ABM TUMOR MODEL EQUATIONS

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Equations for the agent-based tumor model.

1. MODEL

1.1. **Assumptions.**

- No oxygen dependence.
- Cell growth depends on growth signal with half-saturation constant K_s.
- Bulk concentration of growth signal is constant.
- Diffusion of solute (growth signal) is physically modeled.
- Cells grow to a maximum radius then divide.
- Begin with only cheaters, with probability of mutation to cooperator upon division equal to λ. There is no mutation from cooperator to cheater.
- Cooperators produce growth signal at a rate R_s and cost c.
- Cells at edges of tumor detach from the main tumor mass at rate proportional to r^2 where r is the distance to the center of the simulation space. This simulates detachment of cells to form metastases and death due to distance from the initial location of tumorigenesis with favorable growth conditions. Detachment coefficient is the constant R_{det}.
- Cells push each other so as not to overlap.

1.2. **Stoichiometry table.**

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Reaction	S	X (cooperator)	Y (cheater)	Rate
X growth	$-1/Y_s$	1		$\mu_{max}\frac{S}{K_s+S}X$
Y growth	$-1/Y_s$		1	$\mu_{max}\frac{S}{K_s+S}Y$
S produce	1	$-c$		R_sX
Mutate		1	-1	λY

Erosion speed function (dimensionality is $[LT^{-1}]$):

$$V_{ero} = \frac{-R_{det}r^2}{\rho} \tag{1}$$

1.3. Time derivatives.

$$\frac{\delta X}{\delta t} = \mu_{max}\frac{S}{K_s+S}X - \frac{R_{det}2\pi r^3}{\rho}X - R_scX + \lambda Y \tag{2}$$

$$\frac{\delta Y}{\delta t} = \mu_{max}\frac{S}{K_s+S}Y - \frac{R_{det}2\pi r^3}{\rho}Y - \lambda Y \tag{3}$$

$$\frac{\delta S}{\delta t} = D\nabla^2 S - \frac{\mu_{max}}{Y_s}\frac{S}{K_s+S}(X+Y) + R_sX \tag{4}$$

1.4. Nondimensionalization.

1.4.1. *Parameters.*

μ_{max}	max growth rate	$[T^{-1}]$
c	signal production cost	dimensionless
D	signal diffusion coeff.	$[L^2T^{-1}]$
ρ	biomass density	$[ML^{-2}]$ if 2D, $[ML^{-3}]$ if 3D
h	boundary layer thickness	$[L]$
S_0	bulk signal concentration	$[ML^{-3}]$
K_s	growth with signal half-saturation constant	$[ML^{-3}]$
λ	mutation rate	$[T^{-1}]$
R_s	signal production rate coeff.	$[T^{-1}]$
R_{det}	detachment rate coeff.	$[ML^{-3}T{-}1]$ (r-square detachment)
Y_s	yield of biomass produced per signal consumed	dimensionless
Q	ext. mass transfer rate $\equiv D/h^2$	$[T^{-1}]$

1.4.2. *Variables.*

$$\begin{gathered}\hat{X} = X/\rho = fM/\rho = \pi h^2 \hat{r}^2 f \\ \hat{Y} = Y/\rho = \pi \hat{r}^2(1-f) \\ \hat{S} = S/S_0 \\ \hat{r} = r/h \\ \hat{t} = t * \mu_{max}\end{gathered}$$

1.4.3. *Time derivatives:*

$$\frac{1}{\mu_{max}\rho}\frac{\delta X}{\delta t} = \frac{\delta \hat{X}}{\delta \hat{t}} = \frac{\hat{S}}{K_s/S_0 + \hat{S}}\hat{X} - \frac{2\pi R_{det} h^3}{\mu_{max}}\hat{r}^3\hat{X} - \frac{R_s c}{\mu_{max}}\hat{X} + \frac{\rho\lambda}{\mu_{max}}\hat{Y} \tag{5}$$

$$\frac{1}{\mu_{max}\rho}\frac{\delta Y}{\delta t} = \frac{\delta \hat{Y}}{\delta \hat{t}} = \frac{\hat{S}}{K_s/S_0 + \hat{S}}\hat{Y} - \frac{2\pi R_{det} h^3}{\mu_{max}}\hat{r}^3\hat{Y} - \rho\lambda\hat{Y} \tag{6}$$

$$\frac{1}{S_0\mu_{max}}\frac{\delta S}{\delta t} = \frac{\delta \hat{S}}{\delta \hat{t}} = \frac{D}{h^2\mu_{max}}\nabla^2\hat{S} - \frac{\rho}{Y_sS_0}\frac{\hat{S}}{K_s/S_0+\hat{S}}(\hat{X}+\hat{Y}) + \frac{\rho R_s}{S_0\mu_{max}}\hat{X} \tag{7}$$

