Problem 9.2 of Shuler & Kargi. Batch fermentor operated in two stages.
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Cell growth parameters:

$\mu_{m1} := 0.3\ h^{-1}$ $\mu_{m2} := 0$ $K_s := 0.1$ g/liter $Y_x := 0.4$ g cell/g substrate

$\mu_1(s) := \frac{\mu_{m1} \cdot s}{K_s + s}$ $\mu_2(s) := \frac{\mu_{m2} \cdot s}{K_s + s}$

Product formation parameters:

$Y_p := 0.6$ g product/g substrate $q_p := 0.02$ g product/(g cell·h)

Initial condition $x_0 := 0.1$ $s_0 := 5$ $y_0 := 0$ $p_0 := 0$ $n := 100$ $xsp_0 := \begin{pmatrix} x_0 \\ s_0 \\ p_0 \end{pmatrix}$

Dynamic equations for the first phase of batch fermentor.

$dx1dt(x,s) := (0 \le s)\cdot(0 \le x)\cdot\mu_1(s)\cdot x$

$ds1dt(x,s) := (0 \le s)\cdot(0 \le x)\cdot -\frac{1}{Y_x}\cdot\mu_1(s)\cdot x$

$dp1dt(x,s) := 0$

$dxs1dt(t,xs) := \begin{pmatrix} dx1dt(xs_0, xs_1) \\ ds1dt(xs_0, xs_1) \\ dp1dt(xs_0, xs_1) \end{pmatrix}$

Dynamic equations for the second phase of batch fermentor.

$dx2dt(x,s) := (0 \le s)\cdot(0 \le x)\cdot\mu_2(s)\cdot x$

$ds2dt(x,s) := (0 \le s)\cdot(0 \le x)\cdot\left(-\frac{1}{Y_x}\cdot\mu_2(s)\cdot x - \frac{1}{Y_p}\cdot q_p\cdot x\right)$

$dp2dt(x,s) := (0 \le s)\cdot(0 \le x)\cdot q_p\cdot x$

$dxsp2dt(t,xsp) := \begin{pmatrix} dx2dt(xsp_0, xsp_1) \\ ds2dt(xsp_0, xsp_1) \\ dp2dt(xsp_0, xsp_1) \end{pmatrix}$

Integrate 2 ODEs sequentially

$txsp(t_{f1}, t_{f2}) :=$
- $txsp1 \leftarrow rkfixed(xsp_0, 0, t_{f1}, n, dxs1dt)$
- $txsp2 \leftarrow rkfixed\left[\begin{pmatrix} txsp1_{n,1} \\ txsp1_{n,2} \\ txsp1_{n,3} \end{pmatrix}, t_{f1}, t_{f2}, n, dxsp2dt\right]$
- return stack(txsp1, txsp2)

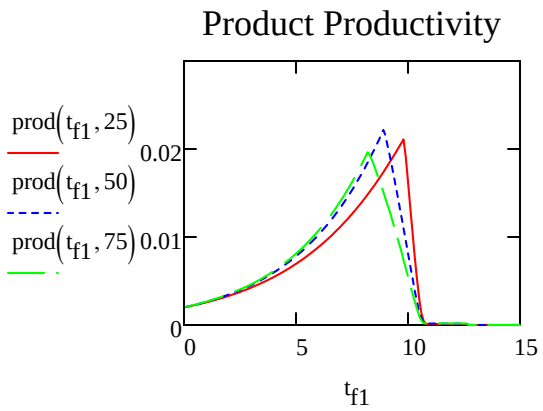
$final := 2\cdot n + 1$

$p_f(t_{f1}, t_{f2}) := txsp(t_{f1}, t_{f2})_{final,3}$

$prod(t_{f1}, t_{f2}) := \frac{p_f(t_{f1}, t_{f2})}{t_{f2}}$

Maximize product productivity

$t_{f1} := 0, 0.1 .. 15$

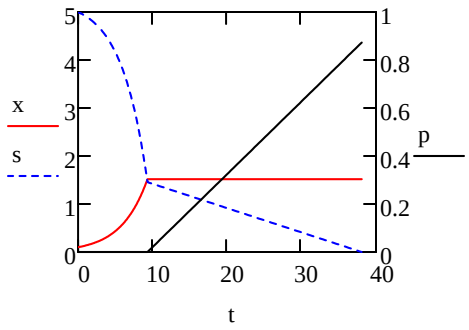


Provide initial guess $t_{f1} := 10$ $t_{f2} := 50$ $prod(t_{f1}, t_{f2}) = 8.147 \times 10^{-3}$

