ACTIVATION OF GLYCOGENOLYSIS WITHOUT AN ACTIVATION OF ATP CONSUMPTION CAN CAUSE CELL DEATH

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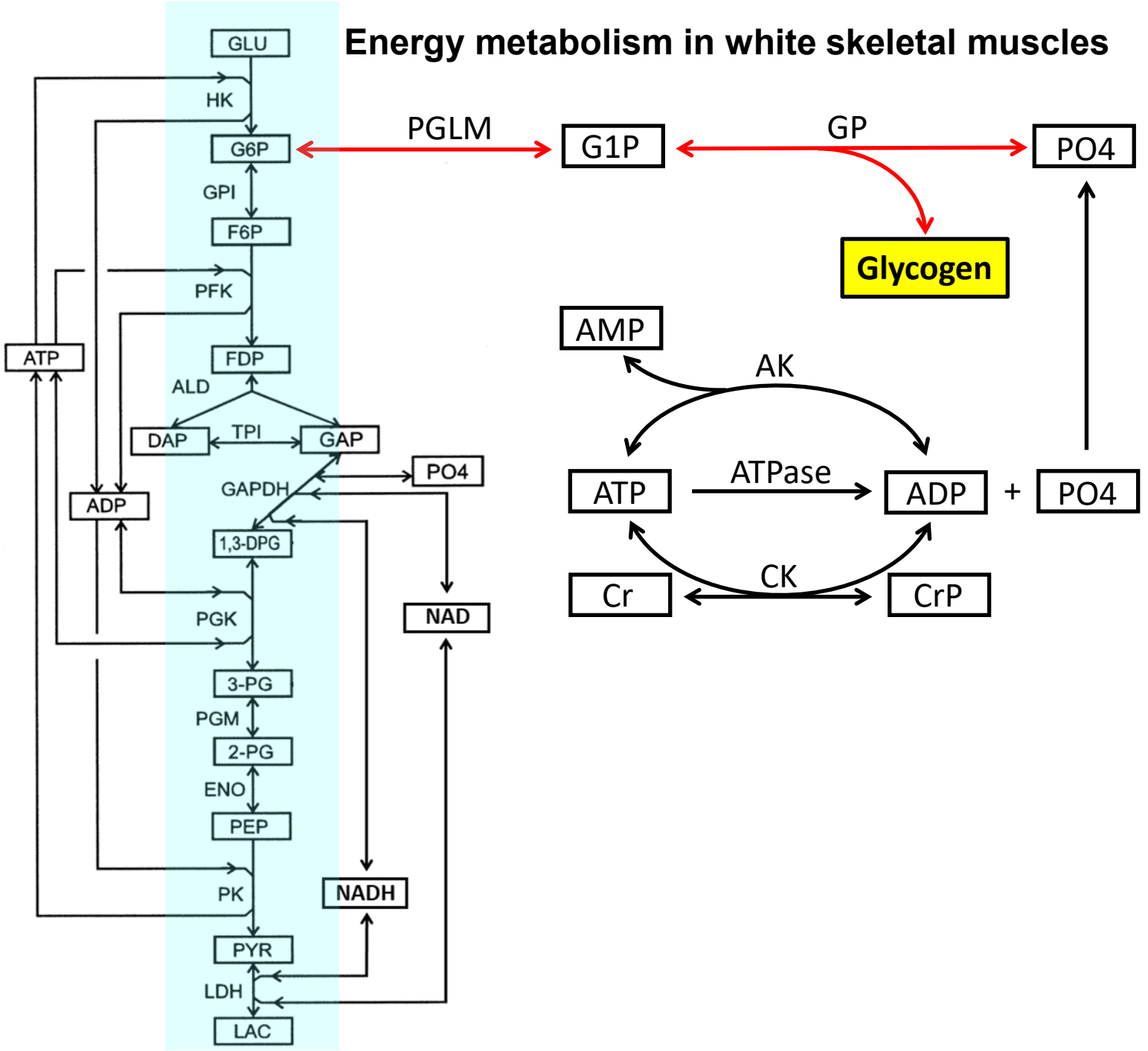
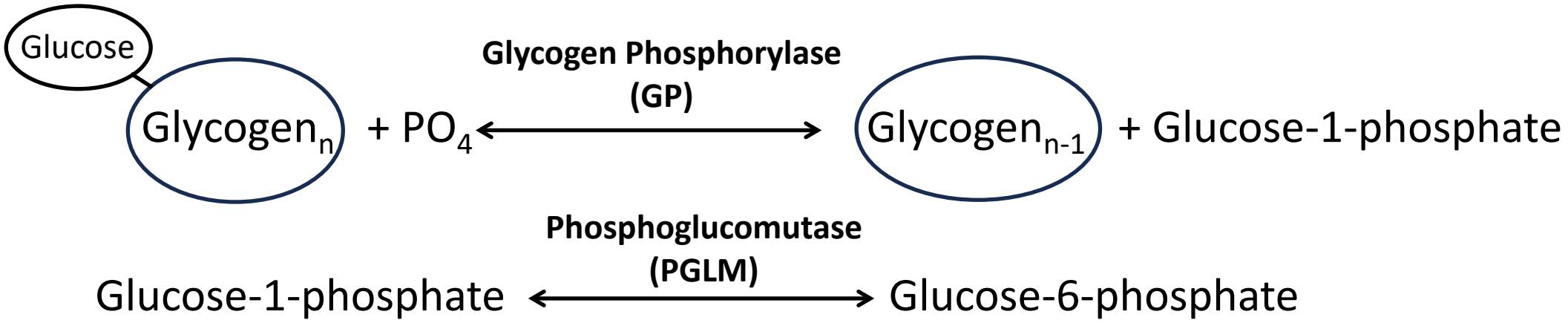
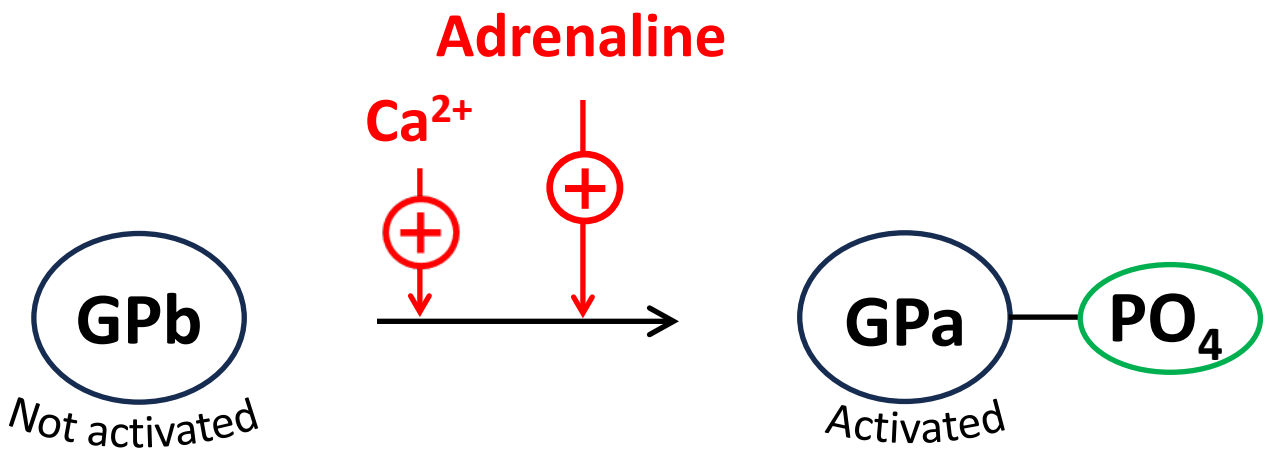
Energy metabolism in white skeletal muscles

