Online Resource 1

Article Title: Glioma Growth Modeling based on the Effect of Vital Nutrients and Metabolic Products

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Online Resource 1 contains the supplementary mathematical formulas, which also have been used in the proposed model. It also includes a multi-page table where the parameter values used for the model simulations are listed.

Additional Mathematical Equations

- Relative oxygen concentration coefficient: $O = 1\text{-}(\mathrm{b_h} + \mathrm{a_n}) \cdot n_h$
- Coefficient related to the critical oxygen concentration for the proliferative cells to turn to hypoxic $\begin{Bmatrix} n_h = 0, o(l,t) > 0 \\ n_h = 1, o(l,t) \le 0 \end{Bmatrix}$
- Conversion rate of proliferative cells to hypoxic: $\mathrm{b_h} = (1\text{-}\dfrac{o_{tmp}(l,t)}{o_0}) / 20$
- Relative glucose concentration coefficient: $Gl = 1\text{-}(\mathrm{b_q} + \mathrm{a_n}) \cdot gl_q$
- Coefficient related to the critical glucose concentration for the proliferative cells to turn to hypoglycemic $\begin{Bmatrix} gl_q = 0, gl(l,t) > 0 \\ gl_q = 1, gl(l,t) \le 0 \end{Bmatrix}$
- Conversion rate of proliferative cells to hypoglycemic: $\mathrm{b}_q = (1\text{-}\dfrac{gl_{tmp}(l,t)}{gl_0}) / 20$
- Relative lactate concentration: $La = \dfrac{la(l,t) - la_0}{la(l,t)}$
- Relative H^+ concentration: $H_{ions} = \dfrac{h(l,t) - h_0}{h(l,t)}$
- Coefficient related to the pH threshold that determines the beginning of the proliferation rate decrease: $pH_{pr} = \mathrm{pH}_{val\,\mathrm{Pr}} - (-\log(h(l,t) \cdot 10^6)$ and $\begin{Bmatrix} pH_{pr} > 0 \Rightarrow pH_{pr} = 1 \\ pH_{pr} < 0, pH_{pr} = 0 \end{Bmatrix}$
- Coefficient related to the pH threshold for the proliferative cells to turn to quiescent (stop proliferating): $pH_q = -\log(h(l,t) \cdot 10^6 - \mathrm{pH}_{valQ}$ and $\begin{Bmatrix} pH_q > 0 \Rightarrow pH_q = 1 \\ pH_q < 0, pH_q = 0 \end{Bmatrix}$
- Coefficient related to the pH threshold for the acidic cells to turn to necrotic: $pH_n = -\log(h(l,t) \cdot 10^6 - \mathrm{pH}_{valN}$ and $\begin{Bmatrix} pH_n > 0 \Rightarrow pH_n = 1 \\ pH_n < 0, pH_n = 0 \end{Bmatrix}$
- Conversion rate of proliferative to acidic cells and acidic to proliferative: $b_a = g_a = 1\text{-}(\mathrm{b_h} \cdot n_h + \mathrm{b}_q \cdot \mathrm{gl}_q + \mathrm{N(l,t)} \cdot \mathrm{a}_n)$

- Threshold for the hypoxic cells to turn to necrotic due to the absence of oxygen:
$$\left.\begin{cases}\dfrac{H(l,t)}{H(l,t)+C(l,t)+Q(l,t)+A(l,t)} > 0.9 \\ n_h = 1\end{cases}\right\} \Rightarrow n_{hn} = 1$$
- Threshold for the hypoxic cells to turn to necrotic due to the absence of glucose:
$$\left.\begin{cases} n_h = 1 \\ gl_q = 1\end{cases}\right\} \Rightarrow gl_{hn} = 1$$
- Threshold for the hypoglycemic cells to turn to necrotic due to the absence of glucose:
$$\left.\begin{cases}\dfrac{Q(l,t)}{H(l,t)+C(l,t)+Q(l,t)+A(l,t)} > 0.75 \\ gl_q = 1\end{cases}\right\} \Rightarrow gl_{qn} = 1$$
- Threshold for the hypoglycemic cells to turn to necrotic due to the absence of oxygen:
$$\left.\begin{cases} n_h = 1 \\ gl_q = 1\end{cases}\right\} \Rightarrow n_{qn} = 1$$
- Concentration change of hypoglycemic cells:

$$\frac{\partial Q(l,t)}{\partial t} = \nabla\cdot(D_{ql}(l,t)\cdot(1-T)\nabla Q(l,t)) + (C(l,t)\cdot b_q\cdot gl_q + A(l,t)\cdot b_q\cdot gl_q - Q(l,t)\cdot g_q\cdot(1-gl_q)$$
$$-Q(l,t)\cdot a_q\cdot n_{qn} - Q(l,t)\cdot a_{glq}\cdot gl_{qn} - Q(l,t)\cdot N(l,t)\cdot a_n)\cdot pH_n - Q(l,t)\cdot(1-pH_n)$$

