Supplemental information

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Oscillations in K(ATP) Conductance Drive Slow Calcium Oscillations in Pancreatic *β*-Cells

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Supporting Material

1. Linear mixed effects modelling

To quantify the steepness and the direction of change in measured Perceval-HR fluorescence ratio of the three experiments described in Figs. 7, 8, and 9 in the main text, we employ a linear mixed-effects model (MATLAB function `fitlme`) to estimate the slope of the traces corresponding to each measurement.

We label the experiments described in Figs. 7, 8, and 9 as Experiment [1], Experiment [2], and Experiment [3], respectively. In each experimental set up, the measurements are recorded from several islets belonging to different mice. Therefore, we employ linear mixed-effects modeling to handle the hierarchical structure in the data resulting from the non-independence of islets from the same mouse and the variability due to unknown factors, such as Perceval-HR expression level, among islets. The response variable of interest is thus modelled as a function of predictors (time and experiment) that were treated as fixed effects, whereas the variance shared among hierarchical groupings (mice and islets) were treated as random effects. In our analysis, the response variable of interest is the Perceval-HR fluorescence ratio, the predictor variables are Time (in minutes) and Experiment (which identifies each of the three experiments), while the random effects are due to the Islet and Mouse corresponding to the recording. The resulting linear mixed-effects model is described by the model formula:

$$\text{Ratio (493/403)} \sim \text{Time * Experiment} + (1|\text{Islet}) + (1|\text{Mouse}).$$

The term Time * Experiment represents the interaction of Time and Experiment, and thus reports the variation in slope for each experimental condition.

The goal of our statistical analysis is to assess whether the slope is null in Fig. 7 (when the β-cell is bursting), positive in Fig. 8 (in diazoxide) and negative in Fig. 9 (in diazoxide and high KCl). As a control for drift possibly due to photobleaching, we recorded the Perceval-HR fluorescence ratio at 5 mM glucose, where β-cells are expected to be silent. Panel A in Fig. S1 illustrates the measurements, where each panel corresponds to an experiment from a different mouse and each trace to a different islet. This experiment is labelled as Experiment [0], and the estimated slope is used as a reference to judge whether the slope in the other experiments is null, positive, or negative.

Table S1 summarizes the results of the linear regression, while Fig. S1 illustrates the recordings organized by experiment and with the model regression lines superimposed on the data. The reference slope (Experiment [0]) is given by the value *Estimate* corresponding to the predictor Time. The slope is numerically very small and statistically not different from 0 (*p-value* = 0.1). The value of *Estimate* corresponding to the term Time:Experiment [x] (where x is either 1, 2, or 3) represents the deviation from the reference of the estimated slope for Experiment x as a function of Time. Therefore, if Time:Experiment [x] is positive, Ratio (492/403) increases with time relative to the reference for the recordings in Experiment x, while if it is negative it decreases.

The slope in Experiment [1] (corresponding to Fig. 7) is not statistically different from the reference value (*p-value* = 0.6), and therefore, there are no statistically significant changes in ATP/ADP over time. In contrast, the slopes for Experiment [2] (Fig. 8) and Experiment [3] (Fig. 9) are statistically different from the baseline with positive (*estimation* = 0.0021 min^{-1}, *p-value* < 0.001) and negative (*estimation* = -0.0033 min^{-1}, *p-value* < 0.001) slope, respectively. Thus, the Ratio (492/403) increases with time in Fig. 8 and decreases with time in Fig. 9.

