Configuração de redes metabólicas.

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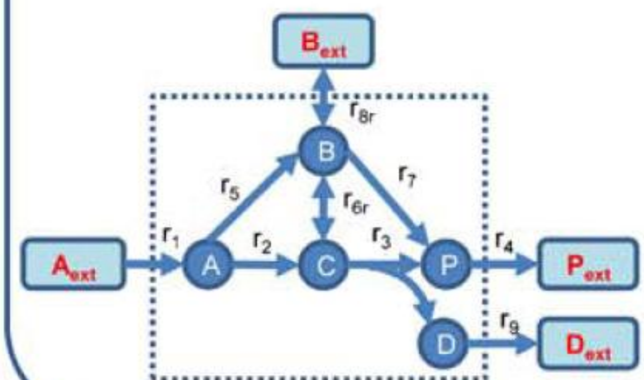
analysis of cellular metabolism

A

Problem statement

Network



Stoichiometric reactions

r_1: $A_{ext} \rightarrow A$
r_2: $A \rightarrow C$
r_3: $C \rightarrow P + D$
r_4: $P \rightarrow P_{ext}$
r_5: $A \rightarrow B$
r_{6r}: $B \leftrightarrow C$
r_7: $B \rightarrow 2P$
r_{8r}: $B \leftrightarrow B_{ext}$
r_9: $D \rightarrow D_{ext}$

Stoichiometric matrix

$\underline{\underline{S}} =$

	r_1	r_2	r_3	r_4	r_5	r_{6r}	r_7	r_{8r}	r_9
A	1	-1	0	0	-1	0	0	0	0
B	0	0	0	0	1	-1	-1	-1	0
C	0	1	-1	0	0	1	0	0	0
D	0	0	1	0	0	0	0	0	-1
P	0	0	1	-1	0	0	2	0	0

$\underline{r} = [r_1\ r_2\ r_3\ r_4\ r_5\ r_{6r}\ r_7\ r_{8r}\ r_9]^T$

Equations to solve

$\underline{\underline{S}} \cdot \underline{r} = \underline{0}$

Thermodynamic constraints:
$r_{1\text{-}5,7,9} \geq 0$

$$\frac{\mathrm{d}}{\mathrm{d}t}\underline{C} = \underline{\underline{S}} \times \underline{r} - \mu \times \underline{C},$$

μ.C (negligible)

dC/dt = 0 (steady state)

S.r = 0 (Eq 2)

ri $\geq$ 0 (Eq 3)

Tools for analysis of cellular metabolism can be grouped into three categories, all of them developed from the same mathematical model:

(1) Metabolic flux analysis,

(2) Flux balance analysis and

(3) Metabolic pathway analysis (Elementary mode analysis).

$$\begin{bmatrix} & X.W & \end{bmatrix} \bullet \begin{bmatrix} Z.Y \\ \\ \end{bmatrix} = \begin{bmatrix} X.Y \end{bmatrix}$$

$$\begin{bmatrix} a_1 & a_2 & a_3 & a_4 \\ b_1 & b_2 & b_3 & b_4 \\ c_1 & c_2 & c_3 & c_4 \end{bmatrix} \bullet \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{bmatrix} = \begin{bmatrix} \frac{da}{dt} \\ \frac{db}{dt} \\ \frac{dc}{dt} \end{bmatrix}$$

