Error correction through catastrophes

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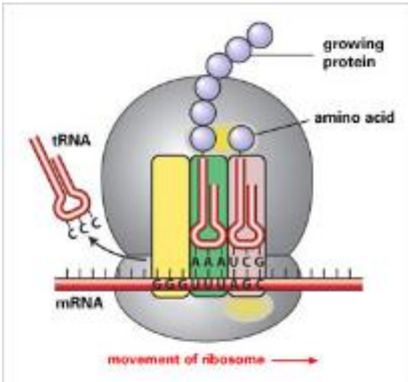
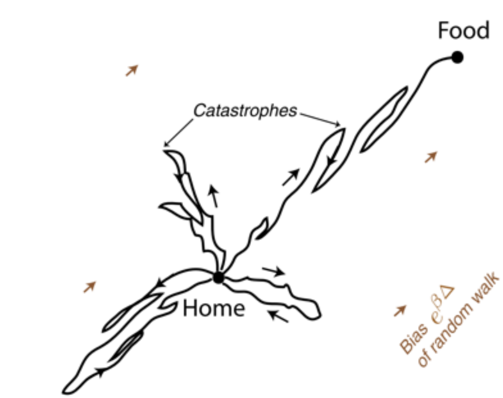
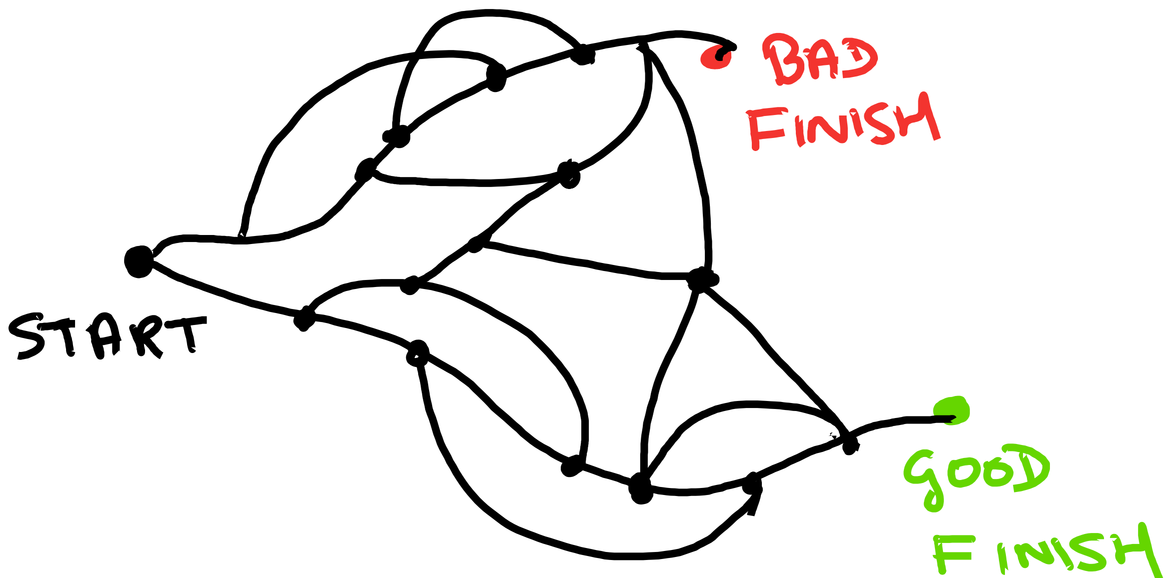
Kinetic Proofreading