The result of the statistical analysis confirms that if the β-cell is bursting, we do not observe any systematic increase in ATP/ADP as glucose is increased (Fig. 7), but an increase is observed when the β-cell is not bursting (Fig. 8). Finally, ATP/ADP declines if the β-cell is silent and the ATP consumption is increased (Fig. 9).
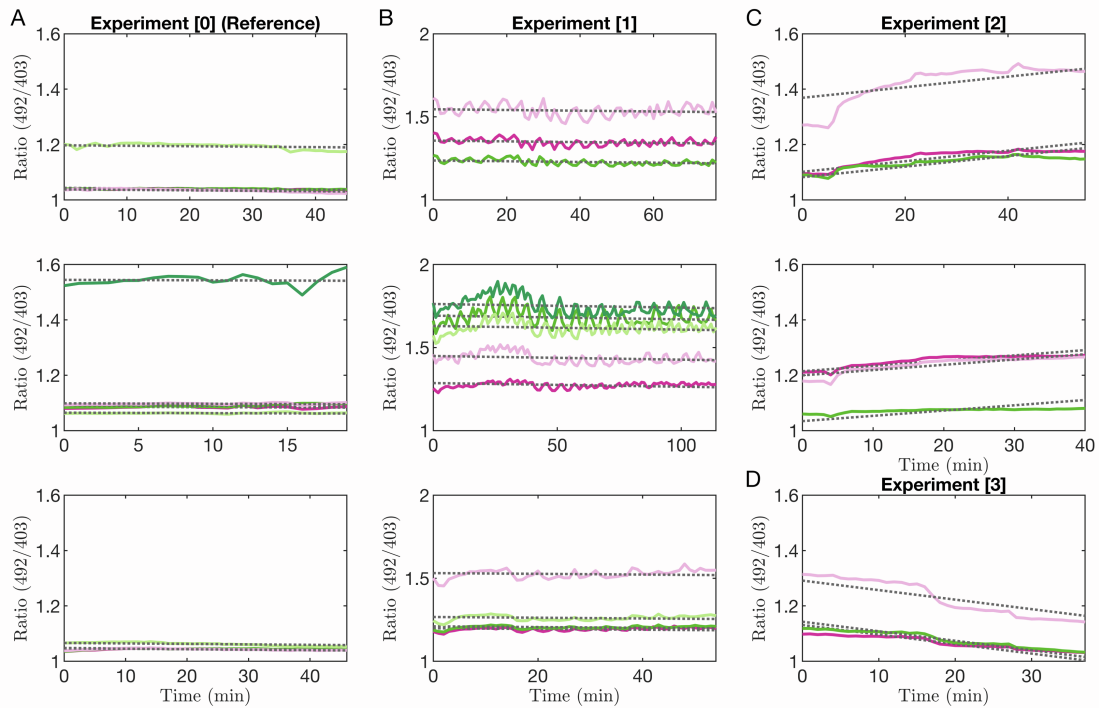
Figure S1: Measurement of Perceval-HR fluorescence ratio and fitted lines (gray). Experiments in which (A) glucose is kept at 5 mM (Experiment [0]); (B) glucose concentration is increased in steps from 9 mM to 13 mM (Experiment [1], Fig. 7); (C) islets were exposed to Dz (200 μM) and KCl (30 mM) and glucose was increased in steps from 5 mM to 13 mM (Experiment [2], Fig. 8); (D) islets were exposed to Dz (200 μM) and 5 mM glucose, and the KCl concentration was increased in steps from 5 mM to 30 mM (Experiment [3], Fig. 9). Each panel corresponds to a different experiment from a Swiss-Webster mouse and each trace to a different islet.

Ratio (492/403)			
Predictors	*Estimate*	*CI*	*p-value*
(Intercept)	1.11	[1.02, 1.19]	**<0.001**
Time	-0.0002	[-0.000361, 3-05]	0.10
Experiment [1]	0.32	[0.19, 0.45]	**<0.001**
Experiment [2]	0.059	[-0.094, 0.212]	0.45
Experiment [3]	0.081	[-0.117, 0.279]	0.42
Time:Experiment [1]	-5e-05	[-0.00026, 0.00015]	0.60
Time:Experiment [2]	0.0021	[0.0018, 0.0024]	**<0.001**
Time:Experiment [3]	-0.0033	[-0.0037, -0.0028]	**<0.001**

Random effects covariance parameters (95% CIs):

Name		*Estimate*	*CI*
σ^2		0.0265	[0.0256, 0.0273]
τ_{00}		0.144 (Islet)	[0.111, 0.189]
		0.0348 (Mouse)	[0.0030, 0.4005]
N	34 Islet		
	9 Mouse		
Observations	1906		

Table S1. Summary of the linear mixed-effects modelling of Measurement of Perceval-HR fluorescence ratio. The model formula is: Ratio (493/403) ~ Time * Experiment + (1|Islet) + (1|Mouse). Estimates, 95% confidence intervals, and p-value (bold, *p-value* <0.001) for each predictor of Ratio (493/403) are shown. σ^2, mean variance of random effects; τ_{00}, random intercept variance (between subject variance) for each random effect; N, number of groups per random effect; Observations, total number of recordings of islets in any combination of fixed effects.

