

1. Extension of Equations (1)-(4) to include oxidative phosphorylation of glucose

Our system of equations is as follows:

$$C_t = \overbrace{\frac{\Delta_C}{r^2} [r^2 C_r]_r}^{\text{diffusion}} + \overbrace{\rho C \left(1 - \frac{C}{C_*}\right)}^{\text{logistic growth}} - \overbrace{\delta (\psi_G + \psi_A + \psi_N) C}^{\text{loss by glucose deprivation, acidosis, or severe anoxia}} \quad (1)$$

$$G_t = \overbrace{\frac{\Delta_G}{r^2} [r^2 G_r]_r}^{\text{diffusion}} - \overbrace{\kappa_G \frac{G}{G + \eta_G} \psi_L C}^{\text{consumption of glucose by glycolysis}} - \overbrace{\kappa_O \frac{\alpha_G G}{\alpha_G G + \alpha_L L + \eta_O} \psi_O C}^{\text{consumption of glucose by OXPHOS}} \quad (2)$$

$$L_t = \overbrace{\frac{\Delta_L}{r^2} [r^2 L_r]_r}^{\text{diffusion}} + \overbrace{2\kappa_G \frac{G}{G + \eta_G} \psi_L C}^{\text{production of lactate by glycolysis}} - \overbrace{\kappa_L \frac{\alpha_L L}{\alpha_G G + \alpha_L L + \eta_L} \psi_O C}^{\text{consumption of lactate by OXPHOS}} \quad (3)$$

$$O_t = \overbrace{\frac{\Delta_O}{r^2} [r^2 O_r]_r}^{\text{diffusion}} - \overbrace{6\kappa_O \frac{\alpha_G G}{\alpha_G G + \alpha_L L + \eta_O} \psi_O C}^{\text{consumption of oxygen by OXPHOS of glucose}} - \overbrace{3\kappa_L \frac{\alpha_L L}{\alpha_G G + \alpha_L L + \eta_L} \psi_O C}^{\text{consumption of oxygen by OXPHOS of lactate}} \quad (4)$$

with the subscript t denoting differentiation with respect to time and r differentiation with respect to radial distance from the tumour core. All parameters are the same as in the main text, except that here we have the additional parameters κ_O and η_O , which represent the maximum rate and half-saturation point, respectively, of OXPHOS of glucose. We also have a new switch function ψ_L ; this captures sensitivity of glycolysis to the concentration of tissue lactate, such that glycolysis becomes suppressed if tissue lactate becomes too high:

$$\psi_L = \begin{cases} 1 & \text{if } L < \sigma_L, \\ 0 & \text{otherwise,} \end{cases} \quad (5)$$

where σ_L is the concentration of lactate above which the cells switch to OXPHOS. Furthermore, the parameters α_G and α_L now represent a sub-cellular (rather than governed by surface membrane protein expression) preference for processing glucose vs. lactate through the mitochondria. As the metabolite concentrations G , L , and O are all in mM, the above equations preserve the stoichiometry of glycolysis and oxidative phosphorylation.

In keeping with the main text, we make the slight simplification of scaling the tumour cell density by the tissue carrying capacity, such that $\tilde{C} = C/C_*$. Further letting $a = \alpha_L/\alpha_G$, $n_G = \eta_G/\alpha_G$, $n_L = \eta_L/\alpha_L$,

$k_G = \kappa_G C_*$, and $k_L = \kappa_L C_*$, and dropping the tilde for convenience, we have

$$C_t = \overbrace{\frac{\Delta C}{r^2} [r^2 C_r]_r}^{\text{diffusion}} + \overbrace{\rho C (1 - C)}^{\text{logistic growth}} - \overbrace{\delta (\psi_G + \psi_A + \psi_N) C}^{\text{loss by glucose deprivation, acidosis, or severe anoxia}} \quad (6)$$

$$G_t = \overbrace{\frac{\Delta G}{r^2} [r^2 G_r]_r}^{\text{diffusion}} - \overbrace{k_G \frac{G}{G + n_G} \psi_L C}^{\text{consumption of glucose by glycolysis}} - \overbrace{k_O \frac{G}{G + aL + n_O} \psi_O C}^{\text{consumption of glucose by OXPHOS}} \quad (7)$$

$$L_t = \overbrace{\frac{\Delta L}{r^2} [r^2 L_r]_r}^{\text{diffusion}} + \overbrace{2k_G \frac{G}{G + n_G} \psi_L C}^{\text{production of lactate by glycolysis}} - \overbrace{k_L \frac{L}{G/a + L + n_L} \psi_O C}^{\text{consumption of lactate by OXPHOS}} \quad (8)$$

$$O_t = \overbrace{\frac{\Delta O}{r^2} [r^2 O_r]_r}^{\text{diffusion}} - \overbrace{6k_O \frac{G}{G + aL + n_O} \psi_O C}^{\text{consumption of oxygen by OXPHOS of glucose}} - \overbrace{3k_L \frac{L}{G/a + L + n_L} \psi_O C}^{\text{consumption of oxygen by OXPHOS of lactate}} \quad (9)$$