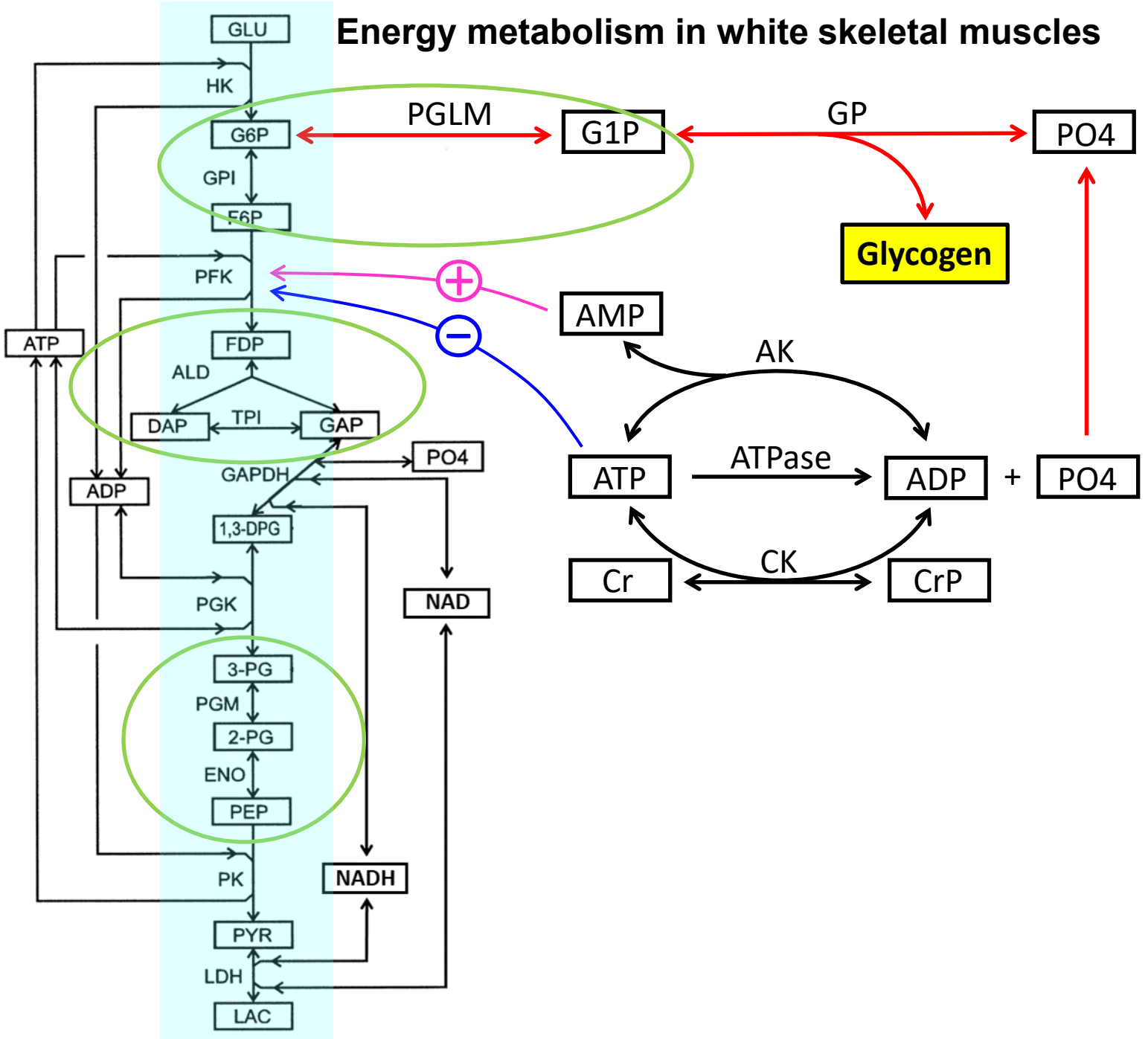


Glycogen consumption is provided by glycogen phosphorylase (GP) and phosphoglucomutase (PGLM)

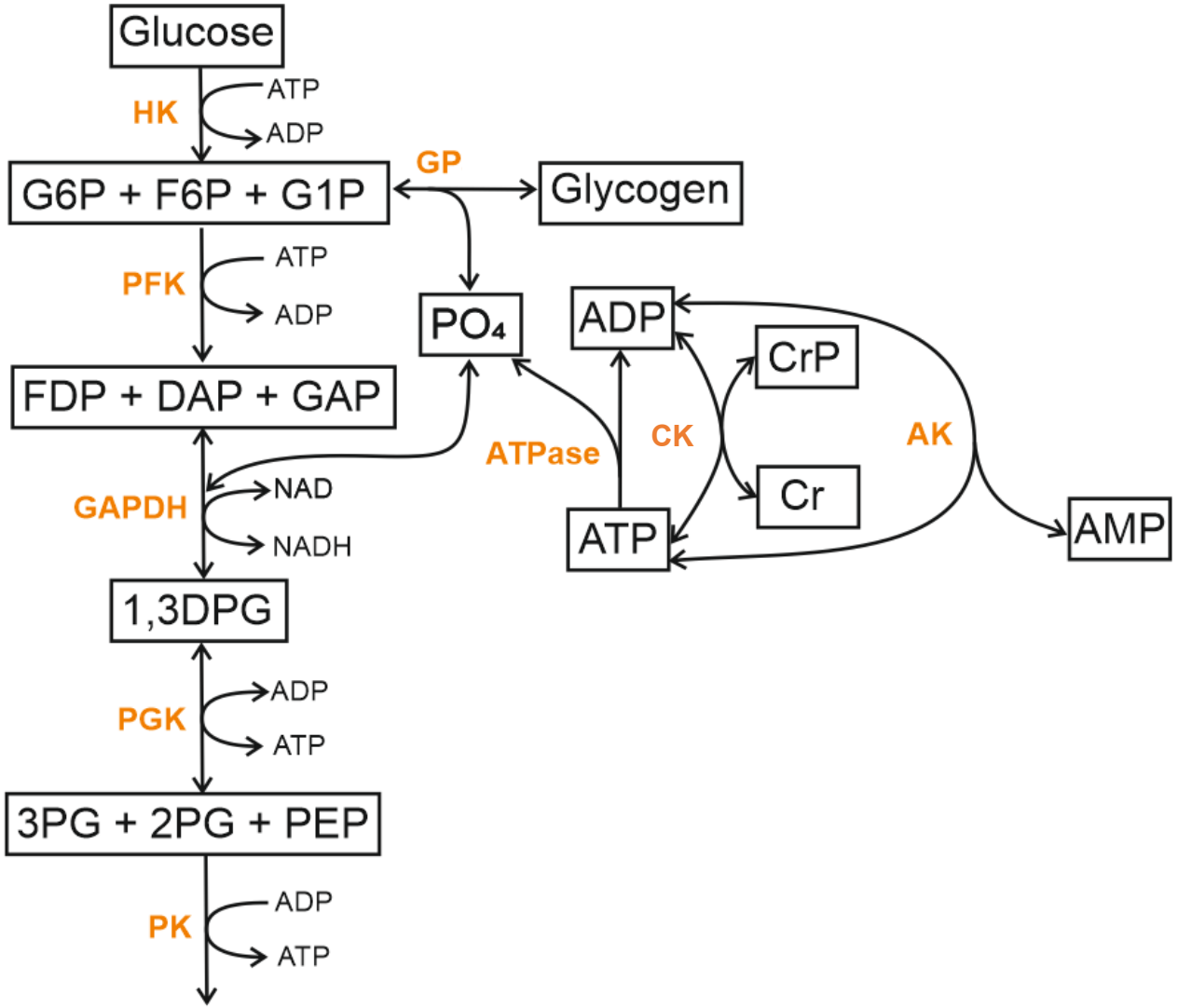




Energy metabolism in white skeletal muscles



Metabolic scheme described by the model



The model equations

$$\begin{cases} \frac{d}{dt}([G6P]+[F6P]+[G1P]) = V_{HK} + V_{GPa} - V_{PFK} \\ \frac{d}{dt}(2[FDP]+[DAP]+[GAP]) = 2V_{PFK} - V_{GAPD} \\ \frac{d}{dt}[1{,}3DPG] = V_{GAPDH} = V_{PGK} \\ \frac{d}{dt}([3PG]+[2PG]+[PEP]) = V_{PGK} - V_{PK} \\ \frac{d}{dt}(2[ATP]+[ADP]+[CrP]) = -V_{HK} + 3V_{PFK} - V_{ATPase} \end{cases}$$