2. Homogeneous steady-state approximation

2.1. **Assumptions.**

- Cooperator and cheater biomass are well-mixed and constant across the tumor radius.
- Growth signal concentration is constant across the tumor.
- Steady-state tumor radius reflects tumor size at which growth rate is exactly equal to detachment rate.

2.2. **Setup.**

Total mass of tumor: $M = X + Y = \rho\pi r^2$
Fraction of cooperators $f \equiv X/M$
r^* is total tumor radius at steady state

$$\mu = \mu_{max}\frac{S}{S+K_s} \sim \begin{cases} S\frac{\mu_{max}}{K_s} & \text{if } S \ll K_s \\ \mu_{max} & \text{if } S \gg K_s \end{cases}$$

$$k = \frac{K_s}{S_0}$$

$$\frac{dS}{dt} = 0 = R_s\rho f - \frac{\mu}{Y_s}\rho + \frac{D_s}{hr}(S_0 - S) \tag{8}$$

Nondimensionalized:

$$\frac{1}{\mu_{max}S_0}\frac{dS}{dt} = \frac{d\hat{S}}{d\hat{t}} = 0 = \frac{R_s\rho}{\mu_{max}S_0}f - \frac{\hat{S}}{k+\hat{S}}\frac{\rho}{S_0Y_s} + \frac{2D_S}{\mu_{max}h^2\hat{r}}(1-\hat{S}) \tag{9}$$

$$\frac{dM}{dt} = 0 = \mu M - R_{det}2\pi r^3 - cfMR_s \tag{10}$$

Nondimensionalized:

$$\frac{1}{\mu_{max}\pi\rho h^2}\frac{dM}{dt} = \frac{d\hat{r}^2}{d\hat{t}} = 0 = \frac{\hat{S}}{k+\hat{S}}\hat{r}^2 - \frac{R_{det}2h}{\mu_{max}\rho}\hat{r}^3 - \frac{cR_s}{\mu_{max}}f\hat{r}^2 \tag{11}$$

$$\frac{dX}{dt} = 0 = \mu fM - R_{det}2\pi r^3 f - cfMR_s + \lambda(1-f)M \tag{12}$$

Nondimensionalized:

$$\frac{1}{\mu_{max}\rho\pi h^2}\frac{dX}{dt} = \frac{d\hat{r}^2 f}{d\hat{t}} = 0 = \frac{\hat{S}}{k+\hat{S}} f\hat{r}^2 - \frac{R_{det}2h}{\mu_{max}\rho} f\hat{r}^3 - \frac{cR_s}{\mu_{max}} f\hat{r}^2 + \frac{\lambda}{\mu_{max}}(1-f)\hat{r}^2 \tag{13}$$

2.3. **Solutions.**

(For: $f^*, \hat{s}^*, \hat{r}^*$) From 9:

$$0 = -\hat{s}^* + (\frac{Rs\rho}{2QS_0} f\hat{r} - \frac{\rho\mu_{max}}{2S_0Y_s}\hat{r} + 1 - k)\hat{s}^* + k(\frac{R_s\rho}{2QS_0} f\hat{r} + 1) \tag{14}$$

Define

$$\alpha \equiv \frac{R_s\rho}{2QS_0}[\text{dimensionless}]$$

Which can be regarded as the normalized ratio of signal synthesis to external transfer.

$$\beta \equiv \frac{\rho\mu_{max}}{2S_0Y_sQ}[\text{dimensionless}]$$

Which can be regarded as the normalized ratio of signal consumption to external transfer.