2. Linear mixed effects modelling: mean, amplitude, peaks, and nadirs

To test the invariance of ATP/ADP mean, amplitude, peak, and nadir values of Perceval-HR fluorescence ratio oscillations with changes in the stimulatory glucose concentration (Fig. 7, Experiment [1]), we again use a linear mixed-effects model. The predictor variable is now glucose, and the resulting model formula is:

$$Response \sim Glucose + (1|Islet) + (1|Mouse)$$

where the variables *Response* represents the value of the mean, amplitude, peaks, or nadirs of ATP/ADP (see Fig. S2).

Tables S2, S3, S4 and S5 summarize the results of the linear regression done using the MATLAB function `fitlme`, for mean, amplitude, peak, and nadir values, respectively. In the experimental set up, the islets are initially silent ($G = 5$ mM) and enter the bursting regime when the level of glucose is increased to 9 mM. Analysis is then performed on the data following an initial transition period. We identify this moment as the point in time when the oscillation period reaches 75% of the (mean) period observed in 11 mM and 13 mM. The analysis showed no significant impact of changes in glucose in the mean, nadir, or amplitude of oscillations. There was a small, but significant, decline in the oscillation peak as a function of glucose (with *p-value* = 0.0044).
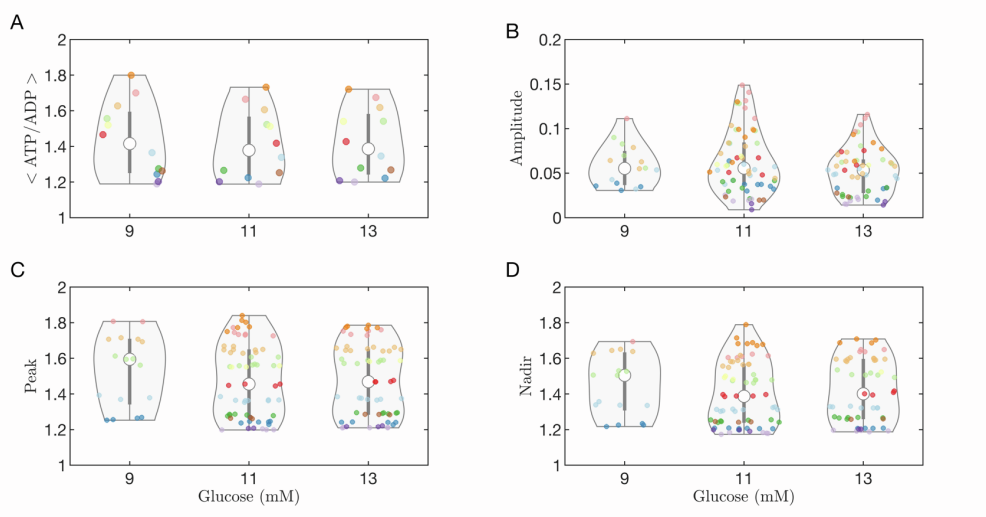
Figure S2: Perceval-HR fluorescence ratio values of mean (A), amplitude (B), peaks (C), and nadirs (D) for different values of glucose. Each islet is identified by a different color.

| | **Mean** | | |
Predictors	Estimate	CI	p-value
(Intercept)	1.452	[1.311, 1.593]	**<0.001**
Glucose	-0.00339	[-0.00685, 7e-05]	0.055

Random effects covariance parameters (95% CIs):

Name	Estimate	CI
σ^2	0.017	[0.013, 0.022]
τ_{00}	0.171 (Islet)	[0.109, 0.270]
	0.076 (Mouse)	[0.013, 0.451]
N	12 Islet	
	3 Mouse	
Observations	36	

Table S2. Summary of the linear mixed-effects modelling of the mean of Perceval-HR fluorescence ratio. The model formula is: Mean ~ Glucose + (1|Islet) + (1|Mouse). Estimates, 95% confidence intervals, and p-value (bold, *p-value* <0.05) for each predictor of Mean are shown. σ^2, mean variance of random effects; τ_{00}, random intercept variance (between subject variance) for each random effect; N, number of groups per random effect; Observations, total number of recordings of islets in any combination of fixed effects.

