Cancer cells phenotype evolution in hypoxic conditions.

Modelli matematici per la biomedicina

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1859

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The biological problem

- Phenotypic heterogeneity in vascularized tumors;
- The role of intratumoral oxygen concentration:
  - Hypoxia-inducible factors (**HIF-1**α);
  - Warburg effect.
- Biomedical needs and models in literature.

Aim of the work

Describing the transition of tumor cells from an aerobic to an anaerobic metabolism in hypoxic environment with the use of different spatial domain dimensions and abiotic factor concentrations.

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2 Methods

Cancer cell dynamics

- $\mathbf{x} \in \Omega \subset \mathbb{R}^d$, in which $d = 1, 2$;
- $h \in [0, 1]$: phenotype of cancer cells;
- $f(t, \mathbf{x}, h)$: local phenotype distribution of cancer cells with $t \in [0, T]$, $T > 0$;
- volume fraction of cancer cells:

$$\phi(t, \mathbf{x}) = \int_0^1 f(t, \mathbf{x}, h) dh \tag{1}$$

- average phenotype distribution:

$$H(t, \mathbf{x}) = \frac{1}{\phi(t, \mathbf{x})} \int_0^1 h f(t, \mathbf{x}, h) dh \tag{2}$$

Cancer cells dynamics

Evolution of $f(t, \mathbf{x}, h)$

$$\partial_t f + \nabla_{(\mathbf{x})} \cdot (f\mathbf{v}) + \partial_h(fw) - \beta\partial^2_{hh} f = Gf \tag{3}$$

$$G = (p(\bar{\phi} - \phi))_+ - d \tag{4}$$

- effective proliferation: $(p(\bar{\phi} - \phi))_+,\ p \equiv p(h, c_o(t, \mathbf{x}), c_g(t, \mathbf{x}))$;
- cells death: $d,\ d \equiv d(h, c_o(t, \mathbf{x}), c_g(t, \mathbf{x}))$.

How G is modelled

$$G(h, c_o(t,\mathbf{x}), c_g(t,\mathbf{x})) =$$
$$\eta(\bar{\phi} - \phi(t,\mathbf{x}))_+(\tilde{q}(h, c_o(t,\mathbf{x}), c_g(t,\mathbf{x})) - 1)_+ - \xi - \xi_q(1 - \tilde{q}(h, c_o(t,\mathbf{x}), c_g(t,\mathbf{x})))_+ \quad (5)$$

- $(\tilde{q} - 1)_+$: available quantity of ATP;
- $\tilde{q} := \dfrac{q}{\theta}$

Rate of total energy produced by a single cell with phenotype h

$$q \equiv q(h, c_o(t,\mathbf{x}), c_g(t,\mathbf{x})) = n_o(h)q_o(c_o(t,\mathbf{x}), c_g(t,\mathbf{x})) + n_g(h)q_g(c_g(t,\mathbf{x})) \quad (6)$$

Qualitative analysis

Hypothesis

- Cells motions and induced phenotype variation are slower than cell proliferation and death;
- Spontaneous epimutations are slower than induced ones.

$$\begin{cases} \varepsilon\partial_t f_\varepsilon - \varepsilon\mu(h)\nabla_{\mathbf{x}} f_\varepsilon \left[\nabla_{\mathbf{x}}(\phi_\varepsilon)\right] - \varepsilon\mu(h) f_\varepsilon \nabla^2_{\mathbf{x}}(\phi_\varepsilon) + \varepsilon\partial_h(w f_\varepsilon) = G f_\varepsilon + \varepsilon^2 \partial^2_{hh} f_\varepsilon \\ \phi_\varepsilon = \int_0^1 f_\varepsilon(t, \mathbf{x}, h) dh \end{cases} \tag{7}$$

$$f(t, \mathbf{x}, h) \approx \phi(t, \mathbf{x})\delta(h - \bar{h}(\mathbf{x})), \qquad \varepsilon \to 0 \tag{8}$$

$\bar{h} : \Omega \to [0, 1]$: phenotype in which the majority of the cancer cell population is found to be at.

