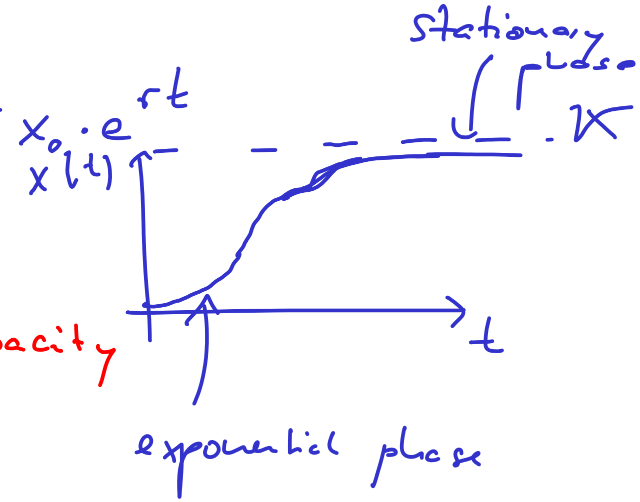
25-3-2020

- Exponential growth $\qquad \dot{x} = r x \longrightarrow x(t) = x_0 \cdot e^{rt}$

Parameter: growth

- Logistic growth $\qquad \dot{x} = r x \cdot \left(1 - \frac{x}{K}\right) \longrightarrow$

Parameter: capacity



Lotka-Volterra

predator-prey

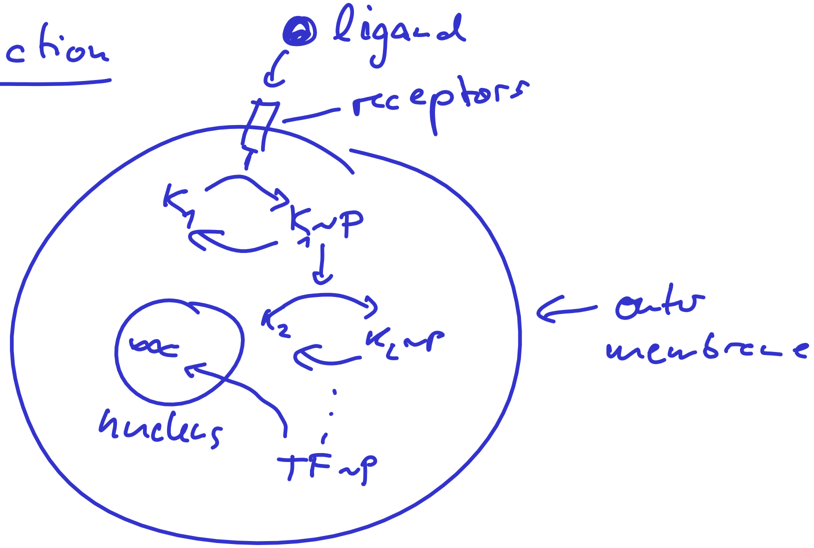
$$\dot{x} = r_1 x - a_1 x y \quad \text{prey}$$
$$\dot{y} = a_2 x y - r_2 y \quad \text{predator}$$

.... $\longrightarrow$ generalised Lotka-Volterra $\quad x_1, \dots, x_n$

.... $\longrightarrow$ dynamics of population <u>and</u> resources

.... $\longrightarrow$ MacArthur consumer resource models

Signal Transduction



Prototype Model

$$R \xrightarrow{\lambda} \emptyset$$

(receptor)

$$K_1 \underset{b_1}{\overset{a_1}{\rightleftharpoons}} K_1 \sim P \qquad \text{kinase 1 (protein kinase)}$$

dephosphorylation

$$K_2 \underset{b_2}{\overset{a_2}{\rightleftharpoons}} K_2 \sim P \qquad \text{kinase 2}$$

$$\vdots$$

$$K_n \underset{b_n}{\overset{a_n}{\rightleftharpoons}} K_n \sim P \Longrightarrow \text{cellular response}$$