$$\frac{da}{dt} = a_1v_1 + a_2v_2 + a_3v_3 + a_4v_4$$

$$\frac{db}{dt} = b_1v_1 + b_2v_2 + b_3v_3 + b_4v_4$$

$$\frac{dc}{dt} = c_1v_1 + c_2v_2 + c_3v_3 + c_4v_4$$

Embden
Meyerhoff
Parnas

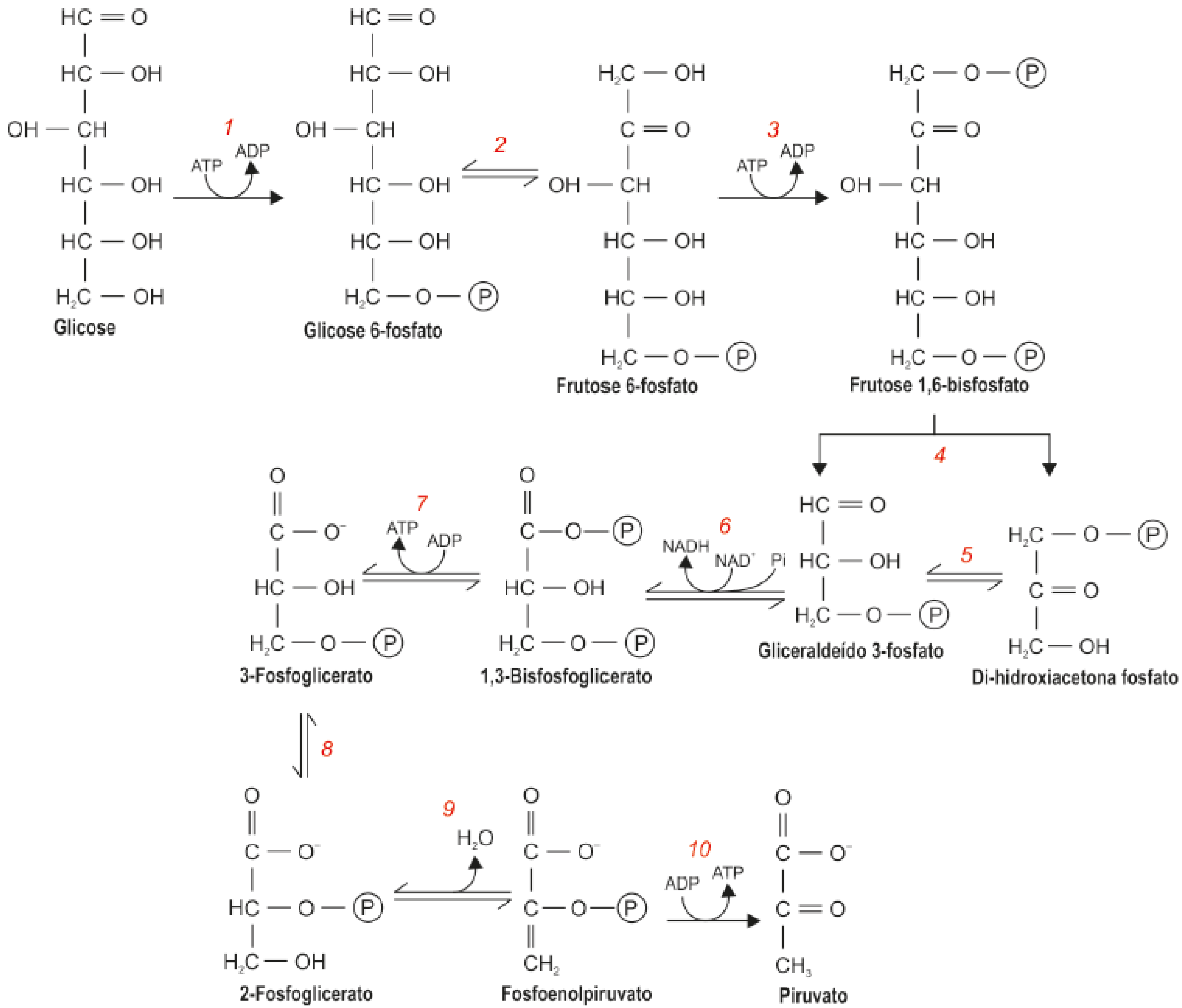


Figura 3.4 Via de Embden-Meyerhoff-Parnas.

Embden-Meyerhoff-Parnas

EMP1 : Gliext + ATP = G6P + ADP .

EMP2 : G6P = F6P .

EMP3 : F6P + ATP = F16P + ADP .

EMP4 : F16P = G3P + DHP .

EMP5 : DHP = G3P .

EMP6 : G3P + NAD = BPG13 + NADH .

EMP7 : BPG13 + ADP = PG3 + ATP .

EMP8 : PG3 = PG2 .

EMP9 : PG2 = PEP .

EMP10 : PEP + ADP = PIR + ATP .

CPD : PIR + NAD + CoASH = AcCoA + NADH + CO2 .

OXNAD : NADH + 3 ADP + O = NAD + 3 ATP .

