A mathematical dissection of the adaptation of cancer cell populations to fluctuating oxygen levels

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Mathematical Biology: Modeling, Analysis and Simulation
IMS, National University of Singapore
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Plan of the talk

Statement of the biological problem

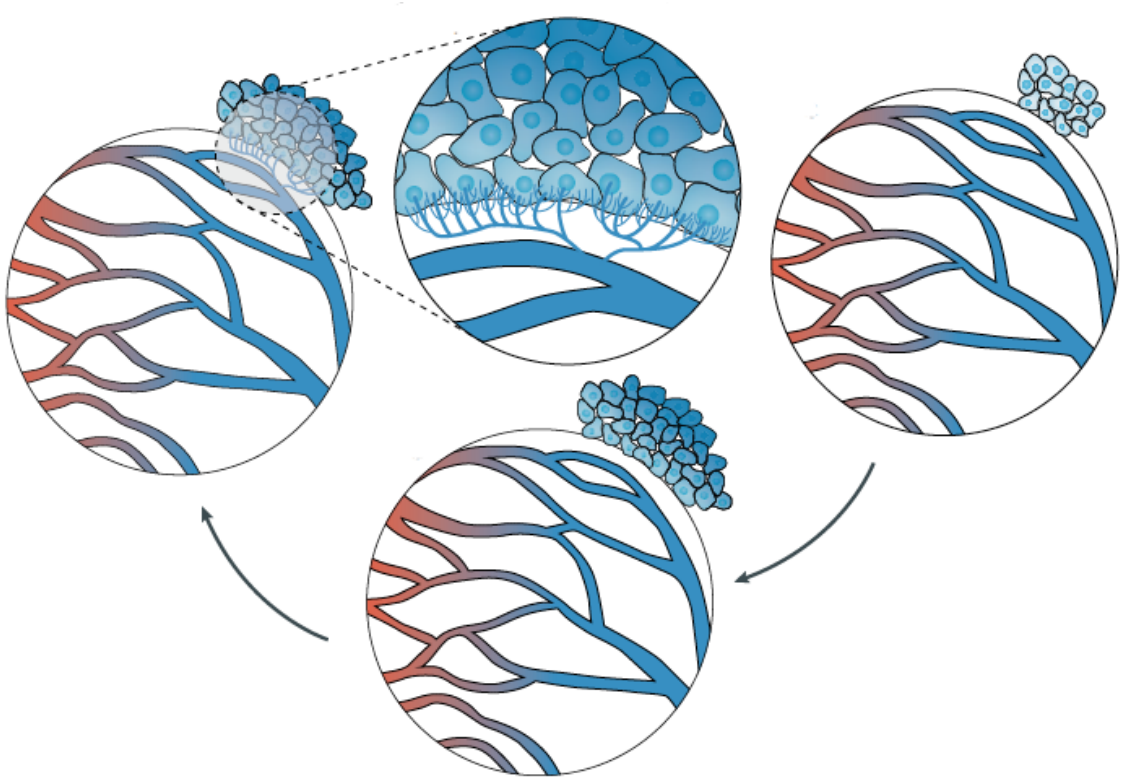
Mathematical model

Main results

Research perspectives

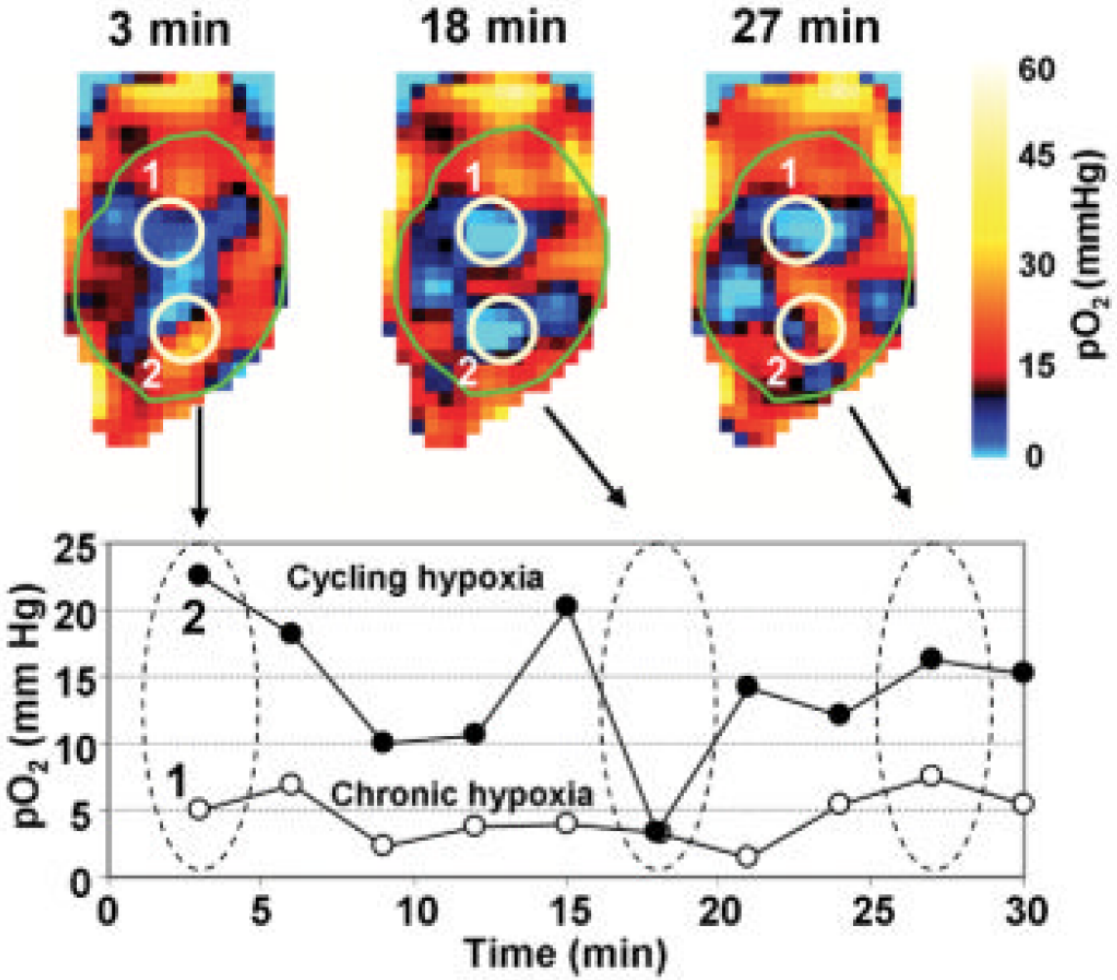
Statement of the biological problem

Tumour angiogenesis and emergence of fluctuating oxygen levels in tumours



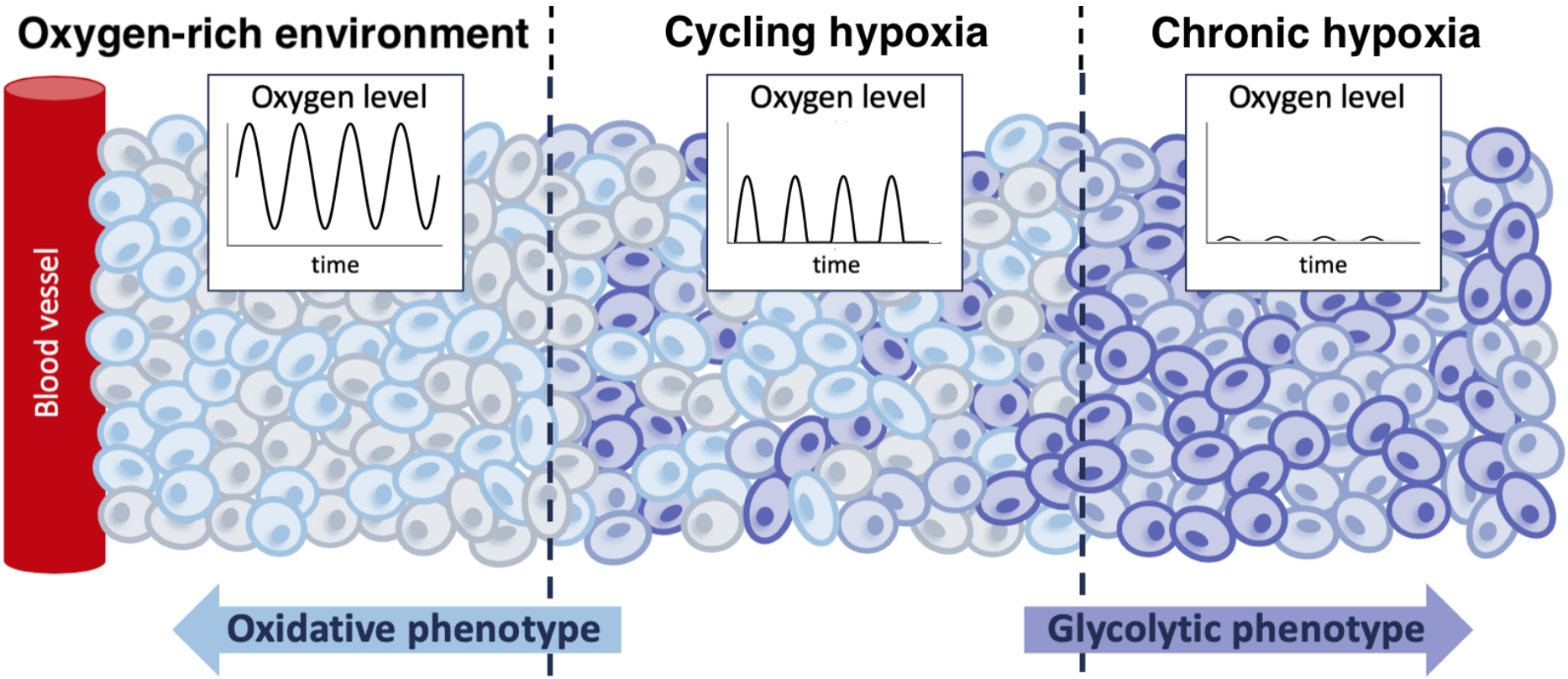
Adapted from Gillies et al., Nature Reviews Cancer, 2018

