# Evolutionary dynamics of glucose-deprived cancer cells: insights from experimentally-informed mathematical modelling<sup>\*</sup> Supplementary Material

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# S1 Mathematical model

Building on the modelling strategies presented in [19], we develop a mathematical model that describes the evolutionary dynamics of a population of MCF7-sh-WISP2 cells, structured by the level of MCT1 expression, under the environmental conditions determined by the levels of glucose and lactate in the extracellular environment. The model relies on the following assumptions, justified by the literature or our experimental observations:

- A1 There is a low level of MCT1 expression endowing cells with the highest proliferation rate via glycolysis, and a higher level of MCT1 expression endowing cells with the highest rate of proliferation via lactate reuse when glucose is scarce cf. the experimental results underlying our study.
- A2 There is a threshold level of glucose above which cells prioritise glucose uptake [15].
- A3 Lactate binding to the membrane of cancer cells triggers regulatory pathways increasing the transcriptional activity – and thus level of expression – of MCT1 and, conversely, the interruption of lactate signalling induces a reduction in MCT1 expression levels [14, 18].
- A4 MCT1 expression levels may undergo fluctuations due to epigenetic changes interfering with the transcriptional activity detailed in assumption A3 [13], and the rate at which these changes occur increases with lactate uptake [34].
- A5 Cancer cells proliferate and die according to their fitness in relation to the environmental conditions they are exposed to, and may also die due to competition for space [19].
- A6 The rate of cell proliferation via glycolysis and the corresponding rates of glucose consumption and lactate production are proportional to the rate of glucose uptake, whereas the rate of cell proliferation via lactate reuse and the corresponding rate of lactate consumption are proportional to the rate of lactate uptake. Furthermore, lactate consumption is mediated by the cells' MCT1 expression level [16, 30].
- A7 Glucose and lactate uptake by cancer cells are mediated by ligand-receptor dynamics [28].

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A8 The MCT1 expression distribution at day 0 is in a Gaussian form – cf. the experimental results underlying our study.

#### S1.1 Preliminaries

We introduce the cell population density function n(t, y), which represents the number of MCF7-sh-WISP2 cells with level of MCT1 expression  $y \in \mathbb{R}$  at time  $t \in \mathbb{R}_+$  (i.e. the MCT1 expression distribution of MCF7-sh-WISP2 cells at time t). The cell number, the mean level of MCT1 expression and the related variance, which provides a possible measure for the level of intercellular variability in MCT1 expression, are then computed, respectively, as

$$\rho(t) = \int_{\mathbb{R}} n(t, y) \, \mathrm{d}y, \quad \mu(t) = \frac{1}{\rho(t)} \int_{\mathbb{R}} y \, n(t, y) \, \mathrm{d}y, \quad \sigma^2(t) = \frac{1}{\rho(t)} \int_{\mathbb{R}} y^2 \, n(t, y) \, \mathrm{d}y - \mu^2(t). \tag{S1}$$

We also introduce the functions G(t) and L(t), which model, respectively, the concentrations of glucose and lactate in the extracellular environment.

The results of *in vitro* experiments (cf. Sec. 3.2 in the Main Manuscript) indicate that the mean of the MCT1 expression distribution of MCF7-sh-WISP2 cells moves from lower to higher expression levels when cells are rescued from glucose deprivation. Hence, we assume that there is a level of MCT1 expression (i.e. the fittest level of MCT1 expression) endowing cells with the highest fitness depending on the environmental conditions determined by the concentrations of glucose and lactate. Moreover, the results of *in vitro* experiments (cf. Sec. 3.1 in the Main Manuscript) support the idea that proliferation and survival of MCF7-sh-WISP2 cells correlate with glucose uptake when glucose levels are sufficiently high and with lactate uptake when glucose levels are low. Therefore, we further assume that there are a level of MCT1 expression,  $y_L$ , endowing cells with the highest rate of proliferation via glycolysis and a higher level of MCT1 expression,  $y_H > y_L$ , endowing cells with the highest rate of proliferation via lactate reuse when glucose is scarce (cf. assumption A1) – i.e. if the concentration of glucose in the extracellular environment is lower than a threshold level  $G^*$  above which cells stop taking lactate from the extracellular environment in order to prioritise glucose uptake (cf. assumption A2). We then introduce the following change of variable

$$x = \frac{y - y_L}{y_H - y_L},\tag{S2}$$

so that the rescaled level of MCT1 expression x = 0 corresponds to the level of MCT1 expression  $y = y_L$ and the rescaled level of MCT1 expression x = 1 corresponds to the level of MCT1 expression  $y = y_H$ . Under the change of variable defined by Eq. (S2), representing the rescaled MCT1 expression distribution of MCF7-sh-WISP2 cells at time t by the cell population density function  $n_r(t, x) = (y_H - y_L) n(t, y)$ , we compute the cell number, the mean rescaled level of MCT1 expression and the related variance, respectively, as

$$\rho_r(t) = \int_{\mathbb{R}} n_r(t,x) \, \mathrm{d}x, \quad \mu_r(t) = \frac{1}{\rho_r(t)} \int_{\mathbb{R}} x \, n_r(t,x) \, \mathrm{d}x, \quad \sigma_r^2(t) = \frac{1}{\rho_r(t)} \int_{\mathbb{R}} x^2 \, n_r(t,x) \, \mathrm{d}x - \mu_r^2(t).$$
(S3)

**Remark S1.1** Note that the following relations hold between the quantities defined via Eq. (S3) and Eq. (S1):

$$\rho(t) = \rho_r(t), \quad \mu(t) = y_L + \mu_r(t)(y_H - y_L), \quad \sigma^2(t) = \sigma_r^2(t)(y_H - y_L)^2.$$
(S4)

#### S1.2 Cell dynamics

The dynamics of the population density function  $n_r(t, x)$  is governed by the following partial integrodifferential equation (PIDE)

$$\begin{cases} \frac{\partial n_r}{\partial t} - \Phi(G(t), L(t)) \frac{\partial^2 n_r}{\partial x^2} + \Psi(G(t), L(t), \mu_r(t)) \frac{\partial n_r}{\partial x} = R(x, G(t), L(t), \rho_r(t)) n_r, & x \in \mathbb{R} \\ \rho_r(t) = \int_{\mathbb{R}} n_r(t, x) \, \mathrm{d}x, & \mu_r(t) = \frac{1}{\rho_r(t)} \int_{\mathbb{R}} x \, n_r(t, x) \, \mathrm{d}x, \end{cases}$$
(S5)

where:

- the advection term  $\Psi(G, L, \mu_r) \frac{\partial n_r}{\partial x}$  models the effects of environment-induced changes in MCT1 expression mediated by lactate-associated signalling pathways, i.e. SPCs (cf. assumption A3);
- the diffusion term  $\Phi(G, L) \frac{\partial^2 n_r}{\partial x^2}$  models the effects of fluctuations in MCT1 expression due to epigenetic changes, i.e. FECs (cf. assumption **A4**);
- the reaction term  $R(x, G, L, \rho_r) n_r$  models the effects of cell proliferation and death under environmental selection on MCT1 expression (cf. assumption **A5**).

The modelling strategies underlying the PIDE (S5) are detailed in the following.

#### Modelling cell proliferation and death under environmental selection on MCT1 expression

The fitness of cells with rescaled level of MCT1 expression x at time t is modelled by the function

$$R(x, G, L, \rho_r) = p(x, G, L) - d\rho_r.$$
(S6)

Definition (S6) translates in mathematical terms to the following biological ideas: all else being equal, cells die due to intracellular competition at rate  $d\rho_r$ , with the parameter d > 0 being related to the carrying capacity of the *in vitro* system in which the cells are contained (cf. assumption **A5**); cells with the rescaled level of MCT1 expression x proliferate and die under environmental selection on MCT1 expression at rate p(x, G, L) (i.e. the function p is a net proliferation rate). Based on the considerations and assumptions introduced so far, we define

$$p(x,G,L) = p_G(x,G) + p_L(x,G,L)$$
(S7)

with

$$p_G(x,G) = \gamma_G U_G(G) (1-x^2), \quad p_L(x,G,L) = \gamma_L U_L(G,L) \left[1 - (1-x)^2\right],$$
(S8)

$$U_G(G) = \frac{G^m}{(\alpha_G)^m + G^m} \quad \text{and} \quad U_L(G, L) = (1 - H(G - G^*)) \frac{L^c}{(\alpha_L)^c + L^c}.$$
 (S9)

The function  $p_G$  models the net rate of cell proliferation via glycolysis and the function  $p_L$  models the net rate of cell proliferation via lactate reuse. The fact that these functions are negative for values of xsufficiently far from 0 (i.e. the rescaled level of MCT1 expression endowing cells with the highest rate of proliferation via glycolysis) and 1 (i.e. the rescaled level of MCT1 expression endowing cells with the highest rate of proliferation via lactate reuse when glucose is scarce) captures the idea that cells with less fit levels of MCT1 expression are driven to extinction by environmental selection (cf. assumptions A1, A2 and A5). Moreover, the functions  $U_G$  and  $U_L$  model glucose and lactate uptake, respectively (cf. assumptions A6 and A7). In the definitions given by Eqs. (S8) and (S9): •  $H(G - G^*)$  is the Heaviside step function centred at the threshold level of glucose  $G^*$  (i.e. the level of glucose above which cells stop taking lactate from the extracellular environment and reusing it to produce energy for fuelling their proliferation), that is,

$$H(G - G^*) = \begin{cases} 0, & \text{if } G < G^* \\ 1, & \text{if } G \ge G^*; \end{cases}$$
(S10)

- $\gamma_G > 0$  and  $\gamma_L > 0$  are the maximum rates of cell proliferation via glycolysis and lactate reuse;
- $\alpha_G > 0$  and  $\alpha_L > 0$  are the glucose and lactate concentrations at half receptor occupancy [28];
- m > 0 and c > 0 are the Hill coefficients for glucose and lactate ligand-receptor dynamics [28].