As in the main text, these equations are subject to spatially uniform initial conditions such that C is at half-carrying capacity and the metabolite concentrations $G, L, O(t = 0, r)$ are equal to their values in the vessels, denoted $G_v, L_v,$ and O_v . The boundary conditions are zero-flux in the tumour core (at $r = 0$), and metabolites are permitted to exchange with the capillary shell as follows (for a generic metabolite, M):

$$M_r|_{r=R} = J_M (M_v - M), \quad (10)$$

where J_M is the coefficient of exchange for metabolite M and M_v its concentration in the vessels. For glucose, lactate, and oxygen, the exchange coefficients are $J_G, J_L,$ and J_O , respectively.

We can define symbiosis by first letting

$$\phi_o = k_O \frac{G}{G + aL + n_O} \psi_O C, \quad (11)$$

$$\phi_l = k_L \frac{L}{G/a + L + n_L} \psi_O C, \quad (12)$$

$$\phi_g = k_G \frac{G}{G + n_G} \psi_L C, \quad (13)$$

such that $\phi_o, \phi_l,$ and ϕ_g represent the rates of consumption of glucose by OXPHOS, consumption of lactate by OXPHOS, and consumption of glucose by glycolysis, respectively, over time and space. Under the unrealistic but simplifying assumption that these pathways together comprise the cell's entire metabolism, we define

the metabolic proportions

$$\Phi_o = \frac{\phi_o}{\phi_o + \phi_l + \phi_g}, \quad (14)$$

$$\Phi_l = \frac{\phi_l}{\phi_o + \phi_l + \phi_g}, \quad (15)$$

$$\Phi_g = \frac{\phi_g}{\phi_o + \phi_l + \phi_g}, \quad (16)$$

where Φ_o denotes the proportion of metabolism consisting of OXPHOS of glucose, Φ_l the proportion of metabolism consisting of OXPHOS of lactate, and Φ_g the proportion of metabolism consisting of glycolytic consumption of glucose. We note that here, and also throughout the main text, "glycolysis" refers to the anaerobic, extra-mitochondrial portion of the full pathway for glucose catabolism; that is, conversion of glucose to pyruvate and then to lactate in the cytosol.

Symbiosis then concerns the dominance of glycolysis vs. lactate OXPHOS in the core and near the edge, as in the main text. That is, we consider symbiosis to occur when glycolysis dominates over lactate OXPHOS in the hypoxic core, and lactate OXPHOS dominates over glycolysis in the oxygenated region near the tumour edge. Further, we carry over from main text our definitions of the 'strength' of symbiosis, amount of necrosis in the core, and extent of tissue hypoxia (see Equations (18)-(20) in the main text).

We take 10^4 samples of the multidimensional parameter space defined by Table 1 in the main text, additionally varying the parameters k_O and n_O such that k_O varies between 1 and 10^5 , analogously to k_G and k_L , while n_O varies between 0.01 and 10, analogously to n_G and n_L . With these sampled parameter values, we numerically solve Equations (6)-(9) to steady state (i.e. to $t = 200$ days), under both the wildtype scenario and under anti-MCT1 treatment. The latter is simulated by using the same sampling points as for the wildtype scenario, but with $k_L = 0$.

Figures 1 and 2 show the long-time system behaviours over space in the symbiotic parameter regime and the weakly- or non-symbiotic parameter regime, respectively. These figures are analogous to Figures 7 and 8 in the main text, and indeed the qualitative results are very similar. OXPHOS of glucose appears to act as a kind of background (though variable) consumption, with the expected dynamics between glycolysis and OXPHOS of lactate occurring against it.