$K_{CK}[H^+] = K'_{CK} = \frac{[Cr][ATP]}{[CrP][ADP]}$; $\quad K_{AK} = \frac{[ATP][AMP]}{[ADP]^2}$

$[ATP]+[ADP]+[AMP] = const$; $\quad [Cr]+[CrP] = const$

$[PO_4]+[G1P]+[G6P]+[F6P]+2[FDP]+[DAP]+[GAP]+$
$+2[1{,}3DPG]+[3PG]+[2PG]+[PEP]+2[ATP]+[ADP]+[CrP] = const$

$[Glucose] = const$; $\quad [Glycogen] = const$; $\quad [NAD] = const$; $\quad [NADH] = const$

Equation for the reaction rate catalyzed by activated GP in the model

$$V_{GP} = \frac{\boldsymbol{A_{GP}}\, K_{G1P}\left([PO_4] - \frac{[G1P]}{K_{eq}}\right)}{K_{G1P}K_P + [G1P]K_P + [PO_4]K_{G1P}}$$

Parameter A_{GP} represents the enzyme activity. It was changed from 0 to 3000 mM/h, K_{G1P} = 2.7 mM, K_P = 4 mM, K_{eq} = 0.33

Gold A.M. et al., *J. Biol. Chem.* 1970; Cori G.T., Cori C.F. *J.Biol. Chem.* 1940

Calculation methods

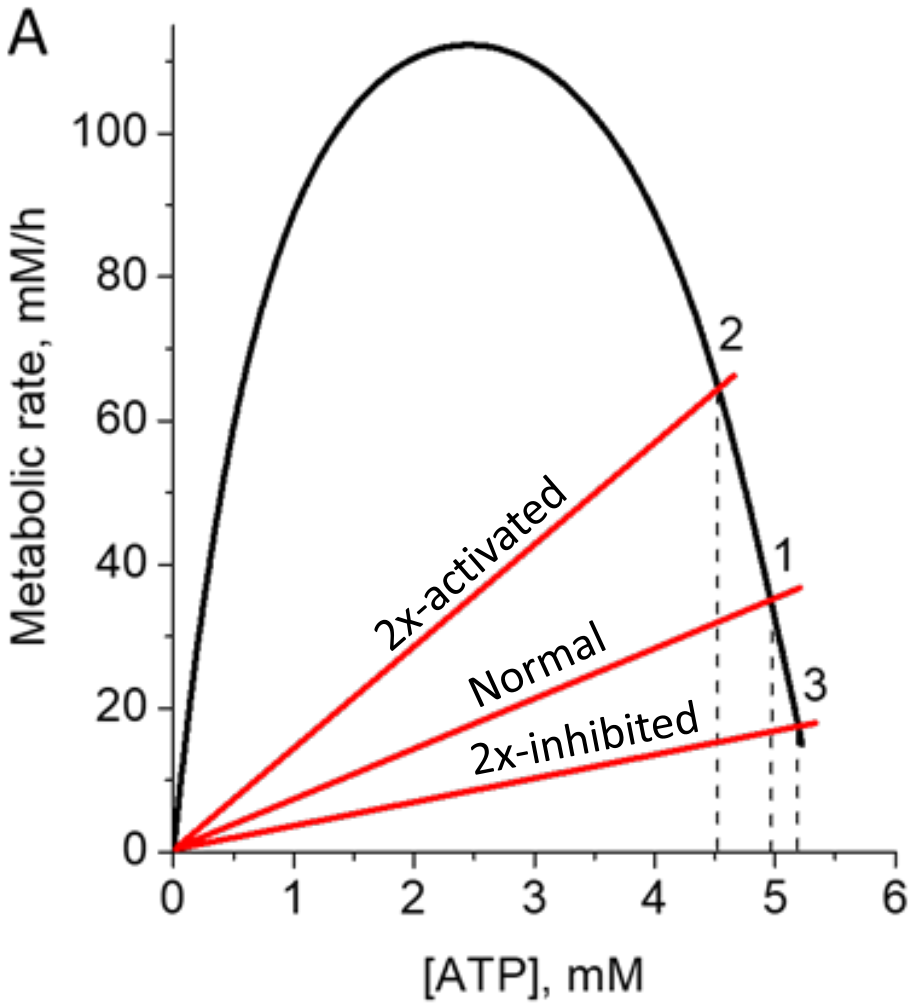
The kinetics of the mathematical model were calculated using the CVODE package:

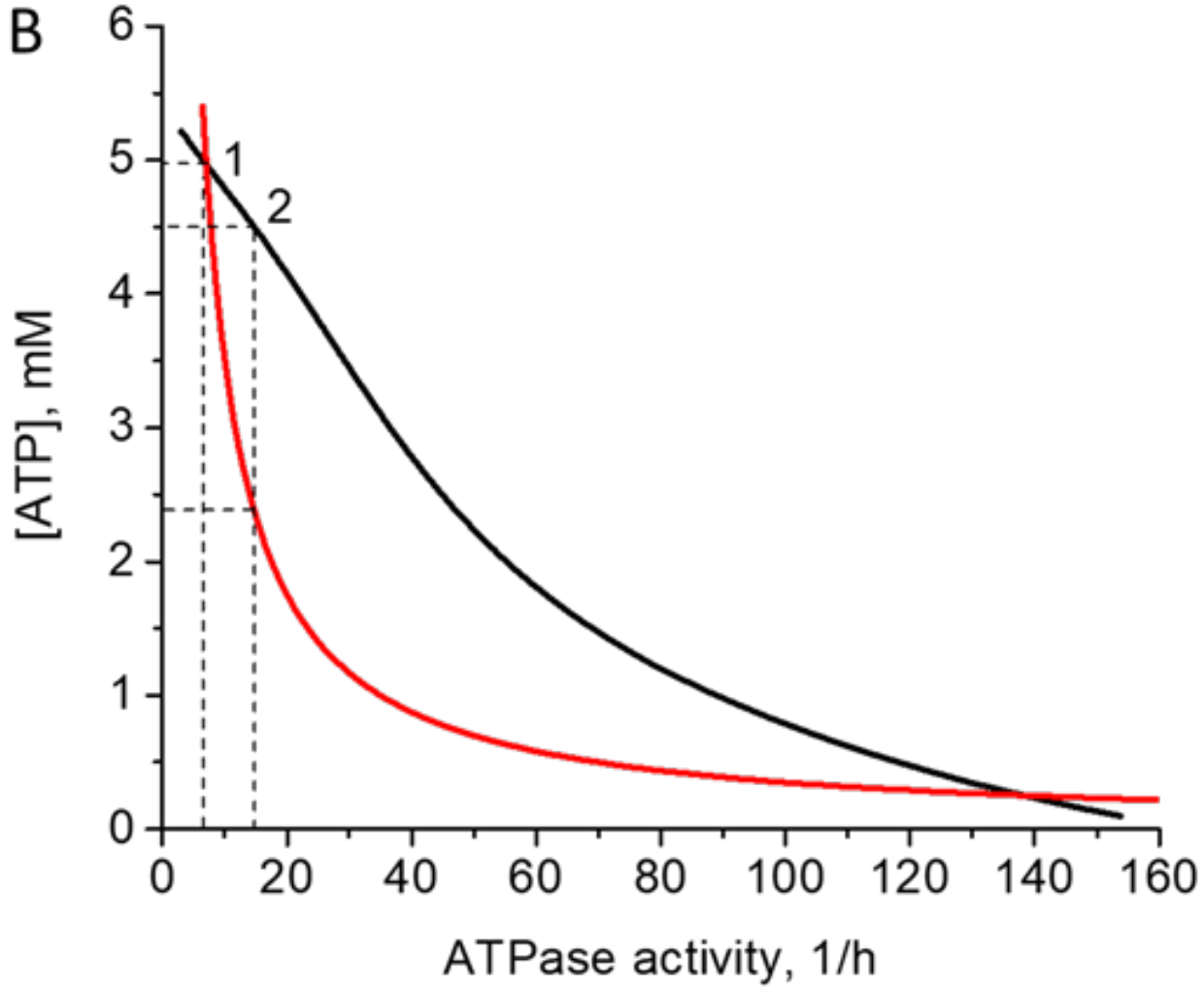
(Cohen, C.D.; Hindmarsh, A.C. CVODE, A Stiff/Nonstiff ODE Solver in C. Computers in Physics 1996, 10, 138–143.)

Steady states of the model were explored using AUTO 2000 software:

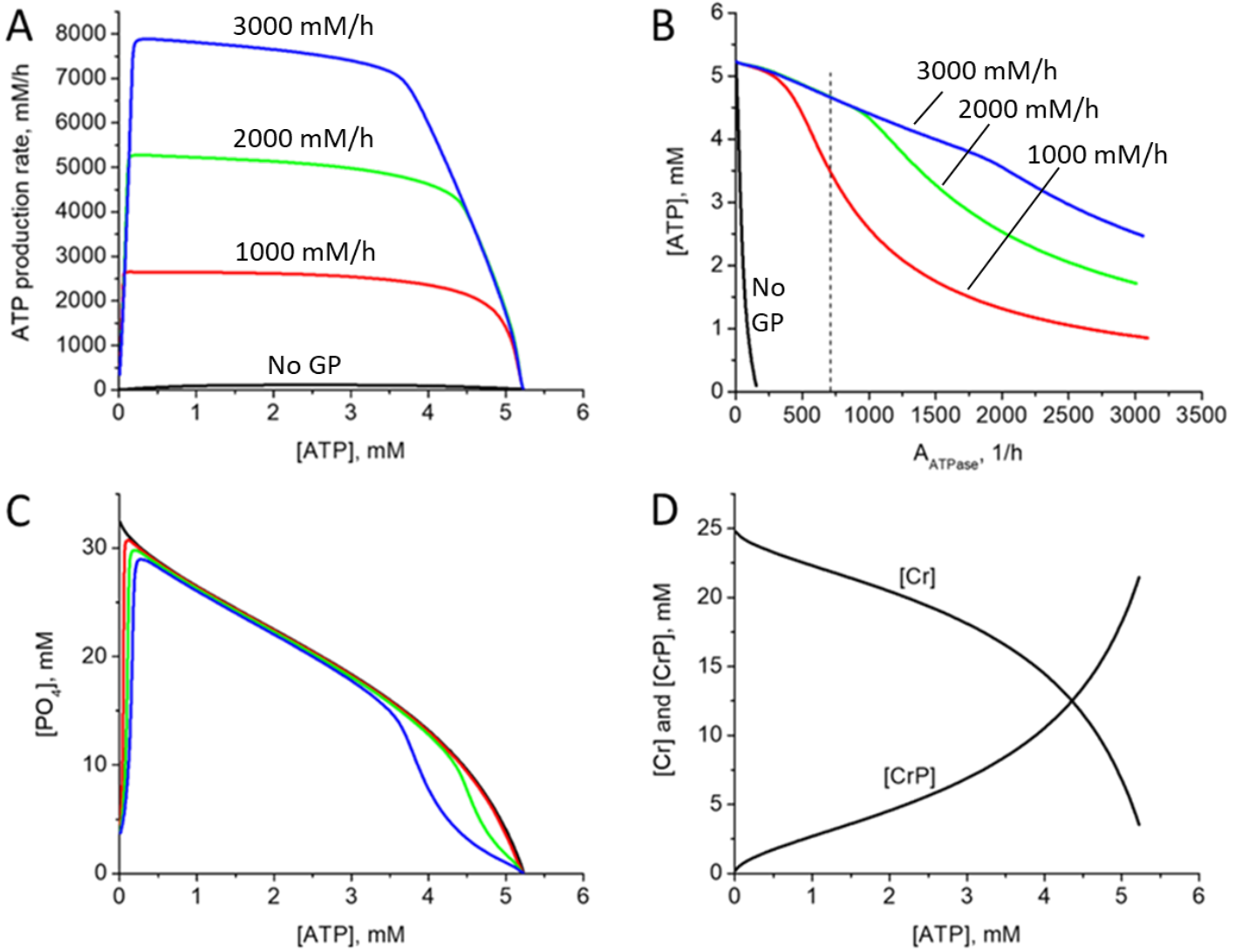
(Doedel, E.J.; Paffenroth, R.C.; Champneys, A.R.; Fairgrieve, T.F.; Kuznetsov, Y.A.; Sandstede, B.; Wang, X. AUTO 2000: Continuation and Bifurcation Software for Ordinary Differential Equations (with HomCont). Technical Report, California Institute of Technology 2001.)

Steady-state characteristics of muscle energy metabolism at zero activity of glycogen phosphorylase