$\begin{pmatrix} t_{f1} \\ t_{f2} \end{pmatrix} := Maximize(prod, t_{f1}, t_{f2}) = \begin{pmatrix} 9.318 \\ 38.063 \end{pmatrix}$ $prod(t_{f1}, t_{f2}) = 0.023$

The productivity in 2 CSTRs in series was 0.027 g/(L·h)

profile $txsp := txsp(t_{f1}, t_{f2})$ $(t \ x \ s \ p) := \left(txsp^{\langle 0 \rangle} \ txsp^{\langle 1 \rangle} \ txsp^{\langle 2 \rangle} \ txsp^{\langle 3 \rangle}\right)$



The product is encoded in a plasmid. Upon cell division, there is a small probability P=0.001 of a plasmid-bearing cell x producing a plasmid-free offspring y.

$P := 0.001$

$dx1_{dt}(x, y, s) := (0 \le s) \cdot (0 \le x) \cdot (1 - P) \cdot \mu_1(s) \cdot x$

$dy1_{dt}(x, y, s) := (0 \le s) \cdot (0 \le x) \cdot \mu_1(s) \cdot y + P \cdot \mu_1(s) \cdot x$

$ds1_{dt}(x, y, s) := (0 \le s) \cdot (0 \le x) \cdot \left(-\frac{1}{Y_x} \cdot \mu_1(s) \cdot x - \frac{1}{Y_x} \cdot \mu_1(s) \cdot y\right)$

$dp1_{dt}(x, y, s) := 0$

I.C. $xysp_0 := \begin{pmatrix} x_0 \\ y_0 \\ s_0 \\ p_0 \end{pmatrix}$

$$dxysp1_{dt}(t, xysp) := \begin{pmatrix} dx1_{dt}(xysp_0, xysp_1, xysp_2) \\ dy1_{dt}(xysp_0, xysp_1, xysp_2) \\ ds1_{dt}(xysp_0, xysp_1, xysp_2) \\ dp1_{dt}(xysp_0, xysp_1, xysp_2) \end{pmatrix}$$

$$dx2_{dt}(x, y, s) := (0 \le s)\cdot(0 \le x)\cdot(1 - P)\cdot\mu_2(s)\cdot x$$

$$dy2_{dt}(x, y, s) := (0 \le s)\cdot(0 \le x)\cdot\mu_1(s)\cdot y + P\cdot\mu_2(s)\cdot x$$

$$ds2_{dt}(x, y, s) := (0 \le s)\cdot(0 \le x)\cdot\left(-\frac{1}{Y_x}\cdot\mu_2(s)\cdot x - \frac{1}{Y_x}\cdot\mu_1(s)\cdot y - \frac{1}{Y_p}\cdot q_p\cdot x\right)$$

$$dp2_{dt}(x, y, s) := (0 \le s)\cdot(0 \le x)\cdot q_p\cdot x$$

$$dxysp2_{dt}(t, xysp) := \begin{pmatrix} dx2_{dt}(xysp_0, xysp_1, xysp_2) \\ dy2_{dt}(xysp_0, xysp_1, xysp_2) \\ ds2_{dt}(xysp_0, xysp_1, xysp_2) \\ dp2_{dt}(xysp_0, xysp_1, xysp_2) \end{pmatrix}$$

$$txysp(t_{f1}, t_{f2}) := \left| \begin{array}{l} txysp1 \leftarrow rkfixed(xysp_0, 0, t_{f1}, n, dxysp1_{dt}) \\ txysp2 \leftarrow rkfixed\left[\begin{pmatrix} txysp1_{n,1} \\ txysp1_{n,2} \\ txysp1_{n,3} \\ txysp1_{n,4} \end{pmatrix}, t_{f1}, t_{f2}, n, dxysp2_{dt}\right] \\ return\ \ stack(txysp1, txysp2) \end{array} \right.$$

