Stoichiometry Of Tumor Dynamics: Models And Analysis

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Our objective here is to integrate natural selection driven by competition for resources, especially phosphorus $P$, into mathematical models consisting of delay differential equations. Mathematical and numerical analysis of these models show that tumor population growth and sizes are more sensitive to total phosphorous amount than their growth rates. Our simulation results show that if an artificial mechanism (treatment) can half the tumor cells’ $P$ uptake, then it may lead to a three quarter reduction in ultimate tumor size, indicating the excellent potential of such a treatment.
Tumor growth with nutrient limitation

The phosphorus is distributed into two compartments: extracellular, including blood plasma and interstitial fluid; and intracellular, which contains fraction $f$ (approximately $2/3$) of the total fluid within a typical organ (Ganong 1999). Let $n$ represent mean phosphorus content (millimoles/g) in 1 gram of healthy cells, including VECs, within the tumor stroma. Similarly, let $m$ be mean phosphorus content of 1 gram of tumor tissue. Then $P - nx - my - nz \equiv P_e$ is extracellular phosphorus within the organ. We cast $n$ and $m$ in similar units to facilitate comparisons between tumor and healthy cells.
In this model, reproduction of both healthy and tumor cells is a function of amount of extracellular phosphorus. In a phosphorus-rich environment, healthy cells and tumor cells can proliferate at maximum per capita rates $a$ and $b$, respectively. However, if the extracellular phosphorus concentration drops below a threshold value, then growth rates of both healthy and tumor cells are impaired. For healthy cells, if the extracellular phosphorus concentration $\frac{P_e}{f k_h}$(millimoles/kg) is less than $n$, the mean phosphorus content (millimoles/g) in healthy cells, then the per capita growth rate, without crowding effects, becomes

$$a \frac{P_e}{f n k_h}.$$
Homogeneous Tumor

The tumor proliferation rate begins to decrease whenever vascularization drops below a certain threshold. In particular, whenever \( g(z - \alpha y) < 1 \), then the maximum proliferation rate of the tumor becomes \( g(z - \alpha y) \), where \( \alpha \) represents the mass of tumor tissue that one unit of blood vessels can just barely maintain, and \( g \) measures sensitivity of tumor tissue to lack of blood.

The tumor’s growth rate decelerates as it approaches its carrying capacity \( k_t \). This value is determined by the physiological status of the host and in human lung cancer is approximately 3kg.
Homogeneous Tumor

The growth rate of healthy tissue decelerates as the mass of both the healthy and tumor tissue approaches $k_h$. A similar situation does not apply to the tumor. Blood vessel dynamics are much simpler. First, we assume that new microvessels arise from activated VEC precursor cells within the tumor stroma at per capita rate $c$. Furthermore, we assume there is a delay between activation of vascular precursor cells and construction of functional vessels (Ji et al. 1998). Some evidence suggests that the vascular network within tumors is constantly being remodeled (Columbo et al. 1996). To reflect this observation, we assume that mature vessels die at a constant rate $d_z$. 
Homogeneous Tumor

To explore the dynamic effect of a possible tumor cell $P$ uptake regulation, we introduce a parameter $\beta$ to measure the efficiency of such an artificial regulation in the tumor growth equation. These considerations lead to the following model:

$$\frac{dx}{dt} = x\left(a \min\left(1, \frac{Pe}{f nk_h}\right) - dx - (a - dx) \frac{x + y + z}{k_h}\right),$$

$$\frac{dy}{dt} = y\left(b \min\left(1, \beta \frac{Pe}{f mk_h}\right) \min(1, L) - dy - (b - dy) \frac{y + z}{k_t}\right),$$

$$\frac{dz}{dt} = c \min\left(1, \frac{Pe}{f nk_h}\right) y(t - \tau) - dz z,$$

$$L = \frac{g(z - \alpha y)}{y}.$$

(2.1)
In actual malignant tumors, one often finds a variety of cell types coexist. Although actual tumors can contain many cell types, we simplify the system to only two competing varieties, the masses of which are represented by $y_1$ and $y_2$. We assume that tumor cell types can differ from each other in only two ways: they may have different intrinsic birth and death rates, $b_1$ and $b_2$, $d_1$ and $d_2$, respectively; and they may differ in their efficiency of phosphorus use, meaning that in general $m_1 \neq m_2$, where $m_i$ is the mean phosphorus content of the $i$-th cell type.
These assumptions lead to the following model of a heterogeneous tumor with two competing cell types:

\[
\begin{align*}
\frac{dx}{dt} &= x \left( a \min \left( 1, \frac{Pe}{f nk_h} \right) - d_x - (a - d_x) \frac{x + y_1 + y_2 + z}{k_h} \right), \\
\frac{dy_1}{dt} &= y_1 \left( b_1 \min \left( 1, \frac{\beta_1 Pe}{f m_1 k_h} \right) \min(1, L) - d_1 - (b_1 - d_1) \frac{y_1 + y_2 + z}{k_t} \right), \\
\frac{dy_2}{dt} &= y_2 \left( b_2 \min \left( 1, \frac{\beta_2 Pe}{f m_2 k_h} \right) \min(1, L) - d_2 - (b_2 - d_2) \frac{y_1 + y_2 + z}{k_t} \right), \\
\frac{dz}{dt} &= c \min \left( 1, \frac{Pe}{f nk_h} \right) (y_1 (t - \tau) + y_2 (t - \tau)) - dz, \\
L_1 &= g \frac{z - \alpha (y_1 + y_2)}{y_1 + y_2},
\end{align*}
\]
where $P_e = P - nx - m_1y_1 - m_2y_2 - nz$. Again, we introduced parameters $\beta_1$ and $\beta_2$ to measure the efficiencies of an artificial tumor cell $P$ uptake regulation in the tumor growth equations. Note that model (9) reduces to model (7) when $y_2(0) = 0$, with the obvious modifications of subscripts. The recent work of Loladze et al. (2000) suggests that stoichiometry constraint promote coexistence among competing species. It is interesting to see if such statement can be made in the case of heterogeneous tumor growth. The answer is no (mathematically).
Tumor model with dietary regulation

We assume that a proportion $\gamma$ of the dead cells are removed away from the organ through blood flow. Assume also that the organ $P$ intake through food consumption is $r$ (millimoles/day), then in the setting of a heterogeneous tumor of (9), this yields an equation that tracks the total $P$ amount in the organ:

$$\frac{dP}{dt} = r - \gamma \left( n(dx + dz) + (a - dx)nx \frac{x + y_1 + y_2 + z}{k_h} \right.
\left. + \sum_{i=1}^{2} m_i d_i y_i + \frac{y_1 + y_2 + z}{k_i} \sum_{i=1}^{2} m_i (b_i - d_i) \right).$$

Together with the assumptions of model (9), we obtain the following model of a heterogeneous tumor growth with varying total $P$ amount:
Tumor model with dietary regulation

\[
\begin{align*}
\frac{dx}{dt} &= x \left( a \min \left( 1, \frac{P_e}{fnk_h} \right) - d_x - (a - d_x) \frac{x + y_1 + y_2 + z}{k_h} \right), \\
\frac{dy_1}{dt} &= y_1 \left( b_1 \min \left( 1, \frac{P_e}{fm_1k_h} \right) \min(1, L) - d_1 - (b_1 - d_1) \frac{y_1 + y_2 + z}{k_t} \right), \\
\frac{dy_2}{dt} &= y_2 \left( b_2 \min \left( 1, \frac{P_e}{fm_2k_h} \right) \min(1, L) - d_2 - (b_2 - d_2) \frac{y_1 + y_2 + z}{k_t} \right), \\
\frac{dz}{dt} &= c \min \left( 1, \frac{P_e}{fnk_h} \right) \left( y_1(t - \tau) + y_2(t - \tau) \right) - d_z z, \\
\frac{dP}{dt} &= r - \gamma \left( n(d_xx + d_z z) + (a - d_x)n_x \frac{x + y_1 + y_2 + z}{k_h} + \sum_{i=1}^{2} m_i d_i y_i + \frac{y_1 + y_2 + z}{k_t} \sum_{i=1}^{2} m_i (b_i - d_i) \right), \\
L &= g \frac{z - \alpha(y_1 + y_2)}{y_1 + y_2},
\end{align*}
\]
Simulation analysis of the models

For realistic parameter values and initial conditions, the ultimate outcome of all three models is the same: solutions tend to a positive steady state where phosphorus limits both healthy and tumor cell growth. One nonintuitive phenomenon is that at this steady state, tumor growth is no longer limited by its blood vessel infrastructure.
Simulation analysis of the models

