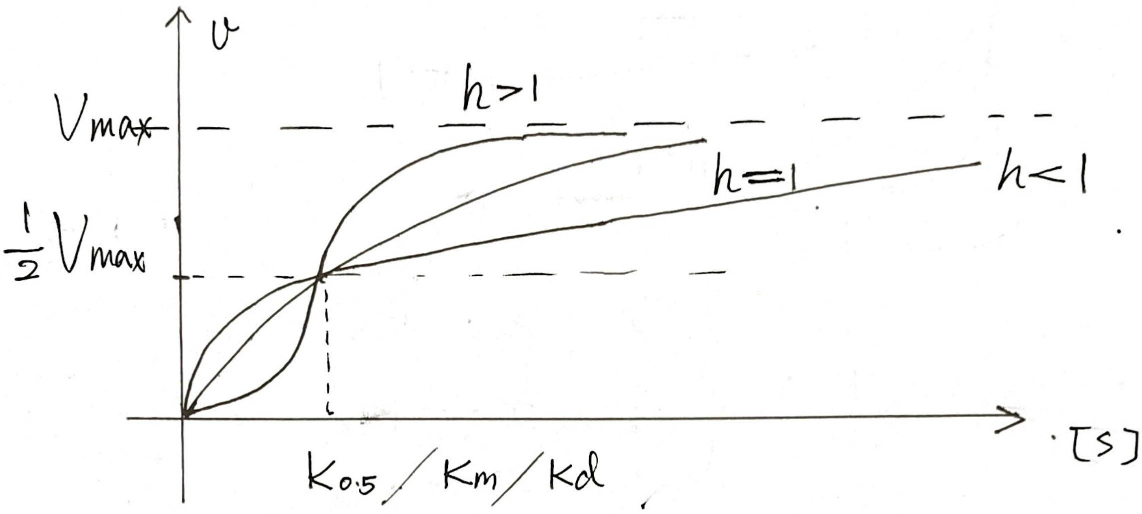
# From Michaelis-Menten to Hill Equation.

Michaelis-Menten Equation. Hill Equation.

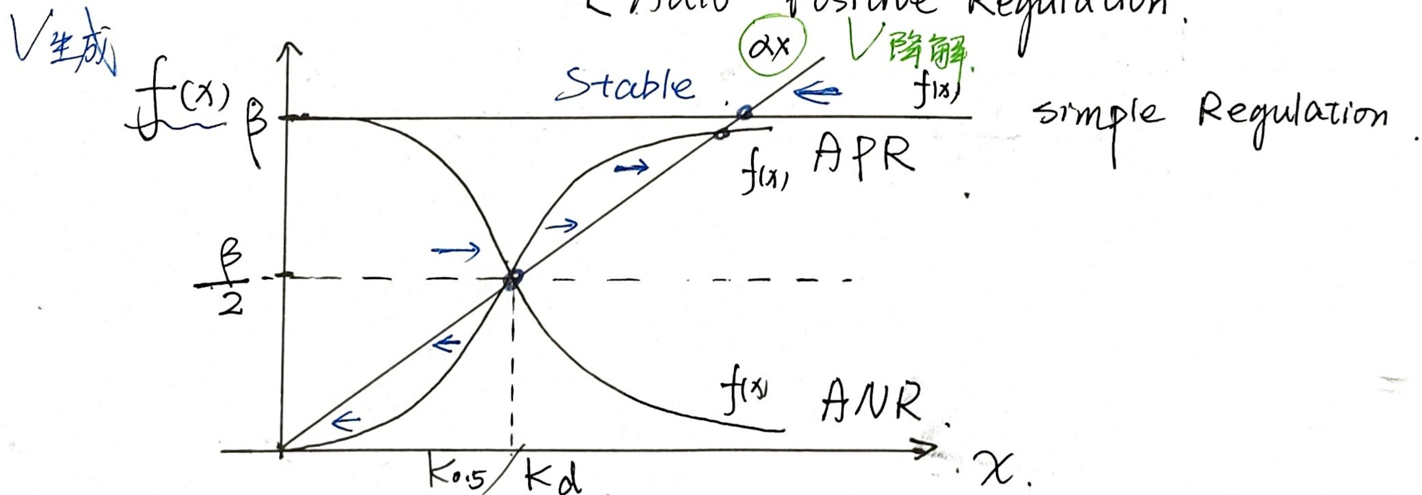
$$v = \frac{V_{max} \cdot [S]}{K_m + [S]} \approx \frac{V_{max}[S]}{K_d + [S]} \; ; \; V = \frac{V_{max} \cdot [S]^h}{K_d^h + [S]^h}$$




