Aspects of Biothermodynamics (D)

A Thermostatics & Thermodynamics of Irreversible Processes

B Biofluids (Theory)

C Biofluids (Experiments)

D Protein Adsorption

E Microbioreactors / Bacteria

F Technical Bioreactors

D Protein Adsorption

D1 Thermodynamic Models
Equilibria (PAE), Kinetics
Multicontacts (MCA), Replacement

D2 Aggregation of Proteins (PA)
Solidification

D3 Denaturation of Proteins
Hydratization

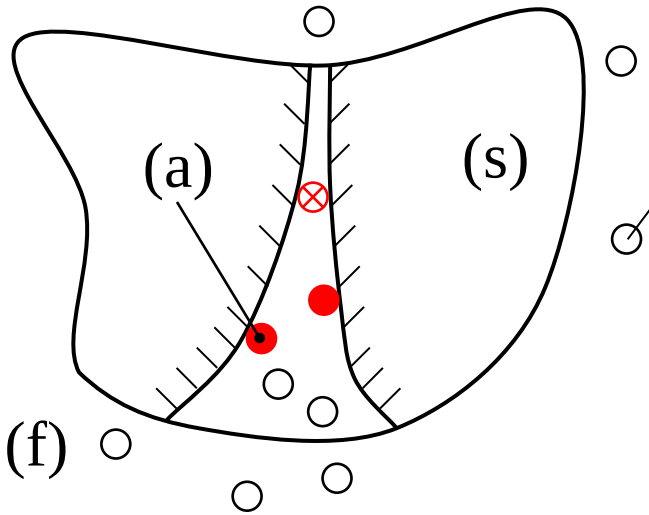
D4 Adsorption Induced Defolding Processes (AUP, PAS)

D5 Adsorption Columns with Incomplete Breakthrough (BK)

Adsorption of Proteins (L)

- Enzyme immobilization
- Biosensors, Diagnostics
- Biofouling, Contamination
- Drug targeting, controlled release
- Downstream processing Chromatography

Basic Concepts



Stationary Phase

Sorbent: $V^s = 1 - \varepsilon \; V_{part}$

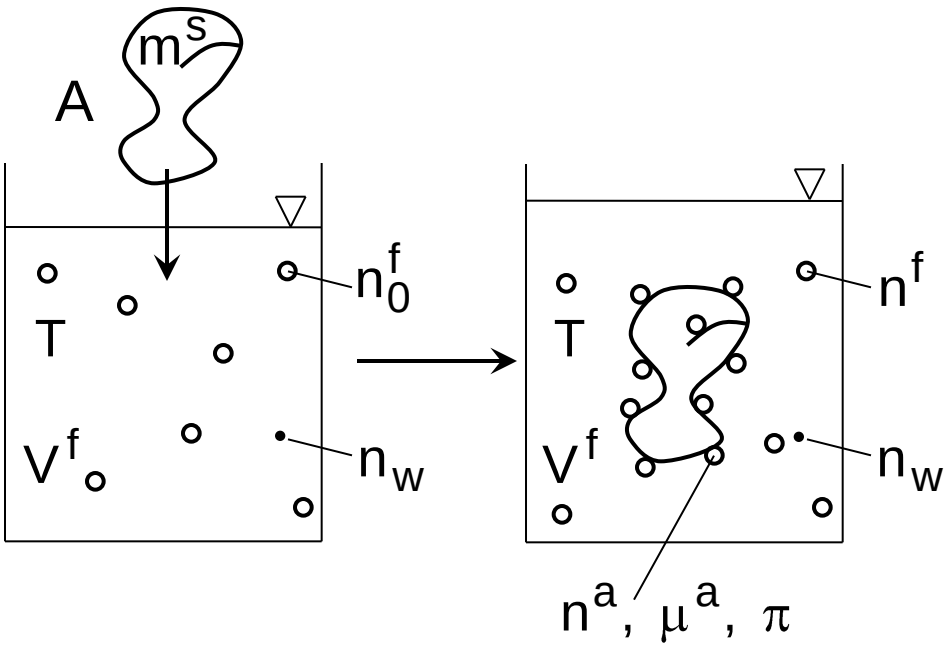
Mobile Phase

Sorbate a, ipf : $V^a = \varepsilon V_{part}$

Sorptive epf : $V^f = V^* - V_{part}$

Porosity : $0 \le \varepsilon \le 1$

Liquid Phase Adsorption



Measurement methods (c_0,c):

- Spectroscopy
  Fluorescence
  Light scattering
  Light absorption
- Dielectric permittivity
- Calorimetry
  enthalpy, temperature
  heat capacity
- Release of ion, atomic groups etc. by protein upon adsorption

Protein molar balance

$$n_0^f = n^f + n^a \qquad 1$$

$$n_0^f = c_0 V_0^f$$

$$n^f = c V^f$$

$$n^a = c_0 V_0^f - c V^f \qquad 2 \qquad \rightarrow$$

$$n^a = n^a\ c, T, m^s \quad \ldots \text{ AI} \qquad 2a$$

Liquid Phase Adsorption Thermodynamics (1)

Adsorbate a ,DoF:2

$n^a,\ \mu^a,\ A,\ \pi,\ T$

EOS: $\pi = \pi\ (n^a, A, T)$ 3

$A = A\ (m^s, T)$

$dG^a = -S^a dT + A\, d\pi + \mu^a dn^a$

Gibbs-Duhem

$A\, d\pi = n^a d\mu^a$ 4

Sorptive phase f as solute n^f , in solvent n_w ,DoF:3

$n^f\ ,\ p^f = \dfrac{n^f R T}{V^f} = c R T\ ,\ T$ 5

$V^f = V^f\ (n_w, n^f, p, T)$ 6

$dG^f = -S^f dT + V^f dp + \mu^f dn^f$

Liquid adsorption equilibria (LAE):

$G = G^f + G^a \rightarrow \mathrm{Min}$

$T = \mathrm{const}, p^f = \mathrm{const}$

$\pi = \mathrm{const}, n_0^f = \mathrm{const}$

$\mu^a\ (n^a, m^s, T) = \mu^f\ (p^f, T)$ 7

Liquid Phase Adsorption Thermodynamics (2)

Liquid adsorption equilibria (LAE)

Example

Ideal adsorbate

$$a: \quad n^a R T = \pi A \quad m^s, T \qquad 3a$$

$$4: \mu^a - \mu_0^a = R T \ln\left(\frac{n^a}{n_0^a}\right) \qquad 4a$$

LAE $7: \mu^a = \mu^f$

Choice of ref. state

$$\mu_0^a = \mu^f \quad p^+, T$$

$$7 \qquad n^a = K \quad T \quad c$$

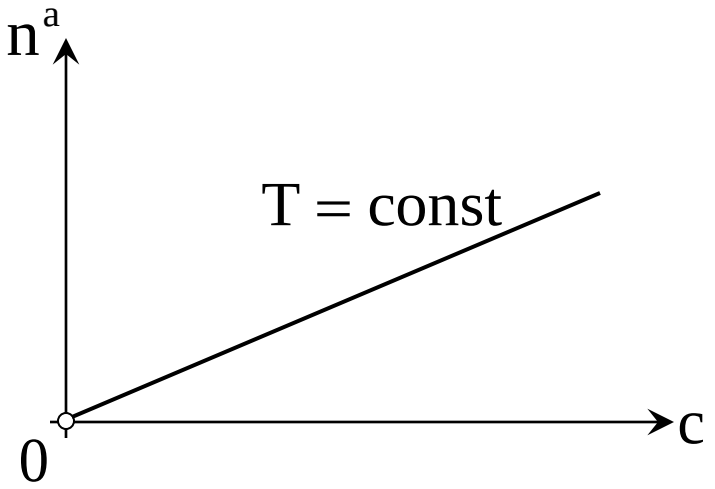
$$K \quad T = n_0^a R T / p^+$$

Protein solved in water:

Dilute solution

Ideal fluid phase

$$f \quad \mu^f \quad p^f, T = \mu^f \quad p^+, T + R T \ln\left(\frac{p^f}{p^+}\right)$$



Protein Adsorption Isotherms (AI)*), N=1

Linear AI

$$\frac{n}{m^s} = K\ t\ \frac{n^f}{V^f} \qquad 1$$

$$q = K c$$

Freundlich AI

$$\frac{n}{m^s} = \left[K\ t\ \frac{n^f}{V^f} \right]^{\alpha}, \quad \alpha > 0 \qquad 2$$

$$q = K c^{\alpha}$$

$$K\ T = K_{\infty} \sqrt{\frac{T_0}{T}} \exp\ q_{fa}/RT \qquad 3$$

Langmuir AI (1916)

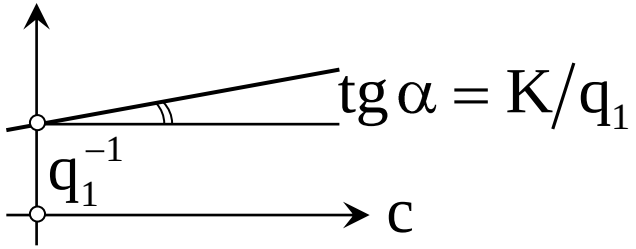
$$\frac{n}{m^s} = \frac{n_{\infty}}{m^s} \frac{K c}{1 + K c} \qquad 4$$

$$q = q_1 \frac{K c}{1 + K c}$$

$$c = 1/K : q = q_1/2 \qquad 5$$

Linear representation

$$\frac{K_c}{q} = \frac{1}{q_1}\ 1 + K c \qquad 4a$$



*) Ref.: Keller J.U., Staudt R., Gas Adsorption Equilibria, Springer, 2005

Protein Adsorption Isotherms (AI), N ≥ 1

Freundlich AI, $i,k = 1...N$

$$\frac{n_i}{m^s} = \left[K_i \; t \; \frac{n_i^f}{V^f} \right]^{\alpha_i} \prod_{k \neq 1}^{N} 1 - y_k \;^{\alpha_{ik}} \qquad 6$$

$$q_i = K_i c_i \;^{\alpha_i} \prod_{k \neq 1}^{N} 1 - y_k \;^{\alpha_{ik}}$$

$$y_k = \frac{c_k}{\sum_j c_j} \;, \quad k = 1...N$$

Langmuir AI

$$\frac{n_i}{m^s} = \frac{n_{i\infty}}{m^s} \cdot \frac{K_i c_i}{1 + \sum_j K_j c_j} \qquad 7$$

$$q_i = q_{i1} \cdot \frac{K_i c_i}{1 + \sum_j K_j c_j}$$

Representation Theorem (JUK)

$$n_i \; c_1 ... c_N, T = \qquad 8$$

$$= n_\infty \; T \left[\alpha_i \; \bar{c}_i \;^{\alpha_i} + \frac{f_i}{R\,T} \sum_{k=1}^{N} \alpha_k \; \bar{c}_k \;^{\alpha_k} \left(\frac{\partial q_k}{\partial p_i} \right) \right] \phi \; c^*$$

$$\bar{c}_i = \frac{f_i}{c_{i0}} \exp\left(\frac{q_i}{R\,T} \right)$$

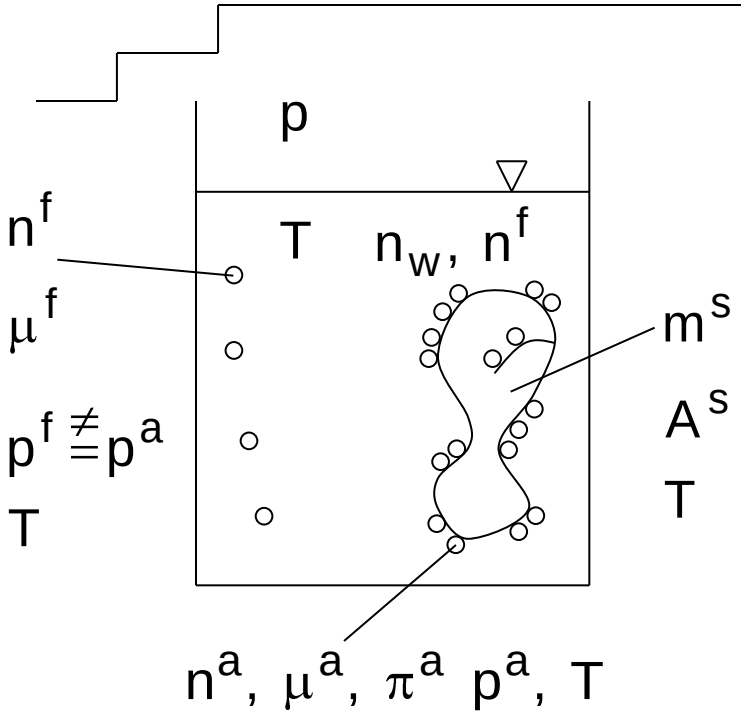
$$q_i = q_i \; f_i ... f_N, T$$

$$f_i = f_i \; c_i ... c_N, T$$

$$c^* = \sum_k \bar{c}_k \;^{\alpha_k} \;, \quad \alpha_i = \alpha_0 \left(\frac{r_i}{r_0} \right)^{-D}$$

$$\phi \; x \; > 0 \;, \quad \frac{d}{dx} \; x \phi \; x \; \geq 0$$

Langmuir: $\phi \; x \; = \frac{1}{1 + x}$



Sorptive Sorbate Sorbent

Adsorption equilibrium:

$$\mu^f\ p^f,T\ = \mu^a\ \pi^a,T \qquad 1$$

Protein Solution EOS

Protein/Water ≅ Ideal gas molecule/Vacuum

Osmotic pressure, dilute solutions

$$p^f = y^f p^* = y^f \frac{nRT}{V^f\ n^f,n_w,p,T} \qquad 2$$

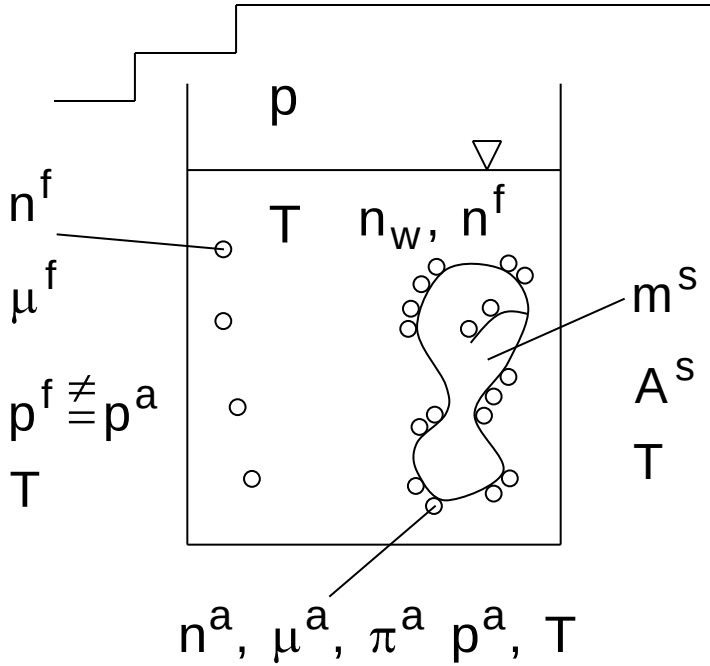
$$y^f = \frac{n^f}{n}\ ,\ n = n^f + n_w$$

$$\mu^f\ p^f,T\ = \mu^f\ p^+,T\ + RT\ln\left[\frac{f^f\ p^f,T}{p^+}\right] \qquad 3$$

$$f^f\ p^f,T\ = p^f\left[1 + B\ T\ p^f + C\ T\ p^{f2} + ...\right]$$

$$\cong p^f\ \text{... dilute solutions} \qquad 4$$

Kinetics of Protein Adsorption (N=1), Thermodynamic Model (1)