Homogeneous tumor growth

- half healthy cells mass
- tumor cells mass
- tumor microvessels mass
- $P$ limitation indicator ($0 \leq s \leq 1$)
- blood supply limitation indicator ($0 \leq g_s \leq 2$)
Simulation analysis of the models

Homogeneous tumor growth with 20% reduction of $P, \beta=1$

- half healthy cells mass
- tumor cells mass
- tumor microvessels mass
- $P$ limitation indicator ($0 \leq s \leq 1$)
- blood supply limitation indicator ($0 \leq gs \leq 2$)
Simulation analysis of the models

Heterogeneous tumor growth, $\beta_1 = \beta_2 = 1$

- 1/4 healthy cells mass (kg)
- tumor cells type 1 mass
- tumor cells type 2 mass
- tumor microvessels mass
- total tumor cells
- $P$ limitation indicator ($0 \leq s \leq 1$)
- blood supply limitation indicator ($0 \leq g_s \leq 2$)
Simulation analysis of the models

Heterogeneous tumor growth with varying $P$

- half healthy cells mass (kg)
- tumor cells type 1 mass
- tumor cells type 2 mass
- tumor microvessels mass
- 2% of total $P$
- $P$ limitation indicator ($0 \leq s \leq 1$)
- blood supply limitation indicator ($0 \leq gs \leq 2$)
Simulation analysis of the models

Here we assume no treatment blocking phosphorus uptake by tumor cells ($\beta = 1$) and the construction of blood vessel is NOT phosphorus limited. Notice that $\frac{P_e}{f n k_h} < 1$ and $L > 1$ at $E^*$ for model (4.1).
Simulation analysis of the models

Here we assume a treatment yielding a 64% reduction in phosphorus uptake by tumor cells, and the construction of blood vessel is NOT phosphorus limited.
We assume that (A1): The construction of blood vessels is NOT limited by phosphorus supply.
With (A1), model (2.1) becomes the following simplified model:

\[
\begin{align*}
\frac{dx}{dt} &= x \left( a \min \left(1, \frac{Pe}{fnk_h} \right) - d_x - (a - d_x) \frac{x + y + z}{kh} \right), \\
\frac{dy}{dt} &= y \left( b \min \left(1, \frac{Pe}{fmk_h} \right) \min(1, L) - d_y - (b - d_y) \frac{y + z}{kt} \right), \\
\frac{dz}{dt} &= cy(t - \tau) - dz, \\
L &= g(z - \alpha y) \frac{z - \alpha y}{y}.
\end{align*}
\]
Mathematical Results

Our main concern is the stability of $E^*$ of (4.1). Our analysis is simplified by the following observation: in both models (2.1) and (4.1), at this steady state $E^*$, \[ \frac{P_e}{f n k_h} < 1 \text{ and } L > 1. \]

Hence we also assume (A2): For model (4.1), \[ \frac{P_e}{f n k_h} < 1 \text{ and } L > 1 \text{ at } E^*. \]

Clearly (A2) implies that \[ \frac{\beta P_e}{f m k_h} < 1. \]

We obtain

\[
x^* = \frac{k_h}{a - d_x} \left[ \frac{a n}{\beta b m} \left( d_y + (b - d_y) \frac{y^* + z^*}{k_t} \right) - d_x \right] - y^* - z^*,
\]

\[
y^* = d z k_t N / D,
\]

\[
z^* = c k_t N / D.
\]
Mathematical Results

where

\[ N = aPb\beta - d_xPb\beta - d_yk_hma - afmk_hd_y + b\beta nd_xk_h + fd_xmk_hd_y \]

and

\[ D = -fd_xd_zmk_hb - ad_zf mk_hd_y - fd_xcmk_hb - acfmk_hd_y - ad_zmk_hd_y + ad_zmk_hb + acfmk_hb + ad_zmk_tb\beta + fd_xd_zmk_hd_y - d_xd_zmk_tb\beta + ad_zf mk_hb - k_t b\beta d_za + k_t b\beta d_znd_x + fd_xcmk_hd_y + acmk_hb - acmk_hd_y. \]
Mathematical Results