Entner

Doudoroff

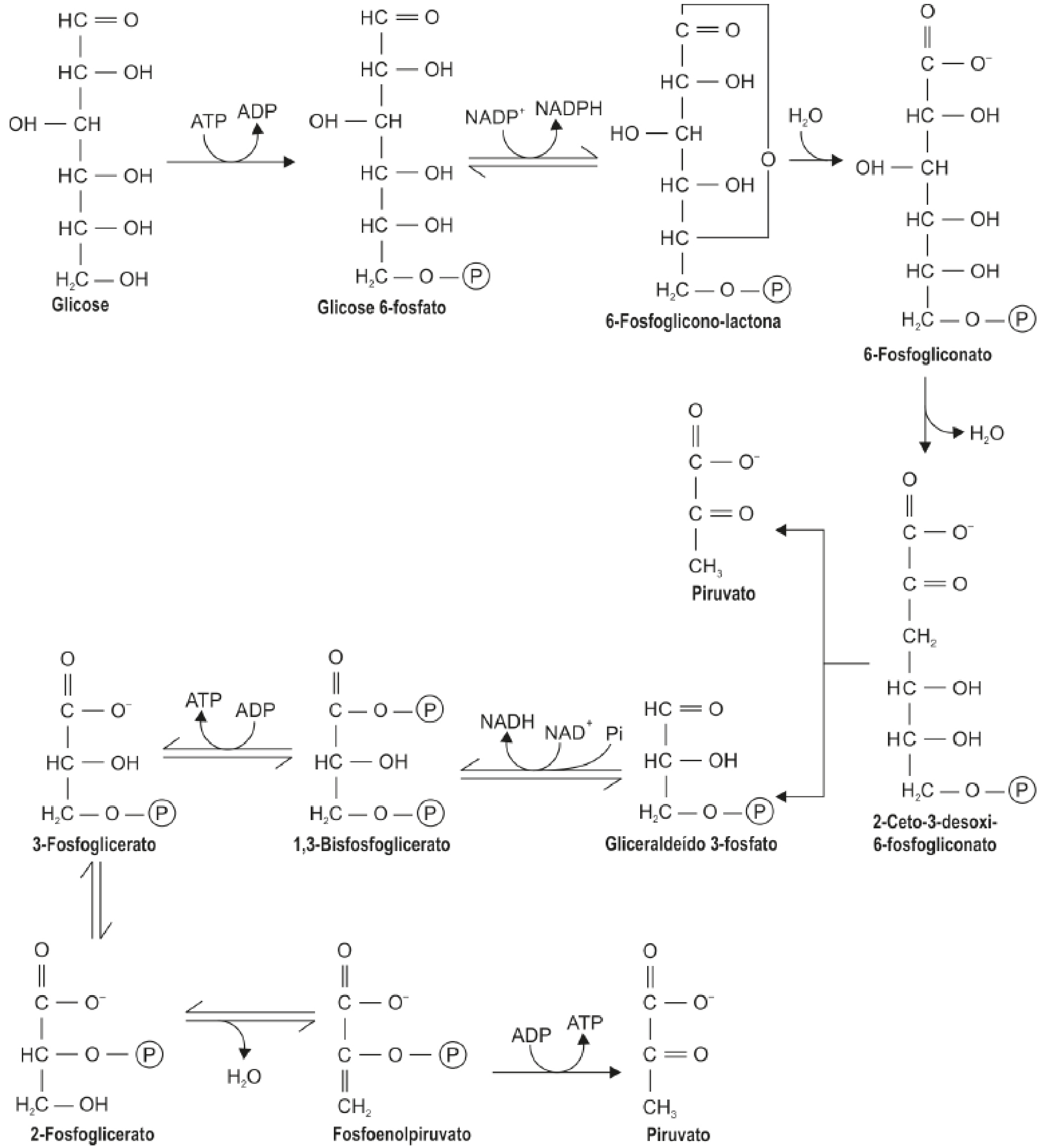


Figura 3.5 Via de Entner-Doudoroff.

Entner-Doudoroff

EMP1 : Gliext + ATP = G6P + ADP .

VP1 : G6P + NADP = PG6 + NADPH .

ED1 : PG6 = KDPG2 .

ED2 : KDPG2 = PIR + G3P .

EMP6 : G3P + NAD = BPG13 + NADH .

EMP7 : BPG13 + ADP = PG3 + ATP .

EMP8 : PG3 = PG2 .

EMP9 : PG2 = PEP .

EMP10 : PEP + ADP = PIR + ATP .