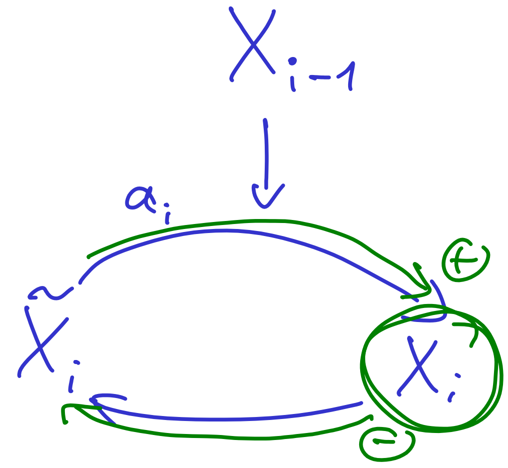
(e.g. expression of certain genes)

e.g. MAPK

Mathematical description

Let X_i denote the amount of activated kinase i

and $\tilde{X}_i$ denote the amount of inactive kinase i



Assumption 1

X_{i-1} activates $\tilde{X}_i$

with a rate proportional to X_{i-1} and $\tilde{X}_i$

$$\Rightarrow \; V_{a,i} = a_i \cdot X_{i-1} \cdot \tilde{X}_i$$

Assumption 2

De-activation by a phosphorylase is constitutive [and unspecific]

$$\Rightarrow \; V_{d,i} = b_i \cdot X_i$$

rate of de-activation

$$\Rightarrow \; \boxed{\frac{dX_i}{dt} = \dot{X}_i = V_{a,i} - V_{d,i} = a_i X_{i-1} \cdot \tilde{X}_i - b_i X_i}$$

$\boxed{\text{Assumption 3}}$ Total amount of a kinase (activated + inactive) remains constant

Important: this assumption is only fulfilled if the signalling process is considerably faster than protein turnover

$$X_i + \tilde{X}_i = C_i$$

constant: total kinase amount

$$\Rightarrow \tilde{X}_i = C_i - X_i$$

$\alpha_i := a_i \cdot C_i$

$$v_{a,i} = a_i X_{i-1} \cdot (C_i - X_i) = a_i C_i X_{i-1} \cdot \left(1 - \frac{X_i}{C_i}\right) = \alpha_i X_{i-1} \cdot \left(1 - \frac{X_i}{C_i}\right)$$

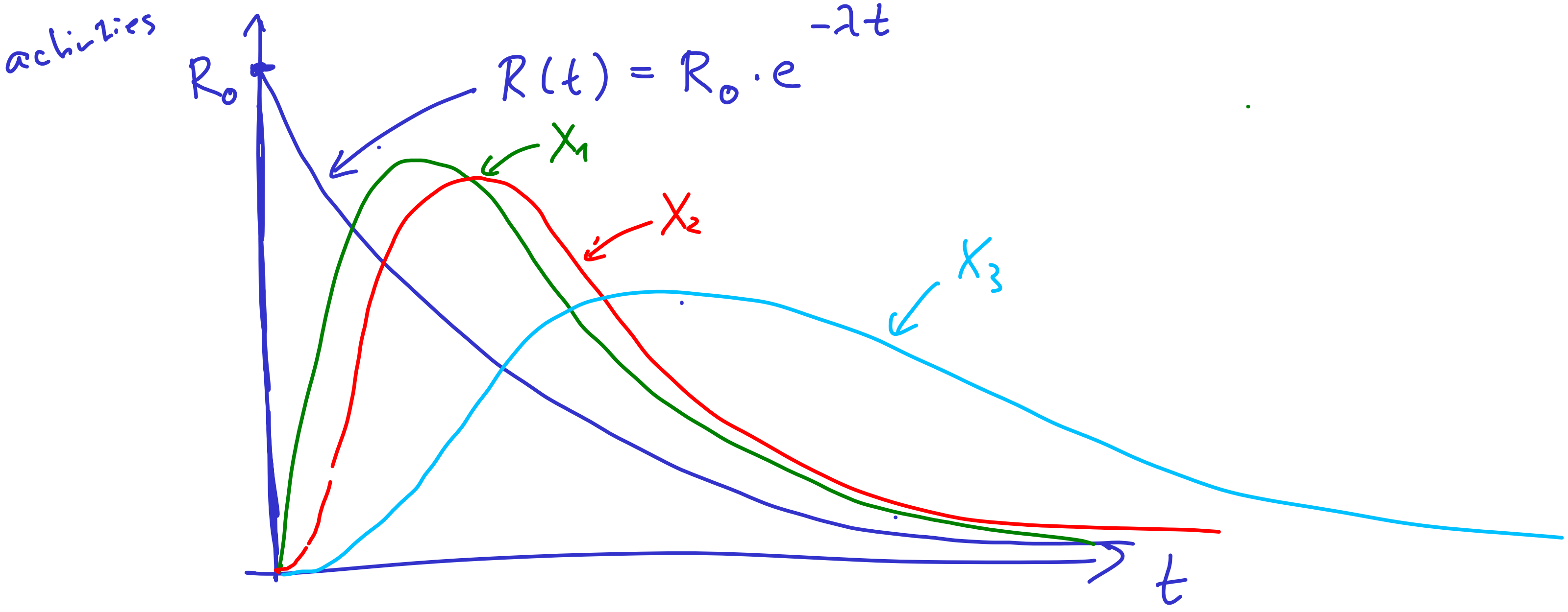
$$\Rightarrow \dot{X}_i = \alpha_i X_{i-1} \cdot \left(1 - \frac{X_i}{C_i}\right) - \underbrace{b_i}_{\beta_i} X_i$$