Qualitative analysis

Limits of $\phi(t,\mathbf{x})$ and $\bar{h}(t,\mathbf{x})$ for $t \to \infty$

- $\phi^{\infty}(\mathbf{x})$ and $h^{\infty}(\mathbf{x})$: asymptotic values to which $\phi(t,\mathbf{x})$ and $\bar{h}(t,\mathbf{x})$ converge for $t \to \infty$
- $\phi^{\infty}(\mathbf{x})$ and $\bar{h}^{\infty}(\mathbf{x})$ need to satisfy the following:

$$G(\mathbf{x}, \bar{h}^{\infty}, \phi^{\infty}) = 0, \quad \mathbf{x} \in \operatorname{supp}(\phi^{\infty}) \tag{9}$$

$$\Downarrow$$

Final result

$$\phi^{\infty}(\mathbf{x}) = \max\left\{0, \bar{\phi} - \frac{\xi}{\eta}\frac{1}{(\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1)}\right\} \tag{10}$$

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Case study - only spontaneous phenotype changes

Evolution of $f(t, \mathbf{x}, h)$

$$\partial_t f + \nabla_{(\mathbf{x})} \cdot (f\mathbf{v}) + \partial_h (fw) - \beta \partial^2_{hh} f = Gf \tag{11}$$

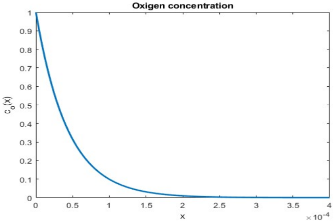
- No motion in physical space: $\mathbf{v} \equiv 0$,
- No induced phenotype changes: $w \equiv 0$.

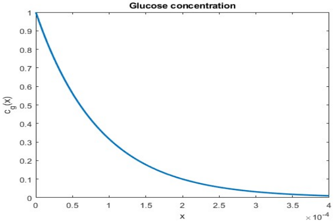
$$\partial_t f - \beta \partial^2_{hh} f = Gf \tag{12}$$

Mono-dimensional case

- $\Omega = [0, L], h \in [0, 1]$;
- fixed oxygen and glucose concentrations (comparison with formal asymptotic analysis results);
- abiotic factors concentrations (with the vessel in $x_v = 0$):

$$\tilde{c}_o = \exp\left(\frac{x}{L}\ln\left(\underline{\tilde{c}}_o\right)\right) \qquad \tilde{c}_g = \exp\left(\frac{x}{L}\ln\left(\underline{\tilde{c}}_g\right)\right)$$

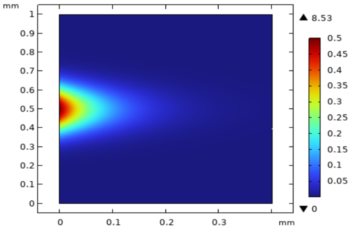


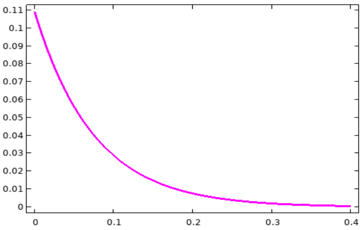


Mono-dimensional case

Initial condition for function f given by

$$f(0,x,h) = f_0(x,h) := 0.5\exp\left(-\frac{x}{\sigma_1} - \frac{(h-0.5)^2}{\sigma_2}\right)$$





