

FIGURE S1: Average values of key variables and fluxes vs.  $[IP_3]$  as complementary figures to the bifurcation diagrams shown in Fig. 2D and Fig. 3B bottom and portrait phases in Fig. 4C. Note that  $\bar{J}_{IDH}$  and  $\bar{J}_{KGDH}$  are indistinguishable. Empty and filled dots correspond to steady-state or period-averaged quantities, respectively. Parameter values are the same as in Fig. 2D.

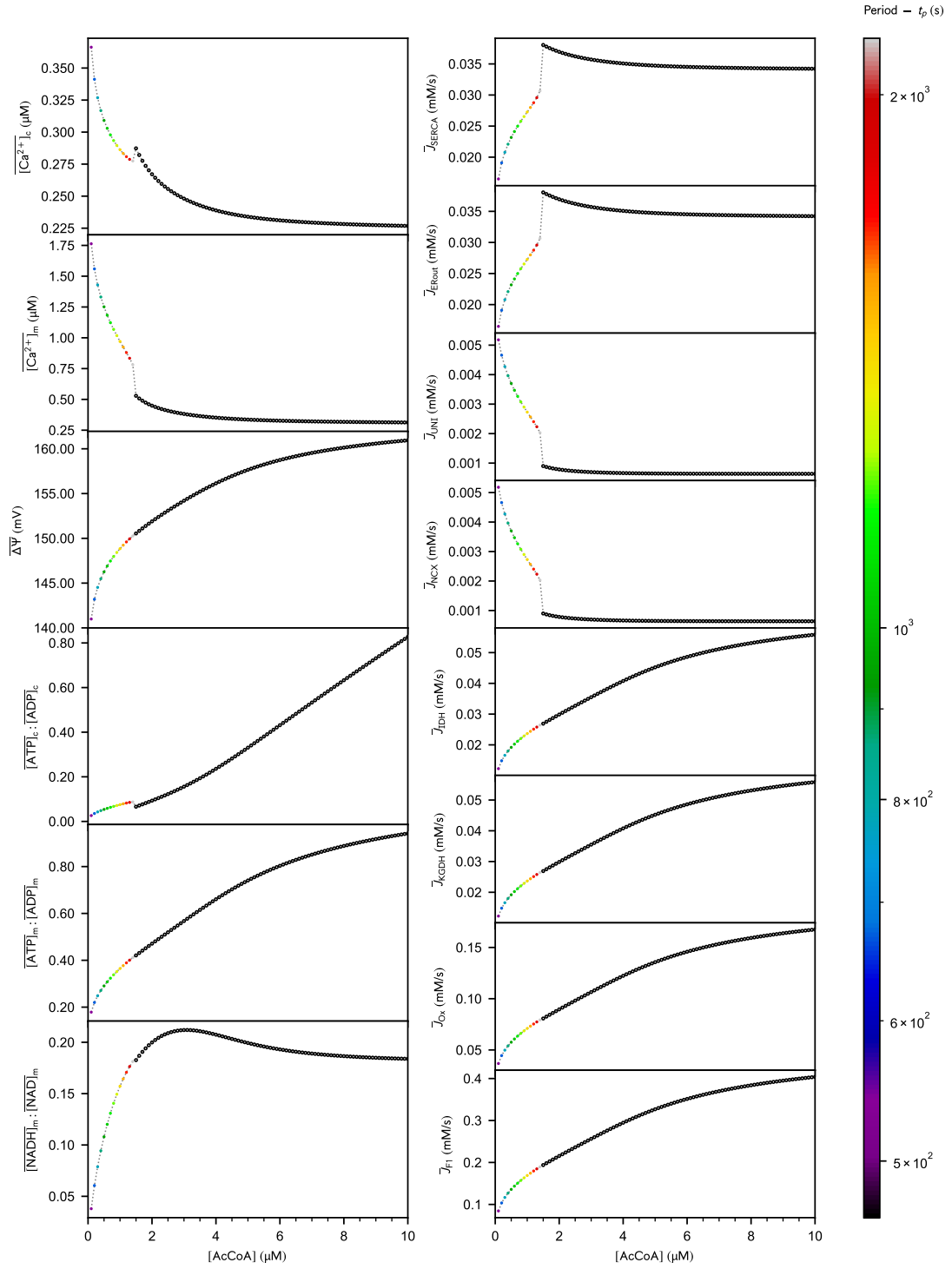


FIGURE S2: Average values of key variables and fluxes vs.  $[\text{AcCoA}]$  as complementary figures to the bifurcation diagrams shown in Fig. 2E and Fig. S3B bottom. Note that  $J_{\text{IDH}}$  and  $J_{\text{KGDH}}$  are indistinguishable. Empty and filled dots correspond to steady-state or period-averaged quantities, respectively. Parameter values are the same as in Fig. 2E.

