

Teoría Variacional del Estado de Transición: Fundamentos y aplicaciones a las reacciones químicas y bioquímicas



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Salou, 9 de Novembre de 2016

TEORIA DEL ESTADO DE TRANSICIÓN

- ❑ Teoría más útil i más extendida de la Química
- ❑ Teoría que da el marco con el que se pueden entender mejor la totalidad de las reacciones químicas.
- ❑ Permite calcular las **constantes de velocidad de sistemas reactivos en función de la temperatura y la presión.**
- ❑ Permite calcular con gran exactitud las $k(T)$ de reacciones de **10-15 átomos en fase gas**: reacciones unimoleculares i **bimoleculares.**
- ❑ Permite calcular constantes de velocidad de reacciones en disolución, procesos moleculares en sistemas sólidos y **catálisis enzimática.**

Svante August Arrhenius



Henry Eyring

$$v = k(T)[A][B]$$



$$k(T) = Ae^{-Ea/RT}$$

81 años

TST

"Everything should be made as simple as possible, but not simpler."

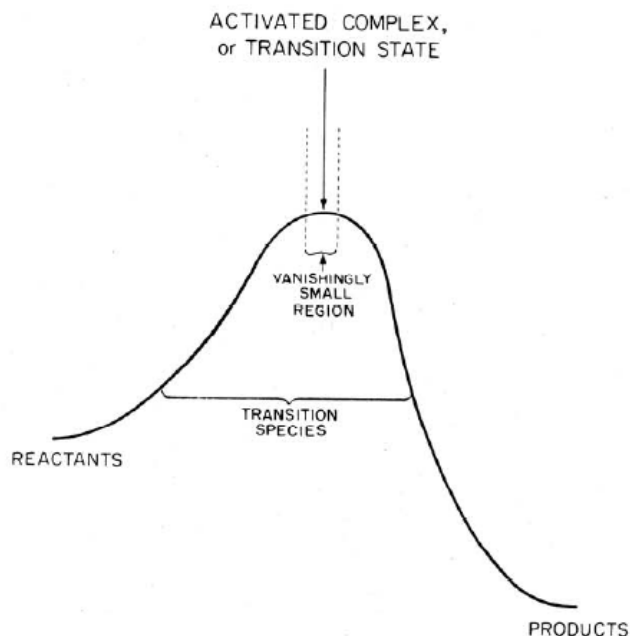
Albert Einstein

The Activated Complex in Chemical Reactions

HENRY EYRING, *Frick Chemical Laboratory, Princeton University*

(Received November 8, 1934)

I. Rates can be calculated by focusing attention on the activated complexes, which lie at the saddle point of the potential energy surface.



$$v = \frac{dP}{dt} = \frac{N_{R \rightarrow P}^\ddagger}{\partial t} = k(T)[A][B]$$

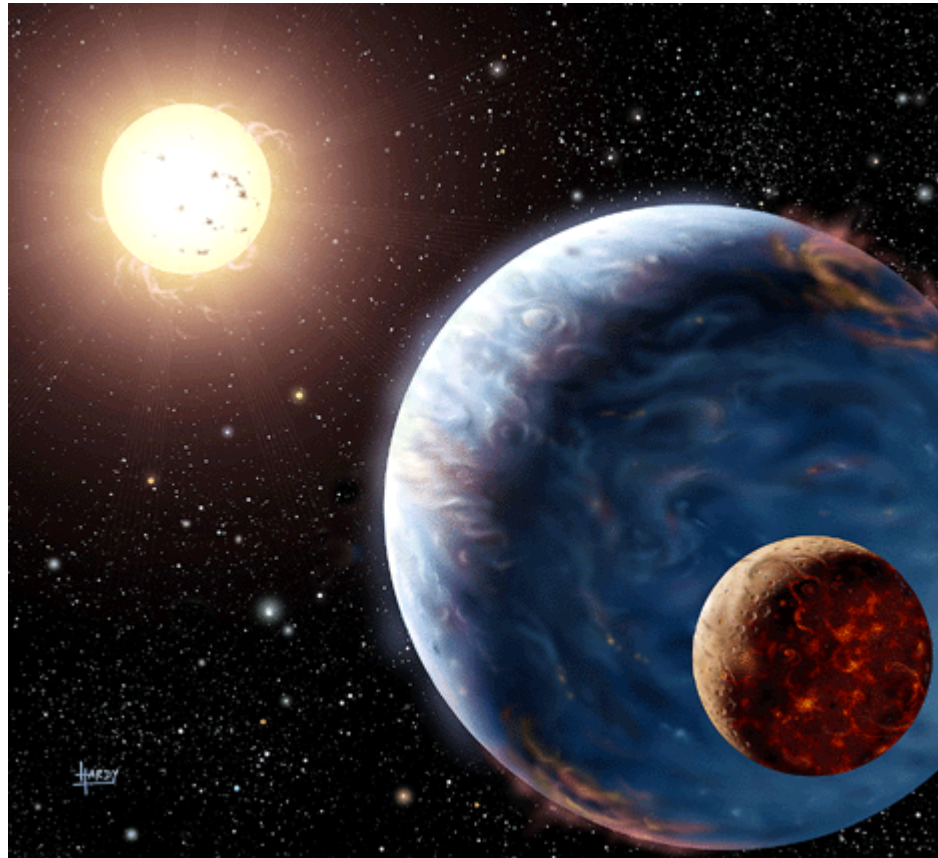
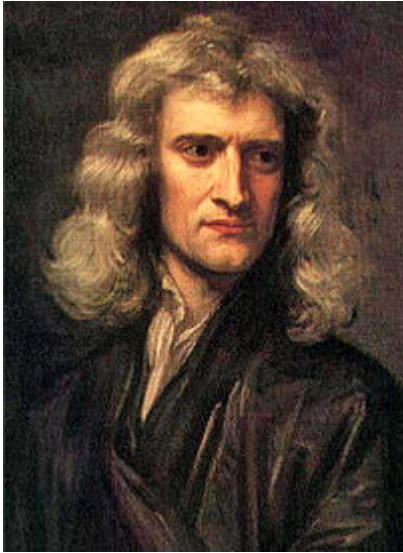
Lifetime of the transition state is in the range of the period of molecular vibrations, which is of the order of 1 picosecond (ps), or even less.

Figure 1. Schematic potential-energy profile for a reaction, showing the activated complex (transition state) and transition species.

MECÁNICA CLÁSICA

Estado de un sistema: $\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N$ $\mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_N$

Segunda Ley de Newton (1687): $\mathbf{F}_i = m_i \mathbf{a}_i = m_i \frac{d^2 \mathbf{r}_i}{d^2 t}$



MECÁNICA CUÁNTICA

Estado de un sistema:

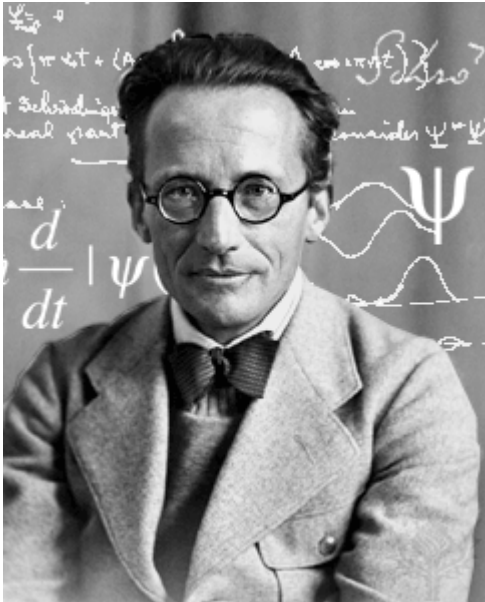
$$\Psi(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N, t)$$

$$\mathbf{x}_i = (\mathbf{r}_i, \omega_i)$$

Equación de Schrödinger (1926):

$$i\hbar \frac{\partial \Psi}{\partial t} = \hat{H}\Psi$$

$$\hat{H}\Psi = E\Psi$$



$\hat{H} \Rightarrow$

3 N derivadas parciales segundas

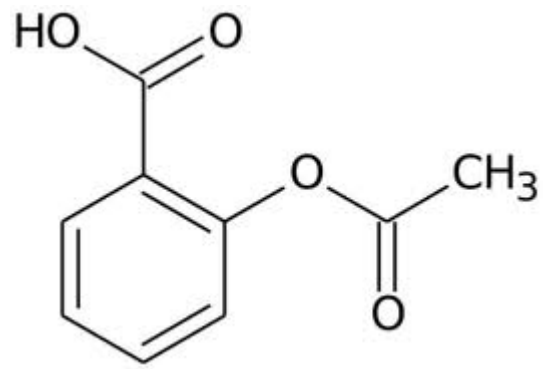
$\frac{1}{2} N(N-1) = O(N^2)$ interacciones potenciales

Ψ

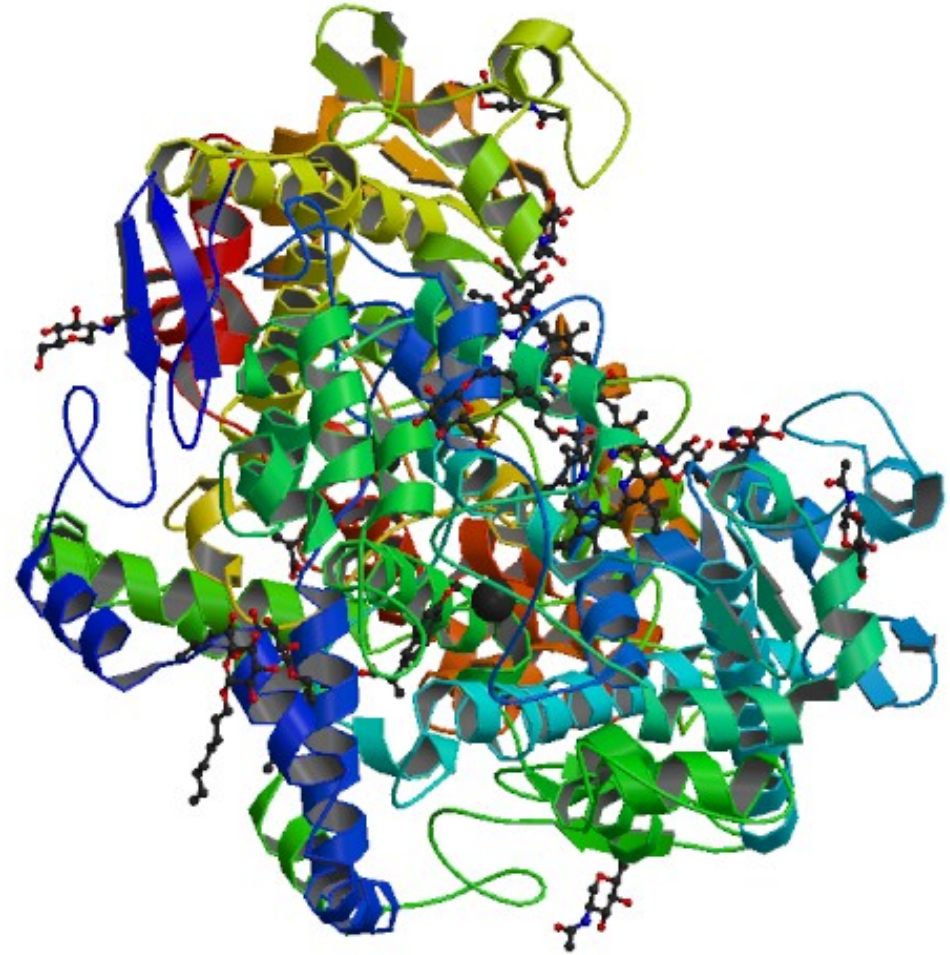
depende de 3 N coordenadas espaciales

Aspirina: $\text{CH}_3\text{COOC}_6\text{H}_4\text{COOH}$

21 núcleos + 94 electrones = 115 partículas = 345 coordenadas

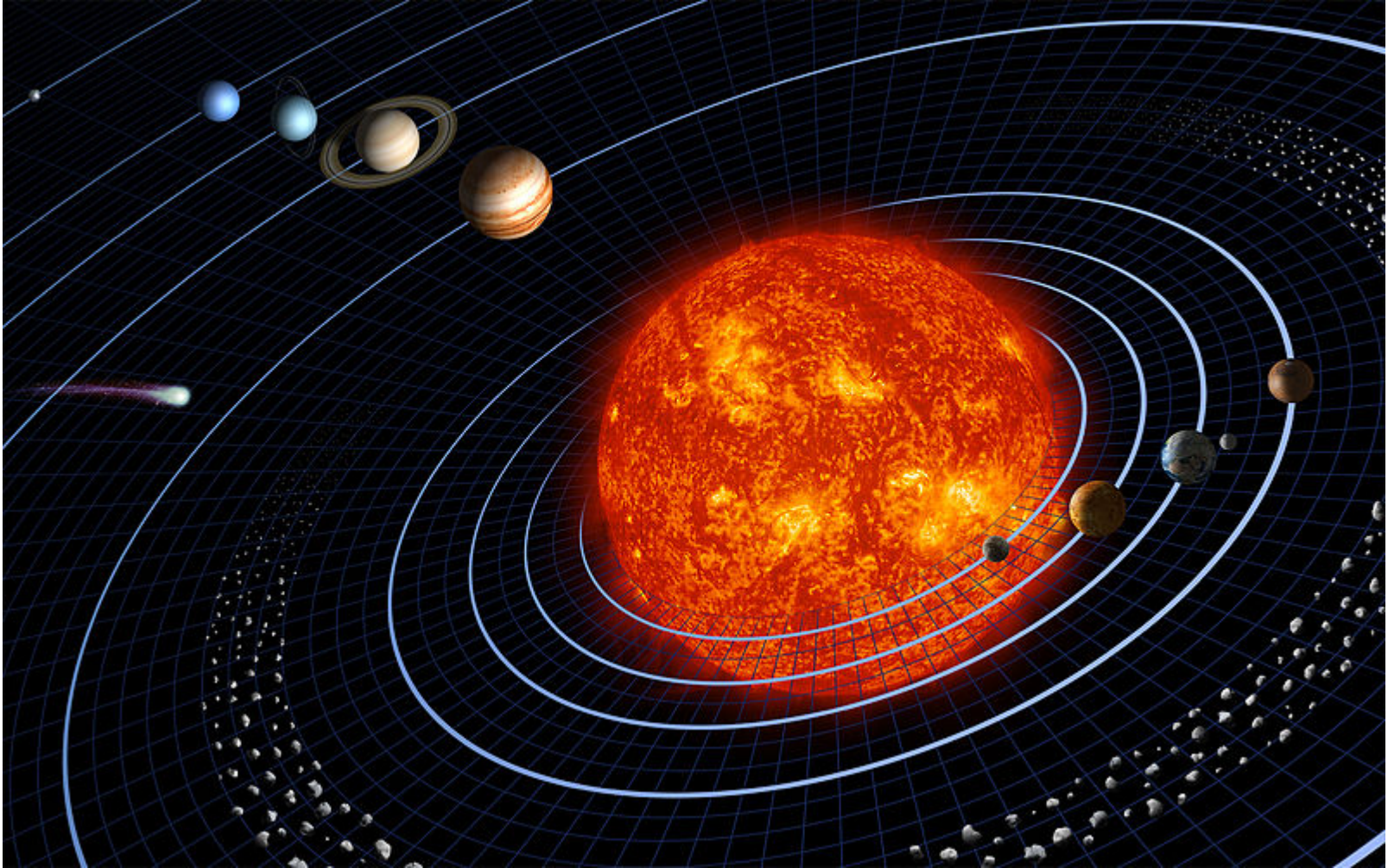


COX 2



Enzima solvatada:
≈ 200.000 partículas (núcleos +
electrones) = 600.000 coordenadas

Enzima solvatada: ≈ 200.000 partículas (núcleos + electrones) =
600.000 coordenadas



*“The fundamental laws necessary for the **mathematical** treatment of a large part of **physics** and the whole of **chemistry** are thus completely known, and the difficulty lies only in the fact that application of these laws leads to equations that are too complex to be solved”.*

Paul M. Dirac

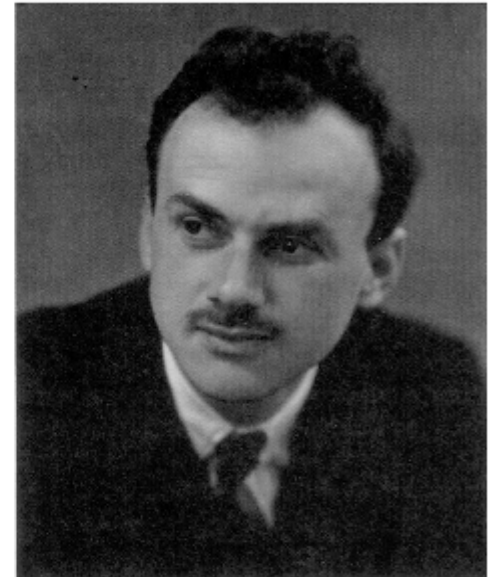
Premi Nobel de Física l'any 1933

amb Erwin Schrödinger

"A theory with mathematical beauty is more likely to be correct than an ugly one that fits some experimental data."

Paul A.M. Dirac (1902-1984)

Dirac gave general formulation of quantum mechanics, and his relativistic equation for the electron had profound and long-lasting consequences. (Photo Ramsey & Muspratt, 1934.)



Aproximación de Born-Oppenheimer (1927):



Nobel de Física 1954



Ec. de Schrödinger electrónica: $\Psi_{el}(\mathbf{r}; \mathbf{R}), U(\mathbf{R})$

Ec. de Schrödinger nuclear: $\Psi_N(\mathbf{R}), E$ **Dinámica**

Aspirina: Ψ_{el} depende de 94 electrones = 282 coordenadas

$$\hat{H}\Psi(\vec{r}, \vec{R}) = E\Psi(\vec{r}, \vec{R})$$

$$\begin{aligned}\hat{H} &= \hat{T}_N + \hat{T}_e + V_{Ne}(\vec{r}, \vec{R}) + V_{ee}(\vec{r}) + V_{NN}(\vec{R}) \\ &= \hat{T}_N + \hat{H}_e + V_{NN}(\vec{R})\end{aligned}$$

$$\hat{H}_e\Psi_{e,n}(\vec{r}; \vec{R}) = E_{e,n}(\vec{R})\Psi_{e,n}(\vec{r}; \vec{R})$$

$$\Psi(\vec{r}, \vec{R}) = \sum_n \Psi_{N,n}(\vec{R}) \Psi_{e,n}(\vec{r}; \vec{R})$$

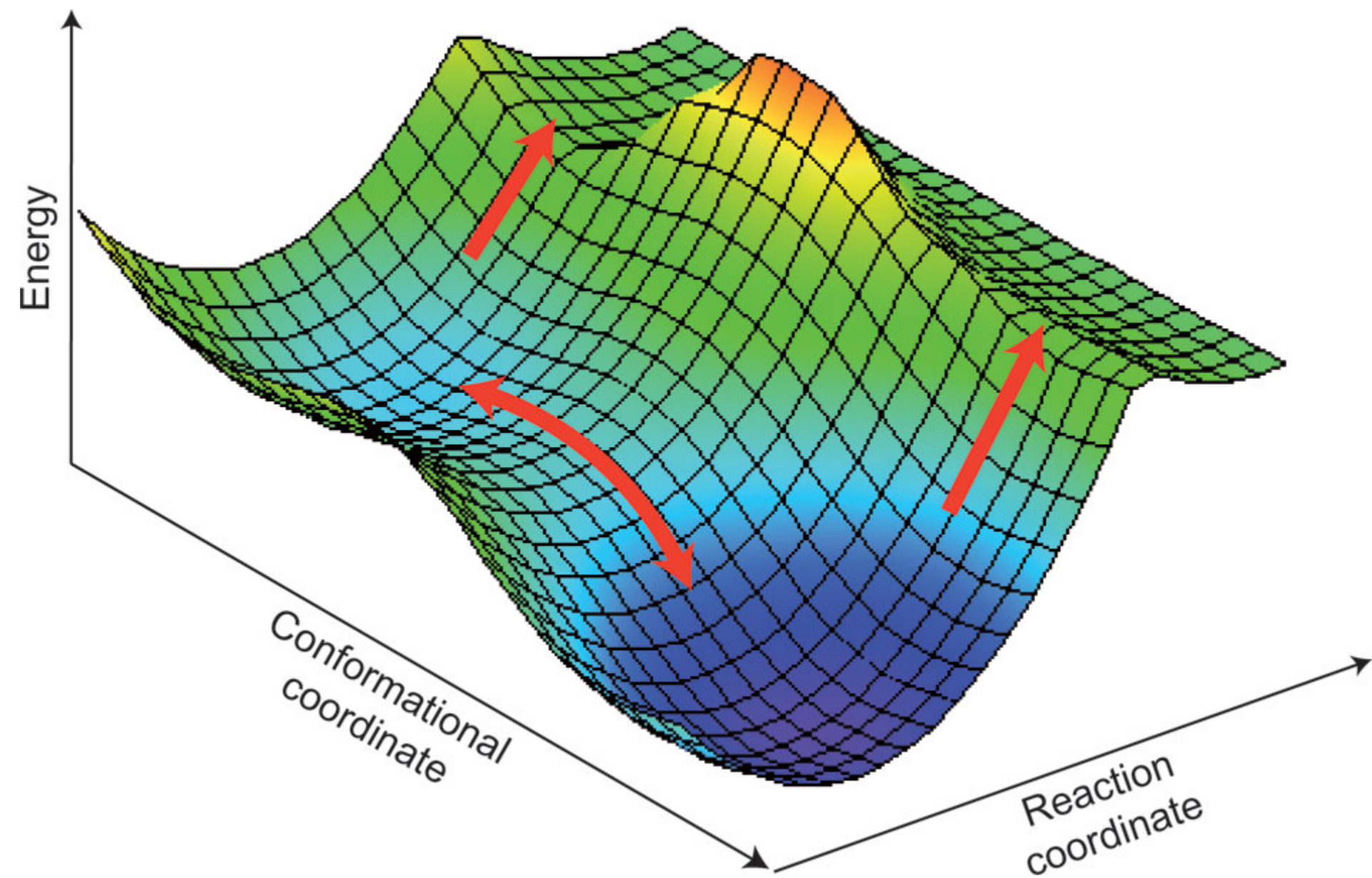
$$\begin{aligned}(\hat{T}_N + E_{e,n}(\vec{R}) + V_{NN}(\vec{R}) + C_{nn}(\vec{R}) - E)\Psi_{N,n}(\vec{R}) \\ + \sum_{n' \neq n} \hat{C}_{n,n'}(\vec{R}, \vec{P}) \Psi_{N,n'}(\vec{R}) = 0\end{aligned}$$

