Modellbildung

1. Modellierung biologischer Systeme

Mathematische Beschreibung

- Modelle mit konzentrierten Parametern
- Modelle mit verteilten Parametern
- Stochastische Modelle

2. Compartment Modelle

$$\frac{dq_i}{dt} = \sum R_{ij} - \sum R_{ji}$$

ΣR_{ij} Summe aller Massenflüsse *in* das Compartment *i*

ΣR_{ji} Summe aller Massentransfers *aus* dem Compartment *i*

3. Modelle von geregelten Systemen

$$\dot{Q}_i(t) = R_{i0} + \sum_{\substack{j=1 \\ j \neq i}}^{n} R_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^{n} R_{ji} - R_{0i}$$

$$R_{ij} = R_{ij}\left(Q_j ; Q_a, Q_b, \ldots\right)$$

$$R_{ij} = l_{ij} Q_a + d_{ij} \dot{Q}_a$$

$$R_{ij} = h_{ij} Q_a Q_j$$

$$R_{ij} = a_{ij}\left(1 - \frac{Q_i}{s_i}\right)$$

$$R_{ij} = R_{ij0} + a_{ij} \tanh\left[b_{ij}\left(Q_j - Q_{j0}\right)\right]$$

4. Theoretische (a priori) Identifizierbarkeit

$$\dot{\mathbf{x}}(t) = \mathbf{f}\big(\mathbf{x}(t,\mathbf{p}),\mathbf{u}(t),t;\mathbf{p}\big) \qquad \mathbf{x}_0 = \mathbf{x}_0(t_0,\mathbf{p})$$

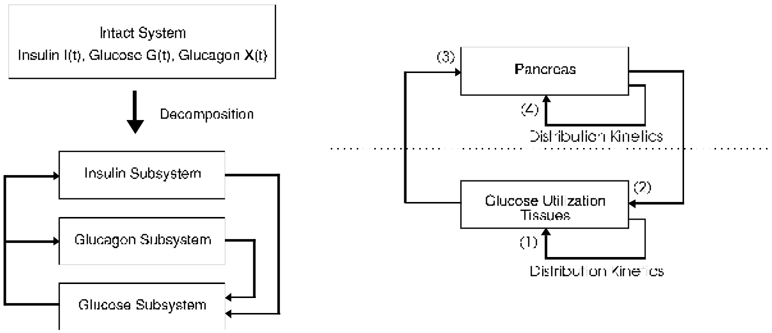
$$\mathbf{y}(t) = \mathbf{g}\big(\mathbf{x}(t,\mathbf{p});\mathbf{p}\big) \qquad t_0 \le t \le T$$

$$\mathbf{h}\big(\mathbf{x}(t,\mathbf{p}),\mathbf{u}(t);\mathbf{p}\big) \ge 0$$

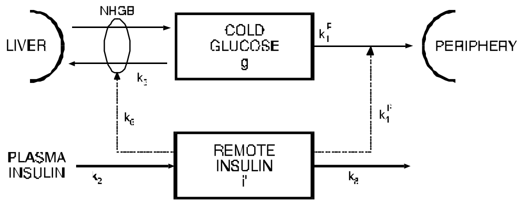
Pohjanpalo:

$$\frac{d^k \mathbf{y}\big(\mathbf{x}(t_0,\mathbf{p})\big)}{dt^k} = \mathbf{c}_k(t_0) \qquad k = 0,1,2,\ldots,L$$

Beispiel: Glucose-Minimalmodell



Beispiel: Glucose-Minimalmodell



$$\frac{di'}{dt} = -k_3 i' + k_2 (i - i_b)$$

$$\frac{dg}{dt} = R_a - R_{dL} - R_{dP}$$

$$\frac{dg}{dt} = NHGB - R_{dP}$$

$$NHGB = B_0 - k_6 i' g - k_5 g$$

$$R_{dP} = k_1^P g + k_4^P i' g$$

$$\frac{dg}{dt} = -(k_1^P + k_5) g - (k_4^P + k_6) i' g + B_0$$

$$\frac{di'}{dt} = -k_3 i' + k_2 (i - i_b)$$

Beispiel: Glucose-Minimalmodell

$$x = (k_4^P + k_6) i'$$

$$p_1 = k_1^P + k_5$$

$$p_2 = k_3$$

$$p_3 = k_2 (k_4^P + k_6)$$

$$p_4 = B_0$$

$$\frac{dg}{dt} = -\left(p_1 + x\right) g + p_4$$

$$\frac{dx}{dt} = -p_2 x + p_3 \left(i - i_b\right)$$

Beispiel: Glucose-Minimalmodell

$$\frac{dg}{dt} = -(p_1 + x)g + p_4 + G_{\text{inf}}$$

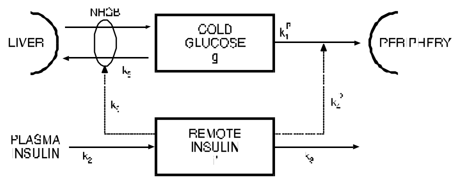
$$\frac{dx}{dt} = -p_2 x + p_3(i_e - i_b)$$