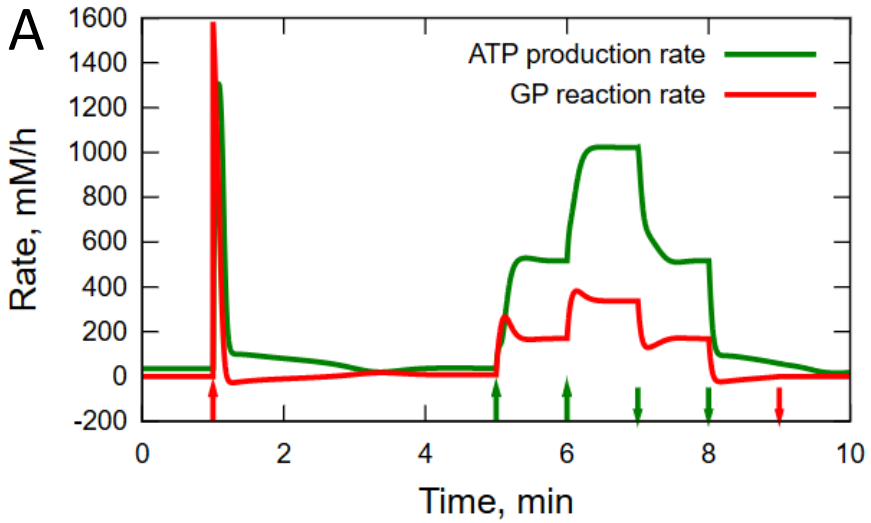


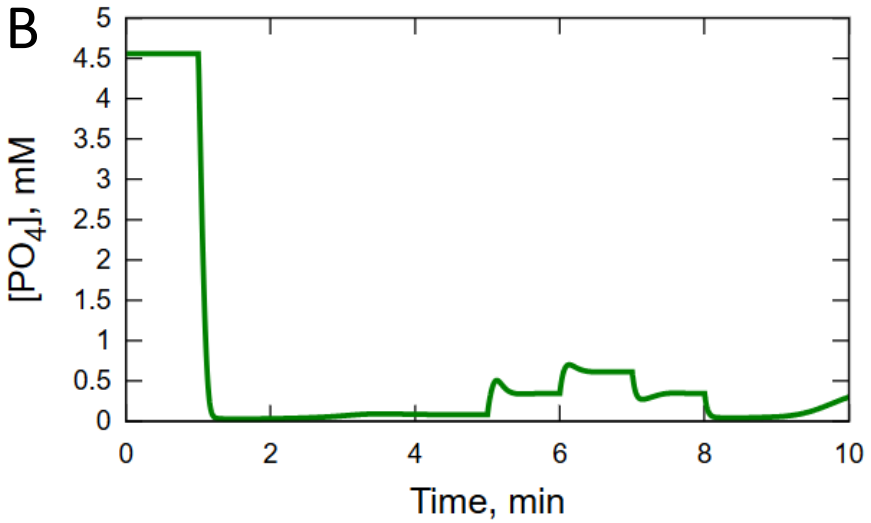


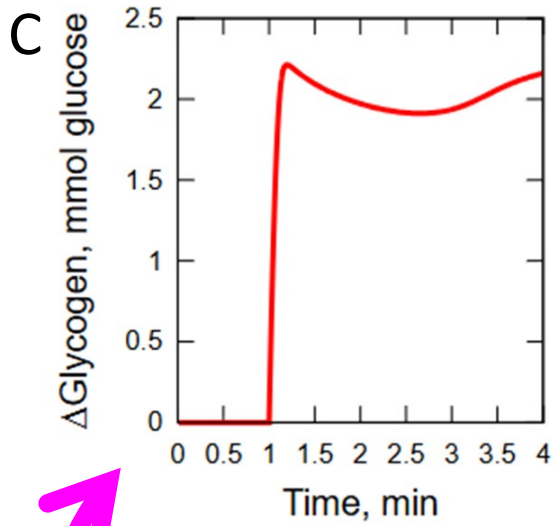
Effect of GP activation on steady-state characteristics of muscle energy metabolism

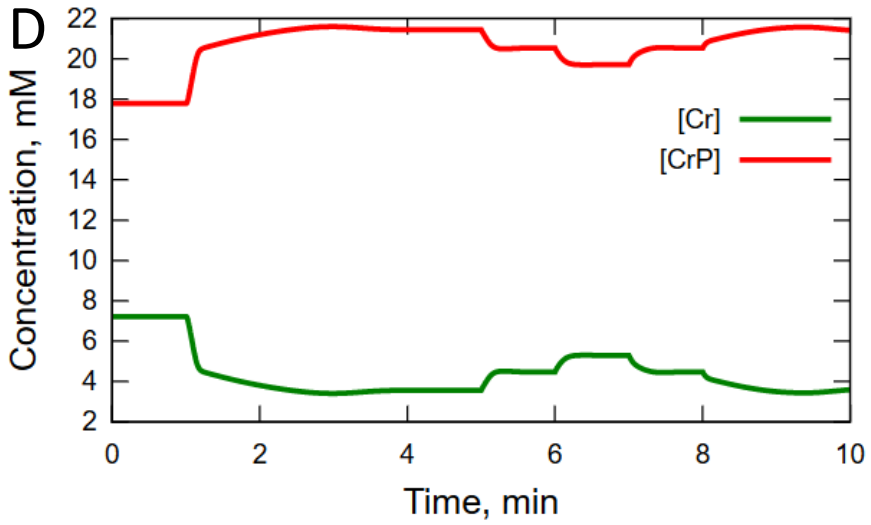


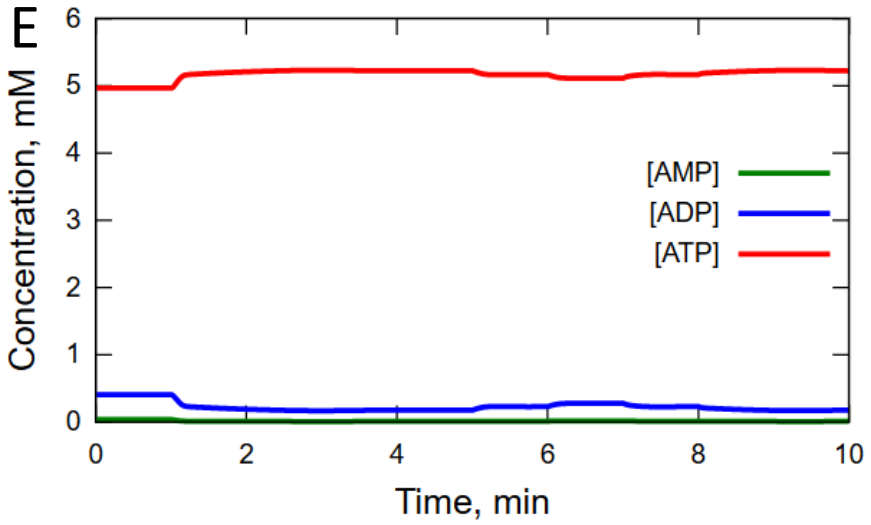
Effect of GP activation on energy metabolism in resting and contracting muscles