Mass Transfer Process (TIP)

$$\dot{n}^a = \alpha A^s \left[\mu^f \; p^f, T \; - \mu^a \; \pi^a, T \right] \qquad 7$$

$$1 : \mu^a \; \pi^a, T \; = \mu^f \; p^a, T$$

p^a ... equiv. equilibrium pressure corresponding to n t

$$7,3,4 : \quad \dot{n}^a = \alpha A^s R T \ln p^f / p^a$$

$$2,6 : \quad \dot{n}^a \; t \; = \alpha A^s R T \ln \left[\frac{y^f \; t \; p^* \; t}{\frac{1}{b} \cdot \frac{n^a / n^a_\infty}{1 - \; n^a / n^a_\infty}} \right]$$

Adsorption Isotherm / Equilibrium:

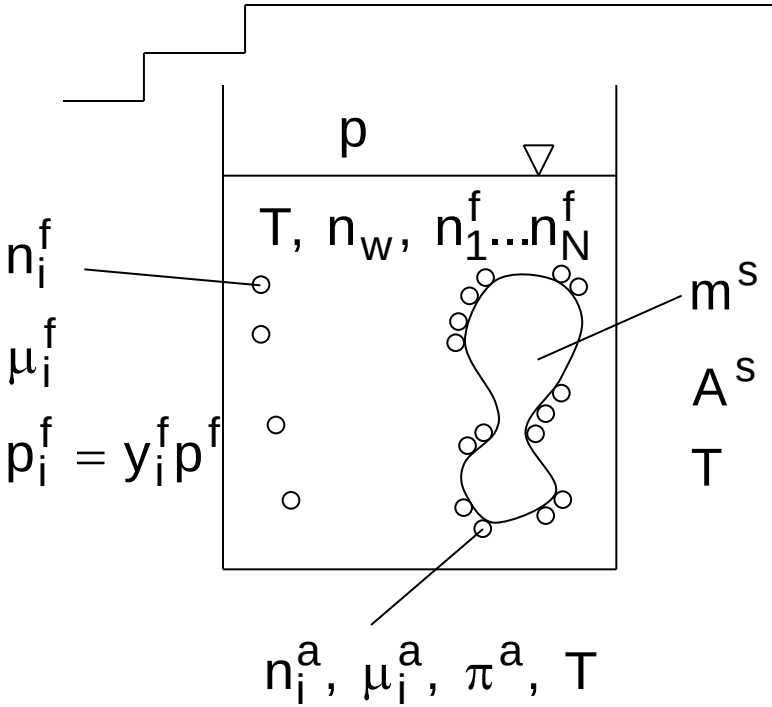
$$n^a = n^a_\infty \; T, m^s \; \frac{b p^a}{1 + b p^a} \qquad 5$$

$$p^a = \frac{1}{b} \cdot \frac{n^a / n^a_\infty \; T, m^s}{1 - \; n^a / n^a_\infty} \qquad 6$$

$$\dot{n}^a + \alpha A^s R T \ln \left[\frac{1}{b} \cdot \frac{n^a / n^a_\infty}{1 - \; n^a / n^a_\infty} \right] = \alpha A^s R T \ln \left[y^f \; \; ^* \; \right]$$

n^a = n^a_0 ... initial adsorption

Kinetics of Protein Adsorption (N=1), Thermodynamic Model (2)



Sorptive Sorbate Sorbent

Adsorption Equilibria

$$\mu_i^f\ p^f, y_1^f ... y_N^f, T\ = \mu_i^a\ \pi^a, x_1 ... x_N, T \quad 1$$

$$i = 1...N$$

Protein Solution EOS

Proteins/Water ≅ Ideal gas mixture/Vacuum

Osmotic partial pressures (p_i^f), dilute solutions

$$p_i^f = y_i^f p^* = y_i^f \frac{nRT}{V\ n_w, n_1^f ... n_N^f, T} \quad 2$$

$$y_i^f = \frac{n_i^f}{n}\ ,\ n = n_w + \sum_k^N n_k^f$$

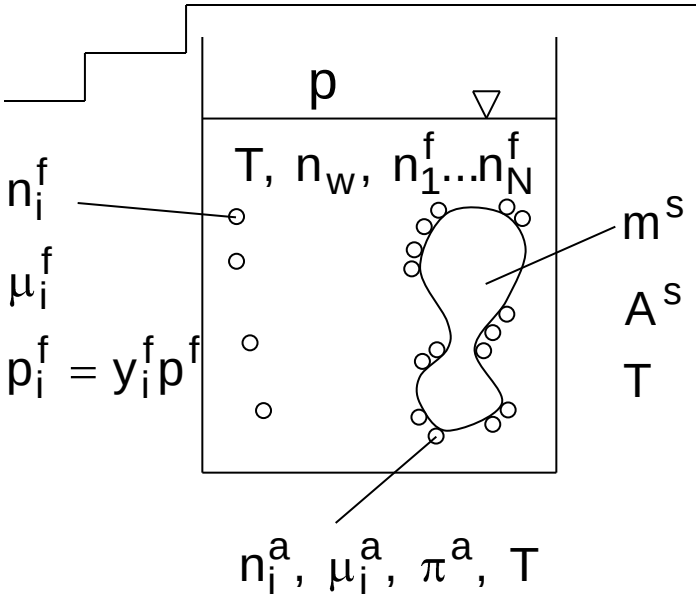
$$\mu_i^f\ p^*, y_1^f ... y_N^f, T\ = \mu_{i0}\ p^+, T\ +$$

$$+ RT \ln \left[f_i \left(\underbrace{p^*, y_1^f ... y_N^f, p^+, T} \right) \Big/ p^+ \right] \quad 3$$

$$f_i = p_i^f \left[1 + \sum_k^N B_{ik}\ \%\ p_k^f + ... \right] \cong p_i^f$$

$$\mu_i^f = \mu_{i0}^+ + RT \ln\ y_i^f p^* \Big/ p^+ \quad 4$$

Kinetics of Protein Adsorption (N≥1), Thermodynamic Model (3)



Sorptive Sorbate Sorbent

Adsorption Isotherm / Equilibria:

$$n_i^a = n_{i\infty}^a \left(T, m^s, \frac{b_i p_i^a}{1+\sum_{k=1}^{N} b_k p_k^a}\right), \quad i = 1...N \qquad 5$$

$$p_i^a = \frac{1}{b_i} \cdot \frac{n_i^a / n_{i\infty}^a}{1-\sum_{k=1}^{N} n_k^a / n_{k\infty}^a} = y_i^a p^a \qquad 6$$

Mass Transfer Process (f↔a) (TIP)

$$\dot{n}_i^a = A^s \sum_{k=1}^{N} \alpha_{ik} \left[\mu_k^f \left(p^*, y_1^f ... y_N^f, T\right) - \mu_k^a \left(\pi^a, x_1 ... x_N, T\right) \right] \qquad 7$$

Accompanying adsorption equilibria

$$\mu_k^a \left(\pi^a, x_1 ... x_N, T\right) = \mu_k^f \left(p^a, y_1^a ... y_N^a, T\right) \qquad 8$$

$$7,4,8: \quad \dot{n}_i^a = A^s RT \sum_{k=1}^{N} \alpha_{ik} \ln\left(\frac{y_k^f p^f}{y_k^a p^a}\right)$$

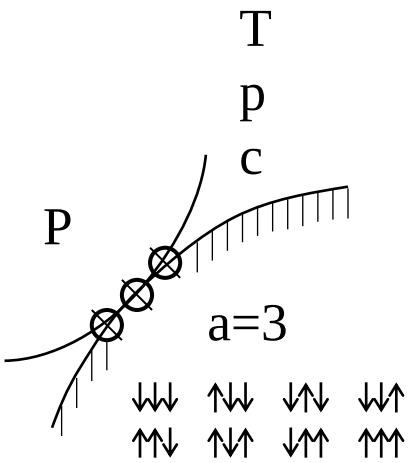
$$6: \dot{n}_i^a(t) = A^s RT \sum_{k=1}^{N} \alpha_{ik} \ln\left[\frac{y_k^f(t)\, p^*(t)}{\frac{1}{b_k} \cdot \frac{n_k^a / n_{k\infty}^a}{1-\sum_{l=1}^{N} n_l^a / n_{l\infty}^a}}\right], \quad i = 1...N$$

$$n_i^a(0) = n_{i0}^a \quad \text{... initial conditions} \qquad 9$$

Kinetics of Protein Adsorption (N≥1), Thermodynamic Model (4), ODE

Ref.: Keller, J.U., Thermodynamics of Non – Isothermal Coadsorption Processes, Ber. Bunsenges. 91 (1987), p. 528

Multicontact Adsorption of Proteins from Aqueous Solution



Open surfaces

Protein concentration: $c = \frac{n_p}{n_w + n_p}$

Single layer adsorption process

$$dn^+ = k_1^+ c \; n^s - a\, n \; dt$$

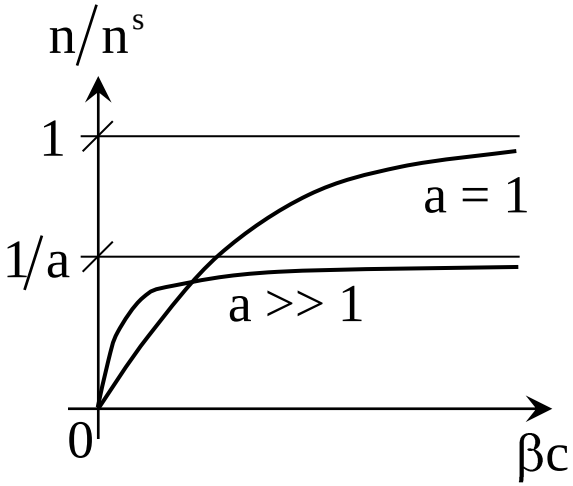
Desorption process

$$dn^- = k_1^- n \frac{1}{2^{a-1}} dt$$

Half load concentration

$$a\, n \; c = \frac{n^s}{2}$$

$$c_{1/2} = \frac{1}{a\beta} \ll 1$$



Adsorption equilibria:

$$dn^+ = dn^-$$

$$n \; c = n^s \frac{\beta c}{1 + a\beta c}$$

$$\beta = 2^{a-1} k_1^+ / k_1^-$$

Special cases

$$a = 1 \quad : \; n \; c = \frac{b c}{1 + b c}$$

$$a \to \infty : \; \frac{n}{n^s} \to \emptyset$$

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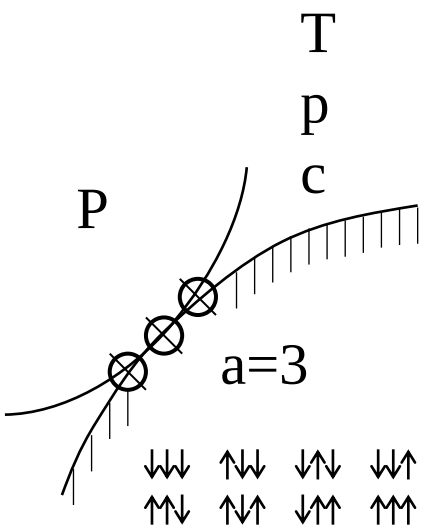
Multicontact Adsorption of Proteins from Aqueous Solution



Open surfaces

Adsorption Kinetics (Langmuir, Rudzinski)

$$dn = dn^{+} - dn^{-}$$

$$\dot{n} = k_1^{+} c \; n^{s} - a\, n \; - k_1^{-} \frac{n}{2^{a-1}}$$

$$\underline{\tau \dot{n} + n = C} \;\; \overbrace{n^{s} \beta c}$$

$$n\;t\; = \frac{n^{s} \beta c}{1 + a \beta c} \cdot \left(1 - e^{-t/\tau}\right)$$

$$\tau = \frac{2^{a-1}}{k_1^{-}\; 1 + 2^{a-1} a\, b\, c}$$

$$\lim_{a \to \infty} \tau \cong \frac{1}{k_1^{-} a\, b\, c} \to \emptyset$$

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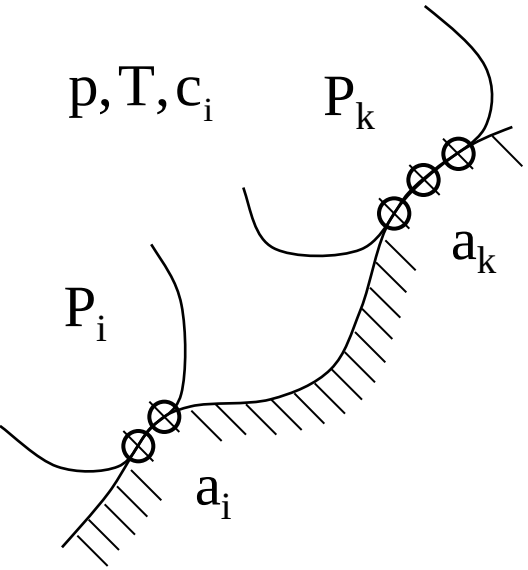
Multicomponent - Multicontact - Adsorption of Proteins from Aqueous Solution

Protein concentration: $c_i = \frac{n_{pi}}{n_w + \sum_k n_{pk}} \quad , \quad i = 1...N$



