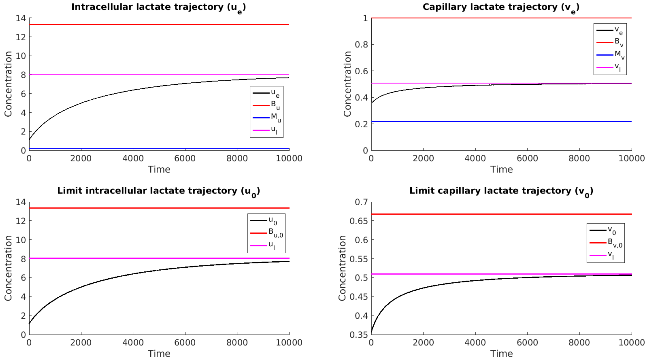




Left : intracellular. Right : capillary.

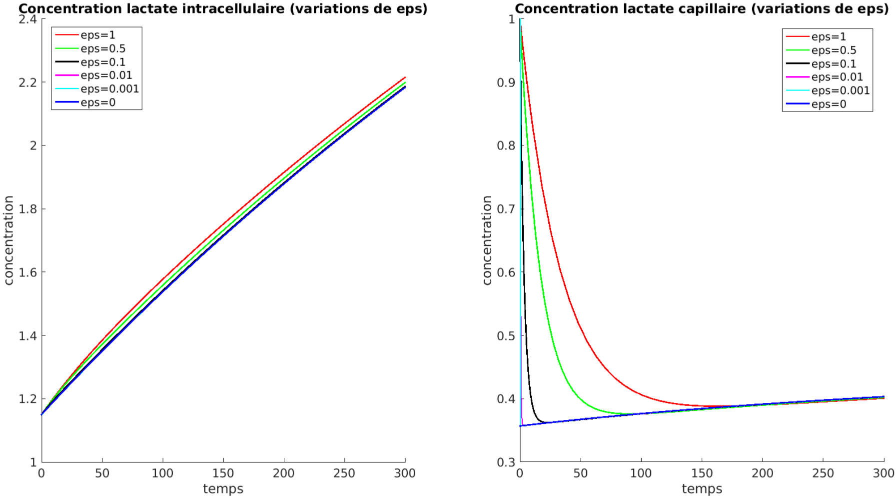
Red : upper bound
Magenta : equilibrium
Black : trajectoiry

Comparaison of dynamics

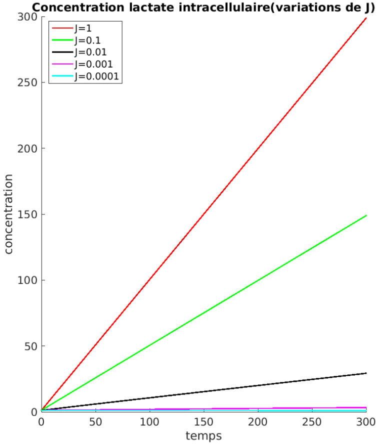


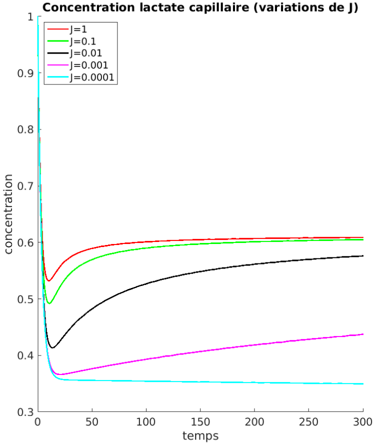
Up : $\varepsilon > 0$. Bottom : $\varepsilon = 0$

Comparaison of dynamics for different ε's



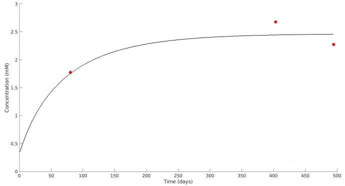
Comparaison of dynamics for different J's

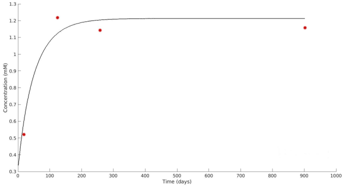


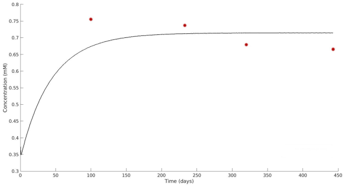


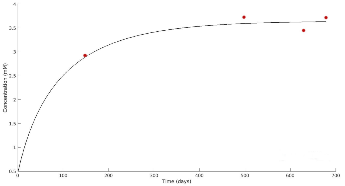
An equilibrium exists for $J < 0.00851 \text{ mM.s}^{-1}$

