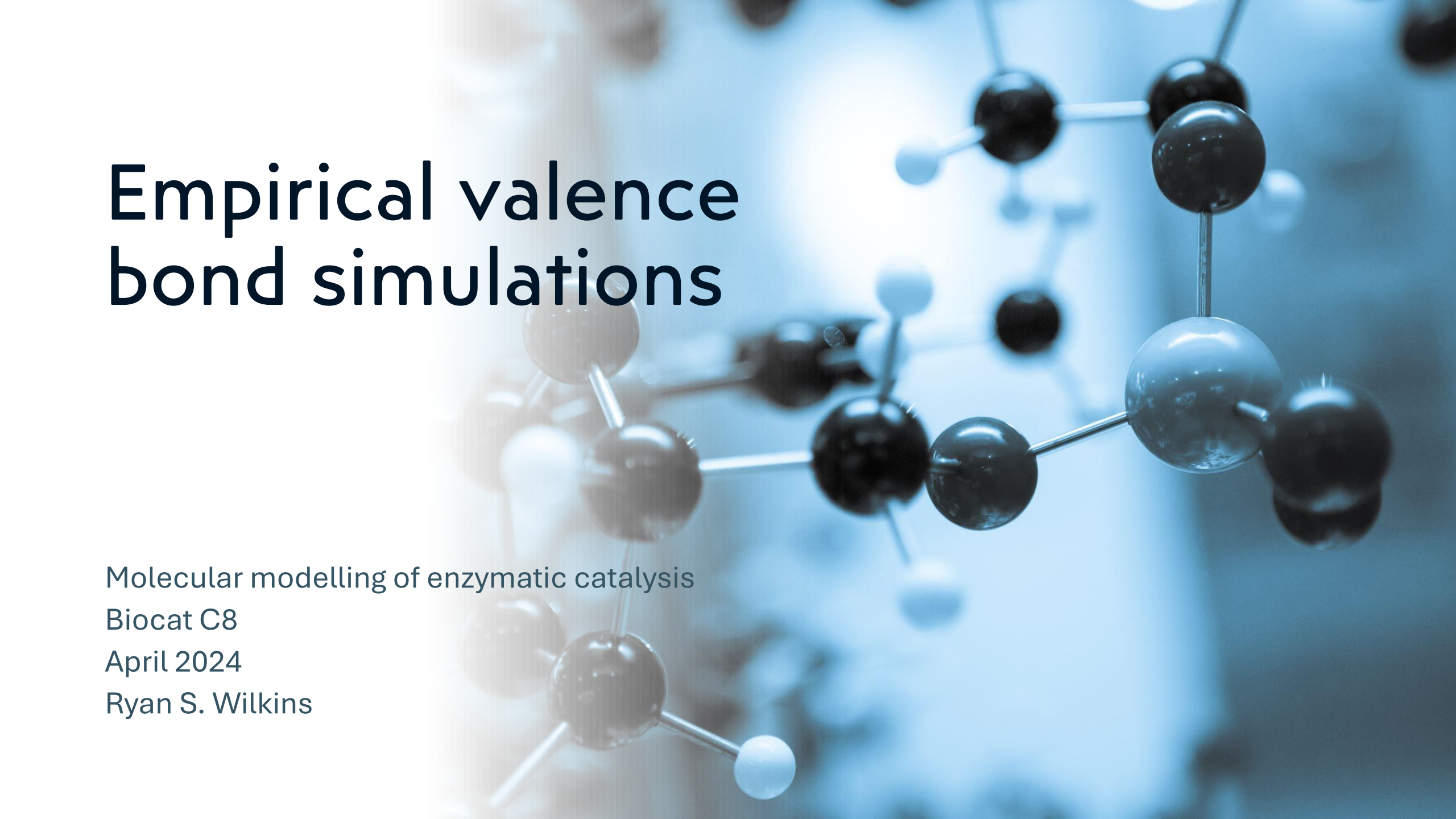
Empirical valence bond simulations



Molecular modelling of enzymatic catalysis

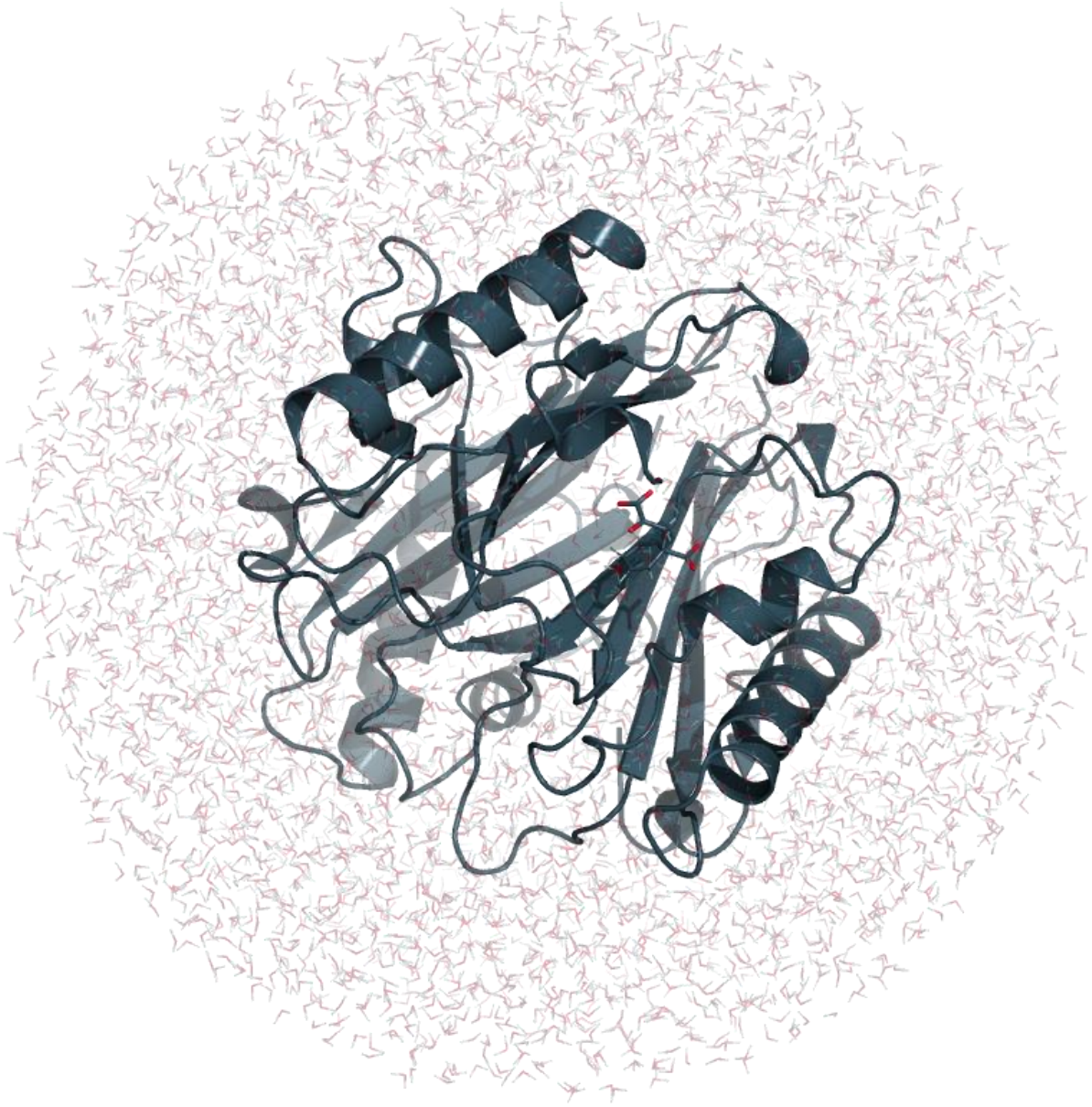
Biocat C8

April 2024

Ryan S. Wilkins

Outline

- History of EVB
- What is EVB?
- Theory behind EVB
- How do we use EVB?
- What's next?



A (very) brief history of EVB

- Developed in 1980
  - Goal: compare solution reactions to enzymatic reactions

Arieh Warshel
Photo from:
Nobel Media AB.

- Many contributions to enzyme catalysis
  - Origins of enzyme catalysis
  - Enzyme adaptation to extreme environments

An Empirical Valence Bond Approach for Comparing Reactions in Solutions and in Enzymes