Under the definitions given by Eq. (S8), after a little algebra, the definition given by Eq. (S7) can be rewritten as

$$p(x, G, L) = a(G, L) - b(G, L) (x - X(G, L))^{2}$$
(S11)

with

$$a(G,L) = \gamma_G U_G(G) + \frac{(\gamma_L U_L(G,L))^2}{\gamma_G U_G(G) + \gamma_L U_L(G,L)}, \quad b(G,L) = \gamma_L U_L(G,L) + \gamma_G U_G(G)$$
(S12)

and

$$X(G,L) = \frac{\gamma_L U_L(G,L)}{\gamma_G U_G(G) + \gamma_L U_L(G,L)}.$$
(S13)

Under the environmental conditions defined by the concentrations of glucose G and lactate L: X(G, L) represents the fittest rescaled level of MCT1 expression; a(G, L) is the corresponding maximum fitness (i.e. the proliferation rate of cells exhibiting the fittest rescaled level of MCT1 expression); b(G, L) can be seen as a nonlinear selection gradient that quantifies the strength of environmental selection on MCT1 expression.

**Remark S1.2** Note that the definition given by Eq. (S13) implies that  $0 \le X(G, L) \le 1$  for all  $G \ge 0$ and  $L \ge 0$ . In particular, coherently with the considerations and assumptions introduced in Sec. S1.1, under this definition and the definitions given by Eq. (S9), we have that if G = 0 then X(G, L) = 1 for any L > 0, while if  $G \ge G^*$  then X(G, L) = 0 for any  $L \ge 0$ .

**Remark S1.3** The fittest level of MCT1 expression, Y(G, L), is obtained from the definition of the fittest rescaled level of MCT1 expression, X(G, L), given by Eq. (S13) through the change of variable defined by Eq. (S2), that is,

$$Y(G,L) = y_L + X(G,L)(y_H - y_L) = y_L + \frac{\gamma_L U_L(G,L)}{\gamma_G U_G(G) + \gamma_L U_L(G,L)}(y_H - y_L).$$
 (S14)

#### Modelling FECs and SPCs in MCT1 expression

The rate of FECs in MCT1 expression is modelled by the function

$$\Phi(G,L) = \beta (1 + \zeta U_L(G,L)), \tag{S15}$$

where the lactate uptake function  $U_L$  is defined via Eq. (S9). Under the definition given by Eq. (S15), the minimum rate of FECs,  $\beta > 0$ , is increased proportionally to lactate uptake with constant of proportionality  $\zeta > 0$  (cf. assumption A4). This translates in mathematical terms to the idea that, since lactate has been shown to be responsible for histone modifications [5, 35], the rate of FECs in MCT1 expression may be enhanced under glucose-deprivation.

Moreover, the rate of environment-induced changes in MCT1 expression mediated by lactate-associated signalling pathways (cf. assumption A3) is modelled by the function

$$\Psi(G, L, \mu_r) = \Psi^+(G, L) - \Psi^-(G, \mu_r),$$
(S16)

with

$$\Psi^{+}(G,L) = \lambda_L U_L(G,L) \quad \text{and} \quad \Psi^{-}(G,\mu_r) = \lambda_G H(G-G^*) (\mu_r)_{+},$$
(S17)

where the lactate uptake function  $U_L$  is defined via Eq. (S9), while  $H(G - G^*)$  is the Heaviside step function defined via Eq. (S10). The definitions given by Eqs. (S16) and (S17) translate in mathematical terms to the idea that environment-induced changes mediated by lactate-associated signalling pathways lead to: an increase in MCT1 expression at rate  $\Psi^+$ , which is proportional to lactate uptake, under glucose deprivation (i.e. when  $G < G^*$ ); to a decrease in MCT1 expression at rate  $\Psi^-$  when the glucose level is sufficiently high (i.e. when  $G \ge G^*$ ). The parameters  $\lambda_L > 0$  and  $\lambda_G > 0$  model the corresponding maximum rates of environment-induced increase and decrease in MCT1 expression. Moreover, the dependence of  $\Psi^-$  on  $(\mu_r)_+ = \max\{0, \mu_r\}$  captures the fact that interruption of lactateassociated signalling pathways may occur when  $G \ge G^*$  if the mean rescaled level of MCT1 expression of the cells is below the fittest level x = 0 (cf. Remark S1.2).

#### S1.3 Glucose and lactate dynamics

The dynamic of the glucose concentration G(t) is governed by the following ordinary differential equation (ODE)

$$\frac{\mathrm{d}G}{\mathrm{d}t} = -k_G U_G(G) \,\rho_r(t) \,, \tag{S18}$$

where the glucose uptake function  $U_G$  is defined via Eq.(S9). The ODE (S18) relies on the assumption that glucose is consumed by the cells at a rate proportional to glucose uptake (cf. assumption A6), with constant of proportionality  $k_G > 0$ . Moreover, the dynamic of the lactate concentration L(t) is governed by the following ODE

$$\frac{\mathrm{d}L}{\mathrm{d}t} = k_L U_G(G) \rho_r(t) - \eta_L \int_{\mathbb{R}} \left( p_L(x, G, L) \right)_+ n_r(t, x) \,\mathrm{d}x \,, \tag{S19}$$

where  $(p_L)_+ = \max\{0, p_L\}$ , with  $p_L$  being the function that models the net rate of cell proliferation via lactate reuse, which is defined via Eq. (S8). Based on earlier studies indicating that most tumours release lactate in quantities linearly related to glucose consumption [32], and coherently with the way in which the effect of glucose consumption is incorporated into the ODE (S18), the ODE (S19) relies on the assumption that lactate is produced by the cells at a rate proportional to glucose uptake (A6), with constant of proportionality  $k_L > 0$ . Moreover, the ODE (S19) relies on the additional assumption that lactate is absorbed only by the cells whose rescaled levels of MCT1 expression make them capable of reusing lactate to produce the energy required for their proliferation when glucose is scarce (i.e. cells with rescaled levels of MCT1 expression x corresponding to positive values of  $p_L(x, G, L)$ ), which absorb lactate at a rate proportional to their net proliferation rate (cf. assumption A6), with constant of proportionality (i.e. conversion factor for lactate consumption)  $\eta_L > 0$ .

#### S1.4 Initial conditions

Informed by the experimental data reported in Fig.2(A) in the Main Manuscript, we define the initial MCT1 expression distribution of MCF7-sh-WISP2 cells as (cf. assumption A8)

$$n(0,y) = n_0(y)$$
 with  $n_0(y) = \frac{\rho_0}{\sqrt{2\pi\sigma_0^2}} \exp\left(-\frac{(y-\mu_0)^2}{2\sigma_0^2}\right),$  (S20)

where the initial cell number,  $\rho_0$ , the initial mean level of MCT1 expression,  $\mu_0$ , and the related variance,  $\sigma_0^2$ , are defined as

$$\rho_0 = 1.5 \times 10^6, \quad \mu_0 = 15.57 \times 10^3, \quad \sigma_0^2 = 8 \times 10^6.$$
(S21)

Hence, under the change of variable defined by Eq. (S2), the initial rescaled MCT1 expression distribution of MCF7-sh-WISP2 cells is

$$n_r(0,x) = n_{r0}(x)$$
 with  $n_{r0}(x) = \frac{\rho_{r0}}{\sqrt{2\pi\sigma_{r0}^2}} \exp\left(-\frac{(x-\mu_{r0})^2}{2\sigma_{r0}^2}\right),$  (S22)

where (cf. the relations given by Eq. (S4))

$$\rho_{r0} = \rho_0, \quad \mu_{r0} = \frac{\mu_0 - y_L}{y_H - y_L}, \quad \sigma_{r0}^2 = \frac{\sigma_0^2}{(y_H - y_L)^2}.$$
(S23)

**Remark S1.4** Note that under the relations given by Eq. (S23), we have that  $n_{r0}(x)$  in Eq. (S22) and  $n_0(y)$  in Eq. (S20) are related by  $n_{r0}(x) = (y_H - y_L)n_0(y)$ , i.e. we retrieve the relation between  $n_r(t, x)$  and n(t, y) introduced in Sec.S1.1.

Moreover, in order to match the experimental data reported in Fig.1(B) in the Main Manuscript, we define the initial concentrations of glucose and lactate, respectively, as

$$G(0) = G_0, \quad L(0) = L_0,$$
 (S24)

with  $G_0 = 5.52$  mM and  $L_0 = 1.67$  mM being the average values recorded at day 0 of the glucosedeprivation experiments.

#### S1.5 Parameter values

The values of the model parameters obtained, through the calibration procedure detailed in Section S2.2, using data from 'glucose-deprivation' experiments conducted on MCF7-sh-WISP2 cells are summarised in Tab. S1, with the associated bootstrap statistics reported in Tab. S2. Moreover, Tab. S3 displays the parameter values, along with the corresponding bootstrap statistics, recovered by repeating the calibration procedure using data from both 'glucose-deprivation' and 'rescue' experiments, which are employed to obtain the numerical results in Fig. S10.

# S2 Further details of materials and methods

#### S2.1 In vitro experiments

Two breast cancer cell lines are considered: MCF7 (human breast cancer cell line, epithelial phenotype) and MCF7-sh-WISP2 (MCF7 cells invalidated for WISP2 by sh-RNA plasmid, mesenchymal pheno-type) [9, 12].

