Investigating physical constraints underlying catalysis and their impact on metabolic systems

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CRI Research Symposium

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https://git.io/vd2x0

Once upon a time...

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Research questions

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

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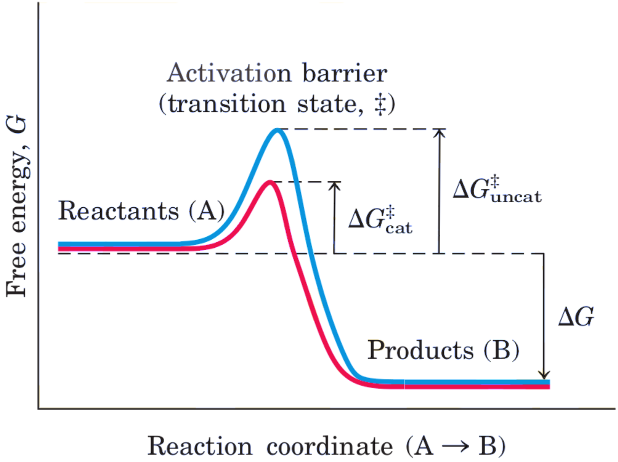
- What is the physical limit for lowering the activation energy barrier of a given reaction
- How is the affinity of an enzyme affected by the requirement to be selective

Textbook illustration



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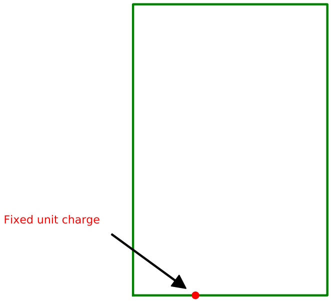
Modeling energy landscape modification in a classical system



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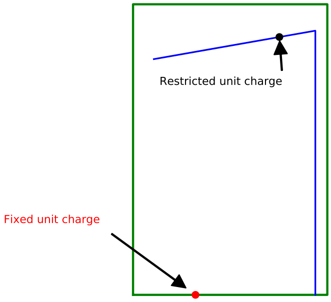

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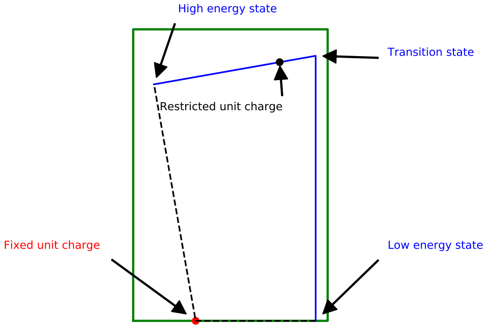

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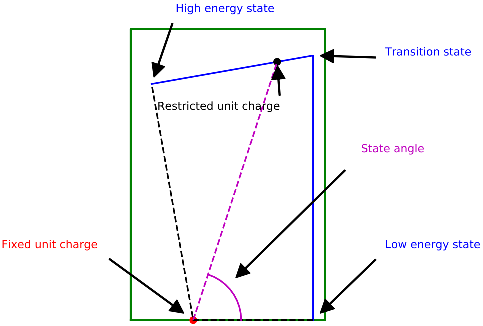

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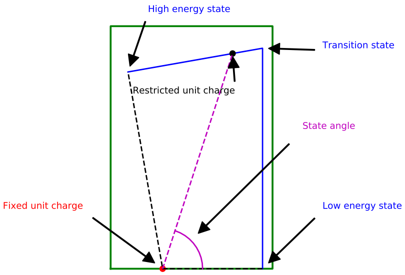
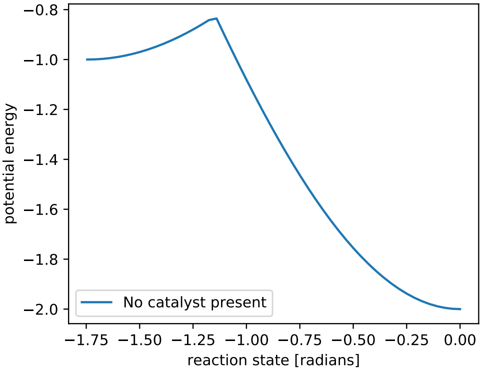
Reaction energy landscape of model substrate





