Quaternary Inhibition

Onsite → $q_j = \frac{q_j}{q_j^r} \neq 0$

Offsite → $q_j = 0$

Equations are exactly the same.

Reactions

$$x_{i,j} \xrightarrow{r_{i,j}} g_{i,j} + x_{i,j} \qquad \boxed{I}$$

$$g_{i,j} \xrightarrow{\delta_g} \phi$$

$$g_{i,j} + dtm \underset{K^-_{i,j}}{\overset{K^+_{i,j}}{\rightleftharpoons}} c_{i,j} \qquad \boxed{II}$$

$$c_{i,j} + D_i \underset{q^-_{i,j}}{\overset{q^+_{i,j}}{\rightleftharpoons}} C_{i,j} \qquad \boxed{III}$$

$C_{i,j} + D_{i,j} \xrightarrow{q^-_{i,j}} C_{i,j}$ III

$C_i \xrightarrow{k_i} G + C_i$ IV

$D_j \xrightarrow{k_j} G + D_j$ V

$G \xrightarrow{\delta_G} \phi$

Math - Rate Eqns

$$\dot{x}_{i,j} = 0 \quad (1)$$

$$\dot{g}_{i,j} = \gamma_{i,j} x_{i,j} + \mu_{i,j} - \delta_g g_{i,j} - k^+_{i,j} g_{i,j} dm + k^-_{i,j} c_{i,j} \quad (2)$$

$$\dot{c}_{i,j} = k^+_{i,j} g_{i,j} dm - k^-_{i,j} c_{i,j} - q^+_{i,j} c_{i,j} D_{i,j} + q^-_{i,j} C_{i,j} \quad (3)$$

$$\dot{C}_{i,j} = q^+_{i,j} c_{i,j} D_{i,j} - q^-_{i,j} C_{i,j} \quad (4)$$

$$\dot{G} = k_i C_i + k_j D_j - \delta_G G \quad (5)$$

Math- QSSA

↳ Complex reaction rates are really fast

↳ Reaction II & III describe two different complex formation reactions

↳ QSSA :- $\dot{c}_{ij} = 0$ [$\dot{C}_{ij} = 0$

(a) (b)

(b) + (4)

↳ $0 = q^{+}_{ij} c_{ij} D_{ij} - q^{-}_{ij} C_{ij}$

$\Rightarrow C_{ij} = q_{ij} c_{ij} D_{ij}$ $\left(q_{ij} = \frac{q^{+}_{ij}}{q^{-}_{ij}}\right)$ (6)

(a) + (2)

↳ $0 = K^{+}_{ij} g_{ij} dm - K^{-}_{ij} c_{ij}$

$- q^{+}_{ij} c_{ij} D_{ij} + q^{-}_{ij} C_{ij}$

④ → = 0

$$\Rightarrow \underbrace{C_{ij} = K_{ij}\, g_{ij}\, dm}_{⑦} \quad \left(K_{ij} = \frac{K_{ij}^{+}}{K_{ij}^{-}}\right)$$

② + ⓐ + ⓑ

$$\dot{g}_{ij} = r_{ij}\, x_{ij} + \mu_{ij} - \delta_g\, g_{ij} + \underbrace{(\quad 0 \quad)}_{ⓐ} + \underbrace{(\quad 0 \quad)}_{ⓑ}$$

$$\Rightarrow \dot{g}_{ij} = r_{ij}\, x_{ij} + \mu_{ij} - \delta_g\, g_{ij}$$

Math - Competition btw Chemicals

↳ Since dCosq & MCP-SoxS has a limited availability, we need to make sure that total dCosq (d_t) & total MCP-SoxS concentrations are always a constant

$$d_t = d + c_i + c_j + C_i + C_j \quad ⑧$$

(d → free dCosq)

$$m_t = m + c_i + c_j + C_i + C_j \quad ⑨$$

↳ free MCP-sons

Also free DNA is limited as well.

$$\hookrightarrow \quad D_{i,j}^{t} = D_{i,j} + e_{i,j}$$

from ⑥ & ⑦

$$q_{i,j}\, K_{i,j}\, g_{i,j}\, dm\, D_{i,j}$$

$$\rightarrow D_{i,j}^{t} = D_{i,j}\,(1 + q_{i,j}\, K_{i,j}\, g_{i,j}\, dm)$$

$$\Rightarrow D_{i,j} = \frac{D_{i,j}^{t}}{1 + q_{i,j}\, K_{i,j}\, g_{i,j}\, dm} \qquad (10)$$