Amplitude			
Predictors	*Estimate*	*CI*	*p-value*
(Intercept)	0.072	[0.042, 0.103]	**<0.001**
Glucose	-0.00164	[-0.00353, 0.00024]	0.086

Random effects covariance parameters (95% CIs):

Name	*Estimate*	*CI*
σ^2	0.014	[0.013, 0.016]
τ_{00}	0.027 (Islet)	[0.017, 0.043]
	0.012 (Mouse)	[0.002, 0.070]
N	12 Islet	
	3 Mouse	
Observations	135	

Table S3. Summary of the linear mixed-effects modelling of the amplitude of Perceval-HR fluorescence ratio oscillations. The model formula is: Amplitude ~ Glucose + (1|Islet) + (1|Mouse). Estimates, 95% confidence intervals, and p-value (bold, *p-value* <0.05) for each predictor of Mean are shown. σ^2, mean variance of random effects; τ_{00}, random intercept variance (between subject variance) for each random effect; N, number of groups per random effect; Observations, total number of recordings of islets in any combination of fixed effects.

	Peak		
Predictors	*Estimate*	*CI*	*p-value*
(Intercept)	1.481	[1.338, 1.624]	**<0.001**
Glucose	-0.00322	[-0.00541, -0.00102]	**0.0044**

Random effects covariance parameters (95% CIs):

Name	*Estimate*	*CI*
σ^2	0.017	[0.015, 0.020]
τ_{00}	0.186 (Islet)	[0.118, 0.293]
	0.080 (Mouse)	[0.013, 0.507]
N	12 Islet	
	3 Mouse	
Observations	145	

Table S4. Summary of the linear mixed-effects modelling of the peaks of the Perceval-HR fluorescence ratio oscillations. The model formula is: Peak ~ Glucose + (1|Islet) + (1|Mouse). Estimates, 95% confidence intervals, and p-value (bold, *p-value* <0.05) for each predictor of Mean are shown. σ^2, mean variance of random effects; τ_{00}, random intercept variance (between subject variance) for each random effect; N, number of groups per random effect; Observations, total number of recordings of islets in any combination of fixed effects.

| | **Nadir** | | |
Predictors	Estimate	CI	p-value
(Intercept)	1.408	[1.283, 1.532]	**<0.001**
Glucose	-0.00158	[-0.00412, 0.00095]	0.219

Random effects covariance parameters (95% CIs):

Name	Estimate	CI
σ^2	0.020	[0.017, 0.022]
τ_{00}	0.161 (Islet)	[0.3, 0.254]
	0.068 (Mouse)	[0.010, 0.448]
N	12 Islet	
	3 Mouse	
Observations	142	

Table S5. Summary of the linear mixed-effects modelling of the nadirs of the Perceval-HR fluorescence ratio oscillations. The model formula is: Nadir ~ Glucose + (1|Islet) + (1|Mouse). Estimates, 95% confidence intervals, and p-value (bold, *p-value* <0.05) for each predictor of Mean are shown. σ^2, mean variance of random effects; τ_{00}, random intercept variance (between subject variance) for each random effect; N, number of groups per random effect; Observations, total number of recordings of islets in any combination of fixed effects.

3. The Integrated Oscillator Model: equations and parameters

The first module in the Integrated Oscillator Model (IOM) describes the cellular electrical activity and intracellular Ca^{2+} dynamics. The second module describes the components of the metabolic pathway included in our model: glycolysis and mitochondrial metabolism.

The electrical and calcium module

The rate of change of the cellular membrane potential, V_M, is expressed by

$$\frac{dV_M}{dt} = \frac{1}{C}\left[I_{Ca} + I_{K(Ca)} + I_{K(ATP)} + I_K\right], \tag{S1}$$

where C is the membrane capacitance, I_{Ca} is the V_M-dependent Ca^{2+} current, $I_{K(Ca)}$ is the Ca^{2+}-activated K^+ current, $I_{K(ATP)}$ is the ATP-dependent K^+ current, and I_K is the delayed-rectifying K^+ current:

$$I_{Ca} = g_{Ca}m_\infty(V_M)(V_M - V_{Ca}) \ , \tag{S2}$$
$$I_{K(Ca)} = g_{K(Ca)}q_\infty(c)(V_M - V_K) \ , \tag{S3}$$
$$I_{K(ATP)} = g_{K(ATP)}o_\infty(ADP, ATP)(V_M - V_K) \ , \tag{S4}$$
$$I_K = g_K n(V_M - V_K) \ . \tag{S5}$$

The upstroke and downstroke of action potentials are mediated by I_{Ca} and I_K, respectively. The K(Ca) and K(ATP) currents are involved in clustering action potentials into bursts.