In vivo experimental results showing the emergence of fluctuating oxygen levels in tumours



Adapted from Matsumoto et al., Cancer Research, 2010

Fluctuations in oxygen levels promote the creation of distinct fluctuating local environments in tumours



Underlying biological questions

How do cancer cells adapt to fluctuating oxygen levels?

What is the role played by phenotypic variations
in the adaption of cancer cells to fluctuating oxygen levels?

Mathematical model

Mathematical representation of the biological system

- Two competing populations of cancer cells in a well-mixed system exposed to given oxygen levels

Mathematical representation of the biological system

- Two competing populations of cancer cells in a well-mixed system exposed to given oxygen levels
- The two populations undergo phenotypic variations at different rates;
  - ▷ population with *higher* rate of phenotypic variations : $i = H$
  - ▷ population with *lower* rate of phenotypic variations : $i = L$

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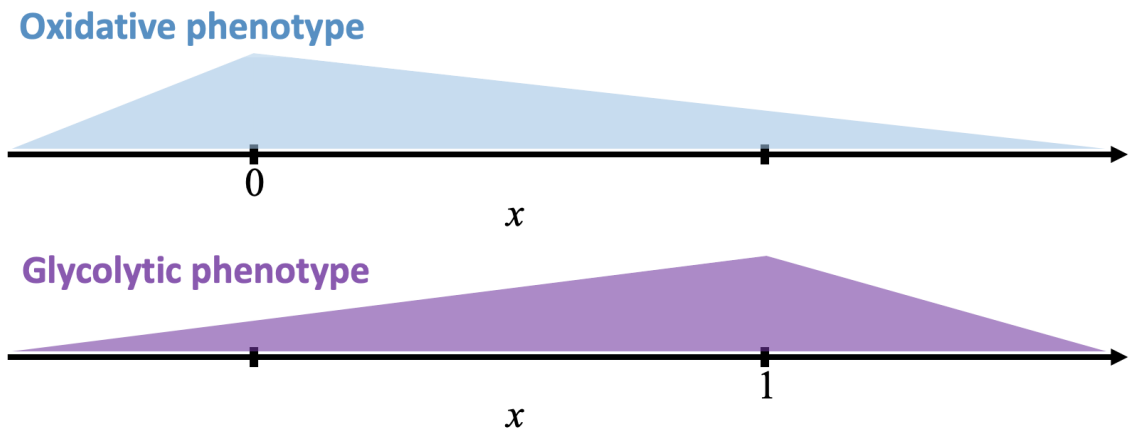
- Phenotypic state : $x \in \mathbb{R}$



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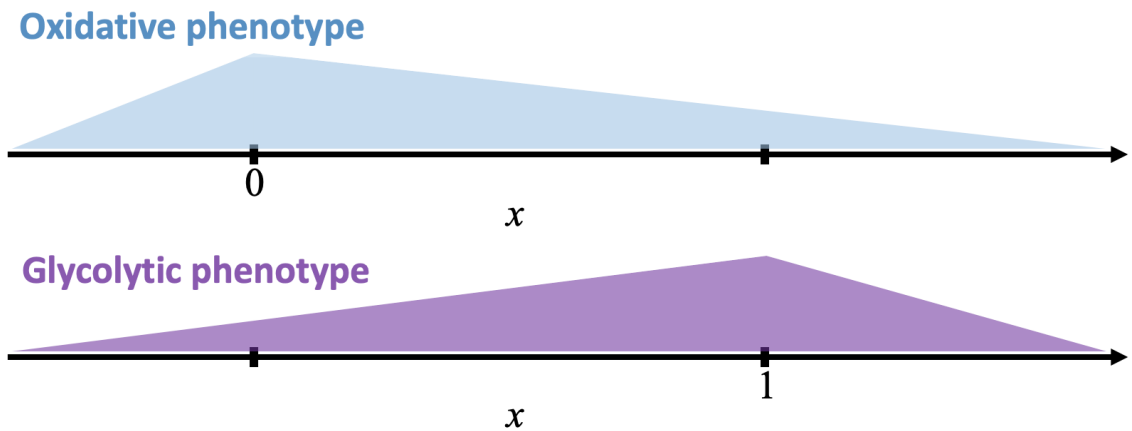