Math - Overall

Clubbing all the math equations together should basically lead us to...

$$\dot{g}_{i,j} = \gamma_{i,j}\, x_{i,j} + \mu_{i,j} - \delta_g\, g_{i,j} \qquad (1)$$

$$C_{ij} = K_{ij}\, g_{ij}\, dm \quad (2)$$

$$\mathcal{C}_{ij} = \frac{q_{ij}\, K_{ij}\, g_{ij}\, dm\, D_{ij}^{t}}{1 + q_{ij}\, K_{ij}\, g_{ij}\, dm} \quad (3)$$

$$D_{ij} = \frac{D_{ij}^{t}}{1 + q_{ij}\, K_{ij}\, g_{ij}\, dm} \quad (4)$$

$$d = d_t - d \cdot m \left(K_i g_i + K_j g_j \right) - d \cdot m \left(\frac{q_i K_i g_i D_i^{t}}{1 + q_i K_i g_i\, dm} + \frac{q_j K_j g_j D_j^{t}}{1 + q_j K_j g_j\, dm} \right) \quad (5)$$

$$m = m_t - d \cdot m \left(K_i g_i + K_j g_j \right) - d \cdot m \left(\frac{q_i K_i g_i D_i^{t}}{1 + q_i K_i g_i\, dm} + \frac{q_j K_j g_j D_j^{t}}{1 + q_j K_j g_j\, dm} \right) \quad (6)$$

$$\dot{G} = K_i \mathcal{C}_i + K_j D_j - \delta_G G \quad (7)$$

* For Offsite, the only difference is $q_j = 0$

Ternary Inhibition

- Onsite → $q_{i,j} \neq 0$
- Offsite → $q_j = 0$

Reactions

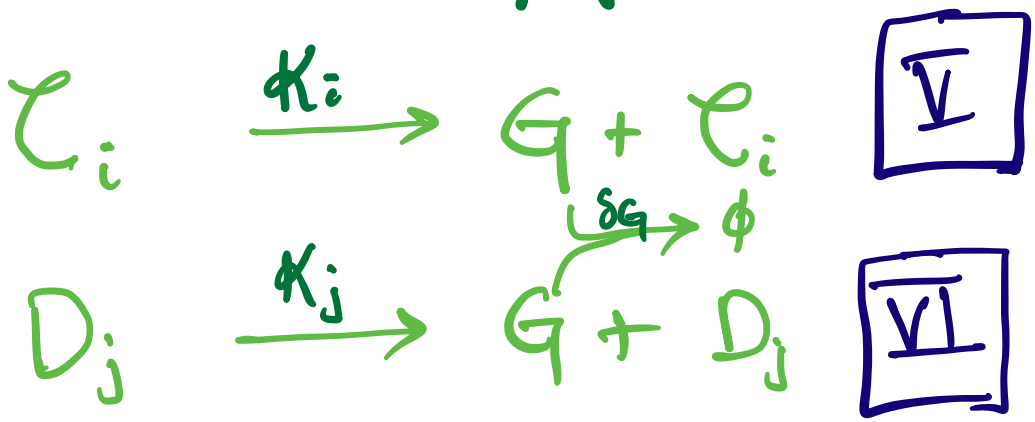
$$x_{i,j} \xrightarrow{r_{i,j}} g_{i,j} + x_{i,j} \quad \text{I}$$

$$g_{i,j} \xrightarrow{\delta_g} \phi$$

$$g_i + dtm \underset{K_i^-}{\overset{K_i^+}{\rightleftharpoons}} c_i \quad \text{II}$$

$$g_j + d \underset{K_j^-}{\overset{K_j^+}{\rightleftharpoons}} c_j \quad \text{III}$$

$$c_{i,j} + D_{i,j} \underset{q^-_{i,j}}{\overset{q^+_{i,j}}{\rightleftharpoons}} C_{i,j} \quad \text{IV}$$