- Concentration change of glucose:

$$\frac{\partial gl(l,t)}{\partial t} = D_{gl}\nabla^2 gl(l,t) + \beta_{gl}\cdot e(l,t) - (\gamma_{cgl1}\cdot(1-n_h) + \gamma_{cgl1}\cdot n_h)\cdot C(l,t)$$
$$-\gamma_{hgl}\cdot H(l,t) - \gamma_{qgl}\cdot Q(l,t) - \gamma_{agl}\cdot A(l,t) - \varepsilon_{gl}\cdot gl(l,t)$$

Table 1 - Parameter Values

Parameters	Symbols	Values	Units
Tissue maximum carrying capacity	C_m	$2.39*10^5$	cells/mm^3
Initial spherical tumor cell density	C_0	$3*10^4$	cells/mm^3
Initial real tumor cell density	C_{0r}	$5*10^4$	cells/mm^3
Initial spherical tumor cell density for model validation	C_{0v}	10^5	cells/mm^3
Initial spherical tumor radius	r_0	1	mm
Initial Diffusion coefficient of proliferative cells	$D_c = D_w$	0.005, 0.3	mm^2/day
Initial Diffusion coefficient of hypoxic cells	D_h	D_c*10	mm^2/day
Initial Diffusion coefficient of hypoglycemic cells	D_q	D_c	mm^2/day
Initial Diffusion coefficient of acidic cells	D_a	D_c	mm^2/day
Low and high cell-diffusion coefficients for model validation (spherical tumor)	D_{cv}	0.01, 0.06	mm^2/day
Cell-diffusion coefficient for model validation (real tumor)	D_{cvr}	0.01	mm^2/day
Proliferation rate constant	ρ	0.0025, 0.04	1/day
Low and high cell-proliferation rates for model validation (spherical tumor)	ρ_v	0.013, 0.033	1/day
Cell-proliferation rate for model validation (real tumor)	ρ_{vr}	0.005	1/day
Initial ECM concentration outside the tumor	f_0	10^{-9}	mol/mm^3
Initial intratumoral ECM concentration	f_{0tumor}	$0.9*10^{-9}$	mol/mm^3
Initial MDEs concentration outside the tumor	m_0	0	mol/mm^3
Initial intratumoral MDEs concentration	m_{0tumor}	$0.5*C_0$	mol/mm^3
Initial oxygen concentration outside the tumor	o_0	$0.28*10^{-9}$	mol/mm^3
Initial intratumoral oxygen concentration (spherical geometry)	o_{0tumor}	o_0*e^{-dr}	mol/mm^3
Initial intratumoral oxygen concentration (real geometry)	o_{0tumor}	$0.5* o_0$	mol/mm^3
Initial glucose concentration outside the	gl_0	$16.5*10^{-9}$	mol/mm^3

tumor			
Initial intratumoral glucose concentration (spherical geometry)	gl_{0tumor}	$gl_0 * e^{-d(r)}$	mol/mm^3
Initial intratumoral glucose concentration (real geometry)	gl_{0tumor}	$0.5 * gl_0$	mol/mm^3
Initial lactate concentration outside the tumor	la_0	10^{-10}	mol/mm^3
Initial intratumoral lactate concentration	la_{0tumor}	$10 * la_0$	mol/mm^3
Initial H^+ concentration outside the tumor (Extra-tumoral pH=7.4)	h_0	$3.98 * 10^{-14}$	mol/mm^3
Initial intratumoral H^+ concentration (Intratumoral pH=7.1)	h_{0tumor}	$7.94 * 10^{-14}$	mol/mm^3
Reduced proliferation rate pH value	pH_{valPr}	6.8	-
Quiescent acidic pH value	pH_{valQ}	6.4	-
Necrotic pH value	pH_{valN}	6	-
Diffusion coefficient of MDEs	D_m	0.00864	mm^2/day
Diffusion coefficient of oxygen	D_o	157.248	mm^2/day
Diffusion coefficient of glucose	D_{gl}	9.504	mm^2/day
Diffusion coefficient of lactate	D_{la}	15.379	mm^2/day
Diffusion coefficient of H^+	D_{ph}	155.52	mm^2/day
Oxygen natural decay rate	ε_o	0.0375	1/day
Oxygen production rate	β_o	0.5025	1/day
Glucose natural decay rate	α_{gl}	0.11	1/day
Glucose production rate	β_{gl}	1.1	1/day
Lactate excretion rate	ε_{la}	0.8	1/day
H^+ excretion rate	ε_{ph}	2592	1/day
Oxygen consumption rate by proliferative cells under normoxic conditions (60% glycolysis)	γ_{co1}	$5.52 * 10^{-12}$	mol/cell*day
Oxygen consumption rate by proliferative cells under hypoxic conditions (75% glycolysis)	γ_{co2}	$5.175 * 10^{-12}$	mol/cell*day
Oxygen consumption rate by hypoxic cells (99% glycolysis)	γ_{ho}	$6.9 * 10^{-13}$	mol/cell*day
Oxygen consumption rate by hypoglycemic cells under normoxic conditions (60%	γ_{qo1}	$0.8125 * \gamma_{cn1}$	mol/cell*day