# From ODE to non-ODE.

$$\frac{dx}{dt} = \beta - \alpha x. \quad \text{simple regulation.}$$

$$\frac{dx}{dt} = f(x) - \alpha x. \quad \begin{cases} \text{Auto Negtive Regulation.} \\ \text{Auto Positive Regulation.} \end{cases}$$

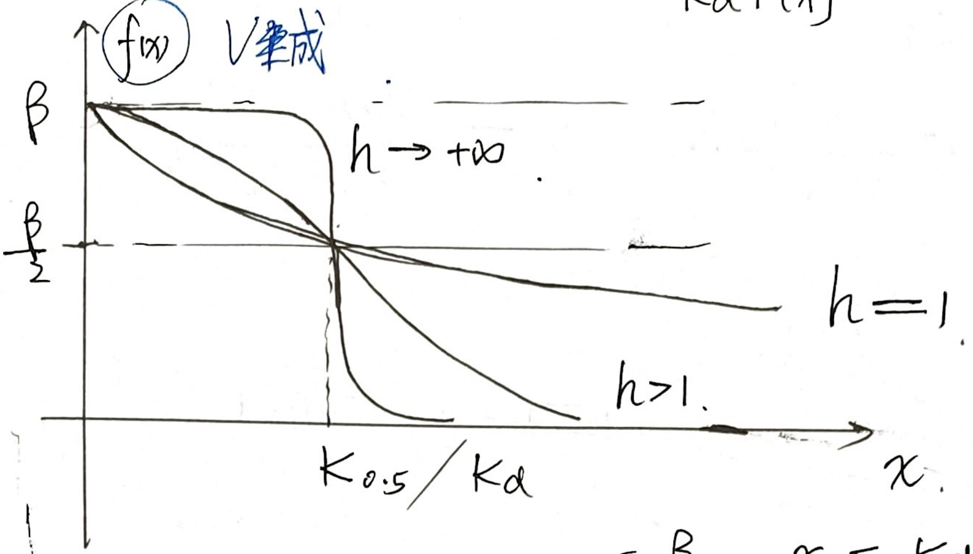



$f(x)$ : SR: $f(x) = \beta$

ANR: $f(x) = \frac{K_d^n}{K_d^h + [x]^h} \cdot \beta$ Unbinding fraction.

APR: $f(x) = \frac{[x]^h}{K_d^n + [x]^h} \cdot \beta$ binding fraction.

for ANR. $f(x) = \frac{\beta \cdot K_d^h}{K_d^h + [x]^h}$

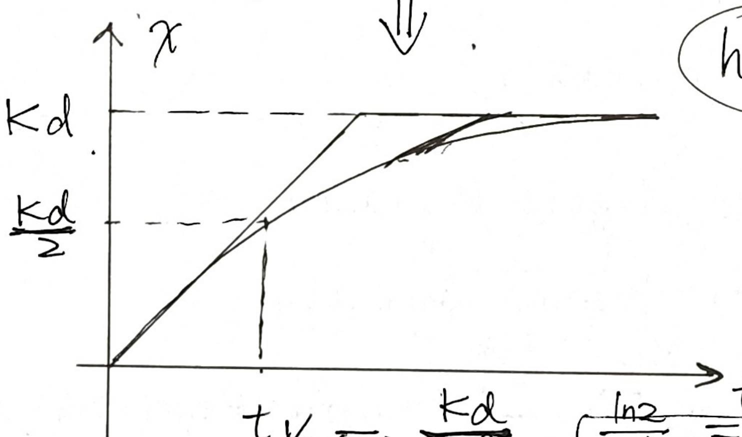



当 $h \to +\infty$. $f(x) = \begin{cases} \beta, & x < K_d \longrightarrow \text{ODE} \\ \frac{\beta}{2}, & x = K_d \\ 0, & x > K_d \end{cases}$

$\frac{dx}{dt} = f(x) - \alpha x \Rightarrow \beta - \alpha x$ $\left( \frac{\beta}{2} = \alpha K_d,\ \alpha = \frac{\beta}{2K_d} \right)$

$\Downarrow$

$h \to +\infty$




$t_{1/2} = \frac{K_d}{2\beta}$ $\cancel{\left( \frac{\ln 2}{\alpha} = \frac{2\ln 2\, K_d}{\beta} \right)}$

关于 $\frac{dx}{dt} = f(x) - \alpha x$.