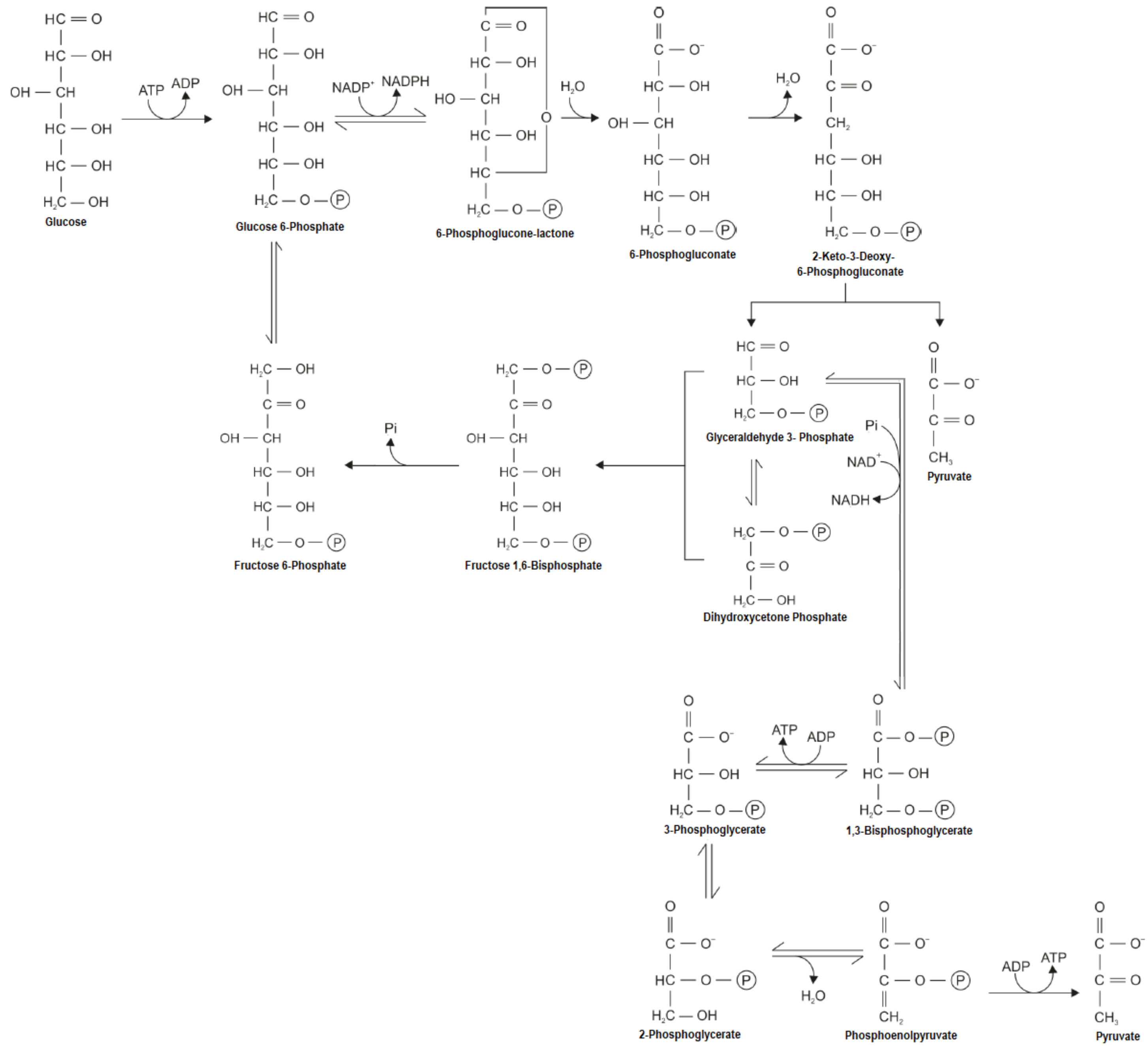
CPD : PIR + NAD + CoASH = AcCoA + NADH + CO2 .

OXNAD : NADH + 3 ADP + O = NAD + 3 ATP .

Entner

Doudoroff

cíclica



Entner-Doudoroff cíclica

EMP1 : Gliext + ATP = G6P + ADP .

VP1 : G6P + NADP = PG6 + NADPH .

ED1 : PG6 = KDPG2 .

ED2 : KDPG2 = PIR + G3P .

GLN1 : G3P = DHP .

GLN2 : G3P + DHP = F16P .

GLN3 : F16P = F6P + Pi .

GLN4 : F6P = G6P .

EMP6 : G3P + NAD = BPG13 + NADH .

EMP7 : BPG13 + ADP = PG3 + ATP .

EMP8 : PG3 = PG2 .

EMP9 : PG2 = PEP .