Arieh Warshel* and Robert M. Weiss

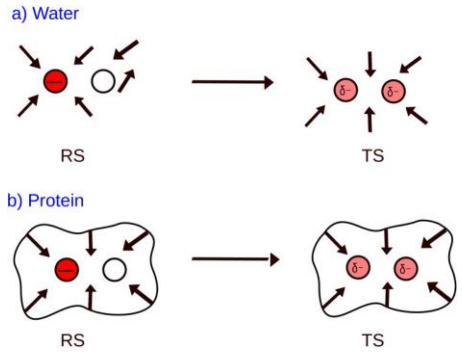
Contribution from the Department of Chemistry, University of Southern California, Los Angeles, California 90007. *Received March 3, 1980*

Origins of enzyme catalysis

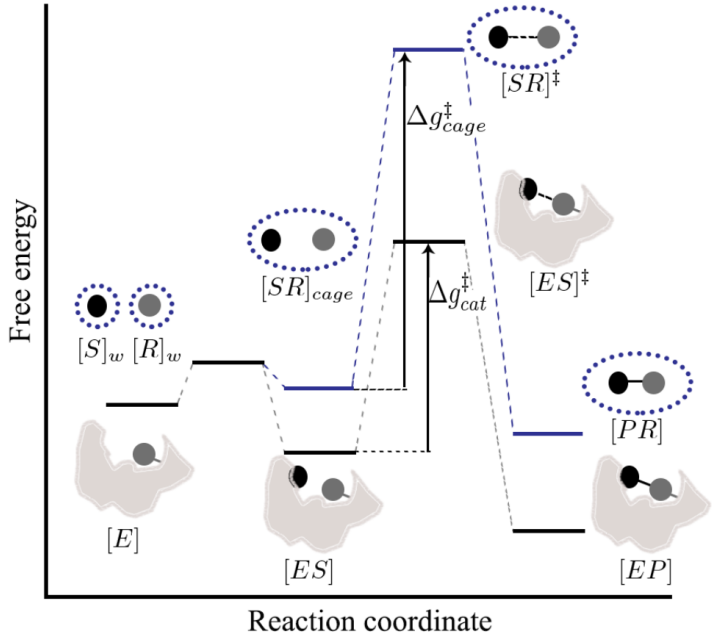
- Electrostatic stabilisation of [ES]‡
- Reorientation of dipoles

$$\Delta G_{\mathrm{sol}} \cong \langle \Delta U_{q\mu} \rangle + \langle \Delta U_{\mu\mu} \rangle \cong \frac{1}{2} \langle \Delta U_{q\mu} \rangle$$

- $\Delta U_{\mu\mu}$ repulsion energy paid during protein folding
  - Reorganization energy
  - Enzymes are preorganized