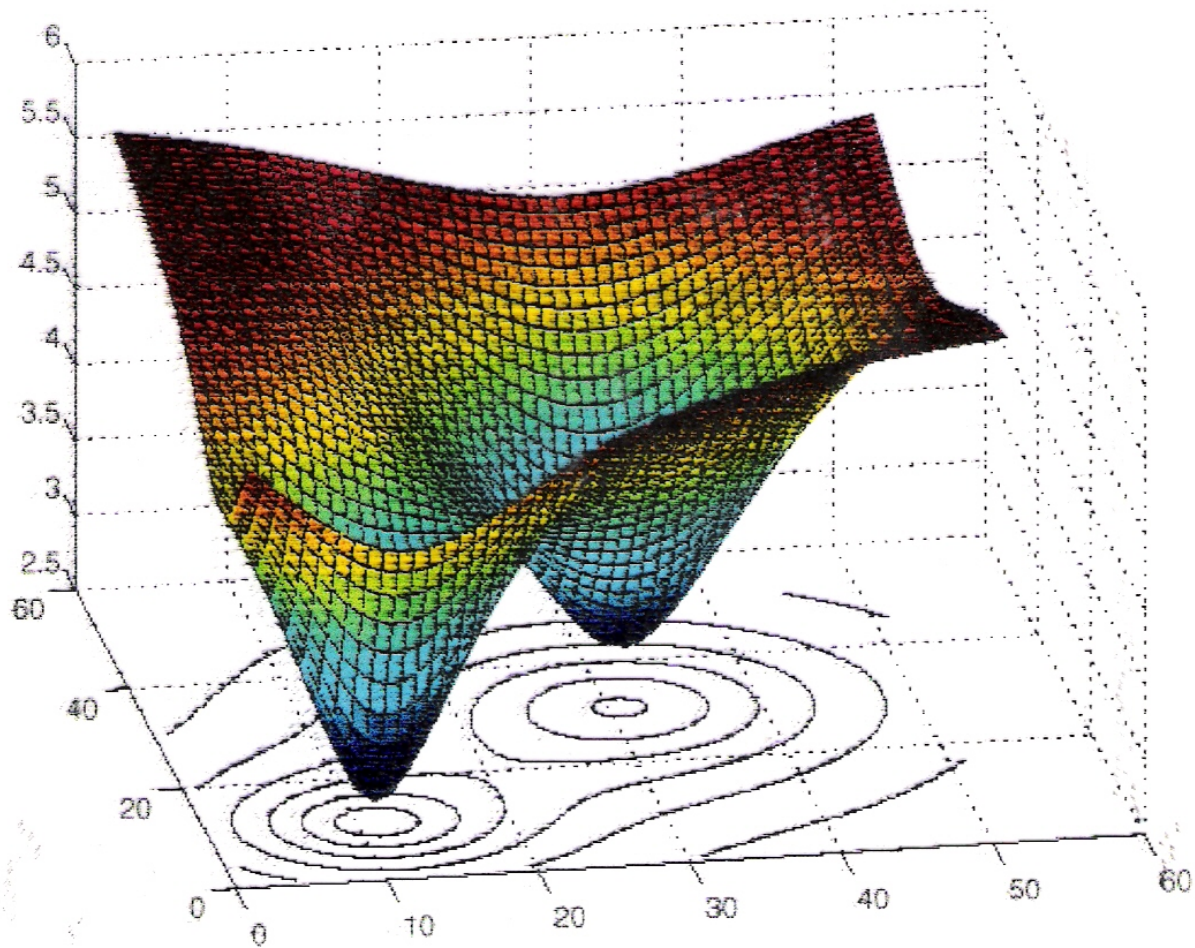
$$C_{nn}(\vec{R}) = \langle \Psi_{e,n}(\vec{r}; \vec{R}) | \hat{T}_N | \Psi_{e,n}(\vec{r}; \vec{R}) \rangle$$

$$\left(\hat{T}_N + U_n(\vec{R}) \right) \Psi_{N,n}(\vec{R}) = E \Psi_{N,n}(\vec{R})$$

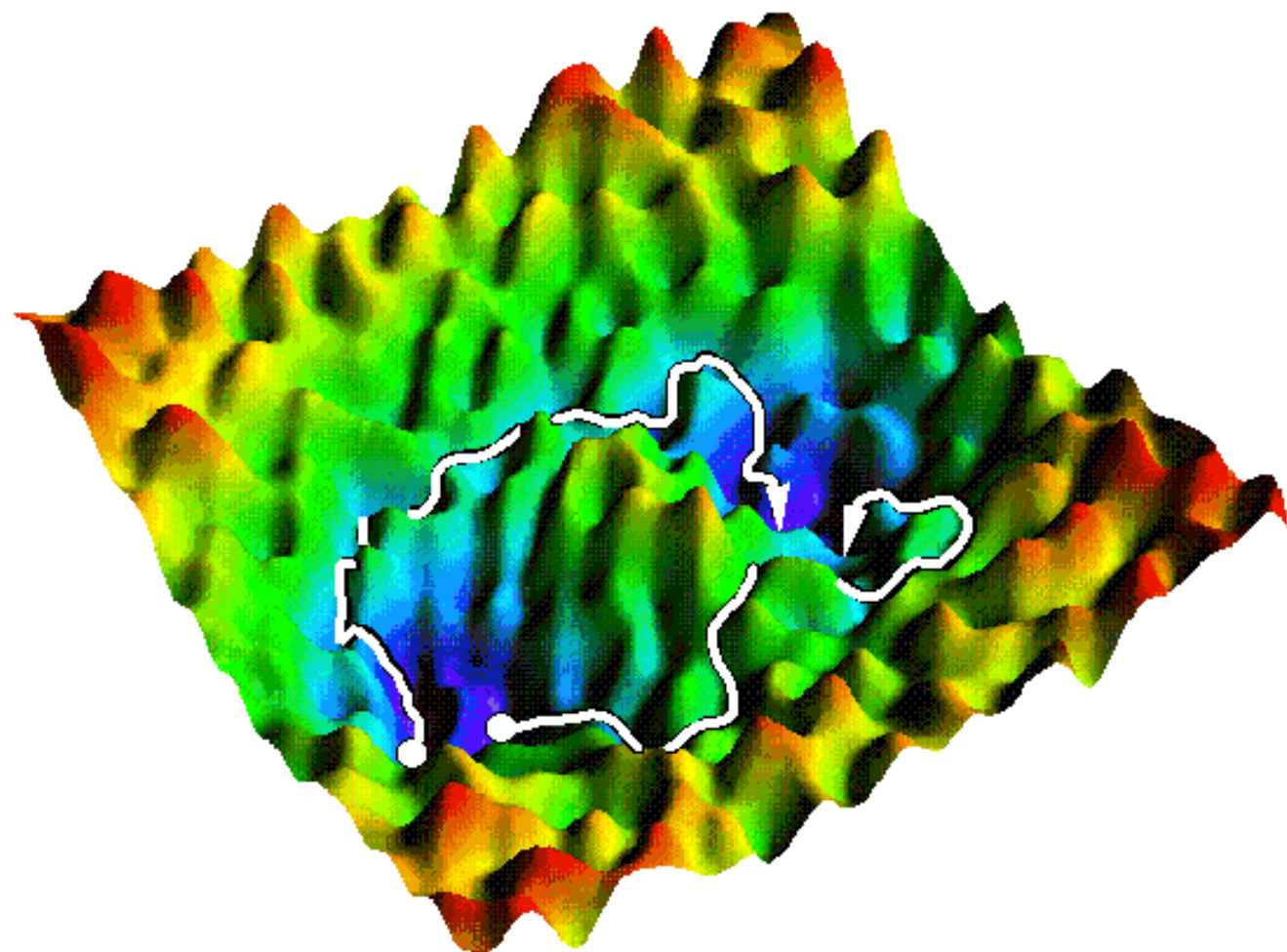
$U_n(\vec{R})$ **Superficie de energía potencial**

$$E = E_{trans} + E_{rot} + E_{vib} + U(\vec{R}_e)$$





Superfície d'energia potencial bidimensional per a una reacció química



FORMULACIÓN DINÁMICA DE LA TEORÍA DEL ESTADO DE TRANSICIÓN

Un sistema reactivo formado por un conjunto de N núcleos clásicos puede ser representado en un instante dado t por un punto

$$(\vec{q}, \vec{p})$$

en el espacio de las fases $6N$ dimensional

La función Hamiltoniana del sistema viene dada por:

$$H(\vec{q}, \vec{p}) = V(\vec{q}) + T(\vec{p})$$

Donde $V(\vec{q})$ y $T(\vec{p})$ representan la energía potencial y cinética del sistema, respectivamente

$$\rho(\vec{q}, \vec{p})$$

Es la densidad de puntos en el espacio de las fases, donde cada punto representa un sistema de N núcleos.

La reacción química puede tratarse como un movimiento de los N núcleos sobre una única superficie de energía potencial (Aproximación de Born-Oppenheimer).

El sistema reactivo puede encontrarse, en un instante dado, en la región del espacio de las fases correspondiente a reactivos, en la región de productos o en una región intermedia.

A partir del seguimiento del **flujo de puntos** entre regiones específicas del espacio de las fases, podemos estudiar el curso de una reacción química en el colectivo de sistemas reactivos.

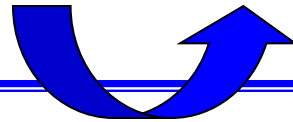
$$-\frac{\delta \rho}{\delta t} = \vec{\nabla} (\rho \vec{v})$$

Ecuación de Liouville

$$-\frac{\delta}{\delta t} \int_R \rho d^{6N} \tau = \int_R \vec{\nabla} (\rho \vec{v}) d^{6N} \tau$$

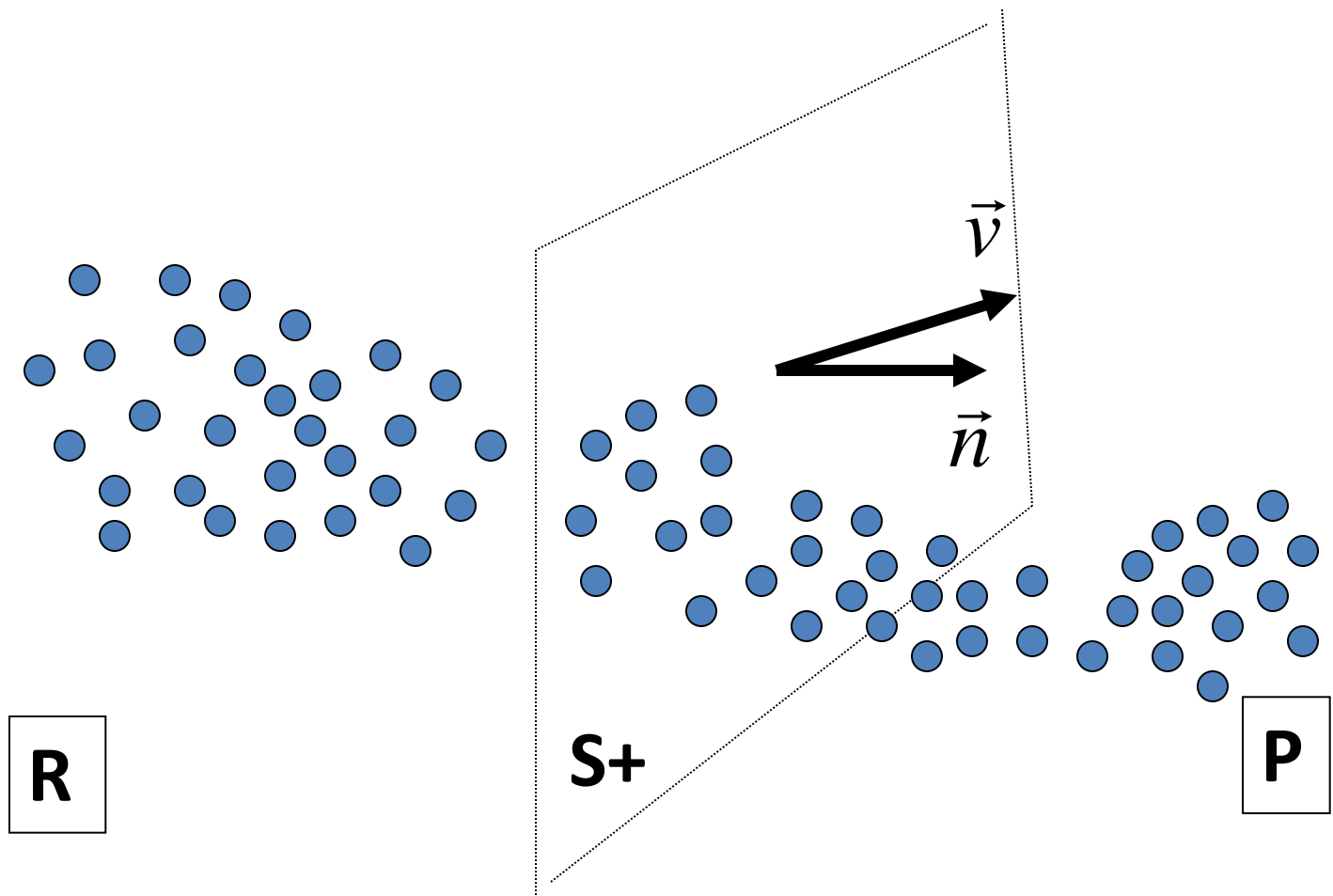
$$N^R = \int_R \rho d^{6N} \tau$$

$$-\frac{\delta N^R}{\delta t} = \int_R \vec{\nabla} (\rho \vec{v}) d^{6N} \tau = \int_S \rho (\vec{v} \vec{n}) d^{6N-1} S = F(T)$$



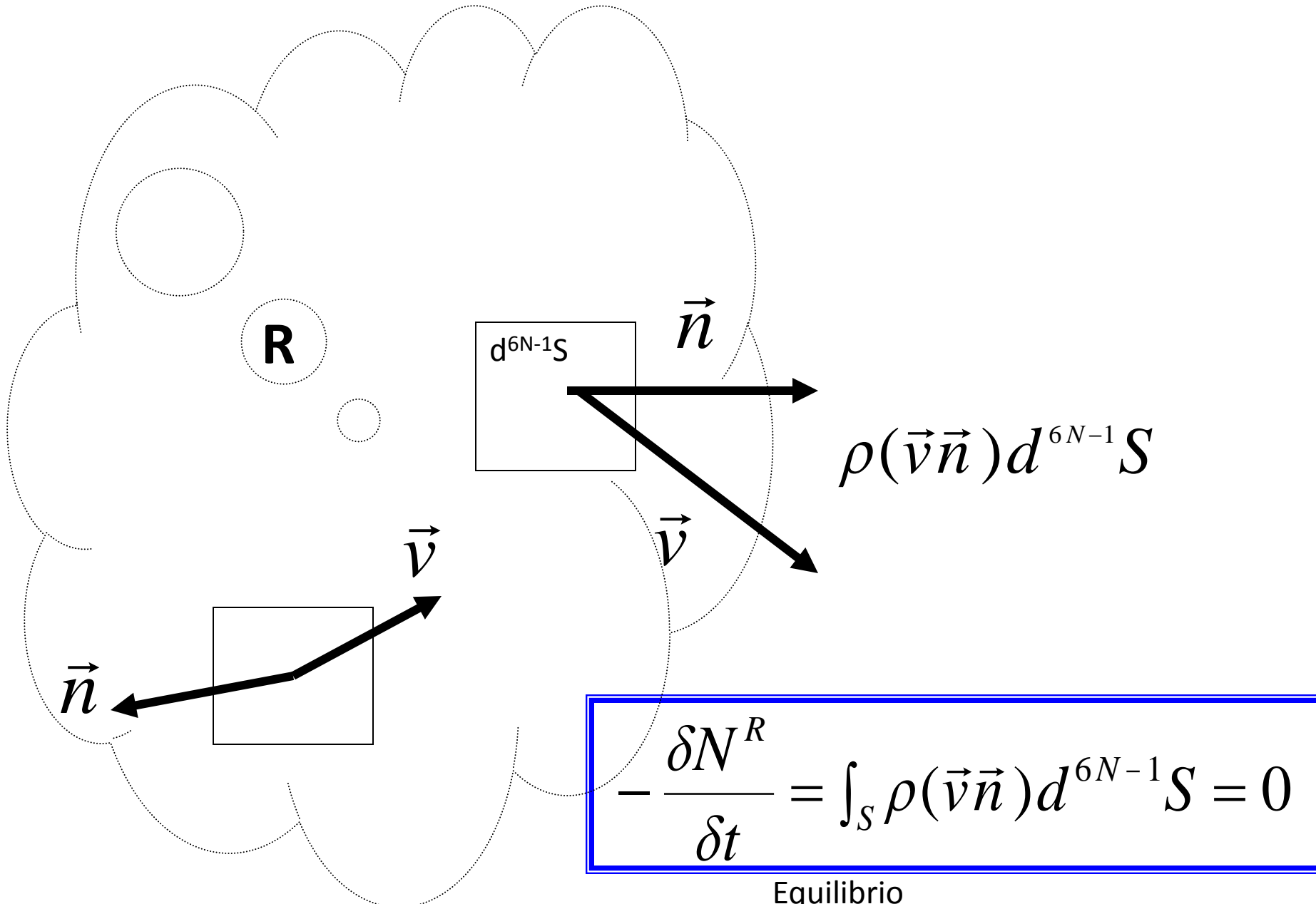
Teorema de Gauss

FLUJO NETO a través
de una superficie



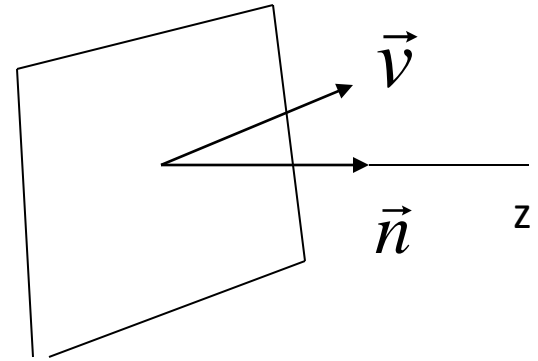
$$F^+ = \int_{S^+} \rho(\vec{v}\vec{n}) d^{6N-1} S \quad (\vec{v} \cdot \vec{n} > 0)$$

FLUJO "one-way"



$$\vec{v} \cdot \vec{n} = \frac{dz}{dt} = \frac{p_z}{\mu} = \frac{p_{3N}}{\mu}$$

$$\vec{v} \cdot \vec{n} > 0 \Rightarrow p_z > 0$$



$$d^{6N-1}S = dq_1 dq_2 \dots dq_{3N-1} dp_1 dp_2 \dots dp_{3N-1} dp_z =$$

$$= d^{6N-2}S dp_z$$

$$F^+ = \int_{S^+} \rho(\vec{v}\vec{n}) d^{6N-1}S = \int_{S^+} \rho \frac{p_z}{\mu} d^{6N-2}S dp_z =$$

$$\rho = \rho_0 e^{-H/k_B T}$$

$$F^+ = \rho_0 \int_{S^+} \frac{p_z}{\mu} e^{-H/k_B T} d^{6N-2}S dp_z$$

$$F^+ = \rho_0 \int_{S^+} \frac{p_z}{\mu} e^{-H/k_B T} d^{6N-2} S dp_z$$

$$H = \frac{p_z^2}{2\mu} + H^{GT}(q_1, \dots, q_{3N-1}, p_1, \dots, p_{3N-1}; z)$$

$$F^{GT}(T, z^*) = \rho_0 k_B T \int e^{-H^{GT}(\vec{u}, \vec{p}_u; z=z^*)/k_B T} d^{6N-2} S$$