EMP10 : PEP + ADP = PIR + ATP .

CPD : PIR + NAD + CoASH = AcCoA + NADH + CO2 .

OXNAD : NADH + 3 ADP + O = NAD + 3 ATP .

Via das Pentoses

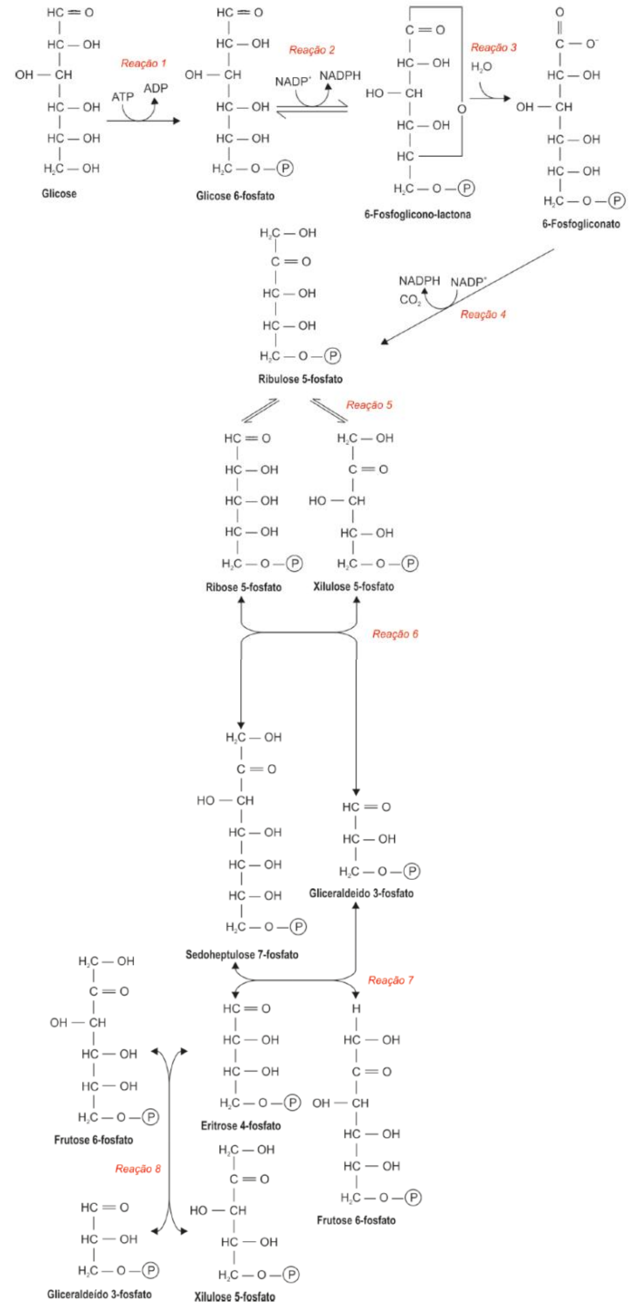


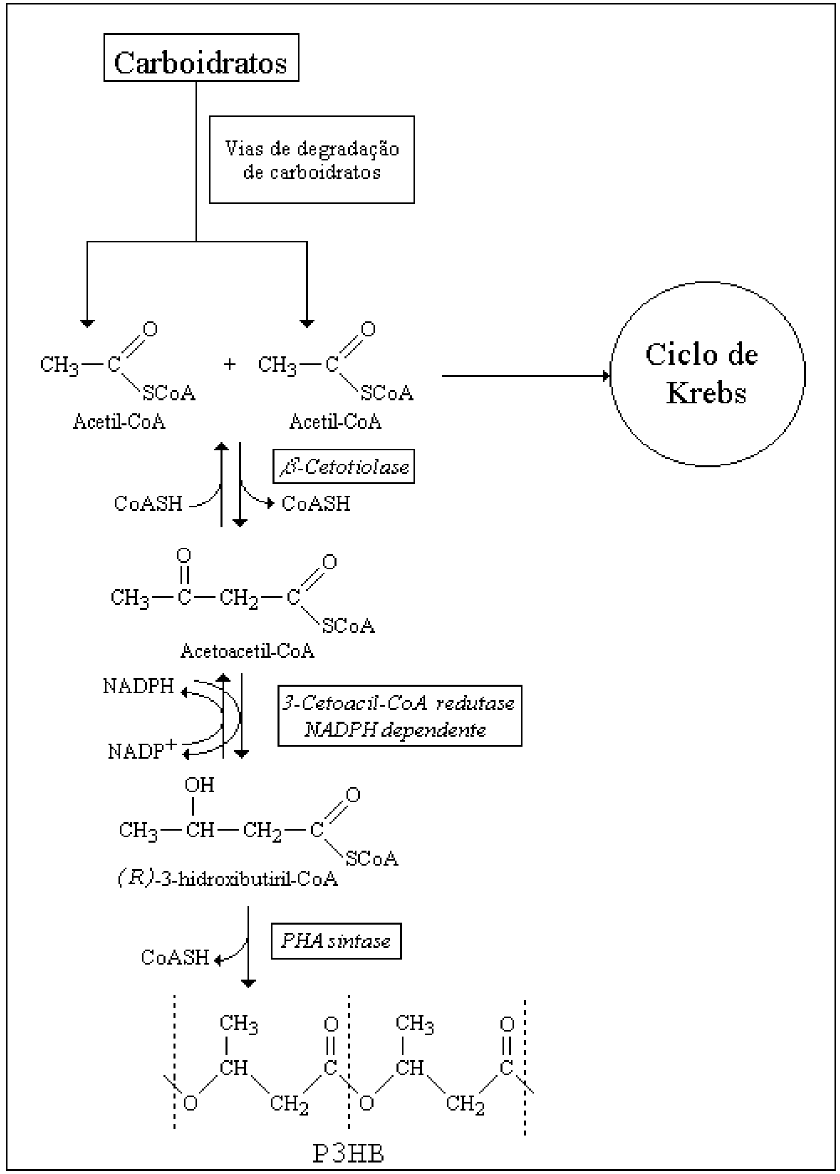
Figura 3.6 Via das pentoses.

Via das Pentoses

EMP1 : Gliext + ATP = G6P + ADP .
VP1 : G6P + NADP = PG6 + NADPH .
VP5 : PG6 + NADP = NADPH + Rbl5P + CO2 .
VP6 : Rbl5P = Rb5P .
VP7 : Rbl5P = X5P .
VP8 : Rb5P + X5P = S7P + G3P .
VP9 : G3P + S7P = E4P + F6P .
VP10 : X5P + E4P = F6P + G3P .
EMP2 : G6P = F6P .
EMP6 : G3P + NAD = BPG13 + NADH .
EMP7 : BPG13 + ADP = PG3 + ATP .
