# Potential Energy Surfaces, Newton Trajectories and Catch Bonds in Theoretical Chemistry

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# Abstract

The talk begins with a discussion of the reaction pathway, in particular the steepest descent, the intrinsic reaction coordinate (IRC). As an alternative, we propose Newton trajectories (NT).[1] An NT is a curve where the gradient of the PES points in the same direction at every point. NTs connect stationary points of the PES, so they can be used to find saddle points.

Application: NTs describe the curves of the change of stationary points under an external linear force.

A special application is the study of so-called catch bonds: counterintiutive bonds that become stronger under a mechanochemical force[2]. Two example PES will be explained.

[1] W.Quapp, M.Hirsch, O.Imig, D.Heidrich, J.Computat.Chem. 19 (1998) 1087; Theor.Chem.Acc. 100 (1998) 285.

[2] W.Quapp, J.M.Bofill, J.Phys.Chem.B 128 (2024) 4097; J.Math.Chem xx (2025) xx.

# Background: what is a Reaction Path?

The chemical bonds emerge by the overlapping of electrons in a molecule. Their description is the Schrödinger equation, together with the Born-Oppenheimer approximation, which separates kernels from the electrons. An N-dimensional molecule has 3N-6 internal degrees of freedom of the atoms. One can calculate to any constellation $(x_1, x_2, ..., x_{3N-6})$ the potential energy, as well as derivatives, for example, the second ones for comparison with spectroscopy. However, for medium or larger molecules one cannot calculate a net of raster-points in all dimensions, to get a 'full' potential energy surface (PES).

What one can do is the definition of a one-dimensional curve in the (3N-6)-dimensional configuration space of the molecule

$$\mathbf{x}(s) = (x_1(s), x_2(s), ..., x_{3N-6}(s))$$

and calculation of the PES profile over this curve, in a (3N-6)+1 dimensional space. If this curve, or 'path' is more or less inside a valley of the PES then we name it $\boxed{\text{Reaction Coordinate}}$.

# Definition of a Reaction Pathway

## Reaction path (RP)

- Is a monotone way between Minimum and Transition State
- It looks nice if going through a valley of the PES
- It would be nice if indicating bifurcations of the valley

A synonyme for RP would be Minimum Energy Path.
From the point of view of practical calculations, it would also be helpful if we could calculate the RP beginning at the minimum.

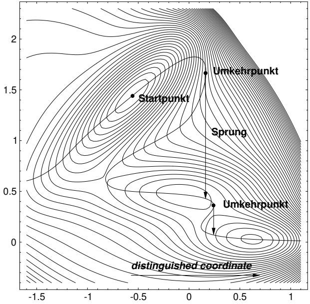
## Examples

- Steepest descent from SP, IRC: no start in Min
- Gradient Extremal $H\,g = \lambda g$ : avoided crossing
- Newton Trajectory

Note: none of the examples fulfills all properties, in all cases.
Thus, we can treat different RP-examples on an equal footing.

# Definition of Newton Trajectory

- W. Quapp M. Hirsch O. Imig D. Heidrich, J Comput Chem **19** 1998, 1087-1100, "Searching for Saddle Points of Potential Energy Surfaces by Following a Reduced Gradient"
- W. Quapp M. Hirsch D. Heidrich, Theor Chem Acc **100** (1998) No 5/6, 285-299 "Following the streambed reaction on potential-energy surfaces: a new robust method"



- Chose a Search Direction $\mathbf{r}$
- Build the Projector Matrix $\mathbf{P}_r = \mathbf{I} - \mathbf{r}\,\mathbf{r}^T$ . It is $\mathbf{P}_r\,\mathbf{r} = \mathbf{0}$.
- Search the Curve $\mathbf{P}_r\,\mathbf{g} = \mathbf{0}$. It is the Newton Trajectory.