#### S2.1.1 Cell proliferation and death

Cells were routinely maintained in Dulbecco's modified Eagle medium containing 4.5g/l of glucose supplemented with 10% fetal bovine serum (FBS), L-Glutamine, and antibiotics. For assessing cell proliferation and death, cells were cultured for four days in a medium initially containing 1g/l of glucose. Viable cells were identified via trypan blue exclusion and counted using Beckman Coulter, while cell death was quantified via annexin V-FITC apoptosis staining.

#### S2.1.2 Flow cytometry analysis

Cells were stained with fluorochrome-conjugated monoclonal antibodies against human MCT1-FITC (Beckman Coulter) at room temperature in the dark for 20 minutes. Cells were then washed with PBS containing 0.5% serum and flow cytometry analysis was carried out. The labelled cells were analysed on a FACS Gallios (Beckman Coulter) and data analysis was performed using the Kaluza software.

#### S2.1.3 Immunofluorescence staining

Cells were plated on chamber slides and fixed in 4% paraformaldehyde. Cells were stained with anti-MCT1 antibody and secondary anti-Rabbit FITC-conjugated antibody (Jackson ImmunoResearch, Cambridgeshire, UK). After immunolabelling, cells were washed, stained with  $1\mu$ g/mL DAPI (Sigma), and observed by fluorescence microscopy (BX61, Olympus).

#### S2.1.4 Real-time RT-qPCR

Total RNA was extracted from cell samples using the TRIzol<sup>®</sup> RNA purification reagent. RNA quantity and purity were assessed by using a Spectrophotometer DS-11 (Denovix, Wilmington, DE, USA). One microgram of total RNA from each sample was reverse transcribed, and real-time RT-qPCR measurements were performed as described in [9], using an apparatus Aria MX (Agilent Technologies, Santa Clara, CA, USA) with the corresponding SYBR<sup>®</sup> Green kit, according to the PROMEGA manufacturer's recommendations.

#### S2.2 Model calibration with experimental data

Experimental data on MCF7-sh-WISP2 cells are used to carry out model calibration through a likelihoodmaximisation method [17, 22, 26, 29]. The likelihood of each parameter set is defined implementing statistical measures obtained from data of replicate experiments, to account for average behaviour. The optimal parameter set (OPS) is obtained by minimising the weighted sum of squared residuals, which corresponds to maximising the likelihood, through an iterative process described in Sec.S2.2.1. At each iteration, we solve numerically the model comprising the PIDE-ODE system (S5), (S18), (S19) subject to the initial conditions defined via Eqs. (S22)-(S24), using methods analogous to those described in Sec.S2.3. Uncertainty quantification is conducted using a bootstrapping algorithm [31, 36], described in Sec.S2.2.2, to obtain emprical 95% confidence intervals of each parameter in the OPS. The MATLAB source codes along with the data used for model calibration have been made available on GitHub<sup>1</sup>. The obtained OPSs are reported in Tab.S1. The bootstrapping statistics are reported in Tab.S2, and the empirical probability distributions of the parameters obtained via the bootstrapping procedure are plotted in Fig.S6.

#### S2.2.1 Calibration procedure

The experimental data used for model calibration. Let  $S_D = \{u_D^{i,k}, i = 1, ..., M, k = 1, ..., K\}$ indicate the set of  $M \times K$  data points  $u_D^{i,k}$ , i.e. the M experimentally obtained summary statistics from each of the K replicate experiments. From these, the average  $\bar{u}_D^i$  and standard deviation  $s_D^i$  of each summary statistic (i = 1, ..., M) are calculated using the standard formulas

$$\bar{u}_D^i = \frac{1}{K} \sum_{k=1}^K u_D^{i,k}, \qquad s_D^i = \frac{1}{\sqrt{K-1}} \sum_{k=1}^K |u_D^{i,k} - \bar{u}_D^i|.$$
(S25)

<sup>&</sup>lt;sup>1</sup>https://github.com/ChiaraVilla/AlmeidaEtAl2023Evolutionary

The likelihood and the weighted sum of square residuals. Let  $S_P \in \Omega \subset \mathbb{R}^N_{\geq 0}$  indicate the set of parameter values in the *N*-dimensional and bounded parameter space  $\Omega$ . Assuming Gaussian measurement noise with zero mean [17, 29], the likelihood of  $S_P$  is given by

$$\mathcal{L}(S_P) = \mathbb{P}(S_D \mid S_P) = \prod_{i=1}^M \frac{1}{\sqrt{2\pi}s_D^i} \exp\left(-\frac{(\bar{u}_D^i - u_P^i)^2}{2(s_D^i)^2}\right),$$
(S26)

where  $\{u_P^i, i = 1, \ldots, M\}$  indicates the summary statistics predicted by the model under  $S_P$ . Since PIDE models provide a mean-field representation of the underlying cellular dynamics, the Gaussian likelihood for each summary statistic  $u_P^i$  is centred at the experimental data average  $\bar{u}_D^i$ . The variance of the Gaussian error measurement – and thus of the Gaussian likelihood – for each summary statistic  $u_P^i$  is assumed to be equal to the variance of the experimental data  $(s_D^i)^2$ , in order to account for the heteroscedasticity [29] suggested by experimental observations. Then the logarithm of the likelihood (S26) is

$$\log \mathcal{L}(S_P) = C_D - R(S_P), \qquad (S27)$$

where  $C_D = -\sum_{i=1}^{M} \log\left(\sqrt{2\pi}s_D^i\right)$  is a constant and

$$R(S_P) = \sum_{i=1}^{M} \frac{(\bar{u}_D^i - u_P^i)^2}{2(s_D^i)^2}$$
(S28)

is the weighted sum of squared residuals, whereby higher/lower variability in the observed data will result in lighter/heavier weights [29].

**Likelihood-maximisation method.** From Bayes Theorem, the posterior distribution of  $S_P$  given the data set  $S_D$  – i.e. the distribution  $\mathcal{P}(S_P | S_D)$  – is such that

$$\mathcal{P}(S_P \mid S_D) \propto \mathcal{P}(S_P) \mathcal{L}(S_P),$$
(S29)

where  $\mathcal{P}(S_P)$  is the prior distribution of  $S_P$ , and  $\mathcal{L}(S_P)$  is the likelihood of  $S_P$  [26]. Due to little knowledge on the prior distribution of the parameters, we assume each of them to be uniformly distributed in a bounded domain, and seek  $S_P$  maximising the likelihood. In practice, for numerical reasons [29], we search for the minimum point of the weighted sum of squared residuals (S28), which corresponds to the maximum of the log likelihood (S27), in the domain assumed for the prior distributions, exploiting the inbuilt MATLAB function **bayesopt**, which is based on Bayesian Optimisation [22]. Due to little knowledge on the parameter values, we take the assumed domain of the prior distributions of most parameters to span several orders of magnitude (see details provided below). These ranges of values are then iteratively updated to ensure that we obtain a good agreement with the experimentally observed MCT1 expression distributions of MCF7-sh-WISP2 cells reported in Fig.2(A) of the Main Manuscript.

Ranges of parameter values considered in the calibration algorithm. We consider values of the maximum rates of proliferation in the range  $\gamma_G$ ,  $\gamma_L \in [0.001, 3]$  /day, to ensure we capture all values recorded in [11] in a variety of environmental conditions for two breast cancer cells lines. Considering this and values of *in vitro* tumour carrying capacities in the range of  $10^5 - 10^7$  cells, as observed here (cf. Fig.1(A) of the Main Manuscript) and in [24], the value of the death rate due to competition for space is taken in the range  $d \in [10^{-8}, 10^{-5}]$  /day /cell. We take values of the glucose consumption and lactate production rates to be in the range  $\kappa_G$ ,  $\kappa_L \in [10^{-7}, 10^{-5}]$  mM /day /cell, considering the values of glucose consumption rates in [23, 24] and those of the tumour carrying capacity range introduced above, knowing that values of  $\kappa_G$  and  $\kappa_L$  are of the same order of magnitude [23]. In the absence of empirically-informed estimates, the value of the conversion factor for lactate consumption is taken in  $\eta_L \in [10^{-12}, 10^{-4}]$  mM /cell, covering a wide range of orders of magnitude, including those used in [10] and references therein. The values of the Hill coefficients c and m are assumed to be in the interval [0.9, 4], since most studies – e.g. [10, 23, 25, 27] – assume Michaelis Menten kinetics (i.e. Hill coefficient equal to 1) but recent works assume positive cooperative binding for glucose uptake [6]. The glucose and lactate concentrations at half receptor occupancy are taken to have values in the range  $\alpha_G$ ,  $\alpha_L \in [0.01, 10]$  mM as in [23, 24]. We take value of the minimum rate of FECs in MCT1 expression  $\beta \in [10^{-4}, 10^{-1}]$  /day, covering the range of values used in [3, 6, 21] and references therein, and consider the value of the lactate-dependency coefficient  $\zeta \in [0, 100]$  to avoid an unrealistic blow up of the rate of FECs. In the absence of further knowledge, we take the maximum rates of SPCs in MCT1 expression to have values in the range  $\lambda_L$ ,  $\lambda_G \in [0,1]$  /day, which includes the range of values considered for  $\beta$  as well as the phenotypic drift magnitude considered in previous phenotype-structured PIDE models for cancer evolution [6]. For consistency with the mean MCT1 expression levels recorded in the experiments (cf. Fig.2(B) of the Main Manuscript), we consider  $y_L \in [0, 15 \times 10^3]$  and  $y_H \in [35 \times 10^3, 100 \times 10^3]$ . Finally, the value of the threshold glucose concentration for lactate uptake is assumed to be above physiological levels, i.e.  $G^* > 5.5$  mM, when calibrating the model with data from 'glucose-deprivation' experiments, and later taken in the interval of experimentallyconsidered glucose concentrations  $G^* \in [0, 25]$  mM to test our initial assumption by calibrating the model with data from both 'glucose-deprivation' and 'rescue' experiments.

