Batch Fermentation /w pH Inhibition. Model parameter estimation from dynamic data.
Instructor: Nam Sun Wang

Model parameters

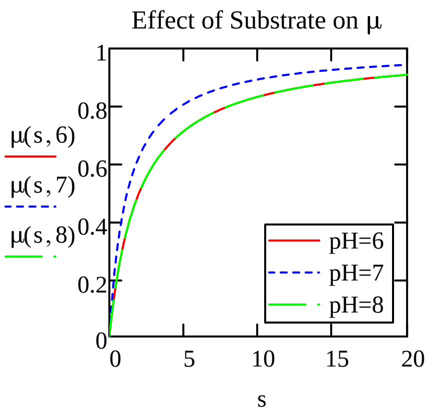
$\mu_m := 1$ hr^{-1} $K_s := 1$ g/L $pK_1 := 6$ $K_1 := 10^{-pK_1}$

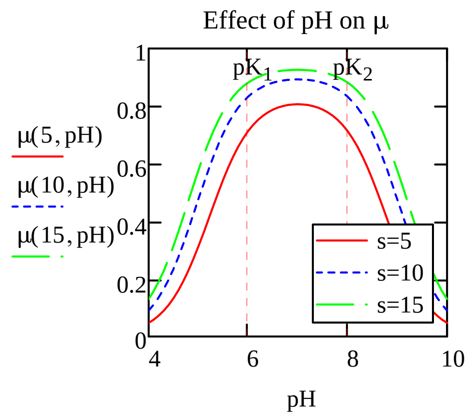
$Y_x := 0.5$ g biomass/g substrate $pK_2 := 8$ $K_2 := 10^{-pK_2}$

$$\mu(s,H) = \frac{\mu_m \cdot s}{K_s \cdot \left(1 + \frac{H}{K_1} + \frac{K_2}{H}\right) + s} \qquad \mu(s,pH) := \frac{\mu_m \cdot s}{K_s \cdot \left(1 + 10^{-pH+pK_1} + 10^{-pK_2+pH}\right) + s}$$

Product formation $\alpha := 10^{-5}$ mole H/g biomass $\beta := 10^{-7}$ mole H/(hr·g biomass)

$s := 0, 0.1 .. 20$ $pH := 4, 4.1 .. 10$





This organism is actually quite pH tolerant. It grows over a very wide pH range.

Simulate batch fermentation. Initial condition $x_0 := 0.1$ g/L $s_0 := 10$ g/L $H_0 := 10^{-9}$ mole/L

ODEs $pH_0 := -\log(H_0) = 9$

$dxdt(x,s,H) := \mu(s,-\log(H)) \cdot x$ ... biomass

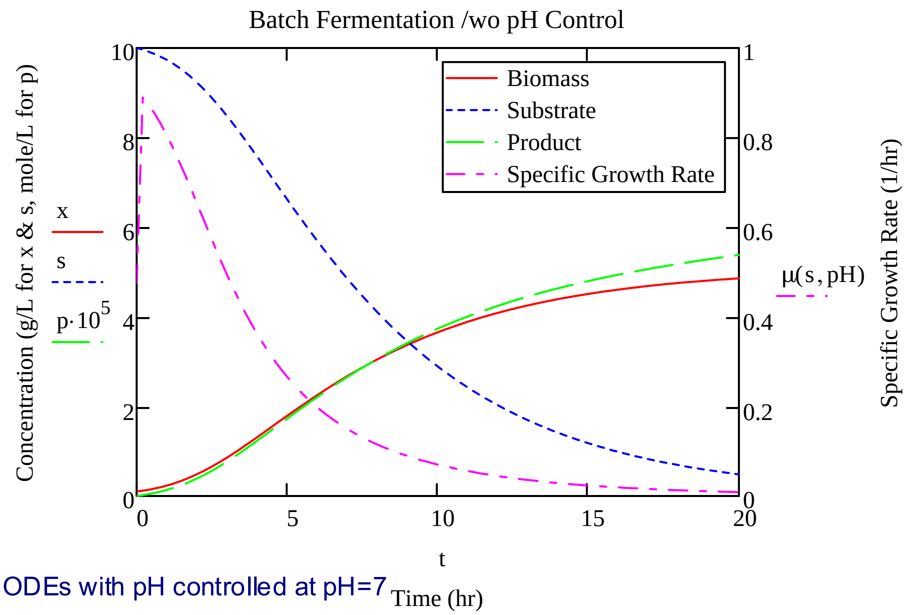
$dsdt(x,s,H) := -\frac{1}{Y_x} \cdot \mu(s,-\log(H)) \cdot x$ ... substrate