# Forces and NTs – linear approach

If a linear force is applied to a molecule then the simplest approach for the potential energy is

$$V_f(\mathbf{x}) = V(\mathbf{x}) \ - F\,\mathbf{f}^T\,\mathbf{x}$$

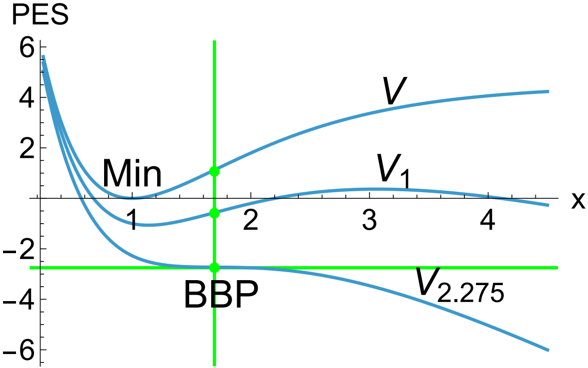
where **f** is the force direction and $F$ its amount. $\mathbf{f}^T\,\mathbf{x}$ is the scalar product of the force and the current coordinate point.
Stationary points of $V_f$ move along the conditions $\frac{\partial V_f}{\partial x_i} = 0$

$$\mathbf{g}(\mathbf{x}) \,||\, \mathbf{f}\ .$$

The curve which describes these force moved stationary points is a Newton trajectory. The search direction **r** of the NT is now the force **f**.

- W.Quapp,J.M.Bofill,J.Ribas-Arino: Int.J.Quant.Chem.118 (2018)e25775 "Towards a Theory of Mechanochemistry – Simple Models from the Early Beginnings"

Usually, an application of a force leads to a decreasing barrier of a reaction. This is the aim: gain of energy for a reaction, or change the direction of a reaction. Action of a force on a 1D Morse pot.

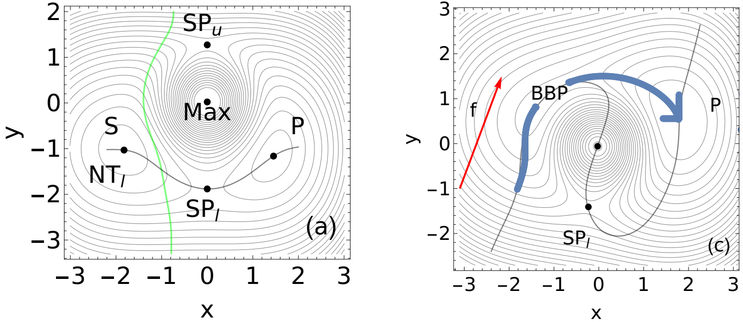


$$V_F = V - F\,x$$

W.Quapp, J.M.Bofill, TCA 135 (2016) 113

BBP means barrier breakdown point, or bond breaking point, where the former PES barrier disappears. It is the aim of many experiments to reach this point. Note: $V_{F\,xx} = 0$ there.

# Change of Reaction Path



(a) The PES has two very different SPs. Left is the ground state, green: BBP line, black: reaction path.
(c) An external excitation in direction of the red arrow changes the reaction channel. The former lower $SP_l$ and the Maximum move together; the former upper $SP_u$ disappears, black: NT to f.

- W.Quapp: J.Math.Chem. 56 (2018) 1339-1347

  A Minimal 2D Model of the Free Energy Surface for a Unidirectional Natural Molecular Motor

# Catch bonds

Mechanical forces play important roles in biology. Biological systems have evolved to address a diverse range of mechanical challenges, including materials with exceptional strength and toughness as well as those that strengthen under load. Mechanochemical reactions enable biological systems to sense mechanical signals and to adapt to changes in their mechanical environment (mechanosensing and mechanotransduction). Key players in these processes are proteins that respond to tensile, compressive or shear forces by undergoing specific conformational changes. They can form catch bonds (bonds that strengthen under load), expose cryptic binding or catalytic sites, or become susceptible to cleavage. These mechanisms are mimicked in synthetic systems and mechanically activated catalysts.
Citation: Moving mechanochemistry forward, J.Batteas et al., RSCMechanochem (2025)

# Catch bonds

Proteins demonstrate a colourful array of multi-phasic bonds, including biphasic catch-slip and triphasic slip-ideal-slip or slip-catch-slip bonds.