（一）化学上，可逆反应.

$$A \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} B. \qquad K = \frac{k_{on}}{k_{off}} = \frac{[B]}{[A]} = \frac{T-[A]}{[A]}$$

$$T = A + B. \qquad A_{st} = [A] = \frac{T}{1+K} = \frac{k_{off}T}{k_{off}+k_{on}}$$

$$\frac{d}{dt}A = -k_{on}A + k_{off}B = -k_{on}A + k_{off}(T-A).$$

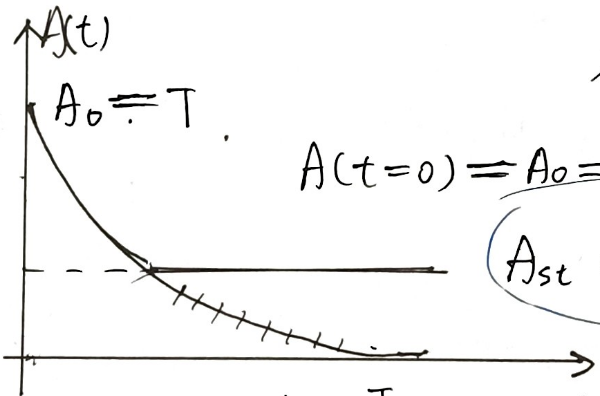
$$\frac{d}{dt}A = k_{off}\cdot T - (k_{on}+k_{off})A. \quad (\frac{d}{dt}x = \beta - \alpha x \ \text{ODE}).$$

通解：$A(t) = \frac{k_{off}T}{k_{on}+k_{off}} \times (1 - C e^{-\frac{t}{(k_{on}+k_{off})^{-1}}})$.

$$A(t) = \frac{\beta}{\alpha}(1 - C\cdot e^{-\alpha t}) = \frac{k_{off}T}{k_{on}+k_{off}}(1 - C\cdot e^{-(k_{on}+k_{off})t})$$

依赖于初始条件的常数.

例.




$A(t=0) = A_0 = T$.

$$A_{st} = \frac{k_{off}}{k_{on}+k_{off}}\cdot T$$

依赖投料总量.

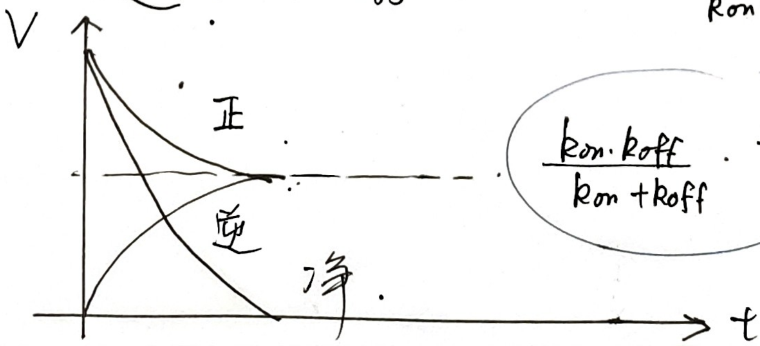
$$A(t) = \frac{k_{off}\cdot T}{k_{on}+k_{off}}\cdot(1 + \frac{k_{on}}{k_{off}} e^{-(k_{on}+k_{off})t})$$

$$V_A(t) = \frac{k_{on}T}{k_{on}+k_{off}}\cdot(+(k_{on}+k_{off}))\cdot e^{-(k_{on}+k_{off})t}) = -\frac{d}{dt}A(t)$$

$V_A(t) = k_{on}T\cdot e^{-(k_{on}+k_{off})t}$. A的净反应速度

$$V_{正}(t) = k_{on}A(t) = \frac{k_{on}k_{off}}{k_{on}+k_{off}}\cdot T\cdot(1 + \frac{k_{on}}{k_{off}} e^{-(k_{on}+k_{off})t}).$$

$$V_{逆}(t) = k_{off}\cdot(T - A(t)) = \frac{k_{on}\cdot k_{off}}{k_{on}+k_{off}}\cdot T\cdot(1 - e^{-(k_{on}+k_{off})t}).$$



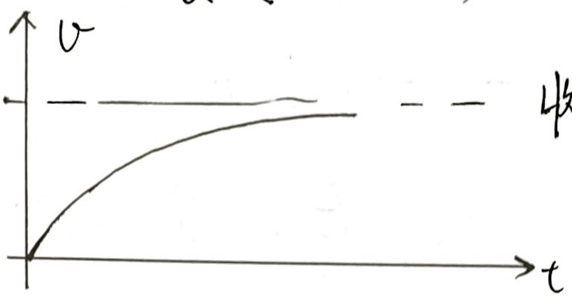

$$\frac{k_{on}\cdot k_{off}}{k_{on}+k_{off}}\cdot T.$$

（二）物理上.（1）雨滴下落（2）.电容电感充放电.