FLUJO “one-way” a través del ESTADO DE TRANSICIÓN GENERALIZADO



Unimolecular

$$k(T) = \frac{F(T)}{V[A]} = \frac{F(T)}{N^A(T)}$$

$$k_C^{GT}(T) = \frac{\rho_0 k_B T \int e^{-H^{GT}(\bar{u}, \bar{p}_u; z=z^*)/k_B T} d^{6N-2} S}{N^A(T)}$$

$$Q_C(T) = \frac{1}{h^{3N}} \int e^{-H(\bar{q}, \bar{p})/k_B T} d^{6N} \tau \quad Q_C^{GT}(T) = \frac{1}{h^{3N-1}} \int e^{-H^{GT}(\bar{u}, \bar{p}_u; z=z^*)/k_B T} d^{6N-2} S$$

$$k_C^{GT}(T, z^*) = \frac{k_B T}{h} \frac{Q_C^{GT}(T, z^*)}{Q_C^A(T)} e^{-V_{RP}(z=z^*)/k_B T}$$



Bimolecular

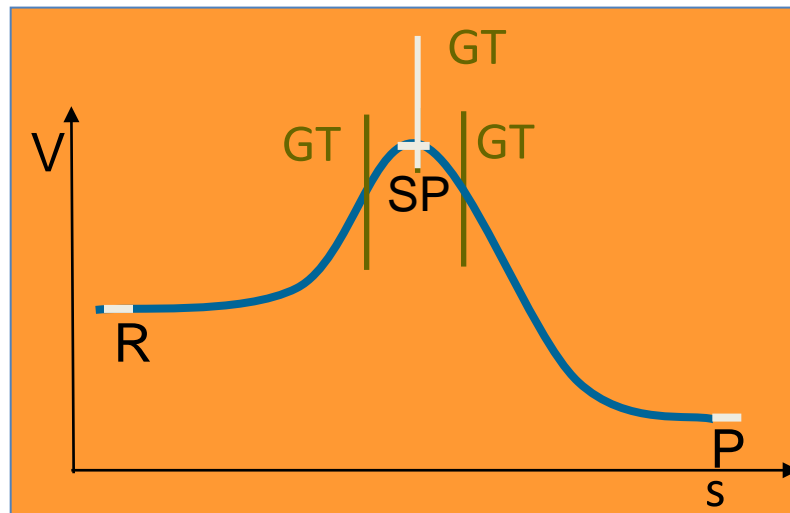
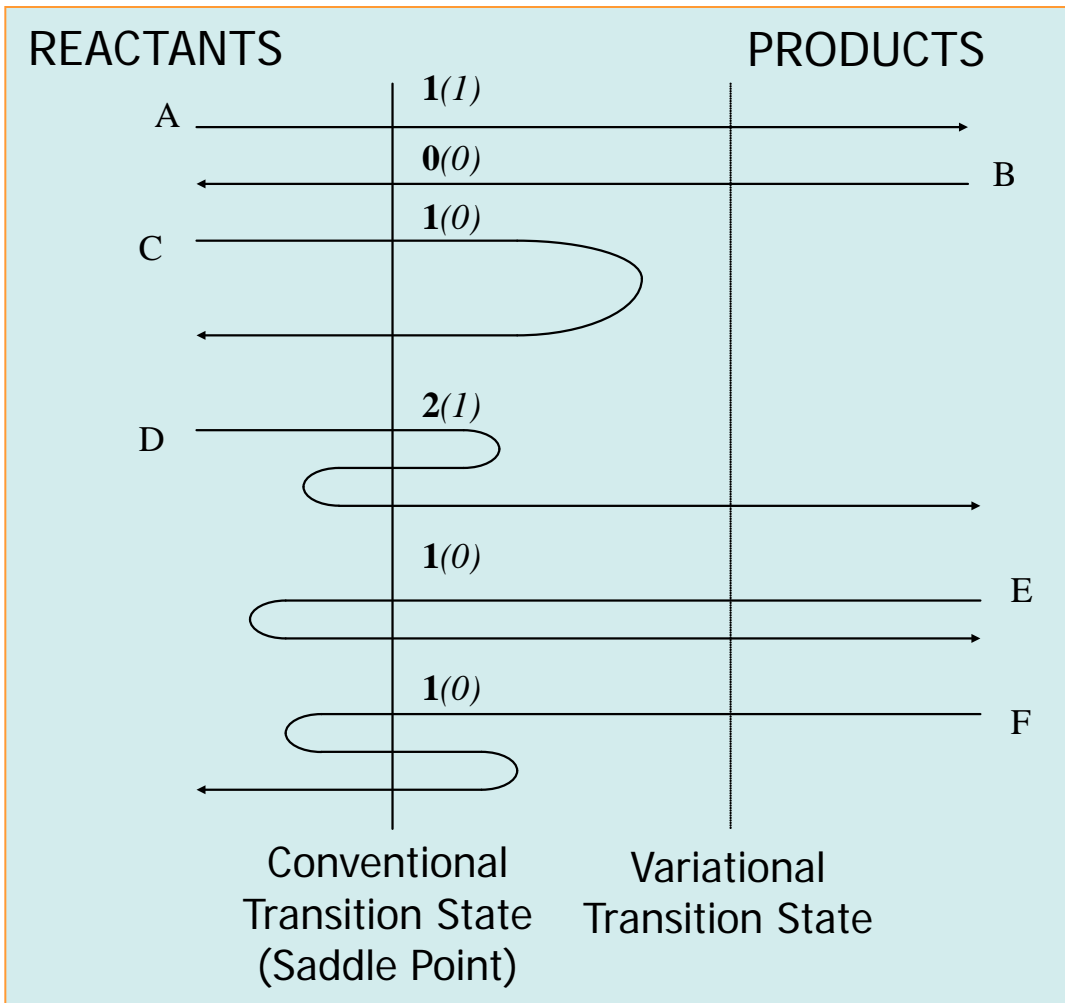
$$k(T) = \frac{F(T)}{V[A][B]} = \frac{F(T)V}{N^{R,A}(T)N^{R,B}(T)}$$

$$k_C^{GT}(T, z^*) = \frac{k_B T}{h} V \frac{Q_C^{GT}(T, z^*)}{Q_C^A(T) Q_C^B(T)} e^{-V_{RP}(z=z^*)/k_B T}$$

TST MAIN PROBLEM: RECROSSING



VARIATIONAL TRANSITION STATE THEORY



$$F^{TST}(T) > F^{GT}(T) > F(T)$$

$$k^{TST}(T) > k^{GT}(T) > k(T)$$

Unimolecular

$$k_C^{GT}(T, z^*) = \frac{k_B T}{h} \frac{Q_C^{GT}(T, z^*)}{Q_C^A(T)} e^{-V_{RP}(z=z^*)/k_B T}$$

$$k_C^{GT}(T, s) = \frac{k_B T}{h} \frac{Q_C^{GT}(T, s)}{Q_C^A(T)} e^{-V_{MEP}(s)/k_B T}$$

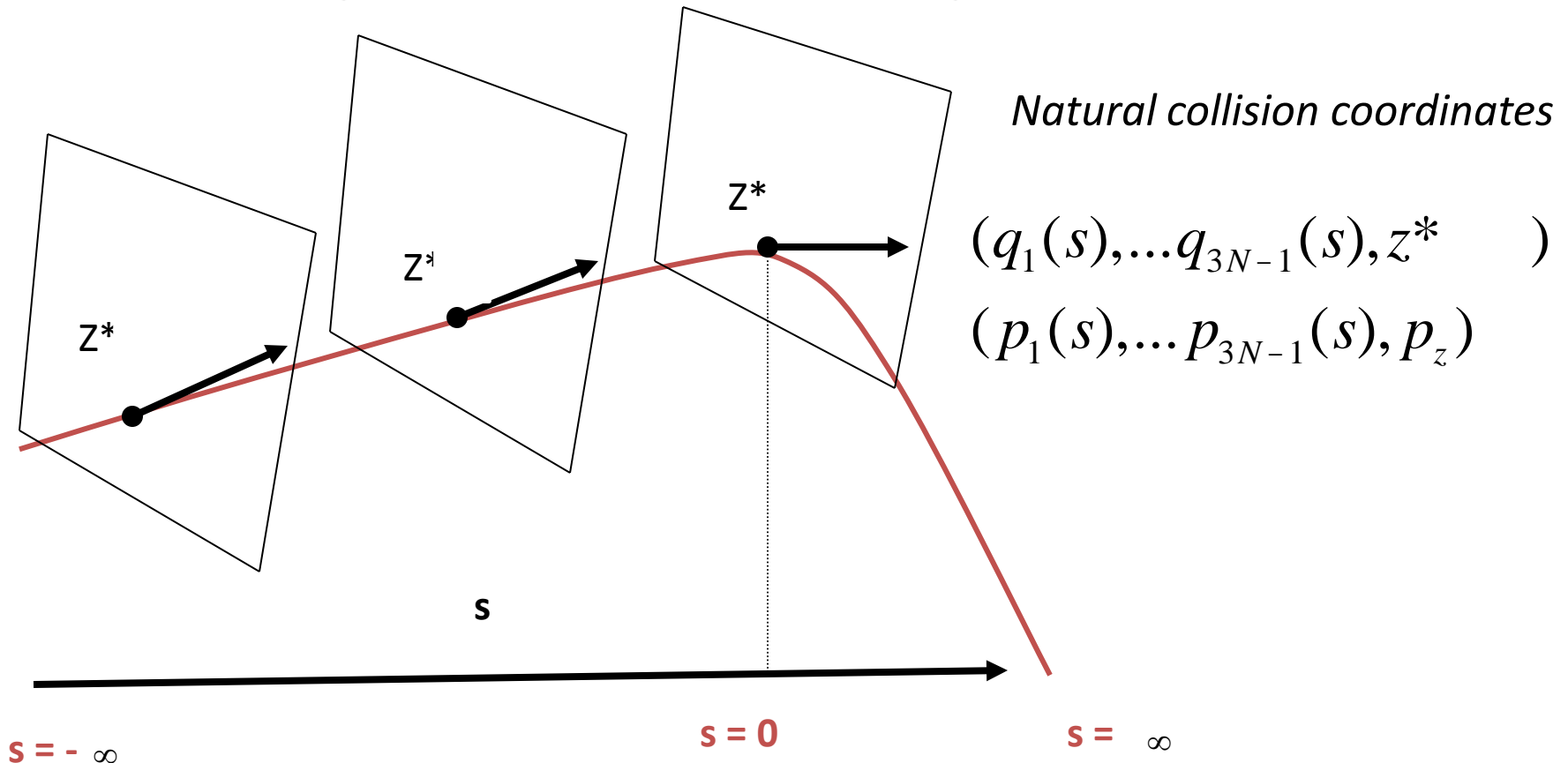
Bimolecular

$$k_C^{GT}(T, z^*) = \frac{k_B T}{h} V \frac{Q_C^{GT}(T, z^*)}{Q_C^A(T) Q_C^B(T)} e^{-V_{RP}(z=z^*)/k_B T}$$

$$k_C^{GT}(T, s) = \frac{k_B T}{h} V \frac{Q_C^{GT}(T, s)}{Q_C^A(T) Q_C^B(T)} e^{-V_{MEP}(s)/k_B T}$$

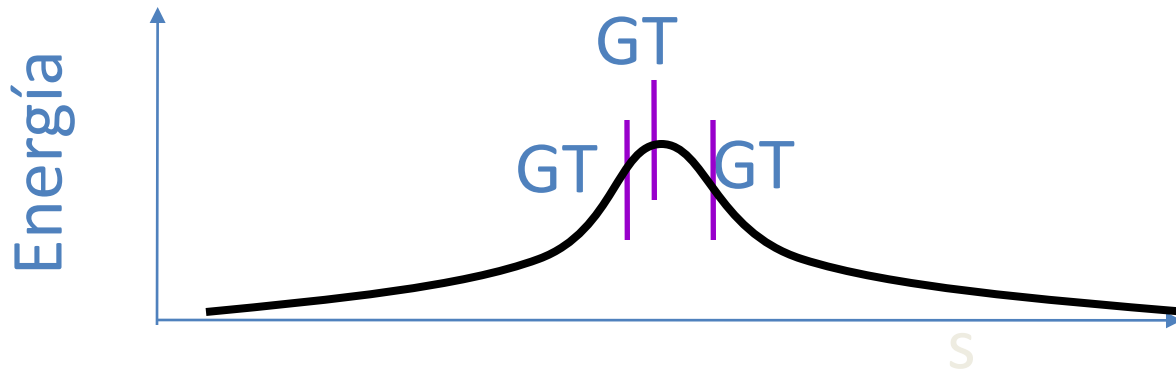
ELECCIÓN DE LA HIPERSUPERFÍCIE DE DIVISIÓN

La hipersuperficie de división de $6N-2$ dimensiones en el espacio de las fases, se asimila a un hiperplano de $3N-1$ dimensiones en el espacio configuracional ortogonal al camino de mínima energía.



Teoría Variacional del Estado de Transición (VTST)

$$k^{GT}(T,s) = \frac{k_B T}{h} K^0 \exp\left(-\frac{\Delta G^{GT,0}(T,s)}{k_B T}\right)$$



$$k^{CVT}(T) = k^{GT}(T, s_*^{CVT}) = \min_s k^{GT}(T, s)$$

$$\min_s k(T, s) \equiv \max_s \Delta G^{GT,0}(T, s) = \Delta G^{GT,0}(T, s_*^{CVT})$$

$$k^{GT}(T,s) = \frac{k_B T}{h} K^0 \exp\left(-\frac{\Delta G^{GT,0}(T,s)}{k_B T}\right)$$

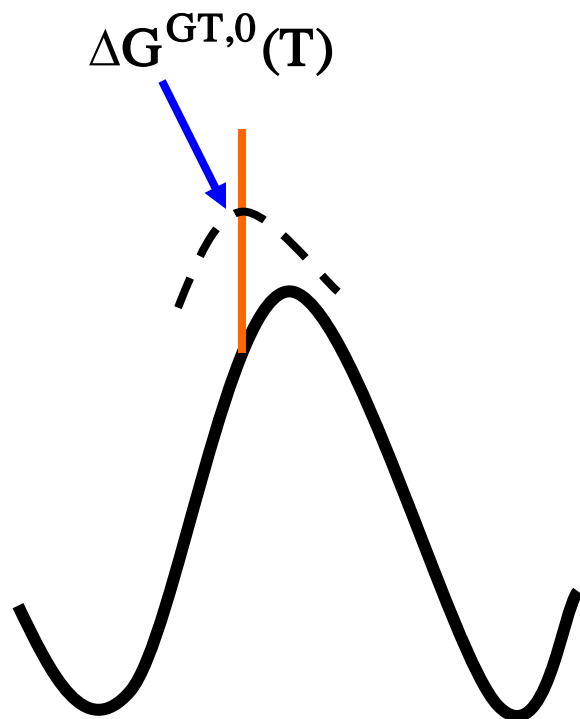
$$k^{GT}(T,s) = \frac{k_B T}{h} V \frac{Q^{GT}(T,s)}{Q_A(T)Q_B(T)} e^{-V_{MEP}(s)/k_B T}$$

Dynamical bottleneck

$$\Delta G^{GT,0}(T,s) = k_B T \left[\frac{V_{MEP}}{k_B T} - \ln \frac{Q^{GT}(T,s)}{\Phi_R(T) K^0} \right]$$

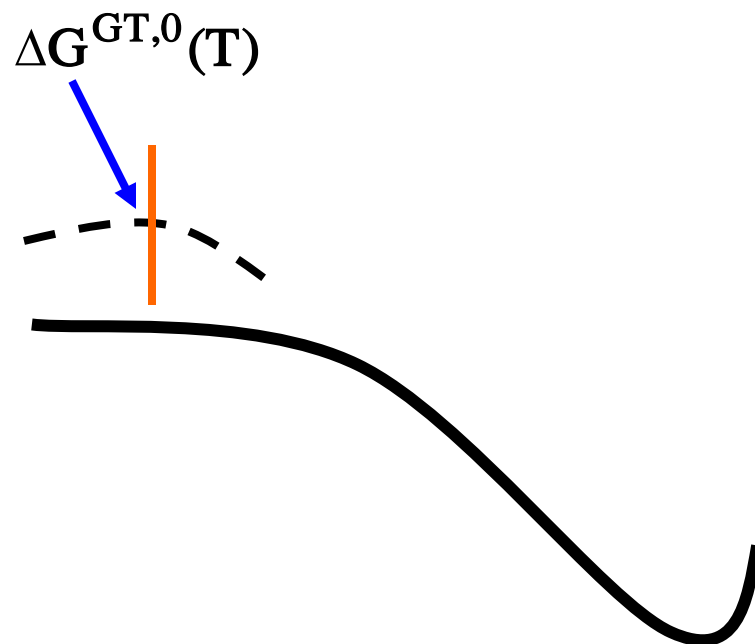
TST

CVT

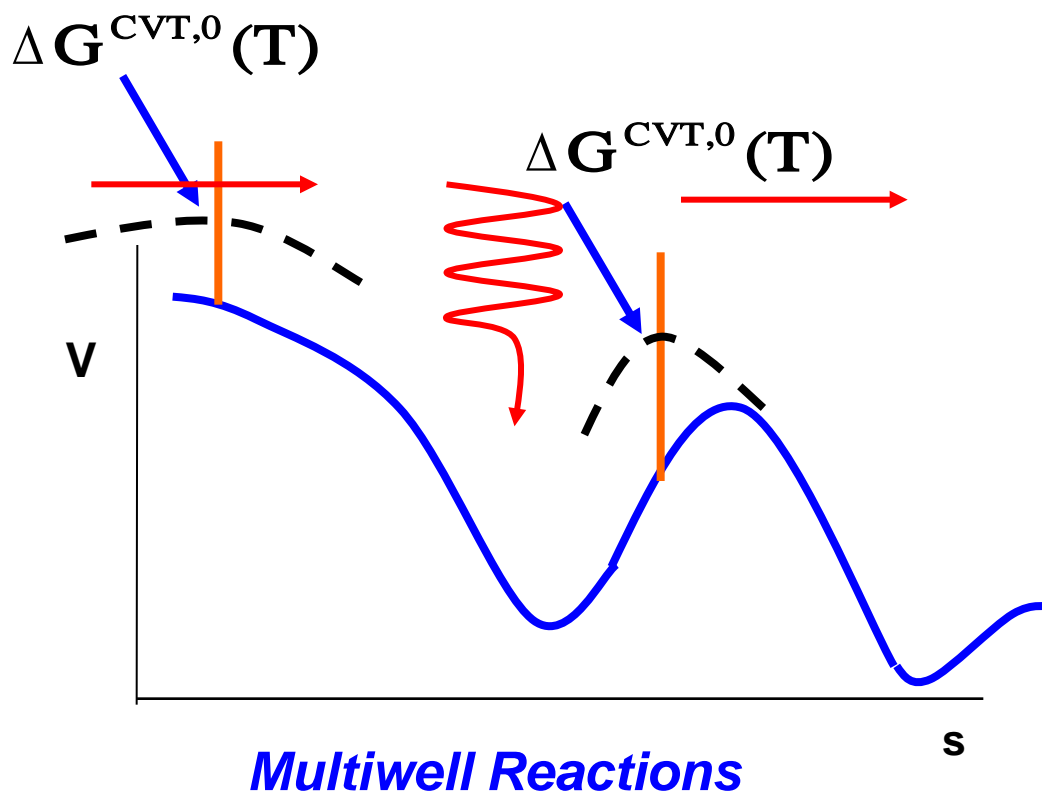
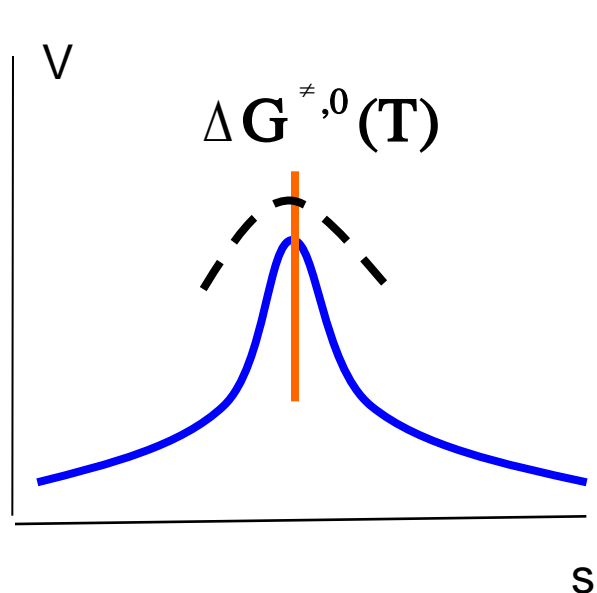
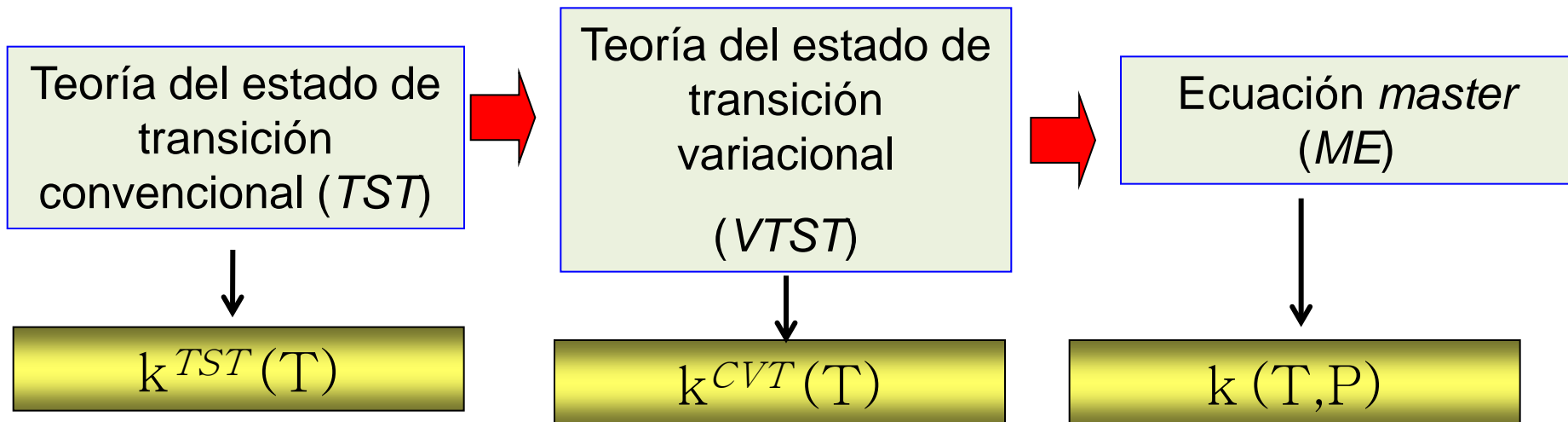


VTST improves TST.