Then

$$0 = -\hat{s}^* + (\alpha f\hat{r} - \beta\hat{r} + 1 - k)\hat{s}^* + k(\alpha f\hat{r} + 1) \tag{15}$$

With the help of Sage:

$$\hat{s}^* = \frac{(\alpha f - \beta)\hat{r} - k + 1 \pm \sqrt{(\alpha^2 f^2 - 2\alpha\beta f + \beta^2)\hat{r}^2 + 2[(\alpha f - \beta)k + \alpha f - \beta]\hat{r} + k^2 + 2k + 1}}{2} \tag{16}$$

But everything under the square root is just:

$$[(\alpha f - \beta)\hat{r} + (k+1)]^2$$

And thus:

$$\hat{s}^* = \begin{cases} -k \\ (\alpha f - \beta)\hat{r} + 1 \end{cases} \tag{17}$$

of which only the latter is relevant.

And so:

$$\frac{\hat{s}^*}{k+\hat{s}^*} = 1 - \frac{k}{(\alpha f - \beta)\hat{r} + k + 1} \tag{18}$$

From 11:

$$\frac{d\hat{r}}{d\hat{t}} = -\frac{R_{det}h}{\mu_{max}\rho}\hat{r}^2 + \frac{1}{2}\frac{\hat{s}}{k+\hat{s}}\hat{r} - \frac{cR_s}{2\mu_{max}}f\hat{r} \tag{19}$$

(Note that this precludes the trivial solution where $\hat{r} = 0$.)

From 13:

$$\begin{aligned}
\frac{d\hat{X}}{d\hat{t}} &= \frac{1}{\mu_{max}\pi\rho h^2}\frac{dX}{dt} && (20)\\
&= \frac{df\hat{r}^2}{d\hat{t}} && (21)\\
&= 2f\hat{r}\frac{d\hat{r}}{d\hat{t}} + \hat{r}^2\frac{df}{d\hat{t}} && (22)\\
&= 2f\hat{r}(-\frac{R_{det}h}{\mu_{max}\rho}\hat{r}^2 + \frac{1}{2}\frac{\hat{s}}{k+\hat{s}}\hat{r} - \frac{cR_s}{2\mu_{max}}f\hat{r}) + \hat{r}^2\frac{df}{d\hat{t}} && (23)\\
&= \frac{\hat{s}}{k+\hat{s}}f\hat{r}^2 - \frac{R_{det}2h}{\mu_{max}\rho}f\hat{r}^3 - \frac{cR_s}{\mu_{max}}f\hat{r}^2 + \frac{\lambda}{\mu_{max}}(1-f)\hat{r}^2 && (24)
\end{aligned}$$

Therefore:

$$\frac{df}{d\hat{t}} = \frac{cR_s}{\mu_{max}}f^2 + (\frac{\lambda}{\mu_{max}} - \frac{cR_s}{\mu_{max}})f + \frac{\lambda}{\mu_{max}} \tag{25}$$

Define:

$$\gamma \equiv \frac{R_{det}h}{\mu_{max}\rho}[\text{dimensionless}]$$

$$\delta \equiv \frac{cR_s}{\mu_{max}}[\text{dimensionless}]$$

$$\epsilon \equiv \frac{\lambda}{\mu_{max}}[\text{dimensionless}]$$

Then:

$$\frac{d\hat{r}}{d\hat{t}} = -\gamma\hat{r}^2 + \frac{1}{2}\left(\frac{\hat{s}}{k+\hat{s}}\hat{r} - \delta f\hat{r}\right) \tag{26}$$

$$\frac{df}{d\hat{t}} = \frac{1}{\mu_{max}}(\lambda - cR_s f)(1-f) \tag{27}$$

2.4. **Fixed points and stability analysis.**

The fixed points of f are found at:

$$f = \begin{cases} 1 \\ \lambda/cR_s \end{cases} \tag{28}$$

Although the fixed points of f are constant for a given λ/cR_s ratio, half time to steady state seems to scale inversely with λ judging by numerical simulations.

2.5. **Parameter lumping and interpretations.**

2.6. **Limitations.**

In reality, $\frac{df}{dt}$ will be dependent on both λ and the [fraction of produced signal received by cooperators/segregation index/relatedness]. $\frac{dX}{dt}$ will be nonlinear for X.