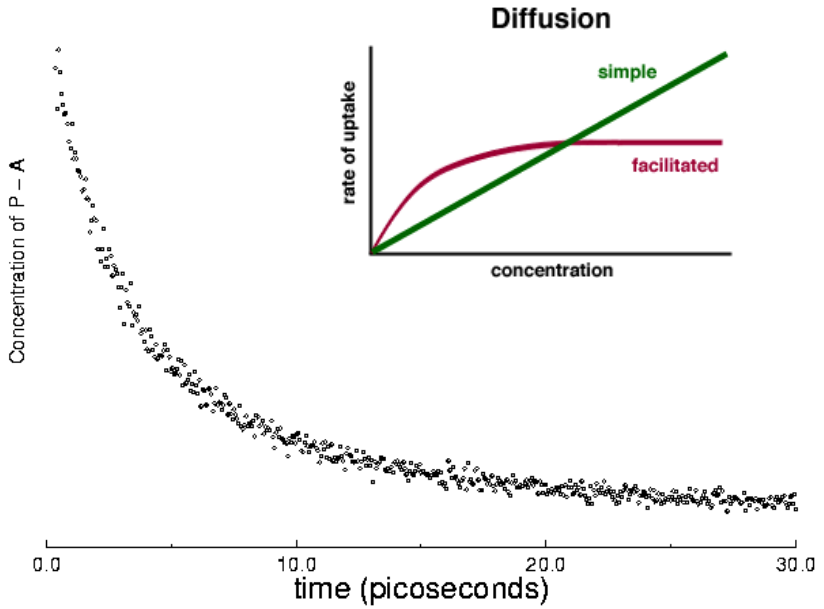
Kinetics, Diffusion, Drug Stability, Pharmacokinetics

- ***Rates*** of drug dissolution, permeation, diffusion, metabolism, binding are controlled by the **laws of chemical *kinetics***
- Liquid (and even solid) dosage drug form is susceptible to time-dependent:
  - **Hydrolysis**
  - **Oxidation**
  - Isomerization
  - Photochemical decomposition
  - Polymerization
  - Precipitation
  - …