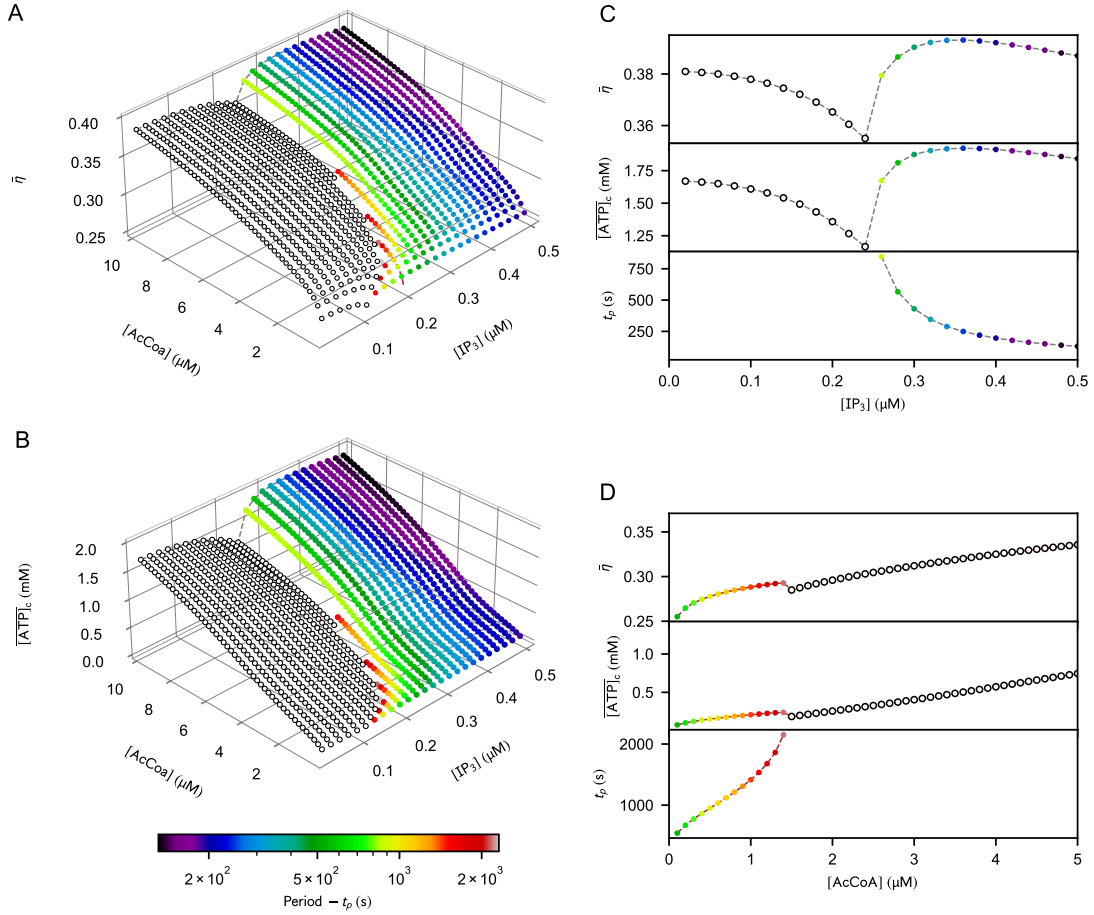


FIGURE S3: Efficiency of mitochondrial metabolism ( $\eta$ ), average cytosolic ATP concentration ( $[ATP]_c$  (mM)) and period of  $Ca^{2+}$  oscillations ( $t_p$ ) as functions of  $[AcCoA]$  and  $[IP_3]$ . (A-B) Summary 3D plots.  $IP_3$  plays a dominant role in the transition between steady-state and oscillations, which usually takes place for concentrations of  $IP_3$  between 0.2 and 0.3  $\mu M$ . The onset of oscillations can be triggered for smaller  $[IP_3]$  in the presence of a very low level of  $AcCoA$  (e.g.  $[AcCoA] \leq 1 \mu M$ ), which supports the role of  $Ca^{2+}$  oscillations as a rescuing mechanism aiming to improve the efficiency of energy production in stressing situations such as substrate-limited. For more clarity, representative behaviors of the efficiency (top panels),  $[ATP]_c$  (mM) (middle panels) and period (low panels) were plot for (grey lines - C)  $[AcCoA] = 10 \mu M$  and (brown lines - D)  $[IP_3] = 0.20 \mu M$ , as complementary figures to the bifurcation diagrams shown in Fig. 2D and 2E, respectively. Note that maxima in efficiency and in  $[ATP]_c$  (mM) can also be observed when  $[AcCoA]$  is varied. Increments in concentrations are of 0.2  $\mu M$  (A-B) or 0.1  $\mu M$  (D) for  $AcCoA$  and of 0.2  $\mu M$  (A – C) for  $IP_3$ .