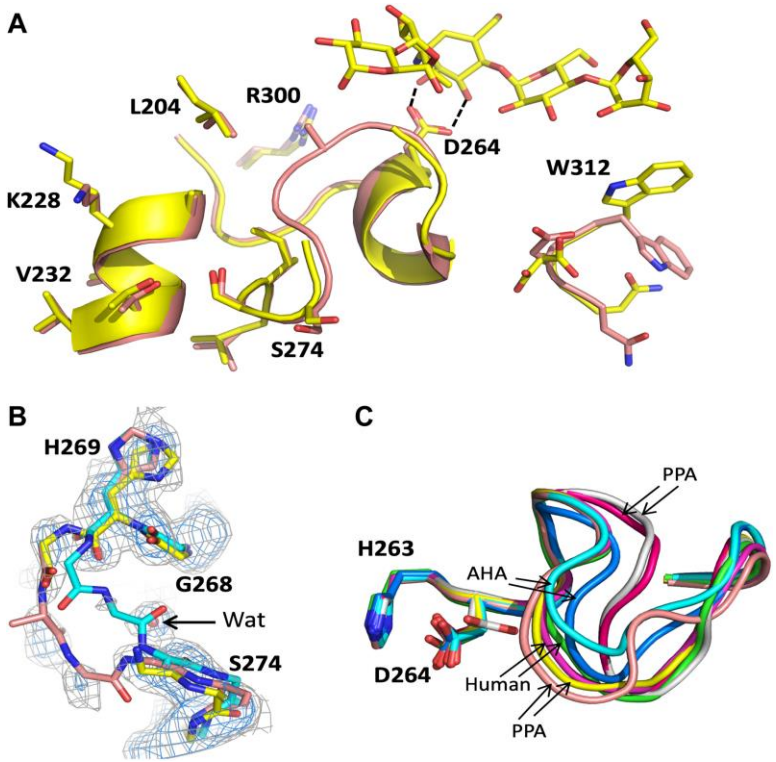


Jindal *et al.*, *Proteins*, 2017

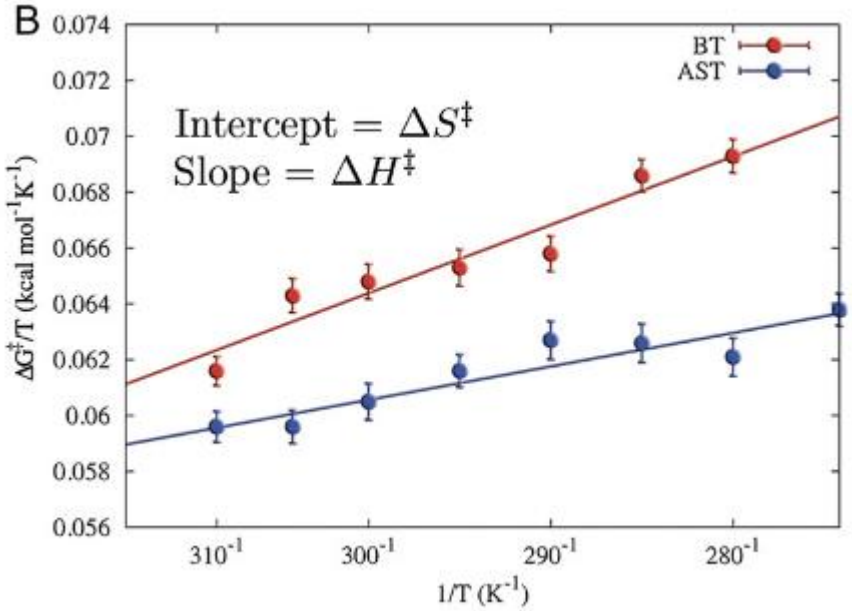


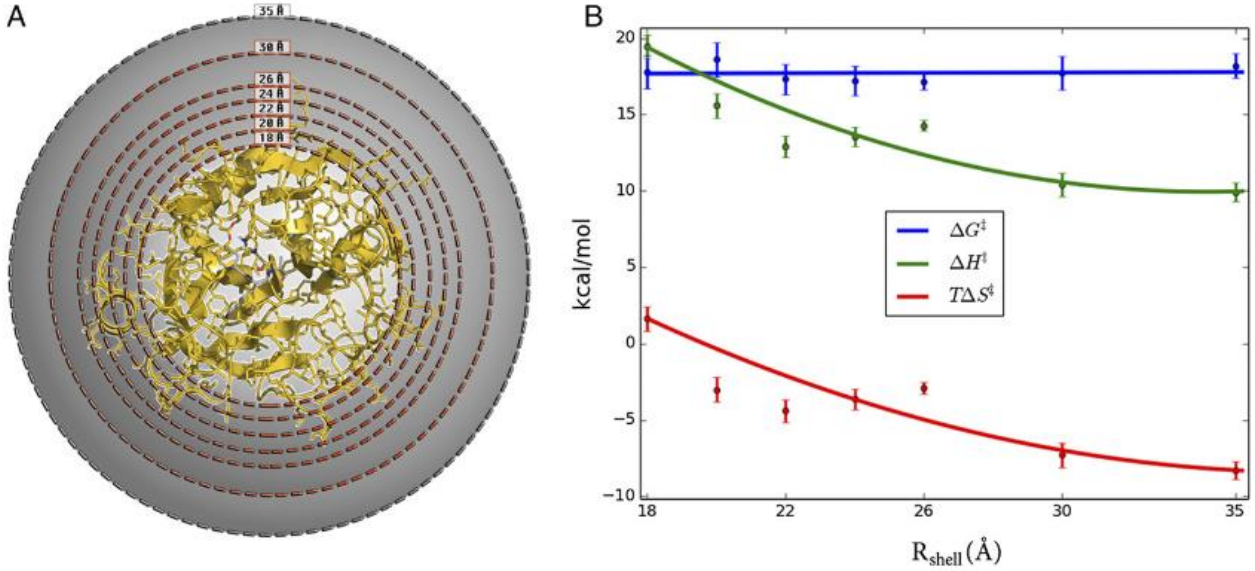
Enzyme adaptation

- Also used to study enzyme adaptation to extreme environments



van der Ent *et al.*, *Science*, 2023

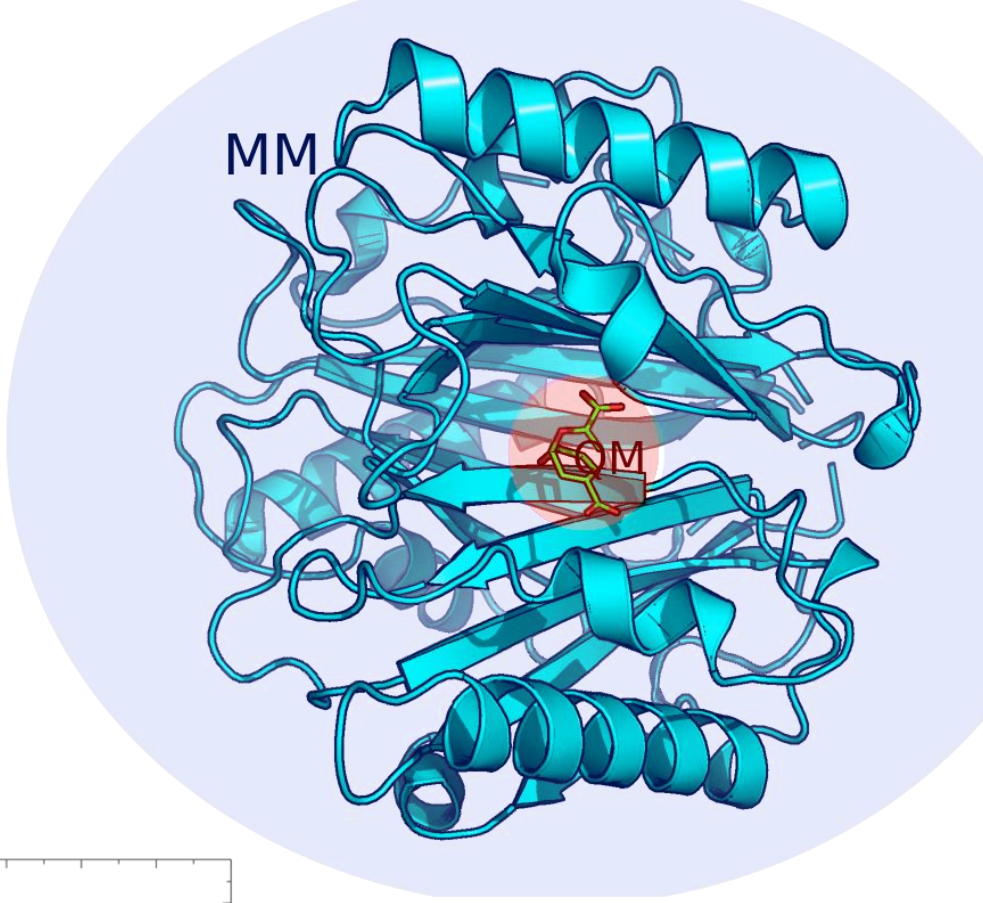


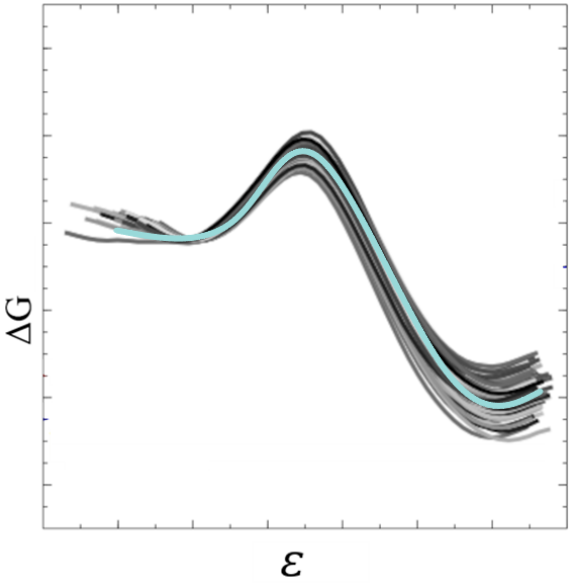


Isaksen *et al.*, *PNAS*, 2016

What is EVB?

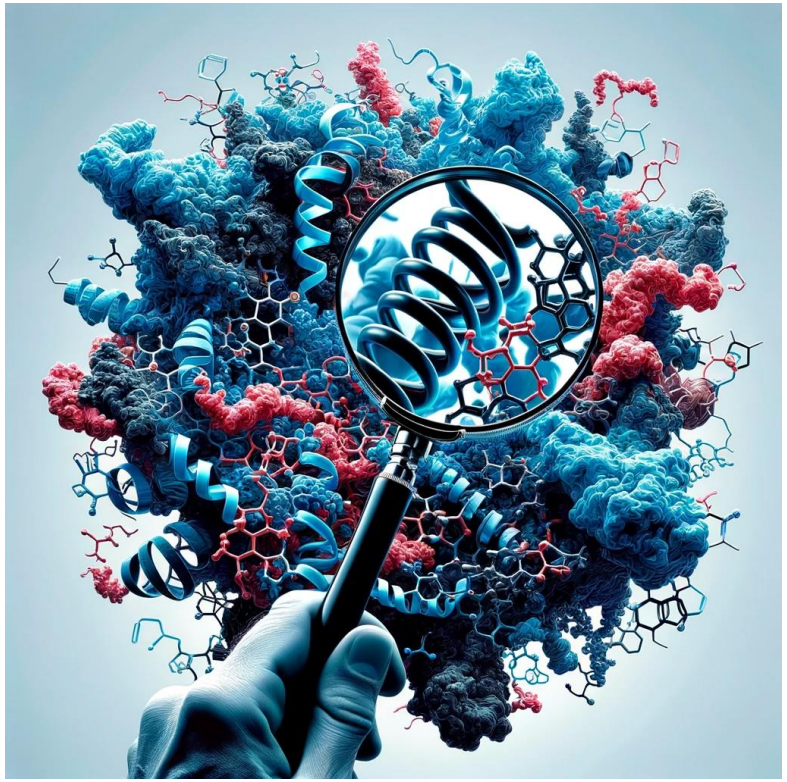
- Semi-empirical quantum mechanical method
- Calculate $\Delta G^{\ddagger}$ for enzyme and solution reactions
- Can treat large and complex systems efficiently





Advantages of EVB

- Directly comparable to experimentally measurable thermodynamics and kinetics of enzymes
- Can dissect energies into contributions:



$$k = \kappa \left(\frac{k_B T}{h}\right) e^{-\Delta G^{\ddagger}/k_B T} = \kappa \left(\frac{k_B T}{h}\right) e^{-\Delta H^{\ddagger}/k_B T} e^{\Delta S^{\ddagger}/k_B}$$

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$$\Delta H^{\ddagger} = \Delta U^{\ddagger} - P\Delta V^{\ddagger}$$

$$\Delta U^{\ddagger} = \Delta U^{\ddagger}_{rr} + \Delta U^{\ddagger}_{rs} + \Delta U^{\ddagger}_{ss}$$

$$\Delta U^{\ddagger}_{ss} = \Delta U^{\ddagger}_{pp} + \Delta U^{\ddagger}_{pw} + \Delta U^{\ddagger}_{ww}$$

r: reacting fragment
s: surroundings
p: protein
w: water

Free energy perturbations

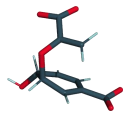
- Want to find free energy difference between two states

$$\Delta G = -\beta^{-1}\ln\langle\exp(-\beta\Delta\epsilon)\rangle_{\varphi_1}$$

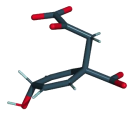
- Potentials must overlap
  - Introduce a set of intermediate mapping potentials