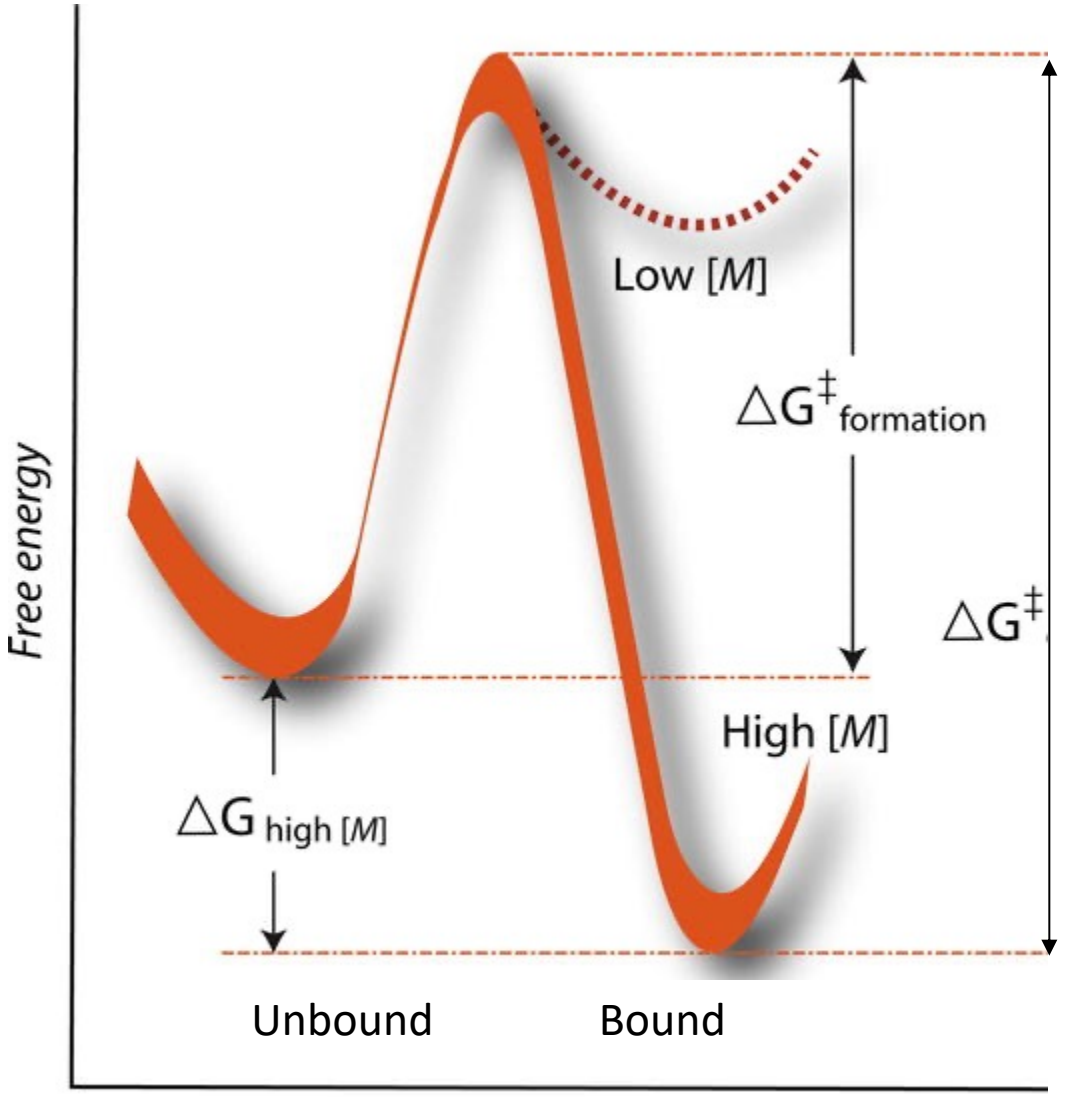


Time

Kinetics vs Thermodynamics

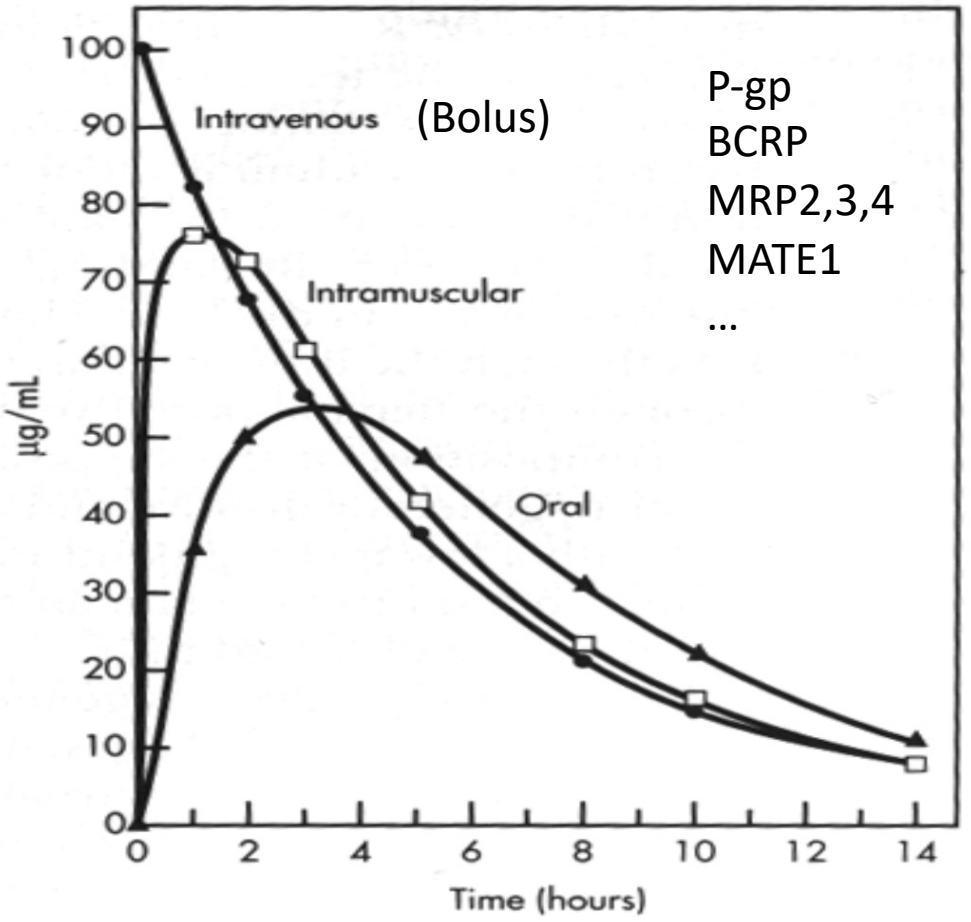
- *Rate* = *Change* per unit time, e.g. moles/*s*
- *Rate of reaction* = the rate at which the reactants are transformed into the products. Kinetics laws: time-dependence of concentrations.