Mono-dimensional case - Results

3 Numerical simulations and results

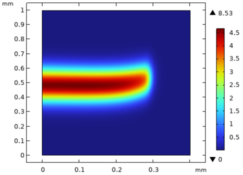


Figure: $f, \; t = 150$

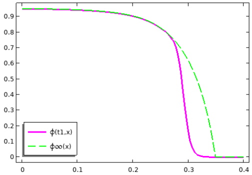


Figure: $\phi, \; t = 150$

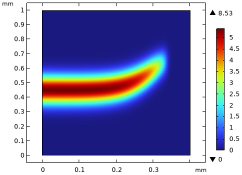


Figure: $f, \; t = 1000$

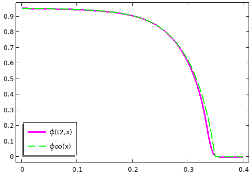


Figure: $\phi, \; t = 1000$

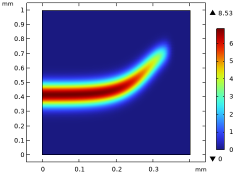


Figure: $f, \; t = 3000$

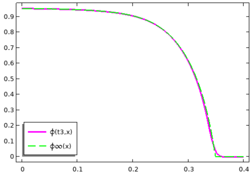


Figure: $\phi, \; t = 3000$

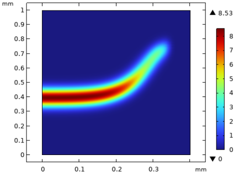


Figure: $f, \; t = 6000$

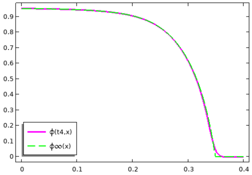
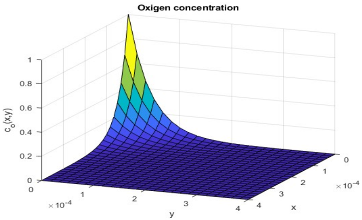


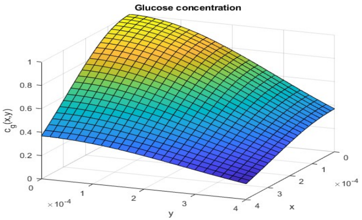
Figure: $\phi, \; t = 6000$

Bi-dimensional case (one vessel)

- **one vessel only**, placed at the origin of the plane $(x_v, y_v) = (0, 0)$
- abiotic factors concentrations:

$$\tilde{c}_o(x,y) = \exp\left(\frac{x+y}{L}\ln\left(\underline{\tilde{c}}_o\right)\right) \qquad \tilde{c}_g(x,y) = \exp\left(\frac{x^2+y^2}{L^2}\ln\left(\underline{\tilde{c}}_g\right)\right)$$



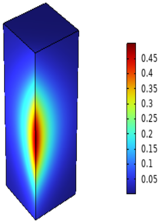


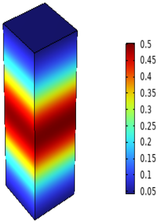
Bi-dimensional case (one vessel)

Two different initial conditions considered:

$$f(0,x,y,h) = f_0(x,y,h) := 0.5 \exp\left(-\frac{x+y}{\sigma_1} - \frac{(h-0.5)^2}{\sigma_2}\right) \tag{13}$$

$$f(0,x,y,h) = f_0(x,y,h) = f_0(h) := 0.5 \exp\left(\frac{(h-0.5)^2}{\sigma_h}\right) \tag{14}$$