Open surfaces

Single layer adsorption process

$$dn_i^+ = k_i^+ c_i \left(n^s - \sum_{k=1}^{N} a_k n_k \right) dt$$

Desorption process

$$dn_i^- = k_i^- n_i \frac{1}{2^{a_i - 1}} dt$$

Adsorption equilibria:

$$dn_i^+ = dn_i^- \quad , \quad i = 1...N$$

$$n_i \; c_1...c_N = n^s \frac{\beta_i c_i}{1 + \sum_k a_k \beta_k c_k}$$

$$\beta_i = 2^{a-1} k_i^+ / k_i^-$$

Single contact:

$$n_i \; c_1...c_N = n^s \frac{b_i c_i}{1 + \sum_k b_k c_k}$$

$$a_i \to \infty : \; \frac{n_i}{n^s} \to 0$$

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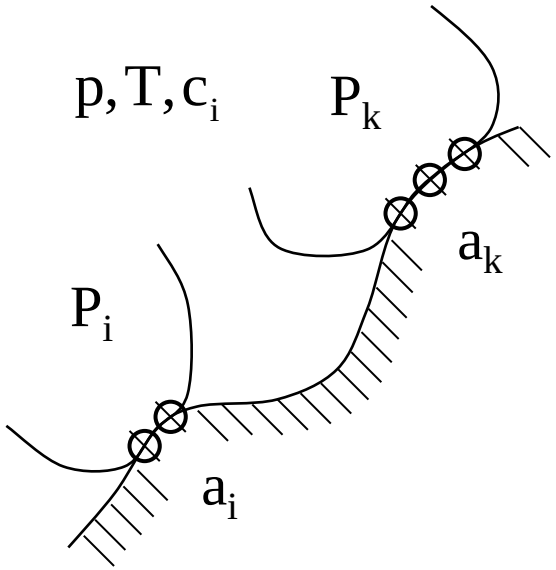
Multicomponent - Multicontact - Adsorption of Proteins from Aqueous Solution



Open surfaces

Adsorption Kinetics

$$dn_i = dn_i^+ - dn_i^- \quad , \quad i = 1...N$$

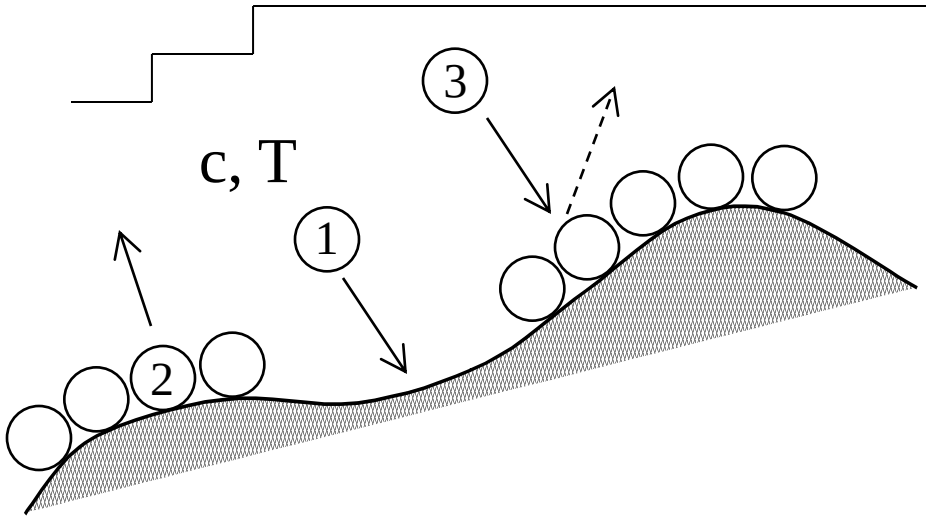
$$\dot{n}_i = k_i^+ c_i \; n^s - \sum_k a_k n_k \; - \frac{k_i^-}{2^{a_i - 1}} n_i$$

$$\tau_i \dot{n}_i + n_i + \beta_i c_i \sum_{k \neq i}^{N} a_k n_k = C_i$$

$$\tau_i = \frac{2^{a_i - 1}}{k_i^- \; 1 + a_i \beta_i c_i} \quad , \quad C_i = \frac{\beta_i c_i n^s}{1 + a_i \beta_i c_i}$$

$$\beta_i = 2^{a_i - 1} \frac{k_i^+}{k_i^-}$$

ODE, Eigenvalues, Implicit numerical methods



Equilibria

$$\frac{n}{n^s} = \frac{bc}{1 + b + d\ c}$$

$$d = 0: \quad \frac{n_0}{n^s} = \frac{bc}{1 + cb}$$

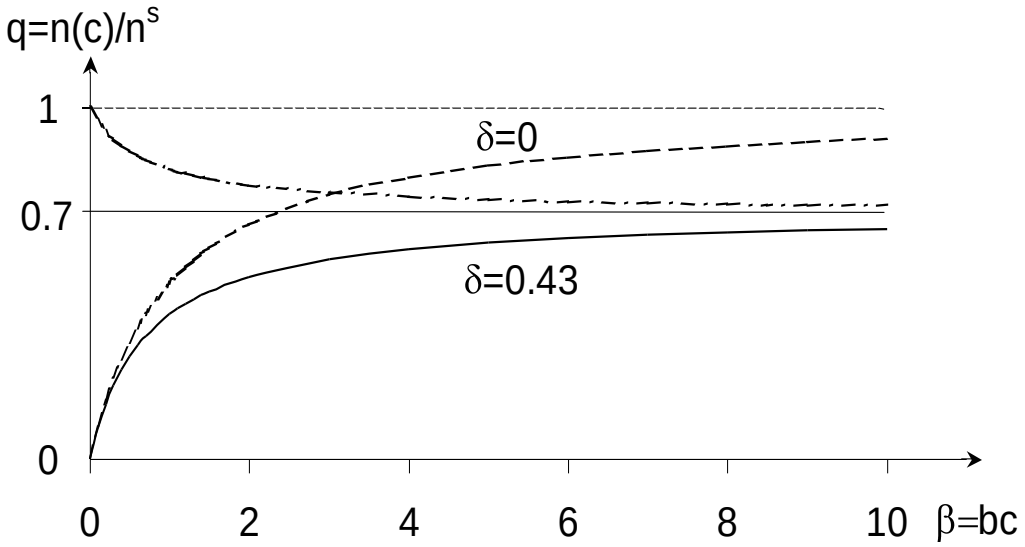
$$\frac{n}{n_0} = \frac{bc}{1 + b + d\ c} < 1$$

$$dn^+ = k^+ c\ n^s - n\ dt \quad ...1$$

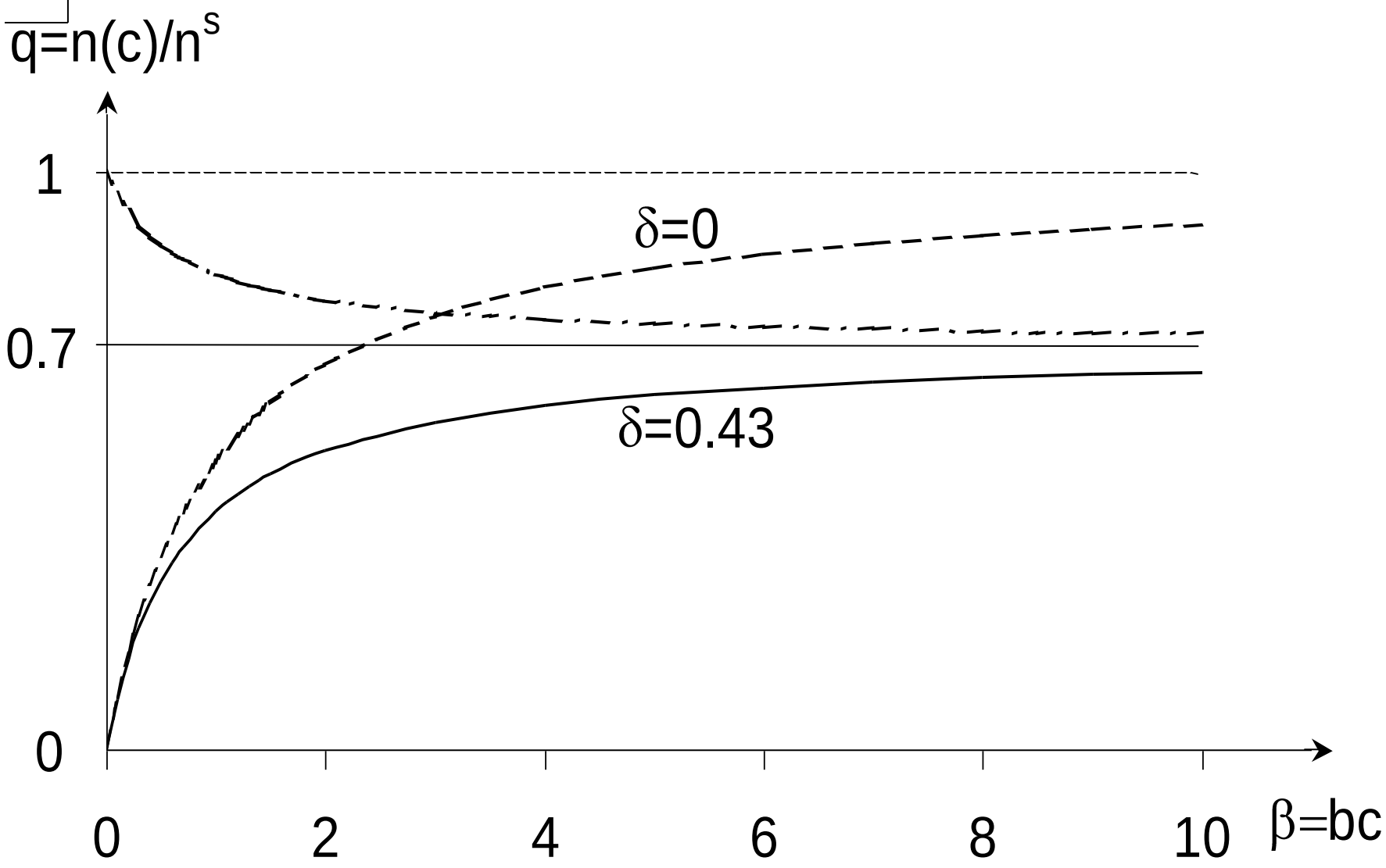
$$dn^- = k^- n + l^- cn\ dt \quad ...2,3$$

$$b = \frac{k^+}{k^-} > 0\ ,\ d = \frac{l^-}{k^-} \geq 0$$

$$\beta = bc\ ,\ \delta = \frac{d}{b} = \frac{l^-}{k^+}$$



Replacement Adsorption, Langmuir Model (N=1), Equilibria



Replacement Adsorption, Langmuir Model, Equilibria

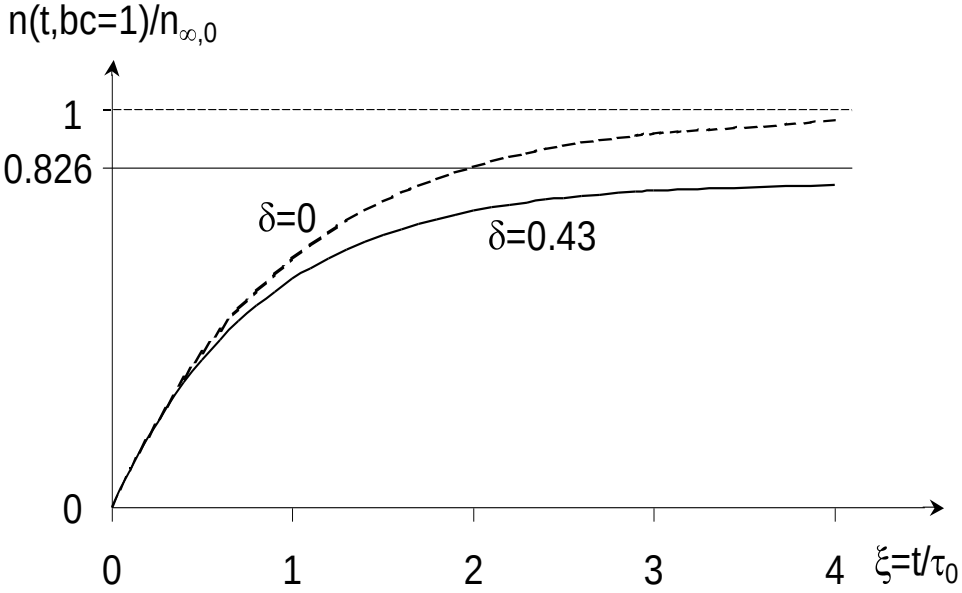
Kinetics of Adsorption Process

$$dn = dn^{+} - dn^{-}$$

$$k^{+} c n^{s} = \dot{n} + \left[1 + b + d\ c\right] k^{-} n$$

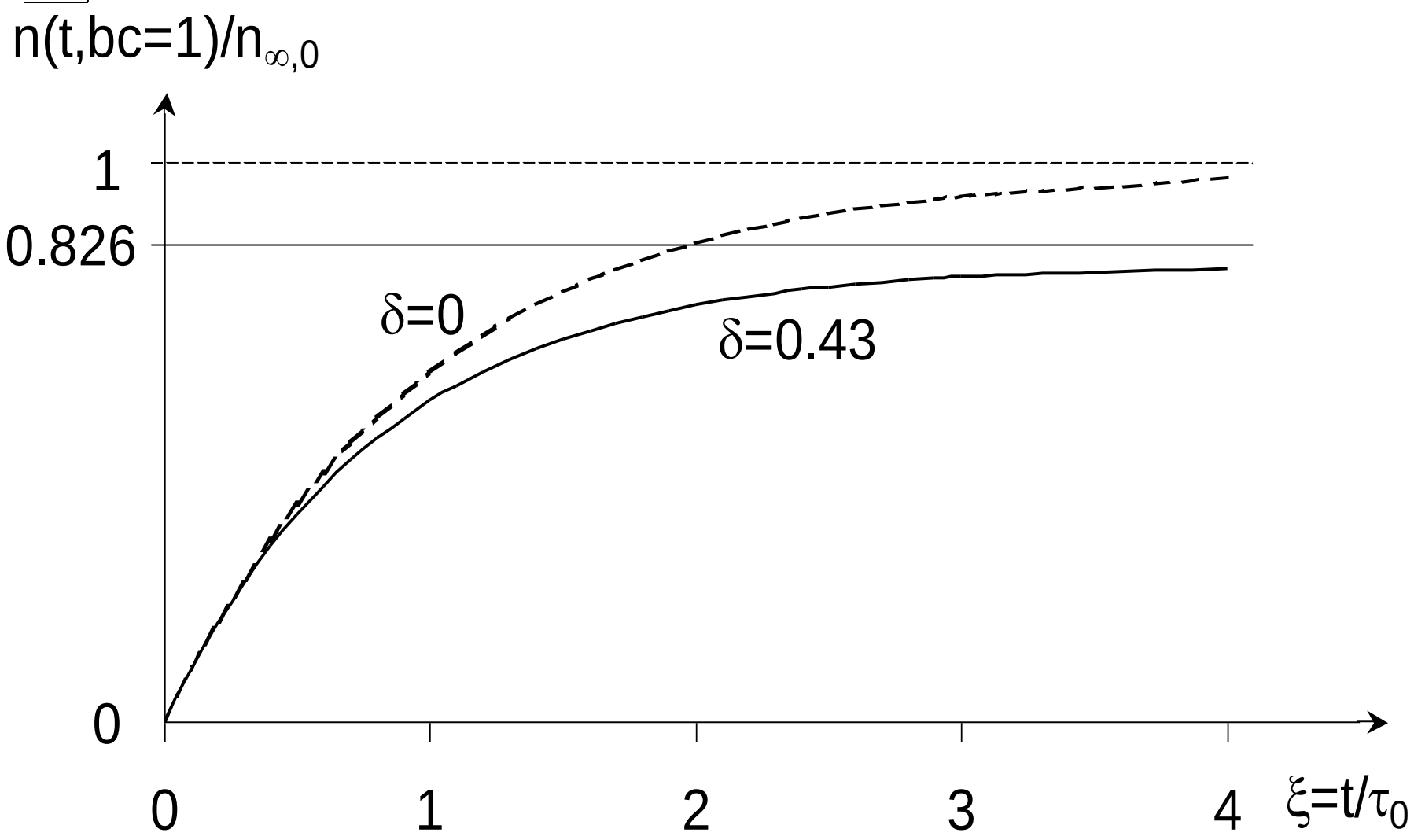
$$n\ t\ = n_{\infty,0} \frac{\tau}{\tau_0} \left(1 - e^{-\frac{\tau_0}{\tau}\left(\frac{t}{\tau_0}\right)} \right)$$