First kinase:

$$\dot{X}_1 = \alpha_1 \cdot R(t) - \beta_1 X_1$$

non-autonomous system

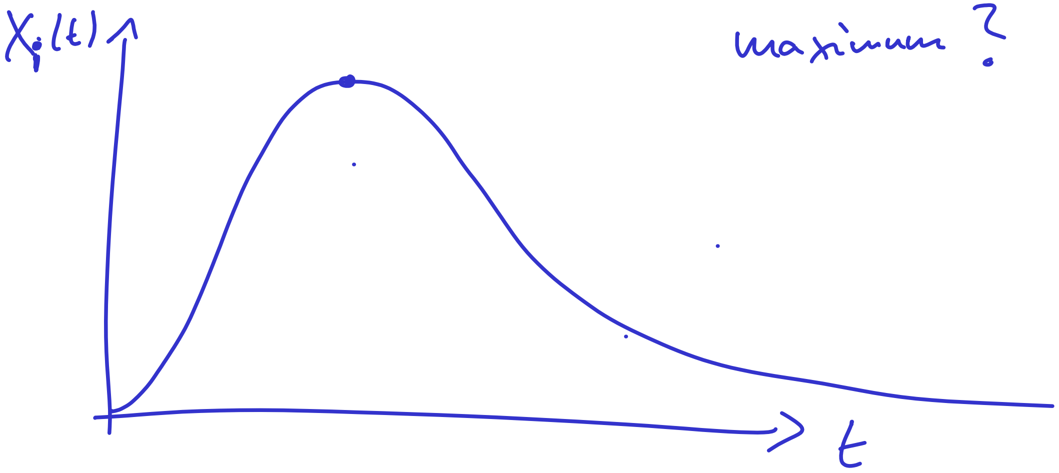
Qualitative behaviour

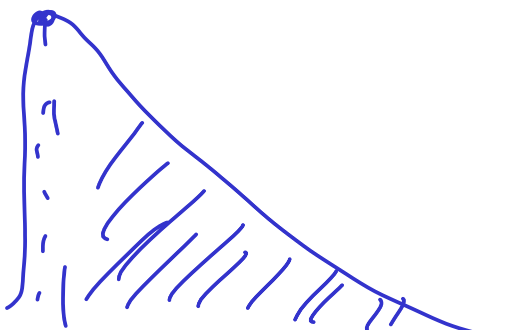


Characteristic quantities

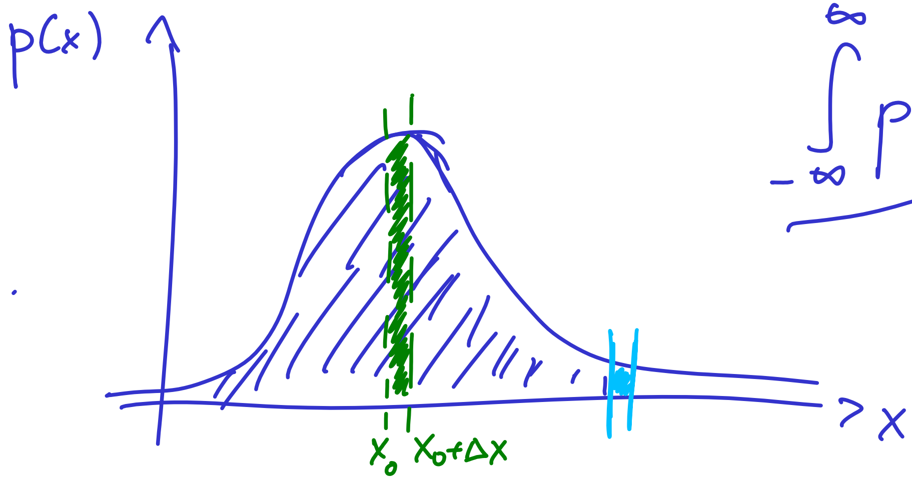
Signal time: when is the "average" time that kinase i is active?