$dHdt(x,s,H) := \alpha \cdot \mu(s,-\log(H)) \cdot x + \beta \cdot x$ ... product (which is directly related to H)

$$dydt(t,y) := \begin{pmatrix} dxdt(y_0,y_1,y_2) \\ dsdt(y_0,y_1,y_2) \\ dHdt(y_0,y_1,y_2) \end{pmatrix} \qquad \text{I.C.} \quad y_{init} := \begin{pmatrix} x_0 \\ s_0 \\ H_0 \end{pmatrix}$$

Length of time to complete fermentation $t_f := 20$ $n := 100$

$ty := rkfixed(y_{init}, 0, t_f, n, dydt)$ $t := ty^{\langle 0 \rangle}$ $x := ty^{\langle 1 \rangle}$ $s := ty^{\langle 2 \rangle}$ $H := ty^{\langle 3 \rangle}$ $pH := \overrightarrow{-\log(H)}$ $p := H$



ODEs with pH controlled at pH=7

$\mathrm{dxdt}(x,s,p) := \mu(s,7)\cdot x$ ... biomass

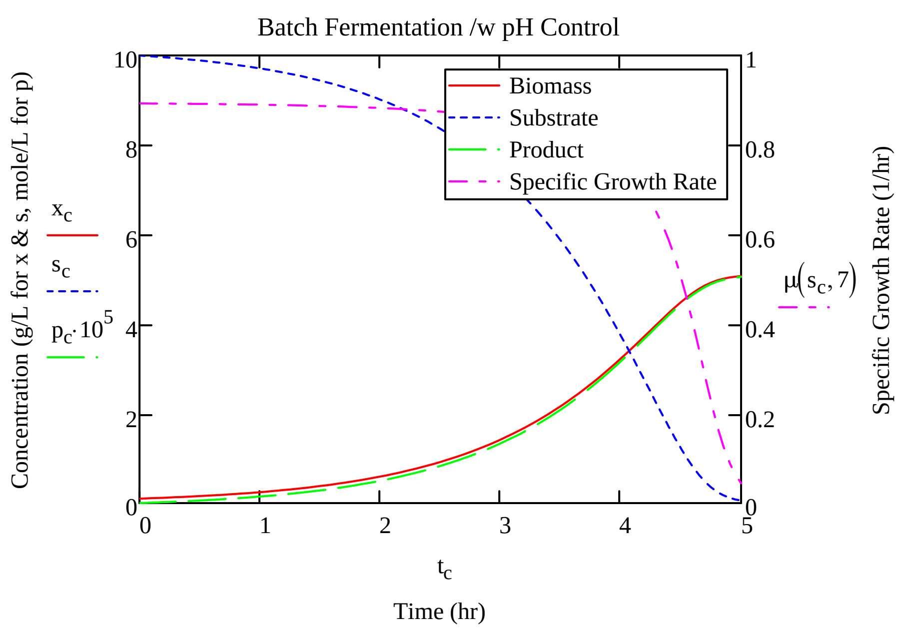
$\mathrm{dsdt}(x,s,p) := -\frac{1}{Y_x}\cdot\mu(s,7)\cdot x$ ... substrate