#### S2.2.2 Uncertainty quantification

Given the little amount of data available for model calibration, we make use of a bootstrapping algorithm [31, 36] to quantify uncertainty in the maximum likelihood estimates obtained from fitting the model to the average values of each summary statistic. The algorithm is composed of the following steps:

- 1. Create the  $j^{th}$  bootstrap data set  $\tilde{S}_D^j = \{u_D^{ij}, i = 1, \dots, M\}$  by randomly resampling with replacement from the original dataset, i.e. by selecting the value of each of the M data points randomly from one of the K replicate experiments  $(u_D^{ij} \equiv u_D^{i,k_i}, \text{ where } k_i \in \{1, \dots, K\}$  for each  $i = 1, \dots, M$ ).
- 2. Find the  $j^{th}$  bootstrap optimal parameter set  $S_B^j$  maximising the bootstrap likelihood  $\mathcal{L}_B^j(S_P)$ , i.e.

$$\mathcal{L}_{B}^{j}(S_{P}) = \mathbb{P}(S_{P} \mid \tilde{S}_{D}^{j}) = \prod_{i=1}^{M} \frac{1}{\sqrt{2\pi}s_{D}^{i}} \exp\left(-\frac{(u_{D}^{ij} - u_{P}^{i})^{2}}{2(s_{D}^{i})^{2}}\right),$$
(S30)

by repeating the calibration procedure described in Sec. S2.2.1 to match the data set  $\tilde{S}_D^j$ .

- 3. Repeat Points 1 and 2 for j = 1, ..., J to obtain J bootstrap samples of the maximum likelihood estimate of each parameter say,  $\hat{\theta}_B^j$ .
- 4. Calculate bootstrap statistics, such as bootstrap mean  $\bar{\theta}_B$ , standard deviation  $s_B^{\theta}$ , and bias of the maximum likelihood estimate obtained during the main calibration procedure (denoted by  $\hat{\theta}_{mle}$ )

$$\bar{\theta}_B = \frac{1}{J} \sum_{j=1}^{J} \hat{\theta}_B^j, \quad s_B^\theta = \frac{1}{\sqrt{J-1}} \sum_{j=1}^{J} |\hat{\theta}_B^j - \bar{\theta}_B|, \quad \text{BIAS} = \hat{\theta}_{mle} - \bar{\theta}_B, \tag{S31}$$

as well as the empirical 95% confidence interval, i.e. the range of values containing the intermediate 95% bootstrap sample values (removing the first and last 2.5% quartiles). Note that positive/negative bias suggests over/under-estimation of the parameter in the optimal parameter set of the main calibration procedure.

### S2.3 Numerical methods for the simulations of the mathematical model

Numerical solutions of the PIDE-ODE system (S5), (S18), (S19) subject to the initial conditions defined via Eqs.(S22)-(S24) are constructed using a uniform discretisation of the interval [0, T], chosen as computational domain of the variable t, with uniform step  $\Delta t = 10^{-5}$ , and a uniform discretisation of the interval [-3,3], chosen as computational domain of the variable x, with uniform step  $\Delta x = 0.002$ . Suitable values of the final time of simulations T > 0 are chosen depending on the scenarios under study. To solve numerically the PIDE (S5), we impose the following zero-flux boundary conditions

$$\begin{cases} \Psi(G(t), L(t)) n_r(t, -3) - \Phi(G(t), L(t), \mu_r(t)) \partial_x n_r(t, -3) = 0, \\ & \forall t \in (0, \mathbf{T}), \\ \Psi(G(t), L(t)) n(t, 3) - \Phi(G(t), L(t), \mu_r(t)) \partial_x n_r(t, 3) = 0, \end{cases}$$

which are implemented by means of first-order forward (at x = -3) and backward (at x = 3) finite difference approximations. We make use of first-order forward difference approximation for the time derivative, second-order central difference approximation for the diffusion term, and a first-order upwind scheme to approximate the advection term. Integral terms are approximated by the corresponding left Riemann sums. Given the numerical values of  $n_r(t, x)$ ,  $\rho_r(t)$ ,  $\mu_r(t)$  and  $\sigma_r^2(t)$ , the corresponding values of n(t, y),  $\rho(t)$ ,  $\mu(t)$  and  $\sigma^2(t)$  are obtained through the change of variable  $n(t, y) = (y_H - y_L)^{-1} n_r(t, x)$ and the relations given by Eq. (S4), respectively.

To solve numerically the ODEs (S18) and (S19), we make use of first-order forward difference approximation for the time derivatives, while integral terms are approximated by the corresponding left Riemann sums.

#### S2.4 Optimal parameter sets obtained through model calibration

The OPSs  $\hat{S}_P$  (with maximum likelihood estimates for each parameter indicated up to 4 d.p.) for the mathematical model defined by the PIDE-ODE system (S5), (S18), (S19), subject to the initial conditions defined via Eqs. (S22)-(S24), in which both FECs and SPCs in MCT1 expression are included (i.e. the model with  $\Phi \neq 0, \Psi^{\pm} \neq 0$  and for reduced models in which only FECs in MCT1 expression are included (i.e. the model with  $\Phi \neq 0$ ,  $\Psi^{\pm} \equiv 0$ ) or only SPCs in MCT1 expression are included (i.e. the model with  $\Phi \equiv 0, \ \Psi^{\pm} \neq 0$  are reported in Tab. S1. The value of the weighted sum of squared residuals  $R(S_P)$ , defined via Eq.(S28), related to each parameter set is provided in the last row of Tab. S1. The units of measure of the parameters are reported in the last column, where '-' is reported for dimensionless parameters. The bootstrap statistics (S31) and empirical 95% confidence interval of each parameter obtained during the uncertainty quantification procedure are reported in Tab. S2, where the BIAS is calculated using the OPS of the full model, i.e. for the values listed in the third column of Tab S1. The bootstrap sampling distributions are plotted, along with bootstrap statistics and the OPS used to calculate the BIAS, in Fig. S6. Maximum likelihood estimates and bootstrap statistics obtained fitting data from 'glucose-deprivation' and 'rescue' experiments are reported in Tab. S3.

Calibration results fitting data from 'glucose-deprivation' experiments. The maximum likelihood estimates of the parameters present in each model variation: (i) are consistent across models; (ii) are found in parameter ranges and orders of magnitude consistent with the current modelling and biological literature; and (iii) all provide a good qualitative agreement with the experimental data. Furthermore, the bootstrap sampling distributions obtained via the uncertainty quantification procedure, conducted on the full model, are in agreement with the estimate of each parameter in the OPS, further supporting the validity of the OPS. In particular, values in the OPS are consistently found in the interval  $\bar{\theta}_B^i \pm s_B^i$  (cf. green vertical lines and red error bars in Fig.S6), i.e. significantly close to the bootstrap mean. The only exceptions are found in the values of the parameters  $\gamma_L$  and d, for both of which we recorded a relatively large negative bias, suggesting the values of these parameter were simultaneously overestimated in the main calibration algorithm. Nonetheless, the value of  $\gamma_G$  is consistently higher than  $\gamma_L$  – of one or 2 orders of magnitude – which is in line with the biologically coherent notion that cell proliferation via glycolysis is more efficient than via alternative metabolic pathways [15], with maximum net proliferation rates via glycolysis being amongst the largest values recorded for cancer cells in [11].

Table S1: Optimal parameter sets  $\hat{S}_P$  obtained through model calibration with data from 'glucose deprivation' experiments. Note that since we assume  $G^* > 5.5$ mM, both the exact value of this parameter and the value of the parameter  $\lambda_G$  are not relevant for predicting dynamics under glucose deprivation and, therefore, they are not provided here – estimates for the values of these parameters are provided in Tab.S3. Bootstrap sampling distributions are plotted in Fig. S6

Parameter	Biological meaning	Model with $\Phi \neq 0, \ \Psi^{\pm} \neq 0$	Model with $\Phi \equiv 0, \ \Psi^{\pm} \not\equiv 0$	Model with $\Phi \neq 0, \ \Psi^{\pm} \equiv 0$	Units of measure
$y_L$	MCT1 level corresponding to the maximum rate of proliferation via glycolysis	$4.1751 \times 10^3$	$6.3798 \times 10^3$	$9.9326 \times 10^3$	-
$y_H$	MCT1 level corresponding to the maximum rate of proliferation via lactate reuse	$49.5822 \times 10^3$	$71.3331 \times 10^3$	$48.6315 \times 10^3$	-
d	Rate of death due to intracellular competition	$4.5232\times 10^{-8}$	$1.6174\times 10^{-8}$	$1.4032\times10^{-7}$	/day /cell
$\gamma_G$	Maximum rate of proliferation via glycolysis	2.8898	2.8307	2.9924	/day
$\gamma_L$	Maximum rate of proliferation via lactate reuse	0.4278	0.1148	0.2921	/day
$\alpha_G$	Glucose concentration at half receptor occupancy	2.7500	3.2362	3.6466	g/l
$\alpha_L$	Lactate concentration at half receptor occupancy	3.6131	5.9826	3.0933	mM
m	Hill coefficient for glucose ligand-receptor dynamics	1.0066	1.0140	1.0294	-
с	Hill coefficient for lactate ligand-receptor dynamics	1.9997	1.6730	2.2783	-
β	Minimum rate of FECs in MCT1 expression	$6.2992 \times 10^{-4}$	/	0.0152	/day
ζ	Lactate-dependency coefficient of the rate of FECs in MCT1 expression	10.8609	/	6.9453	-
$\lambda_L$	Maximum rate of SPCs increasing MCT1 expression	0.0894	0.0905	/	/day
$\kappa_G$	Rate of glucose consumption	$2.4618\times10^{-6}$	$2.6930\times 10^{-6}$	$2.8446\times 10^{-6}$	mM /day /cell
$\kappa_L$	Rate of lactate production	$4.3323 \times 10^{-6}$	$4.4738 \times 10^{-6}$	$4.7253 \times 10^{-6}$	mM /day /cell
$\eta_L$	Conversion factor for lactate consumption	$8.1164 \times 10^{-7}$	$1.4316\times10^{-6}$	$3.0079 \times 10^{-7}$	mM /cell
$R(\hat{S}_P)$	Weighted sum of squared residuals	84.1286	113.8088	195.4532	-