- Phenotype distribution of population i at time $t \geq 0$: $n_i(x,t)$

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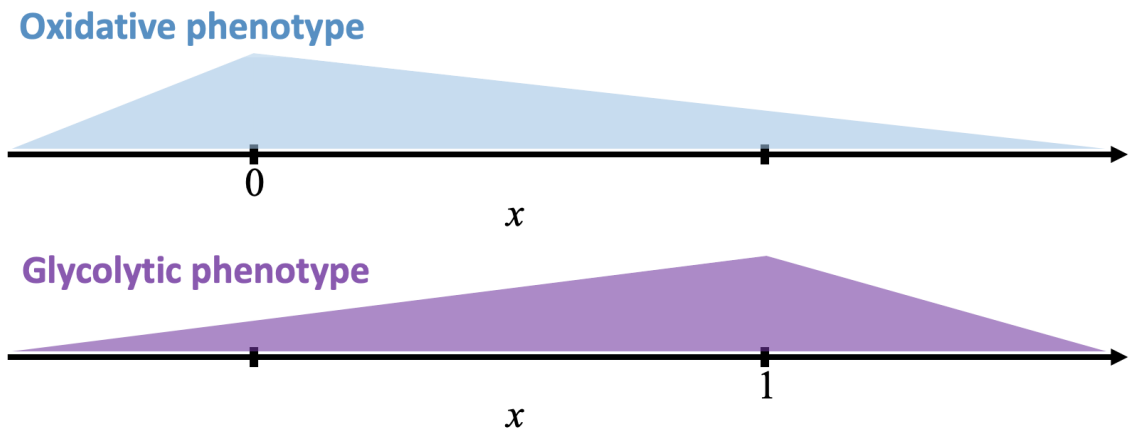

- Phenotype distribution of population i at time $t \geq 0$: $n_i(x,t)$
- Given oxygen level at time t : $S(t)$

Mathematical representation of the biological system

- Size of population i at time t : $\rho_i(t) = \int_{\mathbb{R}} n_i(x,t)\,\mathrm{d}x$
- Total number of cells at time t : $\rho(t) = \rho_H(t) + \rho_L(t)$
- Mean phenotypic state of population i at time t :

$$\mu_i(t) = \frac{1}{\rho_i(t)} \int_{\mathbb{R}} x\, n_i(x,t)\,\mathrm{d}x$$

- Phenotypic variance of population i at time t :

$$\sigma_i^2(t) = \frac{1}{\rho_i(t)} \int_{\mathbb{R}} x^2\, n_i(x,t)\,\mathrm{d}x - \mu_i^2(t)$$

Equations for the phenotype distributions

$$\begin{cases} \dfrac{\partial n_H}{\partial t} = \underbrace{\beta_H \dfrac{\partial^2 n_H}{\partial x^2}}_{\text{phenotypic variations}} + \underbrace{R\big(x, S(t), \rho(t)\big)\, n_H}_{\text{cell division \& death}}, \\ \dfrac{\partial n_L}{\partial t} = \beta_L \dfrac{\partial^2 n_L}{\partial x^2} + R\big(x, S(t), \rho(t)\big)\, n_L, \\ \rho(t) = \rho_H(t) + \rho_L(t), \;\; \rho_i(t) = \displaystyle\int_{\mathbb{R}} n_i(x,t)\,\mathrm{d}x, \;\; i \in \{H, L\}, \end{cases} \qquad (x,t) \in \mathbb{R} \times (0,\infty) \quad (1)$$

$$\beta_i : \text{rate of phenotypic variations,} \qquad (2)$$

$$R\big(x, S, \rho\big) : \text{phenotypic fitness landscape,} \qquad (3)$$

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β_i : rate of phenotypic variations, $\quad \beta_H > \beta_L \qquad (2)$

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β_i : rate of phenotypic variations, $\beta_H > \beta_L$ (2)

$R(x, S, \rho)$: phenotypic fitness landscape, $R(x, S, \rho) = p(x, S) - d\rho$ (3)

$p(x, S)$: net cell-division rate

$d\rho$: rate of death due to intra- and inter-population competition

Phenotypic fitness landscape

- Oxidative phenotypic variants (i.e. $x \to 0$) have a competitive advantage when the oxygen concentration is high (i.e. if $S(t) \to \infty$)
- Glycolytic phenotypic variants (i.e. $x \to 1$) have a competitive advantage when the oxygen concentration is low (i.e. if $S(t) \to 0$)

$$p(x,S) = \gamma \frac{S}{1+S}\left(1-x^2\right) + \zeta\left(1-\frac{S}{1+S}\right)\left[1-(1-x)^2\right] \tag{4}$$