$$d = 0 :\ n_0\ t\ = n_{\infty,0} \left(1 - e^{-\frac{t}{\tau_0}} \right)$$

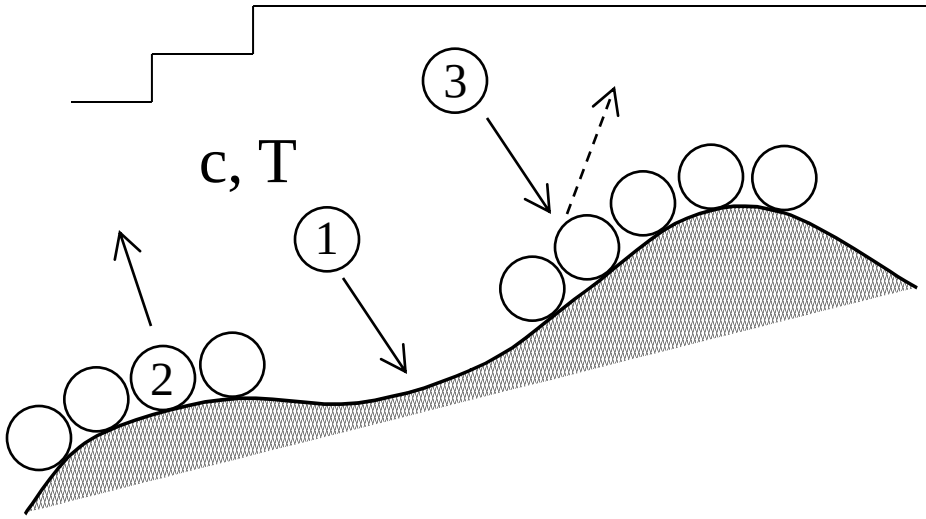


$$\frac{\tau}{\tau_0} = \frac{1 + bc}{1 + b + d\ c} < 1\ ,\ b = \frac{k^{+}}{k^{-}} \geq 0\ ,\ d = \frac{l^{-}}{k^{-}} \geq 0$$

Replacement Adsorption, Langmuir Model (N=1), Kinetics



Replacement Adsorption, Langmuir Model, Kinetics



Equilibria

$$\frac{n}{n^s} = \frac{bc}{1 + b + dn/n^s\ c}\ ,\ d = 0:\ \frac{n_0}{n^s} = \frac{bc}{1+bc}$$

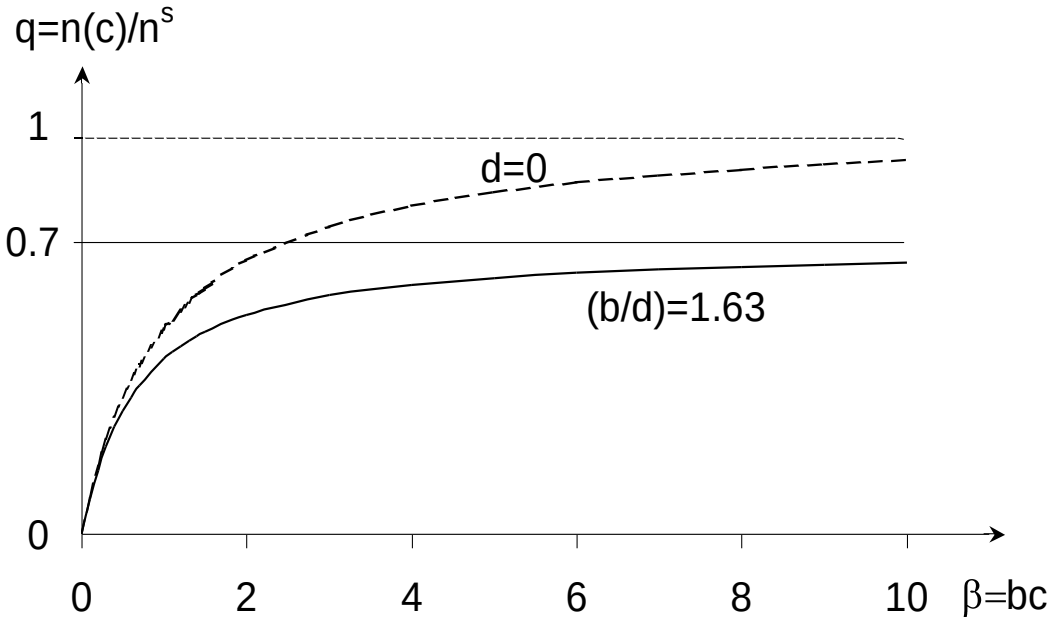
$$\frac{n}{n^s} = -\frac{1+bc}{2dc} \overset{+}{(-)} \sqrt{\left(\frac{1+bc}{2dc}\right)^2 + \frac{b}{d}}$$

$$\frac{n}{n_0} = \frac{bc}{1 + b + dn/n^s\ c} < 1$$

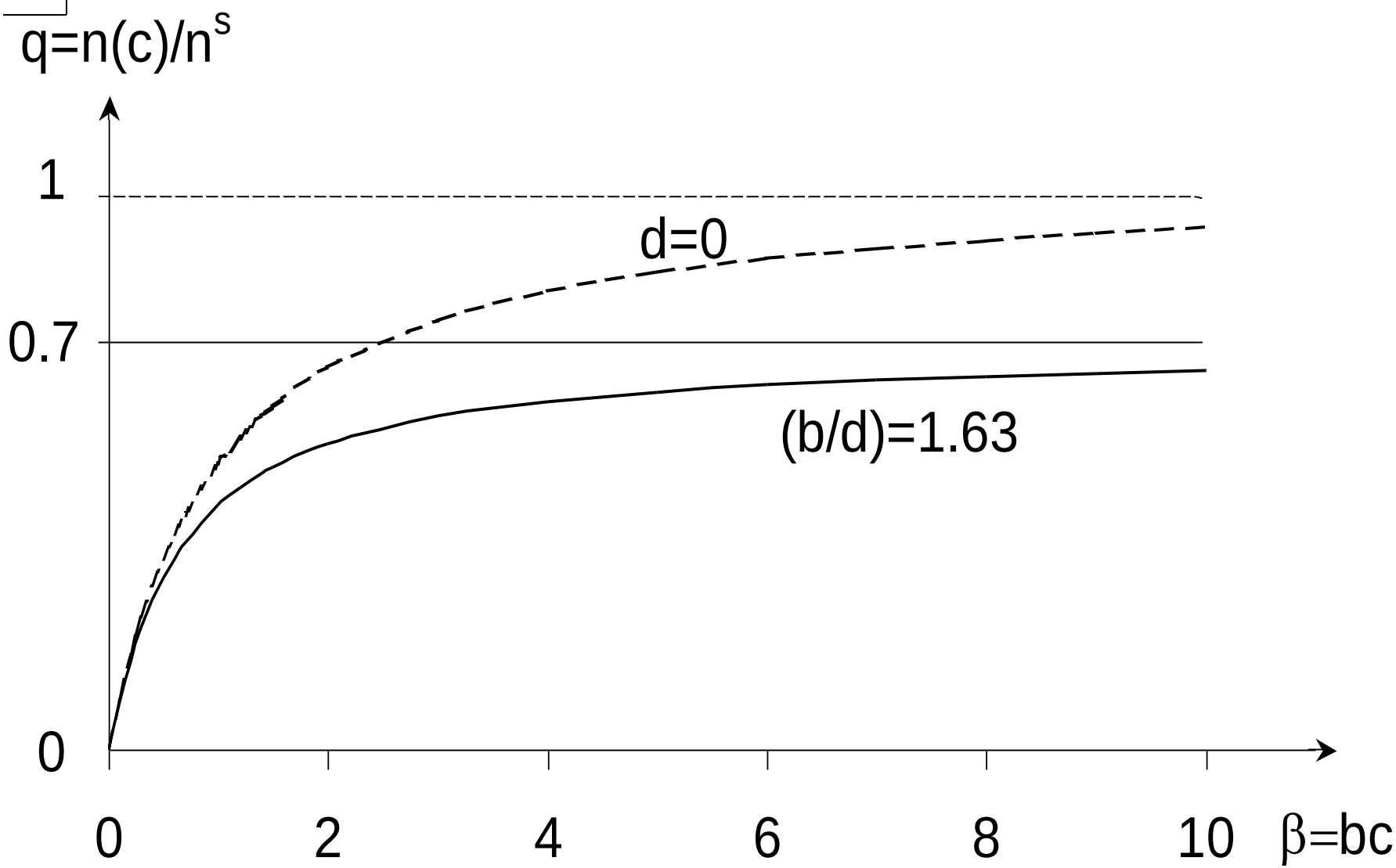
$$dn^+ = k^+ c\ n^s - n\ dt \quad ...1$$

$$dn^- = \left[k^- n + l^- c\left(\frac{n}{n^s}\right) n\right] dt \quad ...2,3$$

$$b = \frac{k^+}{k^-} > 0\ ,\ d = \frac{l^-}{k^-} \geq 0$$



Replacement Adsorption, Non-linear Model (N=1)



Replacement Adsorption, Non-linear Model (N=1)

Kinetics of Adsorption Process

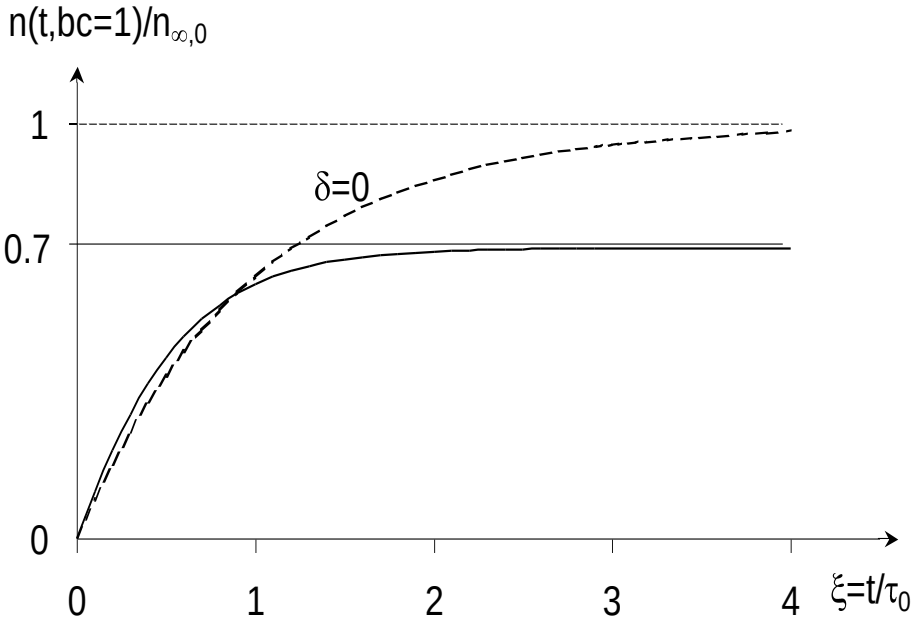
$$dn = dn^{+} - dn^{-}$$

$$k^{-} b c n^{s} = \dot{n} + k^{-}\left[\frac{dc}{n^{s}} n^{2} + (1 + bc)\, n\right]$$

$$n(t, c = \text{const}) = n_{\infty,0}\left(\frac{n_1}{n_{\infty,0}}\right)\frac{1 - e^{-\frac{\tau_0}{\tau}\left(\frac{t}{\tau_0}\right)}}{1 - \frac{n_1}{n_2} e^{-\frac{\tau_0}{\tau}\left(\frac{t}{\tau_0}\right)}}$$

$$d = 0:\ n_0(t, c = \text{const}) = n_{\infty,0}\left(1 - e^{-\frac{t}{\tau_0}}\right)$$