Uncertainty quantification of the maximum likelihood estimates of the Hill coefficients m and c suggests mostly Michaelis-Menten dynamics are at play for glucose uptake, a result supported by many works in the literature –see, for instance, [10, 23, 25, 27] –, and stronger positive cooperative binding for lactate uptake. This can be regarded as an additional evolutionary mechanism of cancer cells to survive glucosedeprivation once they acquire the ability to reuse lactate. Calibration results on the parameters  $\beta$ ,  $\lambda_L$ , and  $\zeta$  confirm the following trends: the rate of FECs in MCT1 expressions can become 10 times larger in the presence of a high concentration of lactate; FECs in MCT1 expression occur at a rate that is 2 orders (or 1 order, under high lactate concentrations) of magnitude smaller than that of SPCs. Finally, we remark that the maximum likelihood estimate for  $\kappa_G$  is consistently about twice as large as  $\kappa_L$ , as supported by the literature [23].

Calibration results fitting data from both 'glucose-deprivation' and 'rescue' experiments. First of all, we note that the value of  $G^*$  in the OPS and the bootstrap sample distributions is close

Parameter	Mean $(\bar{ heta}_B)$	$\begin{array}{c} {\bf Standard} \\ {\bf deviation} \ (s^{\theta}_{B}) \end{array}$	BIAS	Empirical 95% Confidence Interval	Units of measure
$y_L$	$5.5442 \times 10^{3}$	$3.2132 \times 10^3$	$-1.3690 \times 10^3$	$[0.9997, 10.7084] \times 10^3$	-
$y_H$	$52.0074 \times 10^{3}$	$4.6521 \times 10^{3}$	$0.5425 \times 10^{3}$	$[42.0513,\!59.7910]\!\times\!10^3$	-
d	$2.7315\times10^{-8}$	$1.1327 \times 10^{-8}$	$1.7917 \times 10^{-8}$	$[0.1043, 0.4881] \times 10^{-7}$	/day /cell
$\gamma_G$	2.6901	0.2103	0.1996	[2.2339, 2.9833]	/day
$\gamma_L$	0.1802	0.1098	0.2476	[0.0539, 0.4290]	/day
$\alpha_G$	3.6320	1.4511	-0.8820	[1.1456, 6.6794]	g/l
$\alpha_L$	3.0706	1.4633	0.5425	[1.1488, 6.4890]	mM
m	1.1424	0.1414	-0.1358	[0.9568, 1.4324]	-
с	2.6921	0.8918	-0.6924	[ 1.1876,3.9769]	-
β	$5.0096 \times 10^{-4}$	$1.3779 \times 10^{-4}$	$1.2896 \times 10^{-4}$	$[0.2309, 0.6940] \times 10^{-3}$	/day
ζ	8.1224	3.2471	2.7385	[ 2.2757,14.0522]	-
$\lambda_L$	0.0885	0.0112	$9.0230 \times 10^{-4}$	[0.0657,  0.1086]	/day
$\kappa_G$	$2.9733 \times 10^{-6}$	$4.8463 \times 10^{-7}$	$-5.1151 \times 10^{-7}$	$[0.2066, 0.4057] \times 10^{-5}$	mM /day /cell
$\kappa_L$	$4.5190 \times 10^{-6}$	$6.1788 \times 10^{-7}$	$-1.8673 \times 10^{-7}$	$[0.3295, 0.5476] \times 10^{-5}$	mM /day /cell
$\eta_L$	$1.1982 \times 10^{-6}$	$6.2939 \times 10^{-7}$	$-2.9643 \times 10^{-7}$	$[0.5311, 2.7340] \times 10^{-6}$	mM /cell

Table S2: Bootstrap statistics (S31) (J = 200) obtained for uncertainty quantification with data from 'glucose deprivation' experiments. The BIAS is calculated with  $\hat{\theta}_{mle}$  in the optimal parameter set reported in the third column of Tab.S1.

to 5.5mM, i.e. physiological levels of glucose, supporting the assumption made during calibration using 'glucose-deprivation' experiments. The estimated value of the parameter  $\lambda_G$  appears to be as large as, if not more than, the estimated value of  $\lambda_L$  reported in Tab. S2, which is consistent with the analogous nature of the biological mechanisms to which these parameters are linked. Similar conclusions to those reported above can be drawn, with the remarkable exception of the relation between values of  $\gamma_G$  and  $\gamma_L$ . Nonetheless, the delay in the increase in cell numbers observed using the parameter set in Tab. S3 suggests additional evolutionary mechanisms may be at play when glucose levels are around 20mM. Interestingly, a decrease in net proliferation rates at such large glucose concentrations has been reported in [11], which would explain the inconsistencies between the calibration carried out using data from 'glucosedeprivation' experiments alone and the calibration relying on data from both 'glucose-deprivation' and 'rescue' experiments, and the poorer quantitative fit in Fig. S10.

Table S3: Bootstrap statistics (S31) (J = 200) obtained for uncertainty quantification with data from both 'glucose deprivation' and 'rescue' experiments. The optimal parameter set correlates with weighted sum of squared residuals  $R(\hat{S}_P) = 4.8147 \times 10^5$ . The units of measure of each parameter value are as reported in Tab.S1, values of the parameter  $G^*$  are in units of mM and those of the parameter  $\lambda_G$  are in units of (day)<sup>-1</sup>. Bootstrap sampling distributions are plotted in Fig. S11.

Parameter	$egin{array}{c} \mathbf{Optimal} \ \mathbf{parameter} \ \mathbf{set} \; (\hat{ heta}_{mle}) \end{array}$	$\mathbf{Mean}\;(\bar{\theta}_B)$	$\begin{array}{c} \textbf{Standard} \\ \textbf{deviation} \ (s^{\theta}_{B}) \end{array}$	BIAS	Empirical 95% Confidence Interval
$y_L$	$2.6711 \times 10^{3}$	$2.9773 \times 10^{3}$	$0.9773 \times 10^{3}$	$-0.3061 \times 10^3$	$[1.2317, 4.7918] \times 10^3$
$y_H$	$70.8005 \times 10^{3}$	$69.9811 \times 10^{3}$	$2.2316 \times 10^3$	$0.8194 \times 10^{3}$	$[65.363, 7.3986] \times 10^3$
d	$1.2852 \times 10^{-7}$	$1.6046 \times 10^{-7}$	$2.2275 \times 10^{-8}$	$-3.1935 \times 10^{-8}$	$[1.1003, 1.9221] \times 10^{-7}$
$\gamma_G$	2.0329	1.9956	0.0913	0.0373	[1.8326, 2.1603]
$\gamma_L$	2.0426	2.0147	0.0928	0.0279	[1.8258, 2.1710]
$\alpha_G$	3.0815	3.8164	0.9890	-0.7349	[2.1793, 5.8222]
$\alpha_L$	6.6278	6.3020	1.4101	0.3258	[3.5671, 8.6386]
m	0.9150	1.0024	0.0427	-0.0874	[0.9206, 1.0729]
с	0.9165	0.9895	0.0454	-0.0731	[0.9112, 1.0710]
$G^*$	5.7999	6.0598	0.7747	-0.2599	[4.3033, 7.5067]
β	$3.4736 \times 10^{-4}$	$5.7841 \times 10^{-4}$	$2.2511 \times 10^{-4}$	$-2.3095 \times 10^{-4}$	$[1.6953, 9.1985] \times 10^{-4}$
ζ	9.7698	7.4438	3.3634	2.3261	[1.6020,13.5169]
$\lambda_L$	$4.5879 \times 10^{-2}$	0.1056	0.0326	-0.0597	[0.0477, 0.1831]
$\lambda_G$	0.1012	0.2786	0.0456	-0.1774	[0.1908, 0.3646]
$\kappa_G$	$1.3394 \times 10^{-6}$	$1.6594 \times 10^{-6}$	$3.8485 \times 10^{-7}$	$-3.2002 \times 10^{-7}$	$[0.8632, 2.2686] \times 10^{-6}$
$\kappa_L$	$2.4345 \times 10^{-6}$	$2.1349 \times 10^{-6}$	$8.2256 \times 10^{-7}$	$2.9955 \times 10^{-7}$	$[0.6541, 3.7297] \times 10^{-6}$
$\eta_L$	$2.5557 \times 10^{-7}$	$5.4953 \times 10^{-7}$	$2.1185 \times 10^{-7}$	$-2.9396 \times 10^{-7}$	$[1.4937, 9.4075] \times 10^{-7}$

## S2.5 Analysis of the mathematical model

We build on the analytical methods and results presented in [1, 7, 33]. We first characterise the qualitative and quantitative properties of the solution to the PIDE (S5) subject to the initial condition (S22) (cf. Proposition S2.1) and then study its convergence to equilibrium under fixed concentrations of glucose and lactate (cf. Theorem S2.2).