Comparison with real medical data









Further improvements :

- Different compartments
- Other enegetic mechanisms : oxygen, glutamate, ...
- Growth of the tumor

A simple PDE's model

Lactate concentrations vary according to position ; spatial diffusion

PDE's system (F and J constant) :

$$\frac{\partial u}{\partial t} - \alpha \Delta u + T\left(\frac{u}{k+u} - \frac{v}{k'+v}\right) = J,\ \alpha > 0$$

$$\varepsilon \frac{\partial v}{\partial t} - \beta \Delta v + Fv + T\left(\frac{v}{k'+v} - \frac{u}{k+u}\right) = FL,\ \varepsilon,\ \beta > 0$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma$$

$$u|_{t=0} = \bar{u},\ v|_{t=0} = \bar{v}$$

$u = u_\varepsilon$, $v = v_\varepsilon$, Ω : bounded domain of $\mathbb{R}^n$, $n = 2$ or 3, $\Gamma = \partial\Omega$

Assume that

$$(\bar{u},\bar{v}) \in (H^3(\Omega)\cap H^2_{\mathrm{N}}(\Omega))^2,\ \bar{u}\geq 0,\ \bar{v}\geq 0 \text{ a.e. } x$$

$$H^2_{\mathrm{N}}(\Omega) = \{w \in H^2(\Omega),\ \frac{\partial w}{\partial \nu} = 0 \text{ on } \Gamma\}$$

We recover several qualitative properties of the ODE's model :

• Well-posedness, nonnegativity

• $L^\infty(\Omega)$-bounds on the solutions

• Conditional existence of a unique spatially homogeneous equilibrium, linear stability

• Well-posedness, nonnegativity, linear stability of the spatially homogeneous equilibrium for the limit system

• Estimates on the difference of solutions to original and limit systems on finite time intervals

Nonnegativity of the solutions

System of reaction-diffusion equations

Invariant region : $\{u \geq 0,\ v \geq 0\}$

$\rightarrow$ Nonnegativity

Uniqueness

Uniqueness of nonnegative solutions

Existence

Galerkin scheme to the modified system

$$\frac{\partial u}{\partial t} - \alpha \Delta u + T(\frac{u}{k+|u|} - \frac{v}{k'+|v|}) = J$$

$$\varepsilon \frac{\partial v}{\partial t} - \beta \Delta v + Fv + T(\frac{v}{k'+|v|} - \frac{u}{k+|u|}) = FL$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma$$

$$u|_{t=0} = \bar{u},\ v|_{t=0} = \bar{v}$$

Existence, uniqueness of the solution

Multiply the first equation by $-u^-$ and the second one by $-v^-$ $(x^- = \min(0, -x))$: u and v are nonnegative

$\rightarrow$ Solutions to the initial system

Regularity

We have, $\forall t_m > 0$

$$(u,v) \in L^\infty(0,t_m;(H^3(\Omega)\cap H^2_{\mathrm{N}}(\Omega))^2)\cap L^2(0,t_m;H^4(\Omega)^2)$$

$$(\frac{\partial u}{\partial t},\frac{\partial v}{\partial t}) \in L^\infty(0,t_m;H^1(\Omega)^2)\cap L^2(0,t_m;H^2(\Omega)^2)$$

$L^\infty(\Omega)$-bounds on the solutions

We have

$$\|u(t)\|_{L^\infty(\Omega)} \leq \|\bar{u}\|_{L^\infty(\Omega)} + (J+T)t,\ t \geq 0$$

$$\|v(t)\|_{L^\infty(\Omega)} \leq e^{-\frac{F}{\varepsilon}t}\|\bar{v}\|_{L^\infty(\Omega)} + \frac{FL+T}{F},\ t \geq 0$$

Idea of the proof :

We have

$$\frac{\partial u}{\partial t} - \alpha \Delta u \leq J + T$$

$$\varepsilon \frac{\partial v}{\partial t} - \beta \Delta v + Fv \leq FL + T$$

Multiply the first equation by u^{m+1} and the second by v^{m+1}, $m \in \mathbb{N}$:

$$\|u(t)\|_{L^{m+2}(\Omega)} \leq \|\bar{u}\|_{L^{m+2}(\Omega)} + (J+T)\mathrm{Vol}(\Omega)^{\frac{1}{m+2}} t, \ t \geq 0$$

$$\|v(t)\|_{L^{m+2}(\Omega)} \leq e^{-\frac{F}{\varepsilon}t} \|\bar{v}\|_{L^{m+2}(\Omega)} + \frac{FL+T}{F} \mathrm{Vol}(\Omega)^{\frac{1}{m+2}}, \ t \geq 0$$