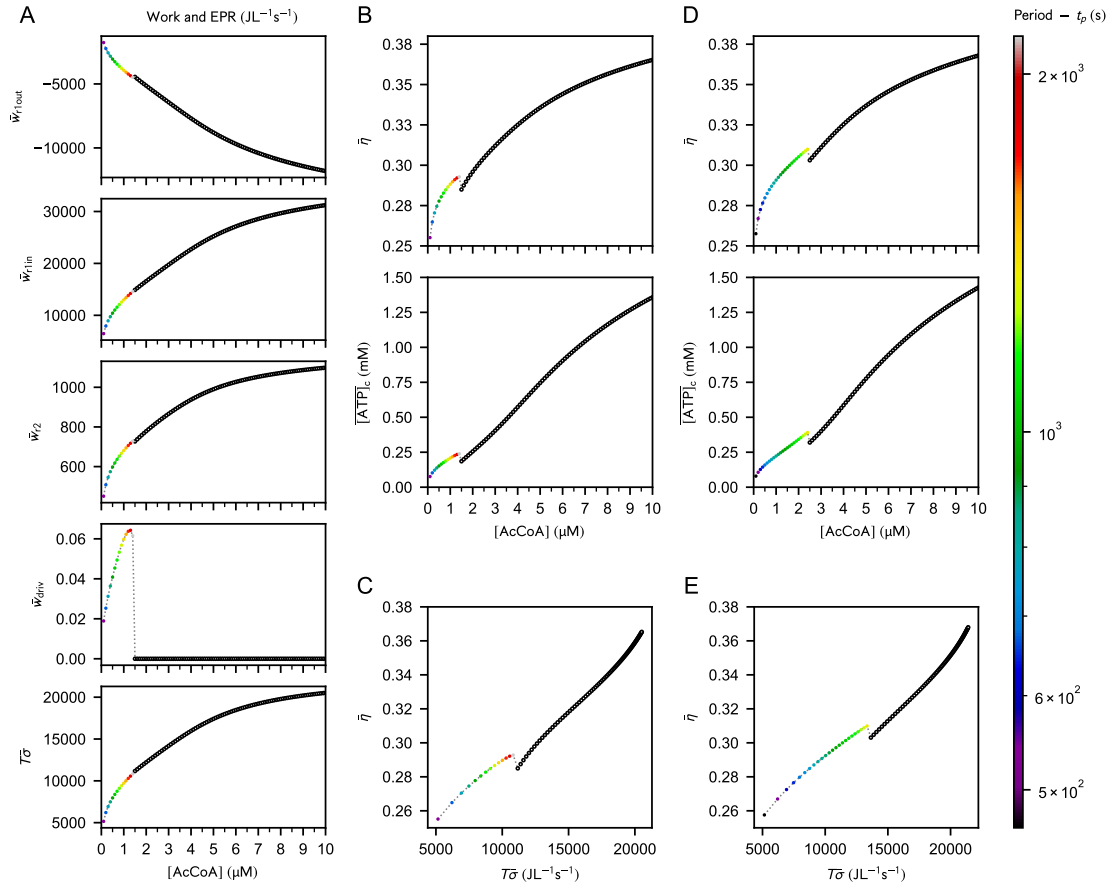


FIGURE S4: Stimulation of mitochondrial metabolism by AcCoA impacts  $\text{Ca}^{2+}$  dynamics *via* the  $\text{Ca}^{2+}$ -metabolism cross-talk. (A) Nonconservative work contributions, driving work and dissipation for different  $[\text{AcCoA}]$ . The driving work represents less than 0.0006% of the EPR. At high stimulation, oscillations disappear in the favor of a nonequilibrium steady-state regime. (B) Efficiency and  $[\text{ATP}]_c$  concentration as a function of  $[\text{IP}_3]$ . (C) Efficiency as a function of the total dissipation for the same range of  $[\text{AcCoA}]$  as in (A) and (B). (D-E) Plots corresponding to (B-C) for  $V_{\text{max}}^{\text{SERCA}} = 0.096 \mu\text{M s}^{-1}$ . Empty and filled dots correspond to steady-state or period-averaged quantities, respectively. Unless specified otherwise, parameter values are the same as in Fig. 2E.