glycolysis)			
Oxygen consumption rate by hypoglycemic cells under hypoxic conditions (60% glycolysis)	γ_{qo2}	0.5* γ_{cn1}	mol/cell*day
Oxygen consumption rate by acidic cells (50% glycolysis)	γ_{ao}	$3.45*10^{-12}$	mol/cell*day
Glucose consumption rate by proliferative cells under normoxic conditions (60% glycolysis)	γ_{cgl1}	$2.3*10^{-12}$	mol/cell*day
Glucose consumption rate by proliferative cells under hypoxic conditions (75% glycolysis)	γ_{cgl2}	0.5* γ_{cgl1}	mol/cell*day
Glucose consumption rate by hypoxic cells	γ_{hgl}	$1.15*10^{-11}$	mol/cell*day
Glucose consumption rate by hypoglycemic cells	γ_{qgl}	0.5* γ_{cgl1}	mol/cell*day
Glucose consumption rate by acidic cells	γ_{agl}	0.5* γ_{cgl1}	mol/cell*day
Lactate consumption rate by proliferative cells under hypoxic conditions	γ_{cla}	0.5* γ_{cgl1}	mol/cell*day
Lactate consumption rate by hypoglycemic cells under normoxic conditions	γ_{qla}	0.25* γ_{cgl1}	mol/cell*day
Lactate production rate by proliferative cells under normoxic conditions (60% glycolysis)	β_{cla1}	1.2* γ_{cgl1}	mol/cell*day
Lactate production rate by proliferative cells under hypoxic conditions (75% glycolysis)	β_{cla2}	0.75* γ_{cgl1}	mol/cell*day
Lactate production rate by hypoxic cells (75% glycolysis)	β_{hla}	1.98* γ_{hgl}	mol/cell*day
Lactate production rate by hypoglycemic cells (60% glycolysis)	β_{qla}	1.2* γ_{qgl}	mol/cell*day
Lactate production rate by acidic cells (50% glycolysis)	β_{ala}	γ_{agl}	mol/cell*day
H^+ production rate by proliferative cells under normoxic conditions (60% glycolysis)	β_{ch1}	$\beta_{cla1}*10^{-3}$	mol/cell*day
H^+ production rate by proliferative cells under hypoxic conditions (75% glycolysis)	β_{ch2}	$\beta_{cla2}*10^{-3}$	mol/cell*day
H^+ production rate by hypoxic cells (75% glycolysis)	β_{hh}	$\beta_{hla}*10^{-3}$	mol/cell*day

H^+ production rate by hypoglycemic cells (60% glycolysis)	β_{qh}	$\beta_{qla}*10^{-3}$	mol/cell*day
H^+ production rate by acidic cells (50% glycolysis)	β_{ah}	β_{ala}	mol/cell*day
ECM degradation rate	δ	0.0022388	mm^3/mol*day
MDEs natural decay rate	λ	0.432	1/day
MDEs production rate by proliferative cells	μ_c	0.006	mol/cell*day
MDEs production rate by hypoxic cells	μ_h	$2*\mu_c$	mol/cell*day
MDEs production rate by hypoglycemic cells	μ_q	μ_c	mol/cell*day
Conversion rate of hypoxic to proliferative or acidic cells	g_h	0.05	1/day
Conversion rate of hypoxic to necrotic cells due to lack of oxygen	a_h	$b_h/10$	1/day
Conversion rate of hypoxic to necrotic cells due lack of glucose	a_{glh}	0.01	1/day
Conversion rate of hypoglycemic to proliferative or acidic cells	g_q	0.05	1/day
Conversion rate of hypoglycemic to necrotic cells due to lack of oxygen	a_q	0.01	1/day
Conversion rate of hypoglycemic to necrotic cells due lack of glucose	a_{glq}	$b_q/10$	1/day
Conversion rate of proliferative, hypoxic, hypoglycemic, acidic to necrotic cells due to contact with necrotic region	a_n	$\log(2)/(50C_m*10^2)$	mm^3/day*cells
Time step	dt	0.0005	days
Spatial grid dimensions of spherical tumor	dr	0.2	mm
Spatial grid dimensions of RIDER-NEURO tumor	dx, dy, dz	1, 1, 1	mm
Spatial grid dimensions of clinical real tumor	dx, dy, dz	0.599, 0.599, 0.725	mm