Let $m \to +\infty$

Remarks :

(i) We do not have a uniform estimate on u

(ii) The estimate on v yields : if $\|\bar{v}\|_{L^\infty(\Omega)} \leq R$ and $\delta > 0$ is given, then there exists $t_0 = t_0(R, \delta) > 0$ such that

$$\|v(t)\|_{L^\infty(\Omega)} \leq \frac{FL+T}{F} + \delta,\ t \geq t_0$$

$\rightarrow$ Dissipative estimate

Comparable with the bound obtained for the ODE's system ($t_0 = 0$, $\delta = 0$)

If M is such that $F(L-M)+T \leq 0$, i.e., $M \geq \frac{FL+T}{F}$, and $\bar{v}$ is such that $0 \leq \bar{v} \leq M$ a.e. x, $0 \leq v \leq M$ a.e. (x,t)

(iii) Uniform bound on u : in the $L^2(\Omega)$-norm only

Assume $J + \frac{Tv}{k'+v} < T$ (v is bounded ; $0 \leq \bar{v} :\leq \frac{FL+\kappa}{F}$) and set $E = \frac{1}{2}\|u\|^2 + k\|u\|_{L^1(\Omega)}$:

$$\frac{dE}{dt} + \alpha\|\nabla u\|^2 + c\|u\|_{L^1(\Omega)} \leq c',\ c > 0$$

$$\frac{dE}{dt} + c\sqrt{E} \leq c',\ c > 0$$

Set $E^* = (\frac{c'}{c})^2$, so that

$$\frac{dE^*}{dt} + c\sqrt{E^*} = c'$$

Comparison arguments yield

$$E(t) \leq \max(E(0), E^*),\ t \geq 0$$

Assume $J \geq T$, $FL \geq T$, $\bar{u} > 0$, $\bar{v} > 0$ a.e. x. Then :

$$u(x,t) \geq \frac{1}{\|\frac{1}{\bar{u}}\|_{L^\infty(\Omega)}},\ v(x,t) \geq \frac{e^{-\frac{F}{\varepsilon}t}}{\|\frac{1}{\bar{v}}\|_{L^\infty(\Omega)}} \text{ a.e. } (x,t)$$

Idea of the proof :

Note that

$$\frac{\partial u}{\partial t} - \alpha \Delta u \geq J - T$$

$$\varepsilon \frac{\partial v}{\partial t} - \beta \Delta v + Fv \geq FL - T$$

Multiply by $\frac{1}{u}$ and $\frac{1}{v}$: positivity

Multiply by $-\frac{1}{u^{m+1}}$ and $-\frac{1}{v^{m+1}}$, $m \in \mathbb{N}$:

$$\|\frac{1}{u(t)}\|_{L^m(\Omega)} \leq \|\frac{1}{\bar{u}}\|_{L^m(\Omega)},\ t \geq 0$$

$$\|\frac{1}{v(t)}\|_{L^m(\Omega)} \leq \|\frac{1}{\bar{v}}\|_{L^m(\Omega)} e^{\frac{F}{\varepsilon}t},\ t \geq 0$$

Let $m \to +\infty$

stability of the unique spatially homogeneous equilibrium

Same as for the ODE's system ; exists under the same condition

Linearized system around the equilibrium

$$\frac{\partial U}{\partial t} - \alpha \Delta U + T(\frac{k}{(k+u_l)^2} U - \frac{k'}{(k'+v_l)^2} V) = 0$$

$$\varepsilon \frac{\partial V}{\partial t} - \beta \Delta V + FV + T(\frac{k'}{(k'+v_l)^2} V - \frac{k}{(k+u_l)^2} U) = 0$$

$$\frac{\partial U}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0 \text{ on } \Gamma$$

$$U|_{t=0} = U_0, \; V|_{t=0} = V_0$$

Well-posedness, regularity, nonnegativity (U_0, V_0 nonnegative)

Theorem : The stationary solution $(\overline{u}, \overline{v})$ is linearly exponentially stable, in the sense that all eigenvalues $s \in \mathbb{C}$ associated with the linear system satisfy $\mathcal{R}e(s) \leq -\xi$, for a given $\xi > 0$.