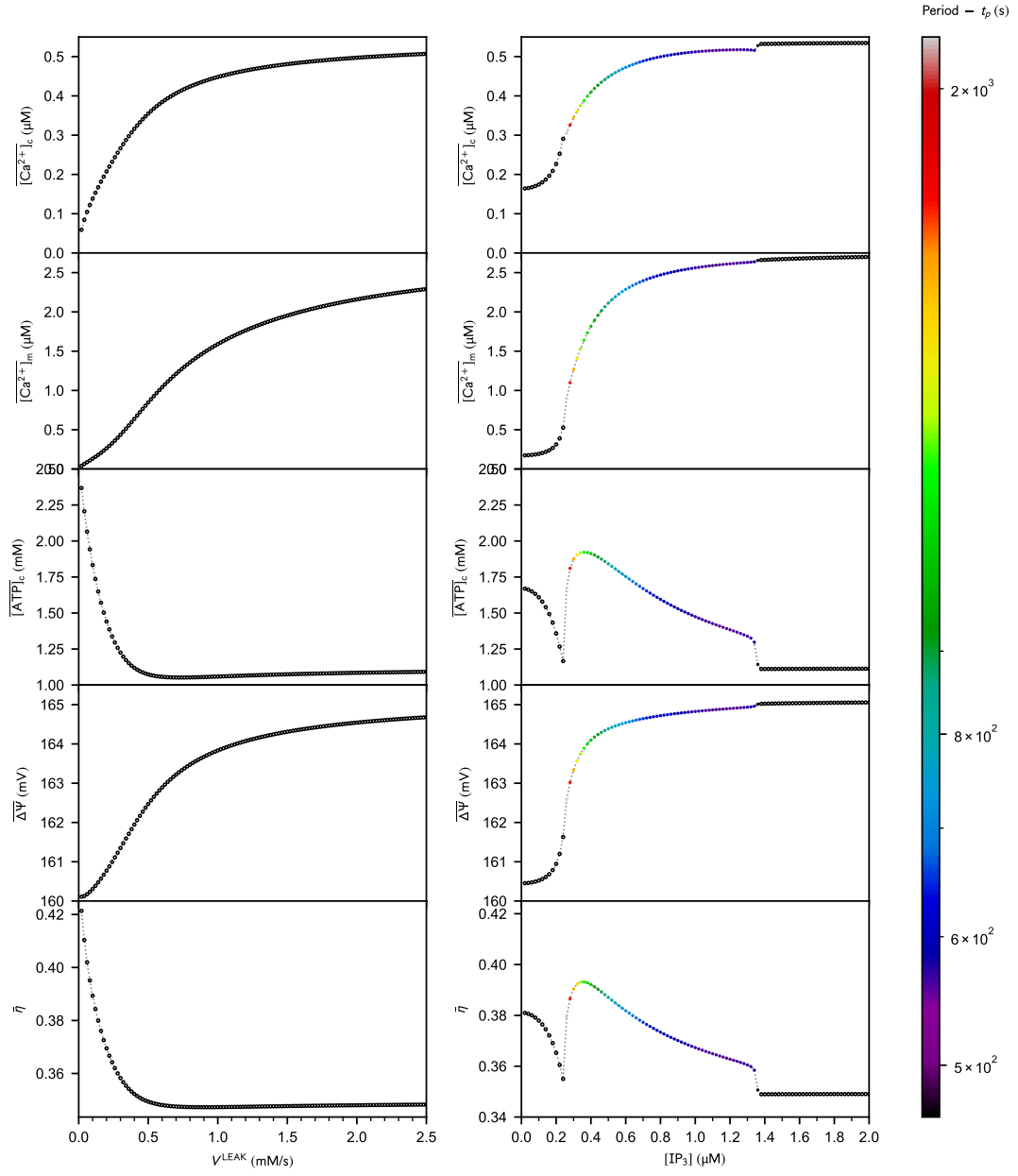


FIGURE S5: Average values of key variables *vs.*  $V^{\text{LEAK}}$  for  $[\text{IP}_3] = 0.10 \mu\text{M}$ . The corresponding plots *vs.*  $[\text{IP}_3]$  for  $V^{\text{LEAK}} = 0.15 \text{ mM s}^{-1}$  (*cf.* Table 4) are shown on the right for comparison. Empty and filled dots correspond to steady-state or period-averaged quantities, respectively. The other parameter values are the same as in Fig. 2D.