γ : maximum cell-division rate of oxidative phenotypic variants

ζ : maximum cell-division rate of glycolytic phenotypic variants

Phenotypic fitness landscape

- After a little algebra, definition (4) can be rewritten as

$$p(x,S) = \gamma\, g(S) - h(S)\,(x-\varphi(S))^2 \tag{5}$$

with

$$\underbrace{g(S) = \frac{1}{1+S}\left(S + \frac{\zeta}{\gamma}\frac{\zeta}{\zeta+\gamma S}\right)}_{\text{rescaled maximum fitness}}, \qquad \underbrace{\varphi(S) = \frac{\zeta}{\zeta+\gamma S}}_{\text{fittest phenotypic state}} \tag{6}$$

and

$$\underbrace{h(S) = \zeta + (\gamma-\zeta)\frac{S}{1+S}}_{\text{nonlinear selection gradient}} \tag{7}$$

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- Henceforth for simplicity we assume $\zeta = \gamma$, which implies

$$g(S) = \frac{1}{1+S}\left(S + \frac{1}{1+S}\right), \quad \varphi(S) = \frac{1}{1+S}, \quad h(S) \equiv \gamma \tag{8}$$

Main results

Gaussian phenotype distributions

Proposition

If the initial phenotype distribution $n_i(x,0)$ for $i \in \{H,L\}$ is of the Gaussian form

$$n_i(x,0) = \rho_i^0 \sqrt{\frac{v_i^0}{2\pi}} \exp\left[-\frac{v_i^0}{2}(x-\mu_i^0)^2\right] \text{ with } \rho_i^0, v_i^0 \in \mathbb{R}_{>0},\ \mu_i^0 \in \mathbb{R}, \quad (9)$$

then the phenotype distribution $n_i(x,t)$ remains of the Gaussian form

$$n_i(x,t) = \rho_i(t) \sqrt{\frac{v_i(t)}{2\pi}} \exp\left[-\frac{v_i(t)}{2}(x-\mu_i(t))^2\right] \quad \forall\ t > 0. \quad (10)$$

Gaussian phenotype distributions

The population size, ρ_i, the mean phenotypic state, μ_i, and the inverse of the phenotypic variance, $v_i = 1/\sigma_i^2$, satisfy the Cauchy problem

$$\begin{cases} v_i'(t) = 2\Big(\gamma - \beta_i v_i^2(t)\Big), \\ \mu_i'(t) = \dfrac{2\gamma}{v_i(t)}\,(\varphi(t) - \mu_i(t)), \\ \rho_i'(t) = (F_i(t) - d\rho(t))\,\rho_i(t), \\ v_i(0) = v_i^0, \quad \mu_i(0) = \mu_i^0, \quad \rho_i(0) = \rho_i^0, \\ \rho(t) = \rho_H(t) + \rho_L(t), \end{cases} \qquad t \in (0,\infty), \quad i \in \{H, L\}, \quad (11)$$

$$F_i(t) \equiv F_i(t, v_i(t), \mu_i(t)) = \gamma\, g(t) - \frac{\gamma}{v_i(t)} - \gamma\,(\mu_i(t) - \varphi(t))^2, \qquad (12)$$

with $g(t) \equiv g(S(t))$ and $\varphi(t) \equiv \varphi(S(t))$.

Evolutionary dynamics under constant oxygen levels

Theorem

Under assumptions (2)-(4), (8) and the additional assumption

$$S(t) \equiv \overline{S} \geq 0, \tag{13}$$

the solution of the system of PDEs (1) subject to the initial condition (9) is of the Gaussian form (10) and satisfies the following:

(i) if $\sqrt{\beta_L} \geq \sqrt{\gamma}\, g(\overline{S})$ then

$$\rho_H(t) \to 0 \quad \text{and} \quad \rho_L(t) \to 0 \quad \text{as } t \to \infty; \tag{14}$$

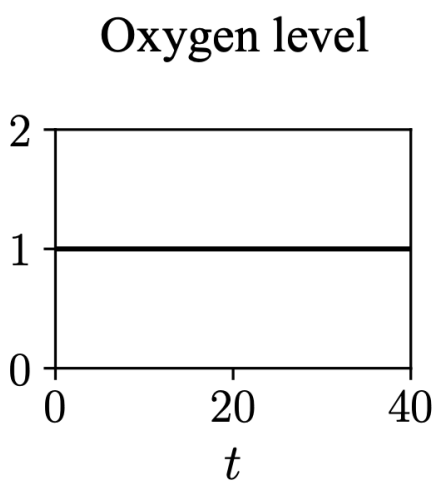
Evolutionary dynamics under constant oxygen levels