$\mathrm{dpdt}(x,s,p) := \alpha\cdot\mu(s,7)\cdot x + \beta\cdot x$ ... product

$$\mathrm{dydt}(t,y) := \begin{pmatrix}\mathrm{dxdt}(y_0,y_1,y_2)\\ \mathrm{dsdt}(y_0,y_1,y_2)\\ \mathrm{dpdt}(y_0,y_1,y_2)\end{pmatrix} \qquad \text{I.C.} \qquad y_{init} := \begin{pmatrix}x_0\\ s_0\\ H_0\end{pmatrix}$$

Length of time to complete fermentation $t_{fc} := 5$

$ty_c := \mathrm{rkfixed}(y_{init}, 0, t_{fc}, n, \mathrm{dydt}) \qquad t_c := ty_c^{\langle 0\rangle} \qquad x_c := ty_c^{\langle 1\rangle} \qquad s_c := ty_c^{\langle 2\rangle} \qquad p_c := ty_c^{\langle 3\rangle}$



Note that biomass and product concentrations closely match, because product formation is dominated by the growth-related term α·μ·x.

Without pH control, fermentation lasted $t_f = 20\,\text{hr}$ Product productivity $\dfrac{H_n - H_0}{t_f} = 2.69 \times 10^{-6}$ mole/(L·l

With pH control, fermentation lasted $t_{fc} = 5\,\text{hr}$ Product productivity $\dfrac{p_n - H_0}{t_{fc}} = 1.076 \times 10^{-5}$ mole/(L·l

Product productivity with pH control is ~5X higher than that without pH control.

Estimate Model Parameter from Dynamic Data. Estimate 4 model parameters simultaneously.

$p := (\mu_m \;\; K_s)^T$

$$
ty(p) := \left|
\begin{array}{l}
(\mu_m \;\; K_s) \leftarrow p^T \\
\mu(s,pH) \leftarrow \dfrac{\mu_m \cdot s}{K_s \cdot \left(1 + 10^{-pH+pK_1} + 10^{-pK_2+pH}\right) + s} \\
dxdt(x,s,H) \leftarrow \mu(s,-\log(H)) \cdot x \\
dsdt(x,s,H) \leftarrow -\dfrac{1}{Y_x} \cdot \mu(s,-\log(H)) \cdot x \\
dHdt(x,s,H) \leftarrow \alpha \cdot \mu(s,-\log(H)) \cdot x + \beta \cdot x \\
dydt(t,y) \leftarrow \begin{pmatrix} dxdt(y_0,y_1,y_2) \\ dsdt(y_0,y_1,y_2) \\ dHdt(y_0,y_1,y_2) \end{pmatrix} \\
ty \leftarrow rkfixed(y_{init}, 0, t_f, n, dydt)
\end{array}\right.
$$

True: $ty_m := ty(p) \quad t := ty_m^{\langle 0 \rangle} \quad x_m := ty_m^{\langle 1 \rangle} \quad s_m := ty_m^{\langle 2 \rangle} \quad H_m := ty_m^{\langle 3 \rangle} \quad pH_m := -\log(H_m)$

$$
sse(p) := \left|
\begin{array}{l}
ty \leftarrow ty(p) \\
(x \;\; s \;\; H) \leftarrow \left(ty^{\langle 1 \rangle} \;\; ty^{\langle 2 \rangle} \;\; ty^{\langle 3 \rangle}\right) \\
pH \leftarrow -\log(H) \\
sse \leftarrow (x - x_m) \cdot (x - x_m) + (s - s_m) \cdot (s - s_m) + (pH - pH_m) \cdot (pH - pH_m)
\end{array}\right.
$$

True value: $p^T = (1 \;\; 1)$

Initial guess: $p := (10 \;\; 10)^T \quad sse(p) = 308.744$

Estimated value: $p := Minimize(sse, p) = \begin{pmatrix} 1 \\ 1 \end{pmatrix} \quad sse(p) = 1.933 \times 10^{-11}$ ... Good!