maximum?





Distribution



$$\int_{-\infty}^{\infty} p(x)\,dx = 1$$

$$\int_{x_0}^{x_0+\Delta x} p(x)\,dx$$

$$\mu = E(x) = \int_{-\infty}^{\infty} x \cdot p(x)\,dx$$

30 people : 100 €

70 : 200 €

how much does everyone have on average?

$$\text{total money: } \frac{30 \times 100 + 70 \times 200}{30+70}$$
$$\text{total people: }$$

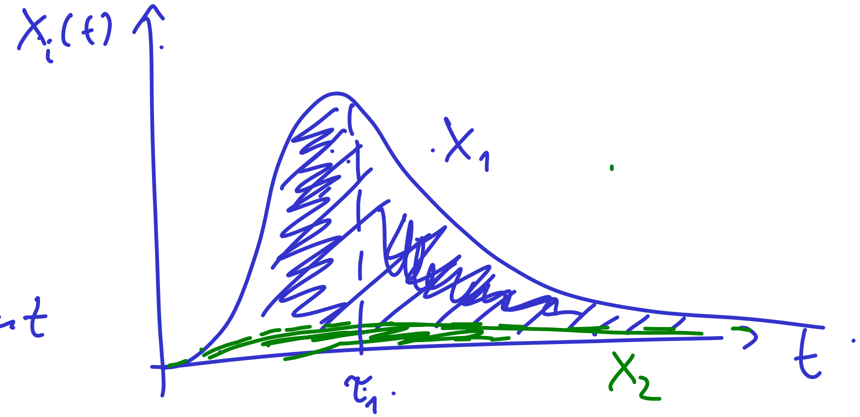
Average time of signal $X_i(t)$:

$$\tau_i = E(t) = \frac{\int_{-\infty}^{\infty} t \cdot X_i(t)\,dt}{\int_{-\infty}^{\infty} X_i(t)\,dt}$$

tau

$$\tau_i = \frac{T_i}{I_i}$$

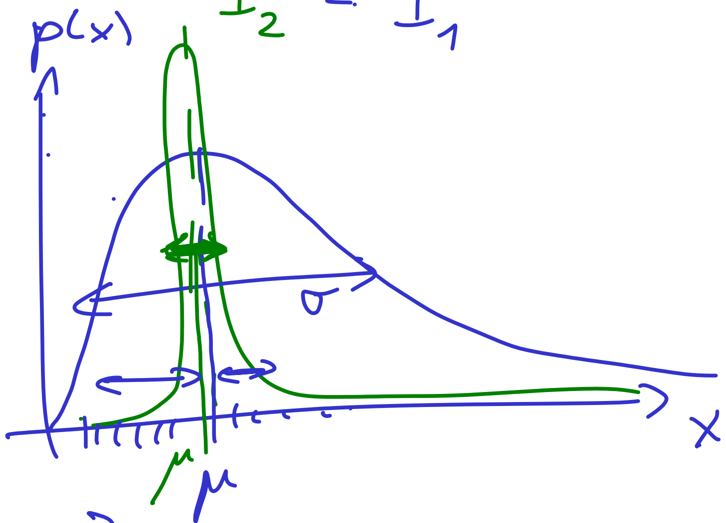
$$I_i = \int_{-\infty}^{\infty} X_i(t)\,dt$$ $\boxed{\text{Integrated response}}$



$$T_i = \int_{-\infty}^{\infty} t \cdot X_i(t)\,dt \quad \Leftarrow \text{First moment}$$