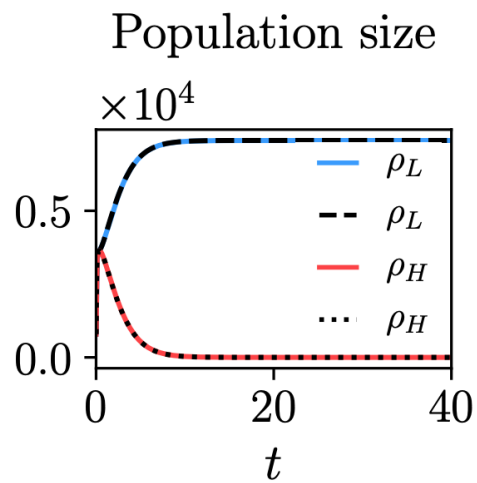
(ii) if $\sqrt{\beta_L} < \sqrt{\gamma}\, g(\overline{S})$ then

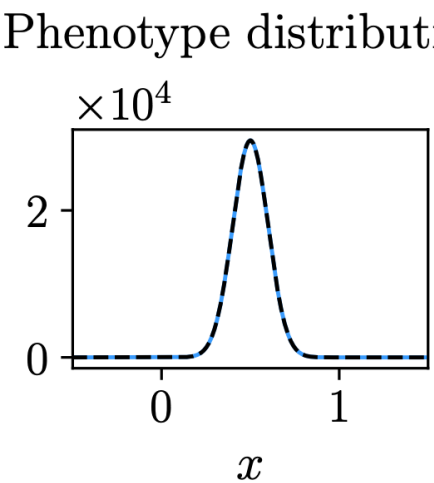
$$\rho_H(t) \to 0, \quad \rho_L(t) \to \frac{\sqrt{\gamma}}{d}\left(\sqrt{\gamma}\, g(\overline{S}) - \sqrt{\beta_L}\right) \quad \text{as } t \to \infty \tag{15}$$

and

$$\mu_L(t) \to \varphi(\overline{S}) = \frac{1}{1+\overline{S}}, \quad \sigma_L^2(t) \to \sqrt{\frac{\beta_L}{\gamma}} \quad \text{as } t \to \infty. \tag{16}$$







Evolutionary dynamics under periodically fluctuating oxygen levels

Theorem

Assume (2)-(4), (8) and

$$S \in \mathrm{Lip}([0,\infty)), \quad S(t+T) = S(t) \quad \forall\, t \geq 0, \quad \text{for some } T > 0. \tag{17}$$

Define

$$\Lambda_i = \sqrt{\beta_i} + \frac{\sqrt{\gamma}}{T} \int_0^T \left(u_i(z) - \varphi(S(z))\right)^2 \mathrm{d}z \quad \text{for} \quad i \in \{H, L\}, \tag{18}$$

where $u_i(t)$ is the unique real T-periodic solution of the problem

$$\begin{cases} u_i'(t) = 2\sqrt{\gamma\beta_i}\,(\varphi(S(t)) - u_i(t)), & \text{for } t \in (0,T), \\ u_i(0) = u_i(T), \end{cases} \tag{19}$$

that is,

$$\begin{aligned} u_i(t) = {} & \frac{2\sqrt{\gamma\beta_i}\exp\left(-2\sqrt{\gamma\beta_i}\,t\right)}{\exp\left(2\sqrt{\gamma\beta_i}\,T\right) - 1} \int_0^T \exp\left(2\sqrt{\gamma\beta_i}\,z\right)\varphi(S(z))\,\mathrm{d}z \\ & + 2\sqrt{\gamma\beta_i}\exp\left(-2\sqrt{\gamma\beta_i}\,t\right)\int_0^t \exp\left(2\sqrt{\gamma\beta_i}\,z\right)\varphi(S(z))\,\mathrm{d}z. \end{aligned} \tag{20}$$

Evolutionary dynamics under periodically fluctuating oxygen levels

The solution of the system of PDEs (1) subject to the initial condition (9) is of the Gaussian form (10) and satisfies the following:

(i) if $\min\{\Lambda_H, \Lambda_L\} \geq \dfrac{\sqrt{\gamma}}{T}\displaystyle\int_0^T g(S(t))\,\mathrm{d}t$ then

$$\rho_H(t) \to 0 \quad \text{and} \quad \rho_L(t) \to 0 \quad \text{as } t \to \infty; \tag{21}$$