Estimate 4 model parameters simultaneously.

$$p := (\mu_m \;\; K_s \;\; pK_1 \;\; pK_2)^T$$

$$ty(p) := \left| \begin{array}{l} (\mu_m \;\; K_s \;\; pK_1 \;\; pK_2) \leftarrow p^T \\ \mu(s,pH) \leftarrow \dfrac{\mu_m \cdot s}{K_s \cdot \left(1 + 10^{-pH+pK_1} + 10^{-pK_2+pH}\right) + s} \\ dxdt(x,s,H) \leftarrow \mu(s,-\log(H)) \cdot x \\ dsdt(x,s,H) \leftarrow -\dfrac{1}{Y_x} \cdot \mu(s,-\log(H)) \cdot x \\ dHdt(x,s,H) \leftarrow \alpha \cdot \mu(s,-\log(H)) \cdot x + \beta \cdot x \\ dydt(t,y) \leftarrow \begin{pmatrix} dxdt(y_0,y_1,y_2) \\ dsdt(y_0,y_1,y_2) \\ dHdt(y_0,y_1,y_2) \end{pmatrix} \\ ty \leftarrow rkfixed(y_{init},0,t_f,n,dydt) \end{array} \right.$$

True: $ty_m := ty(p) \quad t := ty_m^{\langle 0 \rangle} \quad x_m := ty_m^{\langle 1 \rangle} \quad s_m := ty_m^{\langle 2 \rangle} \quad H_m := ty_m^{\langle 3 \rangle} \quad pH_m := -\log(H_m)$

$$sse(p) := \left| \begin{array}{l} ty \leftarrow ty(p) \\ (x \;\; s \;\; H) \leftarrow \left(ty^{\langle 1 \rangle} \;\; ty^{\langle 2 \rangle} \;\; ty^{\langle 3 \rangle}\right) \\ pH \leftarrow -\log(H) \\ sse \leftarrow (x - x_m) \cdot (x - x_m) + (s - s_m) \cdot (s - s_m) + (pH - pH_m) \cdot (pH - pH_m) \end{array} \right.$$

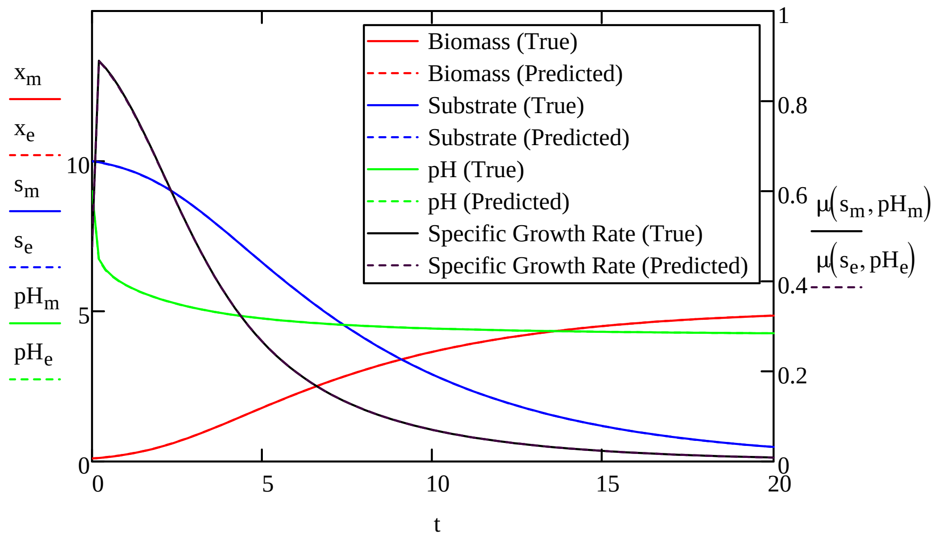
True value: $p^T = (1 \;\; 1 \;\; 6 \;\; 8)$

Initial guess: $p := (2 \;\; 2 \;\; 5 \;\; 10)^T$ $\quad sse(p) = 1.563 \times 10^3$

Estimated value: $p := Minimize(sse,p) = \begin{pmatrix} 1.097 \\ 2.159 \\ 5.697 \\ 9.968 \end{pmatrix}$ $\quad sse(p) = 2.791 \times 10^{-3}$

⟵ K_s, pK_1, pK_2 estimates are off.
Estimated values of x, s, pH are good.