**Proposition S2.1** Let assumptions (S6) and (S11) hold. Then, the PIDE (S5) subject to the initial condition (S22) admits the exact solution

$$n_r(t,x) = \frac{\rho_r(t)}{\sqrt{2\pi\,\sigma_r^2(t)}} \,\exp\left[-\frac{(x-\mu_r(t))^2}{2\,\sigma_r^2(t)}\right],\tag{S32}$$

with  $\rho_r(t)$ ,  $\mu_r(t)$  and  $v_r(t) = 1/\sigma_r^2(t)$  being the components of the solution to the following Cauchy problem

$$\frac{\mathrm{d}v_r}{\mathrm{d}t} = 2\left(b(G,L) - \Phi(G,L)v_r^2\right), 
\frac{\mathrm{d}\mu_r}{\mathrm{d}t} = \frac{2b(G,L)}{v_r}\left(X(G,L) - \mu_r\right) + \Psi(G,L,\mu_r), 
\frac{\mathrm{d}\rho_r}{\mathrm{d}t} = \left[\left(a(G,L) - \frac{b(G,L)}{v_r} - b(G,L)\left(X(G,L) - \mu_r\right)^2\right) - d\rho_r\right]\rho_r, 
\langle v_r(0) = 1/\sigma_{r0}^2, \quad \mu_r(0) = \mu_{r0}, \quad \rho_r(0) = \rho_{r0},$$
(S33)

**Proof.** In the remainder of the proof we use the abridged notation

$$a \equiv a(G,L) \,, \ b \equiv b(G,L) \,, \ X \equiv X(G,L) \,, \ \Phi \equiv \Phi(G,L) \,, \ \Psi \equiv \Psi(G,L,\mu_r)$$

and drop the subscripts r for brevity.

Substituting the definitions given by Eqs.(S6) and (S11) into the PIDE (S5) yields

$$\frac{\partial n}{\partial t} = \Phi \frac{\partial^2 n}{\partial x^2} - \Psi \frac{\partial n}{\partial x} + \left[ a - b \left( x - X \right)^2 - d \rho(t) \right] n, \quad x \in \mathbb{R}.$$
 (S34)

Building upon the results presented in [7, 33], we make the ansatz (S32). Substituting this ansatz into Eq. (S34) and introducing the notation  $v(t) = 1/\sigma^2(t)$  we find

$$\frac{1}{\rho}\frac{d\rho}{dt} + \frac{1}{2v}\frac{dv}{dt} = \frac{1}{2}\frac{dv}{dt}(x-\mu)^2 - \frac{d\mu}{dt}v(x-\mu) + \Phi\left[v^2(x-\mu)^2 - v\right] + \Psi v(x-\mu) + a - b(x-X)^2 - d\rho.$$
(S35)

Equating the second-order terms in x gives the following differential equation for v

$$\frac{\mathrm{d}v}{\mathrm{d}t} + 2\Phi v^2 = 2\,b.\tag{S36}$$

Equating the coefficients of the first-order terms in x, and eliminating  $\frac{\mathrm{d}v}{\mathrm{d}t}$  from the resulting equation, yields

$$\frac{\mathrm{d}\mu}{\mathrm{d}t} = \frac{2b(X-\mu)}{v} + \Psi.$$
(S37)

Choosing  $x = \mu$  in Eq. (S35), and eliminating  $\frac{\mathrm{d}v}{\mathrm{d}t}$  from the resulting equation, we obtain

$$\frac{\mathrm{d}\rho}{\mathrm{d}t} = \left[ \left( a - \frac{b}{v} - b \left( X - \mu \right)^2 \right) - d\rho \right] \rho.$$
(S38)

Under the initial condition given by Eq. (S22), we have

$$v(0) = 1/\sigma_0^2, \quad \mu(0) = \mu_0, \quad \rho(0) = \rho_0,$$

and imposing these initial conditions for the ODEs (S36)-(S38) yields the Cauchy problem (S33).  $\hfill\square$ 

Theorem S2.2 Let assumptions (S6), (S9), (S11), (S13), (S16) and (S17) hold. Let also

$$G(t) \equiv \overline{G} \ge 0 \quad and \quad L(t) \equiv \overline{L} \ge 0.$$
 (S39)

Then, the solution of the PIDE (S5) subject to the initial condition (S22) is such that

$$\rho_r(t) \longrightarrow \rho_{r\infty}(\overline{G}, \overline{L}), \quad \mu_r(t) \longrightarrow \mu_{r\infty}(\overline{G}, \overline{L}), \quad \sigma_r^2(t) \longrightarrow \sigma_{r\infty}^2(\overline{G}, \overline{L}) \quad as \ t \to \infty,$$
(S40)

with

$$\rho_{r\infty}(\overline{G},\overline{L}) = \max\left(0, \frac{1}{d} \left[a(\overline{G},\overline{L}) - \sqrt{\Phi(\overline{G},\overline{L}) b(\overline{G},\overline{L})} - \frac{\left(\Psi^+(\overline{G},\overline{L})\right)^2}{4\Phi(\overline{G},\overline{L})}\right]\right),$$

$$\mu_{r\infty}(\overline{G},\overline{L}) = X(\overline{G},\overline{L}) + \frac{\Psi^+(\overline{G},\overline{L})}{2\sqrt{\Phi(\overline{G},\overline{L}) b(\overline{G},\overline{L})}}, \quad \sigma_{r\infty}^2(\overline{G},\overline{L}) = \sqrt{\frac{\Phi(\overline{G},\overline{L})}{b(\overline{G},\overline{L})}}.$$
(S41)

**Proof.** Proposition S2.1 ensures that for any  $t \in [0, \infty)$  the solution of the PIDE (S5) subject to the initial condition (S22) is of the Gaussian form (S32). Building on the method of proof presented in [7, 33], we thus prove Theorem S2.2 by studying the asymptotic behaviour of the components of the solution to the Cauchy problem (S33) for  $t \to \infty$  under the additional assumption (S39). In the remainder of the proof use the abridged notation

$$a \equiv a(\overline{G}, \overline{L}) \,, \ b \equiv b(\overline{G}, \overline{L}) \,, \ X \equiv X(\overline{G}, \overline{L}) \,, \ \Phi \equiv \Phi(\overline{G}, \overline{L}) \,, \ \Psi^+ \equiv \Psi^+(\overline{G}, \overline{L}) \,, \ \Psi^- \equiv \Psi^-(\overline{G}, \mu_r)$$

and drop the subscript r for brevity.

Asymptotic behaviour of  $v(t) = 1/\sigma^2(t)$  for  $t \to \infty$ . Solving the ODE (S33)<sub>1</sub> subject to the initial condition  $v(0) = v_0$  gives

$$v(t) = \sqrt{\frac{b}{\Phi}} \frac{\sqrt{\frac{b}{\Phi}} + v_0 - \left(\sqrt{\frac{b}{\Phi}} - v_0\right) \exp\left(-4\sqrt{b\Phi}t\right)}{\sqrt{\frac{b}{\Phi}} + v_0 + \left(\sqrt{\frac{b}{\Phi}} - v_0\right) \exp\left(-4\sqrt{b\Phi}t\right)},\tag{S42}$$

which implies that

$$v(t) \longrightarrow \sqrt{\frac{b}{\Phi}}$$
 exponentially fast as  $t \to \infty$ . (S43)

Asymptotic behaviour of  $\mu(t)$  for  $t \to \infty$ . Solving the ODE (S33)<sub>2</sub> subject to the initial condition  $\mu(0) = \mu_0$  with the integrating factor method yields

$$\mu(t) = h + (\mu_0 - X) \exp\left[-\int_0^t \left(\frac{2b}{v(z)} + \Psi^-\right) dz\right] + (\Psi^+ - X\Psi^-) \left\{\int_0^t \exp\left[\int_0^z \left(\frac{2b}{v(\tau)} + \Psi^-\right) d\tau\right] dz\right\} \exp\left[-\int_0^t \left(\frac{2b}{v(z)} + \Psi^-\right) dz\right].$$
(S44)

We compute the integrals in Eq.(S44) using the solution of the ODE  $(S33)_1$  given by Eq.(S42). Introducing the notation

$$\delta = \frac{\sqrt{b/\Phi} - v_0}{\sqrt{b/\Phi} + v_0},\tag{S45}$$

we obtain

$$\begin{split} \mu(t) &= X + \frac{(1-\delta)(\mu_0 - X)}{\exp\left(2\sqrt{b\Phi}\,t\right) - \delta\exp\left(-2\sqrt{b\Phi}\,t\right) + (1-\delta)\Psi^- t} + \\ &+ \frac{(\Psi^+ - X\Psi^-)}{2\sqrt{b\Phi}} \,\frac{\left[\exp\left(2\sqrt{b\Phi}\,t\right) + \delta\exp\left(-2\sqrt{b\Phi}\,t\right) - (1+\delta) + (1-\delta)\Psi^- \sqrt{b\Phi}\,t^2\right]}{\left[\exp\left(2\sqrt{b\Phi}\,t\right) - \delta\exp\left(-2\sqrt{b\Phi}\,t\right) + (1-\delta)\Psi^- t\right]} \,. \end{split}$$

Since, under assumptions (S9), (S13), (S16) and (S17), we have  $X \Psi^- \equiv X(\overline{G}, \overline{L}) \Psi^-(\overline{G}, \mu) = 0$  for any  $\overline{G} \ge 0$ , the latter expression of  $\mu(t)$  allows us to conclude that

$$\mu(t) \longrightarrow X + \frac{\Psi^+}{2\sqrt{b\Phi}} \quad \text{exponentially fast as } t \to \infty.$$
(S46)