Bi-dimensional case (one vessel) - Results

Gaussian initial distribution

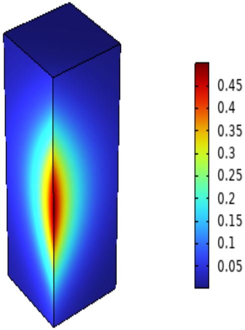


Figure: $f(t, x, y, h),\ t = 0$

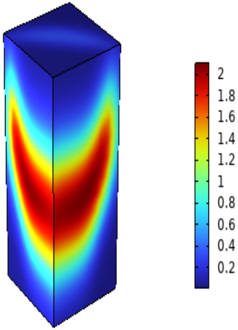


Figure: $f(t, x, y, h),\ t = 50$

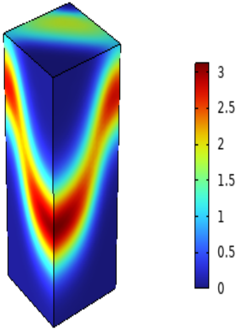


Figure: $f(t, x, y, h),\ t = 700$

Bi-dimensional case (one vessel) - Results

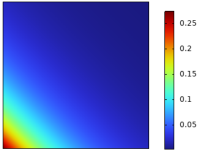


Figure: $\phi, \ t = 0$

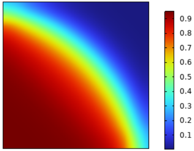


Figure: $\phi, \ t = 50$

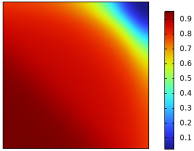


Figure: $\phi, \ t = 700$

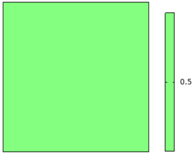


Figure: $H, \ t = 0$

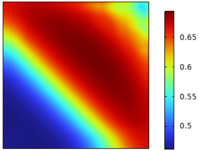


Figure: $H, \ t = 50$

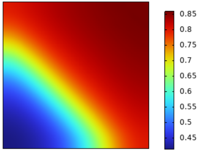


Figure: $H, \ t = 700$

Bi-dimensional case (one vessel) - Results

Uniform initial distribution

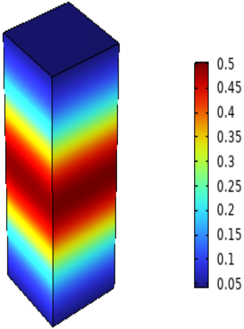


Figure: $f(t, x, y, h),\ t = 0$

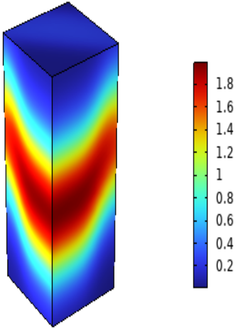


Figure: $f(t, x, y, h),\ t = 50$

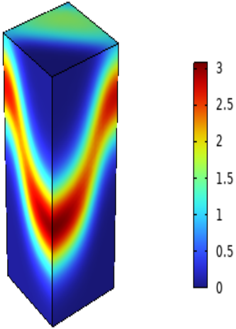


Figure: $f(t, x, y, h),\ t = 700$

Bi-dimensional case (one vessel) - Results

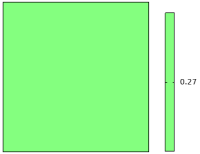


Figure: $\phi, \ t = 0$

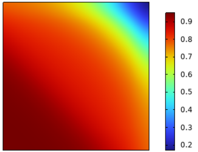


Figure: $\phi, \ t = 50$

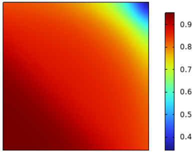


Figure: $\phi, \ t = 700$

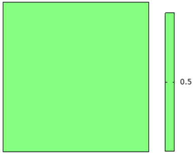


Figure: $H, \ t = 0$

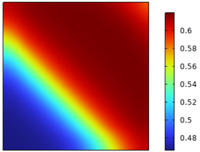


Figure: $H, \ t = 50$

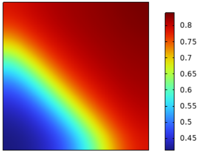


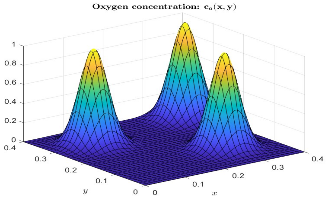
Figure: $H, \ t = 700$

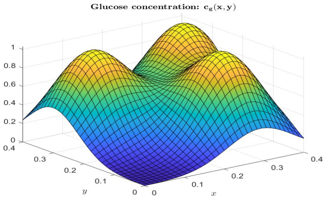
Bi-dimensional case (three vessels)

- **multiple vessels**, placed inside the domain Ω
- abiotic factors concentrations:

$$\tilde{c}_o(x,y) = \sum_{n=0}^{m} \exp\left(\frac{(x-x_n)^2 + (y-y_n)^2}{L^2 \sigma_{c_o}} \ln\left(\underline{\tilde{c}}_o\right) \right)$$

$$\tilde{c}_g(x,y) = \sum_{n=0}^{m} \exp\left(\frac{(x-x_n)^2 + (y-y_n)^2}{L^2 \sigma_{c_g}} \ln\left(\underline{\tilde{c}}_g\right) \right)$$





Bi-dimensional case (three vessels)

Initial conditions considered:

$$f_0(x,y,h) = f_0(h) := 0.5\exp\left(\frac{(h-0.5)^2}{\sigma_h}\right)$$

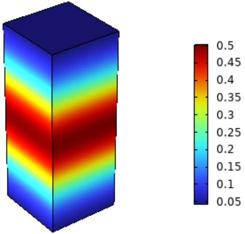


Figure: $f(t,x,y,h)$, $t=0$

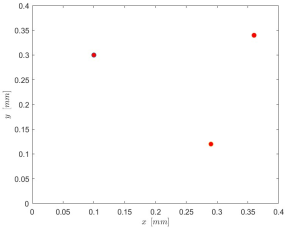


Figure: Blood vessels setting

Bi-dimensional case (three vessels) - Results

Uniform initial distribution

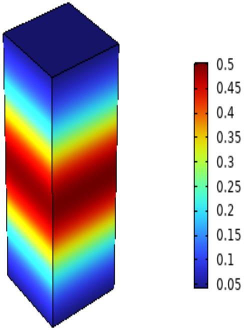


Figure: $f(t,x,y,h),\ t=0$

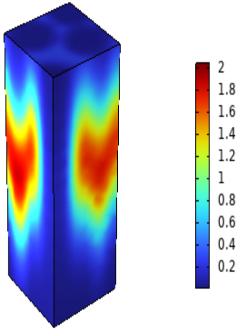


Figure: $f(t,x,y,h),\ t=50$

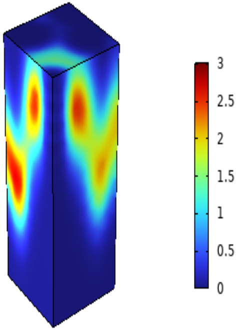


Figure: $f(t,x,y,h),\ t=700$

Bi-dimensional case (three vessels) - Results

3 Numerical simulations and results

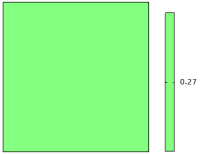


Figure: $\phi, \ t = 0$

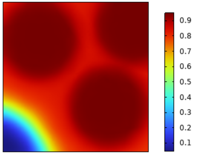


Figure: $\phi, \ t = 50$

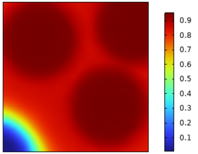


Figure: $\phi, \ t = 700$

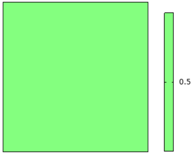


Figure: $H, \ t = 0$

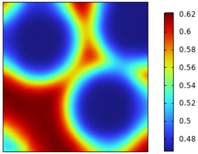


Figure: $H, \ t = 50$

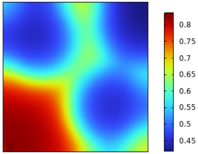


Figure: $H, \ t = 700$

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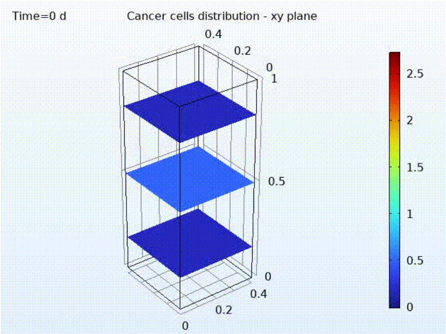
Conclusions

4 Conclusions

- Importance of intra-tumoral heterogeneity;
- Significant difference on the role of abiotic factors;
- Evident metabolic switch, further from the vessel.



Cancer cells phenotype evolution in hypoxic conditions.

Thank you for listening!

Any questions?

- Appendix

- $\Omega = [0, L] \times [0, L]$

Hypothesis

Oxygen and glucose concentrations are at equilibrium

$$c_g(t, \mathbf{x}) = c_g^{\infty}(\mathbf{x}) \qquad\qquad c_o(t, \mathbf{x}) = c_o^{\infty}(\mathbf{x})$$

- Dynamic of $f = f(t, \mathbf{x}, h)$:

$$\begin{cases} \partial_t f - \gamma\hat{\mu}(h)\nabla_{\mathbf{x}}[f\nabla_{\mathbf{x}}(\phi)] + \alpha\partial_h(f\hat{w}) = Gf + \beta\partial^2_{hh}f & \mathbf{x} \in \Omega,\ h \in (0,1), \\ \phi = \int_0^1 f(t, \mathbf{x}, h)dh \end{cases} \tag{15}$$

- $G = G(\mathbf{x}, h, \phi) = \eta(\bar{\phi} - \phi)_+(\tilde{q}(\mathbf{x}, h) - 1)_+ - \xi - \xi_q(1 - \tilde{q}(\mathbf{x}, h))_+$

Rescaled problem

Hypothesis

- Cells motions and induced phenotype variation are slower than cell proliferation and death;
- Spontaneous epimutations are slower than induced ones