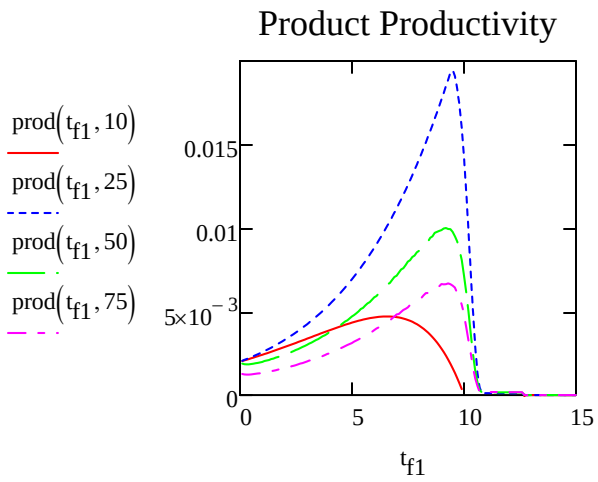
$$final := 2\cdot n + 1$$

$$p_f(t_{f1}, t_{f2}) := txysp(t_{f1}, t_{f2})_{final,4}$$

$$prod(t_{f1}, t_{f2}) := \frac{p_f(t_{f1}, t_{f2})}{t_{f2}}$$

Maximize product productivity

$$t_{f1} := 0, 0.1 .. 15$$



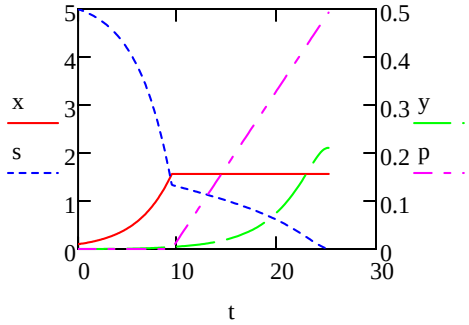
Provide initial guess $t_{f1} := 5$ $t_{f2} := 20$ $prod(t_{f1}, t_{f2}) = 6.505 \times 10^{-3}$

$\begin{pmatrix} t_{f1} \\ t_{f2} \end{pmatrix} := Maximize(prod, t_{f1}, t_{f2}) = \begin{pmatrix} 9.429 \\ 25.24 \end{pmatrix}$ $prod(t_{f1}, t_{f2}) = 0.02$

Optimal profile

$profile := txysp(t_{f1}, t_{f2})$ $(t\ x\ y\ s\ p) := (profile^{\langle 0 \rangle}\ profile^{\langle 1 \rangle}\ profile^{\langle 2 \rangle}\ profile^{\langle 3 \rangle}\ profile^{\langle 4 \rangle})$

Optimum Profile



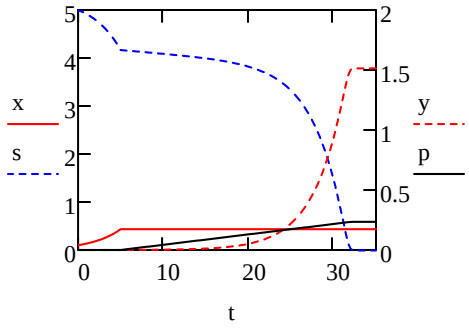
Fraction of plasmid-free cells at end of the run

$\frac{y_{final}}{x_{final} + y_{final}} = 0.119$

Sub optimal profile $t_{f1} := 5$ $t_{f2} := 35$

$profile := txysp(t_{f1}, t_{f2})$ $(t\ x\ y\ s\ p) := (profile^{\langle 0 \rangle}\ profile^{\langle 1 \rangle}\ profile^{\langle 2 \rangle}\ profile^{\langle 3 \rangle}\ profile^{\langle 4 \rangle})$

Induction at 5h



product concentration at end of the run

$p_f := profile_{final,4} = 0.235$ g/L

Fraction of plasmid-free cells at end of the run

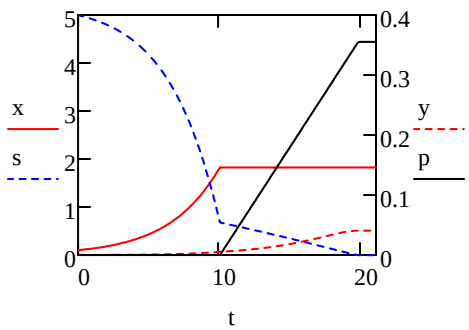
$\frac{y_{final}}{x_{final} + y_{final}} = 0.777$

Fermentation time for 5-h induction was longer than that for 10-h induction (~32h versus ~20h). Product concentration for 5-h induction was lower than that for 10-h induction (0.235 g/L versus 0.355 g/L). 5-h induction led to a fermentor full of nonproductive plasmid-free cells, the fraction of nonproductive plasmid-free cells being 0.777 for 5-h induction versus 0.022 for 10-h induction.

Sub optimal profile $t_{f1} := 10$ $t_{f2} := 21$

$profile := txysp(t_{f1}, t_{f2})$ $(t\ x\ y\ s\ p) := (profile^{\langle 0 \rangle}\ profile^{\langle 1 \rangle}\ profile^{\langle 2 \rangle}\ profile^{\langle 3 \rangle}\ profile^{\langle 4 \rangle})$

Induction at 10h



product concentration at end of the run

$p_f := profile_{final,4} = 0.355$ g/L

Fraction of plasmid-free cells at end of the run

$\frac{y_{final}}{x_{final} + y_{final}} = 0.022$