（1）$mg - kv = ma$ ： $\frac{d}{dt}v = g - \frac{k}{m}v$.

例 当 $t=0$ 时. $v=0$ . $\left(\frac{d}{dt}x = \beta - \alpha x\right)$.

$$v = \frac{\beta}{\alpha}\left(1-e^{-\alpha t}\right) = \frac{mg}{k}\left(1-e^{-\frac{k}{m}t}\right).$$

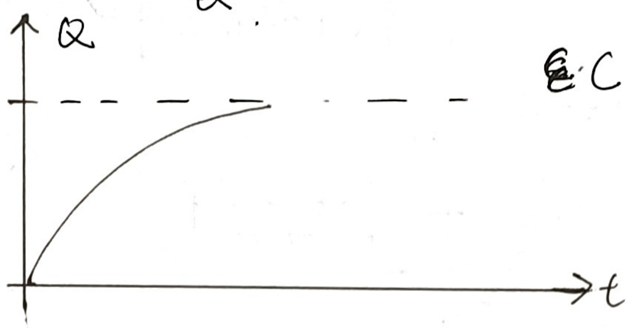



收尾速度.

（2）. $\varepsilon - IR = \frac{Q}{C}$ ： $\frac{d}{dt}Q = \frac{\varepsilon}{R} - \frac{Q}{RC}$

例 当 $t=0$ 时 $Q=0$（充电）.

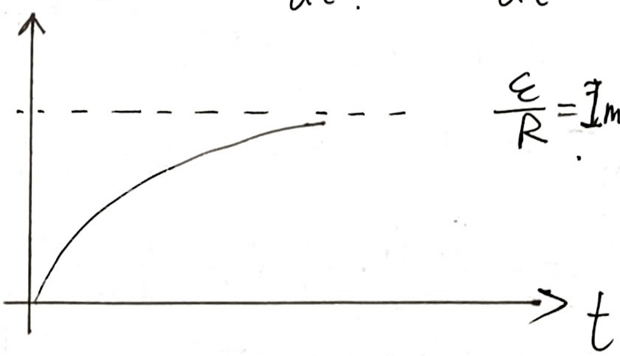
$$Q = \cancel{\varepsilon}\varepsilon C\left(1-e^{-\frac{t}{RC}}\right).$$




$\cancel{\varepsilon} \varepsilon C = Q_{max}$

（3）. $\varepsilon - iR = L\frac{di}{dt}$ ： $\frac{d}{dt}i = \frac{\varepsilon}{L} - \frac{IR}{L}$.