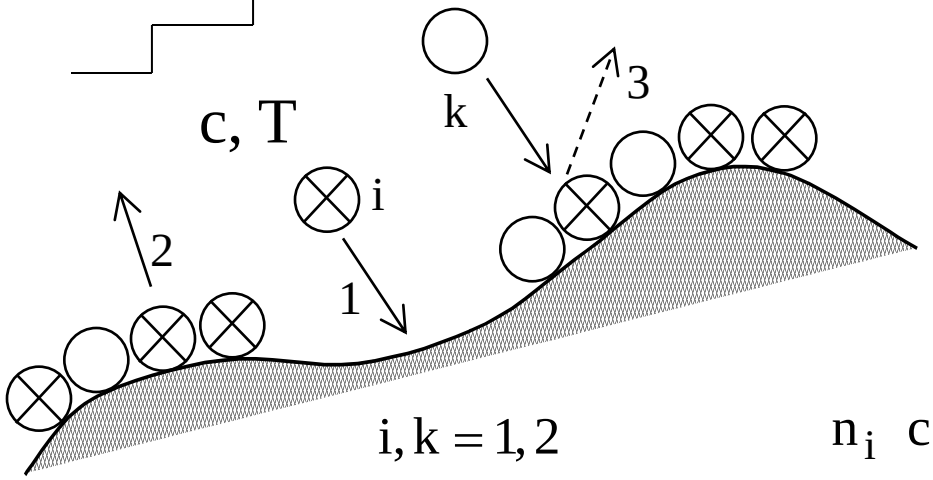
$$n_{\infty,0} = n^{s}\frac{bc}{1 + bc}$$



$$\frac{\tau_0}{\tau} = \sqrt{1 + \frac{d}{b}\left(\frac{2bc}{1 + bc}\right)^{2}}$$

$$n_{1,2} = \frac{n_{\infty,2}}{2}\left[-1 \pm \sqrt{1 + \frac{d}{b}\left(\frac{2bc}{1 + bc}\right)^{2}}\right]$$

Replacement Adsorption, Non-linear Model (N=1), Kinetics



$$i,k = 1,2$$

Equilibria

$$n_i\ c_1, c_2 = n^s \frac{b_i c_i}{1 + d_{i1} c_1 + d_{i2} c_2} \cdot \frac{1}{1+\Sigma} \quad , \quad i = 1,2$$

$$\Sigma = \frac{b_1 c_1}{1 + d_{11} c_1 + d_{12} c_2} + \frac{b_2 c_2}{1 + d_{21} c_1 + d_{22} c_2}$$

$$dn_i^+ = k_i c_i\ n^s - n\ dt \quad ...1$$

$$dn_i^- = k_i^- + l_{i1} c_1 + l_{i2} c_2\ n_i dt \quad ...2,3$$

$$d_{ik} = 0 \quad , \quad i,k = 1,2$$

$$b_i = \frac{k_i^+}{k_i^-} \quad , \quad d_{ik} = \frac{l_{ik}^-}{k_i^-}$$

$$n_i^0\ c_1, c_2 = n^s \frac{b_i c_i}{1 + d_1 c_1 + d_2 c_2}$$

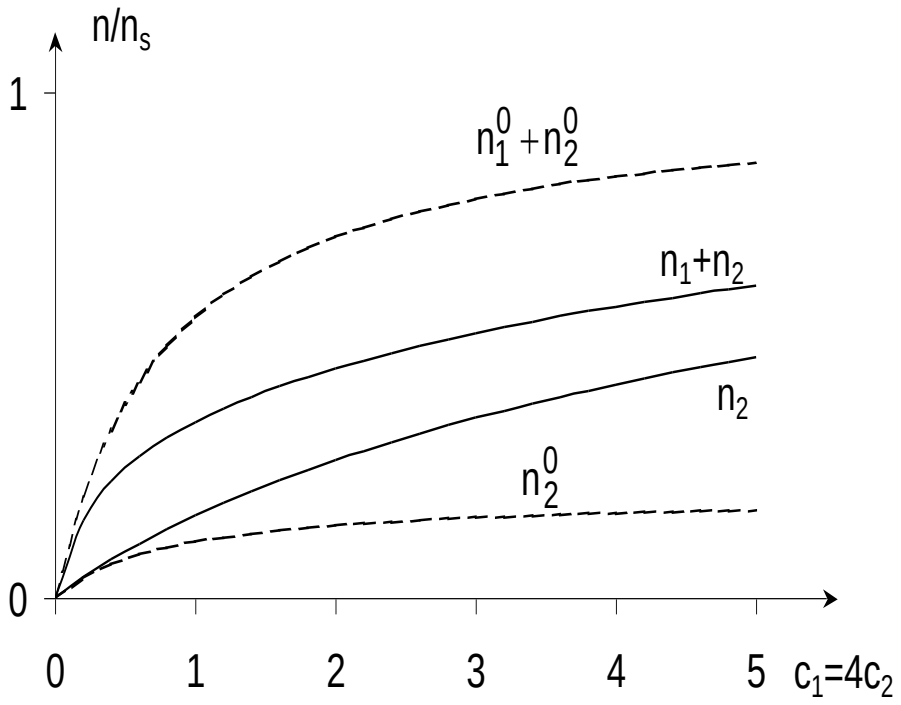
$$n = n_1 + n_2$$

$$\frac{n_i}{n_i^0} \le 1$$

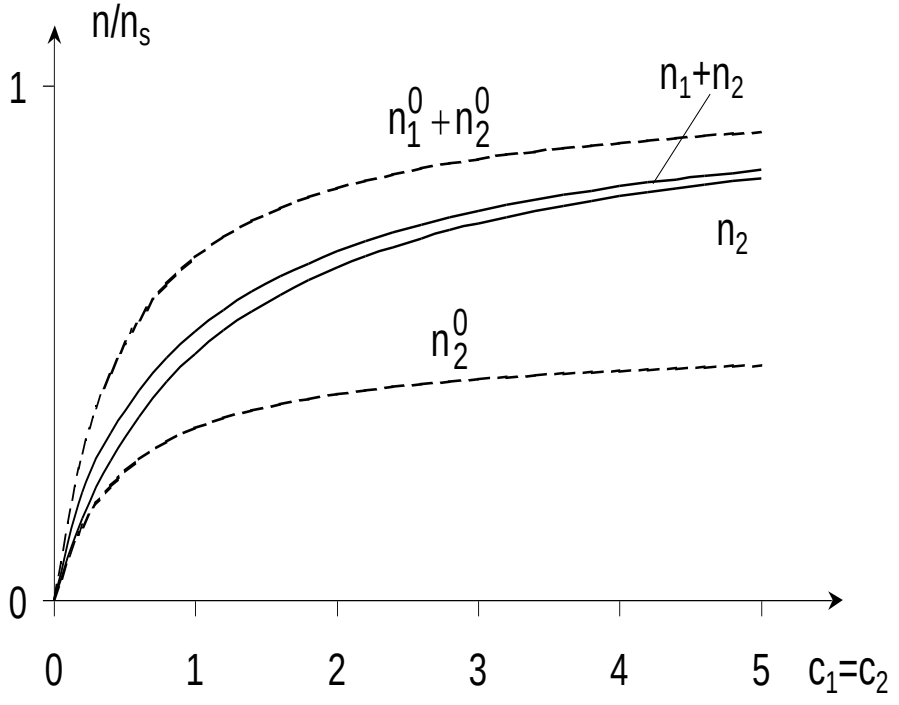
Replacement Adsorption, Langmuir Model (N=2), Equilibria

Coadsorption Equilibria

Example 1

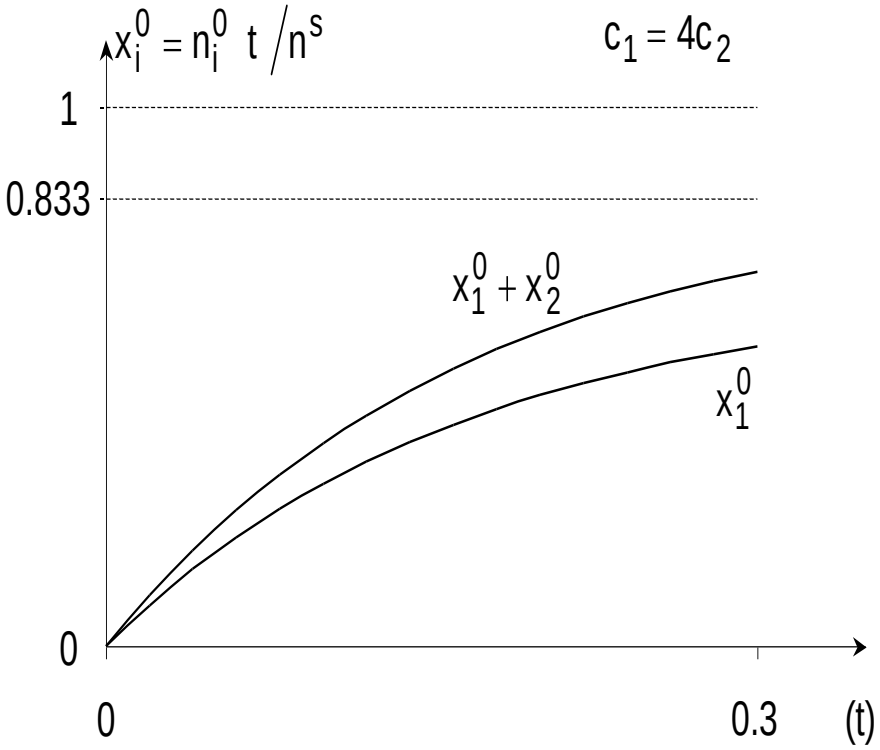


Example 2

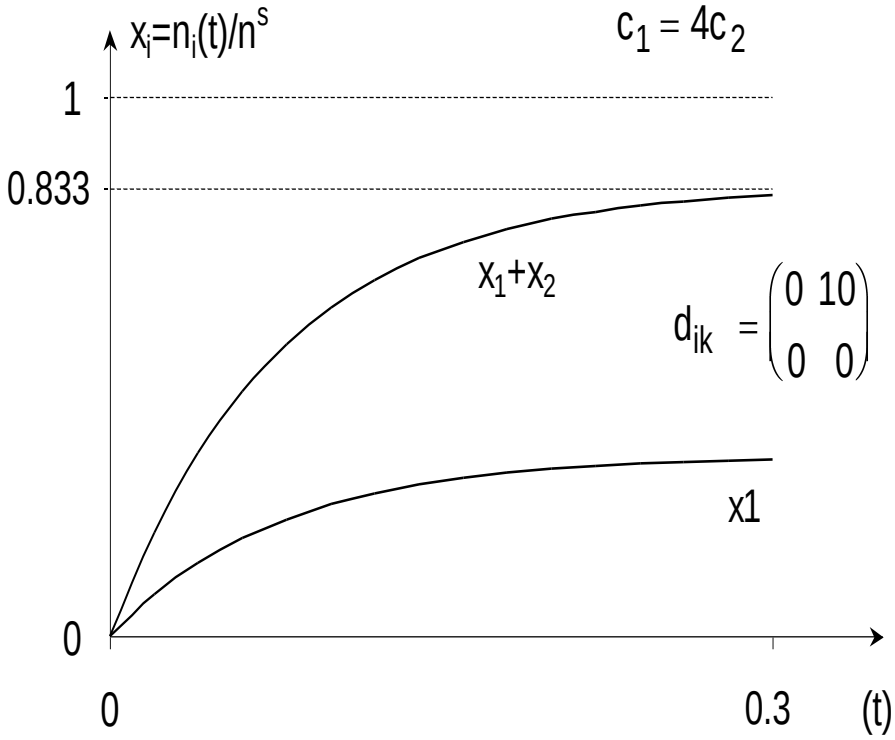


Replacement Adsorption, Langmuir Model (N=2), Equilibria

Coadsorption Kinetics

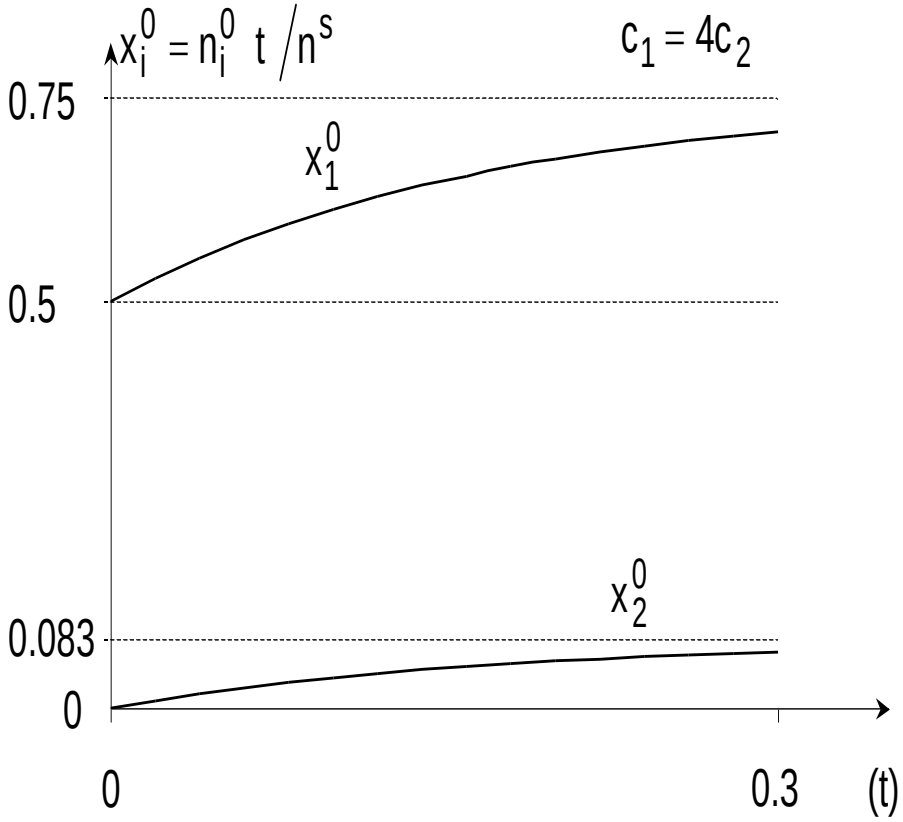


Kinetics of Coadsorption Process with Replacement (1→2)