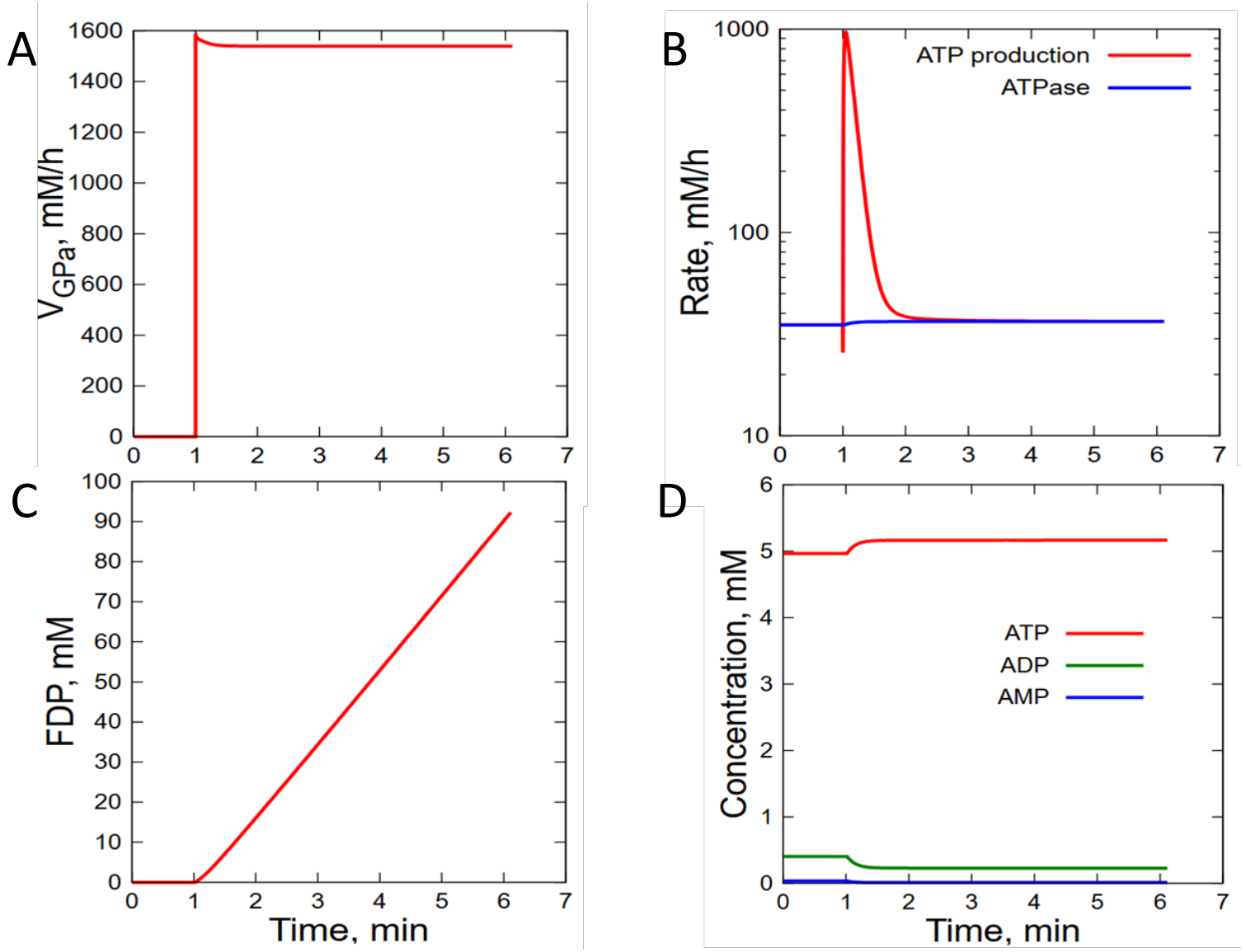






Glycogen consumed in the resting muscles after activation of glycogen phosphorylase

A prolonged increase in the GP reaction rate in the resting muscles may cause catastrophic consequences for cells



Conclusions

A steep decrease in glycolysis rate with increase in ATP concentration provides stabilization of ATP levels in cells at changes in the rate of ATP consumption.

Activation of glycogen phosphorylase in contracting muscles causes activation of glycogen consumption that provides necessary increase in ATP production rate and impoves stabilization of ATP levels.

Activation of glycogen phosphorylase in resting muscles does not cause a prolonged increase in the rate of glycogen consumption due to the rapid depletion of orthophosphate, the substrate of glycogen phosphorylase.

A prolonged increase in the rate of glycogen phosphorylase reaction in resting muscle can lead to muscle cell destruction. It appears that regulation of cellular energy metabolism protects cells from this possibility.

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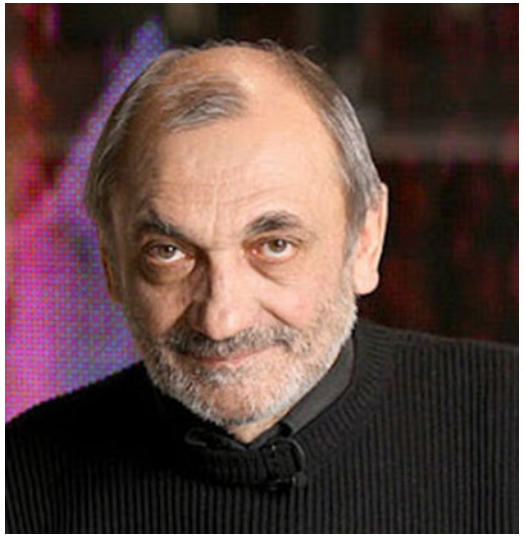

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