The activation functions for I_{Ca}, $I_{K(Ca)}$, and $I_{K(ATP)}$ are given by

$$m_\infty(V_M) = \frac{1}{1 + \exp[(v_m - V_M)/s_m]} \ , \tag{S6}$$

$$q_\infty(Ca) = \frac{Ca^2}{k_d^2 + Ca^2} \ , \tag{S7}$$

$$o_\infty(ADP, ATP) = \frac{0.08 + 0.89\left(\frac{MgADP}{k_{dd}}\right)^2 + 0.16\left(\frac{MgADP}{k_{dd}}\right)}{\left(1 + \frac{MgADP}{k_{dd}}\right)^2\left(1 + \frac{ATP^{4-}}{k_{tt}} + \frac{ADP^{3-}}{k_{td}}\right)} \ , \tag{S8}$$

with MgADP = 0.165 ADP, ATP^{4-} = 0.05 ATP, and ADP^{3-} = 0.135 ADP. The parameters of this module are given in Table S6.

The activation variable for the delayed-rectifying K^+ current, n, is given by

$$\frac{dn}{dt} = \frac{n_\infty(V_M) - n}{\tau_n} \quad , \tag{S9}$$

where

$$n_\infty(V_M) = \frac{1}{1 + \exp[(v_n - V_M)/s_n]} \quad . \tag{S10}$$

The dynamics of the free Ca^{2+} concentration in the cytosol, Ca, in the mitochondria, Ca_m, and in endoplasmic reticulum (ER), Ca_{er}, are given by

$$\frac{dCa}{dt} = f_{Ca}(J_{mem} - J_{er} - J_m) \quad ,$$
$$\frac{dCa_m}{dt} = f_{Ca}\sigma_m J_m \quad , \tag{S11}$$
$$\frac{dCa_{er}}{dt} = f_{Ca}\sigma_{er} J_{er} \quad ,$$

Here, f_{Ca} is the fraction of Ca^{2+} ions not bound to buffers, and J_{mem}, J_m, and J_{er} represent the Ca^{2+} flux densities across the plasma membrane, into the mitochondria, and into the ER, respectively:

$$J_{mem} = -\left[\frac{\alpha}{V_{cyt}}I_{Ca} + k_{PMCA}Ca\right] \quad , \tag{S12}$$
$$J_{er} = k_{SERCA}Ca - k_{NaCa}(Ca_m - Ca) \quad , \tag{S13}$$
$$J_m = J_{uni} - J_{NaCa} \quad . \tag{S14}$$

The terms J_{uni} and J_{NaCa} represent the flux through the Ca^{2+} pumps and through the Na^+/ Ca^{2+} exchanger, respectively:

$$J_{uni} = (p_{21}\psi_m - p_{22})Ca^2 \quad , \tag{S15}$$
$$J_{NaCa} = p_{21}(Ca_m - Ca)\exp(p_{24}\psi_m) \quad . \tag{S16}$$

Parameter	Value	Parameter	Value	Parameter	Value
C	5300 fF	k_d	0.5 µM	σ_{er}	31
g_{Ca}	1000 pS	k_{dd}	17 µM	α	$5.18 \times 10^{-18} \mu mol f A^{-} ms^{-1}$
$g_{K(Ca)}$	150 pS	k_{tt}	1 µM	V_{cyt}	$1.15 \times 10^{-12} l$
$g_{K(ATP)}$	19700 pS	k_{td}	26 µM	k_{PMCA}	0.2 ms^{-1}
g_K	2700 pS	τ_n	20 ms	k_{SERCA}	0.4 ms^{-1}
V_{Ca}	25 mV	v_n	-16 mV	p_{21}	$0.013 \ \mu M^{-1} ms^{-1} mV^{-1}$

V_K	-75 mV	s_n	5mV	p_{22}	1.6 μM^{-1} ms^{-1}
v_m	-20 mV	f_{Ca}	0.01	p_{23}	0.0015 μM ms^{-1}
s_m	12 mV	σ_m	290	p_{24}	0.016 mV^{-1}

Table S6. Parameter values for the electrical and calcium module.

