Problem 6.2 of Shuler. How to find model parameters in μ via regression.
Instructor: Nam Sun Wang

Specific growth rate is a function of s and pH

$$\mu = \frac{1}{x}\cdot\frac{dx}{dt} = \frac{\mu_m\cdot s}{K_s\cdot\left(1+10^{-pH+pK_1}\right)+s} = \frac{\mu_m\cdot s}{K_s\cdot\left(1+\frac{H}{K_1}\right)+s} = \frac{\mu_m\cdot s}{K_{s.app}+s}$$

Linear Regression. Given experimental data (t, x, s) at several pH values, find μ_m, K_s, and K_1.

Step 1. calculate μ $\quad \mu = \frac{1}{x}\cdot\frac{dx}{dt}$

Step 2. for each pH value, find μ_m and $K_{s.app}$ via linear regression.

Regress $1/\mu$ versus $1/s$ (double reciprocal, Lineweaver-Burk, or Eadie-Hofstee, or Hanes-Woolf)

$$\frac{1}{\mu} = \frac{1}{\mu_m} + \frac{K_{s.app}}{\mu_m}\cdot\frac{1}{s} \qquad \mu_m = \frac{1}{intercept} \qquad K_{s.app} = \frac{slope}{intercept}$$

Decreasing pH (increasing H) increases $K_{s,app}$; thus, increases the slope, while the intercept remains unchanged.

Step 3. From $K_{s.app}$ and pH, find K_s and K_1 via linear regression.

Regress $K_{s.app}$ versus H

$$K_{s.app} = K_s + \frac{K_s}{K_1}\cdot H \qquad K_s = intercept \qquad K_1 = \frac{intercept}{slope}$$

Or we can combine Step 2 & Step 3. find μ_m, K_s, & K_1 via linear regression.

Regress $1/\mu$ versus 1, 1/s, and H/s.

$$\frac{1}{\mu} = \frac{1}{\mu_m} + \frac{K_{s.app}}{\mu_m}\cdot\frac{1}{s} = \frac{1}{\mu_m} + \frac{K_s}{\mu_m}\cdot\frac{1}{s} + \frac{K_s}{\mu_m\cdot K_1}\cdot\frac{H}{s} = a_0\cdot 1 + a_1\cdot\frac{1}{s} + a_2\cdot\frac{H}{s} = \begin{pmatrix}1 & \frac{1}{s} & \frac{H}{s}\end{pmatrix}\cdot\begin{bmatrix}a_0\\ a_1\\ a_2\end{bmatrix} = X\cdot a$$

$$a = \left(X^T\cdot X\right)^{-1}\cdot X^T\cdot\frac{1}{\mu} \quad \longrightarrow \quad \mu_m = \frac{1}{a_0} \qquad K_s = \frac{a_1}{a_0} \qquad K_1 = \frac{K_s}{\mu_m\cdot a_2} = \frac{a_1}{a_2}$$

Nonlinear Regression. However, because this is inherently a nonlinear problem, it is far more reliable to estimate model parameters via nonlinear regression in practice. Furthermore, μ values calculated through dx/dt amplify the experimental error in x. Steps in nonlinear regression.

Step 1. Integrate with Euler's method to generate predicted values of x based on the given μ_m, K_s, K_1.

$$\mu\left(s, H, \mu_m, K_s, K_1\right) = \frac{\mu_m\cdot s}{K_s\cdot\left(1+\frac{H}{K_1}\right)+s}$$

Start with $\quad x_{pred_0} = x_0$

for $\quad i = 0 .. n-1 \quad x_{pred_{i+1}} = x_{pred_i} + \mu\left(s_i, H_i, \mu_m, K_s, K_1\right)\cdot x_{pred_i}\cdot\left(t_{i+1}-t_i\right)$

Step 2. Define an error function that returns the sum of squared error.

$$sse(\mu_m, K_s, K_1) = \sum_i \left(x_{pred_i} - x_i\right)^2$$

Step 3. Minimize sse by changing μ_m, K_s, K_1.

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$$\mu = \frac{1}{x}\cdot\frac{dx}{dt} = \frac{\mu_m \cdot s}{K_s \cdot \left(1 + 10^{-pH+pK_1} + 10^{-pK_2+pH}\right) + s} = \frac{\mu_m \cdot s}{K_s \cdot \left(1 + \frac{H}{K_1} + \frac{K_2}{H}\right) + s} = \frac{\mu_m \cdot s}{K_{s.app} + s}$$

Linear Regression. Given experimental data (t, x, s) at several pH values, find μ_m, K_s, and K_1.

Step 1. calculate μ $\quad \mu = \frac{1}{x}\cdot\frac{dx}{dt}$

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Regress $1/\mu$ versus 1/s (double reciprocal, Lineweaver-Burk, or Eadie-Hofstee, or Hanes-Woolf)

$$\frac{1}{\mu} = \frac{1}{\mu_m} + \frac{K_{s.app}}{\mu_m}\cdot\frac{1}{s} \qquad \mu_m = \frac{1}{intercept} \qquad K_{s.app} = \frac{slope}{intercept}$$

For pH<$(pK_1+pK_2)/2$, decreasing pH increases $K_{s,app}$; for $(pK_1+pK_2)/2$<pH, increasing pH increases $K_{s,app}$ thus, increases the slope, while the intercept remains unchanged.

Step 3. From $K_{s.app}$ and pH, find K_s, K_1 & K_2 via linear regression.

Regress $K_{s.app}$ versus 1, H, & 1/H

$$K_{s.app} = K_s \cdot 1 + \frac{K_s}{K_1}\cdot H + K_s \cdot K_2 \cdot \frac{1}{H} = a_0 \cdot 1 + a_1 \cdot H + a_2 \cdot \frac{1}{H} = \begin{pmatrix} 1 & H & \frac{1}{H} \end{pmatrix} \cdot \begin{bmatrix} a_0 \\ a_1 \\ a_2 \end{bmatrix} = X \cdot a$$

$$a = \left(X^T \cdot X\right)^{-1} \cdot X^T \cdot K_{s.app} \quad \longrightarrow \quad K_s = a_0 \qquad K_1 = \frac{a_0}{a_1} \qquad K_2 = \frac{a_2}{a_0}$$

Or we can combine Step 2 & Step 3. find μ_m, K_s, K_1 & K_2 via linear regression.

Regress $1/\mu$ versus 1, 1/s, and H/s, $1/(H\cdot s)$.

$$\frac{1}{\mu} = \frac{1}{\mu_m} + \frac{K_{s.app}}{\mu_m}\cdot\frac{1}{s} = \frac{1}{\mu_m} + \frac{K_s}{\mu_m}\cdot\frac{1}{s} + \frac{K_s}{\mu_m \cdot K_1}\cdot\frac{H}{s} + \frac{K_s \cdot K_2}{\mu_m}\cdot\frac{1}{H\cdot s} = a_0 \cdot 1 + a_1 \cdot \frac{1}{s} + a_2 \cdot \frac{H}{s} + a_3 \cdot \frac{1}{H\cdot s} = \begin{pmatrix} 1 & \frac{1}{s} & \frac{H}{s} & \frac{1}{H\cdot s} \end{pmatrix} \cdot \begin{bmatrix} a_0 \\ a_1 \\ a_2 \\ a_3 \end{bmatrix} = X \cdot a$$

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Start with $x_{pred_0} := x_0$

for $i := 0 .. n-1$ $\quad x_{pred_{i+1}} := x_{pred_i} + \mu(s_i, H_i, \mu_m, K_s, K_1) \cdot x_{pred_i} \cdot (t_{i+1} - t_i)$

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