$$x_{ss} = \frac{p_3}{p_2}(i_e - i_b)$$

$$G_{\text{inf}} = \left(p_1 + \frac{p_3}{p_2}(i_e - i_b)\right)g - p_4$$

$$\frac{\partial G_{\text{inf}}}{\partial g} = p_1 + \frac{p_3}{p_2}(i_e - i_b)$$

$$\frac{\partial^2 G_{\text{inf}}}{\partial g \partial i_e} = \frac{p_3}{p_2}$$



$$S_I = \frac{p_3}{p_2} = \frac{k_2(k_4^L + k_6)}{k_3}$$

$$S_G = p_1 = k_1^P + k_5$$

5. Praktische (*a posteriori*) Identifizierbarkeit

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t,\mathbf{p}),\mathbf{u}(t),t;\mathbf{p})$$

$$y(t) = G(\mathbf{x}(t,\mathbf{p});\mathbf{p})$$

$$z(t_k) = y(t_k,\mathbf{p}) + r(t_k,\mathbf{p})$$

$$\mathbf{r}(t,\mathbf{p}) = \mathbf{z}(t) - \mathbf{G}(t,\mathbf{p})$$

5. Praktische (*a posteriori*) Identifizierbarkeit

$$\mathbf{e} = \mathbf{z} - \mathbf{U}\,\mathbf{p}$$

$$C(\mathbf{p}) = (\mathbf{z} - \mathbf{U}\mathbf{p})^{\mathrm{T}}\,\mathbf{W}\,(\mathbf{z} - \mathbf{U}\mathbf{p})$$

Gradient von $C(\mathbf{p})$: $\nabla C(\mathbf{p}) = -2\left(\mathbf{U}^{\mathrm{T}}\mathbf{W}\mathbf{z} - \mathbf{p}^{\mathrm{T}}\mathbf{U}^{\mathrm{T}}\mathbf{W}\mathbf{U}\right)$

Minimum: $\nabla C(\mathbf{p}) = 0$; $\mathbf{U}^{\mathrm{T}}\mathbf{W}\mathbf{z} = \mathbf{p}^{\mathrm{T}}\mathbf{U}^{\mathrm{T}}\mathbf{W}\mathbf{U}$

$$\hat{\mathbf{p}} = \left(\mathbf{U}^{\mathrm{T}}\mathbf{W}\mathbf{U}\right)^{-1}\mathbf{U}^{\mathrm{T}}\mathbf{W}\mathbf{z}$$

$$\mathbf{V}(\hat{\mathbf{p}}) = \mathbf{Q}\,\mathbf{R}\,\mathbf{Q}^{\mathrm{T}}$$

$$CV(\hat{p}_i) = 100\,\frac{\sqrt{v_{ii}(\hat{p}_i)}}{\hat{p}_i}$$

5. Praktische (*a posteriori*) Identifizierbarkeit

a) Gewichtung mit der Einheitsmatrix **I:** $\mathbf{W} = \mathbf{I}$

$$C(\mathbf{p}) = \mathbf{e}^{\mathrm{T}}\,\mathbf{e}$$

$$\mathbf{Q} = \left(\mathbf{U}^{\mathrm{T}}\mathbf{U}\right)^{-1}\mathbf{U}^{\mathrm{T}}$$

$$\hat{\mathbf{p}} = \left(\mathbf{U}^{\mathrm{T}}\mathbf{U}\right)^{-1}\mathbf{U}^{\mathrm{T}}\,\mathbf{z}$$

$$\mathbf{V}(\hat{\mathbf{p}}_L) = \mathbf{Q}\,\mathbf{R}\,\mathbf{Q}^{\mathrm{T}} = \left(\mathbf{U}^{\mathrm{T}}\mathbf{U}\right)^{-1}\mathbf{U}^{\mathrm{T}}\;\mathbf{R}\;\mathbf{U}\left(\mathbf{U}^{\mathrm{T}}\mathbf{U}\right)^{-1}$$