Evolutionary dynamics under periodically fluctuating oxygen levels

(ii) if $\min\{\Lambda_H, \Lambda_L\} < \dfrac{\sqrt{\gamma}}{T}\displaystyle\int_0^T g(S(t))\,\mathrm{d}t$ and

$$i = \arg\min_{k\in\{H,L\}} \Lambda_k, \quad j = \arg\max_{k\in\{H,L\}} \Lambda_k,$$

then

$$\rho_i(t) \to w_i(t), \quad \rho_j(t) \to 0 \quad \text{as } t \to \infty, \tag{22}$$

and

$$\mu_i(t) \to u_i(t), \quad \sigma_i^2(t) \to \sqrt{\frac{\beta_i}{\gamma}} \quad \text{as } t \to \infty, \tag{23}$$

Evolutionary dynamics under periodically fluctuating oxygen levels

where $w_i(t)$ is the unique real non-negative T-periodic solution of the problem

$$\begin{cases} w_i'(t) = (Q_i(t) - d w_i(t))\, w_i(t), & \text{for } t \in (0, T), \\ w_i(0) = w_i(T) \end{cases} \tag{24}$$

with

$$Q_i(t) = \gamma\, g(S(t)) - \sqrt{\gamma \beta_i} - \gamma\, (u_i(t) - \varphi(S(t)))^2,$$

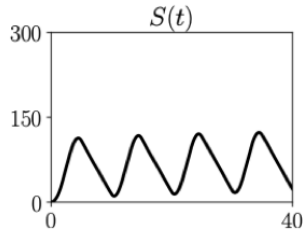
Evolutionary dynamics under periodically fluctuating oxygen levels

that is,

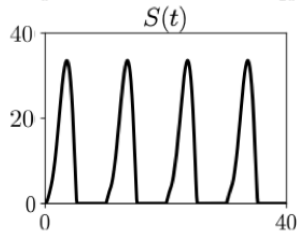
$$w_i(t) = \frac{d^{-1}\exp\left(\int_0^t Q_i(s)\,\mathrm{d}s\right)}{\dfrac{\int_0^T \exp\left(\int_0^s Q_i(z)\,\mathrm{d}z\right)\mathrm{d}s}{\exp\left(\int_0^T Q_i(s)\,\mathrm{d}s\right)-1} + \int_0^t \exp\left(\int_0^s Q_i(z)\,\mathrm{d}z\right)\mathrm{d}s}. \quad (25)$$

Evolutionary dynamics under periodically fluctuating oxygen levels

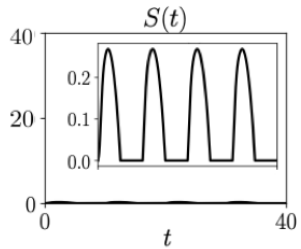
Oxygen-rich environment



Cycling hypoxia

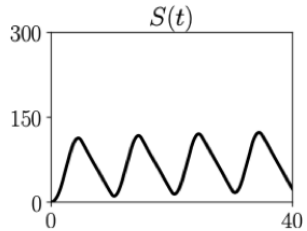


Chronic hypoxia



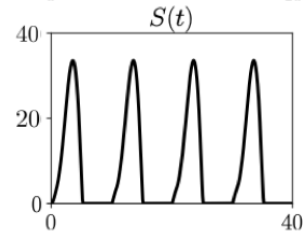
Evolutionary dynamics under periodically fluctuating oxygen levels

Oxygen-rich environment



$$\Lambda_L < \Lambda_H < \frac{\sqrt{\gamma}}{T} \int_0^T g(t)\,\mathrm{d}t$$

Cycling hypoxia



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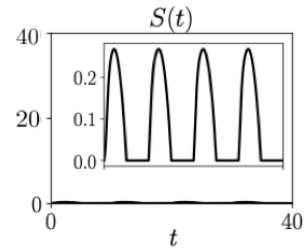