Math - Rate Eqns

$$\dot{x}_{i,j} = 0 \quad (1)$$

$$\dot{g}_i = \mu_i + \gamma_i x_i - \delta_g g_i - K_i^+ g_i dm + K_0^- c_i \quad (2a)$$

$$\dot{g}_j = \mu_j + \gamma_j x_j - \delta_g g_j - K_j^+ g_j d + K_j^- c_j \quad (2b)$$

$$\dot{c}_i = K_i^+ g_i dm - K_i^- c_i - q_i^+ c_i D_i + q_i^- C_i \quad (3a)$$

$$\dot{c}_j = K_j^+ g_j d - K_j^- c_j - q_j^+ c_j D_j + q_j^- C_j \quad (3b)$$

$$\dot{C}_i = q_i^+ c_i D_i - q_i^- C_i \quad (4a)$$

$$\dot{c}_j = q_j^+ c_j D_j - q_j^- c_j \quad (4b)$$

$$\dot{G} = K_i c_i + K_j D_j - s_G G \quad (5)$$

Math - QSSA

Complex reactions → Real FAST!

↳ QSSA → $\dot{c}_i = 0$ (a)

↳ $\dot{c}_j = 0$ (b)

↳ $\dot{c}_{ij} = 0$ (c)

(c) + (4a/b)

↳ $0 = q_{ij}^+ c_{ij} D_{ij} - q_{ij}^- c_{ij}$

$$\Rightarrow \underline{c_{ij} = q_{ij} c_{ij} D_{ij}} \quad (6)$$

(a) + (4a)

↳ $0 = K_i^+ q_i \, dm - K_i^- c_i$

$$-q_i c_i D_i + q_i C_i$$

(c) $\rightarrow = 0$

$$\Rightarrow \quad C_i = k_i g_i dm \qquad (7a)$$

Illy (b) + (b)

$$\hookrightarrow \quad C_j = k_j g_j d \qquad (7b)$$

(2a) + (a) + (c)

$$\hookrightarrow \dot{g}_i = \mu_i + \gamma_i x_i - \delta_g g_i - k_i^+ g_i dm + k_i^- c_i$$

$$= 0$$

$$\Rightarrow \dot{g}_i = \mu_i + \gamma_i x_i - \delta_g g_i$$

Illy (2b) + (b) + (c)

$$\hookrightarrow \underline{g_j = \mu_j + r_j x_j - s_g g_j}$$

Math - Competition btw Chemicals

Similar to Quaternary case, dCas9 & MCP-SoxS are limited. So from the above eqns we can write that ..,

$$\Rightarrow d_t = d + c_i + c_j + \mathcal{C}_i + \mathcal{C}_j \quad (8)$$

$$\Rightarrow m_t = m + c_i + \mathcal{C}_i \quad (9)$$

And also DNA availability is limited too

$$\rightarrow D_{it} = D_i + \underbrace{\mathcal{C}_i}$$

From (6) & (7a) $\rightarrow \mathcal{C}_i = q_i K_i g_i dm D_i$

$$\Rightarrow D_i = \frac{D_{it}}{1 + q_i K_i g_i dm} \quad (10)$$

$$\rightarrow D_{jt} = D_j + C_j$$

from (6) & (7b) $\rightarrow C_j = q_j K_j g_j d D_j$

$$\Rightarrow D_j = \frac{D_{jt}}{1 + q_j K_j g_j d} \quad (11)$$

Math - Overall

Clubbing everything together

$$\dot{g}_{i,j} = \gamma_{i,j} x_{i,j} + \mu_{c,j} - \delta_g g_{i,j} \quad [1]$$

$$c_i = K_i g_i d m \quad [2]$$

$$c_j = K_j g_j d \quad [3]$$

$$C_i = \frac{q_i K_i g_i d m D_{it}}{1 + q_i K_i g_i d m} \quad [4]$$

$$C_j = \frac{q_j k_j g_j d D_{jt}}{1 + q_j k_j g_j d} \quad (5)$$

$$D_i = D_{it} / (1 + q_i k_i g_i dm) \quad (6)$$

$$D_j = D_{jt} / (1 + q_j k_j g_j d) \quad (7)$$

$$d_t = d(1 + k_i g_i m + k_j g_j) + \quad (8)$$

$$d\left(\frac{q_i k_i g_i m D_{it}}{1 + q_i k_i g_i dm} + \frac{q_j k_j g_j D_{jt}}{1 + q_j k_j g_j d}\right)$$

$$m_t = m(1 + k_i g_i) + \quad (9)$$

$$\frac{q_i k_i g_i dm D_{it}}{1 + q_i k_i g_i dm}$$

$$G = k_i C_i + k_j D_j - s_G G \quad (10)$$

* For offsite, the only difference is $q_j = 0$