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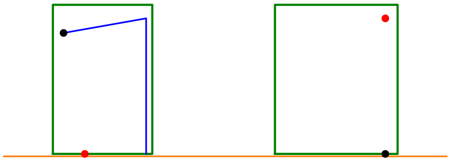
Introducing a model catalyst



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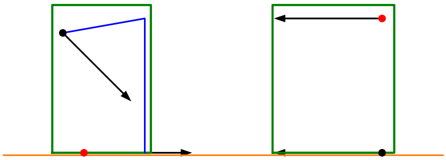

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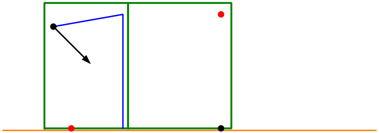
Reaction energy landscape of bound substrate



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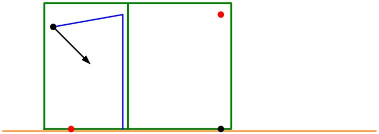

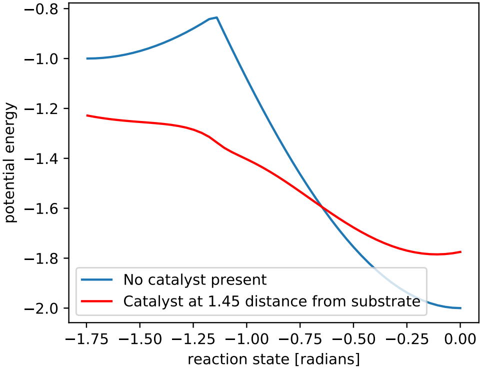

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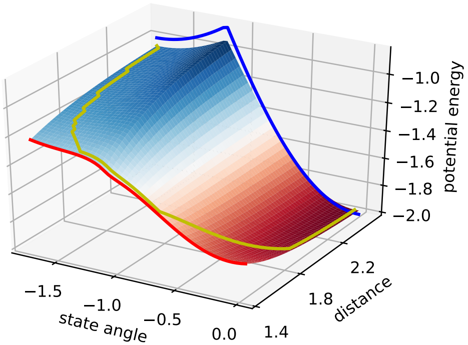
The catalyst creates a bypass to the energy barrier at the transition state



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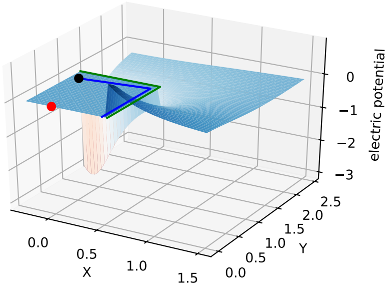
Subtracting the potential field at the transition state from the initial state produces an energy barrier reduction landscape



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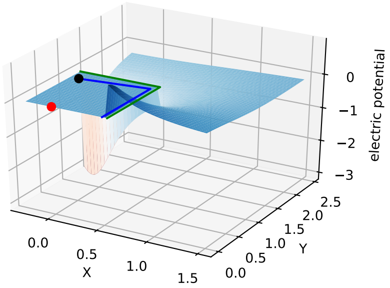

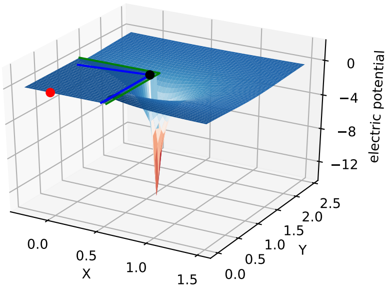

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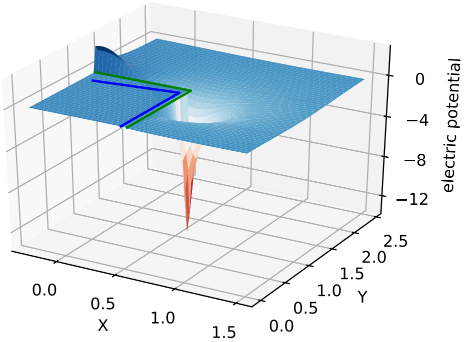

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- The resulting function quantifies the barrier reduction when positioning a positive point charge at any coordinate in space
- Placing charges at extremum points of this function achieves maximal barrier reduction