Predicted: $ty_e := ty(p) \quad t := ty_e^{\langle 0 \rangle} \quad x_e := ty_e^{\langle 1 \rangle} \quad s_e := ty_e^{\langle 2 \rangle} \quad H_e := ty_e^{\langle 3 \rangle} \quad pH_e := -\log(H_e)$



Estimate 5 model parameters simultaneously.

$p := \left(\mu_m \;\; K_s \;\; pK_1 \;\; pK_2 \;\; Y_x\right)^T$

$$ty(p) := \left| \begin{array}{l} \left(\mu_m \;\; K_s \;\; pK_1 \;\; pK_2 \;\; Y_x\right) \leftarrow p^T \\ \mu(s,pH) \leftarrow \dfrac{\mu_m \cdot s}{K_s \cdot \left(1 + 10^{-pH+pK_1} + 10^{-pK_2+pH}\right) + s} \\ dxdt(x,s,H) \leftarrow \mu(s,-\log(H)) \cdot x \\ dsdt(x,s,H) \leftarrow -\dfrac{1}{Y_x} \cdot \mu(s,-\log(H)) \cdot x \\ dHdt(x,s,H) \leftarrow \alpha \cdot \mu(s,-\log(H)) \cdot x + \beta \cdot x \\ dydt(t,y) \leftarrow \begin{pmatrix} dxdt(y_0,y_1,y_2) \\ dsdt(y_0,y_1,y_2) \\ dHdt(y_0,y_1,y_2) \end{pmatrix} \\ ty \leftarrow rkfixed(y_{init}, 0, t_f, n, dydt) \end{array} \right.$$

True: $ty_m := ty(p)$ $\quad t := ty_m^{\langle 0 \rangle}$ $\quad x_m := ty_m^{\langle 1 \rangle}$ $\quad s_m := ty_m^{\langle 2 \rangle}$ $\quad H_m := ty_m^{\langle 3 \rangle}$ $\quad pH_m := -\log(H_m)$

$$sse(p) := \left| \begin{array}{l} ty \leftarrow ty(p) \\ (x \;\; s \;\; H) \leftarrow \left(ty^{\langle 1 \rangle} \;\; ty^{\langle 2 \rangle} \;\; ty^{\langle 3 \rangle}\right) \\ pH \leftarrow -\log(H) \\ sse \leftarrow (x - x_m) \cdot (x - x_m) + (s - s_m) \cdot (s - s_m) + (pH - pH_m) \cdot (pH - pH_m) \end{array} \right.$$

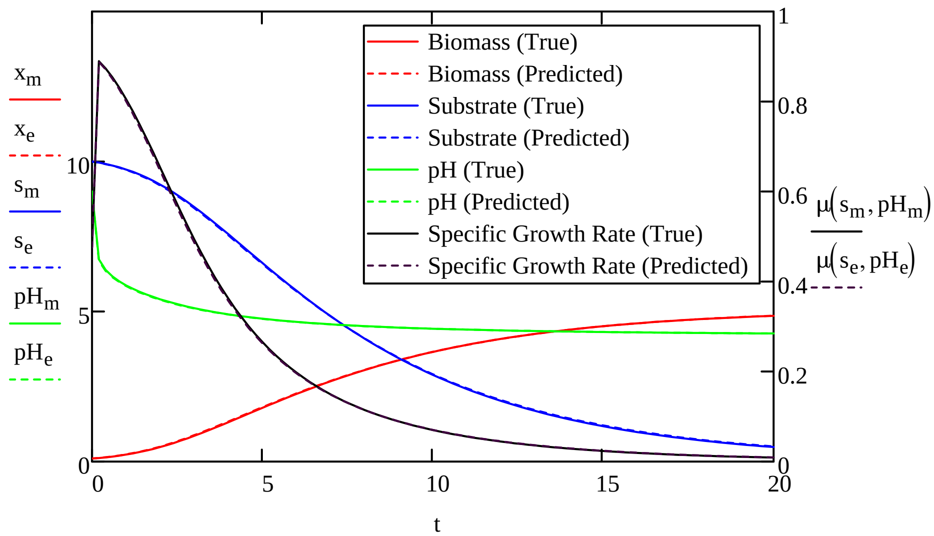
True value: $p^T = (1 \;\; 1 \;\; 6 \;\; 8 \;\; 0.5)$