EMP8 : PG3 = PG2 .
EMP9 : PG2 = PEP .
EMP10 : PEP + ADP = PIR + ATP .
CPD : PIR + NAD + CoASH = AcCoA + NADH + CO2 .
OXNAD : NADH + 3 ADP + O = NAD + 3 ATP .

BIOMASSA : 205 G6P + 71 F6P + 897 Rb5P + 361 E4P + 129 G3P + 1496 PG3 + 519 PEP + 2833 PIR + 3748 AcCoA + 1079 KG2 + 1787 OAA + 3547 NAD + 18225 NADPH + 18485 ATP = 1 g X_R + 18485 ADP + 3547 NADH + 18225 NADP + 3748 CoASH .

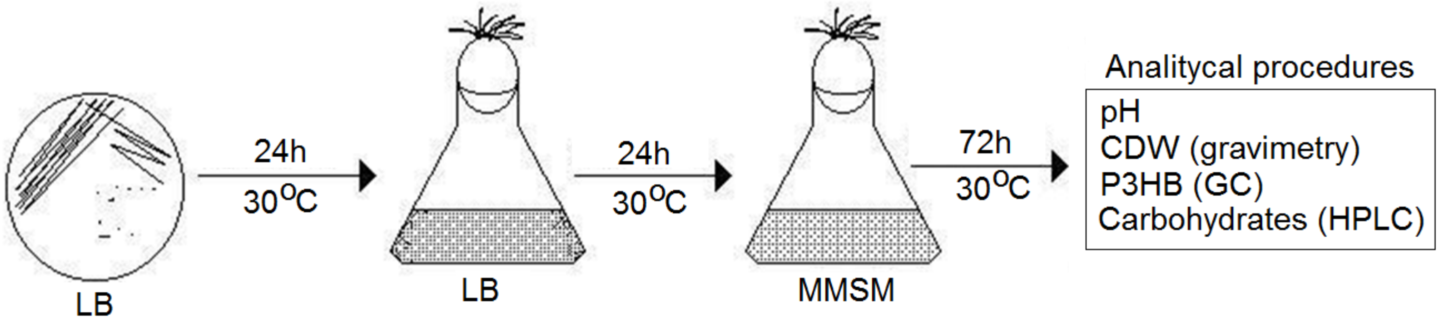
P3HB - biossíntese



P3HB - biossíntese

PHB1 : 2 AcCoA = AcAcCoA + CoASH .
PHB2 : AcAcCoA + NADPH = 3HB-CoA + CoASH + NADP .
PHB3 : 3HB-CoA = 3HB + CoASH .