An examples is the T-cell receptor, a specificity between agonists and antagonists is enhanced 4-fold when tension is applied, a next example is cell polarization during migration which is determined by direction-dependent tension between vinculin and actin, a next is bacterium E. coli which avoids being flushed out by the high shear stress of urinal tracts while retaining mobility under low shear stress. Cadherins and downstream mechanotransduction proteins such as catenins require catch behaviour to regulate cell-cell communication and maintain tissue integrity.

Overall, catch bonds play a pivotal role in cell adhesion, motility, mechanosensing, communication, and organization across a wide spectrum of biological contexts.

Citation: Engineering tunable catch bonds with DNA, M.Yang et al., Nature Communications (2024) 15:8828

# Catch bonds

## Catch bonds

Note that all covalent and H-bonds are slip bonds individuelly. They break faster under stress. So, for catch bond search, only combinations of bonds make sense.

- W. Quapp, J.M.Bofill: J. Phys. Chem. B 128, 17, 4097-4110 (2024)

  "Theory and examples of catch bonds"
- W.Quapp, J.M.Bofill, K.C.Dansuk, S.Keten: J.Math.Chem 2025

  "To a mechanical model of synthetic catch-bonds"

Example: T cell receptor (TCR) interaction

$V_f(L,d) = V(\theta(L)) + B(d,\theta(L)) - F(L+d)$

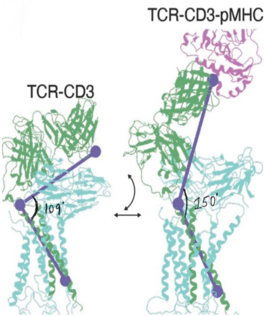
V is a harmonic potential, $\theta$ an angle,

L and d are distances,

B is product of harmonic and Morse pot,

the last term makes a NT to direction (1,1),

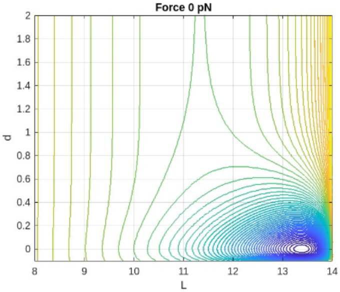
F is the amount of the force.

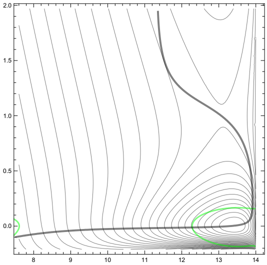


F.J.van Eerden et al. eLife 12 (2023)

# PES T cell receptor

Force 10 pN



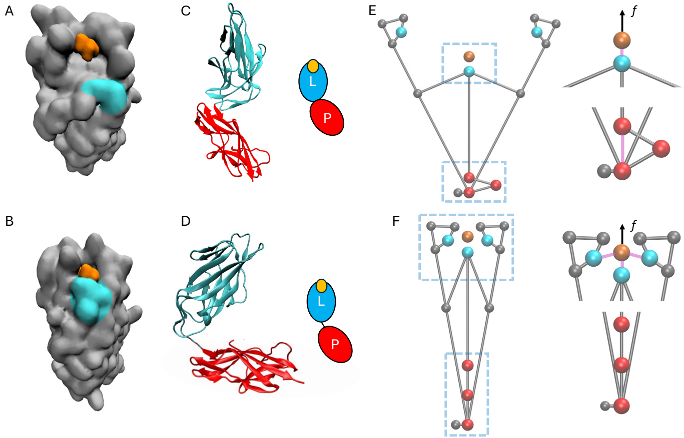


We obtain a PES where the direction (1,1) of the external force points into the ‘mountains’ of the PES. The corresponding NT describes the movement of the minimum and the SP together. However, the hight of the SP increases for moderate forces, in comparison to the MEP in this ‘one-state-model’.