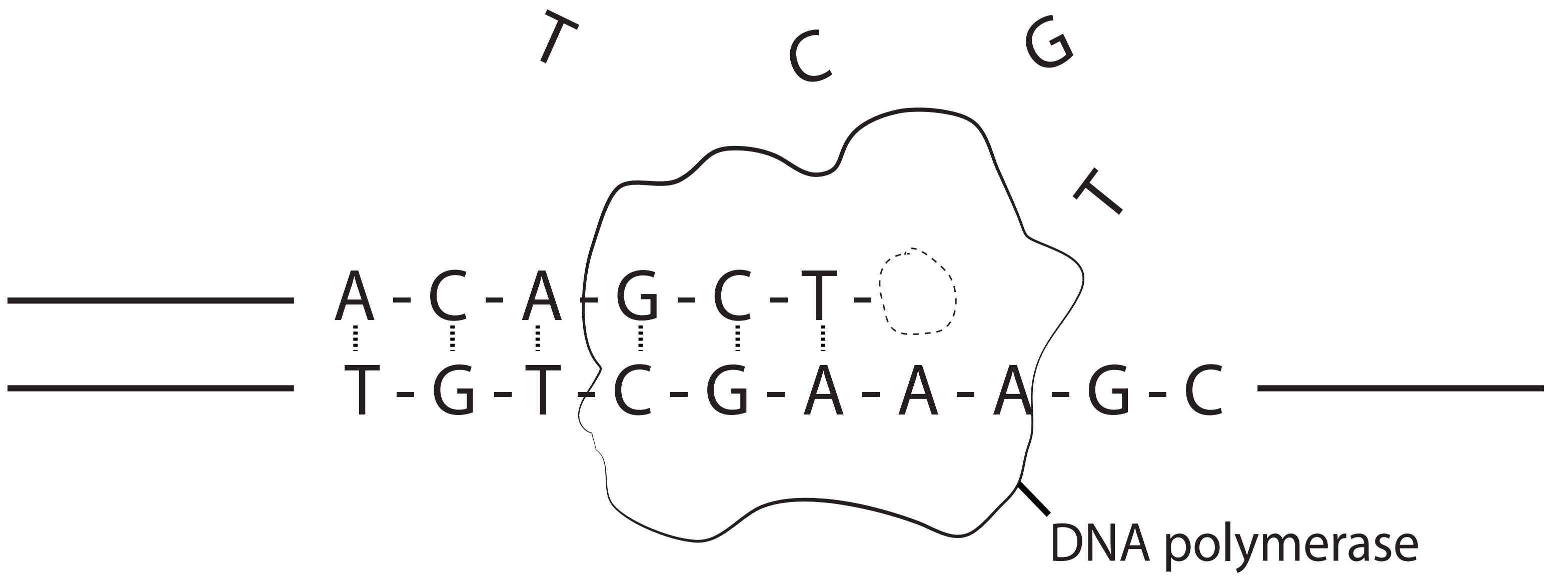


Stochastic algorithms
Search strategies





Errors in enzymatic reactions



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