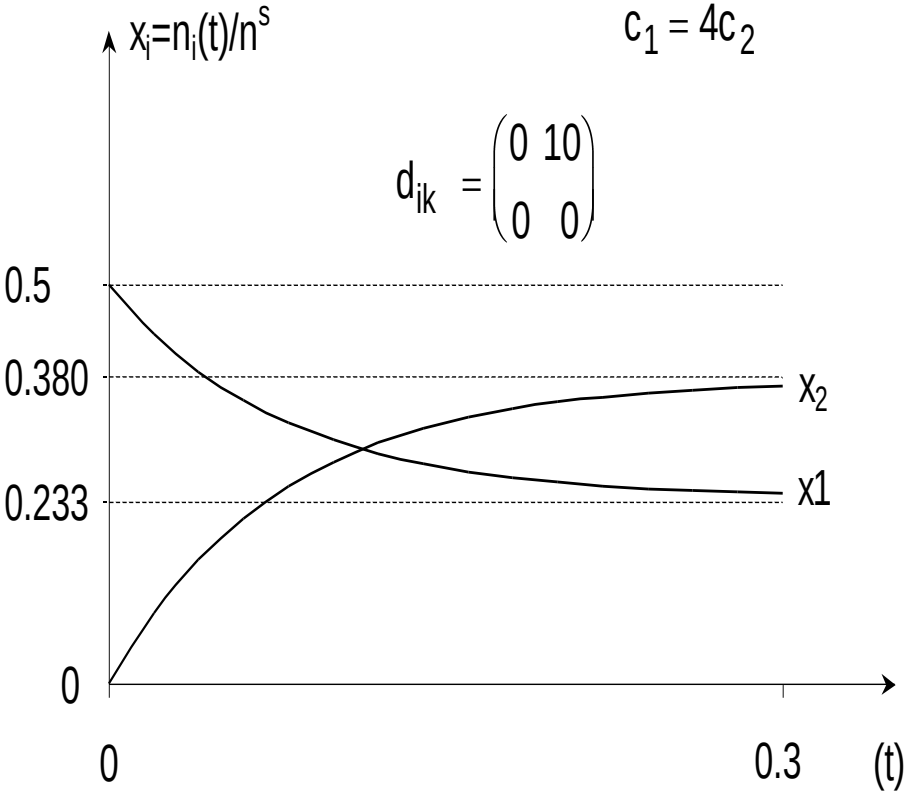


Replacement Adsorption, Langmuir Model (N=2), Kinetics (1)

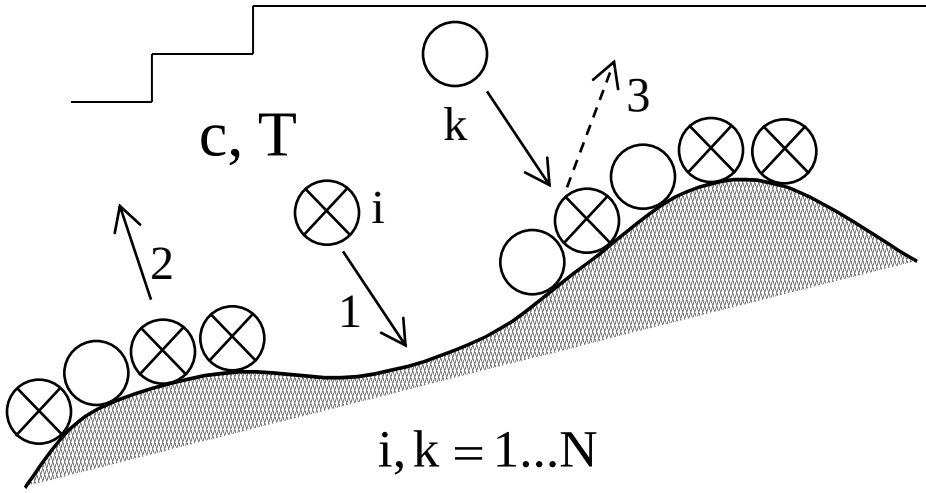
Coadsorption Kinetics



Kinetics of Coadsorption Process with Replacement (1→2)



Replacement Adsorption, Langmuir Model (N=2), Kinetics (2)



$$i,k = 1...N$$

Equilibria

$$n_i\ \ c_1...c_N\ = n^s \frac{b_i c_i}{1+\sum_k^N d_{ik} c_k} \cdot \frac{1}{1+\Sigma}$$

$$\Sigma = \sum_k^N \frac{b_k c_k}{1+\sum_l^N d_{kl} c_l} \quad , \quad i = 1...N$$

$$dn_i^+ = k_i c_i\ \ n^s - n\ \ dt\ \ ...1$$

$$dn_i^- = \left(k_i^- n_i + \sum_k^N l_{ik}^- c_k n_i \right) dt\ \ ...2,3$$

$$d_{ik} = 0 \quad , \quad i,k = 1...N$$

$$b_i = \frac{k_i^+}{k_i^-} > 0 \quad , \quad d_{ik} = \frac{l_{ik}^-}{k_i^-} \geq 0$$

$$n_i^0\ \ c_1...c_N\ = n^s \frac{b_i c_i}{1+\sum_k b_k c_k}$$

$$n = \sum_i^N n_i$$

$$\frac{n_i}{n_i^0} \leq 1$$

Replacement Adsorption, Langmuir Model (N≥1), Equilibria

Institute of Fluid- & Thermodynamics
Prof. Dr. sc. techn. Jürgen U. KELLER

Kinetics of Adsorption Process

$$dn_i = dn_i^+ - dn_i^- \quad , \quad i = 1...N$$

coefficients of replacement

$$k_i^+ c_i n^s = \dot{n}_i + k_i^+ c_i n + \left(k_i^- + \sum_k l_{ik}^- c_k \right) n_i$$

desorption

adsorption

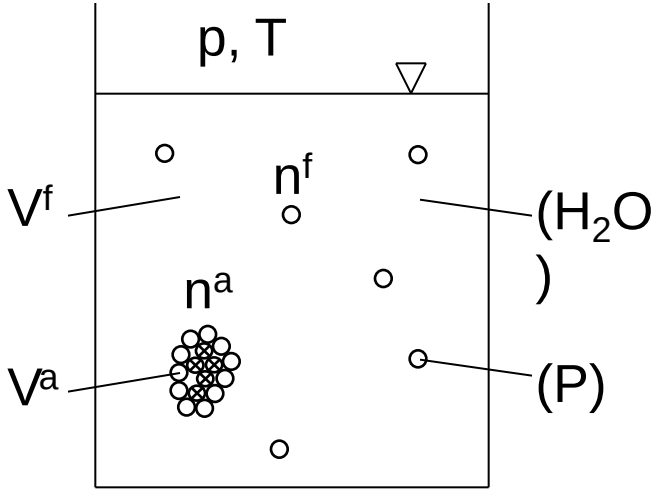
$$n = \sum_i^N n_i$$

$$n_i \ t = \sum_{k=1}^N C_{ik} e^{\lambda_k t} + C_{i0}$$

$$\begin{pmatrix} 1...i-1 & i & i+1...N \\ k_i^+ c_i ... k_i^+ c_i & \left(k_i^+ c_i + k_i^- + \sum_k l_{ik}^- c_k - \lambda \right) & k_i^+ c_i ... k_i^+ c_i \end{pmatrix} = 0 \rightarrow \lambda_k = \lambda_k \ c_1 ... c_i ... c_N, l_{ik}^- \quad , \ k = 1...N$$

Replacement Adsorption, Langmuir Model (N≥1), Kinetics

Protein Aggregation, Thermodynamic Equilibria States



$$n = n^a + n^f \qquad 1$$

$$V = V^a + V^f \qquad 2$$

$$V^a = \varphi n^a \qquad 3$$

$$\varphi = \frac{1}{4} b_w \doteq \frac{1}{12} V_{mc}$$

$$V^f = V^f\ n_w, n^f, p, T \qquad 4$$

Aggregation Model

$$dn^{a+} = k^+\ n^a{}^{\alpha}\ c^f\ dt \qquad 5$$

$$dn^{a-} = k^-\ n^a{}^{\alpha}\ dt \qquad 6$$

$$\alpha \cong \frac{2}{3}\ ,\quad c^f = n^f / V^f$$

Equilibria: $b \doteq k^+ / k^- = b\ T$

$$5,6\quad n^a = \frac{V - nb}{\varphi - b} \qquad 7$$

$$x^a = \frac{n^a}{n} = \frac{V_m - b}{\varphi - b} \qquad 7a$$

$$2,3\quad n^a = n - V^f / b \quad \geq 0 \qquad 8$$

$$x^a \approx 1 - V_m^f / b \quad \geq 0 \qquad 8a$$

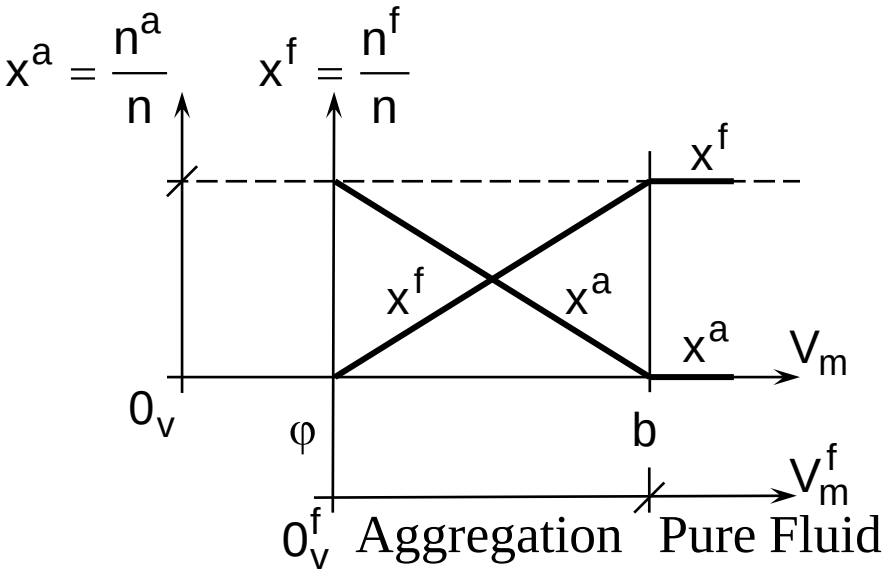
$$x^f = \frac{n^f}{n} = V_m^f / b \leq 1 \qquad 9$$

$$G: n, n_w, p, T; \varphi, b = k^+ / k^-$$

$$U: n^a, n^f, V^a, V^f, V$$

$$4,8 \quad n^a = n - V^f\ n_w, n - n^a, p, T\ /b \quad 10$$

$$n^a \cong n - V^f\ n_w, p, T\ /b \geq 0 \quad 10a$$



Limiting protein concentration for aggregation: $n^a = 0$

$$\rightarrow V^f\ n_w, n, p, T = nb \quad 11$$

$$n = 1$$

$$11 \quad V^f\ n_w^*, n = 1, p, T = b\ T$$

$$n_w^* = n_w^*\ p, T, b \quad 12$$

$$\left[n_w^* \right] = \text{mol } H_2O \ / \text{mol P}$$

Protein Aggregation, Thermodynamic Equilibria States

Dynamic Model

$$dn^a = dn^{a+} - dn^{a-}$$

$$5,6 \quad dn^a = k^+ c^f - k^- \; n^a \;^{\alpha} dt$$

$$\text{ODE:} \quad \dot{n}^a + \left(k^- - k^+ \frac{n - n^a}{V - \varphi n^a} \right) n^a \;^{\alpha} = 0 \quad 13$$

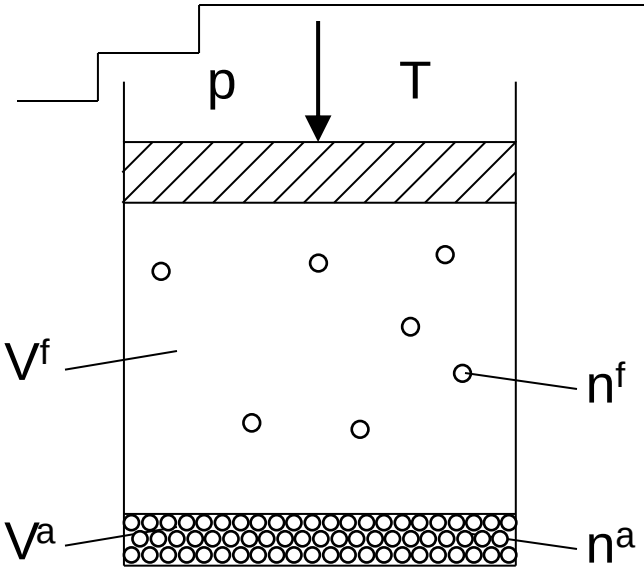
$$P: \; n, V \; n_w, n, p, T \; , \varphi, k^{\pm}, \alpha \cong 2/3$$

$$IC: n^a \; 0 \; = n_0^a$$

Implicit numerical methods

Alzheimer's decease?

Protein Aggregation, Kinetic Theory



Sublimation Model

$$dn^{a+} = k^+ \; n^a \; {}^{\alpha} c^f \, dt \qquad 5$$

$$dn^{a-} = k^- \; n^a \; {}^{\alpha} \, dt \qquad 6$$

$$\alpha \cong \frac{2}{3} \; , \quad c^f = n^f / V^f$$

$$b \; T \doteq k^+ / k^- = V_a^* \exp \; q_{av} / RT$$

$$n = n^a + n^f \qquad 1$$

$$V = V^a + V^f \qquad 2$$

$$V^a = \varphi n^a \qquad 3$$

$$V^f = V^f \; n^f, p, T \qquad 4$$

Equilibria States:

5,6 $\quad V^f \; n^f, p, T = n^f b \qquad 7$

$$n^f = 1$$

7 $\quad V_m^f \; p, T = V_a^* \exp \; q_{af} / RT \qquad 7a$

IG; 7a $\quad p = \dfrac{RT}{V_a^*} \exp \; -q_{af} / RT \qquad 9$

Aggregation / Sublimation of Pure Substances

7 $V_m^f(p,T) = V_a^* \exp(q_{af}/RT)$ 7a

$\lim_{T\to\infty} b(t) = V_a^*$ ... limiting volume for aggr.