Right is shown the NT to this direction for case F=10. The SP has moved along the NT. It is higher: catch bond character.

A biological example is endothelia-selectin (E-selectin).

# Further Example: Tweezer - mechanical model



(A) Lectin domain of FimH: the mannose ligand (orange) is bound to the ligand binding site in both the open and the closed conformations.

(B) During the transition of FimH from its open to the closed conformation, the clamp loop segment (highlighted in cyan) closes on the ligand forming new interactions.

## PES tweezer: geometry

The maximum length of hmax = 22.5. The model starts from the angle of the tweezers

$$\theta(h) = arcsin[\frac{168.75 + h^2}{30h}]\ .$$

Distances (xs,ys) of the tweezer arm from the orange part are

$$xs(h) = 22.5 cos\theta - 2 cos(1.997 - \theta)$$

and

$$ys(h) = 22.5 sin\theta + 2 sin(1.997 - \theta)\ .$$

The distance of the orange atom from the tweezers is

$$\sigma(h, y) = \sqrt{(y + h - ys(h))^2 + xs(h)^2}\ .$$

**PES tweezer: force potentials** We use three potentials for $y$, $h$ and $\sigma$ with

$$pot_1(y) = D_1(1 + Exp[-2\alpha_1(y - \sigma_1)) - 2Exp[-\alpha_1(y - \sigma_1)])$$

$$pot_2(\sigma) = D_2(Exp[-2\alpha_2(\sigma - \sigma_2)] - 2Exp[-\alpha_2(\sigma - \sigma_2)])$$

where $\sigma(h, y)$ is a distance to the side arms, and

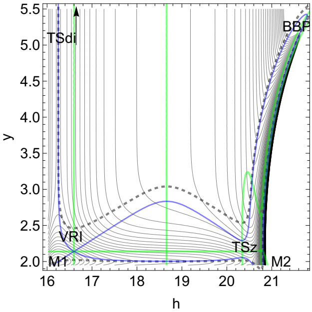
$$pot_3(h) = (1-\frac{h}{10})^{20}+D_3(1+Exp[-2\alpha_3(h-\sigma_3)]-2Exp[-\alpha_3(h-\sigma_3)])$$

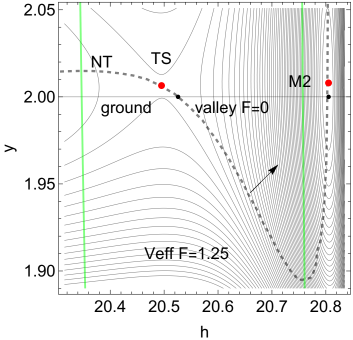
With corresponding parameters adapted to the FimH we get the PES

$$V(h, y) = pot_1(y) + pot_3(h) + 2pot_2(\sigma(h, y)) \ .$$

A sum of different potentials of the molecule is better to accept than a product, like in the former case.

# PES tweezer





↗ (1,1)

Left: PES of the tweezers. Variables are *y* of the orange particle, and *h* of the tweezers length. M1 is the minimum of the open, M2 of the closed form. The two-state model is necessary to explain the catch-slip behaviour of FimH/mannose.
The NT to direction (1,1) is dashed.
Right: effective PES under the force 1.25 units. The barrier M2-TSz becomes higher; forming the catch bond character.

There is no general theory for the existence of a catch bond on a PES. The examples are found by trial and error. Currently we collect further examples to become capable to develop such a theory.