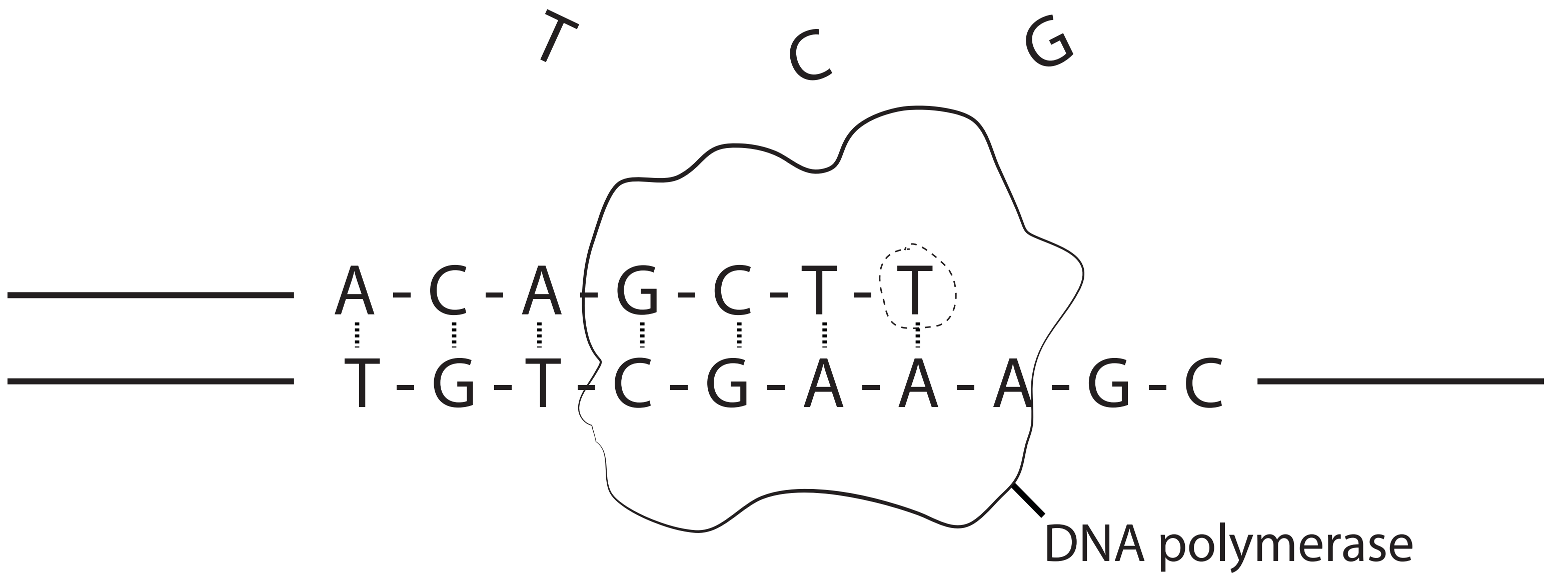
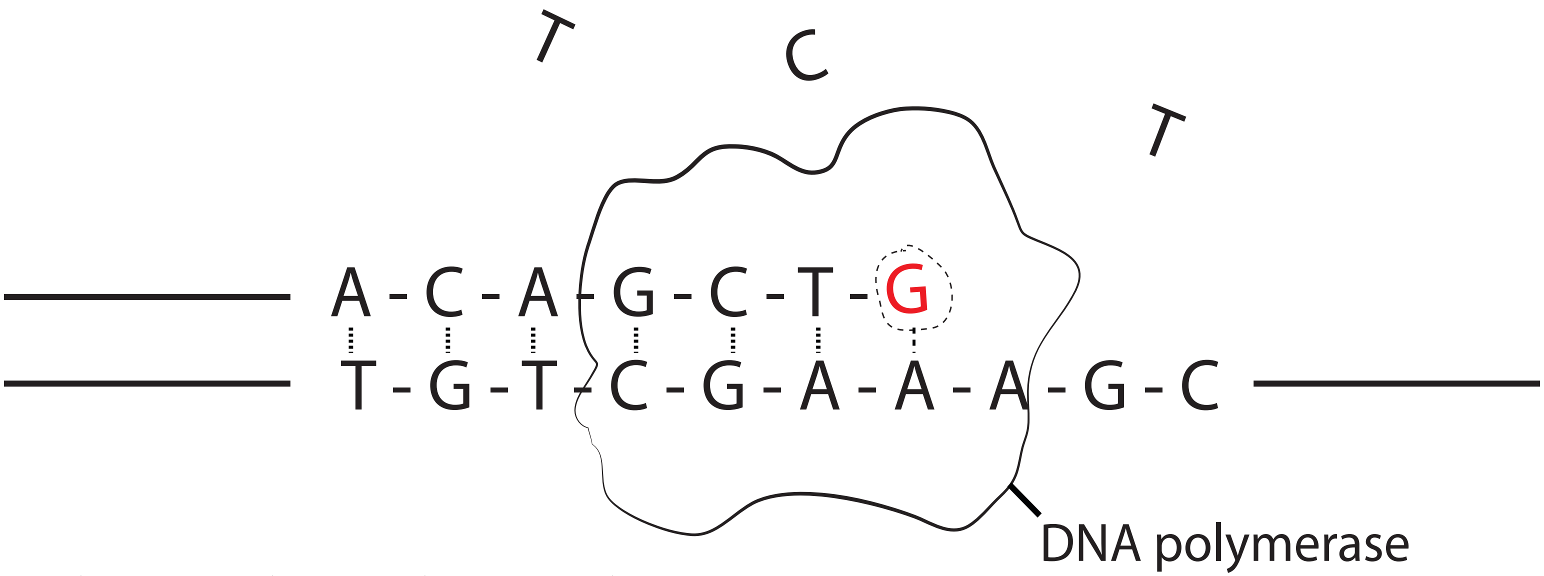
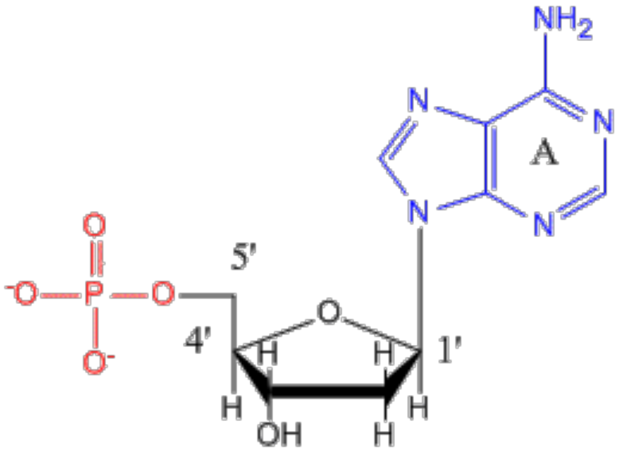