The metabolic module

The cytosolic concentrations of F6P and FBP are described by

$$\frac{dF6P}{dt} = 0.3(J_{GK} - J_{PFK}), \tag{S17}$$

$$\frac{dFBP}{dt} = J_{PFK} - \frac{1}{2}\frac{J_{PDH}}{\sigma_m}, \tag{S18}$$

where J_{GK} is the glucose-dependent glucokinase (GK) reaction rate, J_{PFK} is the phosphofructokinase (PFK) reaction rate, and J_{PDH} is the pyruvate dehydrogenase (PDH) reaction rate. Fluxes through GK, PFK, and PDH are described by

$$J_{GK} = v_{GK}\frac{G^2}{K_{GK}^2 + G^2}, \tag{S19}$$

$$J_{PFK} = v_{PFK}\frac{w_{1110} + k_{PFK}\sum_{i,j,l\in\{0,1\}} w_{ij1l}}{\sum_{i,j,k,l\in\{0,1\}} w_{ijkl}} \tag{S20}$$

$$J_{PDH} = v_{PDH}\frac{1}{K_{NADH_m,PDH} + \frac{NADH_m}{NAD_m}}J_{GPDH}, \tag{S21}$$

where G is the glucose concentration and the weights w_{ijkl}

$$w_{ijkl} = \frac{\left(^{AMP}/K_1\right)^i \left(^{FBP}/K_2\right)^j \left(^{F6P^2}/K_3\right)^k \left(^{ATP^2}/K_4\right)^l}{f_{13}^{ik} f_{23}^{jk} f_{41}^{il} f_{42}^{jl} f_{43}^{kl}}. \tag{S22}$$

The glycerol-3-phosphate dehydrogenase (GPDH) reaction rate, J_{GPDH}, is

$$J_{GPDH} = \frac{Ca_m}{K_{GPDH} + Ca_m}\sqrt{FBP}. \tag{S23}$$

The adenosine diphosphate (ADP) dynamics are given by

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$$\frac{d\text{ADP}}{dt} = J_{\text{hyd}} - \frac{J_{\text{ANT}}}{\sigma_{\text{m}}} \quad , \tag{S24}$$

where J_{hyd} reflects ATP hydrolysis and J_{ANT} is the flux of ATP produced in the mitochondria and transported to the cytosol through the adenine nucleotide translocator (ANT),

$$J_{\text{hyd}} = \left(k_{\text{hyd}}Ca + k_{\text{hyd,bas}}\right)\text{ATP} \quad , \tag{S25}$$

$$J_{\text{ANT}} = p_{19} \frac{\dfrac{\text{ATP}_{\text{m}}}{\text{ADP}_{\text{m}}}}{\dfrac{\text{ATP}_{\text{m}}}{\text{ADP}_{\text{m}}} + p_{20}} \exp\left(\frac{\text{F}}{2\text{RT}}\psi_{\text{m}}\right) \quad . \tag{S26}$$

The hydrolysis term has a Ca^{2+}-independent term that represents ATP hydrolysis for cell homeostasis, and a Ca^{2+}-dependent term that represents hydrolysis by Ca^{2+} pumps present on the plasma and ER membranes.

The model assumes that the total nucleotide concentrations in the cytosol and in the mitochondria (A_{tot} and $A_{\text{tot,m}}$, respectively) is constant, and that the sum of both cytosolic and mitochondrial nucleotides are conserved:

$$\text{ATP} = \frac{1}{2}\left[A_{\text{tot}} + \sqrt{-4\text{ADP}^2 + (A_{\text{tot}} - \text{ADP})^2} - \text{ADP}\right] \quad , \tag{S27}$$

$$\text{ATP}_{\text{m}} = A_{\text{tot,m}}\text{-ADP}_{\text{m}} \quad . \tag{S28}$$

There are two terms for NADH production: production due to pyruvate dehydrogenase (J_{PDH}), and production due to the combined action of dehydrogenases in the citric acid cycle (J_{DH}). The mitochondrial concentration of NADH is then

$$\frac{d\text{NADH}_{\text{m}}}{dt} = J_{\text{PDH}} + J_{\text{DH}} - J_{\text{O}} \quad , \tag{S29}$$

where J_{PDH} is given by (S21) and J_{DH} and the oxygen consumption rate (J_O) are:

$$J_{\text{DH}} = v_{\text{DH}} \frac{Ca_{\text{m}}}{K_{\text{DH}} + Ca_{\text{m}}} \frac{1}{K_{\text{NADH}_{\text{m}},\text{DH}} + \dfrac{\text{NADH}_{\text{m}}}{\text{NAD}_{\text{m}}}} \quad , \tag{S30}$$

$$J_{\text{O}} = p_4 \frac{\text{NADH}_{\text{m}}}{p_5 + \text{NADH}_{\text{m}}} \frac{1}{1 + \exp\left(\dfrac{\psi_{\text{m}} - p_6}{p_7}\right)} \quad . \tag{S31}$$

The model assumes nucleotide conservation:

$$\text{NAD}_{\text{m}} = N_{\text{tot,m}} - \text{NADH}_{\text{m}} \quad , \tag{S32}$$

where $N_{\text{tot,m}}$ is the total concentration in the mitochondria.