- Thermodynamics establishes concentration at an equilibrium.
- Thermodynamics laws define the ratios of equilibrium concentrations



Real **Pharmacokinetics** depends on many concurrent processes (ADME)

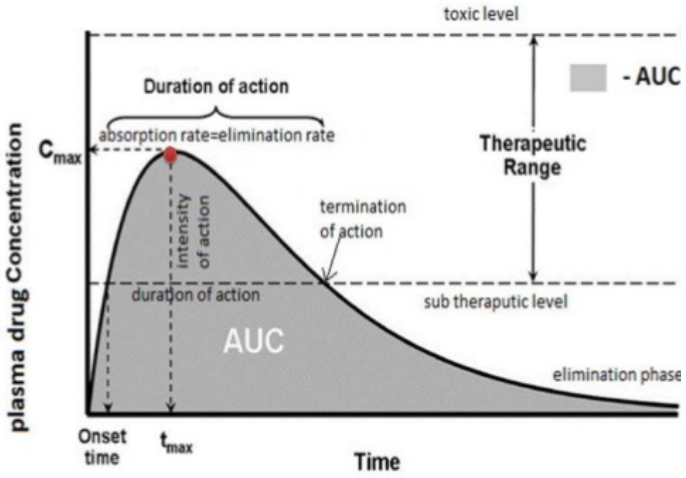
Our goal is characterizing and classifying individual transitions involved in **A**dministration, **D**istribution, **M**etabolism and **E**limination, their types and contributing factors



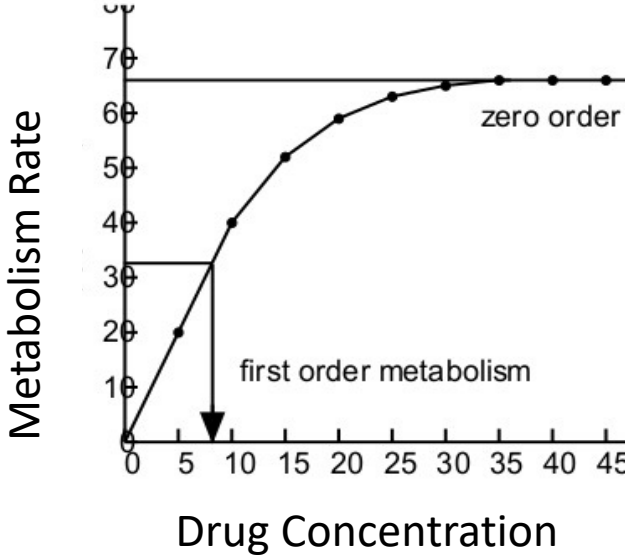
Example: the same amount of drug administered in three different ways