Errors in enzymatic reactions

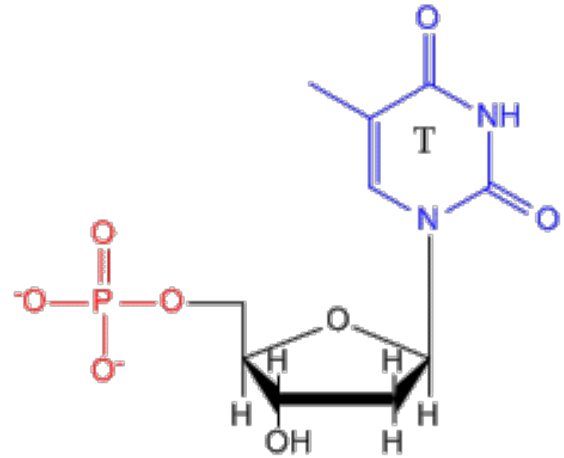


$$\mathtt{E}(A \equiv G) - \mathtt{E}(A \equiv T) = \Delta$$

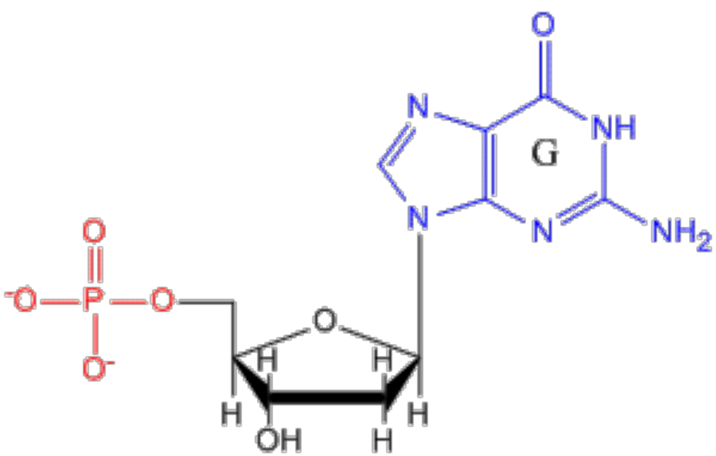
Errors in enzymatic reactions



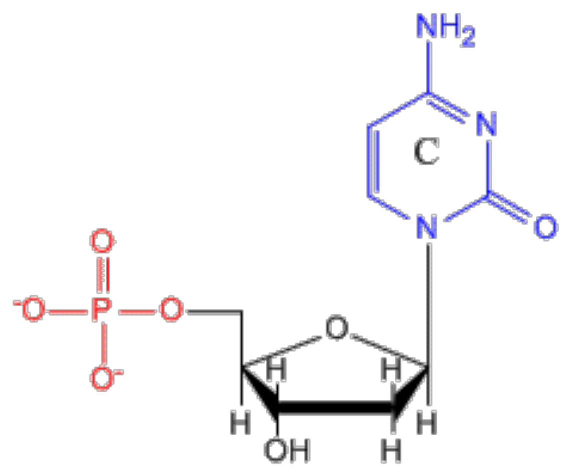
deoxyadenosine 5′-phosphate



deoxythymidine 5′-phosphate

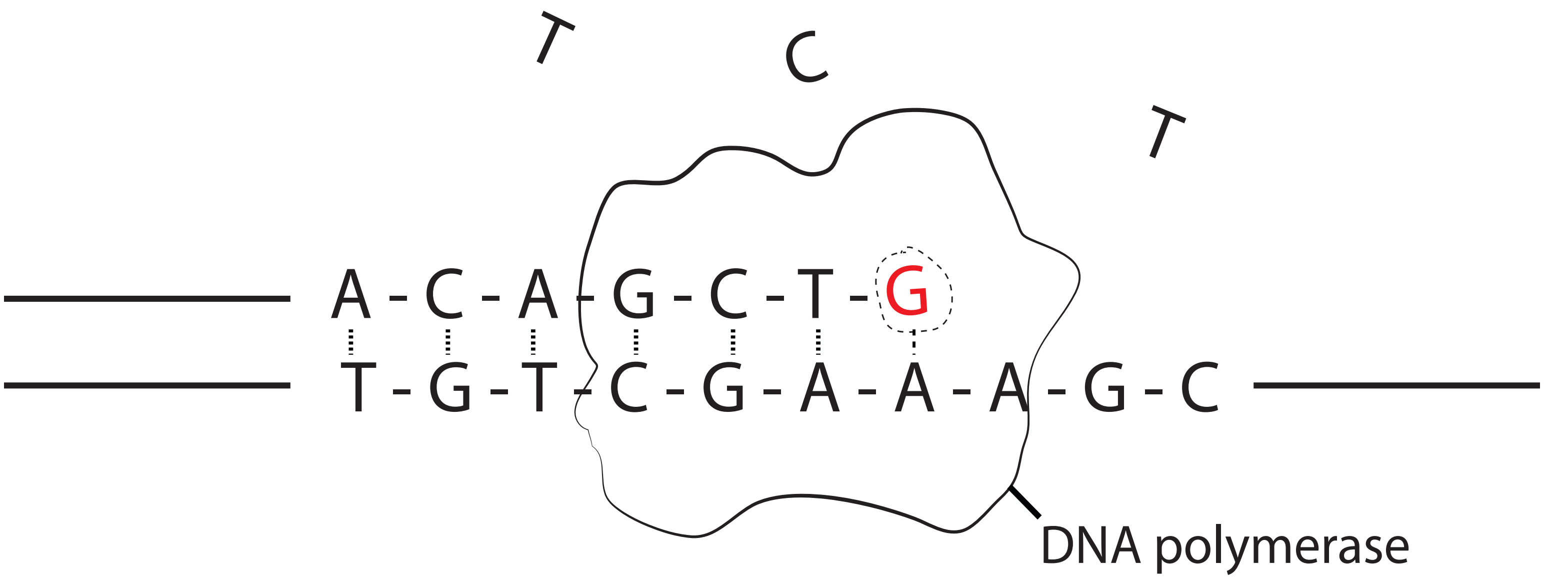


deoxyguanosine 5′-phosphate



deoxycytosine 5′-phosphate

Errors in enzymatic reactions