b) Gewichtung nach Markov: $\mathbf{W} = \mathbf{R}^{-1}$

$$C(\mathbf{p}) = \mathbf{e}^{\mathrm{T}}\mathbf{R}^{-1}\,\mathbf{e}$$

$$\mathbf{Q} = \left(\mathbf{U}^{\mathrm{T}}\mathbf{R}^{-1}\mathbf{U}\right)^{-1}\mathbf{U}^{\mathrm{T}}\mathbf{R}^{-1} \qquad \mathbf{Q}^{\mathrm{T}} = \mathbf{R}^{-1}\mathbf{U}\left(\mathbf{U}^{\mathrm{T}}\mathbf{R}^{-1}\mathbf{U}\right)^{-1}$$

$$\hat{\mathbf{p}} = \left(\mathbf{U}^{\mathrm{T}}\mathbf{R}^{-1}\mathbf{U}\right)^{-1}\mathbf{U}^{\mathrm{T}}\mathbf{R}^{-1}\mathbf{z}$$

$$\mathbf{V}(\hat{\mathbf{p}}_M) = \mathbf{Q}\,\mathbf{R}\,\mathbf{Q}^{\mathrm{T}} = \left(\mathbf{U}^{\mathrm{T}}\mathbf{R}^{-1}\mathbf{U}\right)^{-1}$$

6. Least-Squares Methode zur Schätzung der Modellparameter

Fehlervektor: $\mathbf{r}(\mathbf{p}) = \mathbf{y}_{\text{data}} - \mathbf{y}_{\text{mod}} = \mathbf{z} - \mathbf{G}(\mathbf{p}) = [r_1 \ \cdots r_N]^{\mathrm{T}}$

zu minimierende Zielfunktion C: $C(\mathbf{p}) = f(\mathbf{p}) = \mathbf{r}^{\mathrm{T}}\,\mathbf{r}$

$$\nabla f(\mathbf{p}) = \left(\nabla\, \mathbf{r}^{\mathrm{T}}\right)\mathbf{r} + \left(\nabla\, \mathbf{r}^{\mathrm{T}}\right)\mathbf{r} = 2\left(\nabla\, \mathbf{r}^{\mathrm{T}}\right)\mathbf{r} = 2\,\mathbf{J}^{\mathrm{T}}\,\mathbf{r}$$

$$\mathbf{A}(\mathbf{p}) = \nabla\nabla^{\mathrm{T}} f(\mathbf{p}) = 2\,\mathbf{J}^{\mathrm{T}}\mathbf{J} + 2\left(\mathbf{r}\,\nabla^{\mathrm{T}}\right)^{\mathrm{T}}\mathbf{J}$$

$\mathbf{A}(\mathbf{p}) \approx 2\,\mathbf{J}^{\mathrm{T}}\mathbf{J}$ für kleines $\mathbf{r}$

$$\nabla f(\mathbf{p}) = \begin{pmatrix} \frac{\partial f}{\partial p_1} \\ \frac{\partial f}{\partial p_2} \\ \vdots \\ \frac{\partial f}{\partial p_M} \end{pmatrix} \qquad \mathbf{J} = \left[\nabla\, \mathbf{r}^{\mathrm{T}}\right]^{\mathrm{T}} = \begin{pmatrix} \frac{\partial r_1}{\partial p_1} & \cdots & \frac{\partial r_1}{\partial p_M} \\ \vdots & \ddots & \vdots \\ \frac{\partial r_N}{\partial p_1} & \cdots & \frac{\partial r_N}{\partial p_M} \end{pmatrix}$$

6. Least-Squares Methode zur Schätzung der Modellparameter

Bedingungen für Minimum: $\nabla f(\mathbf{p}) = 0$

$\mathbf{A}(\mathbf{p})$ ist positiv definit

Newton-Raphson-Methode: iterative Bestimmung des Minimums

$$\nabla f(\mathbf{p} + \Delta\mathbf{p}) = \nabla f(\mathbf{p}) + \mathbf{A}(\mathbf{p})\ \Delta\mathbf{p} + \ldots$$

$\nabla f(\mathbf{p} + \Delta\mathbf{p}) \approx 0$ in der Nähe des Minimums

daraus folgt

$$\nabla f(\mathbf{p}) = -\mathbf{A}(\mathbf{p})\ \Delta\mathbf{p}$$

oder $\Delta\mathbf{p} = -\left(\mathbf{A}(\mathbf{p})\right)^{-1}\nabla f(\mathbf{p})$ $\qquad \mathbf{p}_{k+1} = \mathbf{p}_k + \Delta\mathbf{p}_k$