Drug Elimination Kinetics: 0 vs 1

- First order: Metabolism Rate is proportional to drug concentration
- A fixed ***fraction*** is metabolized per time unit.
- Half life is does not depend on the dose



- Zero order: Metabolism Rate is constant
- The rate does not depend on the drug concentration
- Half life depends on the drug concentration



Drug Diffusion

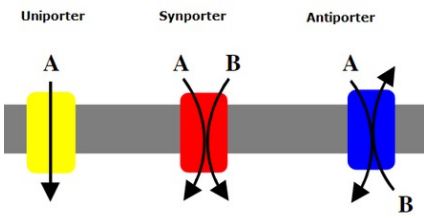
Absorption

Passive Diffusion

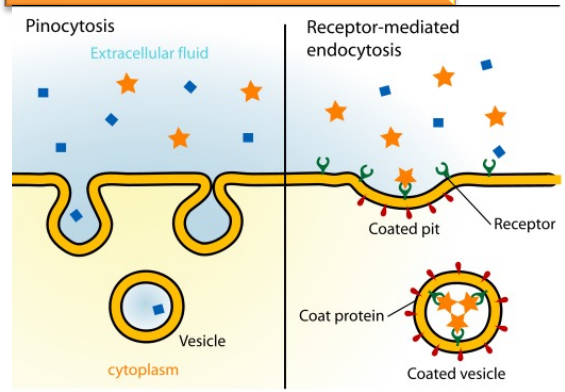
Facilitated Diffusion

Active Transport

Endocytosis

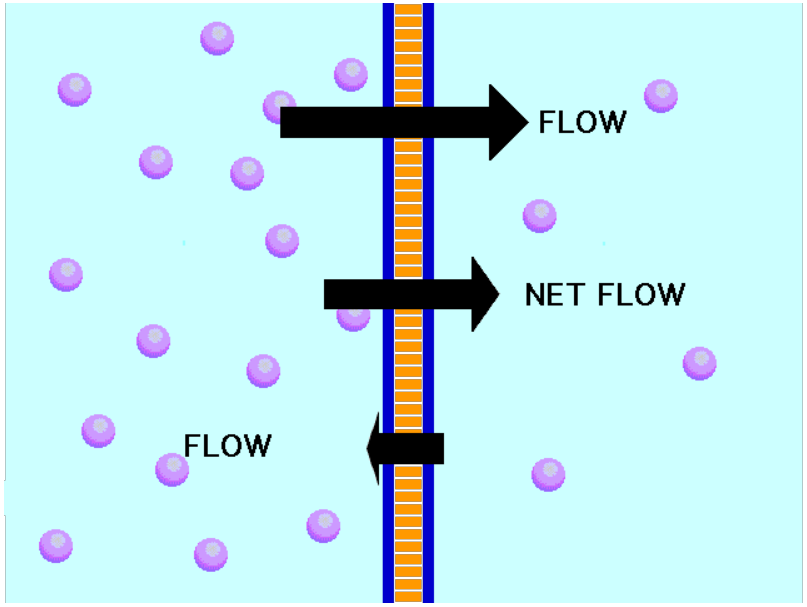


Exporters/Efflux or Importers

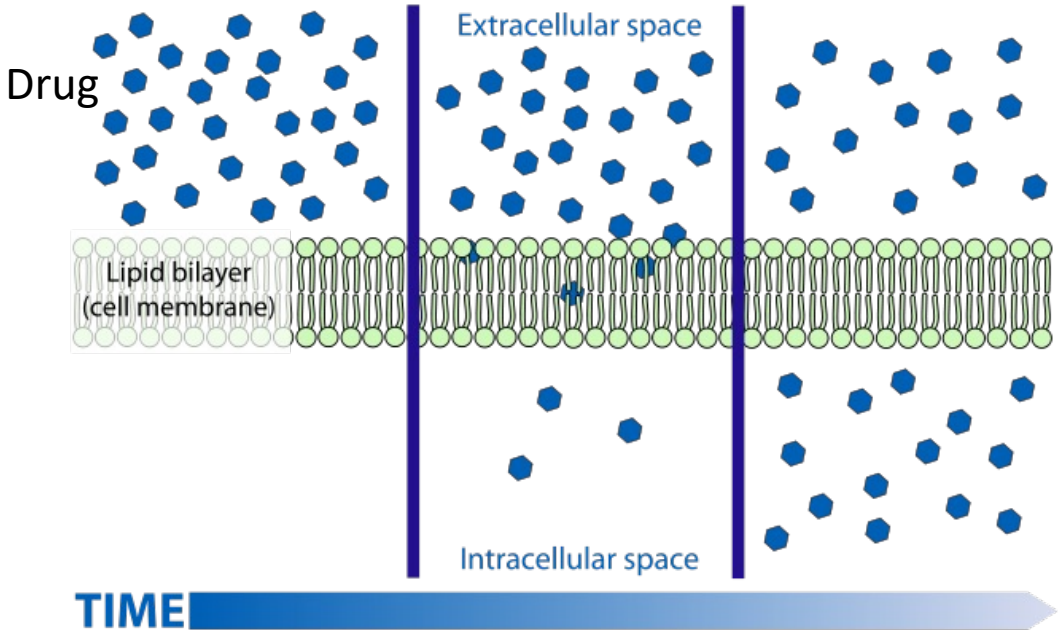


Diffusion: net flow

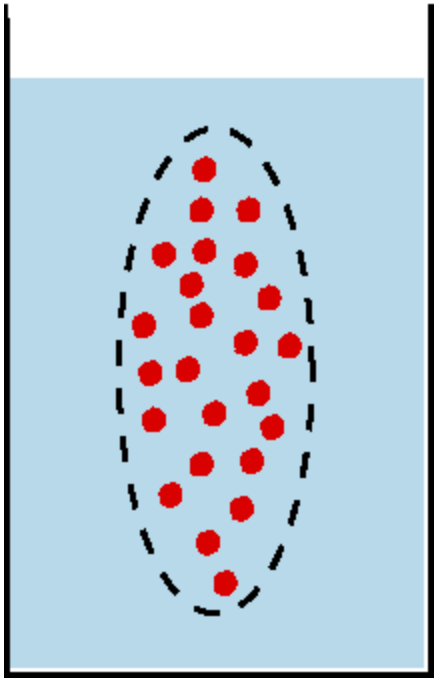
- Diffusion is a random process, and the laws describe the net flow