例. $i$




$\frac{\varepsilon}{R} = I_{max}$

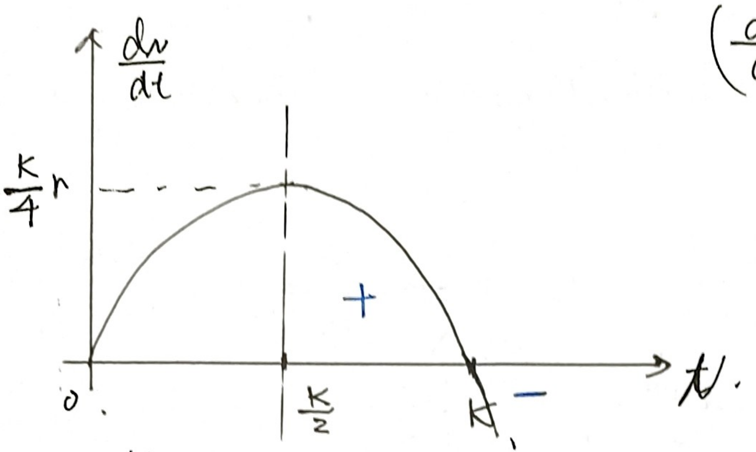
$t=0$ 时. $i=0$（充电）

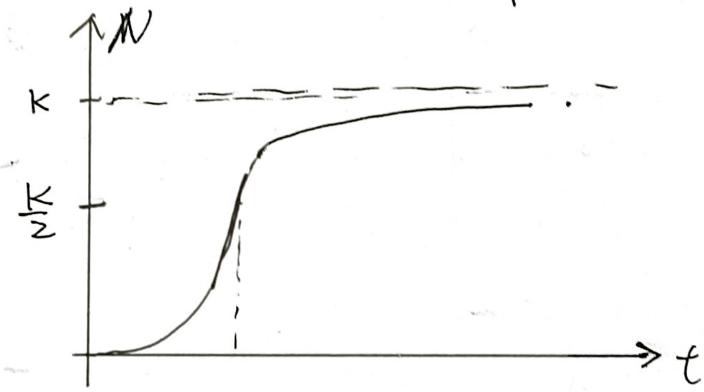
$$i = \frac{\varepsilon}{R}\left(1-e^{-\frac{R}{L}t}\right).$$

（三）生物上 (1) S型增长 (2) 酶催化动力学 (3) 基因转录

(1). $\frac{dN}{dt} = rN\frac{K-N}{K}$ : $\frac{dN}{dt} = \underbrace{-\frac{r}{K}N^2}\ + \underbrace{rN}$

$\left(\frac{dx}{dt} = \quad f(x) \quad -\alpha x\right)$



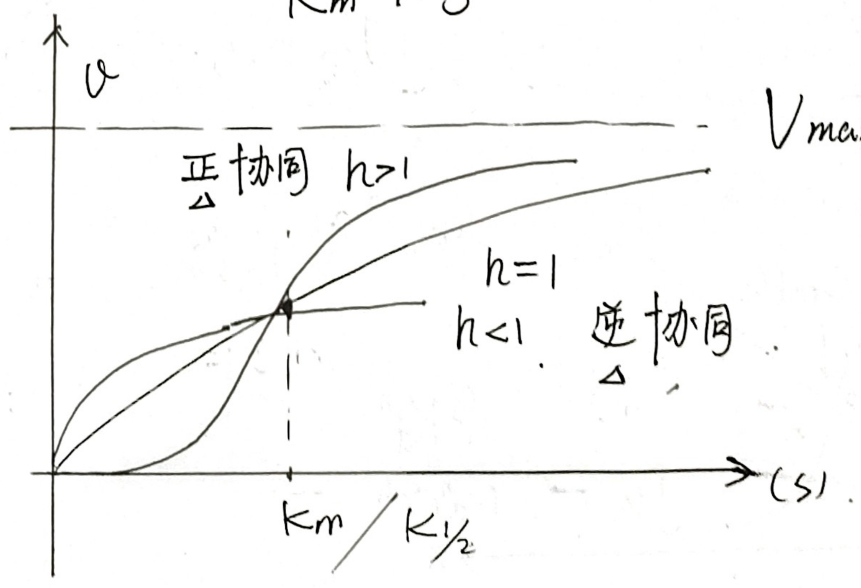




(2). $E_{Enzyme} + S_{Substrate} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} ES$. 快速～近似始终平衡

$ES \xrightarrow{k_{cat}} E + P_{product}$. 慢速

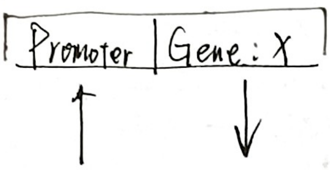
$v \approx k_{cat}\cdot ES = \frac{k_{cat}\cdot E_0\cdot S}{K_m + S}$. Michaelis-Menten

$v = \frac{k_{cat}\cdot E_0\cdot S^h}{K_m^h + S^h}$ Hill Equation

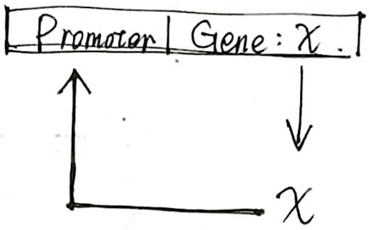



$V_{max} = k_{cat}\cdot E_0$.

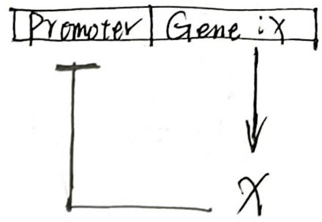
## (3) 转录

① 


Simple Regulation.