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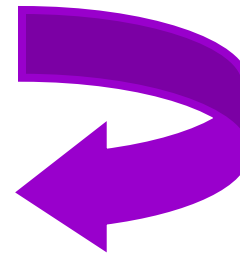


VTST is essential for barrierless reactions.



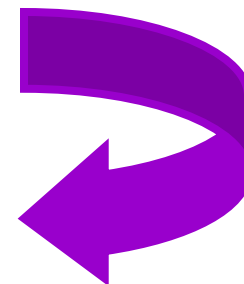
Régimen de baja presión

Las supermoléculas evolucionan manteniendo la distribución de Boltzmann entre los niveles energéticos de reactivos.



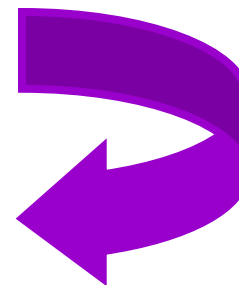
Régimen de presión intermedia

Las supermoléculas adquieren distribuciones energéticas intermedias entre los dos regímenes límite: *MASTER EQUATION*

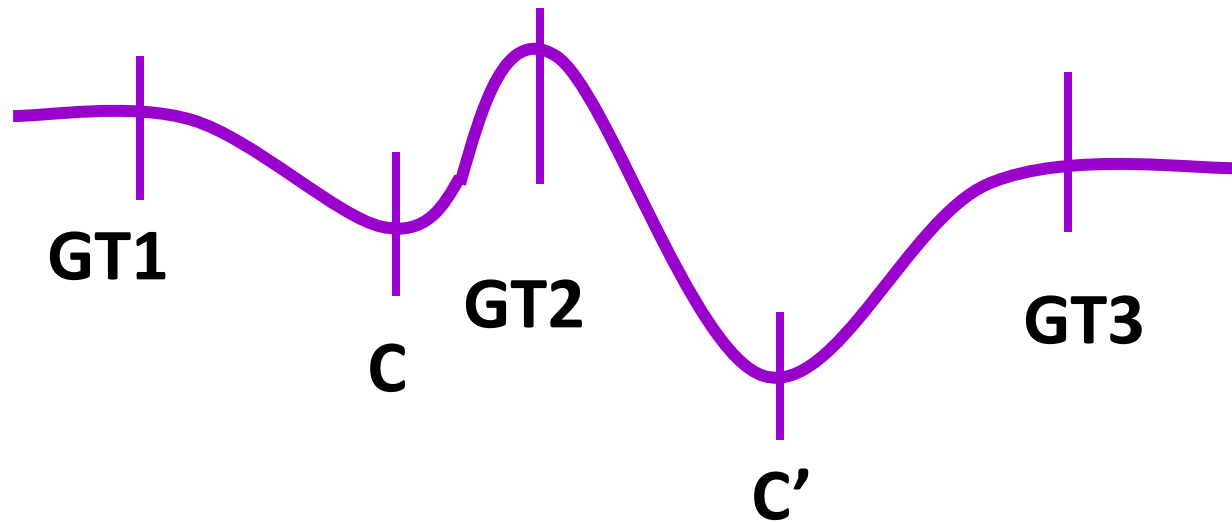


Régimen de alta presión

Las supermoléculas adquieren una distribución de Boltzmann entre los niveles energéticos del complejo.



Teoría Estadística Canónica Unificada (CUS)



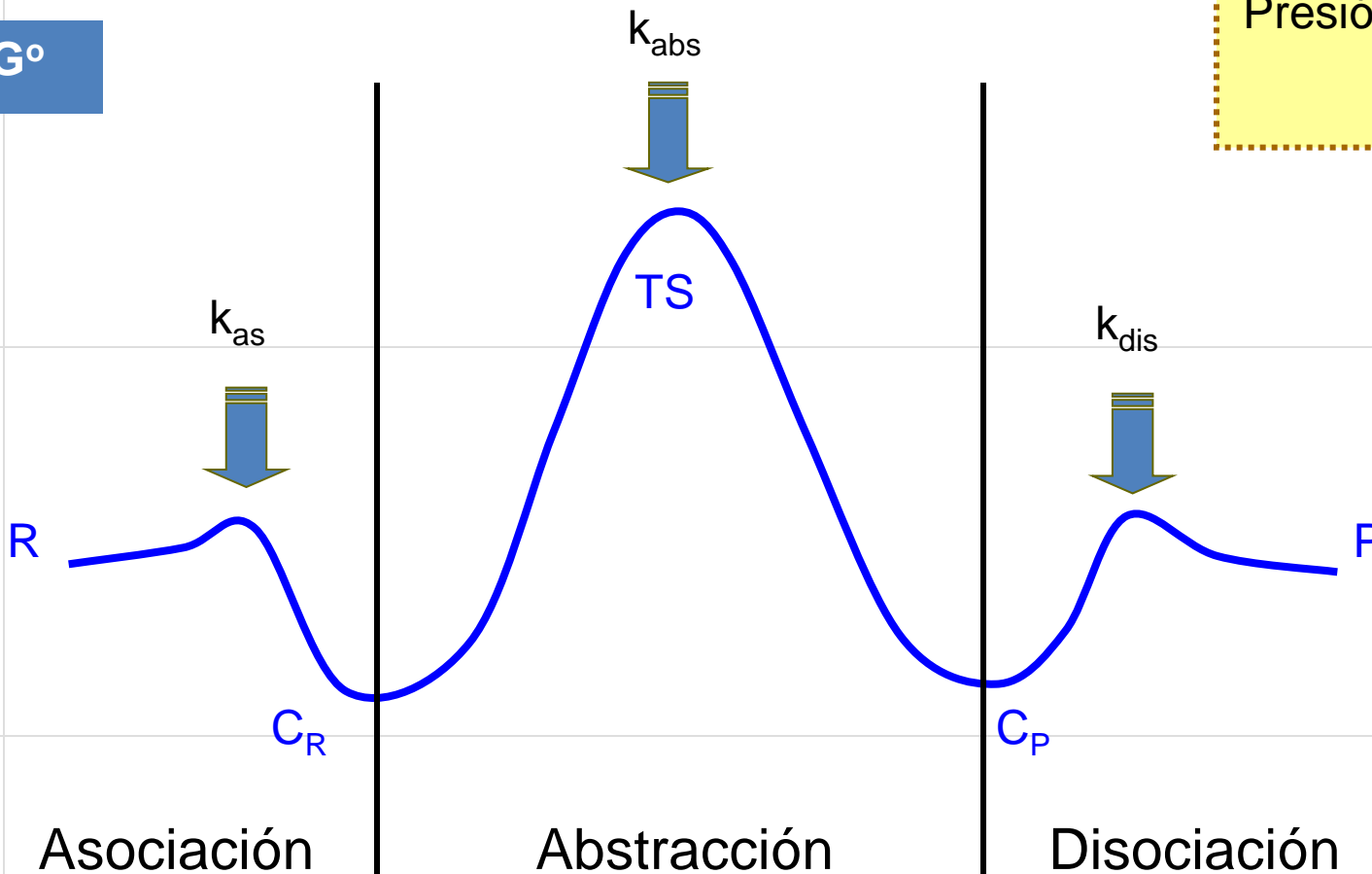
Truhlar et al.

$$\frac{1}{k^{CUS}(T)} = \frac{1}{k_{GT1}(T)} - \frac{1}{k_C(T)} + \frac{1}{k_{GT2}(T)} - \frac{1}{k_{C'}(T)} + \frac{1}{k_{GT3}(T)}$$



Presión baja

ΔG°



INTRODUCCIÓN

RESULTADOS

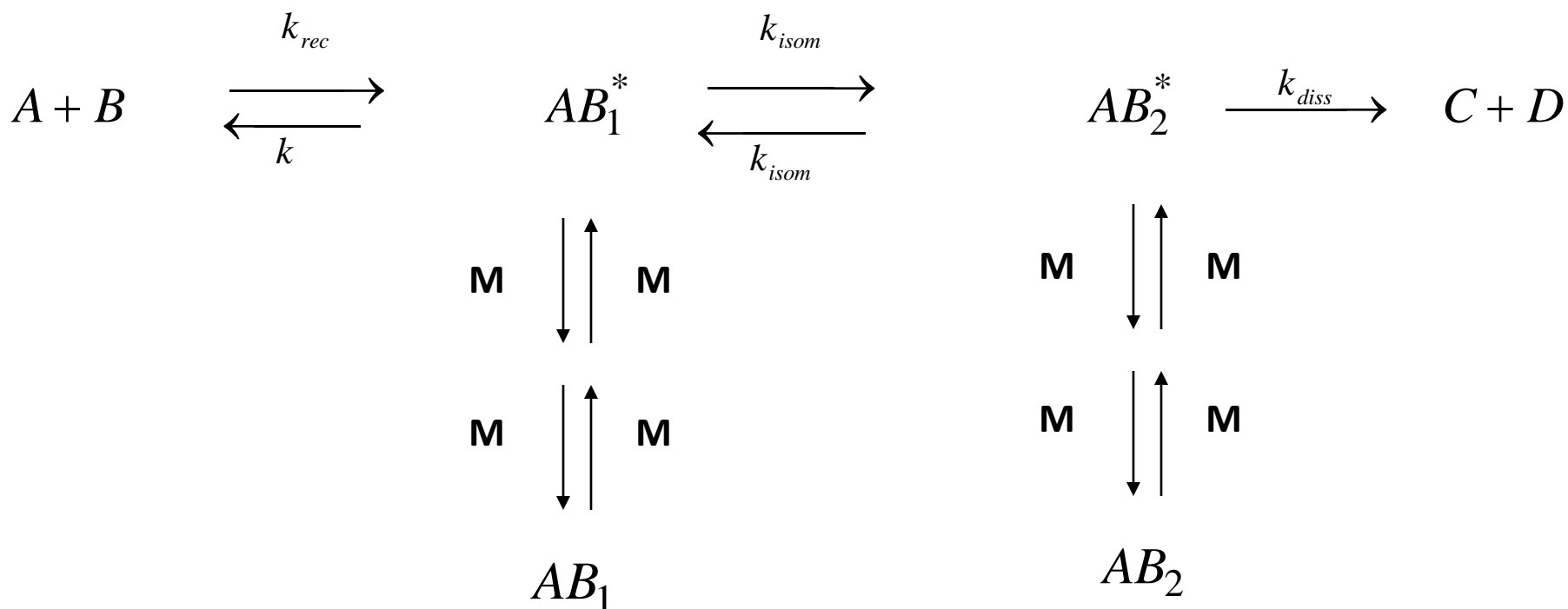
CONCLUSIONES

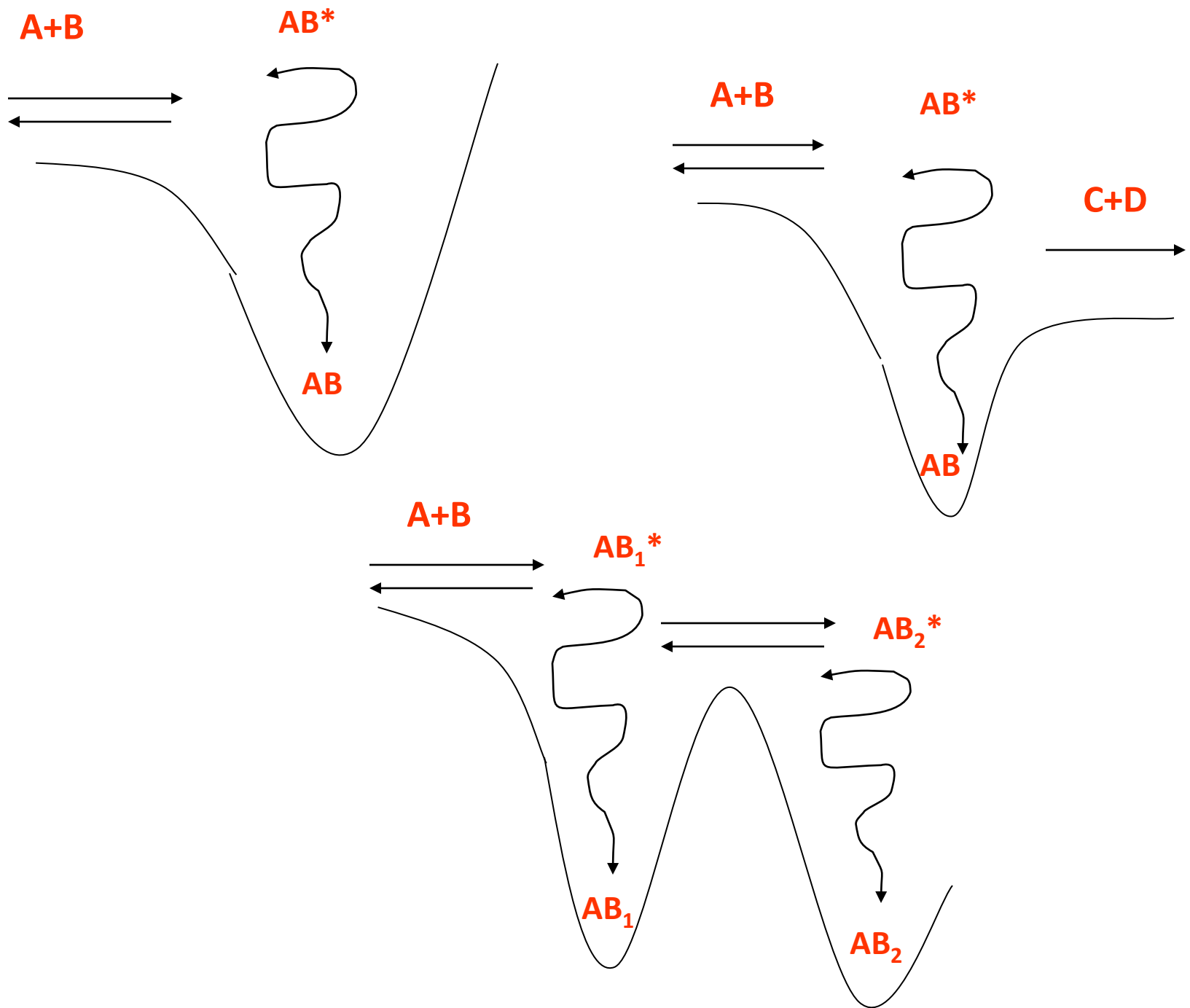
$$\frac{1}{k^{\text{CUS}}(T)} = \frac{1}{k_{\text{as}}(T)} - \frac{1}{k_{C_R}(T)} + \frac{1}{k_{\text{abs}}(T)} - \frac{1}{k_{C_P}(T)} + \frac{1}{k_{\text{dis}}(T)}$$

Reactions are pressure-dependent when the rate of collisional energy transfer is competitive with the rate of a chemical process that depends on internal energy.

Since the rate of energy transfer depends on the total pressure, the overall reaction is pressure-dependent

Classes of pressure dependent reactions





$y(E', t)dE'$ Concentration of species with energy in the range E' to $E'+dE'$

$$\frac{d}{dt}(y(E', t)dE') = \frac{dy(E', t)}{dt}dE'$$

How does the concentration of species change with time?

MASTER EQUATION FOR THE VIBRATIONAL QUASICONTINUM

$$\frac{dy(E',t)}{dt}dE' = \text{Initial energy density} + \text{Rate of collisional energy transfer into states in range } E' \rightarrow E'+dE' - \text{Rate of collisional energy transfer out of states in range } E' \rightarrow E'+dE' - \text{Chemical reaction rate}$$

$$\frac{dy(E',t)}{dt}dE' = f(E',t)dE' + \int_0^\infty [R(E',E)y(E,t)dE]dE' - \int_0^\infty [R(E,E')y(E',t)dE]dE' - \sum_{i=1}^{\text{channels}} k_i(E')y(E',t)dE'$$

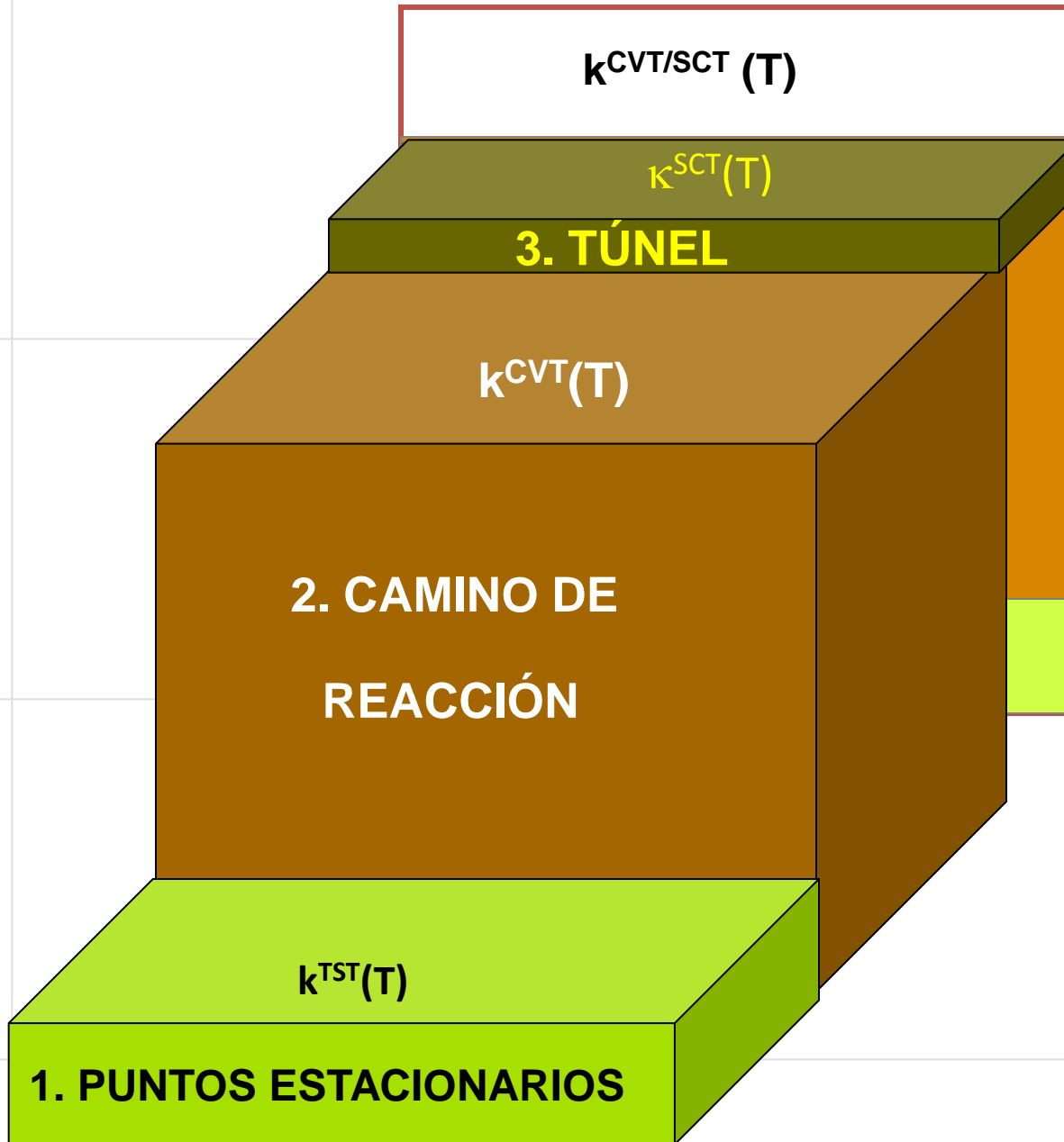
source term

Initial energy density distributions

pseudo-first-order energy transfer rates

Number of collisions with the bath gas per reactant molecule, unit energy and unit time whereby that reactant molecule initially within the energy range $[E, E+dE]$ or $[E', E'+dE']$ ends up with energy $[E', E'+dE']$ or $[E, E+dE]$.

unimolecular chemical reaction rates



Canonical Variational Transition State Calculations.

$$k^{GT}(T, s) = \frac{k_B T}{h} \frac{Q^{GT}(T, s)}{\Phi_R(T)} e^{-V_{MEP}(s)/k_B T}$$

$$Q^{GT,0}(T, s) = Q_{el}^{GT}(T, s) Q_{rot}^{GT}(T, s) Q_{vib}^{GT}(T, s)$$

1. After the initial step in the direction of the normalized imaginary frequency eigenvector **at the saddle point**, an algorithm is used all the way down to the reactants and to the final products.

