~~1~~

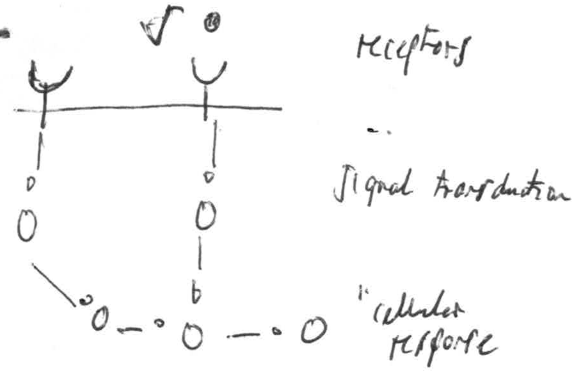


Figure: signal transduction

4

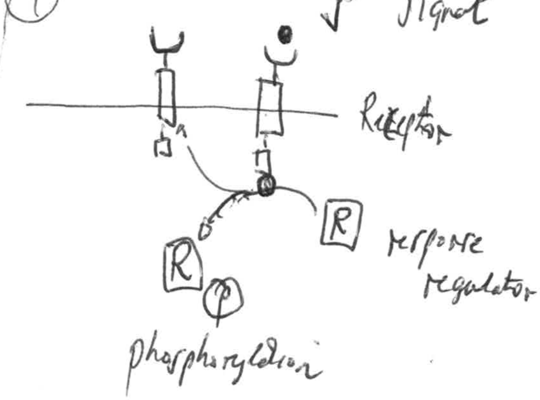
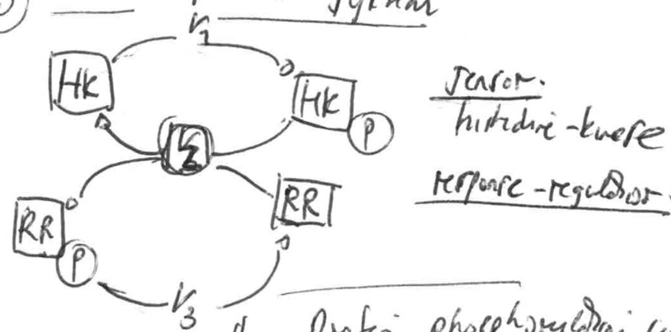
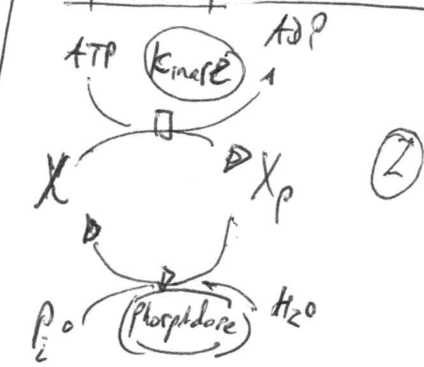


Figure: 2-component system

5 Two component system



Protein phosphorylation cycle



3

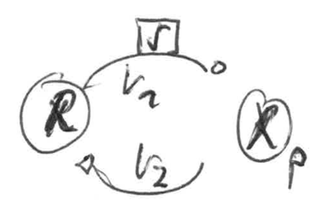


Figure: phosphorylation cycle

$$v_1 = k_1 \cdot R \cdot S$$
$$v_2 = k_2 \cdot R_p$$

$$\dot{R} = -v_1 + v_2 = k_1 R S - k_2 R_p$$
$$\dot{R}_p = v_1 - v_2 = -\dot{R}$$

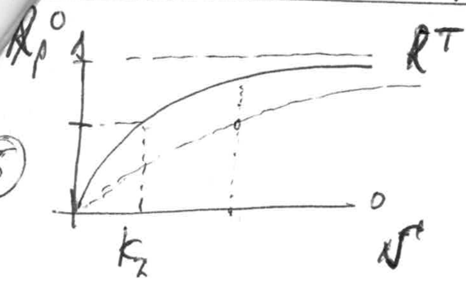
$$R_p + R = R^T = \text{const}$$

Steady state + Erhaltungsbedingung $\dfrac{d(R_p + R)}{dt} = 0$

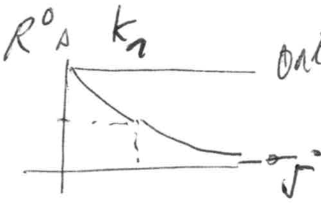
$$k_1 (R^T - R_p) \cdot S - k_2 R_p = 0$$
$$k_1 R^T S - (S k_1 + k_2) R_p = 0$$
$$R_p^0 = \frac{k_1 R^T S}{k_1 S + k_2} = \cancel{k_1 \left(\frac{S}{S + k_2}\right) X^T} = R^T \left(\frac{S}{S + \frac{k_2}{k_1}}\right)$$