P3HB production from sugarcane carbohydrates



$C_T \rightarrow Y^{G}_{P/C} = \frac{X_{HB}}{C_T}$

$C_T \rightarrow C_C \rightarrow Y_{X_R/C_C} = \frac{X_R}{C_C}$

$C_T \rightarrow C_{HA1} \rightarrow Y_{X_{HB}/C_{HB}} = \frac{X_{HB}}{C_{HB}}$

$$Y^{O}_{P/C} = \frac{PHB}{PHB\left(\frac{1}{Y^{T}_{P/C}} - \frac{1}{Y_{X/C}}\right) + \frac{100}{Y_{X/C}}}$$

$C_T = C_C + C_{HB}$

$$\frac{X_{HB}}{Y^{G}_{P/C}} = \frac{X_R}{Y_{X_R/C_C}} + \frac{X_{HB}}{Y_{X_{HB}/C_{HB}}}$$

Dividir por XT e
multiplicar por 100

$$\frac{\%PHB}{Y^{G}_{P/C}} = \frac{\%CEL}{Y_{X_R/C_C}} + \frac{\%PHB}{Y_{X_{HB}/C_{HB}}}$$

$$Y^{G}_{P/C} = \frac{\%PHB}{\frac{100}{Y_{X_R/C_C}} - \frac{\%PHB}{Y_{X_R/C_C}} + \frac{\%PHB}{Y_{X_{HB}/C_{HB}}}}$$

Gomez et al., 1996

$$Y^{O}_{P/C} = \frac{PHB}{PHB\left(\frac{1}{Y^{T}_{P/C}} - \frac{1}{Y_{X/C}}\right) + \frac{100}{Y_{X/C}}}$$