$$\mathrm{E}(A \equiv G) - \mathrm{E}(A \equiv T) = \Delta$$

Expected error rate $\eta \sim e^{-\Delta/kT} \sim 10^{-4}$

Actual error rate $\eta \sim 10^{-8}$

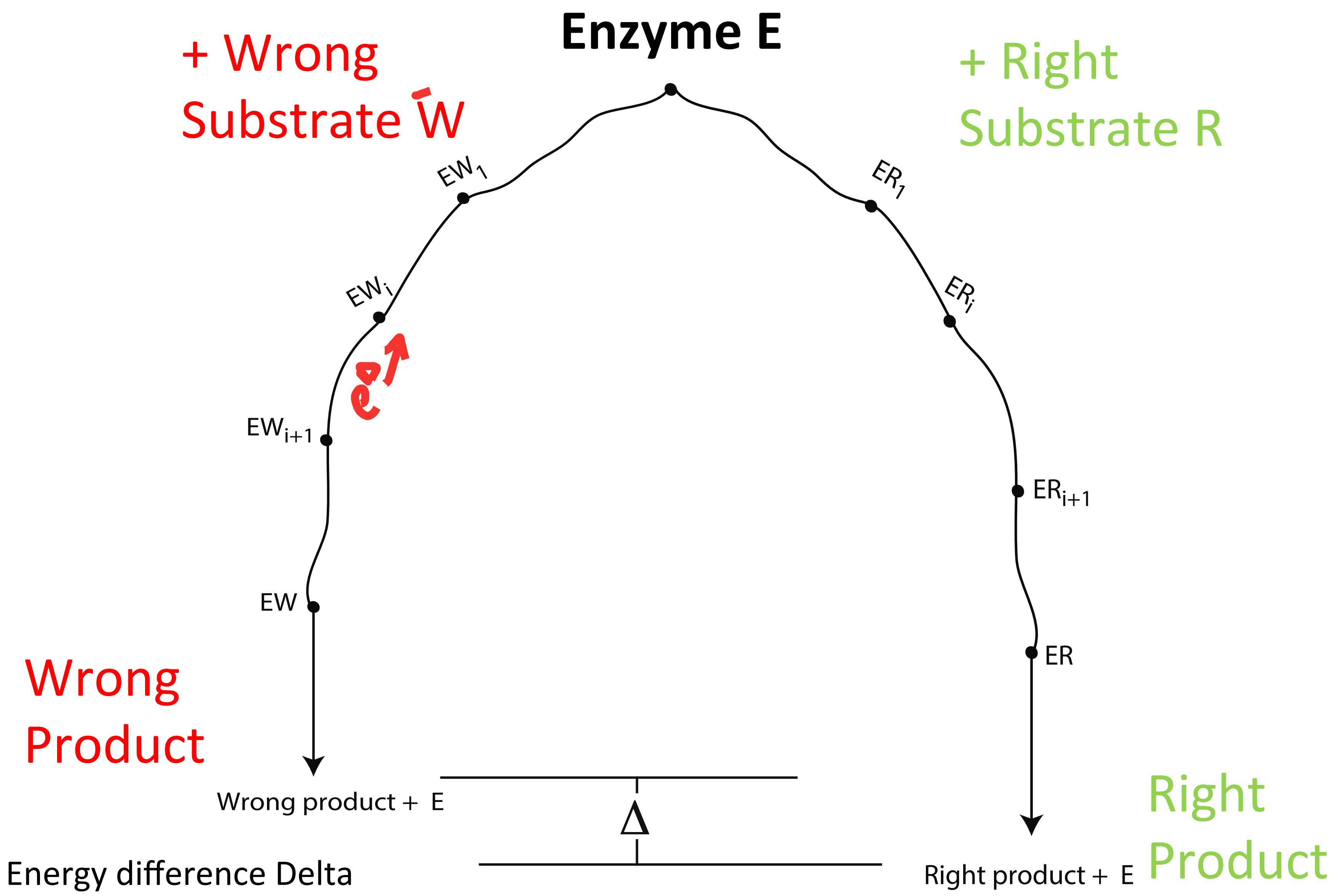
Errors in enzymatic reactions

- Protein synthesis
- tRNA charging
- T-cell receptors
- ….

How do you reduce effective error rate below $e^{-\frac{\Delta}{kT}}$
(Fixed Δ)

Kinetic Proofreading

John Hopfield (1974)
Jacques Ninio (1975)