Initial guess: $p := (2 \;\; 2 \;\; 5 \;\; 10 \;\; 1)^T$ $\quad sse(p) = 4.133 \times 10^3$

Estimated value: $p := \text{Minimize}(sse, p) = \begin{pmatrix} 1.111 \\ 2.024 \\ 5.74 \\ 9.947 \\ 0.501 \end{pmatrix}$ $\quad sse(p) = 0.077$

⟵ K_s, pK_1, pK_2 estimates are off.
Estimated values of x, s, pH are good.

Predicted: $ty_e := ty(p) \quad t := ty_e^{\langle 0 \rangle} \quad x_e := ty_e^{\langle 1 \rangle} \quad s_e := ty_e^{\langle 2 \rangle} \quad H_e := ty_e^{\langle 3 \rangle} \quad pH_e := -\log(H_e)$



Estimate all 7 model parameters simultaneously. Since α & β are not O(1), the sse minimization step will terminate prematurely and return the same set of parameters as the initial guess. Here we adjust the magnitude to bring all parameters to O(1).

$$p := \left(\mu_m \;\; K_s \;\; pK_1 \;\; pK_2 \;\; Y_x \;\; \alpha \cdot 10^5 \;\; \beta \cdot 10^7\right)^T$$

$$\begin{aligned}
ty(p) :=\; & \left(\mu_m \;\; K_s \;\; pK_1 \;\; pK_2 \;\; Y_x \;\; \alpha \;\; \beta\right) \leftarrow p^T \\
& \alpha \leftarrow \alpha \cdot 10^{-5} \\
& \beta \leftarrow \beta \cdot 10^{-7} \\
& \mu(s, pH) \leftarrow \frac{\mu_m \cdot s}{K_s \cdot \left(1 + 10^{-pH + pK_1} + 10^{-pK_2 + pH}\right) + s} \\
& dxdt(x, s, H) \leftarrow \mu(s, -\log(H)) \cdot x \\
& dsdt(x, s, H) \leftarrow -\frac{1}{Y_x} \cdot \mu(s, -\log(H)) \cdot x \\
& dHdt(x, s, H) \leftarrow \alpha \cdot \mu(s, -\log(H)) \cdot x + \beta \cdot x \\
& dydt(t, y) \leftarrow \begin{pmatrix} dxdt\left(y_0, y_1, y_2\right) \\ dsdt\left(y_0, y_1, y_2\right) \\ dHdt\left(y_0, y_1, y_2\right) \end{pmatrix} \\
& ty \leftarrow rkfixed\left(y_{init}, 0, t_f, n, dydt\right)
\end{aligned}$$

True: $ty_m := ty(p)$ $\quad t := ty_m^{\langle 0 \rangle}$ $\quad x_m := ty_m^{\langle 1 \rangle}$ $\quad s_m := ty_m^{\langle 2 \rangle}$ $\quad H_m := ty_m^{\langle 3 \rangle}$ $\quad pH_m := -\log\left(H_m\right)$

$$\begin{aligned}
sse(p) :=\; & ty \leftarrow ty(p) \\
& (x \;\; s \;\; H) \leftarrow \left(ty^{\langle 1 \rangle} \;\; ty^{\langle 2 \rangle} \;\; ty^{\langle 3 \rangle}\right) \\
& pH \leftarrow -\log(H) \\
& sse \leftarrow \left(x - x_m\right) \cdot \left(x - x_m\right) + \left(s - s_m\right) \cdot \left(s - s_m\right) + \left(pH - pH_m\right) \cdot \left(pH - pH_m\right)
\end{aligned}$$