In order to study stability aspects of the steady state $E^*$ of (4.1), we need

**Lemma 1** *(Kuang, p227)* Assume that the parameters are positive, and $x^* > 0$, $y^* > 0$, $z^* > 0$:

\[
\frac{dx}{dt} = -x(A_1(x - x^*) + A_2(y - y^*) + A_3(z - z^*)),
\]

\[
\frac{dy}{dt} = -y(B_1(x - x^*) + B_2(y - y^*) + B_3(z - z^*)),
\]

\[
\frac{dz}{dt} = -(-c(y(t - \tau) - y^*) + d_z(z - z^*)).
\]

If there are positive constants $c_1, c_2$ such that

1): $d_z > c/c_2$,

2): $B_2/c_2 > B_3 + B_1/c_1$,

3): $A_1/c_1 > A_1 + A_2/c_2$

then the steady state $E^* = (x^*, y^*, z^*)$ is G.A.S.
Mathematical Results

For $a = 3, m = 20, n = 10, k_h = 10, f = 0.6667, P = 150, b = 6, d_x = 1, d_y = 1, \beta = 1$, we can chose $c_1 = 0.5$ and $c_2 = 0.2$ to satisfy conditions 1) through 3) in the above Lemma. In other words, we have shown that for this set of parameters, the positive steady state $E^*$ of model (4.1) is locally asymptotically stable. However, simulation suggests that it is actually globally asymptotically stable. So, this mathematical question remains open.
Mathematical Results

Theorem 1  Assume that in model (4.1) there is a unique positive steady state \( E^* = (x^*, y^*, z^*) \). Assume further that there are positive constants \( c_1, c_2 \) such that

1): \( dz > c / c_2 \),
2): \( B_2 / c_2 > B_3 + B_1 / c_1 \),
3): \( A_1 / c_1 > A_1 + A_2 / c_2 \)

where \( A_1, A_2, B_1, B_2, B_3 \) are given by (4.4) and (4.5). Then the steady state \( E^* = (x^*, y^*, z^*) \) is locally asymptotically stable.
Mathematical Results

Special Case: \( ma = nb, d_x = d_y, \beta = 1. \)

\[
y^* = \frac{aP - fnk_h d_x}{fn(a - d_x)(\rho + 1 + \sigma) + a(n\rho + m + n\sigma)}
\]

\[
= \frac{bP - fmk_h d_y}{fm(a - d_y)(\rho + 1 + \sigma) + b(n\rho + m + n\sigma)},
\]

where

\[
\sigma = \frac{c}{dz}, \quad \rho = \left( \frac{b - d_y}{k_t} - \frac{a - d_x}{k_h} \right) \frac{k_h(1 + \sigma)}{a - d_x}.
\]

The tumor dies out if one can increase the tumor’s death rate or the tumor’s \( P \) requirement, or lower the tumor’s birth rate to certain threshold levels.
The most noteworthy insight gained through this modelling exercise is that within the tumor entity, slower-growing tumor cell types, which utilize less phosphorus because their ribosome production demands are not as great, will dominate the tumor over the time. This competitive exclusion pressure always threatens to push faster-growing cell types to extinction, which in turn may provide the evolutionary impetus for these more aggressive tumor cells to metastasize. This result may explain why metastatic tumor cells typically differ from those that dominate the primary tumor. One should explore how this evolutionary insight might be exploited clinically.
One recommendation suggested by this research is to look for ways to selectively reduce the rate of phosphorus uptake by tumor cells. The advantage of such a treatment is that it may dramatically reduce ultimate tumor size while maintaining the organ at a healthy size. This result could be accomplished by applying drugs capable of selectively blocking phosphorus uptake by tumor cells. Alternatively, one could use a nutritionally worthless inhibitor that competes with phosphate for the binding site on membrane phosphate transporters. This strategy is intriguing since it would tend to avoid the toxic effect of excessive phosphorus liberated from dead tumor cells, a situation that causes, in part, “tumor lysis syndrome,” a well known phenomenon that results from destruction of tumor cells during chemotherapy.
Discussion

A second plausible (crazy?) treatment suggested by this research is to implant into the tumor less malignant or benign tumor cells, or simply healthy cells if possible, that require less phosphorus and thus are likely to out-compete the original tumor cells. Alternatively, one can try to genetically manipulate existing tumor cells to generate less malignant or benign tumor cells that will do the same thing.