Kinetic Proofreading

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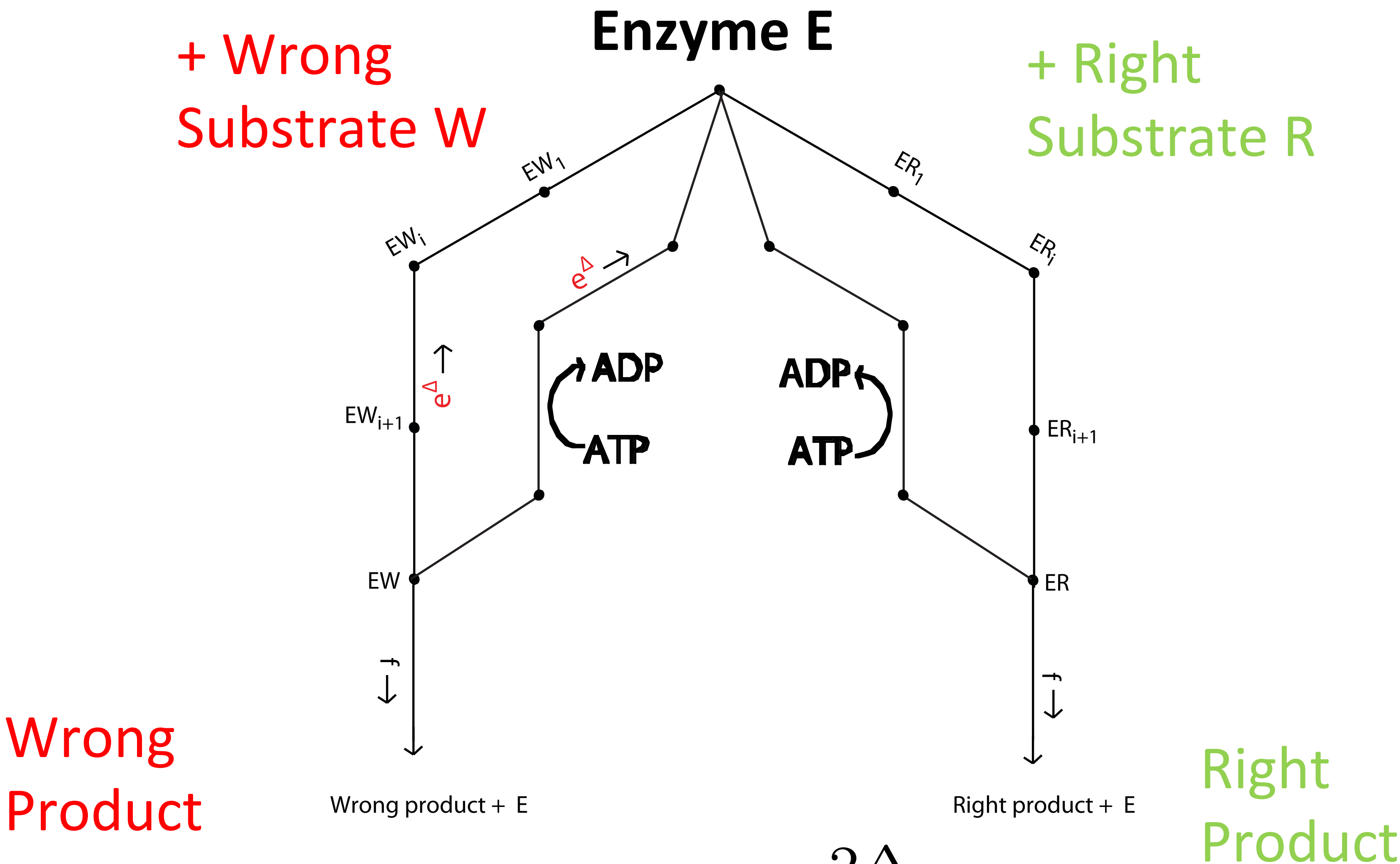
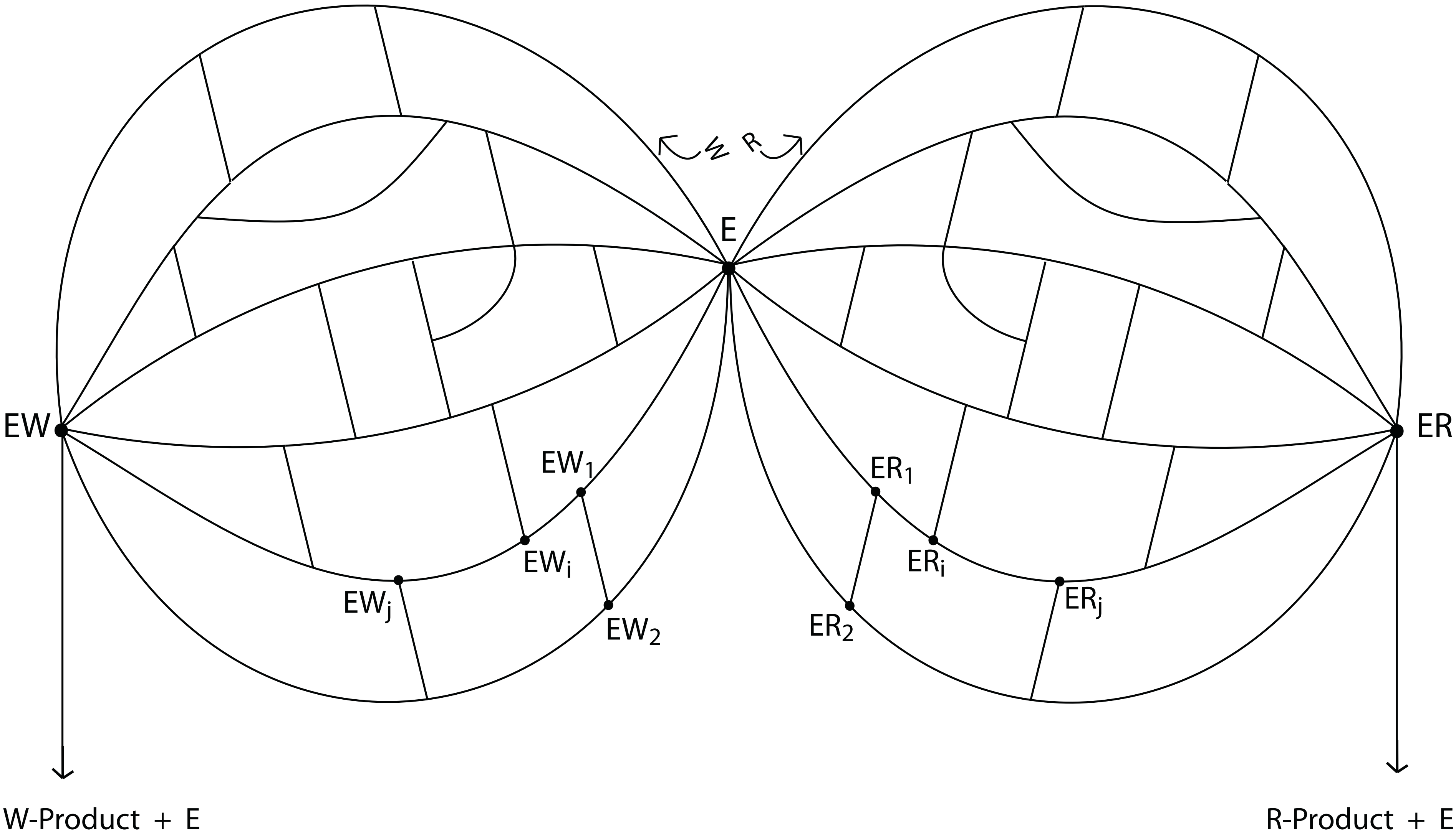