Further references:

- W.E.Thomas et al., Catch-bond model derived from allostery explains force-activated bacterial adhesion. Biophys.J.90, 753 (2006)
- W.E.Thomas, V.Vogel, E.Sokurenko, Biophysics of catch bonds Annu. Rev. Biophys. 37, no.1, 399, 2008
- S.S.M.Konda et al., Molecular catch bonds and the anti-hammond effect in polymer mechanochemistry JACS 135, no. 34, 12722 (2013)
- Y.Suzuki, O.K.Dudko, Biomolecules under mechanical stress: a simple mechanism of complex behavior J. Chem. Phys. 134, no.6, 065102 (2011)
- C.O.Barkan, R.F.Bruinsma, Catch-slip bonding, pathway switching, and singularities in the flow of molecular deformation Phys. Rev. Res. 5, no. 2, 023161 (2023)

# Summary: How to find a RP, If You Must

## Properties of NTs

- Describe the RP by (some) Newton Trajectories:
  it is tractable – in many practical cases.
- Find TS by Newton Trajectories: it is tractable.
- Find a special Newton Trajectory which describes a catch-bond: it is tractable.

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- I thank my collegues over many years
  Prof.Dr.D.Heidrich from Theoretical Chemistry, Leipzig
  Dr.M.Hirsch from Mathematics, Leipzig (now London)
  Prof.Dr.J.M.Bofill from Barcelona

  A row of results (which are presented here)
  are born in discussions with them.

# Appendix: Some References to Newton Trajectories

| | |
|---|---|
| W.Quapp, M.Hirsch, O.Imig, D.Heidrich, J.Computat.Chem.19 (1998) 1087 | (Definition of NTs in chemistry) |
| W.Quapp, M.Hirsch, D.Heidrich, Theor.Chem.Acc.100 (1998) 285 | (Bifurcation of NTs) |
| M.Hirsch, W.Quapp, D.Heidrich, Phys.Chem.Chem.Phys.1 (1999) 5291-9 | (VRI points of water) |
| W.Quapp, M.Hirsch, D.Heidrich, Theoret.Chem.Acc.105 (2000) 145-155 | (Streambed Reactions) |
| W.Quapp, V.Melnikov, PCCP 3 (2001) 2735- 41 | (VRI points, PES of H2S, H2Se, H2CO) |
| J.M.Anglada,E.Besalu,J.M.Bofill,R.Crehuet, J.Comp.Chem.22 (2001) 387 | (Reaction path on reduced PES) |
| J.M.Bofill, J.M.Anglada, Theor.Chem.Acc.105 (2001) 463 | (TSs on reduced PES) |
| R.Crehuet, J.M.Bofill, J.M.Anglada, Theor.Chem.Acc.107 (2002) 130 | (Reduced-gradient-following path) |
| W.Quapp, J.Theor.Comput.Chem. 2, No 3, (2003) 385-417 | (Review to NTs) |
| M.Hirsch, W.Quapp, J.Math.Chem.36 (2004) 307-340 | (Convexity of the PES and NTs) |
| M.Hirsch, W.Quapp, Chem.Phys.Lett.395 (2004) 150-156 | (Reaction Pathway as Curve with Induced Tangent) |
| W.Quapp, J.Computat.Chem.25 (2004) 1277 | (Projection Operators) |
| M.Hirsch, W.Quapp, J.Mol.Struct.THEOCHEM 683 (2004) 1-13 | (Reaction Channels by NTs) |
| W.Quapp, J.Mol.Struct.695-696 (2004) 95-101 | (Reaction Path Branching) |
| W.Quapp, J.Chem.Phys.122 (2005) 174106 | (Growing string method for NTs) |
| W.Quapp, J.Computat.Chem.28 (2007) 1834 | (Growing string method for NTs) |
| W.Quapp, E.Kraka, D.Cremer, J.Phys.Chem.A 111 (2007) 11287 | (TS of quasi barrier-less reactions by NTs) |
| H.Joo, E.Kraka, W.Quapp, D.Cremer, Mol.Phys.105 (2007) 2697 | (Hidden Transition States) |
| W.Quapp, J.Theoret.Computat.Chem.8 (2009) 101 | (Growing string method for NTs) |
| J.M.Bofill, J.Chem.Phys.130 (2009) 176102 | (The reduced gradient following path) |
| W.Quapp, B.Schmidt, Theoret. Chem. Acc. 128 (2011) 47-61 | (Unsymmetric Valley-Ridge Inflection Points) |
| J.M.Bofill, W.Quapp: J. Chem. Phys. 134 (2011) 074101 | (Variational Nature of NTs) |
| W.Quapp, J.M.Bofill, J. Aguilar-Mogas, Theor.Chem.Acc.129 (2011) 803-821 | (Cyclopropyl Ring Opening) |
| W.Quapp, J.M.Bofill, J. Math. Chem. 50 (2012) 2061-2085 | (Valley-Ridge Inflection Points by NTs) |
| W.Quapp, J.M.Bofill, M.Caballero, Chem. Phys. Lett. 541 (2012) 122-127 | (Conical Intersection points by NTs) |
| B.Schmidt, W.Quapp, Theoret. Chem. Acc. 132 (2012) 1305-1313 | (Nonsymmetric VRI Points) |
| W.Quapp, J.M.Bofill, Int.J.Quant.Chem. 115 (2015) 1635-1649 | (SPs of Index two) |
| W.Quapp, J. Math. Chem 54 No.1 (2015) 137-148 | (Branching for more than 2D PES) |
| W.Quapp, J. Chem. Phys. 143 (2015) 177101 | (Bifurcation of reaction pathways by NTs) |
| W.Quapp, J.M.Bofill, J. Phys. Chem. B 120 (2016) 2644-2645 | (NTs for Mechanochemical Transformations) |
| W.Quapp, J.M.Bofill, Theoret. Chem. Acc. 135 (2016) 113-132 | (Mechanochemical Pathways by NTs) |
| W.Quapp, J.M.Bofill, J. Computat. Chem. 37 (2016) 2467-2478 | (Catalysis and Mechanochemistry) |
| W.Quapp, J.M.Bofill, J.Ribas-Arino: J. Phys. Chem. A, 121 (2017) 2820-2838 | (Catalysis and Mechanochemistry) |
| J.M.Bofill, J.Ribas-Arino, S.P.Garcia, W.Quapp, J. Chem. Phys. 147 (2017) 152710 | (Optimal BBPs) |
| W.Quapp, J. M. Bofill, Molecular Physics 117, iss.9-12 (2019) 1541-1558 | (1D Frenkel-Kontorova chain) |