$I_2 < I_1$

$$Q_i = \int_{-\infty}^{\infty} t^2 X_i(t)\,dt \quad \Leftarrow \text{Second moment}$$



Standard deviation

$$\mu = E(x)$$

$$\sigma = \sqrt{Var(x)}$$

$$Var(x) = E\left[(x-\mu)^2\right]$$

$$= E\left[x^2 - \boxed{2x\cdot\mu} + \mu^2\right]$$

$-2E(x)^2$ $\quad + E(x)^2$

$$E(t^2) = \frac{\int_{-\infty}^{\infty} t^2 X_i(t)\,dt}{\int_{-\infty}^{\infty} X_i(t)\,dt} = \frac{Q_i}{I_i}$$

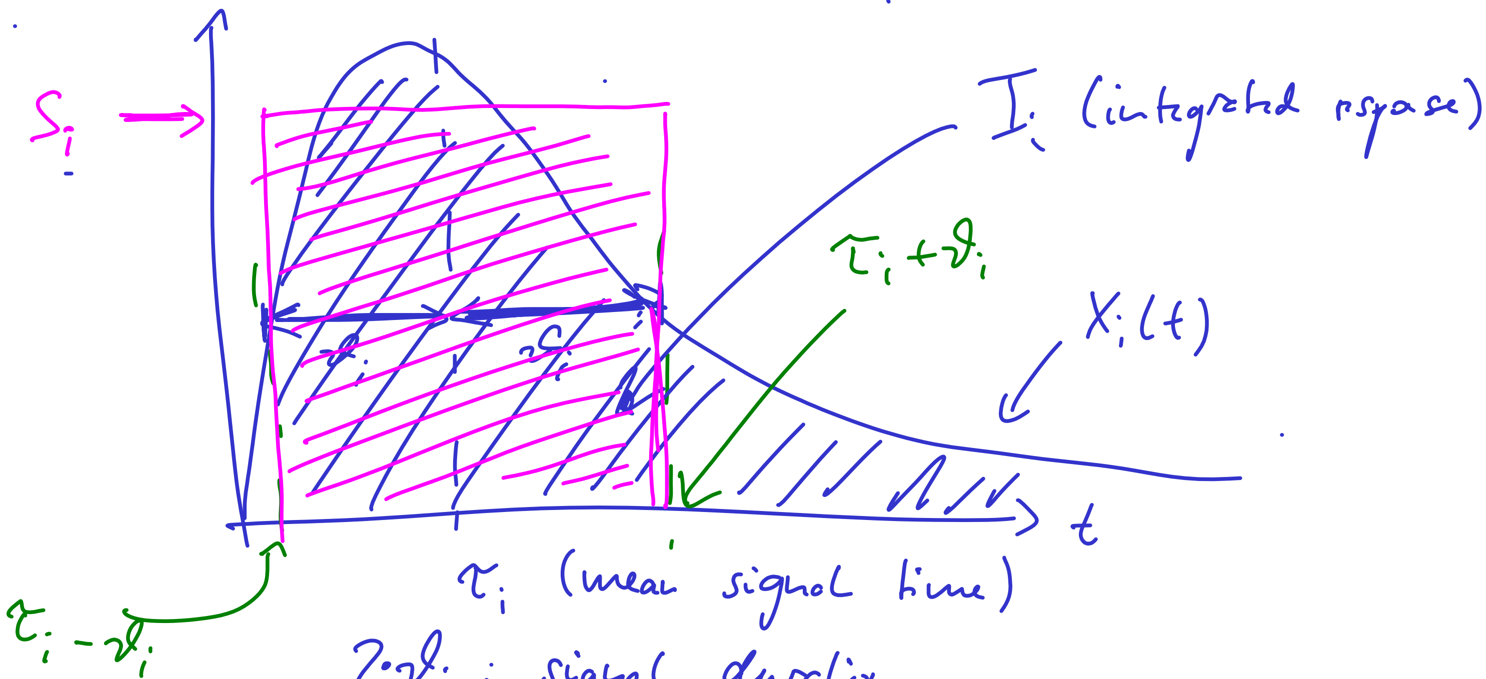
$$= E(x^2) - 2\mu\cdot E(x) + \mu^2$$

$$E(2\cdot x\cdot\mu) = 2\cdot\mu\cdot\overbrace{E(x)}^{\mu}$$
$$= 2\mu^2 = 2(E(x))^2$$

$$= E(x^2) - E(x)^2$$

Signal duration ϑ_i [theta]