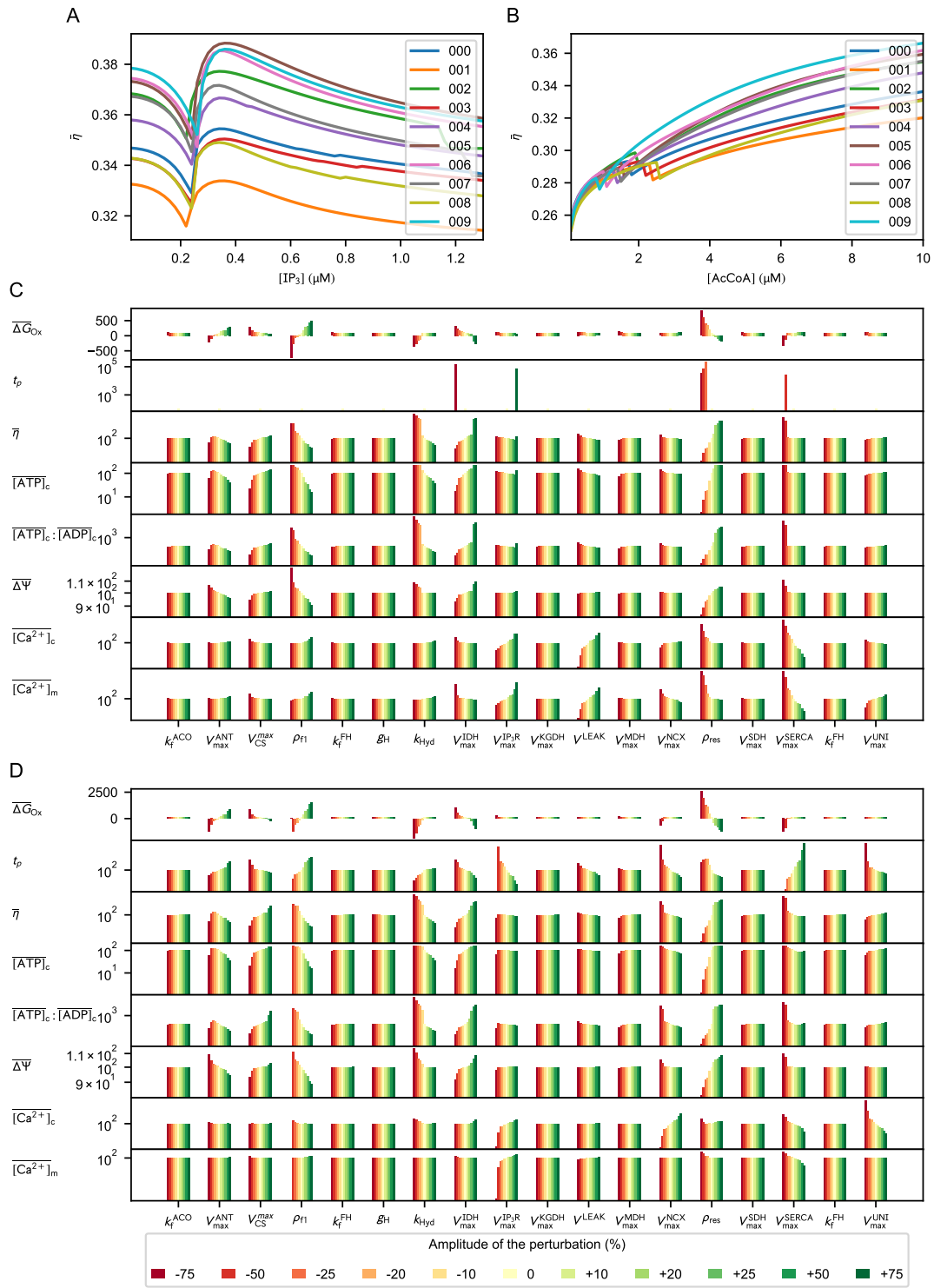


FIGURE S6: Sensitivity analysis. (A – B) Bifurcation diagrams for  $[AcCoA] = 10$  (μM) and  $[IP_3] = 0.2$  (μM). The values of the leading constants can be found in Table 6. (C – D) Fold-change in Gibbs free energy of cellular respiration, thermodynamic efficiency, cytosolic ATP concentration,  $ATP_c:ADP_c$  ratio, mitochondrial membrane potential, cytosolic  $Ca^{2+}$  concentration, mitochondrial  $Ca^{2+}$  concentration, and (change in) absolute period of  $Ca^{2+}$  oscillations. Oscillations can be induced by perturbations of the reference steady-state and *vice-versa*. If oscillations are present, the calculations are based on the period-averaged value of the quantity. For the period bar plot, the absence of a bar indicates a steady-state regime.