$f = v$: Sublimation

$f = l$: Solidification, Freezing

f: IG: $V_m^f = RT/p$ 8

7a,8 $p = \frac{RT}{V_a^*} e^{-q_{av}/RT}$ 9

Reference state (Triple state)

9 $p_{tr} = \frac{RT_{tr}}{V_a^*} e^{-q_{av}/RT_{tr}}$ (9 tr)

(9,9 tr) $p = p_{tr}\left(\frac{T}{T_{tr}}\right) e^{-q_{av}\left(\frac{1}{T}-\frac{1}{T_{tr}}\right)}$ (10)

Example: CO_2

$M = 44\,g/mol$, $p_{tr} = 5.18\,bar$

$T_{tr} = 216.5\,K = -56.6\,°C$

Sublimation enthalpy

Exp: $q_{av}(T_{tr}) = 23.3\,kJ/mol$

Trouton: $q_{av}(T_{tr}) = 21.5\,kJ/mol$

Limiting gas volume 9 tr

$V_a^* = 565\,m^3/mol$

$T = 193\,K$: 10 : $p = 1.07\,bar$

IGA : $p = 1.20\,bar$

Exp : $p = 1.00\,bar$

Aggregation / Sublimation of Pure Substances (CO_2)

Dynamic Model

$$dn^a = dn^{a+} - dn^{a-}$$

5,6 $$dn^a = k^+ c^f - k^- \; n^a \;^{\alpha} dt$$

ODE: $$\dot{n}^a + \left(k^- - k^+ \frac{n - n^a}{V^f \; n - n^a, p, T} \right) n^a \;^{\alpha} = 0 \quad 11$$

$$P: \; n, p, T, k^{\pm}, \alpha \cong 2/3$$

$$IC: n^a \; 0 \; = n_0^a$$

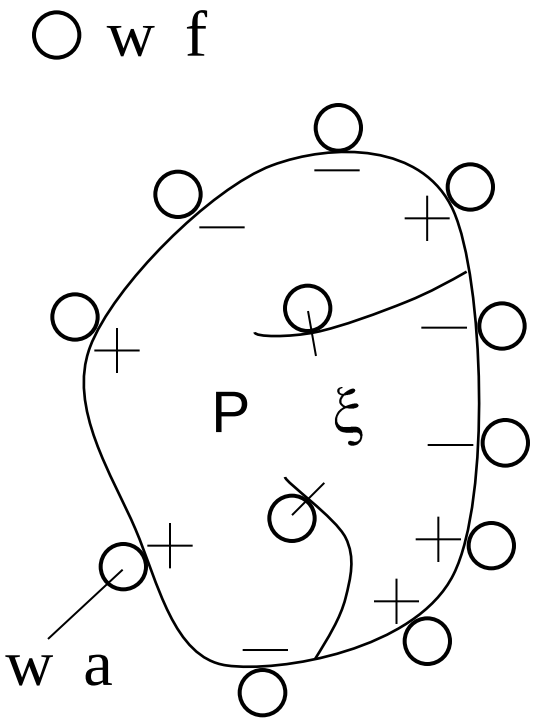
Implicit numerical methods

A. Mersmann, Crystallization

Aggregation / Sublimation, Kinetic Theory

Hydratization Process of Proteins (Water Intrusion) I

Simple Thermodynamic Formalism



Water:

$T, p, \mu_w^f = \mu_w^a = \mu$

Stimulus: Chemical potential of water: $\mu = \mu\ p, T, \ldots$

Response: Adsorption of water on P

AI: $n = n\ \mu, T = \text{const}\ = n_0 + H_0\ T\ \ \mu - \mu_0\ + O\ 2$

Number of Adsorption sites: ξ ... Internal variable!

a) $\xi = \xi_E = \text{const}$ ... equilibrium : $\xi = \xi_E\ (n, T = \text{const}$

b) $\xi \neq \xi_E$ ... variable ... non-equilibrium:

$A = A\ (n, T = \text{const}, \xi) \neq 0$

Affinity: Measure for non-equ. deviation.

Hydratization Process of Proteins (Water Intrusion) II

Thermostatics 1

Free energy of (P, w)-system:

$$F = F\ n, \xi, T\ = -S\,dT + \mu\,dn - A\,d\xi \quad , \quad T = \text{const}$$

$$\mu = \left(\frac{\partial F}{\partial n}\right)_{T,\xi} = \mu\ n, \xi, T\ \ldots \text{AI}$$

$$-A = \left(\frac{\partial F}{\partial \xi}\right)_{T,n} = -A\ n, \xi, T\ \ldots \text{IEOS}$$

External & internal or full equilibrium: $F \rightarrow \text{Min}$, $T = \text{const}$, $n = \text{const}$

$$A\ n, \xi, T\ = 0 \rightarrow \xi_E = \xi_E\ n, T\ = \text{const}$$

External equilibrium only (restricted equilibrium), $T = \text{const}$:

$A \neq 0$ ξ ... arbitrary value

Hydratization Process of Proteins (System: P, w(a))

Free Energy, Taylor Series

$$F\ n,\xi,T\ = F_{00} + F_{10}n + F_{01}\xi + \frac{1}{2!}\ F_{20}n^2 + 2F_{11}n\xi + F_{02}\xi^2\ + O\ 3$$

Thermodynamic Stability (2nd Law): $\left\|\partial^2 F/\partial n\,\partial\xi\right\| > 0\ ,\ F_{ik} = F_{ik}\ T$

$$\rightarrow F_{20} \geq 0\ ,\ \ F_{20}F_{02} - F_{11}^2 > 0\ ,\ \ F_{02} \geq 0$$

Reference State: $Z_0\ \ n_0, \mu_0, \xi_0, A_0 = 0, T$

Equations of State:

$$\mu = \ \partial F/\partial n\ _{\xi,T} \quad : \quad \mu - \mu_0 = F_{20}\ \ n - n_0\ + F_{11}\ \ \xi - \xi_0 \qquad 1$$

$$-A = \ \partial F/\partial \xi\ _{n,T} \quad : \quad -A = F_{11}\ \ n - n_0\ + F_{02}\ \ \xi - \xi_0 \qquad 2$$

Internal Equilibrium: $A\ \ n, \xi_E T\ = 0\ ,\ \xi_E - \xi_0 = -\frac{F_{11}}{F_{02}}\ \ n - n_0$

$$1 : \underline{\underline{n - n_0 = H\ \ \mu - \mu_0}}\ ,\ H = \frac{F_{02}}{F_{20}F_{02} - F_{11}^2} > H_0 = \frac{1}{F_{20}}$$

Hydratization Process of Proteins (System: P, w(a))

Thermodynamics of Processes

1st Law: $dU = dQ + h\,dn + 0$

2nd Law: $dS = \frac{1}{T}dU - \frac{\mu}{T}dn + \frac{A}{T}d\xi$

$$dS = \frac{Q}{T} + s\,dn + dS_{in}$$

$$\mu = h - Ts \qquad P_s = \dot{S}_{\dot{m}} = \frac{A}{T}\dot{\xi} \geq 0$$

Eckart-Onsager: $\Delta\ \dot{\xi} = \alpha\ \ n, \xi, T\ \ A + O\ \ A^2$

Equations of State: $\Delta\mu = F_{20}\Delta n + F_{11}\Delta\xi$

$$-A = F_{11}\Delta n + F_{02}\Delta\xi$$

*

$\Delta\mu\ \ t\ = \mu - \mu_0 \rightarrow \Delta n\ \ t\ = n - n_0\ ,\ \Delta\xi\ \ t\ = \xi - \xi_0\ ,\ A = A\ \ t\ \rightarrow 0!$

Stimulus Adsorption Structure Equilibrium

Hydratization Process of Proteins (System: P, w(a))

Stimulus : $\Delta\mu = \mu\ p, T, \ldots\ - \mu_0$

Adsorption: $\Delta n = n\ t\ - n_0$

Structure : $\Delta\xi = \xi\ t\ - \xi_0$ ... adsorption sites

$$\tau_n \Delta\dot{\mu} + \Delta\mu = E\ \Delta n + \tau_\mu \Delta\dot{n}$$ (Poynting, Elastic Relax.)

* $\tau_n^{-1} = \alpha F_{02} > 0\ ,\ E = F_{20} - \frac{F_{11}^2}{F_{02}} \geq 0\ ,\ \tau_\mu^{-1} = \left(F_{02} - \frac{F_{11}^2}{F_{20}} \right) \alpha > 0$

$\tau_n < \tau_\mu$

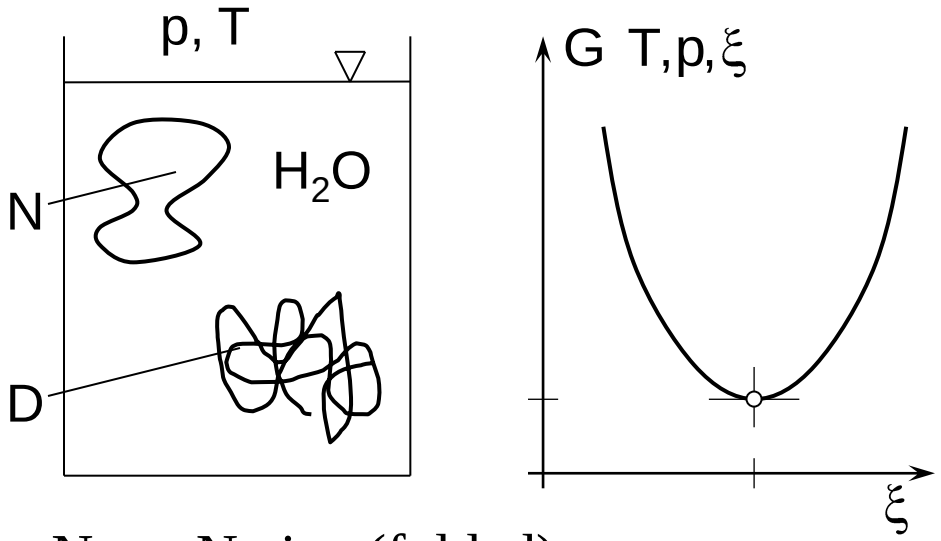
Adsorption Process

$$\Delta n\ t\ = \frac{1}{\tau_\mu E} \int_0^t ds \left[\Delta\mu\ s\ + \tau_n \Delta\dot{\mu}\ s\ \right] e^{-\ t-s\ /\tau_\mu} ds$$

Protein structure / Adsorption sites

$$\Delta\xi\ t\ = \frac{1}{F_{11}} \left\{ \Delta\mu - \alpha F_{20} \int_0^t ds \left[\Delta\mu\ s\ + \tau_n \Delta\dot{\mu}\ s\ \right] \right\} e^{-\ t-s\ /\tau_\mu} ds$$

Denaturation of Proteins, Thermodynamic Analysis, Equilibria



N ... Native (folded) state

D ... Denaturated (unfolded) state

N↔D Quasichemical reaction (ξ)

$$G = G\ T,p,n_N,n_D = \mu_N n_N + \mu_D n_D \quad 1$$

$$dG = -S\,dT + V\,dp + \mu_N\,dn_N + \mu_D\,dn_D \quad 2$$

Equilib.: $G \rightarrow \text{Min}, T = \text{const},$

$$p = \text{const}, n = \text{const}$$

$$dG = 0\ ,\ d^2G > 0 \quad 3$$

Reaction parameter:

$$n_N = n_{N0} - \xi\ ,\ dn_N = -d\xi$$

$$n_D = n_{D0} + \xi\ ,\ dn_D = \ d\xi$$

$$2,3 : dG = \ -\mu_N + \mu_D\ d\xi = 0$$

$$\rightarrow \quad \underline{\mu_N = \mu_D} \quad 4$$

$$\mu_i = \mu_{i0}\ T,p\ + RT\ln\ \gamma_i x_i\ ,\ i = D,N \quad 5$$

$$5\ ,\ 4\ \underbrace{\mu_{N0} - \mu_{D0}} = RT\ln\ \gamma_D x_D / \gamma_N x_N$$

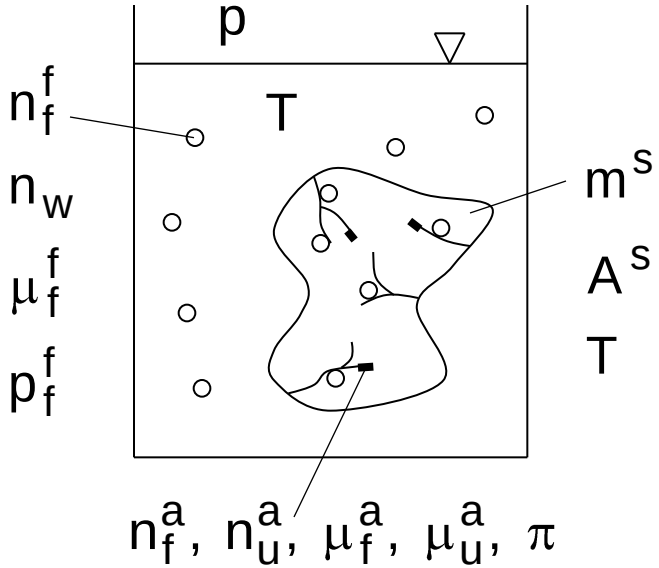
$$-\Delta G = RT\ln K_{eq}\ T,p$$

$$K_{eq} \doteq \frac{\gamma_D x_D}{\gamma_N x_N} = e^{-\Delta G/RT} \quad 6$$

Ideal solution: $\gamma_D = \gamma_N = 1$

Real solution: Margules,van Laar ...

Denaturation of Adsorbed Protein by Unfolding, Thermostatic Equ.



Sorptive Sorbate Sorbent

(f↔u): Chemical equilibrium

$$G^a\ T,\pi^a,n_f^a,n_u^a \rightarrow \text{Min}$$

$$T = \text{const},\ \pi^a = \text{const} \qquad 1$$

$$n^a = n_f^a + n_u^a = \text{const}$$

$$1 \rightarrow \mu_f^a = \mu_u^a \qquad 1A$$

Chemical potentials:

$$\mu_i^a\ T,\pi,n_f^a,n_u^a = \mu_{i0}^a\ T,\pi + RT\ln\ \gamma_i^a x_i^a \qquad 2$$

Adsorption equilibria of pure components (f,u):

$$\mu_{i0}^a\ T,\pi = \mu_i^f\ T,p_i^f\ ,\ i = f,u \qquad 3$$

$$1A,2,3 : \frac{\gamma_f^a x_f^a}{\gamma_u^a x_u^a} = K\ T,p_f^f,p_u^f = \exp\left(-\frac{\mu_f^f - \mu_u^f}{RT}\right) \qquad 4$$

Protein / Water ≅ Ideal gas / Vacuum

$$\mu_i^f\ T,p_i^f = \mu_i^f\ T,p^+ + RT\ln\left(\frac{p_i^f}{p^+}\right) \qquad 5$$

$$p_i^f = \frac{n_i^f}{n}\cdot\frac{nRT}{V\ n_w,n_f,n_u,p,T}\ ,\ i = f,u$$

Denaturation of Adsorbed Protein by Unfolding, Equilibria (2)

Law of Mass Action

$$4,5 \qquad \frac{\gamma_f^a x_f^a}{\gamma_u^a x_u^a} = K\ T,p^+ \left(\frac{p_u^f}{p_f^f}\right)$$

$$6 \rightarrow 8,9 : \frac{\gamma_f^a n_f^a}{\gamma_u^a n_u^a} = \overbrace{\left(K^+ \frac{b_f}{b_u}\right)}^{K_{fu}} \frac{n_u^a / n_{u\infty}}{n_f^a / n_{f\infty}} \left(1 - \frac{n_f^a}{n_{f\infty}}\right) \qquad 10$$

$$n = n_f + n_u = \text{const} \qquad 11$$

$$K^+ = K\ T,p^+ = \exp\left(-\frac{\mu_f^f\ T,p^+ - \mu_u^f\ T,p^+}{RT}\right) \qquad 7$$