Asymptotic behaviour of  $\rho(t)$  for  $t \to \infty$ . We define

$$w \equiv w(t) \equiv w(v(t), \mu(t), \overline{G}, \overline{L}) = \left(\sqrt{b\Phi} - \frac{b}{v}\right) - b\left(\mu - X - \frac{\Psi^+}{2\sqrt{b\Phi}}\right)^2$$

and rewrite the ODE  $(S33)_3$  as

$$\frac{\mathrm{d}\rho}{\mathrm{d}t} = \left[ \left( a + \frac{(\Psi^+)^2}{4\Phi} - \sqrt{b\Phi} - \Psi^+ \sqrt{\frac{b}{\Phi}} (\mu - X) + w \right) - d\rho \right] \rho.$$
(S47)

Solving Eq.(S47) subject to the initial condition  $\rho(0) = \rho_0$  yields

$$\rho(t) = \frac{\rho_0 \exp\left[\left(a + \frac{(\Psi^+)^2}{4\Phi} - \sqrt{b\Phi}\right)t - \Psi^+ \sqrt{\frac{b}{\Phi}} \int_0^t (\mu(z) - X) dz + \int_0^t w(z) dz\right]}{1 + d\rho_0 \int_0^t \exp\left[\left(a + \frac{(\Psi^+)^2}{4\Phi} - \sqrt{b\Phi}\right)z - \Psi^+ \sqrt{\frac{b}{\Phi}} \int_0^z (\mu(\tau) - X) d\tau + \int_0^z w(\tau) d\tau\right] dz}.$$
 (S48)

The asymptotic results (S43) and (S46) ensure that

$$w(t) \longrightarrow 0$$
 exponentially fast as  $t \to \infty$ . (S49)

Furthermore, the asymptotic results (S46) and (S49) imply that in the asymptotic regime  $t \to \infty$  we have

$$\exp\left[\left(a + \frac{(\Psi^{+})^{2}}{4\Phi} - \sqrt{b\Phi}\right)t - \Psi^{+}\sqrt{\frac{b}{\Phi}}\int_{0}^{t}(\mu(z) - X)\mathrm{d}z + \int_{0}^{t}w(z)\,\mathrm{d}z\right] \\ \sim A\,\exp\left[\left(a - \sqrt{b\Phi} - \frac{(\Psi^{+})^{2}}{4\Phi}\right)t\right]\,,$$
(S50)

for some positive constant factor  $A \equiv A(\overline{G}, \overline{L})$ . Therefore, Eq. (S48) allows us to conclude that

if 
$$\sqrt{b\Phi} + \frac{(\Psi^+)^2}{4\Phi} \ge a$$
 then  $\rho(t) \longrightarrow 0$  as  $t \to \infty$ . (S51)

On the other hand, the asymptotic results (S46) and (S49) imply that, if  $\sqrt{b\Phi} + (\Psi^+)^2/(4\Phi) < a$ , in the asymptotic regime  $t \to \infty$  we also have

$$\int_{0}^{t} \exp\left[\left(a + \frac{(\Psi^{+})^{2}}{4\Phi} - \sqrt{b\Phi}\right)z - \Psi^{+}\sqrt{\frac{b}{\Phi}}\int_{0}^{z}(\mu(\tau) - X)d\tau + \int_{0}^{z}w(\tau)d\tau\right]dz$$

$$\sim B\frac{\exp\left[\left(a - \sqrt{b\Phi} - \frac{(\Psi^{+})^{2}}{4\Phi}\right)t\right]}{\left(a - \sqrt{b\Phi} - \frac{(\Psi^{+})^{2}}{4\Phi}\right)},$$
(S52)

for some positive constant factor  $B \equiv B(\overline{G}, \overline{L})$ . The asymptotic relations (S50) and (S52), along with Eq. (S48), allow us to conclude that

if 
$$\sqrt{b\Phi} + \frac{(\Psi^+)^2}{4\Phi} < a$$
 then  $\rho(t) \longrightarrow \frac{1}{d} \left[ a - \sqrt{b\Phi} - \frac{(\Psi^+)^2}{4\Phi} \right]$  as  $t \to \infty$ . (S53)

Taken together, the asymptotic results (S51) and (S53) yield

$$\rho(t) \longrightarrow \max\left(0, \frac{1}{d}\left[a - \sqrt{b\Phi} - \frac{(\Psi^+)^2}{4\Phi}\right]\right) \quad \text{as } t \to \infty.$$
(S54)

Claims (S40) and (S41) follow from the asymptotic results (S43), (S46) and (S54).

**Remark S2.3** The asymptotic results of Theorem S2.2 along with the relations given by Eq. (S4) imply that, when  $(G(t), L(t)) \equiv (\overline{G}, \overline{L})$ ,

$$\rho(t) \longrightarrow \rho_{\infty}(\overline{G}, \overline{L}), \quad \mu(t) \longrightarrow \mu_{\infty}(\overline{G}, \overline{L}), \quad \sigma^{2}(t) \longrightarrow \sigma^{2}_{\infty}(\overline{G}, \overline{L}) \quad as \ t \to \infty,$$
(S55)

where

$$\rho_{\infty}(\overline{G},\overline{L}) = \max\left(0, \frac{1}{d} \left[a(\overline{G},\overline{L}) - \sqrt{\Phi(\overline{G},\overline{L}) b(\overline{G},\overline{L})} - \frac{\left(\Psi^{+}(\overline{G},\overline{L})\right)^{2}}{4\Phi(\overline{G},\overline{L})}\right]\right),$$

$$\mu_{\infty}(\overline{G},\overline{L}) = y_{L} + (y_{H} - y_{L}) \left[X(\overline{G},\overline{L}) + \frac{\Psi^{+}(\overline{G},\overline{L})}{2\sqrt{\Phi(\overline{G},\overline{L}) b(\overline{G},\overline{L})}}\right],$$
(S56)
$$\sigma_{\infty}^{2}(\overline{G},\overline{L}) = (y_{H} - y_{L})^{2} \sqrt{\frac{\Phi(\overline{G},\overline{L})}{b(\overline{G},\overline{L})}}.$$





Figure S1: Dynamics of cell proliferation and glucose and lactate concentrations in 'glucosedeprivation' experiments conducted on MCF7 cells. Dynamics of cell proliferation (panel (A)), glucose concentration (panel (B), red line, left y-axis) and lactate concentration (panel (B), pink line, right y-axis) in 'glucose-deprivation' experiments conducted on MCF7 cells for four days. Cell proliferation was assessed by counting the number of viable cells upon seeding (i.e. day 0) and at the end of each day of culture (i.e. days 1-4). Glucose and lactate concentrations were measured in the culture medium at days 0-4. The figure in panel (A) displays the average (dots) and standard deviation (error bars) of two replicate experiments.



Figure S2: Dynamics of cell death in 'glucose-deprivation' experiments conducted on MCF7 and MCF7-sh-WISP2 cells. Dynamics of cell death in 'glucose-deprivation' experiments conducted on MCF7 cells (blue line) and MCF7-sh-WISP2 cells (red line) for four days. Cell death was assessed by measuring the percentage of apoptotic cells upon seeding (i.e. day 0) and at the end of each day of culture (i.e. days 1-4). This figure displays the average (dots) and standard deviation (error bars) of two replicate experiments.



Figure S3: Dynamics of MCT1 expression in 'glucose-deprivation' experiments conducted on MCF7-sh-WISP2 and MCF7 cells. Comparison between MCT1 protein expression of MCF7-sh-WISP2 cells (panel (A)) and MCF7 cells (panel (B)), assessed through flow cytometry analysis, upon seeding (i.e. on day 0) and on days 3 and 5 of 'glucose-deprivation' experiments conducted for five days (sub-panel D0 and sub-panels D3 and D5). The 'Events' legends indicate the number of events (i.e. the total number of cells analysed) for each distribution plotted on a logarithmic scale.



Figure S4: Dynamics of MCT expression in 'glucose-deprivation' and 'rescue' experiments conducted on MCF7-sh-WISP2 cells. (A) MCT1, MCT2 and MCT4 mRNA expression of MCF7-sh-WISP2 cells, assessed through RT-qPCR, upon seeding (i.e. on day 0) and on days 1-4 of 'glucose-deprivation' experiments conducted for four days (column D0 and columns D1-D4). (B) MCT1 mRNA expression of MCF7-sh-WISP2 cells, assessed through RT-qPCR, upon seeding (i.e. on day 0) and on days 3 and 4 of 'glucose-deprivation' experiments conducted for four days (column D0 and columns D3 and D4). MCT1 mRNA expression during the phase of rescue from glucose deprivation in the corresponding 'rescue' experiments (i.e. on days 3 and 4) is also displayed (column D3-4). The mRNA levels in the plots indicate the abundance of the target gene relative to that of endogenous control Actin used to normalise the initial quantity and purity of total RNA.