MEP calculation $\longrightarrow V_{MEP}(s), \mathbf{x}(s), \mathbf{g}(s)$

$$Q^{GT,0}(T, s) = Q_{el}^{GT}(T, s) Q_{rot}^{GT}(T, s) Q_{vib}^{GT}(T, s)$$

- At every gradient step, the **projected force constant matrix** is computed.
- Generalized vibrational frequencies and generalized normal modes** orthogonal to the reaction path are obtained within the harmonic approximation.

$$\mathbf{F}^P(s) = [\mathbf{1} - \mathbf{P}(s)]\mathbf{F}(s)[\mathbf{1} - \mathbf{P}(s)]$$

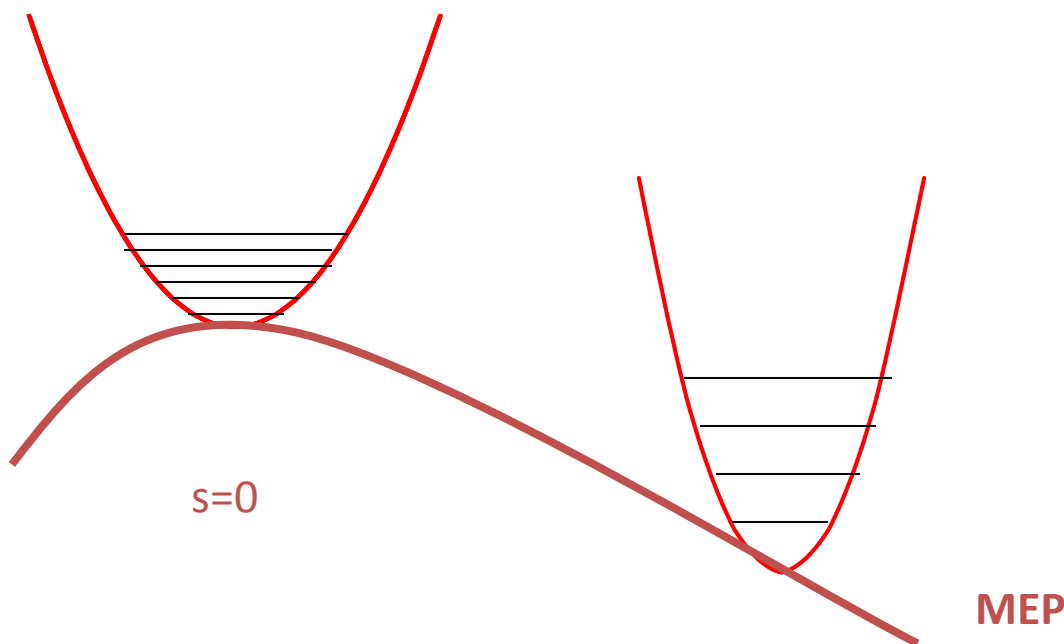
$$\left[\mathbf{L}^{GT}(s)\right]^T \mathbf{F}^P(s)\mathbf{L}^{GT}(s) = \Lambda(s)$$

$$\mathbf{L}_m^{GT}(s), \nu_m(s) \quad m = 1, F - 1 \quad F = 3n - 6 \text{ (or } 3n - 5) \quad F \rightarrow \text{MEP}$$

Generalized normal modes Generalized frequencies

$$Q^{GT,0}(T, s) = Q_{el}^{GT}(T, s)Q_{rot}^{GT}(T, s)Q_{vib}^{GT}(T, s)$$

4. The **harmonic zero-point energy correction** at each step along the path is calculated.



$$V_a^G(s) = V_{MEP}(s) + \varepsilon^G(s)$$

$$\varepsilon^G(s) = \sum_{m=1}^{F-1} \varepsilon_{vib,m}^{GT}(n_m = 0, s) = \frac{1}{2}h \sum_{m=1}^{F-1} \nu_m(s)$$

Canonical Variational Transition State Calculations.

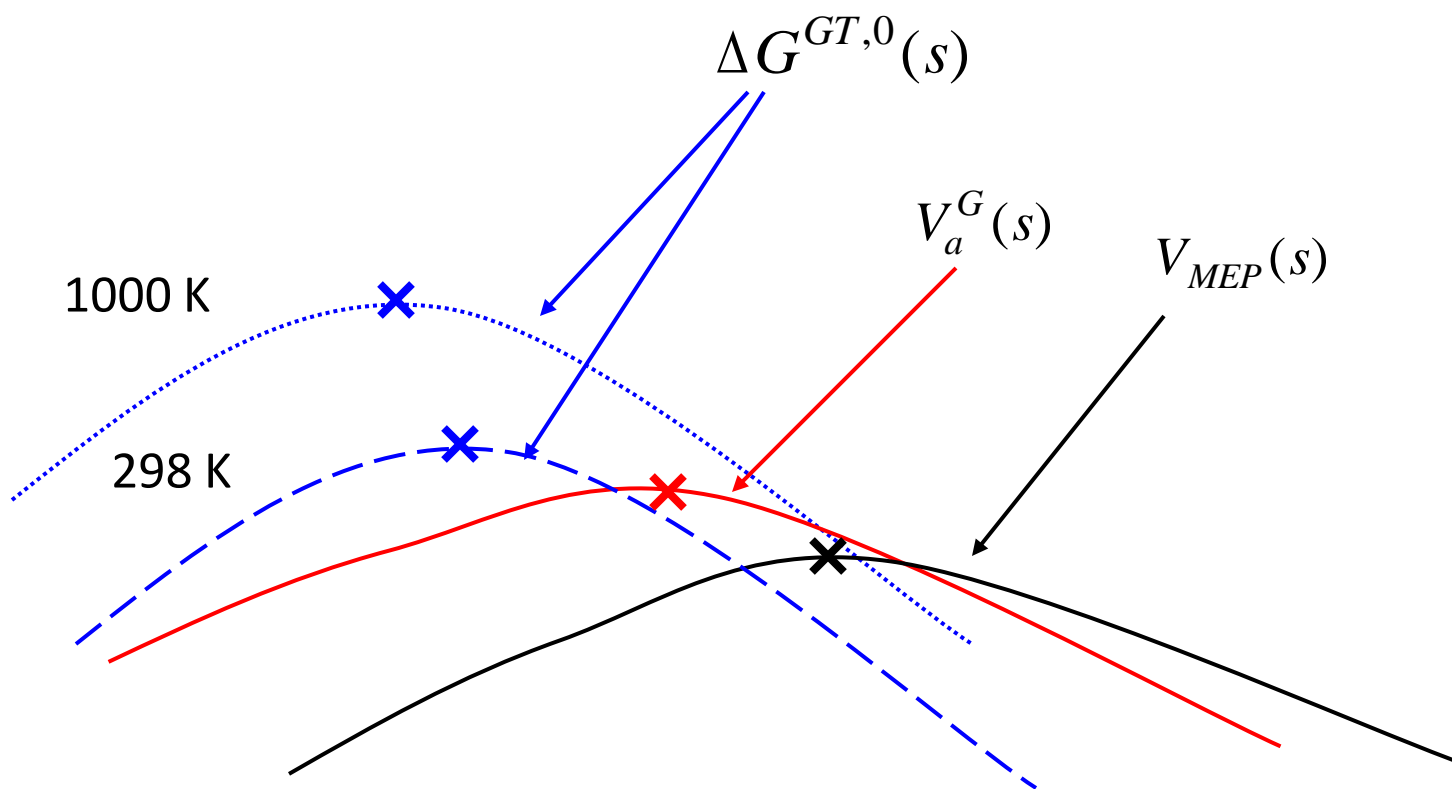
5. The interpolated variational transition state theory by mapping **(IVTST-M)** is used to interpolate the information along the paths and to obtain the **adiabatic ground-state potential energy curve** at each side of the saddle point.

IVTST-M interpolates $V_{\text{MEP}}(s)$, $|\mathbf{I}(s)|$, $v_m(s)$ and $B_{m,F}(s)$ not as functions of s but as functions of z , where z is a new variable that always has a finite value.

$$z = \frac{2}{\pi} \mathit{arctan} \left(\frac{s - s_0}{L} \right)$$

The new $V_{\text{MEP}}(z)$, $|\mathbf{I}(z)|$, $v_m(z)$ and $B_{m,F}(z)$ functions are interpolated using splines under tension.

6. The **generalized activation free energy barrier at s** is calculated and maximized to obtain the **generalized rate constant at each temperature.**



Kinetically equivalent pathways

$$k^{GT}(T, s) = \sigma(s) \frac{k_B T}{h} \frac{Q^{GT}(T, s)}{\Phi_R(T)} e^{-V_{MEP}(s)/k_B T}$$

Symmetry number

$$\sigma(s) = \frac{n^{GT} \sigma^R}{n^R \sigma^{GT}(s)}$$

$$\sigma(s) = \frac{n^{GT} \sigma^R}{\sigma^{GT}(s)}$$

$$\sigma = \frac{n^{SP} \sigma^R}{\sigma^{SP}}$$

$$k^{CVT}(T) = \sigma k(T, s_*^{CVT})$$



$$k(T) = \sum_i k_i(T)$$

$$k_1 = k_1(H)$$

$$k_2 = k_2(H) + k_2(D)$$

$$k_3 = k_3(H) + k_3(D)$$

$$k_4 = k_4(H) + k_4(D)$$

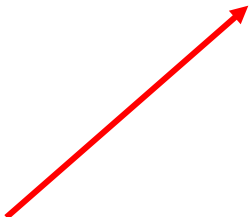
$$k_5 = k_5(D)$$

$$k_6 = k_6(H)$$

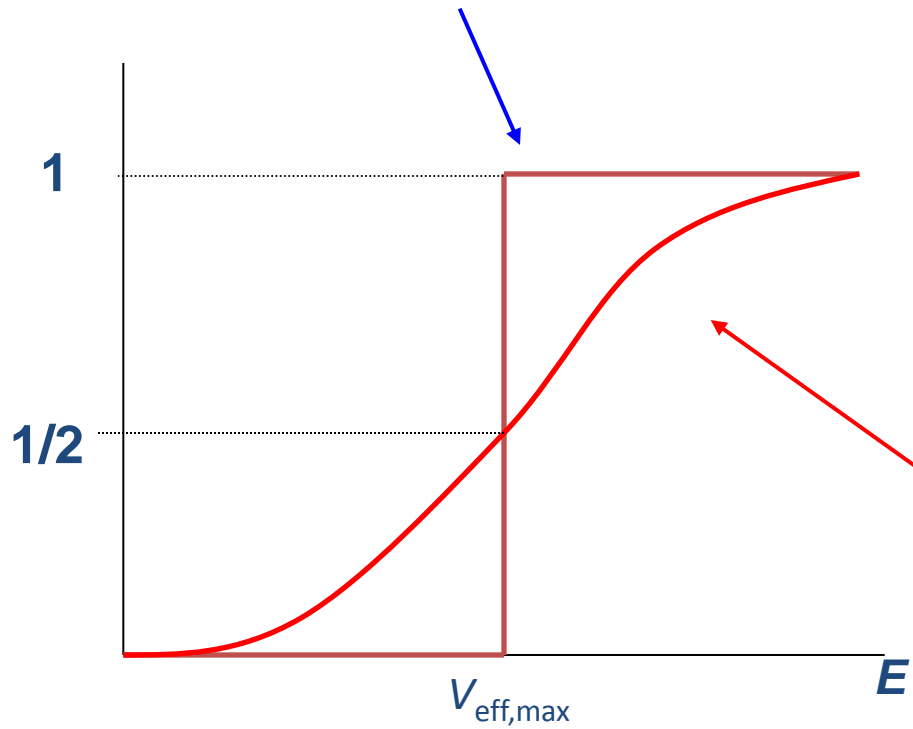
Tunneling transmission coefficient, $\kappa(T)$

$$k^{CVT}(T) = \frac{k_B T}{h} \sigma \frac{Q^{CVT}(T, s_*^{CVT})}{\Phi_R(T)} e^{-V_{MEP}(s_*^{CVT})/k_B T}$$

$$k^{CVT/MT}(T) = \kappa^{MT}(T) k^{CVT}(T)$$


$$\kappa^{MT}(T) = \frac{\text{Prob quantica}}{\text{Prob classica}} = \frac{\int_0^{\infty} P_q(E) \exp(-E/K_B T)}{\int_{V_{eff, \max}}^{\infty} P_C(E) \exp(-E/K_B T)}$$

$$P_c(E) = \Theta\{E - V_a^G(s_*^{CVT}(T))\}$$

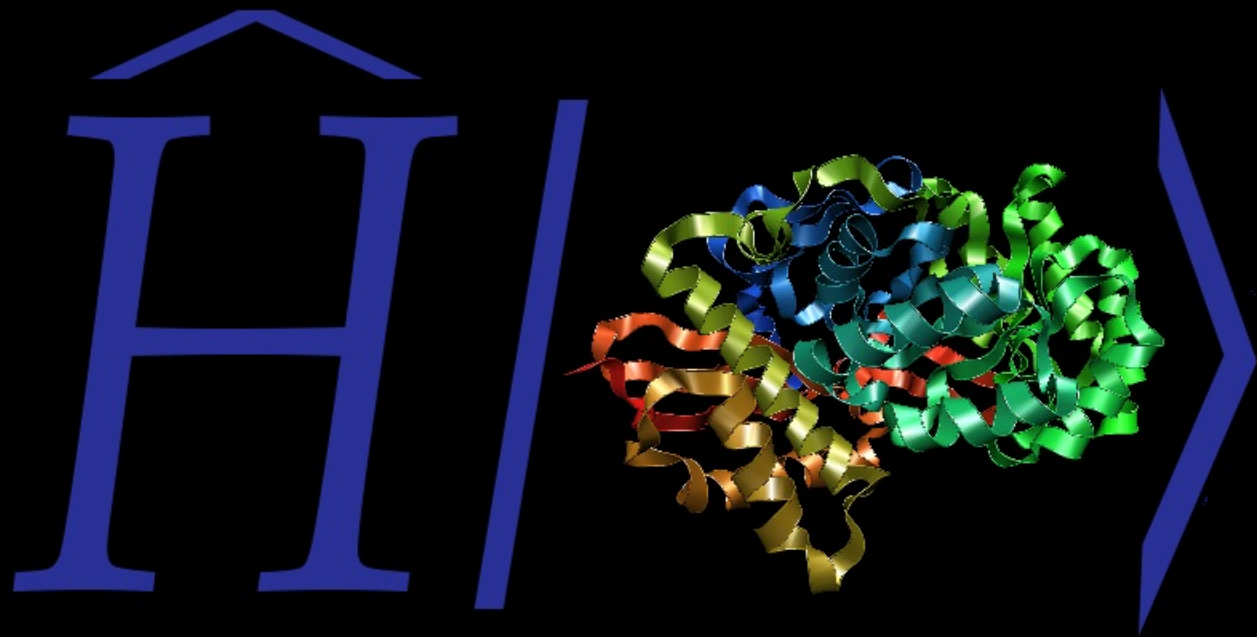


$$\hat{H} = \frac{-\hbar}{2\mu} \frac{d^2}{ds^2} + V_{eff}(s) \longrightarrow V_a^G(s)$$

$$P_{qu}(E) = |\psi|^2 \approx \exp(-2\theta(E))$$

Action along the
tunneling path

Enzyme Catalysis



Problems

- ❑ Thousands of atoms
- ❑ Solvation waters
- ❑ Many conformations
- ❑ Dynamics
- ❑ Huge number of minima and transition state structures
- ❑ Quantum effects (Transfers of H, H⁻ y H⁺)
- ❑ Many steps beyond the simplified Michaelis-Menten mechanism:



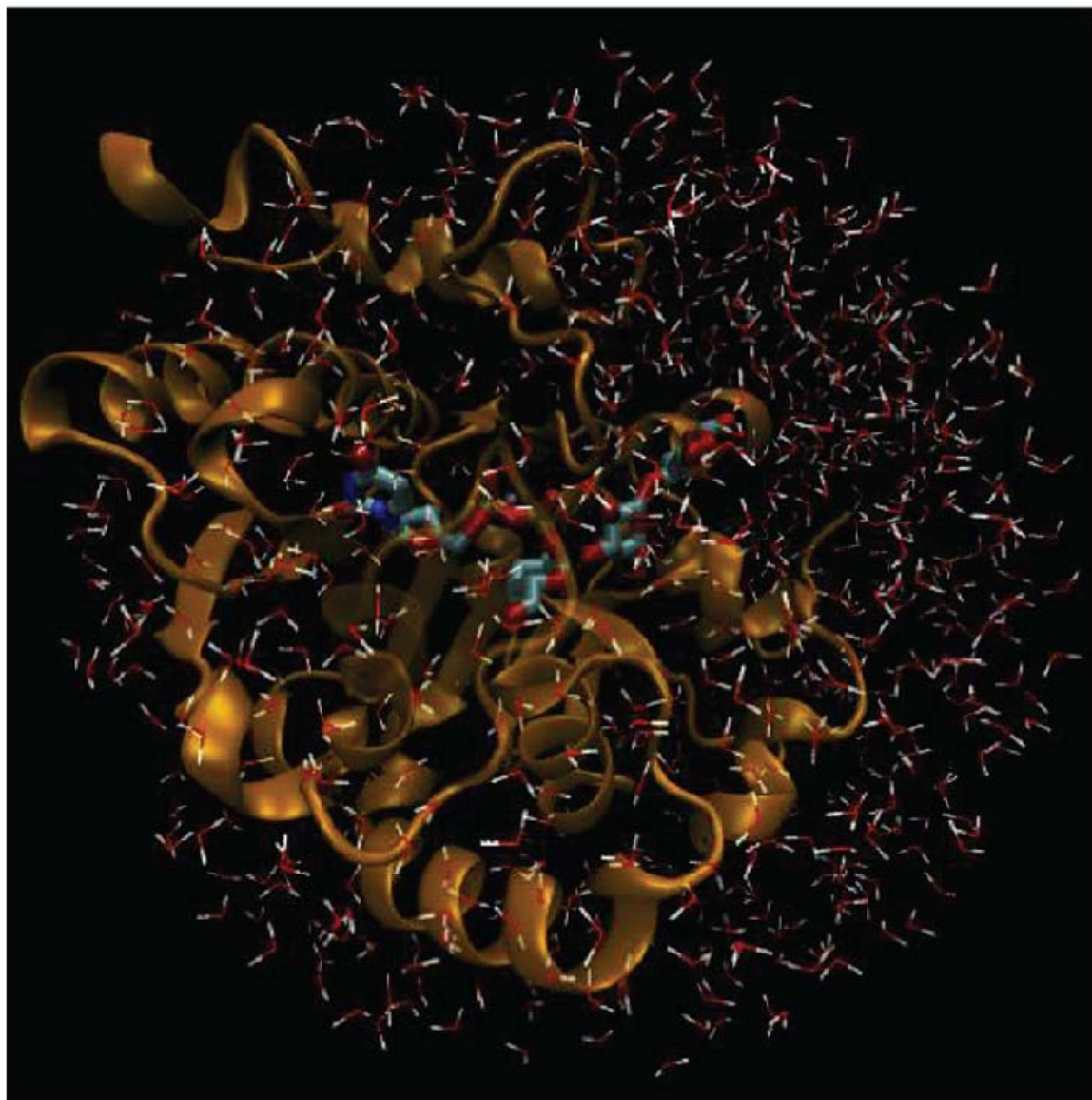


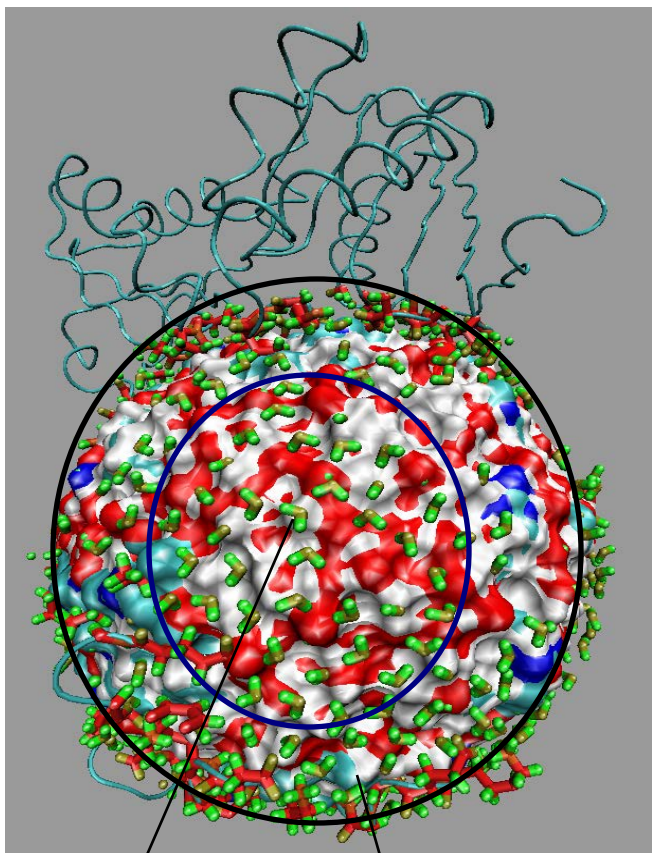
Figure 2. Representation of the system studied: UDP-Gal, LAT, and Mg^{2+} (sticks) bound to LgtC (orange cartoon) and solvated with a 24 Å radius sphere of water molecules.