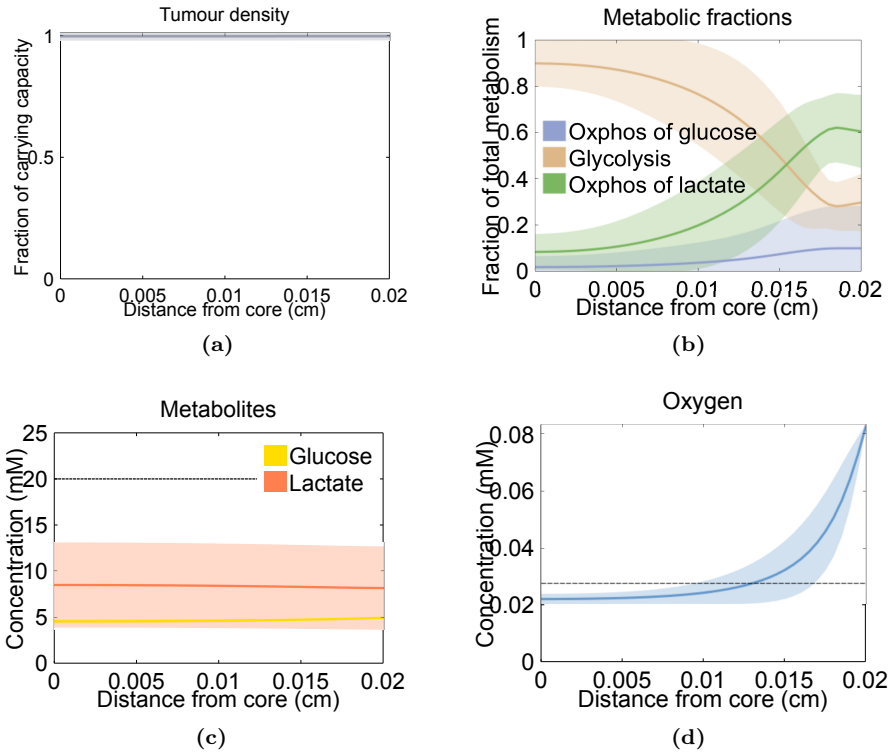


Figure 1: Symbiotic behaviour of Equations (6)-(9). Averaged spatial behaviours of the (a) tumour density, (b) metabolic fractions, (c) metabolite concentrations, and (d) oxygen concentration, at steady state. Shown are the means (curves) and standard deviations (shaded areas) from 10^4 uniformly distributed samples from the parameter region giving rise to symbiotic behaviour. Parameter values can be found in Table 1 of the main text, and additionally $k_O = \text{Unif}(1, 10^5)$ and $n_O = \text{Unif}(0.01, 10)$.

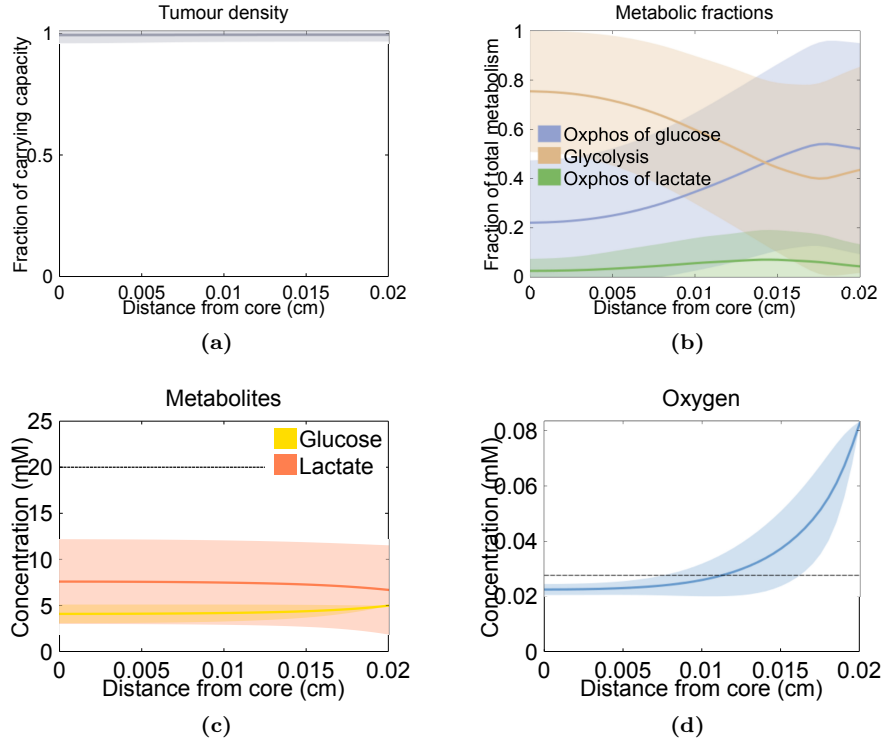


Figure 2: Weakly- or non-symbiotic behaviour of Equations (6)-(9). Averaged spatial behaviours of the (a) tumour density, (b) metabolic fractions, (c) metabolite concentrations, and (d) oxygen concentration, at steady state. Shown are the means (curves) and standard deviations (shaded areas) from 10^4 uniformly distributed samples from the parameter region giving rise to weakly- or non-symbiotic behaviour. Parameter values can be found in Table 1 of the main text, and additionally $k_O = \text{Unif}(1, 10^5)$ and $n_O = \text{Unif}(0.01, 10)$.