$\alpha := \varepsilon \qquad \gamma := \varepsilon \qquad \beta := \varepsilon^2$ where $0 < \varepsilon << 1$

- The problem has been rescaled using the time scaling $t \to \frac{t}{\varepsilon}$.
- $f_\varepsilon(t, \mathbf{x}, h) = f(\frac{t}{\varepsilon}, \mathbf{x}, h)$:

$$\begin{cases} \varepsilon\partial_t f_\varepsilon - \varepsilon\mu(h)\nabla_{\mathbf{x}} f_\varepsilon \left[\nabla_{\mathbf{x}}(\phi_\varepsilon)\right] - \varepsilon\mu(h) f_\varepsilon \nabla^2_{\mathbf{x}}(\phi_\varepsilon) + \varepsilon\partial_h(w f_\varepsilon) = G f_\varepsilon + \varepsilon^2 \partial^2_{hh} f_\varepsilon \\ \phi_\varepsilon = \int_0^1 f_\varepsilon(t, \mathbf{x}, h)dh \end{cases} \tag{16}$$

Asymptotic analysis for $\varepsilon \to 0$

Hypothesis

$f_\varepsilon(0, \mathbf{x}, h)$ is a sufficiently regular function that for any fixed value of $\mathbf{x}$ is a Gaussian in h with little variance

$$f_\varepsilon(0, \mathbf{x}, h) = \exp\left[\frac{u_\varepsilon^0(\mathbf{x}, h)}{\varepsilon}\right] \tag{17}$$

- $u_\varepsilon^0(\mathbf{x}, h)$ is a regular function, strictly concave in h and such that:

$$\exp\left[\frac{u_\varepsilon^0(\mathbf{x}, h)}{\varepsilon}\right] \xrightarrow[\varepsilon\to 0]{*} \phi(0, \mathbf{x})\delta(h - \bar{h}^0(\mathbf{x})) \quad \forall \mathbf{x} \in \Omega \tag{18}$$

- $f(t, \mathbf{x}, h) \approx \phi(t, \mathbf{x})\delta(h - \bar{h}(\mathbf{x}))\ \varepsilon \to 0$
  $\bar{h} : \Omega \to [0, 1]$: phenotype in which the majority of the cancer cell population is found to be at.

Qualitative analysis

WKB ansatz

$$f_\varepsilon(t,\mathbf{x},h) = \exp\left[\frac{u_\varepsilon(t,\mathbf{x},h)}{\varepsilon}\right] \tag{19}$$

Computing:

$$\partial_t f_\varepsilon = \frac{f_\varepsilon}{\varepsilon}\partial_t u_\varepsilon, \quad \nabla_{\mathbf{x}} f_\varepsilon = \frac{f_\varepsilon}{\varepsilon}\nabla_{\mathbf{x}} u_\varepsilon, \quad \partial_h f_\varepsilon = \frac{f_\varepsilon}{\varepsilon}\partial_h u_\varepsilon, \quad \partial^2_{hh} f_\varepsilon = f_\varepsilon\left(\frac{\partial_h u_\varepsilon}{\varepsilon}\right)^2 + \frac{f_\varepsilon}{\varepsilon}\partial^2_{hh} u_\varepsilon$$

substituting (19) in (16) we get:

$$\varepsilon\frac{f_\varepsilon}{\varepsilon}\partial_t u_\varepsilon - \varepsilon\mu(h)\frac{f_\varepsilon}{\varepsilon}\nabla_{\mathbf{x}} u_\varepsilon \nabla_{\mathbf{x}}(\phi_\varepsilon\Sigma(\phi_\varepsilon)) - \varepsilon\mu(h) f_\varepsilon \nabla^2_{\mathbf{x}}(\phi_\varepsilon\Sigma(\phi_\varepsilon)) + \varepsilon w\frac{f_\varepsilon}{\varepsilon}\partial_h u_\varepsilon + \varepsilon f_\varepsilon \partial_h w =$$

$$G f_\varepsilon + \varepsilon^2\left(\frac{\partial_h u_\varepsilon}{\varepsilon}\right)^2 f_\varepsilon + \varepsilon^2\frac{f_\varepsilon}{\varepsilon}\partial^2_{hh} u_\varepsilon \tag{20}$$