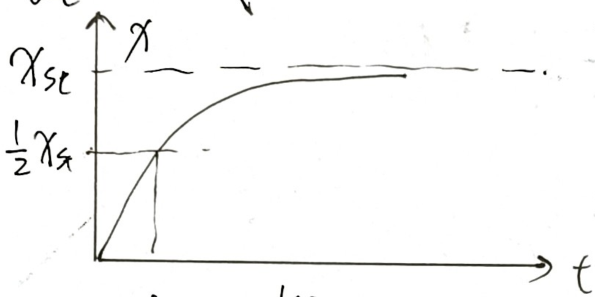
② 


Auto Positive Regulation.

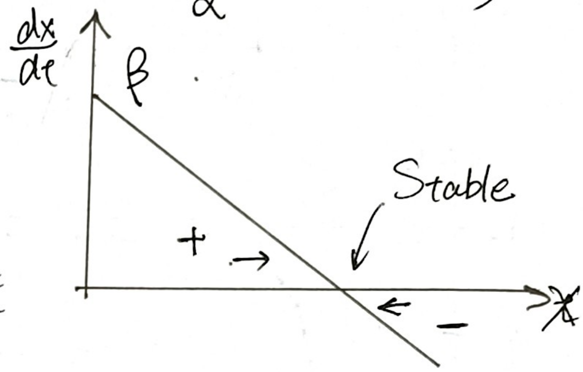
③ 


Auto Negtive Regulation

① $\frac{dx}{dt} = \beta - \alpha x \Rightarrow x = \frac{\beta}{\alpha}(1-e^{-\alpha t})$



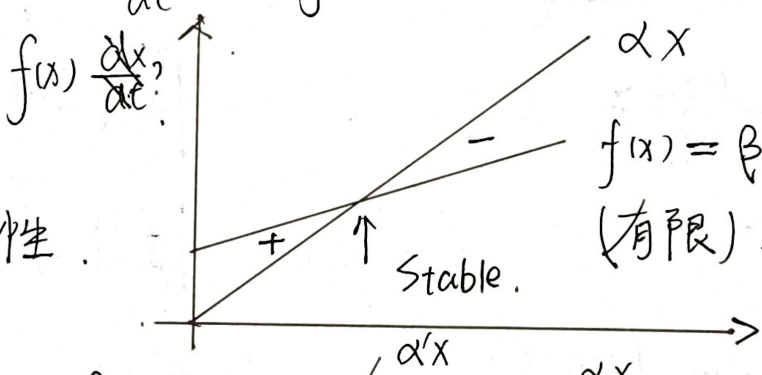

$t_{1/2} = \frac{\ln 2}{\alpha}$.




② $\frac{dx}{dt} = f(x) - \alpha x$.

$\frac{d}{dt}x = \frac{\beta}{\alpha-\beta_1}(1-e^{-(\alpha-\beta_1)t})$.

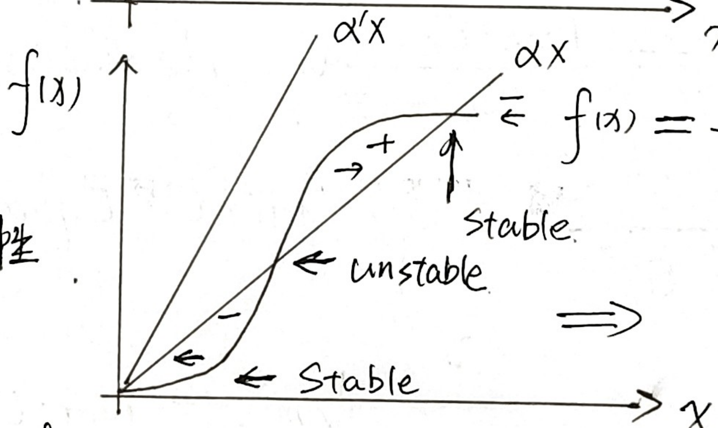
线性.




$f(x) = \beta + \beta_1 x$.

(有限) 正反馈 $\Rightarrow$ Slow.

非线性.