# Appendix: TCR-pMHC Catch bond PES formulae

TCR-pMHC: The PES depends on two main variables: the protein extension $L$ and the distance $d$. To simplify the expression, the extension $L(\theta)$ is used as an alternative to the hinge angle $\theta$

$$L(\theta) = 2Wsin(\theta/2)$$

and inversely

$$\theta(L) = 2arcsin(L/2W) \ .$$

The total free energy of the TCR-pMHC system, $V_f(L, d)$, combines intrinsic hinge energy, binding site interaction, and work by the external force

$$V_f(L, d) = V(\theta(L)) + B(d, \theta(L)) - F\,(L + d) \ .$$

The hinge energy, $V(\theta)$, prefers a bent conformation:

$$V(\theta) = 1/2k(\theta - \theta_0)^2$$

where $\theta_0 \approx 0.6\pi$ radians.

The ligand-binding interaction, $B(d,\theta)$, is modeled using a Morse potential:

$$B(d,\theta) = D(\theta)\,[(1 - Exp(-(d - d_0))^2 - 1]$$

Here, $D(\theta)$, represents the angle-dependent binding strength, uses a Gaussian centered at $\theta_1$:

$$D(\theta) = D_0\, Exp[-\frac{(\theta - \theta_1)^2}{2\sigma^2}]\ .$$

This model captures the allosteric communication between the hinge angle and binding site, crucial for modulating TCR-pMHC interaction strength.
It works also for different selectines, compare

- W. Quapp, J.M.Bofill: J. Phys. Chem. B 128, 17, 4097-4110 (2024) "Theory and examples of catch bonds"

However, the product of two single potential parts is somewhat strange. It is avoided in the tweezer model.