Theoretical treatment for enzyme kinetics

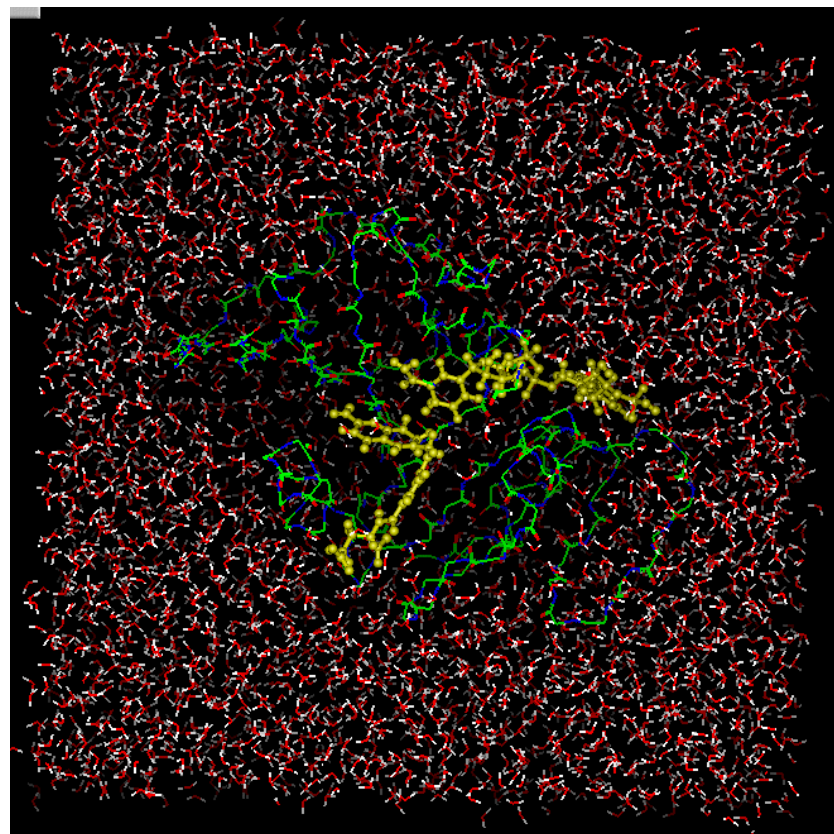
- **Model of the enzymatic system:**
 - Choice of the initial coordinates taken from high-resolution X-ray crystallographic structures (Protein Data Bank)
 - Addition of H atoms
 - Protonation states of the residues (pK_a , pH)
 - Ligand location/binding
 - Addition of solvent water molecules

Choice of solvent model and boundary conditions

Stochastic Boundary MD



Periodic Boundary Conditions



All atoms allowed to move
Forces as being in bulk
(N,P,T) conditions

Newton MD

Langevin MD

Molecular Dynamics Simulations

Newton's equations

$$\vec{F}_i = m_i \frac{d^2 \vec{r}_i(t)}{dt^2}$$

$$\vec{F}_i = - \frac{\partial U(\vec{r}^{(N)})}{\partial \vec{r}_i}$$

The algorithms for integrating the equations of motion assume that the positions and dynamic properties can be approximated as Taylor series expansions.

Most used algorithms: Verlet, leap-frog and velocity Verlet

Stochastic dynamics

Langevin equation of motion for a particle i :

$$m_i \frac{d^2 \vec{r}_i(t)}{dt^2} = \vec{F}_i - \gamma_i \frac{d\vec{r}_i(t)}{dt} m_i + \vec{R}_i(t)$$

1

2

3

1 Force due to the interaction of particle i with the other particles.

2 Frictional drag on the particle i due to the solvent.

γ_i is the collision frequency.

3 Force due to random fluctuations caused by interactions with the solvent molecules.

Quantum Mechanics/Molecular Mechanics methods (QM/MM)

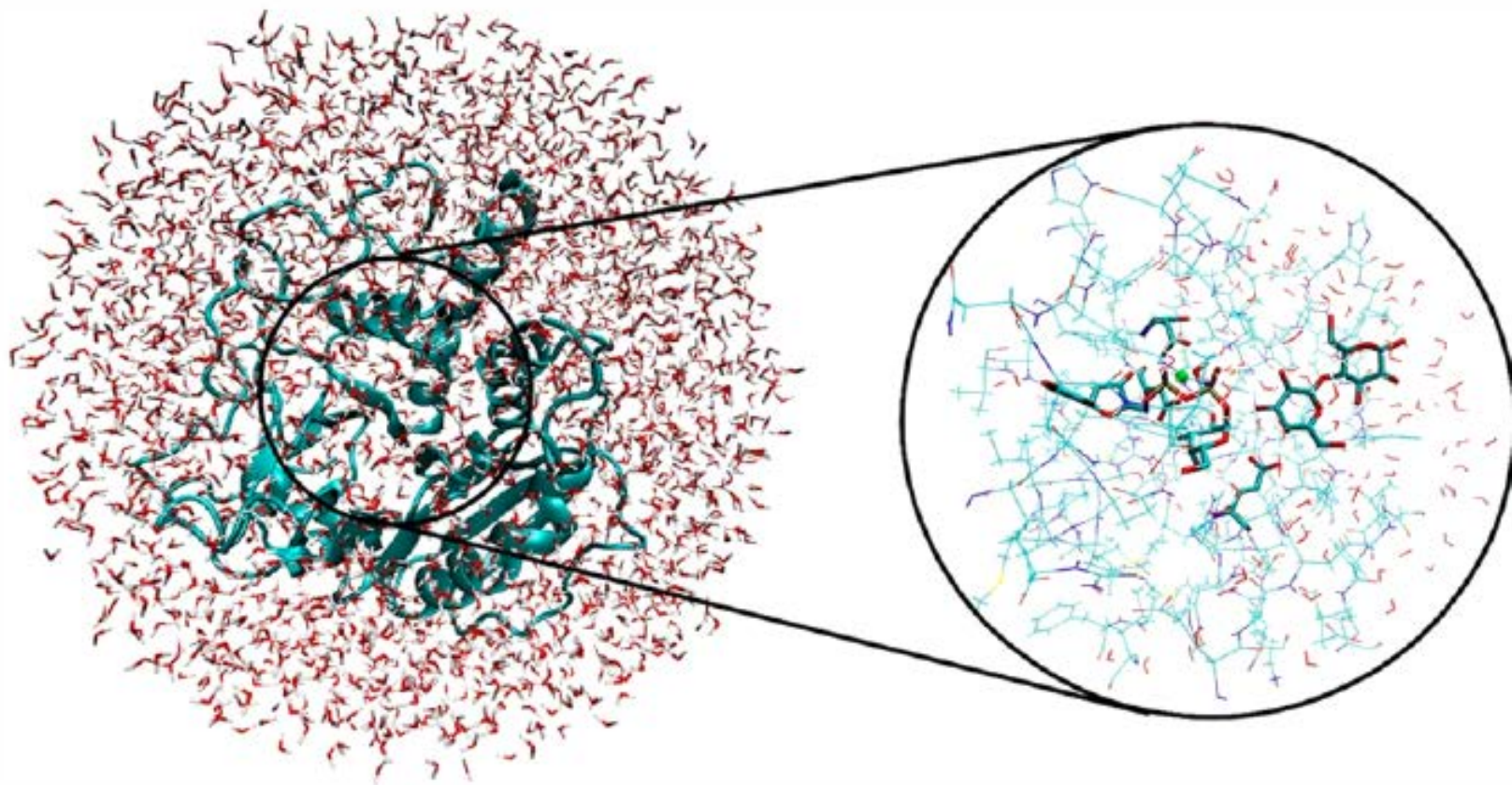
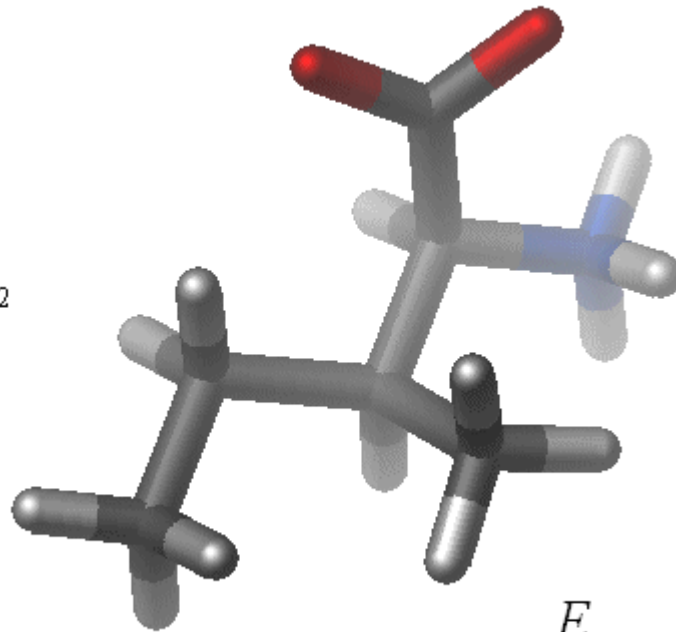


Figure 1. Model system used in the QM/MM calculations. The active region is enlarged and the QM atoms represented in licorice.

$$V(R) = E_{\text{bonded}} + E_{\text{non-bonded}}$$

$$E_{\text{bonded}} = E_{\text{bond-stretch}} + E_{\text{angle-bend}} + E_{\text{rotate-along-bond}}$$

$$E_{\text{bond-stretch}} = \sum_{1,2 \text{ pairs}} K_b (b - b_0)^2$$



$$E_{\text{bond-bend}} = \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2$$

$$E_{\text{rotate-along-bond}} = \sum_{1,4 \text{ pairs}} K_\phi (1 - \cos(n\phi))$$

$$E_{\text{non-bonded}} = E_{\text{van-der-Waals}} + E_{\text{electrostatic}}$$

$$E_{\text{van-der-Waals}} = \sum_{\text{nonbonded pairs}} \left(\frac{A_{ik}}{r_{ik}^{12}} - \frac{C_{ik}}{r_{ik}^6} \right)$$

$$E_{\text{electrostatic}} = \sum_{\text{nonbonded pairs}} \frac{q_i q_k}{D r_{ik}}$$

$$\mathbf{H} = \mathbf{H}_{\text{QM}} + \mathbf{H}_{\text{MM}} + \mathbf{H}_{\text{QM/MM}} \quad (1)$$

$$\mathbf{H}_{\text{QM}} = -\frac{1}{2} \sum_i^{\text{electrons}} \Delta_i - \sum_i^{\text{electrons}} \sum_K^{\text{nuclei}} \frac{Z_K}{r_{iK}} + \sum_i^{\text{electrons}} \sum_{i>j}^{\text{electrons}} \frac{1}{r_{ij}} + \sum_K^{\text{nuclei}} \sum_{K>L}^{\text{nuclei}} \frac{Z_K Z_L}{R_{KL}} \quad (2)$$

$$\mathbf{H}_{\text{MM}} = \sum_{\text{bonds}} k_r (r - r_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} \sum_n \frac{V_n}{2} [1 + \cos(n\phi - \omega)] + \sum_{(i,j)} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]. \quad (3)$$

$$\mathbf{H}_{\text{QM/MM}} = V_{\text{QM/MM}}^{\text{van der Waals}} - \sum_i^{\text{electrons}} \sum_C^{\text{classical}} \frac{Q_C}{r_{iC}} + \sum_K^{\text{nuclei}} \sum_C^{\text{classical}} \frac{Z_K Q_C}{R_{KC}} \quad (4)$$

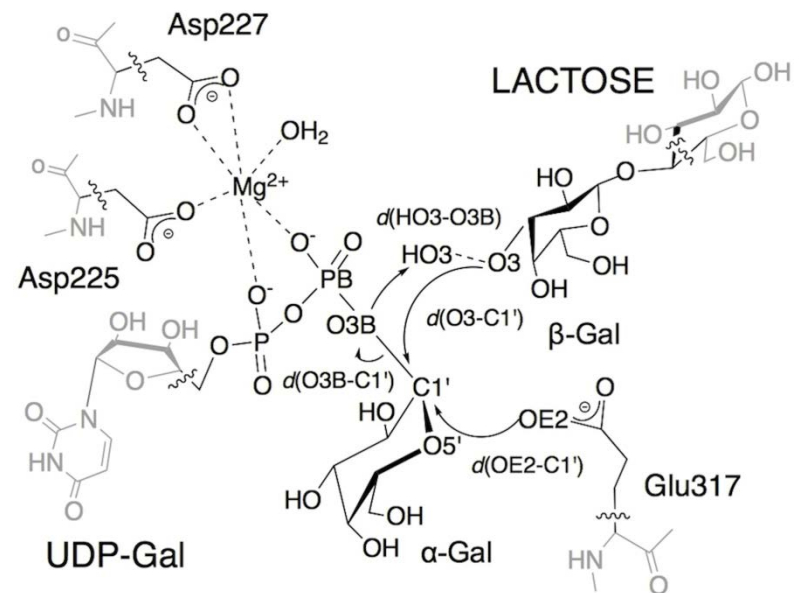
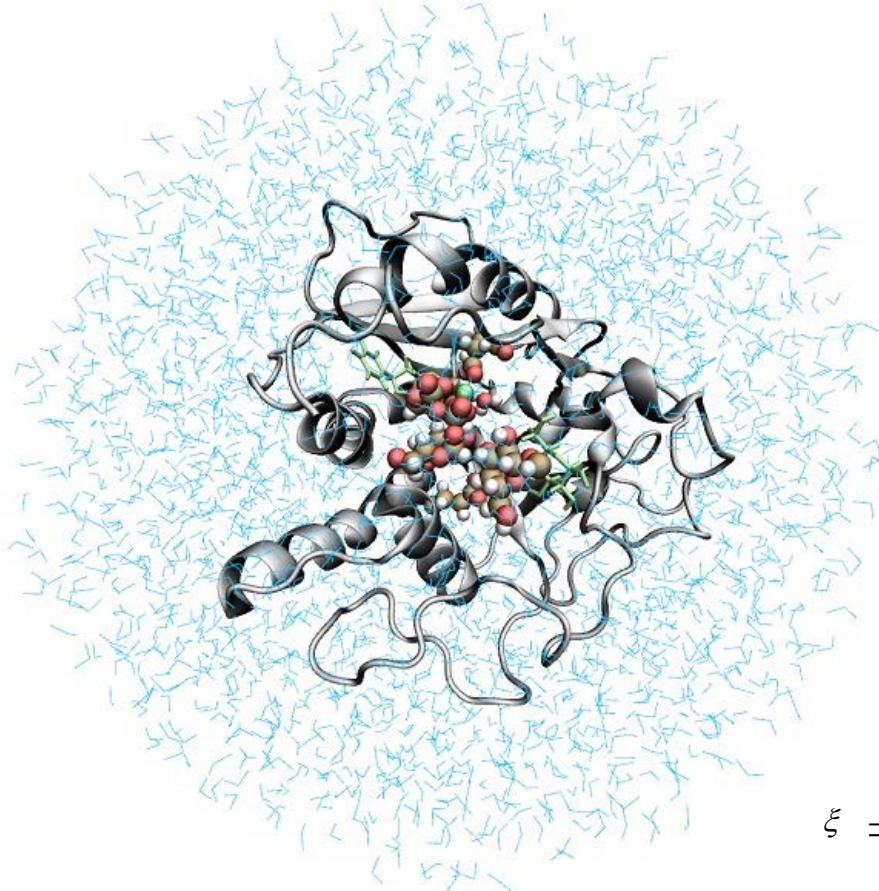
We can group the terms in Eqs. (2), (3), and (4) depending on whether they describe electrons on the quantum part (\mathbf{H}_{elec}) or not ($\mathbf{H}_{\text{non-elec}}$). This gives

$$\begin{aligned}
 \mathbf{H}_{\text{elec}} = & -\frac{1}{2} \sum_i^{\text{electrons}} \Delta_i - \sum_i^{\text{electrons}} \sum_K^{\text{nuclei}} \frac{Z_K}{r_{iK}} \\
 & + \sum_i^{\text{electrons}} \sum_{i>j}^{\text{electrons}} \frac{1}{r_{ij}} - \sum_i^{\text{electrons}} \sum_C^{\text{classical}} \frac{Q_C}{r_{iC}}
 \end{aligned}$$

$$\begin{aligned}
 \mathbf{H}_{\text{non-elec}} = & \mathbf{H}_{\text{MM}} + V_{\text{QM/MM}}^{\text{van der Waals}} \\
 & + \sum_K^{\text{nuclei}} \sum_C^{\text{classical}} \frac{Z_K Q_C}{R_{KC}} + \sum_K^{\text{nuclei}} \sum_{K>L}^{\text{nuclei}} \frac{Z_K Z_L}{R_{KL}} \\
 = & \mathbf{H}_{\text{MM}} + V_{\text{QM/MM}}^{\text{van der Waals}} + V_{\text{QM+QM/MM}}^{\text{nuclei}}.
 \end{aligned}$$

Potential energy methods

- Selection of one (or several) snapshot of the molecular dynamics simulations
- Calculation of the reaction path as a function of a reaction coordinate
- Location of the transition-state structure



$$\xi = [d(O3B-C1') - d(O3-C1') - d(HO3-O3B)]$$

Potential of Mean Force (PMF)

N particles.

$\vec{r}^{(N)}$ denotes the set of $3N$ atomic Cartesian coordinates

$\vec{p}^{(N)}$ denotes the set of their $3N$ conjugate momenta

For an arbitrary generalized coordinate λ , the PMF $W(s)$ at $\lambda = s$:

$$\frac{dW(s)}{ds} = -k_B T \frac{d \ln P(s)}{ds}$$

where $P(s)$ is the probability density:

$$P(s) = \frac{1}{A} \frac{1}{h^{3N}} \int e^{-H(\vec{r}^{(N)}, \vec{p}^{(N)}) / k_B T} \delta[\lambda(\vec{r}^{(N)}) - s] d\vec{r}^{(N)} d\vec{p}^{(N)}$$

where A is a normalization constant

Integrating:

$$W(s) = -k_B T \ln P(s) + B$$

$$W(s) = -k_B T \ln \int e^{-H(\vec{r}^{(N)}, \vec{p}^{(N)})/k_B T} \delta[\lambda(\vec{r}^{(N)}) - s] d\vec{r}^{(N)} d\vec{p}^{(N)} + C$$

The value of C sets the zero of energy. Then it can be taken as zero. This integral involves integration over the momentum along the reaction coordinate λ .