$f(x) = \frac{\beta x^n}{K_d^n + x^n}$

(有限范围/程度)

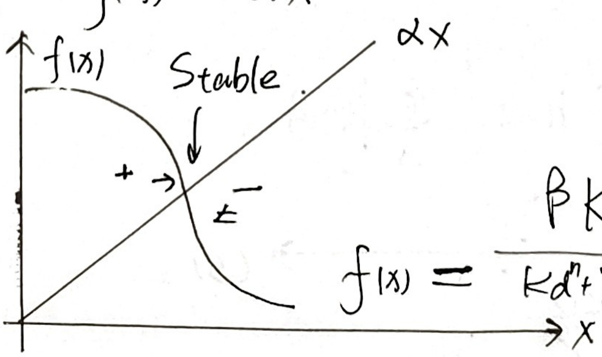
正反馈

$\frac{dx}{dt} = \boxed{f(x)} - \alpha x$

负反馈(整体)

$\Rightarrow$ Switch.

③ $\frac{dx}{dt} = f(x) - \alpha x$




负反馈.

$f(x) = \frac{\beta K_d^n}{K_d^n + x^n}$.

两步：Step1: $x + p \rightleftharpoons xp$. 快速近似平衡

Step2: $xp \longrightarrow$ Protein : $x$ 慢速.

当 $x$ = activator $\quad \eta = \dfrac{xp}{x+xp} = \dfrac{x^n}{Kd^n + x^n}$

binding fraction

$$f(x) = \beta \cdot \eta = \beta \frac{x^n}{Kd^n + x^n}$$ 生成速率 ↑ ⇐ $x$ ↑

当 $x$ = repressor $\quad \eta = \dfrac{x}{x+xp} = \dfrac{Kd^n}{Kd^n + x^n}$

unbinding fraction

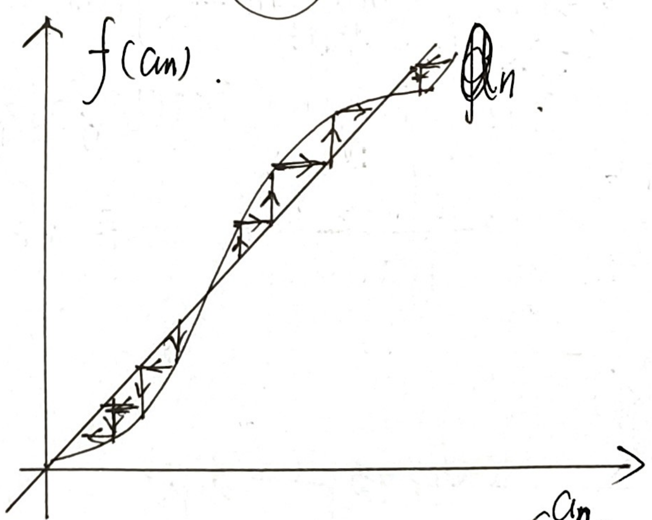
$$f(x) = \beta \cdot \eta = \beta \frac{Kd^n}{Kd^n + x^n}$$ 生成速率 ↓ ⇐ $x$ ↓

(四) 数学上.

$$a_{n+1} = f(a_n). \Rightarrow a_{n+1} - a_n = f(a_n) - a_n.$$

$$\frac{a_{n+1} - a_n}{(n+1) - n} = f(a_n) - a_n$$ , 离散形式 $\frac{d}{dt}x = f(x) - \alpha x$

$$x \sim a_n \;;\; t \sim a_n.$$




不动点法与蛛网图.

*. 找 $g(n)$ 近似 $a_n$ (求通项).