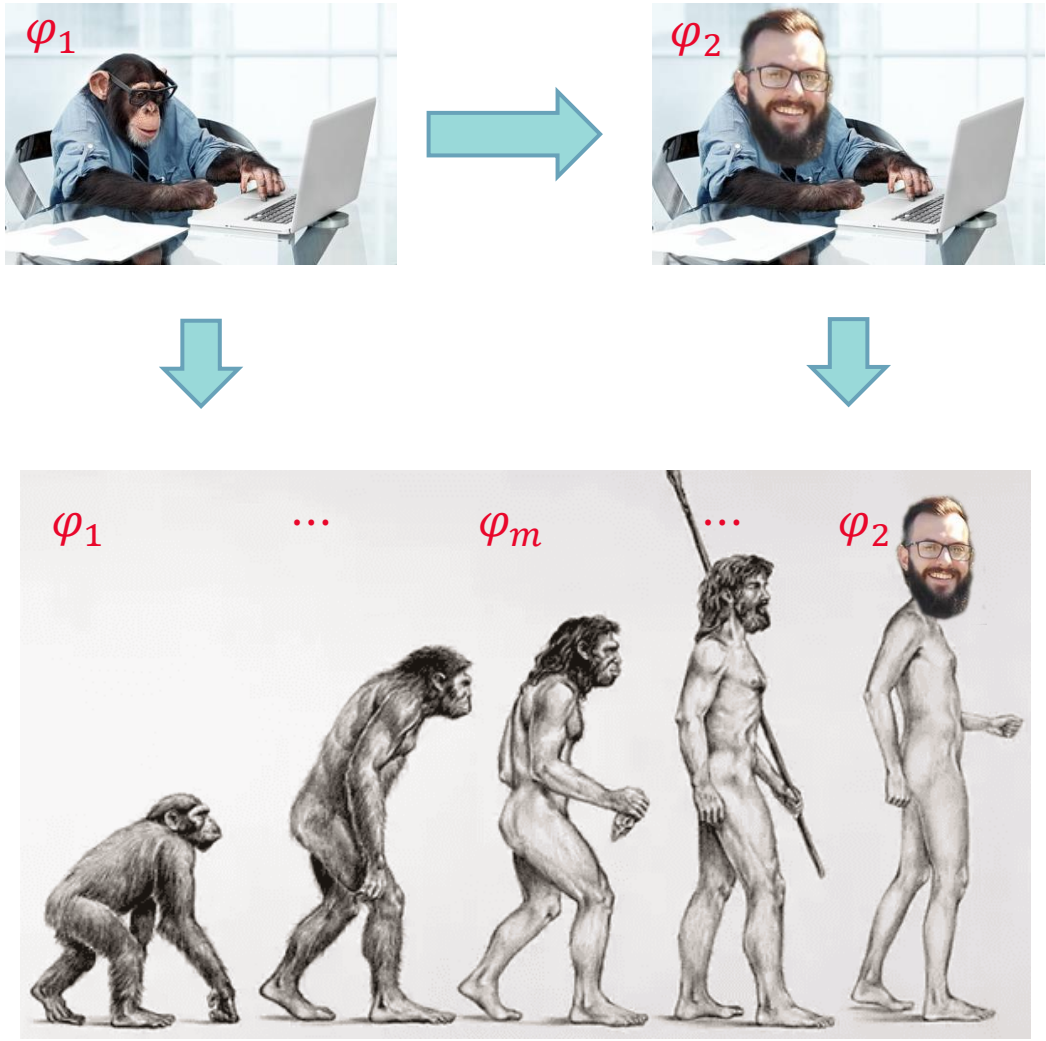
$$\epsilon_m = (1-\lambda_m)\epsilon_1 + \lambda_m\epsilon_2 \qquad \lambda_m \in [0,1]$$

0 =



1 =





Free energy perturbations

- How to calculate $\Delta G^{\ddagger}$?
  - Umbrella sampling:

$$\Delta G = -\beta^{-1}\ln\langle\exp(-\beta\Delta\epsilon)\rangle_{\varphi_1}$$

    - Divided into $m-1$ windows:

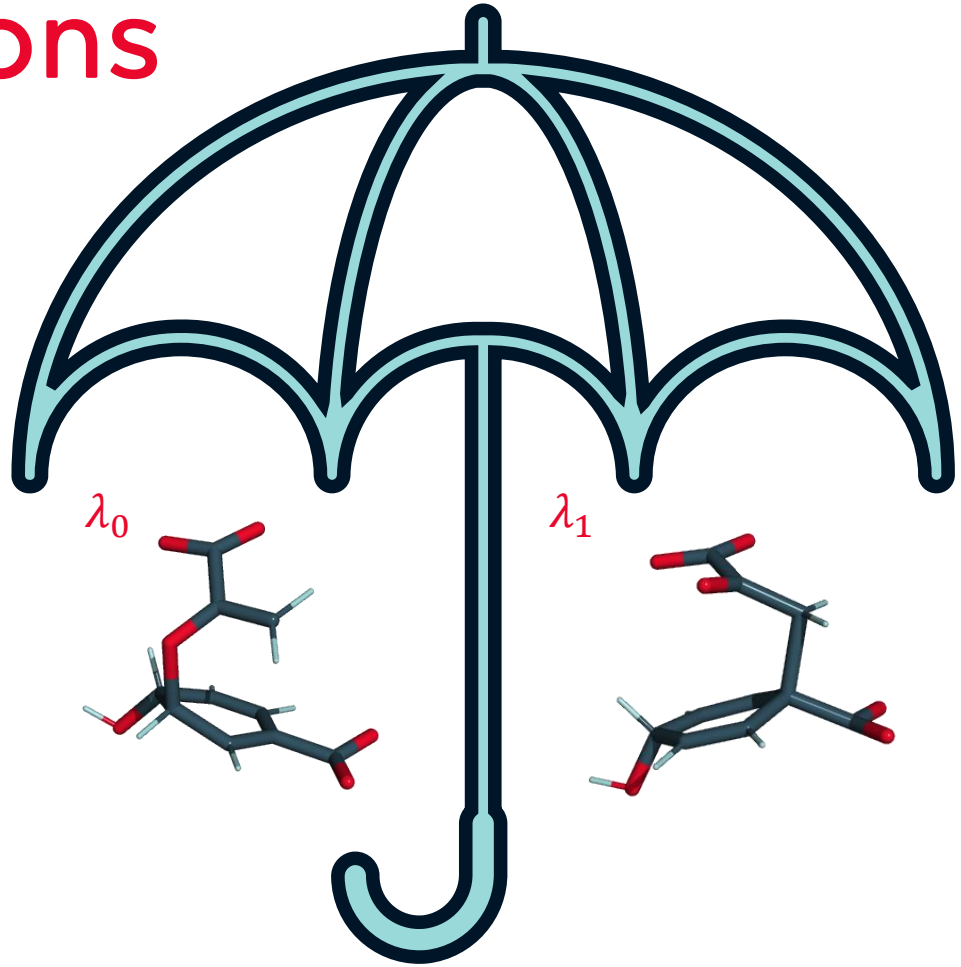
$$\epsilon_m = (1-\lambda_m)\epsilon_1 + \lambda_m\epsilon_2,\ \ \lambda_m \in [0,1]$$

    - $\Delta G^{\ddagger}$ of each window:

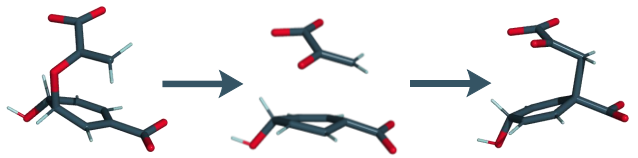
$$\Delta G_m = -\beta^{-1}\ln\left\langle\exp\left(-\beta(\epsilon_{m+1}-\epsilon_m)\right)\right\rangle_{\varphi_1}$$

    - Total $\Delta G^{\ddagger}$:

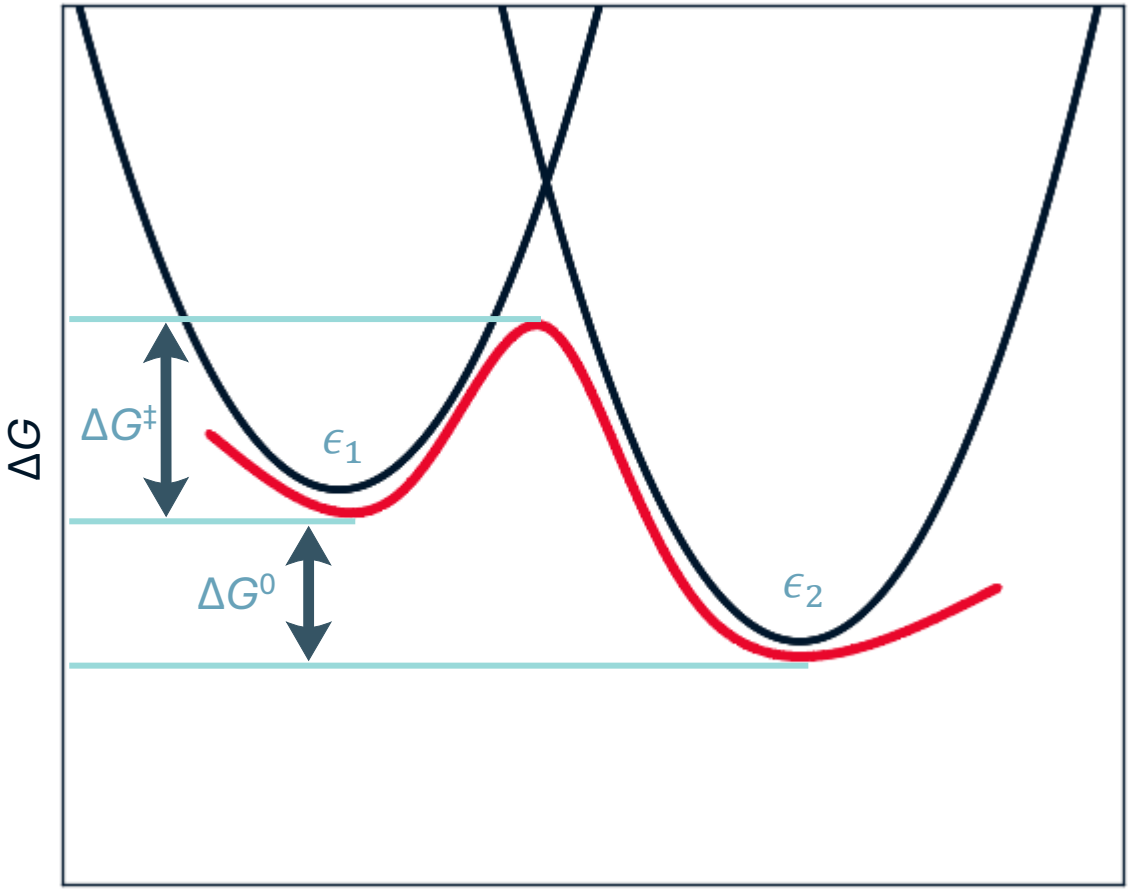
$$\Delta G = \sum_{m=0}^{n-1}\Delta G_m$$



How does EVB work?



- Origins in Marcus electron transfer theory of metals
  - Applied to catalysis in solution
- Solve Schrödinger equation to calculate ground-state energy of a state



The EVB Hamiltonian

- Each state in a reaction in described as a valence bond (VB) states (ϕ_1, ϕ_2, …, ϕ_n)

$$\mathcal{H}_{\mathrm{EVB}} = \begin{bmatrix} H_{ii} & \cdots & H_{ij} \\ \vdots & \ddots & \vdots \\ H_{ji} & \cdots & H_{jj} \end{bmatrix}$$

- Diagonal elements given by:

$$H_{ii} = \epsilon_i = U^i_{bond} + U^i_{ang} + U^i_{tor} + U^i_{imp} + U^i_{nb.rr} + U^i_{nb,rs} + U^i_{ss} + \alpha^i$$

  - α^i = intrinsic gas-phase energy at infinite separation

- And off-diagonals:
  - From adiabatic mixing of states

$$H_{ij} = \sum_{k,l} A^{k,l}_{ij} e^{-\mu_{ij}/r}$$

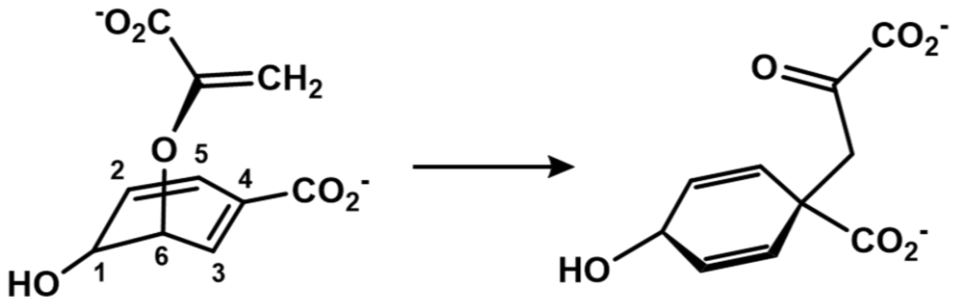
$$H_{ij} = \sum_{k,l} A^{k,l}_{ij}$$

Interpretation of the Hamiltonian

$$H_{ii} = \epsilon_i = U^i_{bond} + U^i_{ang} + U^i_{tor} + U^i_{imp} + U^i_{nb.rr} + U^i_{nb,rs} + U^i_{ss} + \alpha^i$$

$$H_{ij} = \sum_{k,l} A^{k,l}_{ij}$$

2-state EVB



ϕ_1 ϕ_2

$$\mathcal{H}_{\text{EVB}} = \begin{bmatrix} \epsilon_1 & A_{1,2} \\ A_{2,1} & \epsilon_2 \end{bmatrix} = \begin{bmatrix} \epsilon_1 & A_{1,2} \\ A_{1,2} & \epsilon_2 \end{bmatrix}$$