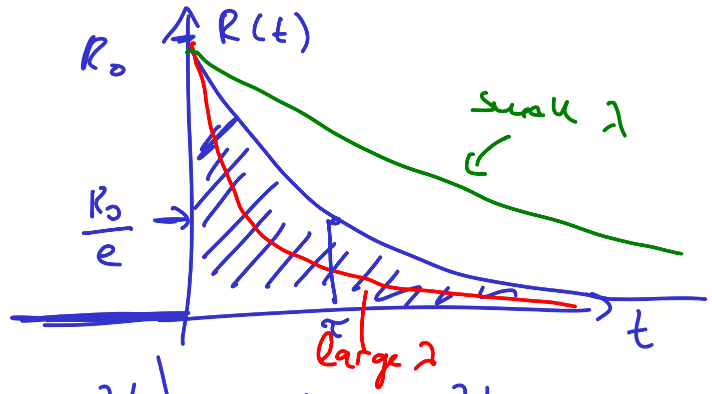
$$\vartheta_i = \sqrt{Var(t)} = \sqrt{E(t^2) - E(t)^2} = \sqrt{\frac{Q_i}{I_i} - \tau_i^2}$$



$2\cdot\vartheta_i$: signal duration

mean signal strength:
$$S_i = \frac{I_i}{2\cdot\vartheta_i}$$

Example: $R(t) = R_0 \cdot e^{-\lambda t}$



$$I = \int_0^\infty R_0 e^{-\lambda t}\, dt = R_0 \cdot \underbrace{\int_0^\infty \boxed{e^{-\lambda t}}\, dt}$$

$$-\frac{1}{\lambda} e^{-\lambda t}$$

$$= -\frac{R_0}{\lambda} \cdot \left[e^{-\lambda t}\right]_0^\infty$$

$$\longrightarrow \frac{d}{dt}\left(-\frac{1}{\lambda} e^{-\lambda t}\right) = -\frac{1}{\lambda} \cdot e^{-\lambda t} \cdot (-\lambda) = e^{-\lambda t} \checkmark$$

$$= -\frac{R_0}{\lambda}\,[\underbrace{0-1}_{-1}] = \frac{R_0}{\lambda}$$

$$T = R_0 \cdot \int_0^\infty t \cdot e^{-\lambda t}\, dt$$

$f(t)$ $g'(t)$

$f'(t) = 1$

$g(t) = -\frac{1}{\lambda} e^{-\lambda t}$

partial integration:

$$\int_a^b f(x) \cdot \underline{g'(x)}\, dx = [f \cdot g]_a^b - \int_a^b f'(x)\, \underline{g(x)}\, dx$$

$$\frac{d}{dx}[f \cdot g] = f' \cdot g + f \cdot g'$$

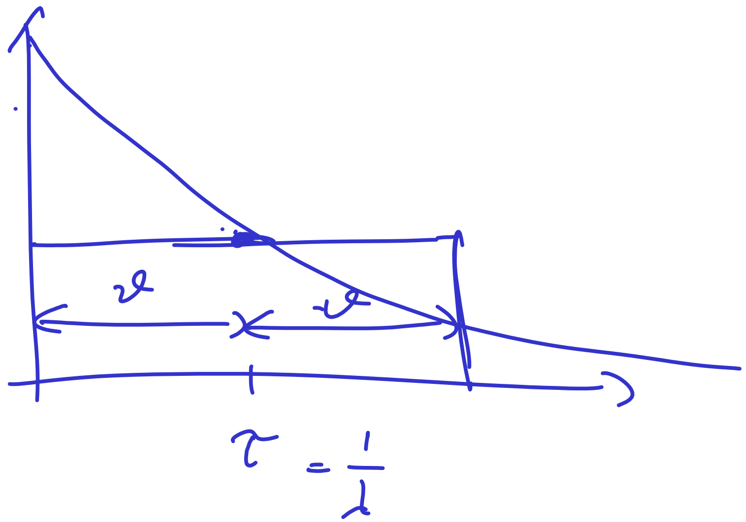
$$[f \cdot g]_a^b = \int_a^b \frac{d}{dx}[f \cdot g]\, dx = \int_a^b f' \cdot g\, dx + \int_a^b f \cdot g'\, dx$$