...chaelis – Menten like response

(5)



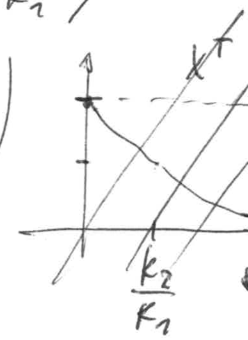
$$R_p^0 = \cancel{R^T}\left(\frac{R^T S}{S+\frac{k_2}{k_1}}\right)$$



only depends on the ratio of the kinetic constants

$$R^0 = R^T - \left(\frac{R^T S}{S+\frac{k_2}{k_1}}\right)$$

$$= R^T\left(1-\frac{S}{S+\frac{k_2}{k_1}}\right)$$



dependence on signal

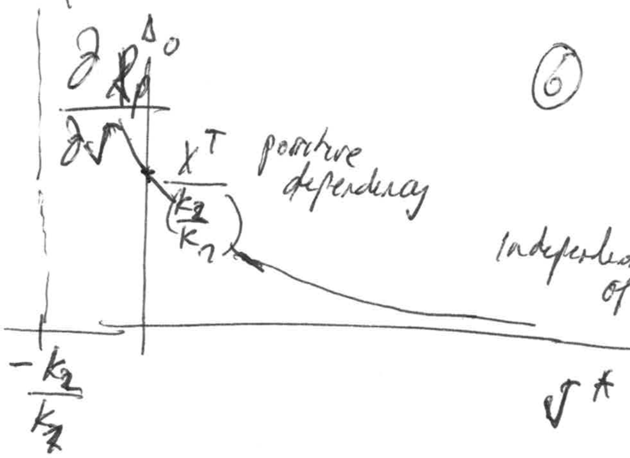
Sensitivity of steady state

$$\left.\frac{\partial R_p^0}{\partial S}\right|_{S^*} = \left.\frac{R^T\left(S+\frac{k_2}{k_1}\right)-R^T S}{\left(S+\frac{k_2}{k_1}\right)^2}\right|_{S^*} \qquad \frac{\partial}{\partial S}\left(\frac{u}{v}\right) = \frac{(u'\cdot v - u\cdot v')}{v^2}$$

$$= \left.\frac{\frac{k_2}{k_1}R^T}{\left(S+\frac{k_2}{k_1}\right)^2}\right|_{S^*}$$

$$= \frac{\frac{k_2}{k_1}R^T}{\left(S^*+\frac{k_2}{k_1}\right)^2}$$

(6)



$\frac{\chi^T}{\left(\frac{k_2}{k_1}\right)}$ positive dependency

independent of S^*

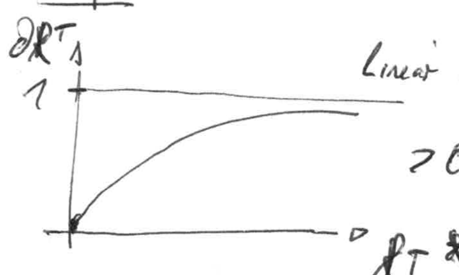
Sensitivity of steady state with respect to S

---

dependency on total concentration

$$\left.\frac{\partial R_p^0}{\partial R^T}\right|_{R^{T*}} = \frac{S}{S+\frac{k_2}{k_1}}$$

$$= \frac{1}{1+\frac{(k_2/k_1)}{S}}$$



Linear dependency

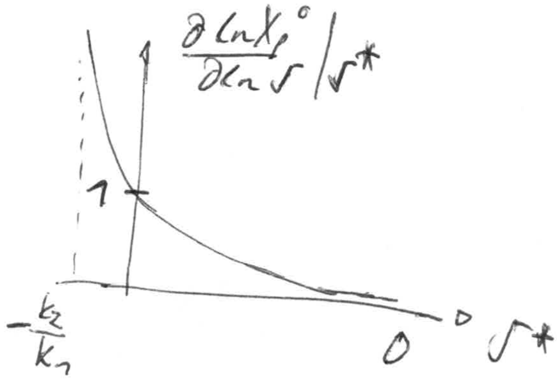
>0

$$\frac{\partial \ln R_p^0}{\partial \ln S}\bigg|_{S^*} = \frac{S}{R_p^0}\,\frac{\partial R_p^0}{\partial S}\bigg|_{S^*}$$