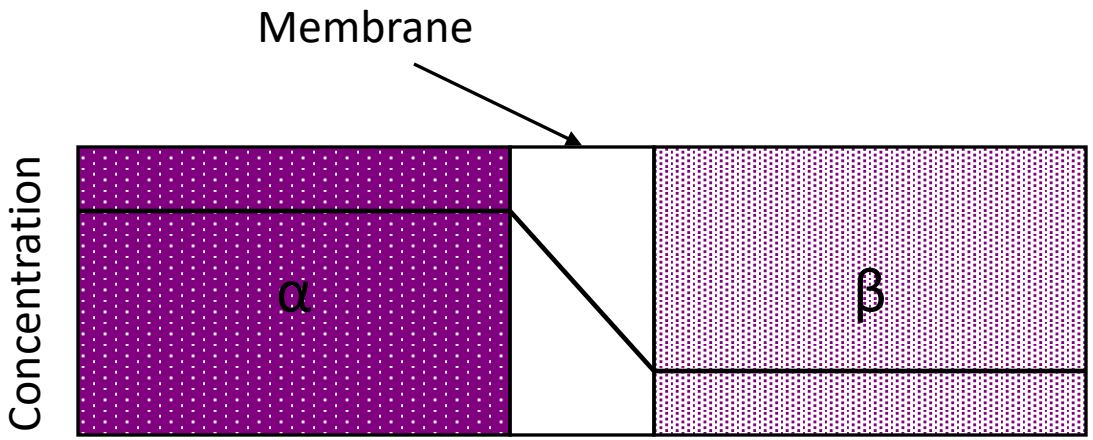
Diffusion vs concentration gradient



- **Diffusion** is the net action of matter, heat, light, .. whose end is to minimize a concentration gradient in space
- **Flux**, $\boldsymbol{J}$, is the amount of substance flowing through unit area per second
- $\boldsymbol{J}$ [mol m^{-2} s^{-1}]
- Question: How does $\boldsymbol{J}$ depend on the concentration difference (or gradient)?



Concentration Gradient



$$\Delta C = C_{\beta} - C_{\alpha}$$

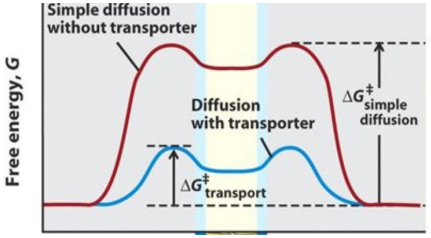
Fick's Laws of Diffusion

Adolf Eugen Fick, 1829-1901, a German physiologist, invented contact lenses

- Relates the flux and the concentration (C) gradient (difference per unit length)
- 1st Law: Steady State
- 2nd Law: time dependence
- ***D*** depends on the diffusion activation energy (barrier).

$$J = -P\,\Delta C$$

$$J = -D\frac{dC}{dx}$$



$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

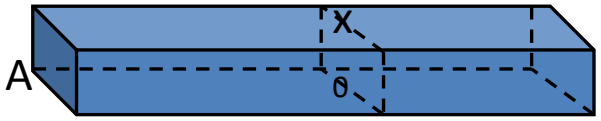
$$D = D_0 e^{-\frac{E_a}{RT}}$$

Total amount diffused

- E.g. from the intestines to the bloodstream through intestinal walls
- The **total *amount*** of drug absorbed is

$$\text{Flux}(\boldsymbol{J}) \bullet \text{Area}(\boldsymbol{A}) \bullet \text{Time}$$

- $\boldsymbol{J}$ [mol m^{-2} s^{-1}]; $\boldsymbol{J} \times \boldsymbol{A}$ [mol s^{-1}]; $\boldsymbol{J} \times \boldsymbol{A} \times \boldsymbol{t}$ [mol]
- Flux is $\boldsymbol{J} = -P(C^{\alpha} - C^{\beta}) = -P\Delta C$
  - where $\boldsymbol{P}$ is permeability (related to diffusion coefficient)



Rates of Chemical Reactions

- Rate Laws and Rate Constants
- Integrated Rate Laws
  - Zero-order Reactions
  - First-order Reactions
  - Second-order Reactions
- Temperature dependence of the

Reaction Rates (Arrhenius)

Reaction Rates

- Molecules or atoms of reactants must collide with each other in chemical reactions (concentrations).
- The molecules must have sufficient energy (discussed in terms of activation energy) to initiate the reaction. That leads to *k(T)*
- In some cases, the orientation of the molecules during the collision must also be considered.