$$= \dots = \frac{R_0}{\lambda^2}$$

$$\Rightarrow \tau = \frac{T}{I} = \frac{1}{\lambda}$$

ϑ $\qquad Q = R_0 \int_0^\infty t^2 e^{-\lambda t}\, dt = \dots = \frac{2}{\lambda^3} \cdot R_0$

$$\vartheta = \sqrt{\frac{Q}{I} - \tau^2} = \sqrt{\frac{2}{\lambda^2} - \frac{1}{\lambda^2}} = \sqrt{\frac{1}{\lambda^2}} = \frac{1}{\lambda}$$



Back to signal transduction cascade:

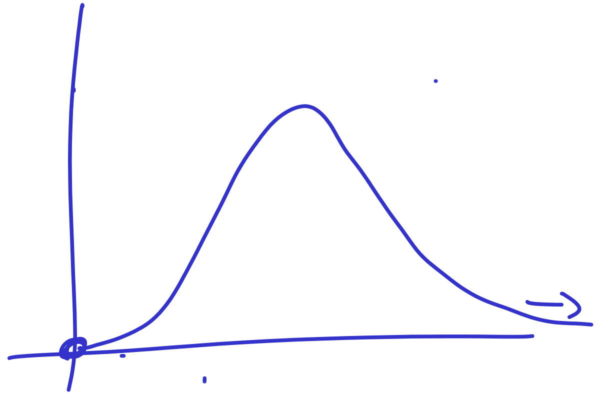
$$\dot{X}_i = \frac{dX_i}{dt} = \alpha_i X_{i-1} \cdot \left(1 - \cancel{\frac{X_i}{C_i}}\right) - \beta_i X_i$$

$\boxed{\text{Assumption 4}}$ weak activation $\quad X_i \ll C_i \iff \frac{X_i}{C_i} \ll 1$

This leads to simpler equations: $\quad \dot{X}_i = \alpha_i \underline{X_{i-1}} - \beta_i \underline{X_i}$

System of linear differential equations

$$\frac{dX_i}{dt} = \alpha_i X_{i-1} - \beta_i X_i$$



$$\underbrace{\int_0^\infty \frac{dX_i}{dt}\,dt}_{[X_i(t)]_0^\infty = 0} = \alpha_i \underbrace{\int_0^\infty X_{i-1}\,dt}_{I_{i-1}} - \beta_i \underbrace{\int_0^\infty X_i\,dt}_{I_i}$$

$$I_i = \int_0^\infty X_i(t)\,dt$$

$$0 = \alpha_i I_{i-1} - \beta_i I_i \iff \boxed{I_i = \frac{\alpha_i}{\beta_i} I_{i-1}}$$

recursion

I_0 : receptor

$$I_0 = \frac{R_0}{\lambda}$$

$$\Rightarrow \boxed{I_i = \frac{R_0}{\lambda} \cdot \prod_{j=1}^{i} \frac{\alpha_j}{\beta_j}}$$

$$\int_0^\infty t \cdot \frac{dX_i}{dt} dt = \int_0^\infty t \cdot \alpha_i X_{i-1} dt - \int_0^\infty t \beta_i X_i dt$$

$$T_i = \int t \cdot X_i(t)\, dt$$

$$\dots \quad \boxed{\tau_i = \frac{1}{\beta_i} + \tau_{i-1}}$$

Time of a signal depends on the phosphatases, but not on the kinases!

rate constant of de-activating phosphorylase

$$\boxed{\vartheta_i^2 = \frac{1}{\beta_i^2} + \vartheta_{i-1}^2}$$

Also the duration depends on phosphatases, but not on kinases

$$\frac{dX_i}{dt} = \alpha_i X_{i-1} - \beta_i X_i \quad \Big| \cdot t$$

$$t \cdot \frac{dX_i}{dt} = \alpha_i \cdot t X_{i-1} - \beta_i \cdot t X_i$$

$$\int t \frac{dX_i}{dt} dt = \alpha_i \cdot \overbrace{\int t X_{i-1} dt}^{T_{i-1}} - \beta_i \overbrace{\int t X_i dt}^{T_i}$$