Solving the Hamiltonian

- Want to solve the Schrödinger equation for the adiabatic ground-state energy

$$\boldsymbol{\mathcal{H}}_{\mathrm{EVB}} E_g = \boldsymbol{C}_g E_g$$

- This is just an eigenvalue/eigenvector problem

$$\left|\boldsymbol{\mathcal{H}}_{\mathrm{EVB}} - \mathbf{I}E_g\right| A = 0$$

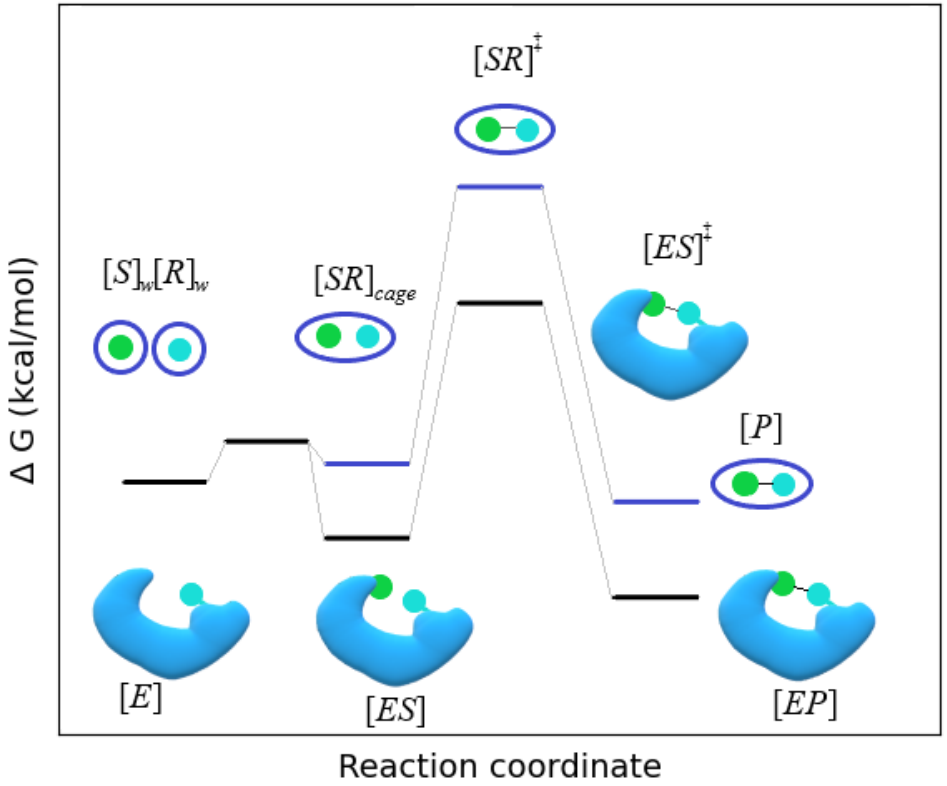
$$\left|\begin{bmatrix} \epsilon_1 & A_{1,2} \\ A_{1,2} & \epsilon_2 \end{bmatrix} - \begin{bmatrix} E_g & 0 \\ 0 & E_g \end{bmatrix}\right| = 0$$

$$E_g{}^2 + E_g(-\epsilon_1 - \epsilon_2) + \epsilon_1\epsilon_2 - A_{1,2}^2 = 0$$

$$E_g = \frac{(\epsilon_1 + \epsilon_2) - \sqrt{(\epsilon_1 - \epsilon_2)^2 - 4A_{1,2}}}{2}$$

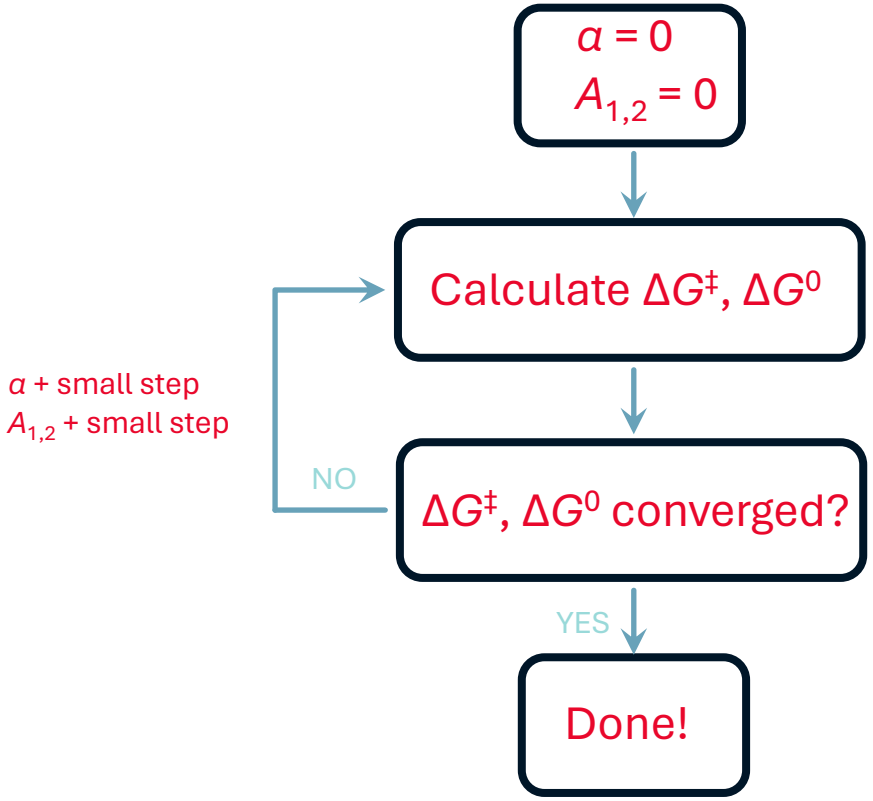
Calibrating the Hamiltonian

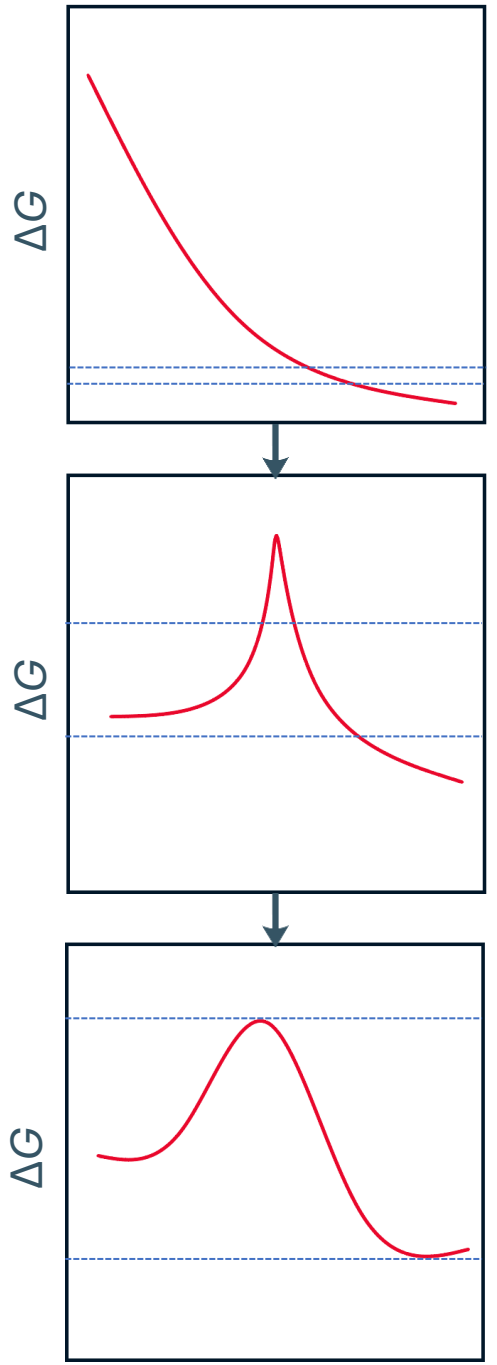
- Key "problem" of EVB: Hamiltonian not fully known (yet)
  - α, $A_{1,2}$ are empirical parameters
- Power of EVB: these parameters are independent of environment
- Can calibrate the Hamiltonian using $\Delta G^{\ddagger}$, ΔG^{0}
  - Experiment or *ab initio*