The changes in the dynamics of the mitochondrial membrane potential, ψ_m, are described by

$$\frac{d\psi_m}{dt} = \frac{1}{C_m} \left[J_{Hres} - J_{Hatp} - J_{Hleak} - J_{ANT} - J_{NaCa} - 2J_{uni} \right] \quad . \tag{S33}$$

Here, C_m is the mitochondrial inner membrane capacitance, J_{Hres} is the flux through respiration-driven proton pumps, J_{Hatp} is the proton flux entering the mitochondria through the ATPase, while J_{Hleak} is the proton flux entering the mitochondria through leakage down the proton gradient:

$$J_{Hres} = p_8 \frac{NADH_m}{p_9 + NADH_m} \frac{1}{1 + \exp\left(\frac{\psi_m - p_{10}}{p_{11}}\right)} \quad , \tag{S34}$$

$$J_{Hatp} = 3J_{F1F0} \quad , \tag{S35}$$

$$J_{Hleak} = p_{17}\psi_m - p_{18} \quad . \tag{S36}$$

The term J_{F1F0} in (S35) is the rate at which the F1F0 ATP synthase phosphorylates ADP to form ATP:

$$J_{F1F0} = p_{16} \frac{p_{13}}{p_{13} + ATP_m} \frac{1}{1 + \exp\left(\frac{p_{14} - \psi_m}{p_{15}}\right)} \quad . \tag{S37}$$

Since mitochondrial ATP production comes at the expense of ADP, the mitochondrial ADP level (ADP_m) is given by

$$\frac{dADP_m}{dt} = J_{ANT} - J_{F1F0} \quad , \tag{S38}$$

with J_{ANT} and J_{F1F0} given in (S26) and (S37), respectively.

Parameter values for the metabolic module are given in Table S7.

Parameter	Value	Parameter	Value	Parameter	Value
J_{GK}	$0.001\mu M\ ms^{-1}$	$K_{NADH_m,PDH}$	1.3	p_{11}	5 mV
v_{GK}	$0.0037\mu M\ ms^{-1}$	K_{GPDH}	$1.5\mu M$	p_{13}	10000 μM
K_{GK}	19mM	k_{hyd}	$1.864 \times 10^{-6}\mu M\ ms^{-1}$	p_{14}	190 mV
v_{PFK}	$0.01\ _{\mu M\ ms}{}^{-1}$	$k_{hyd,\ bas}$	$6.48 \times 10^{-7}\mu M\ ms^{-1}$	p_{15}	8.5 mV
k_{PFK}	0.06	v_{DH}	$1.1\mu M\ ms^{-1}$	p_{16}	$4\ \mu M\ ms^{-1}$
K_1	$30\ _{\mu M}$	$K_{NADH_m,DH}$	1.3	p_{17}	$0.0014\ \mu M\ ms^{-1}mV^{-1}$
K_2	$1\ _{\mu M}$	K_{DH}	$0.8\mu M$	p_{18}	$0.02\ \mu M\ ms^{-1}$
K_3	$5 \times 10^4\ _{\mu M}{}^2$	$\dfrac{F}{2RT}$	0.037	p_{19}	$0.6\mu M\ ms^{-1}$
K_4	$1000\ _{\mu M}{}^2$	p_4	$0.55\ \mu M\ ms^{-1}$	p_{20}	2
f_{13}	0.02	p_5	250 μM	A_{tot}	3000 μM
f_{23}	0.2	p_6	165 mV	$A_{tot,m}$	15000 μM
f_{41}	20	p_7	5mV	$N_{tot,m}$	10000 μM
f_{42}	20	p_8	$7.4\ \mu M\ ms^{-1}$	C_m	180 mV
f_{43}	20	p_9	100 μM		
v_{PDH}	$0.4\mu M\ ms^{-1}$	p_{10}	165 mV		

Table S7. Parameter for the metabolic module.