Adsorption Isotherms of pure components (f,u):

$$n_f^a = n_{f\infty} \frac{b_f p_f^f}{1 + b_f p_f^f} \qquad 8$$

$$n_u^a = n_{u\infty} b_u p_u^f \qquad 9$$

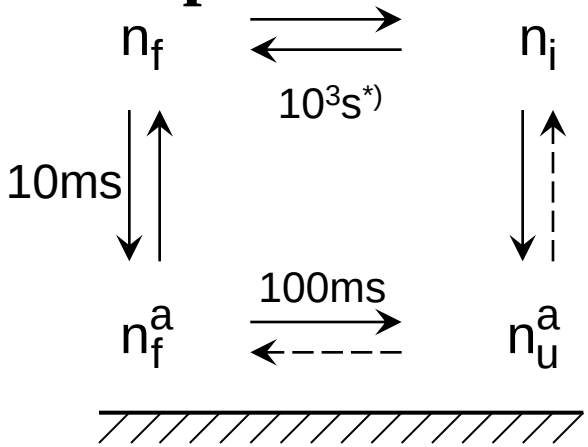
$10,11 \rightarrow n_f, n_u$ .... $K_{fu}, n_{f\infty}, n_{u\infty}$

Ideal adsorbate approx.: $\gamma_f^a = \gamma_u^a = 1$

Calib. exp.: $n_{f\infty}, n_{u\infty}$

1^{st} Meas. : $n_f^a, n_u^a \rightarrow K_{fu}$

Adsorption-Induced Unfolding of Proteins, Basic Concepts



Mole Numbers :

n_f ... folded or native state

n_i ... intermediate or partially unfolded state (molten globule)

n_f^a ... native state adsorbed

n_u^a ... unfolded or denaturated state of adsorbed protein

Measurement Methods

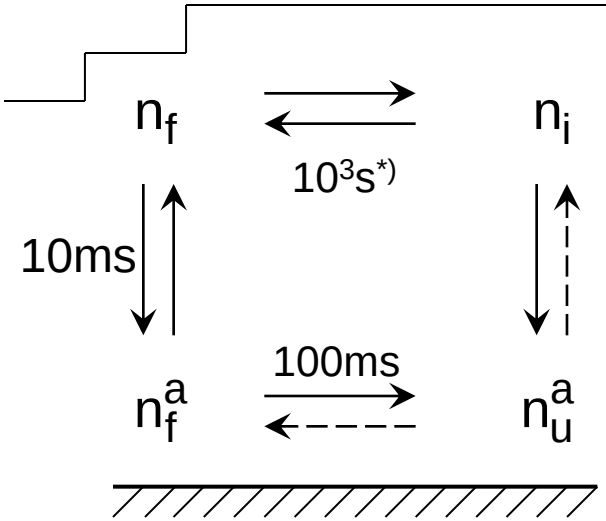
1. Enthalpy changes during defolding
   Intramolecular changes
   Multiple adsorption contacts
   Changes of heat capacity

2. Spectroscopy
   Fluorescence
   Light scattering
   Light absorption

3. Dielctric permittivity

4. Release of ions or atomic groups during (f $\rightarrow$ u)

*) Relax. times for Bovine α-lactalbumin on polystyrene nanospheres (d≅ 100nm), Engel et al., J. Biol. Chem. 277 (2002), 10922



Process equations

$$dn_f = d\xi_{fi} - dn_{fa} \quad 1$$

$$dn_i = -d\xi_{fi} - dn_{ia} \quad 2$$

$$dn_f^a = dn_{fa} - dn_{af}^a \quad 3$$

$$dn_u^a = dn_{fu}^a + dn_{ia} \quad 4$$

n_{xy} ... from phase (x) to phase (y)

Model equations for

Chemical reaction ($f \leftrightarrow i$)

$$d\xi_{fi} = L\ \mu_f - \mu_i\ dt \quad \text{... TIP} \quad 5$$

$$\mu_f = \mu_{f0}\ p^*, T\ + RT \ln x_f$$

$$\mu_i = \mu_{i0}\ p^*, T\ + RT \ln x_i$$

Adsorption / Desorption (f)

$$dn_{fa} = k_f^+\ n_\infty - n_f^a - n_u^a\ c_f\ dt \quad 6$$

$$dn_{af}^a = k_f^- n_f^a\ dt$$

Adsorption (i)

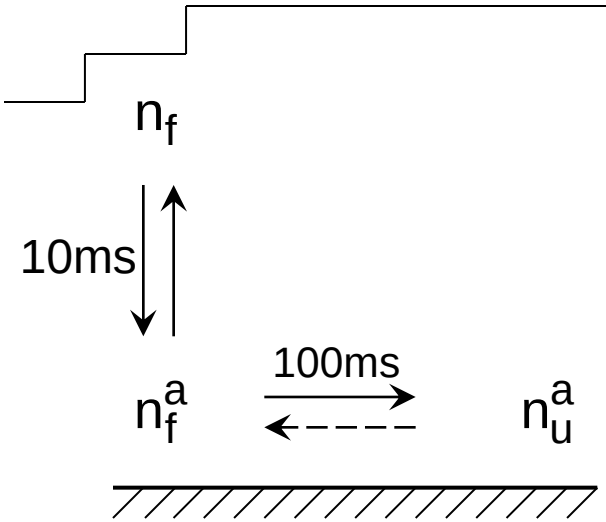
$$dn_{ia} = k_i^+\ n_\infty - n_f^a - n_u^a\ c_i\ dt \quad 7$$

Unfolding process ($f \rightarrow u$)

$$dn_{fu}^a = \frac{1}{\tau_{fu}} n_f^a\ dt \quad 8$$

Adsorption-Induced Unfolding of Proteins, Langmuir Model:

4 ODE n_f, n_f^a, n_i, n_u^a **IC.**



Model equations (5 – 8):

Protein balance (f)

$$\dot{n}_f = -k_f^+ \; n_\infty - n_f^a - n_u^a \; c_f + k_f^- n_f^a \qquad 9$$

Protein balance (a)

$$\dot{n}_f^a = k_f^+ \; n_\infty - n_f^a - n_u^a \; c_f - k_f^- n_f^a - \frac{1}{\tau_{fu}^a} n_f^a \qquad 10$$

Unfolding process (relaxation process)

$$\dot{n}_u^a = \frac{1}{\tau_{fu}^a} n_f^a \qquad 11$$

Process equations

$$dn_f = -dn_{fa} \qquad 1$$

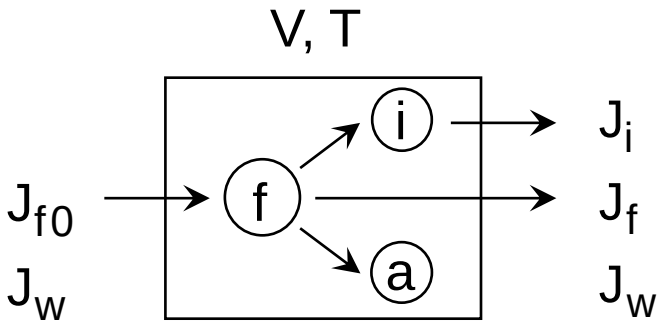
$$dn_f^a = dn_{fa} - dn_{fu}^a \qquad 3$$

$$dn_u^a = dn_{fu}^a \qquad 4$$

Equ. state: $n_f^a = 0$, $n_u^a = n_\infty$, $n_f = n_f \;\; 0 \;\; - n_\infty$

Adsorption-Induced Unfolding of Proteins, Simple Langmuir Model: 3 ODE n_f, n_f^a, n_u^a ,Initial Conditions

Adsorption Reactors with Incomplete Breakthrough (1)

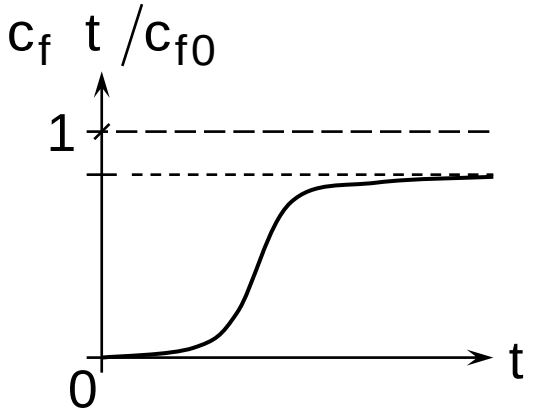


$$N_f, N_i, N_a, N_w = \text{const}$$

Molarities

$$c_{f0} = \frac{N_{f0}}{V}, \quad c_f = \frac{N_f}{V}$$

$$c_i = \frac{N_i}{V}, \quad c_w = \frac{N_w}{V} = \text{const}$$



Molar balances

$$\dot{N}_f = J_{f0} - J_f - J_{fa} + J_{af} - J_{fi} \quad 1$$

$$\dot{N}_i = J_{fi} - J_{if} - J_i \quad 2$$

$$\dot{N}_a = J_{fa} - J_{af} \quad 3$$

Molar flows : $J_\alpha = c_\alpha J_V$

Volume flow: J_V , $\alpha = f, i, w$

$$J = \frac{\text{mol}}{\text{s}}, \quad J_V = \frac{\text{l}}{\text{s}}$$

Model equations for :

Adsorption / Desorption

$$J_{fa} = k^{+} \left(N_{a\infty} - N_a \right) c_f \qquad 4$$

$$J_{af} = k^{-} N_a \qquad 5$$

Mass exchange CSTR

$$J_f = c_f J_V = \frac{N_f}{V} J_V \qquad 6$$

$$J_i = c_i J_V = \frac{N_i}{V} J_V \qquad 7$$

Chemical reaction $f \leftrightarrow i$

$$J_{fi} = k_{fi} x_f \left(1 - x_i \right) \qquad 8$$

$$J_{if} = k_{if} x_i \left(1 - x_f \right) \qquad 9$$

Process equations 1-9 : 3 ODE

$$1 : \dot{N}_f = -\left[k^{+} \left(N_{a\infty} - N_a \right) \frac{N_f}{V} - k^{-} N_a^{-} \right] -$$

$$- \frac{k_{fi}}{N^2} N_f \left(N_f + N_w \right) + \left(N_{f0} - N_f \right) \frac{J_V}{V} \qquad 11$$

$$2 : \dot{N}_i = \frac{k_{fi}}{N^2} N_f \left(N_f + N_w \right) - \frac{k_{if}}{N^2} N_i \left(N_w + N_i \right) -$$

$$- N_i \frac{J_V}{V} \qquad 12$$

$$3 : \dot{N}_a = k^{+} \left(N_{a\infty} - N_a \right) \frac{N_f}{V} - k^{-} N_a \qquad 13$$

Initial conditions: $t = 0, N_{f0}, N_{i0}, N_{a0},$

$N_w = \text{const}$

$x_f = c_f / c = N_f / N, \; x_i = c_i / c = N_i / N, \; c = c_f + c_i + c_w, \; N = N_f + N_i + N_w$

Adsorption Reactors with Incomplete Breakthrough (2)

Stationary States : $\dot{N}_x = 0\ ,\ x = f,i,a$

$$11: N_f\ N_f + N_w\ = K_c\ N_{f0} - N_f\ \ N_f + N_i + N_w\ ^2$$

$$12: N_f\ N_f + N_w\ - K_c N_i\ N_i + N_w\ =$$

$$= K N_i\ N_f + N_i + N_w\ ^2$$

$$13: \quad N_a = N_{a\infty} \frac{k N_f}{1 + k N_f}$$

$$D: \quad K = \frac{J}{V k_{fi}}\ ,\ k = \frac{k^+}{k^- V}$$

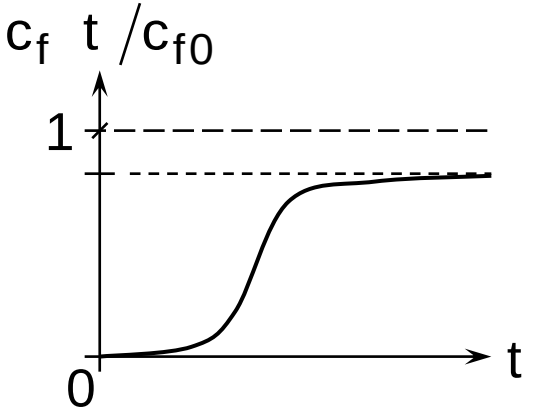
$$K_c = \frac{k_{if}}{k_{fi}}$$

Diluted Solutions : $N_w \gg N_f\ ,\ N_i$

$$14 \rightarrow N_f = \frac{K}{1+K} N_{f0} < N_{f0}$$

$$15 \rightarrow N_i = \frac{N_f}{K N_w + K_c} > 0$$

$$16 \quad \frac{c_f}{c_{f0}} = \frac{N_f}{N_{f0}} = \frac{K}{1+K} < 1$$



Adsorption Reactors with Incomplete Breakthrough (3)

Kinetics: Dilute Solutions Approximation: $N_w >> N_f, N_i, N_w = \text{const}$

$$11: \dot{N}_f = N_{f0} - N_f \frac{J_V}{V} - \left[k^+ N_{a\infty} - N_a \frac{N_f}{V} - k^- N_a \right] - k_{fi} \frac{N_f}{N_w} \qquad 11a$$

$$12: \dot{N}_i = k_{fi} \frac{N_f}{N_w} - k_{if} \frac{N_i}{N_w} - N_i \frac{J_V}{V} \qquad 12a$$

$$13: \dot{N}_a = k^+ N_{a\infty} - N_a \frac{N_f}{V} - k^- N_a \qquad 13a$$

Parameter: $N_{a\infty}, k^+, k^-, N_{f0}, k_{fi}, k_{if}, N_w, J_V/V$

NL-ODE: 3, U: $N_f\ t$, $N_i\ t$, $N_a\ t$

Special Cases

1) No Adsorption

$$11a: \dot{N}_f = N_{f0} - N_f \frac{J_V}{V} - k_{fi} \frac{N_f}{N_w}$$

$$12a: \dot{N}_i = k_{fi} \frac{N_f}{N_w} - k_{if} \frac{N_i}{N_w} - N_i \frac{J_V}{V}$$

2) No Chemical Reaction (f $\leftrightarrow$ i)

$$11a: \dot{N}_f = N_{f0} - N_f \frac{J_V}{V} - \left[k^+ N_{a\infty} - N_a \frac{N_f}{V} - k^- N_a \right]$$

$$13a: \dot{N}_a = k^+ N_{a\infty} - N_a \frac{N_f}{V} - k^- N_a$$