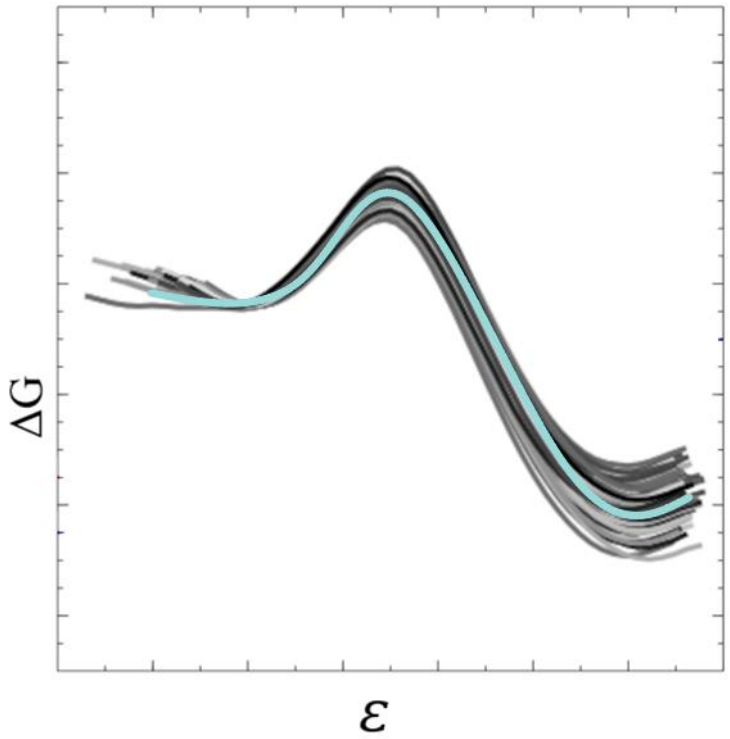
Iterative calibration

- Need $\Delta G^{\ddagger}$, ΔG^{0} targets



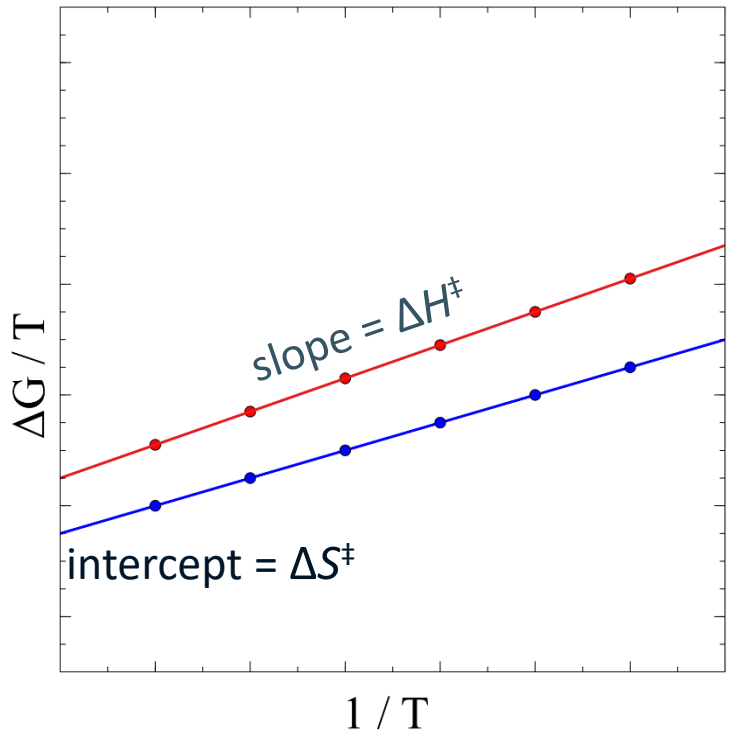


Using EVB for Arrhenius plots

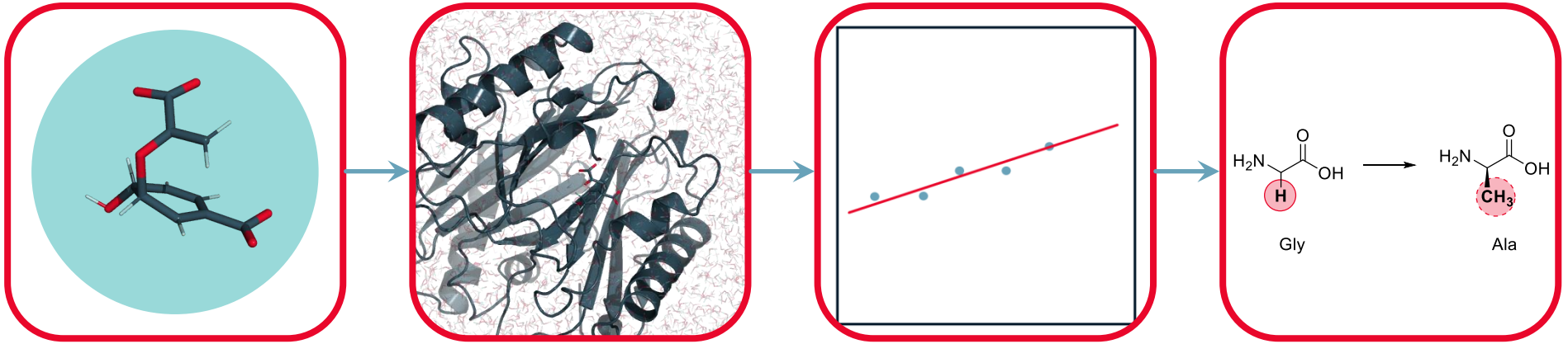


Repeat at multiple *T*

$\Delta G^{\ddagger}/T = \Delta H^{\ddagger}/T - \Delta S^{\ddagger}$



Example EVB workflow



The future of EVB

- EVB has some *problems*...
  - Q v.s. Molaris
- Can it be fixed?

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Efficient Empirical Valence Bond Simulations with GROMACS

Gabriel Oanca,* Florian van der Ent, and Johan Åqvist*

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