

Investigating physical constraints underlying catalysis and their impact on metabolic systems

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CRI Research Symposium

October 11, 2017

Once upon a time...



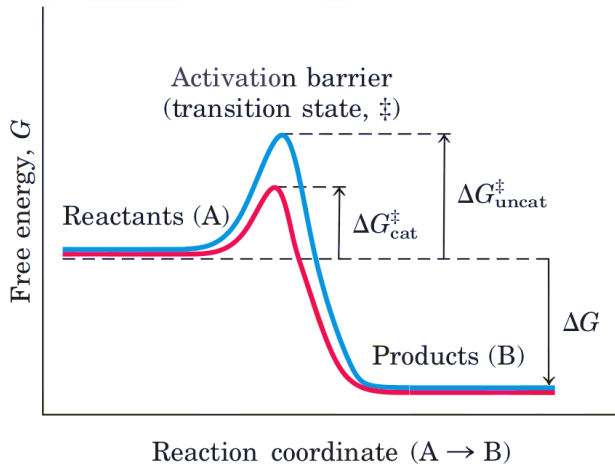
Research questions

- ▶ What is the physical limit for lowering the activation energy barrier of a given reaction

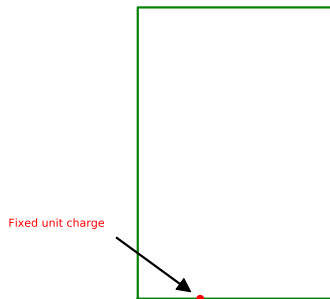
Research questions

- ▶ What is the physical limit for lowering the activation energy barrier of a given reaction
- ▶ How is the affinity of an enzyme affected by the requirement to be selective

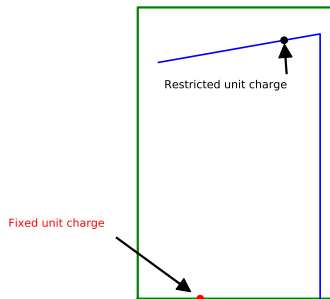
Textbook illustration



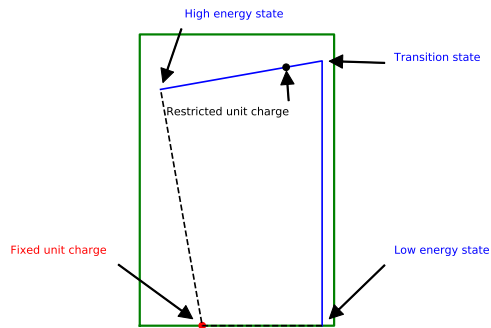
Modeling energy landscape modification in a classical system



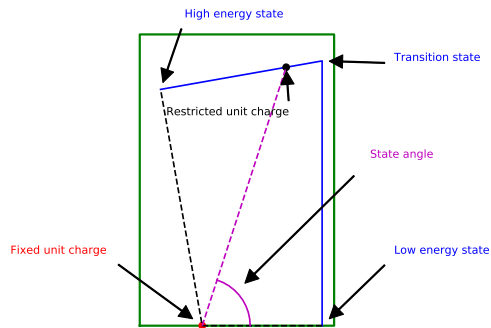
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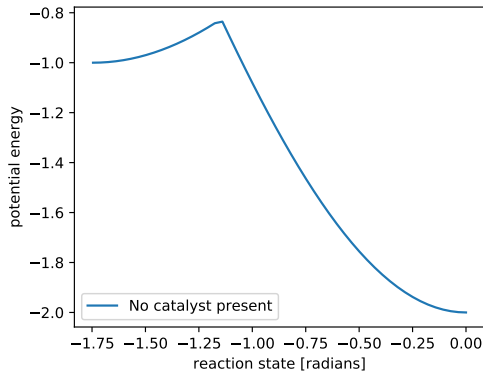
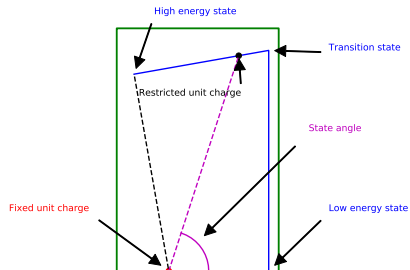
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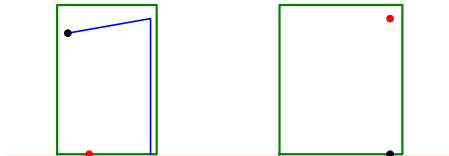
Modeling energy landscape modification in a classical system