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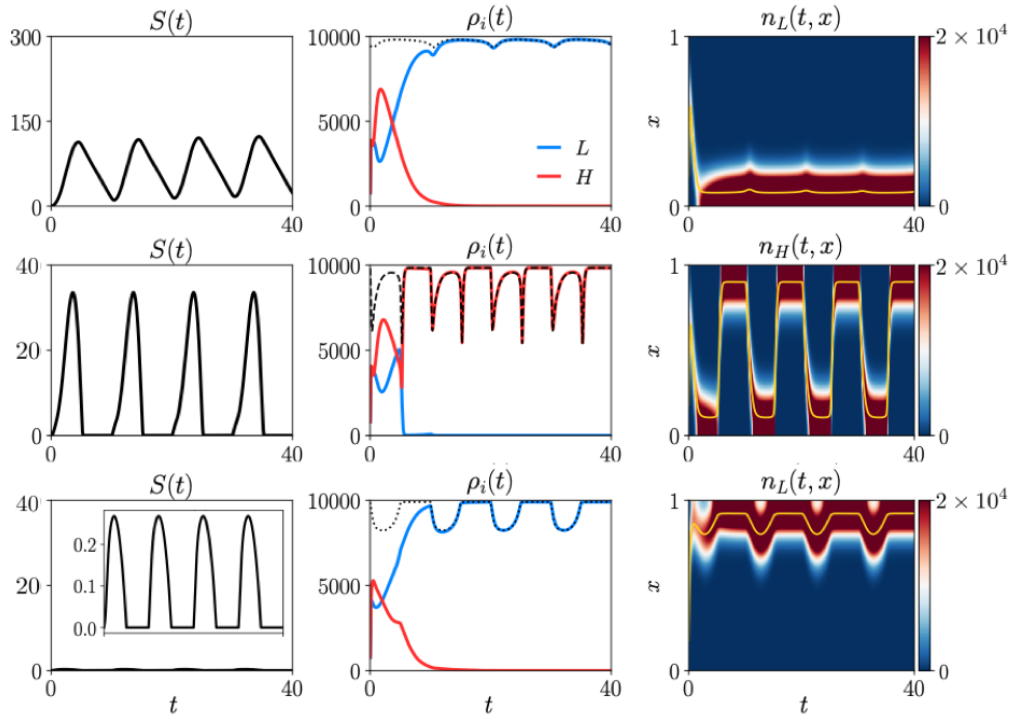

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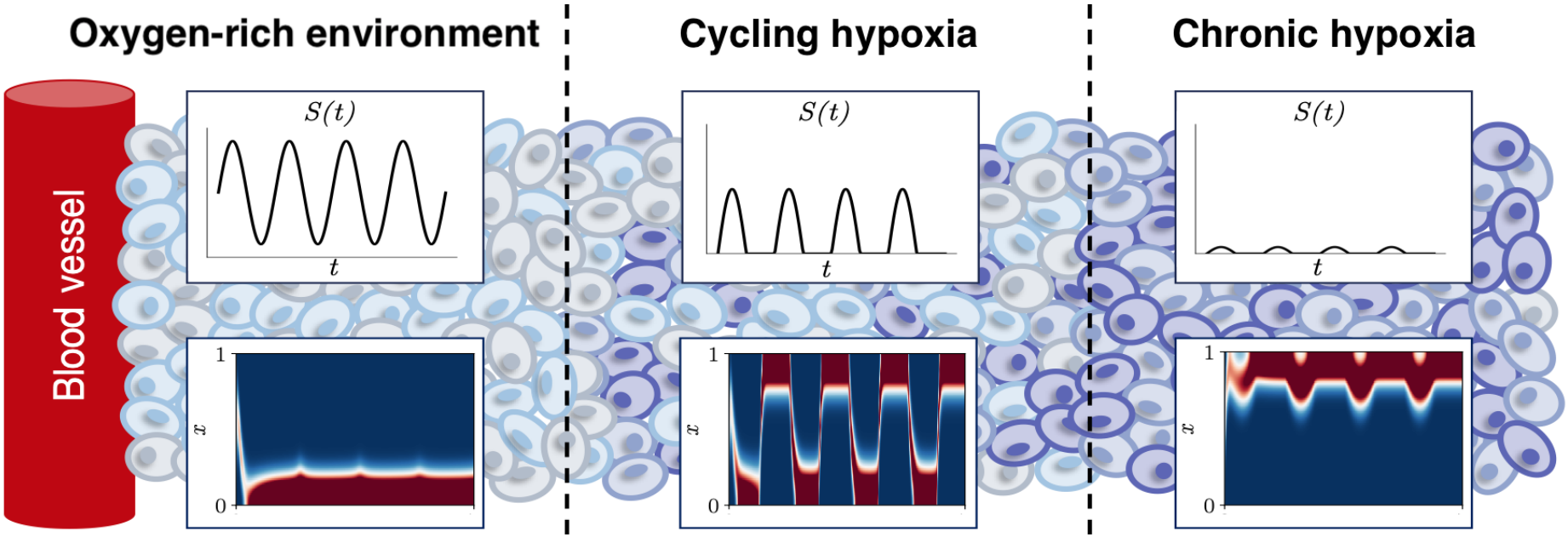
Adaptation of cancer cell populations to fluctuating oxygen levels



- 'Stable' oxidative phenotype
- Lower phenotypic heterogeneity

- 'Switching' between oxidative and glycolytic phenotype (bet-hedging)
- Higher phenotypic heterogeneity

- 'Stable' glycolytic phenotype
- Lower phenotypic heterogeneity

Oxidative phenotype ← → **Glycolytic phenotype**

Research perspectives

- Develop a corresponding stochastic individual-based model → explore stochastic effects that are relevant in the regime of low cell numbers.

- Model oxygen dynamics explicitly → study the impact of oxygen consumption on the evolutionary dynamics of cells.

- Include spatial structure → obtain a more detailed representation of the underlying biological problem.

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