Methodological approach for investigating catalytic constraints

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- Crowd-sourcing platform
  - Challenge existing assumptions
  - Reveal potential catalytic mechanisms

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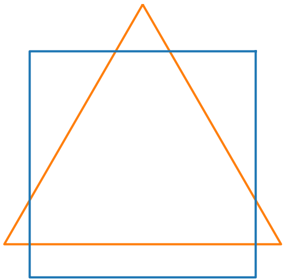
- Most enzymes are substrate-specific
- Structural similarity is used for drug discovery and promiscuous activity tests
- Metabolic networks must contain structurally similar metabolites
  - But can potentially reduce similarities at critical points
- Numerous examples for specificity tradeoffs in the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

Why do we expect selectivity to decrease affinity?



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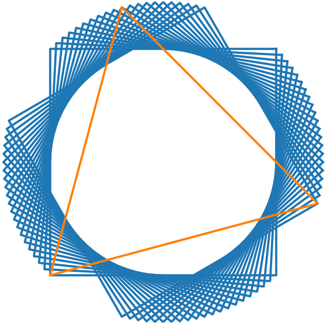

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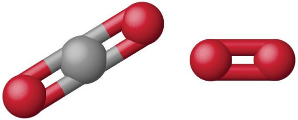
Examples of specificity-affinity challenges

- RuBisCo
  - CO_2 versus O_2



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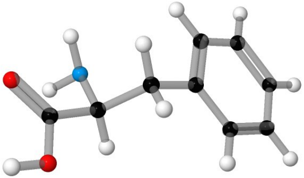

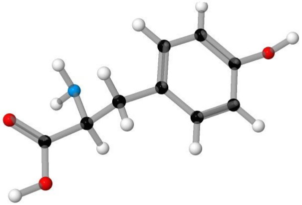

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Examples of specificity-affinity challenges

- RuBisCo
  - CO_2 versus O_2
- Tyrosine ammonia lyase
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- Bacterial DNA methyltransferase
  - Relaxing sequence specificity accelerates rate
- Bacterial hexose phosphate transporter

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Can we formulate a quantitative evaluation of the selectivity challenge?

- Given metabolites concentration data
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  - Quantify expected cost

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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

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- Impact on metabolites concentrations and enzymes
  - BRENDA - identifying weak affinity enzymes
  - Promiscuous activity data from Sauer lab
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- 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
- Impact on network structure
  - Project metabolic networks to chemical space
  - Implement selectivity in constraint based modeling of metabolic networks

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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!

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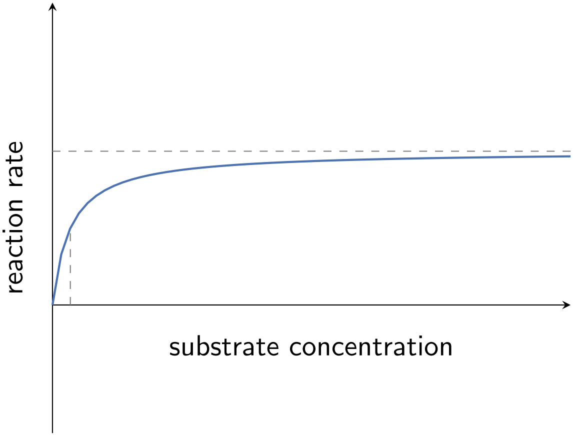
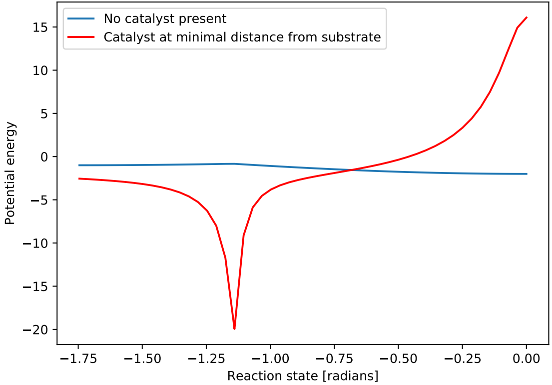
The Michaelis-Menten model for catalyzed chemical reaction rate



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

Catalyst design must track the entire reaction pathway



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Structural similarity inhibits enzymes due to finite structural diversity

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