$$= \frac{S^*}{\left(\frac{R^T S^*}{S^* + \frac{k_2}{k_1}}\right)} \; \frac{\left(\frac{k_2}{k_1} R^T\right)}{\left(S^* + \frac{k_2}{k_1}\right)^2}$$

$$\cancel{= \frac{S^*}{(X^T S^*)}\,\frac{k_2}{k_1} X^T = \frac{k_2}{k_1}}$$

$$= \frac{\frac{k_2}{k_1}}{\left(S^* + \frac{k_2}{k_1}\right)}$$



$$= \frac{1}{\frac{S^*}{(k_2/k_1)} + 1} \in [0,1] \;\forall\; S^* \geq 0$$

Model 2-component system: (robustness of two component systems)

mass-action kinetics

H: histidine kinase

R: response regulator

$V_1 = k_1 \cdot S \cdot H$

$V_2 = k_2\, R \cdot H_p$

$V_3 = k_3 \cdot R_p$

$$\frac{dH_p}{dt} = k_1 S \cdot H - k_2 R H_p = V_1 - V_2$$

$$\frac{dR_p}{dt} = \cancel{k_1}\, V_2 - V_3 = k_2 \cdot R \cdot H_p - k_3 R_p$$

conservation

$H + H_p = H^T$

$R + R_p = R^T$

solution is lengthy (quadratic equation)
..

$$\frac{dH_p}{dt} = k_1 \cdot S\,(H^T - H_p) - k_2\, R \cdot H_p$$
$$= k_1 \cdot S\, H^T - (k_1 S + k_2 R)\, H_p = k_1 S H^T - k_1 S H_p - k_2 (R^T - R_p) H_p$$
$$\cancel{= k_1 S H^T - k_1 S H_p - k_2 R^T H_p + k_2 R_p H_p}$$
$$= k_1 S H^T - (k_1 S + k_2 R^T) H_p + k_2 R_p H_p$$

$$\frac{dR_p}{dt} = k_2 (R^T - R_p) - k_3 R_p$$
$$= k_2 R^T - (k_2 + k_3) R_p$$

...

at steady state:

we know $V_1 = V_3$

$$k_1 \cdot S \cdot H = k_3$$

steady state:

$$\frac{dR_p}{dt} = 0 \qquad R_p^{\,0} = \frac{k_2}{k_2 + k_3} R^T$$

$$\frac{dH}{dt} = 0$$

$$0 = k_1 S \cdot H^T - k_1 S H_p - k_2 \left(R^T - \frac{k_2}{k_2 + k_3} R^T\right) \cdot H_p$$

$$\Rightarrow H_p^{\,0} = \left(\frac{k_1 S H^T}{k_1 S + k_2 \left\{ R^T \cdot \left(1 - \frac{k_2}{k_2 + k_3}\right) \right.} \right)$$

In many two component systems the unphosphorylated form deactivates the response regulator, i.e.

$$V_3 = k_3 \cdot R_p \cdot H$$

at steady state we know

$$V_1 \overset{!}{=} V_3$$

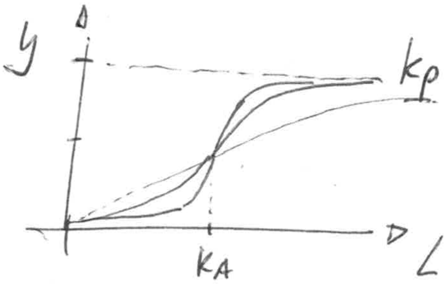
$$k_1\, S \cdot H^0 = k_3 \cdot R_p^{\,0} \cdot H^0$$

$$R_p^{\,0} = \frac{k_1 S}{k_3} = \frac{k_1}{k_3} S$$

$\Rightarrow$ resulting equation is independent of the expression of the proteins (→ robust adaptation → integral feedback etc.)

sensitivity

$$y = \frac{k_p L^n}{k_A^n + L^n}$$



$$\frac{L}{y} \frac{\partial y}{\partial L}\Big|_{L^*} = \frac{L^*}{\left(\frac{k_p L^{n*}}{k_A^n + L^n}\right)} \frac{n L^{n-1} k_p (k_A^n + L^n) - k_p L^n n L^{n-1}}{(k_A^n + L^n)^2}\Big|_{L^*}$$

$$= \frac{1}{k_p} \frac{n k_p L^{n-1} k_A^n}{(k_A^n + L^n)}\Big|_{L^*} = \frac{n L^{n-1} k_A^n}{(k_A^n + L^n)}$$

$$= n k_A^n \frac{L^{n-1}}{k_A^n + L^n}\Big|_{L^*}$$

$$\frac{\partial \ln y}{\partial \ln L}\Big|_{L^*}$$