The CVT rate constant for the dividing surface defined by $\lambda=s_*$ is

$$k(T) = \frac{1}{Q^R} \frac{1}{h^{3N}} \int e^{-H(\vec{r}^{(N)}, \vec{p}^{(N)})/k_B T} \delta[S] \Theta(\dot{S}) \dot{S} d\vec{r}^{(N)} d\vec{p}^{(N)}$$

where the dividing surface is specified by $S = \lambda(\vec{r}^N) - s_*$

$$k(T) = \frac{k_B T}{h} \frac{Q^{GT}(s_*)}{Q^R} =$$

$$\frac{k_B T}{h} \frac{1}{Q^R} \frac{1}{h^{3N-1}} \int e^{-H(\vec{r}^{(N)}, \vec{p}^{(N)})/k_B T} \delta[\lambda(\vec{r}^{(N)}) - s_*] \delta(p_\lambda) d\vec{r}^{(N)} d\vec{p}^{(N)}$$

This integral does not include integration over the momentum along the reaction coordinate λ .

Thermodynamic formulation:

$$k(T) = \frac{k_B T}{h} e^{-[G(s_*) - G(s^R)] / k_B T} \quad (\text{no tunneling})$$

It can be proved (Truhlar and cow., J. Chem. Phys., 119, 5828 (2003)) that

$$k(T) = \frac{k_B T}{h} \frac{\phi(s_*)}{\phi(s^R)} e^{-[\Delta W(s_*) - G(s_\lambda^R)] / k_B T}$$

$$\Delta W(s_*) = W(s_*) - W(s^R)$$

$$\Delta G(s_*) = G(s_*) - G(s^R) = \Delta W(s_*) - G_\lambda^R - k_B T \ln \frac{\phi(s_*)}{\phi(s^R)}$$

Si λ is a rectilinear coordinate (linear combination of atomic Cartesian coordinates) $\phi(s)$ is independent of s , and the last term is nul.

Umbrella sampling

Umbrella sampling uses an artificial biasing potential energy function U' which is added to the actual potential energy U . Then the configurations are selected with a non-Boltzmann configurational probability density:

$$\Pi(\vec{r}^{(N)}, \vec{p}^{(N)}) = \frac{e^{-[H(\vec{r}^{(N)}, \vec{p}^{(N)}) + U'(z)] / k_B T}}{\int e^{-[H(\vec{r}^{(N)}, \vec{p}^{(N)}) + U'(z)] / k_B T} d\vec{r}^{(N)} d\vec{p}^{(N)}}$$

After such simulation, the effect of the non-Boltzmann sampling has to be removed. The true probability density turns out to be:

$$P(z) = \frac{P'(z) e^{U'(z)/k_B T}}{\left\langle e^{U'(z)/k_B T} \right\rangle_{H+U'}} = P'(z) e^{\frac{U'(z) - g}{k_B T}}$$

$P'(z)$ is the biased probability density

The reaction coordinate is divided into intervals (windows), with a specific value z_i and a biasing potential U'_i assigned to each window i , trying that the sampling within each window is as uniform as possible.

The biasing potential often takes the harmonic form:

$$U'_i(z) = \frac{1}{2} K (z - z_i)^2$$

The PMF for each window i can be obtained through:

$$W(z) = -k_B T \ln P'_i(z) - U'_i(z) + g_i$$

$P'_i(z)$ is calculated as normalized histogram of the values of z occurring during the simulation within window i .

The weighted histogram analysis method (WHAM) has been the most used method to combine the contributions of the different windows. WHAM calculates the values g_i iteratively and provides the total $P(z)$ along the reaction coordinate.

$$e^{-\frac{g_i}{k_B T}} = \frac{\sum_{m=1}^{N_w} \sum_{k=1}^{n_m} \frac{e^{-\frac{U'_i(\xi(\vec{r}_{k,m}^{(N)}))}{k_B T}}}{\sum_{j=1}^{N_w} n_j e^{\frac{g_j}{k_B T}} e^{-\frac{U'_j(\xi(\vec{r}_{k,m}^{(N)}))}{k_B T}}}}{\sum_{j=1}^{N_w} n_j e^{\frac{g_j}{k_B T}} e^{-\frac{U'_j(\xi(\vec{r}_{k,m}^{(N)}))}{k_B T}}}}$$

$$P(z) = \frac{\sum_{m=1}^{N_w} \sum_{k=1}^{n_m} \frac{\delta(\xi(\vec{r}_{k,m}^{(N)}) - z)}{\sum_{j=1}^{N_w} n_j e^{\frac{g_j}{k_B T}} e^{-\frac{U'_j(\xi(\vec{r}_{k,m}^{(N)}))}{k_B T}}}}{\sum_{j=1}^{N_w} n_j e^{\frac{g_j}{k_B T}} e^{-\frac{U'_j(\xi(\vec{r}_{k,m}^{(N)}))}{k_B T}}}}$$

EA-VTST/MT rate constants: activation free energy barriers

$$k^{EA-VTST/MT}(T) = \gamma \frac{k_B T}{h} \exp\left(-\frac{\Delta G_{act}^{QC}(z_*^{QC})}{RT}\right)$$

$$\Delta G_{act}^{CM}(z) = W^{CM}(z) - [W^{CM}(z_R) + G_{R,T,F}^{CM}]$$

Classical mechanical
activation free energy profile

$$\Delta G_{act}^{QC}(z) = W^{QC}(z) - [W^{CM}(z_R) + G_{R,T,F}^{CM} + \Delta W_{vib,R}]$$

Quasiclassical activation
free energy profile

$$\Delta G_{act}^{CM}(z_*^{CM}) = \max(\Delta G_{act}^{CM}(z))$$

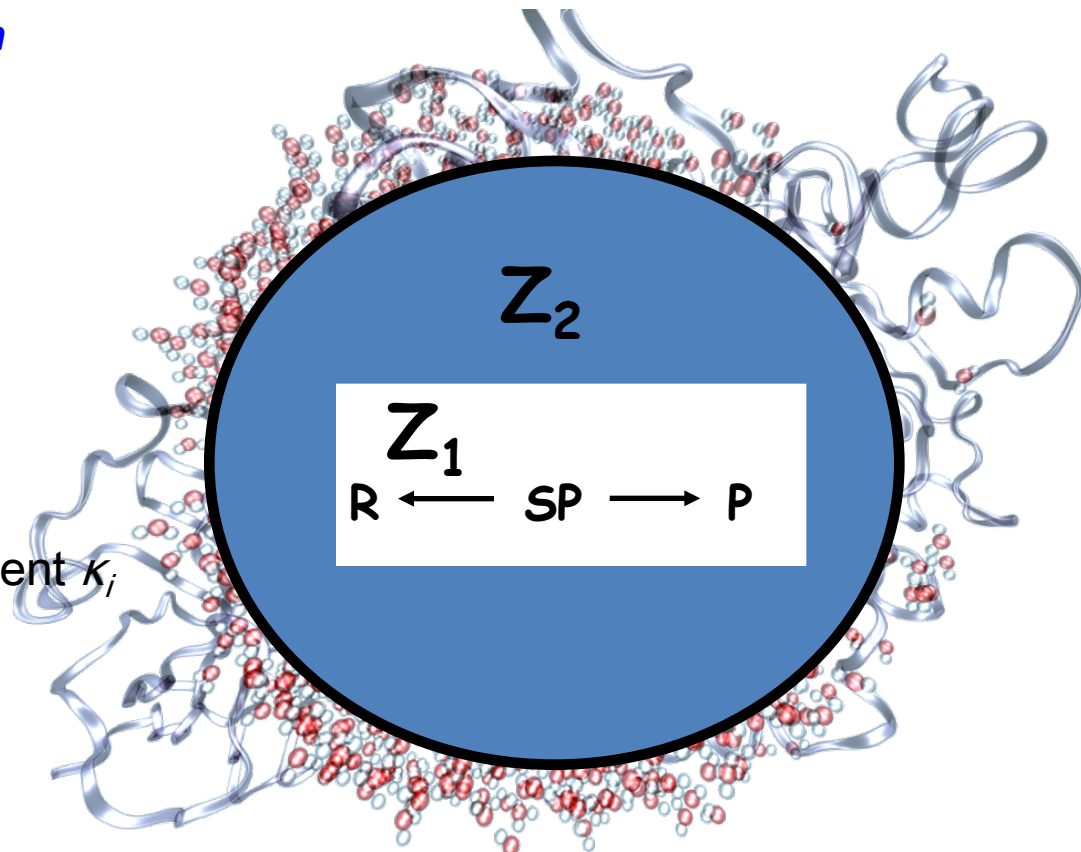
$$\Delta G_{act}^{QC}(z_*^{QC}) = \max(\Delta G_{act}^{QC}(z)) \quad (\text{kcal/mol})$$

Average net transmission coefficient γ

For each variational transition state configuration i at z_*^{QC} :

Static-Secondary Zone approximation
(Frozen Bath)

- 1) SP location
- 2) MEP
- 3) Quassiclassical transmission factor Γ_i
- 4) Semiclassical transmission coefficient κ_i

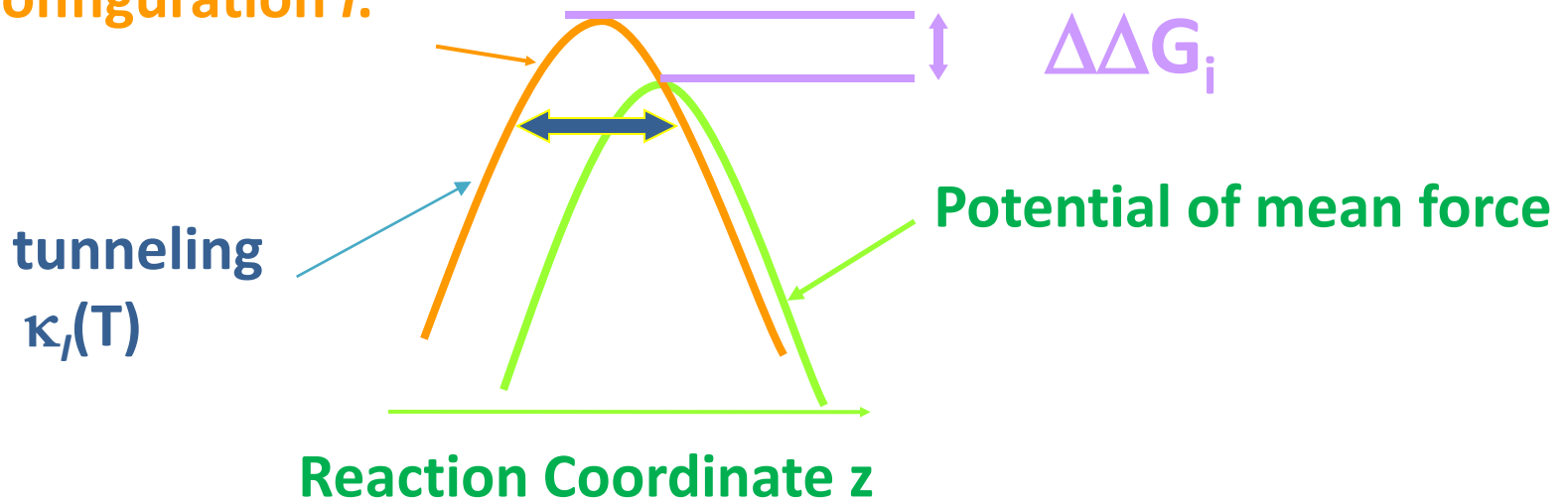


$$\gamma(T) = \langle \Gamma_i(T) \kappa_i(T) \rangle$$

Quassiclasical Transmission Factor Γ

$V_i(s)$
for configuration i .

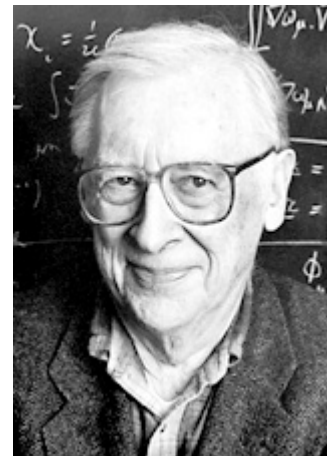
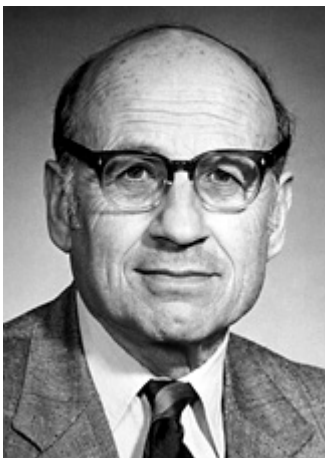
$$\Gamma_i(T) = \exp\{-\beta\Delta\Delta G_i\}$$



*“**Chemistry** is already in a new era where experiment and theory can work together in the exploration of the properties of molecular systems. **Chemistry** is no longer a purely experimental science”.*

Swedish Academy of Sciences

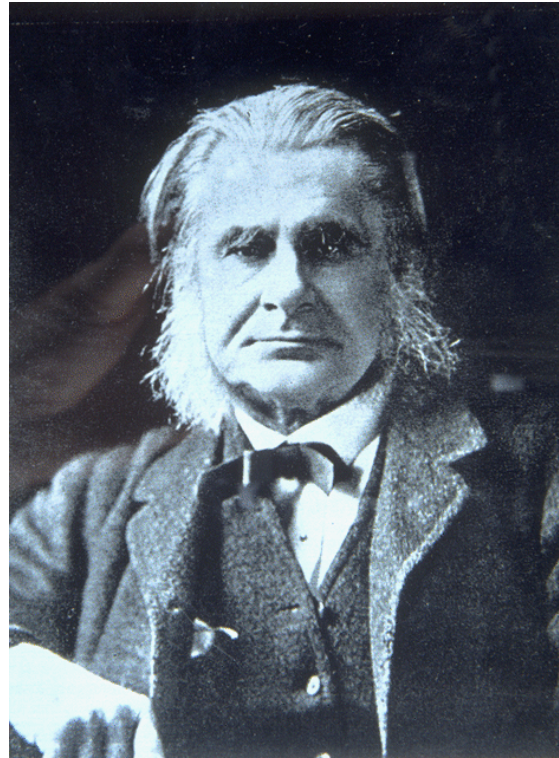
Concesión del Premi Nobel de Química 1998 a Walter Kohn (*“for his development of Density Functional Theory”*) y a John Pople (*“for his development of computational methods in quantum chemistry”*)



*“Nothing can be more incorrect than the assumption one sometimes meets with, that **physics** has one method, **chemistry** another, and **biology** a third”.*

Thomas Huxley

(Segele XIX)



*“**Biology** is no longer a purely experimental science”.*

Métodos de estructura electrónica **QM/MM** +
Métodos dinámicos **MD** + **VTST** +
Superordenadores



Sistemas biomoleculares cada vez más **grandes** y
fenómenos biológicos de más **larga duración**,
con resultados cada vez más **precisos** y
detallados, obtenidos con **menos tiempo** de cálculo real.

Estructura y función de:

- Proteínas
- Enzimas
- Ácids nucleicos (ARN i ADN)



Complejos supramoleculares: Virus, ribosomas



Célula

2013 NOBEL PRIZE IN CHEMISTRY

Martin Karplus
Michael Levitt
Arieh Warshel



© The Nobel Foundation. Photo: Lovisa Engblom.



1930, Vienna, Austria.
Université de Strasbourg,
Strasbourg, France,
Harvard University,
Cambridge, MA, USA



1947, Pretoria, South
Africa.
Stanford University
School of Medicine,
Stanford, CA, USA

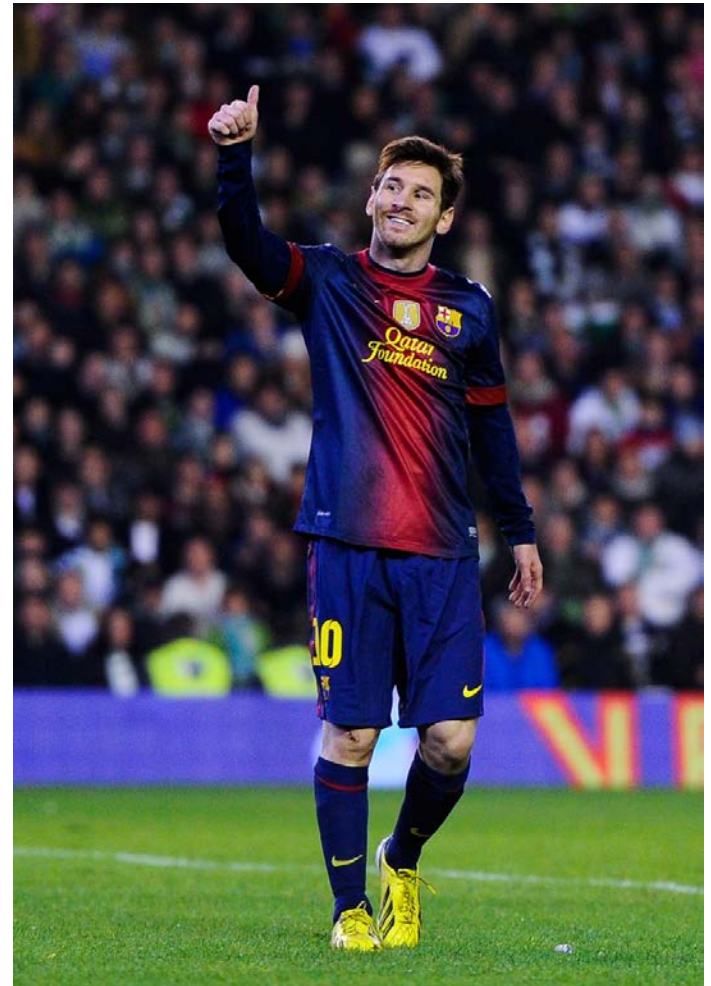
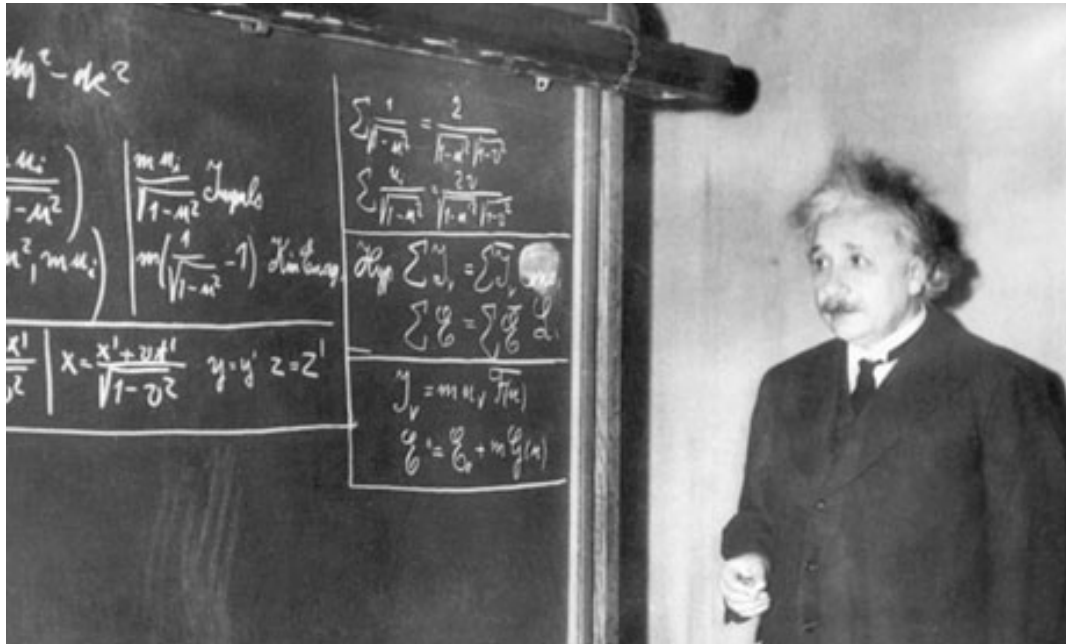


1940, Kibbutz Sde-Nahum,
Israel.
University of Southern
California,
Los Angeles, CA, USA

Prize motivation: "for the development of multiscale models for complex chemical systems"

Michael Levitt's dream:

To simulate a living organism on a molecular level



All our dreams can come true, if we have the courage to pursue them.