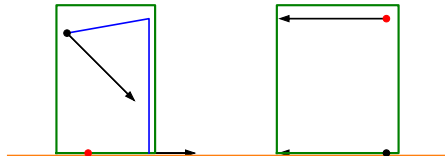
Reaction energy landscape of model substrate



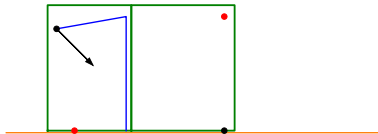
Introducing a model catalyst



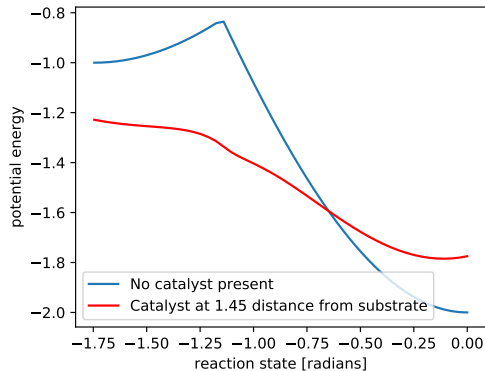
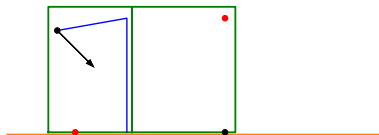
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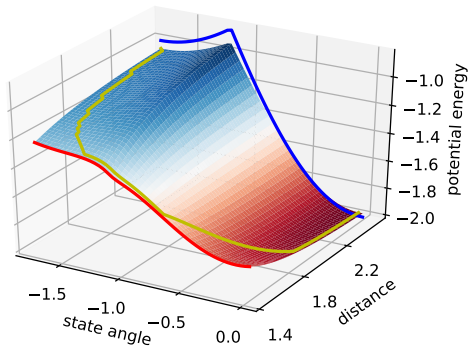
Reaction energy landscape of bound substrate



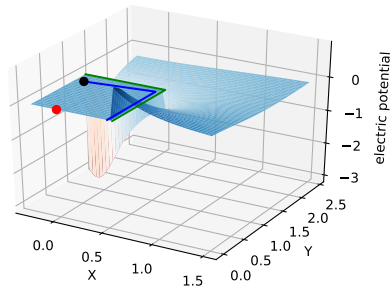
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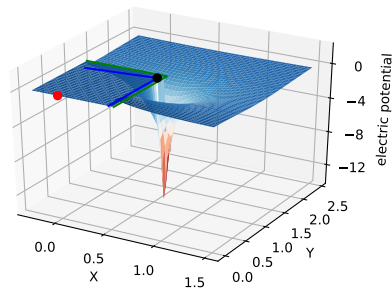
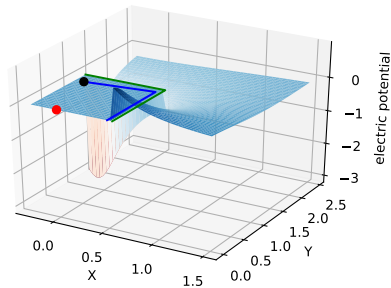
The catalyst creates a bypass to the energy barrier at the transition state



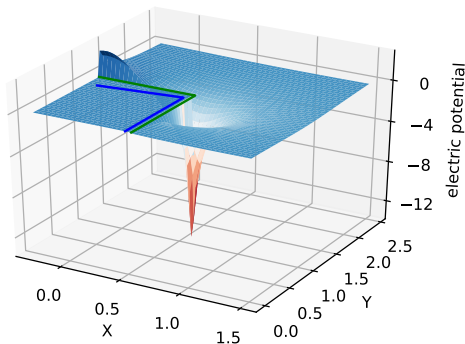
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- ▶ The resulting function quantifies the barrier reduction when positioning a positive point charge at any coordinate in space
- ▶ Placing charges at extremum points of this function achieves maximal barrier reduction

Methodological approach for investigating catalytic constraints

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 - ▶ Challenge existing assumptions
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- ▶ Apply theoretical framework to molecular domain
- ▶ Investigate metabolic network design implications
 - ▶ Synthetic biology applications
 - ▶ Origins of life metabolism

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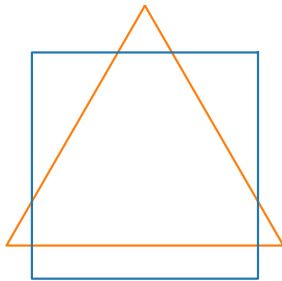
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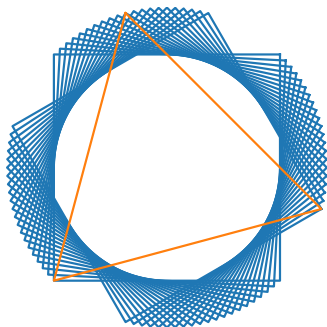
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- ▶ Most enzymes are substrate-specific
- ▶ Structural similarity is used for drug discovery and promiscuous activity tests
- ▶ Metabolic networks must contain structurally similar metabolites
 - ▶ But can potentially reduce similarities at critical points
- ▶ Numerous examples for specificity tradeoffs in the literature

Why do we expect selectivity to decrease affinity?