Rates of a Chemical Reaction

Example:

A + 2B → 3C + D

$$-\frac{d[A]}{dt} = -\frac{1}{2}\frac{d[B]}{dt} = +\frac{1}{3}\frac{d[C]}{dt} = +\frac{d[D]}{dt}$$

Rate of Consumption

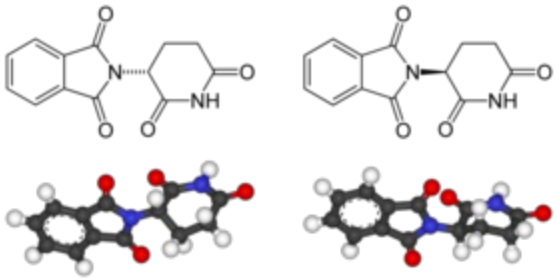
$$-\frac{d[A]}{dt} = -\frac{1}{2}\frac{d[B]}{dt}$$

Rate of Formation

$$\frac{1}{3}\frac{d[C]}{dt} = \frac{d[D]}{dt}$$

Reversible reactions: connection between kinetic and thermodynamic constants

- Examples:
  - Epimerization of tetracyclines
  - Chiral transition of thalidomide



$$A \underset{k_r}{\overset{k_f}{\longleftrightarrow}} B$$

At equilibrium

$$\frac{\mathrm{d[A]}}{\mathrm{d}t} = -k_f[\mathrm{A}] + k_r[\mathrm{B}] = 0$$

$$\mathrm{K_{eq}} = \frac{[B]}{[A]} = \frac{k_f}{k_r}$$

Rates and Equilibrium Constant

- A ⇔ B
- Forward rate: k_f[A]
- Reverse rate: k_r[B]
- Equilibrium:

k_f[A] = k_r[B]

$$K_{eq} = \frac{[B]}{[A]} = \frac{k_f}{k_r}$$

- P + L ⇔ PL
- Forward rate: k_{on}[P][L]
- Reverse rate: k_{off}[PL]
- Equilibrium (stationary):

k_{on}[P][L] = k_{off}[PL]

$$K_{bind} = \frac{[PL]}{[P][L]} = \frac{k_{on}}{k_{off}}$$

$$K_d = \frac{[P][L]}{[PL]} = \frac{k_{off}}{k_{on}}$$

The Unique Rate of a Chemical Reaction

The unique Rate of Reaction is defined as:

$$rate = \frac{1}{\nu_j} \frac{d[\mathbf{c}_j]}{dt}$$

where $\mathbf{c}_j$ is a generic participant to the reaction and ν_j its stoichiometric number.

Reaction Rates are reported in [mol L^{-1} s^{-1}]

Rate Laws

The Rate Law is an experimentally determined equation that expresses the rate of reaction, r, as a function of concentrations:

$$r = k \cdot f([A],[B],etc.)$$

The coefficient k is called rate constant.

It is *often* possible to write the function as a product of concentrations with constant exponents:

$$r = k[A]^x[B]^y[C]^z$$

Reaction Order

$$v = k[A]^x[B]^y[C]^z$$

The reaction is said to be of order *x* with respect to [A], etc. The overall order of the reaction is

x + y + z

The orders are generally unrelated to the stoichiometric coefficients in the reaction equation. E.g.,

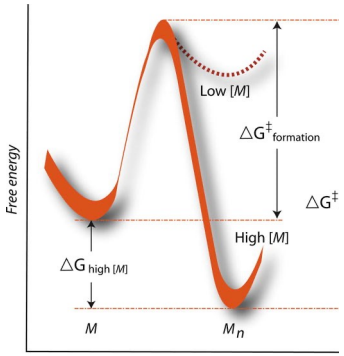
$$2N_2O_5(g) \rightarrow 4NO_2(g) + O_2(g), \quad v = k[N_2O_5]$$

Arrhenius

- The **rate constant** of chemical reaction, k

$$k = (Pf)e^{-\frac{G_{activation}}{RT}}$$

- Pf is the pre-exponential factor (pre-factor),
- R is the gas constant



Svante Arrhenius, Swedish physical chemist. In 1903 he became the first Swede to be awarded the Nobel Prize in chemistry.

The equilibrium constant of a reaction, K

$$K = e^{-\frac{G_{AB}}{RT}}$$

Jacobus van't Hoff