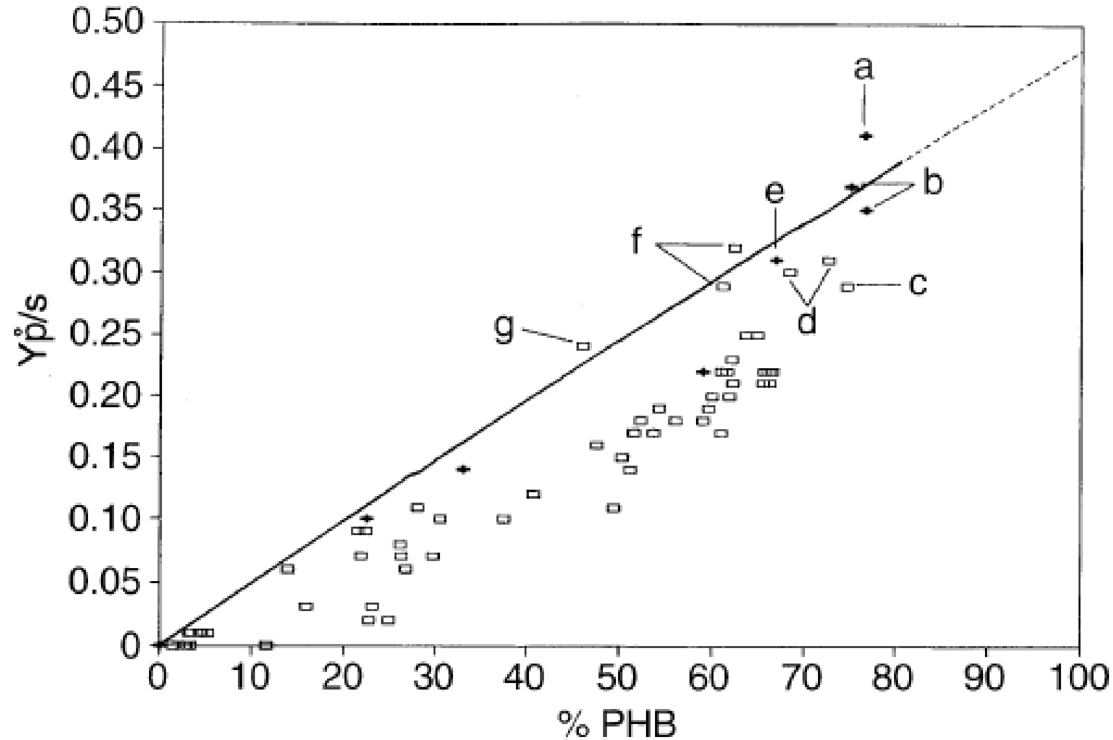


Fig. 1 Relation between $Y^{O}_{P/C}$ and poly-(3-hydroxybutyrate) (*PHB*) content for different strains isolated from soil (□) or obtained from the culture collection (+) when glucose plus fructose was used as the carbon source. The line represents the values expected when $Y^{T}_{P/C} = 0.48$ g/g and $Y_{X/C} = 0.50$ g/g. Points related to strains *A. latus* DSM 1123 (*a*), *A. eutrophus* DSM 545 (*b*), IPT-101 (*c*), IPT-083 (*d*), *A. eutrophus* DSM 428 (*e*), IPT-086 (*f*), and IPT-055 (*g*) are indicated

Gomez et al., 1996

$$Y_{P/C}^{O} = \frac{PHB}{PHB\left(\frac{1}{Y_{P/C}^{T}} - \frac{1}{Y_{X/C}}\right) + \frac{100}{Y_{X/C}}}$$

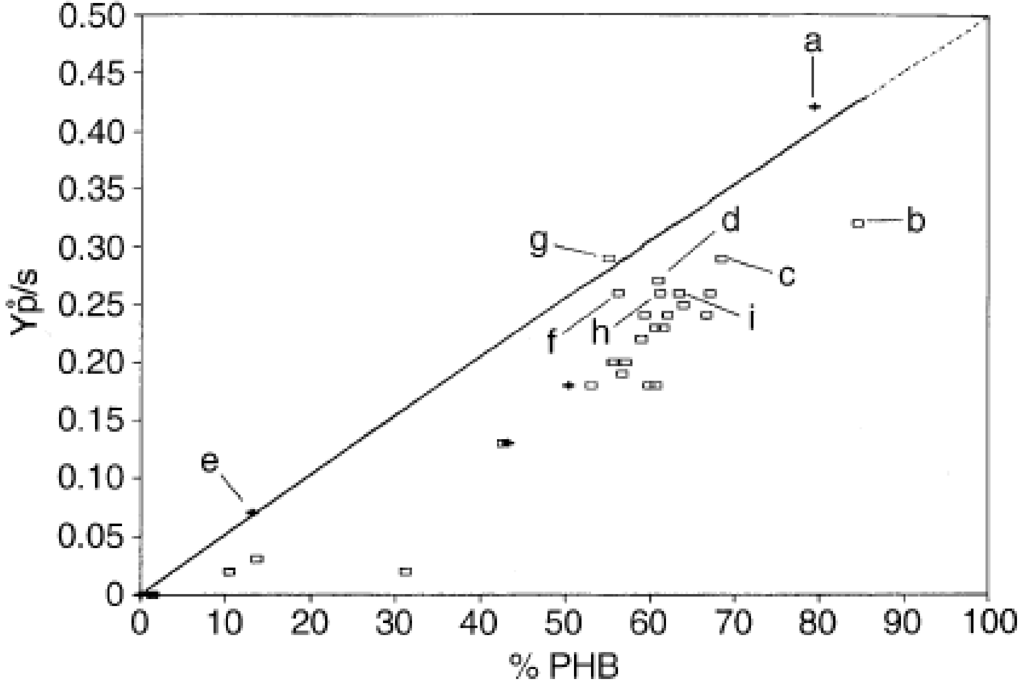


Fig. 2 Relation between $Y_{P/C}^{O}$ and PHB content for different strains isolated from soil (□) or obtained from the culture collection (+) when sucrose was used as the carbon source. The line represents the expected values when $Y_{P/C}^{T} = 0.50$ g/g and $Y_{X/C} = 0.52$ g/g. Points related to strains *A. latus* DSM 1123 (*a*), IPT-044 (*b*), IPT-101 (*c*), IPT-083 (*d*), *A. latus* DSM 1122 (*e*), IPT-076 (*f*), IPT-055 (*g*), IPT-040 (*h*), and IPT-045 (*i*) are indicated

Gomez et al., 1996