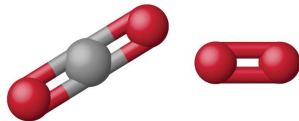


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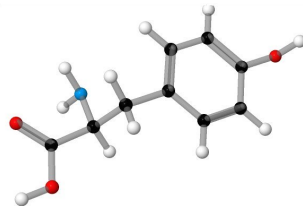
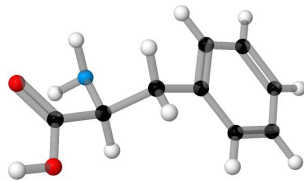
Examples of specificity-affinity challenges

- ▶ RuBisCo
 - ▶ CO_2 versus O_2



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- ▶ RuBisCo
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 - ▶ Tyr versus Phe
- ▶ Bacterial DNA methyltransferase
 - ▶ Relaxing sequence specificity accelerates rate
- ▶ Bacterial hexose phosphate transporter

Can we formulate a quantitative evaluation of the selectivity challenge?

- ▶ Given metabolites concentration data
 - ▶ Identify challenging reactions
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- ▶ Given metabolites concentration data
 - ▶ Identify challenging reactions
 - ▶ Quantify expected cost
- ▶ Given reaction possibilities
 - ▶ Find biases in metabolic network structure maximizing structural differences

Methodological approach for investigating selectivity tradeoffs

- ▶ Impact on metabolites concentrations and enzymes
 - ▶ BRENDA - identifying weak affinity enzymes
 - ▶ Promiscuous activity data from Sauer lab
 - ▶ Structural similarity metrics comparison with measured metabolites concentrations

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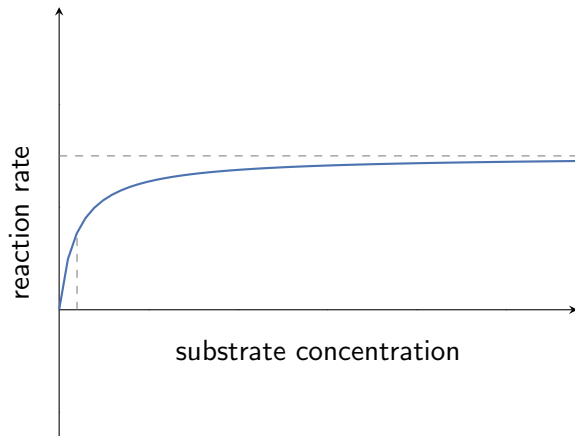
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 - ▶ BRENDA - identifying weak affinity enzymes
 - ▶ Promiscuous activity data from Sauer lab
 - ▶ Structural similarity metrics comparison with measured metabolites concentrations
- ▶ Impact on network structure
 - ▶ Project metabolic networks to chemical space
 - ▶ Implement selectivity in constraint based modeling of metabolic networks

Summary

- ▶ Basic challenges of biological systems are rarely investigated theoretically
- ▶ Transforming key problems to simplified models in accessible platforms can leverage innovation of wider audience and reveal novel principles
- ▶ Recently available datasets allow evaluation of hypotheses
- ▶ Mapping metabolic networks into the chemical space can highlight metabolic network motifs

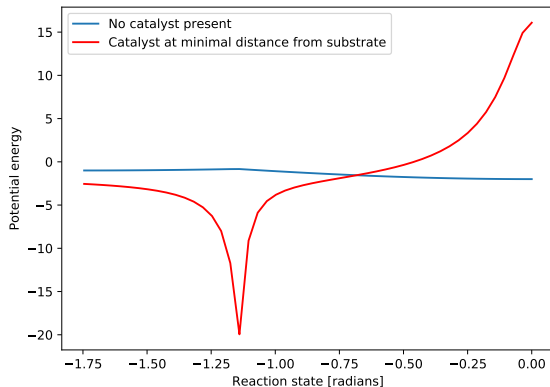
Thank You!

The Michaelis-Menten model for catalyzed chemical reaction rate



$$V = \frac{k_{\text{cat}}[X]}{k_M + [X]}$$

Catalyst design must track the entire reaction pathway



Structural similarity inhibits enzymes due to finite structural diversity