$a_n = g(n)$. 即是解微分方程

$a_{n+1} - a_n = f(a_n) - a_n$

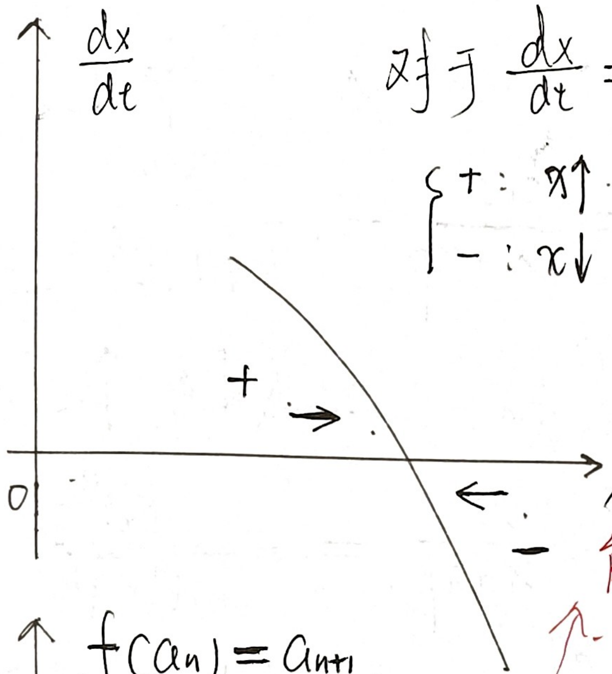
⇓

$$\frac{d\, a_n}{dn} = f(a_n) - a_n$$

$$\frac{dx}{dt} = f(x) - x.$$

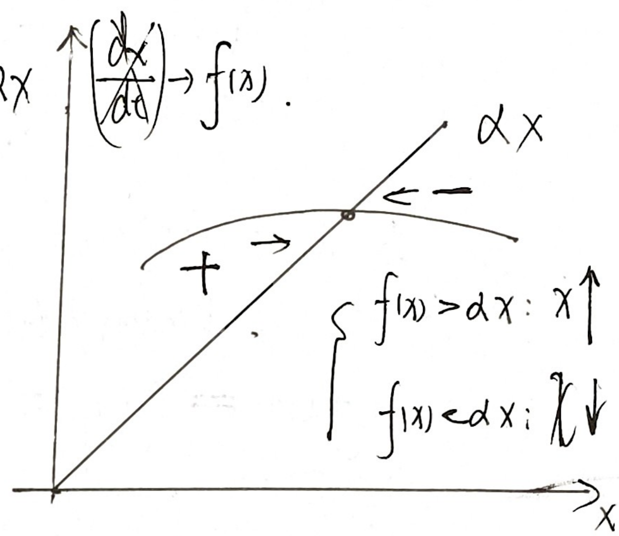
$$\int_0^n dn = \frac{da_n}{f(a_n) - a_n} = \int_{a_1}^{a_n} \frac{dx}{f(x) - x}.$$

# （五）相图

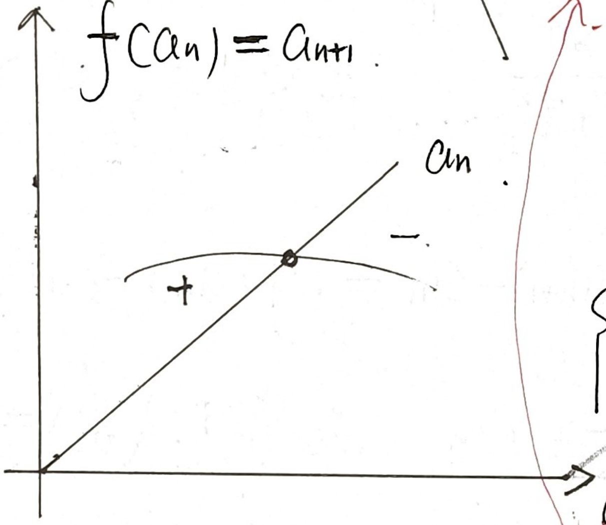



对于 $\frac{dx}{dt} = f(x) - \alpha x$

$\begin{cases} + : x\uparrow \\ - : x\downarrow \end{cases}$




解微分方程 由 $\frac{dx}{dt}$ 求 $x(t)$.




$$\frac{a_{n+1}-a_n}{(n+1)-n} = f(a_n) - a_n$$

$\Uparrow$ $\{a_n\}$ 增减性；"导数" $\begin{cases} x(t) \sim a_n \\ t \sim n \end{cases}$

$\begin{cases} f(a_n) > a_n : a_n\uparrow \\ f(a_n) < a_n : a_n\downarrow \end{cases}$

求数列通项 由 $a_{n+1} = f(a_n)$ 求 $a_n = g(n)$

由于 $\frac{dx}{dt} = f(x) - \alpha x$ 等价 $\frac{a_{n+1}-a_n}{(n+1)-n} = f(a_n) - a_n$

求 $x(t)$ 之方法　　等价 求 $g(n)$ 通项之方法

$$\int \frac{dx}{f(x)-\alpha x} = \int dt \qquad \int \frac{da_n}{f(a_n)-a_n} = \int dn$$

可用 $x(t) = x$ 近似 $g(n) = a_n$

离散 → 连续 → 求解

例：$a_{n+1} = a_n + \frac{1}{a_n}$，$a_1 = 1$ 对应 $\frac{dx}{dt} = \frac{1}{x}$

$\int x\,dx = \int dt \Rightarrow \frac{1}{2}x^2 = t$ 对应 $\frac{1}{2}a_n^2 = n$

$a_n = \sqrt{2n}$（近似通项）.