- For u_ε the equation becomes

$$\partial_t u_\varepsilon - \mu(h)(\nabla_{\mathbf{x}} u_\varepsilon)(\nabla_{\mathbf{x}}(\phi_\varepsilon)) - \varepsilon\mu(h)\nabla^2_{\mathbf{x}}(\phi_\varepsilon) + w\partial_h u_\varepsilon + \varepsilon\partial_h w = G + (\partial_h u_\varepsilon)^2 + \varepsilon\partial^2_{hh} u_\varepsilon \tag{21}$$

- Taking $\varepsilon \to 0$ equation for f becomes:

$$\partial_t u - \mu(h)(\nabla_{\mathbf{x}} u)(\nabla_{\mathbf{x}}(\phi)) + w\partial_h u = G + (\partial_h u)^2 \quad , \quad (\mathbf{x}, h) \in \Omega \times (0, 1) \tag{22}$$

in which u and ϕ are the zero-order terms of the u_ε and ϕ_ε expansions, respectively.

Qualitative analysis

- $u_\varepsilon^0(\mathbf{x},h) = u_\varepsilon(0,\mathbf{x},h)$ uniformly strictly concave function in h.
  If G is also concave, *then* $u(t,\mathbf{x},h)$ is also uniformly strictly concave in h;
- $\forall \mathbf{x} \in \Omega$ there exist a *unique* phenotype, $(\bar{h}(\mathbf{x},t))$, such that:

$$u(t,\mathbf{x},\bar{h}(\mathbf{x})) =: \max_{h\in[0,1]} u(t,\mathbf{x},h) \qquad \forall \mathbf{x} \in \Omega$$

  and

$$\partial_h u(t,\mathbf{x},\bar{h}(\mathbf{x})) = 0 \qquad \forall \mathbf{x} \in \Omega$$

- Constraints to be satisfied:

$$\max_{h\in[0,1]} u(t,\mathbf{x},\bar{h}) = u(t,\mathbf{x},\bar{h}) = 0, \ \forall \mathbf{x} \in \text{supp}(\phi) \tag{23}$$

- Therefore:

$$\partial_h u(t, \mathbf{x}, \bar{h}(\mathbf{x})) = 0 \qquad \nabla_{\mathbf{x}} u(t, \mathbf{x}, \bar{h}) = 0 \quad , \quad \forall \mathbf{x} \in \mathrm{supp}(\phi) \tag{24}$$

- Computing equation (22) in $\bar{h}(t, \mathbf{x})$ it can be found that:

$$G(\mathbf{x}, \bar{h}(t, \mathbf{x}), \phi) = 0 \quad , \quad \forall \mathbf{x} \in \mathrm{supp}(\phi(t, \cdot)) \tag{25}$$

Transport equation for $\bar{h}(t, \mathbf{x})$

- $\mathbf{x} \in \text{supp}(\phi(t, \cdot))$. Differentiating in h equation (22) and evaluating it in $\bar{h}$, an equation for $\bar{h}$ can be found:

$$\partial^2_{ht} u(t, \mathbf{x}, \bar{h}) - \mu(\bar{h})(\nabla_{\mathbf{x}}(\phi))\partial_h \left[\nabla_{\mathbf{x}} u(t, \mathbf{x}, \bar{h})\right] + \partial_h(w\partial_h u)(t, \mathbf{x}, \bar{h}) = \partial_h G \qquad (26)$$

- Differentiating equations found in (24) with respect to t and h respectively, substituting them in (26) and recalling that u is strictly concave in h ($\partial^2_{hh} u < 0$), a transport equation for $\bar{h}(t, \mathbf{x})$ can be found:

$$\partial_t \bar{h} - \mu(\bar{h})(\nabla_{\mathbf{x}} \phi)(\nabla_{\mathbf{x}} \bar{h}) = (-\partial^2_{hh} u(t, \mathbf{x}, \bar{h}))^{-1}(\partial_h G(\mathbf{x}, \bar{h}, \phi) - \partial_h(w\partial_h u)(t, \mathbf{x}, \bar{h})) \quad (27)$$