Figure S5: Numerical simulations of 'glucose-deprivation' experiments conducted on MCF7sh-WISP2 cells. Simulated dynamics of the cell number  $\rho(t)$  (panel (a)), the glucose concentration G(t) (panel (b)), the lactate concentration L(t) (panel (c)), the mean level of MCT1 expression  $\mu(t)$  (panel (d)), the related variance  $\sigma^2(t)$  (panel (e)), and the MCT1 expression distribution n(t, y) (panel (f), t = 0 - t = 5) in 'glucose-deprivation' experiments conducted on MCF7-sh-WISP2 cells. Numerical simulations were carried out for the calibrated model in which both SPCs and FECs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \neq 0$ ) and for calibrated reduced models in which only FECs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \equiv 0$ ) or only SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \equiv 0$ ) or only SPCs in MCT1 expression are included (i.e.  $\Phi \equiv 0, \Psi^{\pm} \equiv 0$ ) or only SPCs in MCT1 expression are included (i.e.  $\Phi \equiv 0, \Psi^{\pm} \equiv 0$ ) or only SPCs in MCT1 expression are included (i.e.  $\Phi \equiv 0, \Psi^{\pm} \equiv 0$ ) or only SPCs in MCT1 expression are included (i.e.  $\Phi \equiv 0, \Psi^{\pm} \equiv 0$ ) or only SPCs in MCT1 expression are included (i.e.  $\Phi \equiv 0, \Psi^{\pm} \equiv 0$ ) and for calibrated reduced models in which only FECs in MCT1 expression are included (i.e.  $\Phi \equiv 0, \Psi^{\pm} \equiv 0$ ) are included in Tab.S1. The MCT1 expression are included (i.e.  $\Phi \equiv 0, \Psi^{\pm} \equiv 0$ ) are included to a logarithmic scale as for the outputs of flow cytometry analyses (panel (g)) to facilitate visual comparison. The red markers highlight experimental data that are used to carry out model calibration. The values of t are in days, while the values of G(t) and L(t) are in mM.



Figure S6: Bootstrap sampling distributions of the model parameters obtained by fitting data from 'glucose-deprivation' experiments. Parameter distributions obtained through the bootstrapping algorithm described in Sec.S2.2.2 for the model in which both FECs and SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \neq 0$ ), setting  $G^* > 5.5$ mM (and thus ignoring  $\lambda_G$  as irrelevant for predicting dynamics under glucose deprivation), generating J = 200 bootstrap samples. For each parameter the following statistics are displayed: the probability density function (PDF) of the samples (orange histogram); the kernel density estimation (KDE), i.e. the smooth PDF obtained from the bootstrap samples by applying the MATLAB function ksdensity (blue line); the empirical 95% confidence interval (blue area); the bootstrap mean (red dot) and standard deviation (red line); the parameter value in the optimal parameter set (OPS) listed in the second column of Tab.S1 (green line), for comparison.



Figure S7: Numerical simulations of long-term dynamics of the mean level of MCT1 expression of glucose-deprived MCF7-sh-WISP2 cells. Long-term dynamics of the mean level of MCT1 expression of MCF7-sh-WISP2 cells  $\mu(t)$  in 'glucose-deprivation' experiments simulated through the calibrated model in which both FECs and SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \neq 0$ ) and through calibrated reduced models in which only SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \neq 0$ ) and through calibrated reduced models in which only SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \neq 0$ ) or only FECs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \equiv 0$ ), under the OPS reported in Tab.S1. Dynamics are shown for  $t \in [0, t^*]$  (in days), with  $t^*$  being the first time instant when the mean level of MCT1 expression attains the value  $y_H$ , which in our modelling framework is the level endowing MCF7-sh-WISP2 cells with the maximum capability of taking lactate from the extracellular environment and reusing it to produce the energy required for their proliferation under glucose deprivation. The value of  $t^*$  is marked by a star, i.e.  $t^* = 72$  for the model with  $\Phi \neq 0$  and  $\Psi^{\pm} \neq 0$ ,  $t^* = 325$  for the model with  $\Phi \equiv 0$  and  $\Psi^{\pm} \equiv 0$ .



Figure S8: Additional numerical simulations of 'glucose-deprivation' experiments conducted on MCF7-sh-WISP2 cells. Simulated dynamics of the cell number  $\rho(t)$  (first column), the mean level of MCT1 expression  $\mu(t)$  (second column), the related variance  $\sigma^2(t)$  (third column), and the lactate concentration L(t) (fourth column) in 'glucose-deprivation' experiments conducted on MCF7-sh-WISP2 cells. Numerical simulations were carried out for the calibrated model in which both FECs and SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \neq 0$ ), under the OPS reported in Tab.S1 but for different values of the parameter  $\beta$  (panel (a)) or different values of the parameter  $\zeta$  (panel (b)), which correspond to different values of the rate of FECs in MCT1 expression  $\Phi$  (cf. the definition given by Eq.(S15)), or different values of the parameter  $\lambda_L$  (panel (c)), which correspond to different values of the rate at which SPCs lead to an increase in MCT1 expression  $\Psi^+$  (cf. the definition given by Eq.(S17)). In particular: in panel (a),  $\beta = 0.0004$  (blue lines),  $\beta = 0.002$  (orange lines),  $\beta = 0.005$  (yellow lines),  $\beta = 0.01$  (purple lines), and  $\beta = 0.02$  (green lines); in panel (b),  $\zeta = 7.9143$  (blue lines),  $\zeta = 40$  (orange lines),  $\zeta = 120$ (yellow lines),  $\zeta = 200$  (purple lines), and  $\zeta = 400$  (green lines); in panel (c),  $\lambda_L = 0.0693$  (blue lines),  $\lambda_L = 0.1$  (orange lines),  $\lambda_L = 0.18$  (yellow lines),  $\lambda_L = 0.25$  (purple lines), and  $\lambda_L = 0.32$  (green lines). The values of t are in days, while the values of L(t) are in mM.



Figure S9: Numerical simulations of long-term dynamics of glucose-deprived MCF7-sh-WISP2 cells under constant concentrations of glucose and lactate. Top row. Simulated dynamics of the cell number  $\rho_r(t)$  (first column), the rescaled mean level of MCT1 expression  $\mu_r(t)$ (second column), and the related variance  $\sigma_r^2(t)$  (third column) under constant concentrations of glucose and lactate, i.e.  $(G(t), L(t)) \equiv (\overline{G}, \overline{L})$  with  $(\overline{G}, \overline{L}) = (5.52, 0)$  (red lines),  $(\overline{G}, \overline{L}) = (2.76, 4.8225)$  (blue lines) and  $(\overline{G}, \overline{L}) = (0, 9.645)$  (green lines). Numerical simulations were carried out for the calibrated model in which both FECs and SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0, \Psi^{\pm} \neq 0$ ), under the OPS for cell dynamics reported in Tab.S1. The black, dashed lines highlight the dynamics of the same quantities obtained by solving numerically the Cauchy problem (S33) complemented with Eq. (S23) and with  $(G(t), L(t)) \equiv (\overline{G}, \overline{L})$ , while the coloured stars mark the analytical equilibrium values computed via Eq.(S41). Bottom row. Corresponding dynamics of the rescaled MCT1 expression distribution  $n_r(t, x)$ for  $(\overline{G}, \overline{L}) = (5.52, 0)$  (left panel),  $(\overline{G}, \overline{L}) = (2.76, 4.8225)$  (central panel) and  $(\overline{G}, \overline{L}) = (0, 9.645)$  (right panel). Coloured, solid lines refer to different times t and the black, dashed lines highlight the rescaled MCT1 expression distribution given by Eq. (S32) whereby  $\rho_r(t), \mu_r(t)$  and  $\sigma_r^2(t)$  are obtained by solving numerically the Cauchy problem (S33) complemented with Eq. (S23) and with  $(G(t), L(t)) \equiv (\overline{G}, \overline{L})$ . The values of t are in days, while the values of  $\overline{G}$  and  $\overline{L}$  are in mM



Figure S10: Numerical simulations of 'glucose-deprivation' and 'rescue' experiments conducted on MCF7-sh-WISP2 cells. Simulated dynamics of the cell number  $\rho(t)$  (top-left panel), the glucose concentration G(t) (top-central panel), the lactate concentration L(t) (top-right panel), the mean level of MCT1 expression  $\mu(t)$  (bottom-left panel, solid line), the related variance  $\sigma^2(t)$  (bottom-central panel), and the MCT1 expression distribution n(t, y) (bottom-right panel, t = 0 - t = 5) in 'glucosedeprivation' experiments conducted on MCF7-sh-WISP2 cells. Numerical simulations were carried out for the calibrated model in which both FECs and SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0$ and  $\Psi^{\pm} \neq 0$ , under the OPS reported in Tab.S3 (blue line), and under 200 parameter sets generated by random sampling from the empirical 95% confidence interval (CI) of the bootstrap sampling distributions (green area) – see Fig. S11. The MCT1 expression distribution obtained under the OPS is plotted on a logarithmic scale as for the outputs of flow cytometry analyses to facilitate visual comparison. The MCT1 expression distribution during the phase of rescue from glucose deprivation in the corresponding simulations of 'rescue' experiments is also displayed (bottom-right panel, t = 4 R and t = 5 R) along with the mean level of MCT1 expression (bottom-left panel, dashed blue line and light green area). The red markers highlight average (scatter points) and standard deviation (error bars) of the experimental data that are used to carry out model calibration, with circles and triangles corresponding to 'glucosedeprivation' and 'rescue' experiments, respectively. The values of t are in days, while the values of G(t)and L(t) are in mM.



Figure S11: Bootstrap sampling distributions of the model parameters obtained by fitting data from 'glucose-deprivation' and 'rescue' experiments. Parameter distributions obtained through the bootstrapping algorithm described in Sec.S2.2.2 for the model in which both FECs and SPCs in MCT1 expression are included (i.e.  $\Phi \neq 0$ ,  $\Psi^{\pm} \neq 0$ ), generating J = 200 bootstrap samples. For each parameter the following statistics are displayed: the probability density function (PDF) of the samples (orange histogram); the kernel density estimation (KDE), i.e. the smooth PDF obtained from the bootstrap samples by applying the MATLAB function ksdensity (blue line); the empirical 95% confidence interval (blue area); the bootstrap mean (red dot) and standard deviation (red line); the parameter value in the optimal parameter set (OPS) listed in the second column of Tab. S3 (green line), for comparison.

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