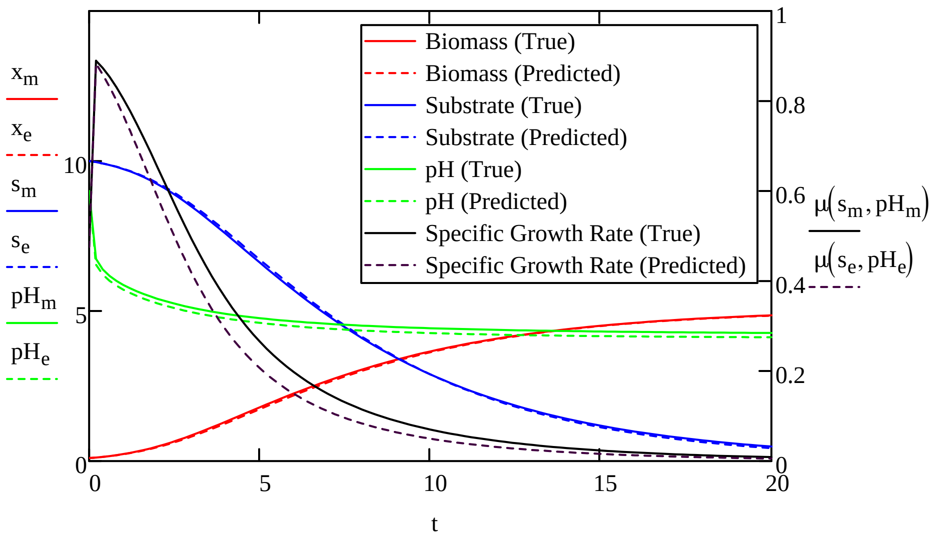
True value: $p^T = (1 \;\; 1 \;\; 6 \;\; 8 \;\; 0.5 \;\; 1 \;\; 1)$

Initial guess: $p := (2 \;\; 2 \;\; 5 \;\; 10 \;\; 1 \;\; 2 \;\; 0.5)^T$ $\qquad sse(p) = 3.276 \times 10^3$

Estimated value: $p := \text{Minimize}(sse, p) = \begin{pmatrix} 1.049 \\ 2.167 \\ 5.495 \\ 9.958 \\ 0.496 \\ 1.512 \\ 0.496 \end{pmatrix}$ $\qquad sse(p) = 2.86$

⟵ K_s, pK_1, pK_2, α, & β estimates are off.
The estimated values of x, s, pH are ok.

Predicted: $ty_e := ty(p)$ $t := ty_e^{\langle 0 \rangle}$ $x_e := ty_e^{\langle 1 \rangle}$ $s_e := ty_e^{\langle 2 \rangle}$ $H_e := ty_e^{\langle 3 \rangle}$ $pH_e := -\log(H_e)$



In general, μ_m and Y_x are estimated well. The estimated pK_1 value is adjusted from the initial guess toward the true value, but the estimated pK_2 value does not change much from the initial guess, because the pH dynamic data do not stay around the pK_2 range. Likewise, the K_s value is not estimated well, because the dynamic data for s do not hover around the K_s range for long. The value of α & β estimates are off with α been adjusted toward the true value more than β, because the growth-rated term α·μ·x overshadows the maintenance-related term β·x in dp/dt. If we let fermentation run longer such that the term the term β·x becomes more significant than the term α·μ·x, we will be able to estimate β better. The predicted values of x, s, pH are all quite good. **In summary, to achieve better estimates of all the model parameters, we need to have data from more runs that cover the range of the model variables being estimated.**