with $\mathbf{x} \in \text{supp}(\phi)$

Limits of $\phi(t,\mathbf{x})$ and $\bar{h}(t,\mathbf{x})$ for $t \to \infty$

- $\phi^\infty(\mathbf{x})$ and $h^\infty(\mathbf{x})$: asymptotic values to which $\phi(t,\mathbf{x})$ and $\bar{h}(t,\mathbf{x})$ converge for $t \to \infty$
- $\phi^\infty(\mathbf{x})$ and $\bar{h}^\infty(\mathbf{x})$ need to satisfy:

$$\begin{cases} G(\mathbf{x},\bar{h}^\infty,\phi^\infty) = 0 \quad (\textit{defines} \quad \phi^\infty) \\ [-\mu(h)(\nabla_{\mathbf{x}}\phi^\infty)\nabla_{\mathbf{x}}h]_{h=\bar{h}^\infty} = \mathcal{F}(\mathbf{x},\bar{h}^\infty,u^\infty,\phi^\infty) \quad (\textit{defines} \quad \bar{h}^\infty) \end{cases}, \quad \mathbf{x} \in \mathrm{supp}(\phi^\infty) \tag{28}$$

in which

$$\mathcal{F}(\mathbf{x},h^\infty,u^\infty,\phi^\infty) := -(\partial^2_{hh}u(\mathbf{x},h))^{-1}(\partial_h G(\mathbf{x},h,\phi^\infty) - \partial_h(w\partial_h u^\infty)(\mathbf{x},h))$$

- u^∞ satisfies the steady state transport equation (22) subject to (23) which is

$$\begin{cases} G(\mathbf{x}, h, \phi^\infty) + (\partial_h u^\infty(\mathbf{x}, h))^2 - w\partial_h u^\infty(h) = 0 \\ \max_{h\in[0,1]} u^\infty(\mathbf{x}, h) = u^\infty(\mathbf{x}, \bar{h}^\infty(\mathbf{x})) = 0 \end{cases} \quad \mathbf{x} \in \text{supp}(\phi^\infty) \tag{29}$$

- The first equation of system (28) is analyzed after substituting the definition of G:

$$G(\mathbf{x}, \bar{h}^\infty, \phi^\infty) = 0 \implies \eta(\bar{\phi} - \phi^\infty(\mathbf{x}))(\tilde{q}(\mathbf{x}, \bar{h}^\infty(\mathbf{x})) - 1)_+ - \xi - \xi_q(1 - \tilde{q}(\mathbf{x}, \bar{h}^\infty(\mathbf{x})))_+ = 0 \tag{30}$$

for $\mathbf{x} \in \text{supp}(\phi^\infty)$.

- $\tilde{q}(\mathbf{x}, \bar{h}^{\infty}) = 1 \quad \Longrightarrow \quad (1 - \tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})))_{+} = (\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1)_{+} = 0$
- $(\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1)_{+} = 0 \quad \Longrightarrow \quad (1 - \tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})))_{+} > 0$
- $(\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1)_{+} > 0 \quad \Longrightarrow \quad (1 - \tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})))_{+} = 0$

The first and second cases result as absurd statements. The third one, instead, results in an equation for $\phi^{\infty}(\mathbf{x})$

$$\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) > 1 \quad , \quad \mathbf{x} \in \text{supp}(\phi^{\infty}) \tag{31}$$

$$\Downarrow$$

$$0 = \eta(\bar{\phi} - \phi^{\infty}(\mathbf{x}))(\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1)_{+} - \xi \tag{32}$$

Since $\phi^{\infty}(\mathbf{x}) \geq 0 \quad \forall \mathbf{x} \in \Omega$,*if*

$$\bar{\phi} - \frac{\xi}{\eta} \frac{1}{\left(\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1\right)} < 0$$

then (32) does not allow non-negative solutions $\phi^{\infty}(\mathbf{x})$ and consequently $\mathbf{x} \notin \mathrm{supp}(\phi^{\infty})$, that is $\phi^{\infty}(\mathbf{x}) = 0$. *Otherwise*

$$\phi^{\infty}(\mathbf{x}) = \bar{\phi} - \frac{\xi}{\eta} \frac{1}{\left(\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1\right)} \tag{33}$$

Final result

$$\phi^{\infty}(\mathbf{x}) = \max\left\{0, \bar{\phi} - \frac{\xi}{\eta} \frac{1}{\left(\tilde{q}(\mathbf{x}, \bar{h}^{\infty}(\mathbf{x})) - 1\right)}\right\} \tag{34}$$