The case $\varepsilon = 0$

Limit problem :

$$\frac{\partial u}{\partial t} - \alpha \Delta u + T(\frac{u}{k+u} - \frac{v}{k'+v}) = J$$

$$-\beta \Delta v + Fv + T(\frac{v}{k'+v} - \frac{u}{k+u}) = FL$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma$$

$$u|_{t=0} = \bar{u}$$

$u = u_0$, $v = v_0$

Parabolic-elliptic system

Remark : $-\beta \Delta v(0) + Fv(0) + T(\frac{v(0)}{k'+v(0)} - \frac{\bar{u}}{k+\bar{u}}) = FL$

Assume that

$$u_0 \in H^2_{\mathrm{N}}(\Omega),\ u_0 \geq 0 \text{ a.e. } x$$

Well-posedness for an auxiliary system

Modified problem :

$$\frac{\partial u}{\partial t} - \alpha \Delta u + T\left(\frac{u}{k + |u|} - \frac{v}{k' + |v|}\right) = J$$

$$-\beta \Delta v + Fv + T\left(\frac{v}{k' + |v|} - \frac{u}{k + |u|}\right) = FL$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma$$

$$u|_{t=0} = \bar{u}$$

Variational formulation :
Find $(u, v) : [0, t_m] \to H^1(\Omega)^2$ such that

$$\frac{d}{dt}((u, \phi)) + \alpha((\nabla u, \nabla \phi)) + ((\varphi_k(u), \phi)) - ((\varphi_{k'}(v), \phi))$$

$$= ((J, \phi)),\ \forall \phi \in H^1(\Omega)$$

$$\beta((\nabla v, \nabla \psi)) + F((v, \psi)) + ((\varphi_{k'}(v), \psi)) - ((\varphi_k(u), \psi))$$

$$= ((FL, \psi)),\ \forall \psi \in H^1(\Omega)$$

$$u(0) = \bar{u} = \text{ in } L^2(\Omega)$$

$$\varphi_c(s) = \frac{Ts}{c + |s|}$$

Well-posedness : Galerkin scheme

Well-posedness and regularity for the original problem

Nonnegativity, well posedness

We have, $\forall t_m > 0$

$$u \in L^\infty(0, t_m; H^2_{\mathrm{N}}(\Omega)) \cap L^2(0, T; H^3(\Omega))$$

$$v \in L^\infty(0, t_m; H^3(\Omega) \cap H^2_{\mathrm{N}}(\Omega)) \cap \mathcal{C}([0, t_m]; L^2(\Omega))$$

$$\frac{\partial u}{\partial t} \in L^\infty(0, t_m; L^2(\Omega)) \cap L^2(0, t_m; H^1(\Omega))$$

Bounds on the solutions

We have

$$\|u(t)\|_{L^\infty(\Omega)} \leq \|\bar{u}\|_{L^\infty(\Omega)} + (J + T)t,\ t \geq 0$$

$$\|v(t)\|_{L^\infty(\Omega)} \leq \frac{FL + T}{F},\ t \geq 0$$

Regularity of $\frac{\partial v}{\partial t}$

Essential to study the limit $\varepsilon \to 0$

We can define the mapping

$$\mathcal{F} : H^1(\Omega) \to H^1(\Omega),\ w \mapsto z = \mathcal{F}(w)$$

where z is the unique solution to

$$\alpha((\nabla z, \nabla \phi)) + F((z, \phi)) + ((\varphi_{k'}(z), \phi)) = ((FL + \varphi_k(w), \phi)),\ \forall \phi \in H^1(\Omega)$$

$\to v(t) = \mathcal{F}(u(t))$

$\mathcal{F}$ is differentiable (for the $L^2(\Omega)$ and $H^1(\Omega)$-norms)

$\rightarrow \frac{\partial v}{\partial t} = \mathcal{F}'(u) \cdot \frac{\partial u}{\partial t}$

$\rightarrow \frac{\partial v}{\partial t} \in L^\infty(0, t_m; H^1(\Omega))$, $\|\frac{\partial v}{\partial t}\|_{H^1(\Omega)} \leq c\|\frac{\partial u}{\partial t}\|$ a.e. $t \geq 0$

Stability of the unique spatially homegeneous equilibrium

As in the case $\varepsilon > 0$

Convergence to the limit problem as $\varepsilon \to 0$

Convergence on finite time intervals :

$$\|u_\varepsilon(t) - u_0(t)\|_{H^1(\Omega)} \leq Q(t_m, \|\bar{u}\|_{H^1(\Omega)})\varepsilon$$

$$\|v_\epsilon(t) - v_0(t)\|_{H^1(\Omega)} \leq Q(t_m, \|\bar{u}\|_{H^1(\Omega)})\sqrt{\varepsilon},$$

$t \in [0, t_m]$, $u_\varepsilon(0) = u_0(0) = \bar{u}$, $v_\varepsilon(0) = v_0(0) = \mathcal{F}(\bar{u})$