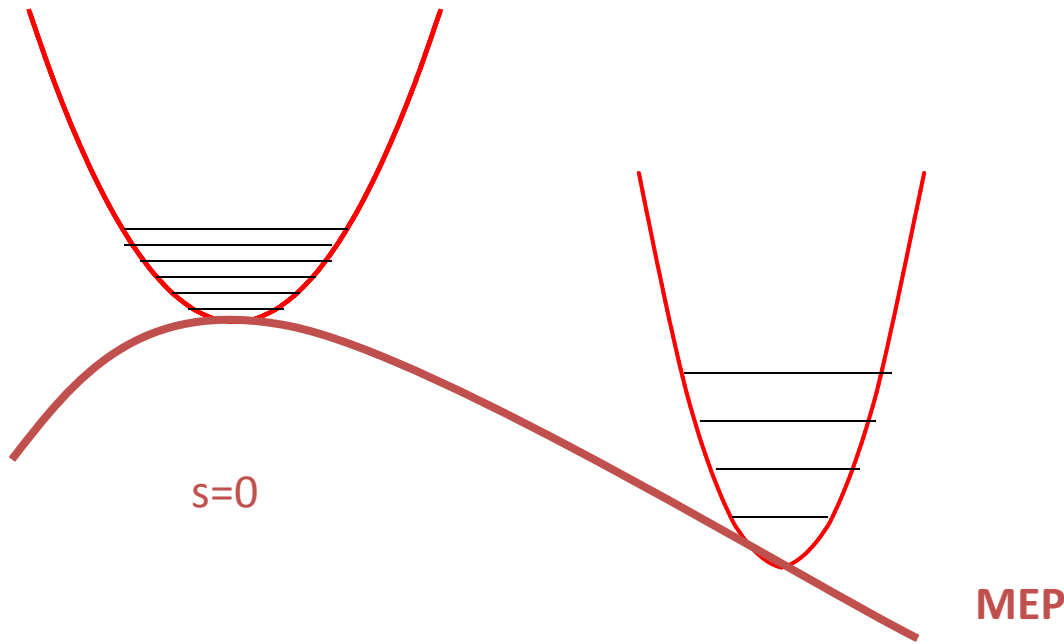
Walt Disney

**In order to make dreams come into reality,
it takes an awful lot of determination,
dedication, self-discipline, and effort.**

Jesse Owens



Modos normales generalizados



$$\Delta G^{GT,0}(T,s)$$

crece



Factor "entálpico"



Factor "entrópico"

crece

If the rate coefficients $R(E, E')$ do not depend on the initial quantum states of the collider bath molecules, they can be written as the product of the **total rovibrationally inelastic collisional frequency** (ω) multiplied by the **collision step-size distribution** $P(E, E')$, which expresses the probability that a molecule initially in the energy range from E' to $E'+dE'$ will undergo an inelastic transition to the energy range E to $E+dE$.

$$R(E, E')dE = \int_0^\infty R(E, E')dE \left\{ \frac{R(E, E')dE}{\int_0^\infty R(E, E')dE} \right\} = \omega P(E, E')dE$$

$$\frac{dy(E', t)}{dt}dE' = f(E', t)dE' + \int_0^\infty [R(E', E)dE y(E, t)]dE' - \int_0^\infty [R(E, E')dE y(E', t)]dE' - \sum_{i=1}^{\text{channels}} k_i(E')y(E', t)dE' =$$

$$= f(E', t)dE' + \int_0^\infty [\omega P(E', E)dE y(E, t)]dE' - \int_0^\infty \omega P(E, E')dE y(E', t)dE' - \sum_{i=1}^{\text{channels}} k_i(E')y(E', t)dE' =$$

$$= f(E', t)dE' + \omega \int_0^\infty [P(E', E)y(E, t)dE]dE' - \omega y(E', t)dE' \int_0^\infty P(E, E')dE - \sum_{i=1}^{\text{channels}} k_i(E')y(E', t)dE' =$$

$$= f(E', t)dE' + \omega \int_0^\infty [P(E', E)y(E, t)dE]dE' - \omega y(E', t)dE' - \sum_{i=1}^{\text{channels}} k_i(E')y(E', t)dE' \rightarrow \text{Normalisation}$$

1

Constante de velocidad de la reacción unimolecular para el

$$k(E) = \sigma \frac{1}{h} \frac{G^\ddagger(E - E_0)}{\rho(E)}$$

Correcciones
centrífugas

$$E_0 = E_0 - k_B T \left\{ 1 - \frac{I_A}{I_A^\ddagger} \right\}$$

Constante de velocidad para la transferencia de energía vib

$$R(E, E') dE = \int_0^\infty R(E, E') dE \left\{ \frac{R(E, E') dE}{\int_0^\infty R(E, E') dE} \right\} = \omega P(E, E') dE$$

ω : parámetros
de Lennard
Jones

Gas circundante: He

$$P(E, E') = \frac{1}{N(E')} \exp \left[- \left(\frac{E' - E}{\alpha} \right)^\gamma \right]$$

La ecuación
master

ecuación diferencial fenomenológica de primer orden que describe la evolución en el tiempo de la probabilidad de un sistema de ocupar cada conjunto de estados E

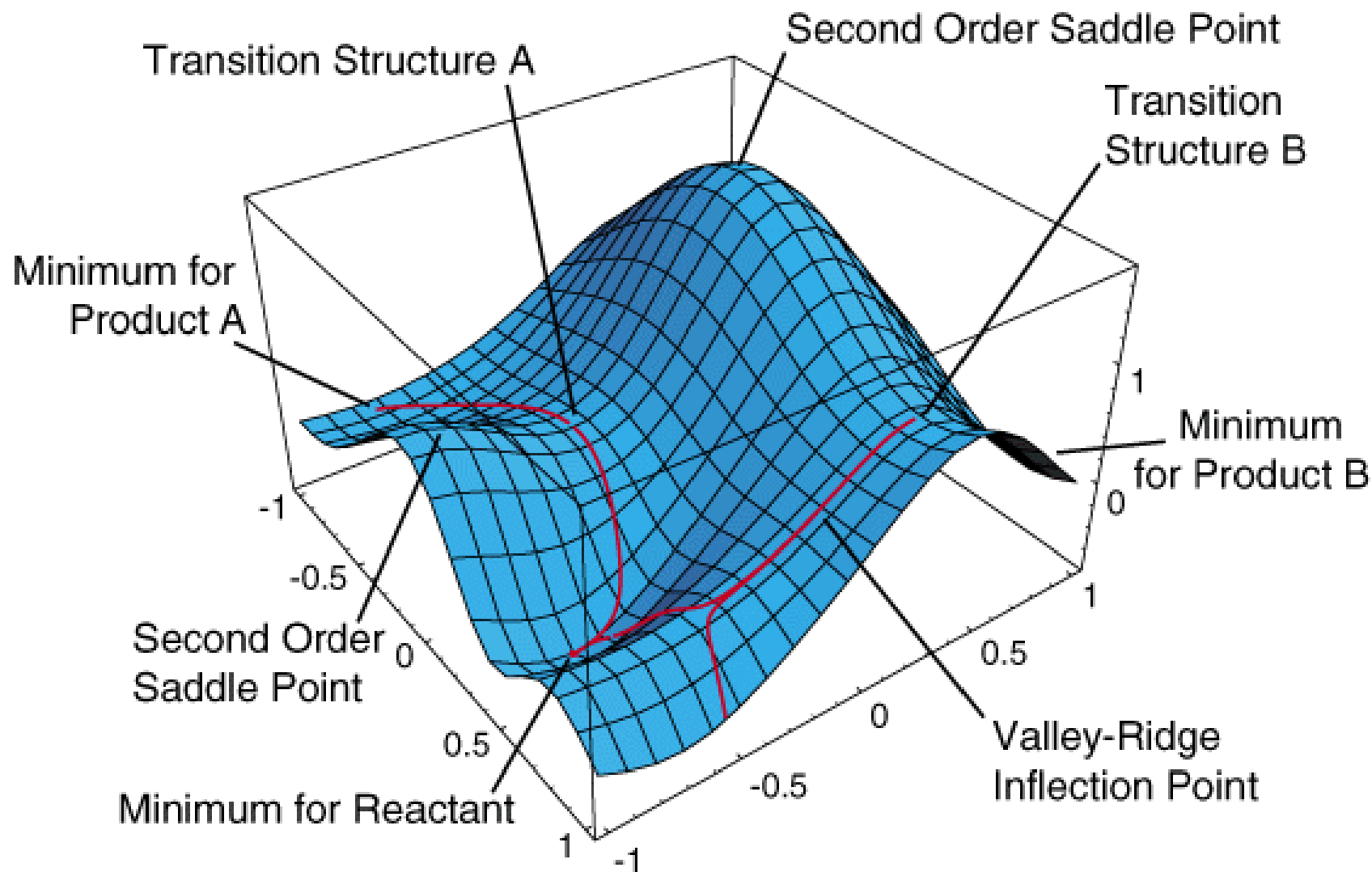
$$\frac{dy(E', t)}{dt} dE' = f(E', t) dE' + \int_0^{\infty} [R(E', E) dE' y(E, t)] dE - \int_0^{\infty} [R(E, E') y(E, t)] dE - \sum_{i=1}^{\text{canales}} k_i(E') y(E', t) dE'$$

término de distribución de densidad de energía inicial

constante de velocidad de pseudo primer orden para la transferencia de energía vibracional de la energía E hasta la energía E'

constante de velocidad de la reacción unimolecular para el canal i .

Minimum Energy Paths (MEPs):
 Conectividad entre los puntos estacionarios



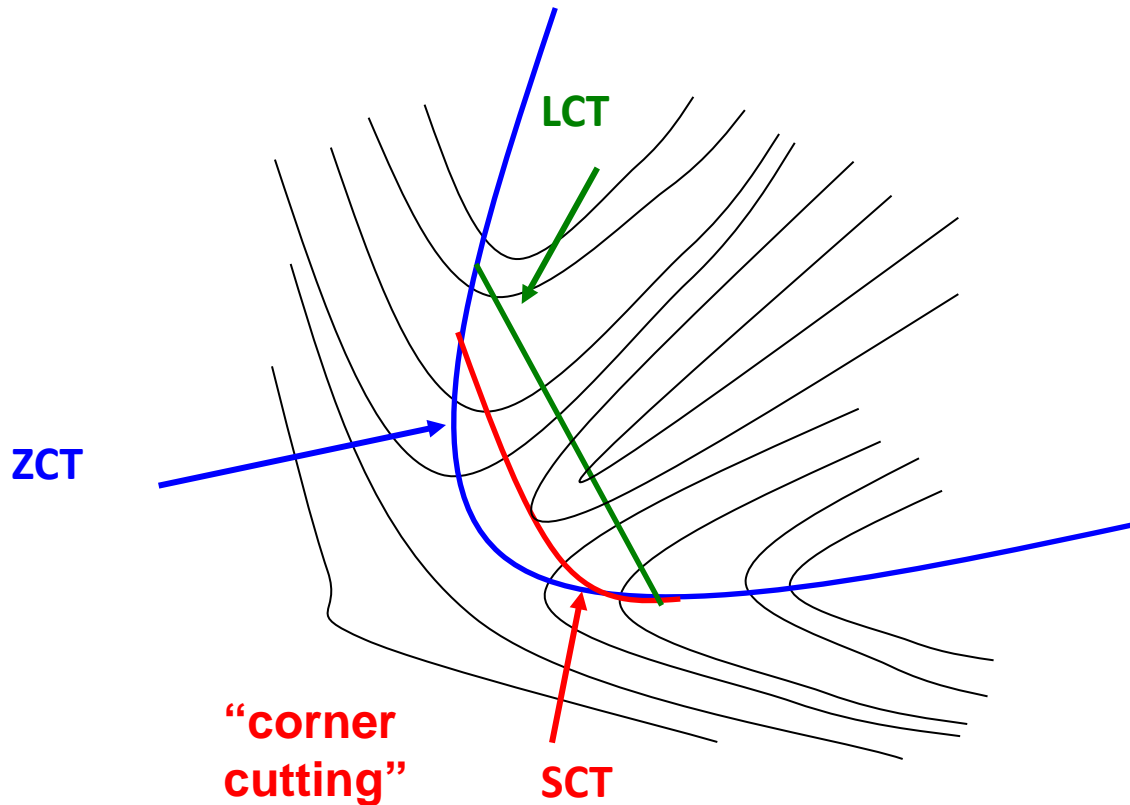
Canonical Variational Transition State Calculations.

1. After the initial step in the direction of the normalized imaginary frequency eigenvector **at the saddle point**, an algorithm is used all the way down to the reactants and to the final products.
2. At every gradient step, the **projected force constant matrix** is computed.
3. **Generalized vibrational frequencies and generalized normal modes** orthogonal to the reaction path are obtained within the harmonic approximation.
4. The **harmonic zero-point energy correction** at each step along the path is calculated.
5. The interpolated variational transition state theory by mapping **(IVTST-M)** is used to interpolate the information along the paths and to obtain the **adiabatic ground-state potential energy curve** at each side of the saddle point.
6. The **generalized rate constant at s** is calculated and minimized to obtain the **generalized activation free energy barrier at each temperature**.

$$P_{\text{qu}}(E) = |\psi|^2 \approx \exp(-2\theta(E))$$

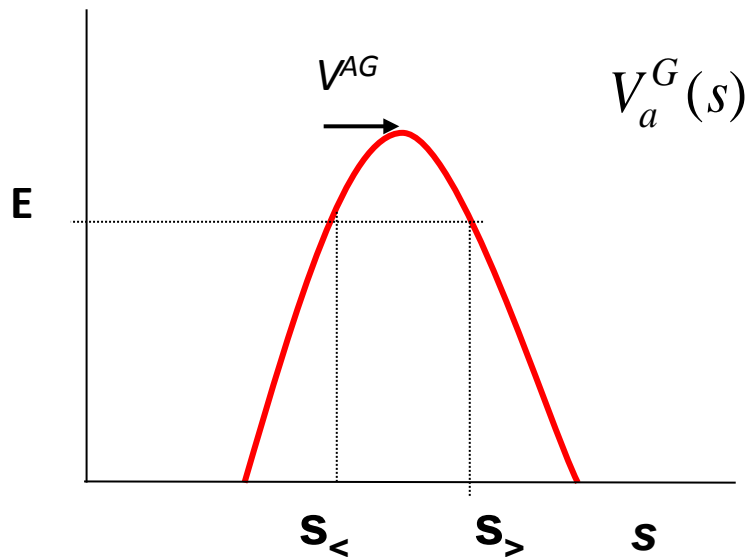
$$\theta(E) = \hbar^{-1} \int_{s_<}^{s_>} \{2\mu[V_{\text{eff}}(s) - E]\}^{1/2} ds$$

Turning points

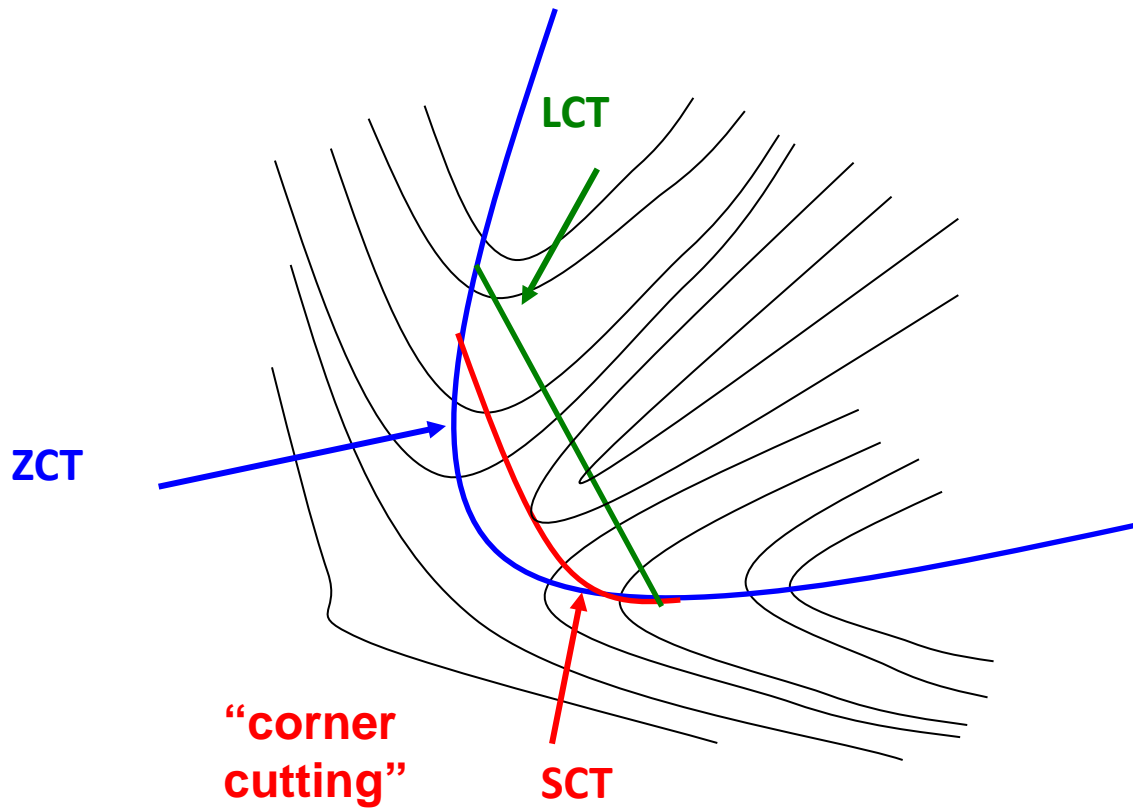


$$P^{SAG}(E) \left\{ \begin{array}{l} 0 \quad E < E_0 \\ \{1 + \exp[2\theta E]\}^{-1} \quad E_0 \leq E \leq V^{AG} \\ 1 - P^{SAG}(2V^{AG} - E) \quad V^{AG} \leq E \leq 2V^{AG} - E_0 \\ 1 \quad 2V^{AG} - E_0 < E \end{array} \right\}$$

$$E_0 = \max \left\{ \begin{array}{l} V_a^G(s = -\infty) \\ V_a^G(s = \infty) \end{array} \right\}$$



$$P^{\mu OMT}(E) = \max \begin{matrix} P^{LCT}(E) \\ P^{SCT}(E) \end{matrix}$$



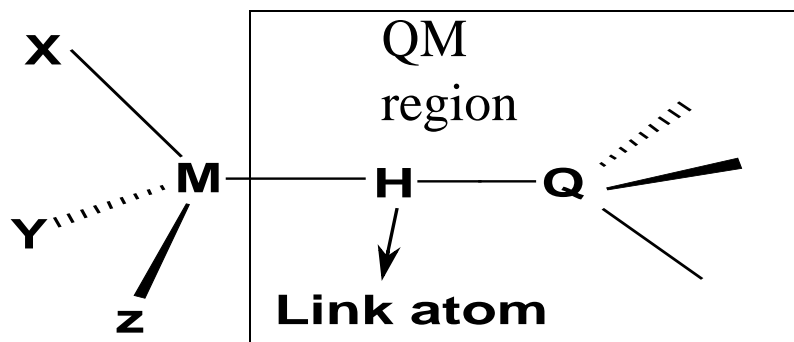
[http:// www.youtube.com/watch?v=Y79XI0LfYI4](http://www.youtube.com/watch?v=Y79XI0LfYI4)

\mathbf{H}_{elec} and $V_{\text{QM+QM/MM}}^{\text{nuclei}}$ can be computed using a standard quantum mechanics code. The term describing the electrons–classic charge interaction is incorporated into the core Hamiltonian of the quantum subsystem.

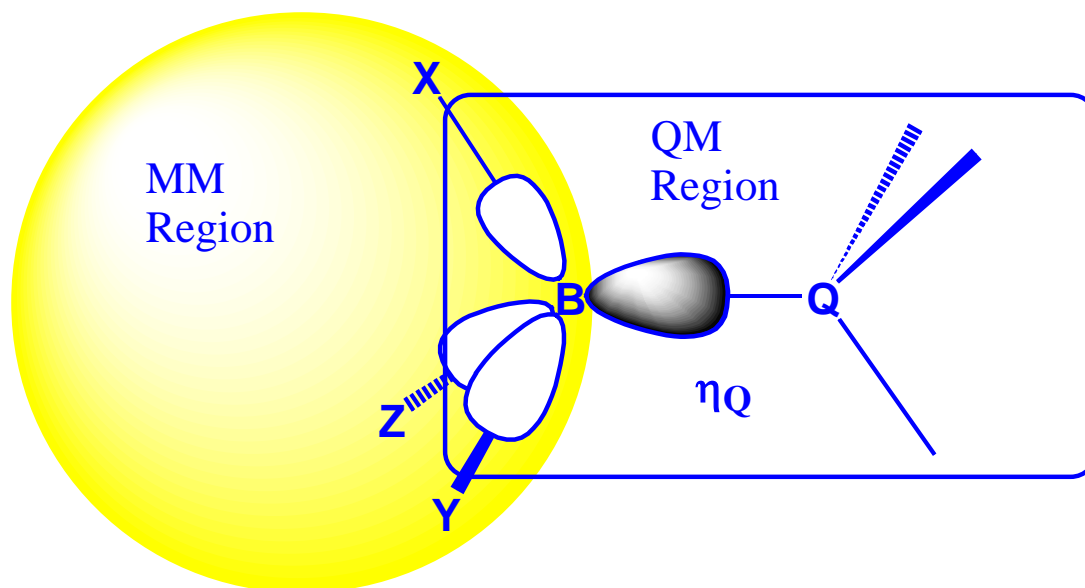
\mathbf{H}_{MM} and $V_{\text{QM/MM}}^{\text{van der Waals}}$ are computed using standard molecular mechanics code and are relatively easy to implement.

QM-MM boundary

- Link atom method¹



- Generalized Hybrid Orbital (GHO) method.²



² Gao J, et al. *J.Phys.Chem. A* 1998, 102, 4714.