$$\eta \sim e^{-2\Delta}$$

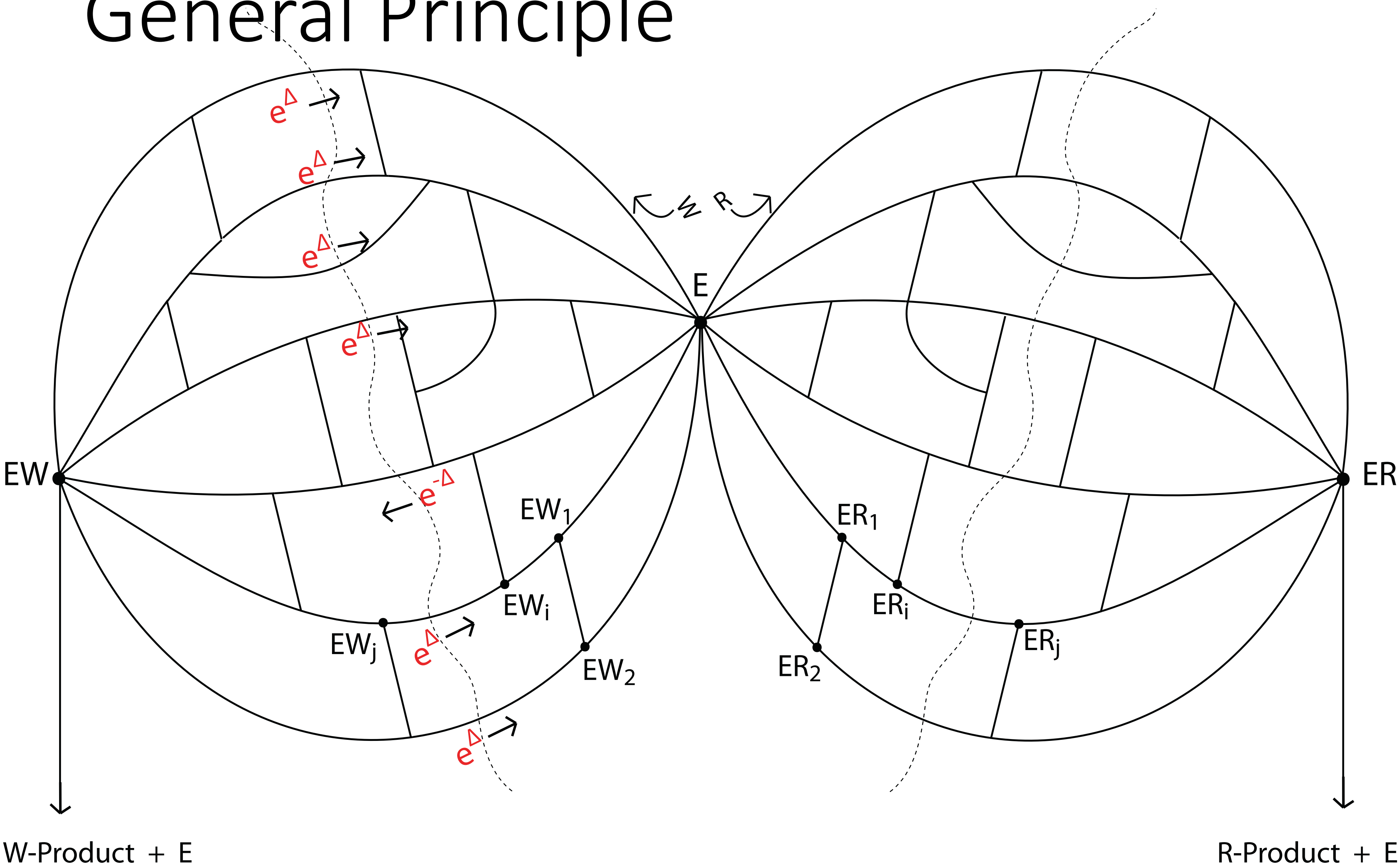
A.M, D.Huse, S.Leibler, PNAS 2012

General Principle

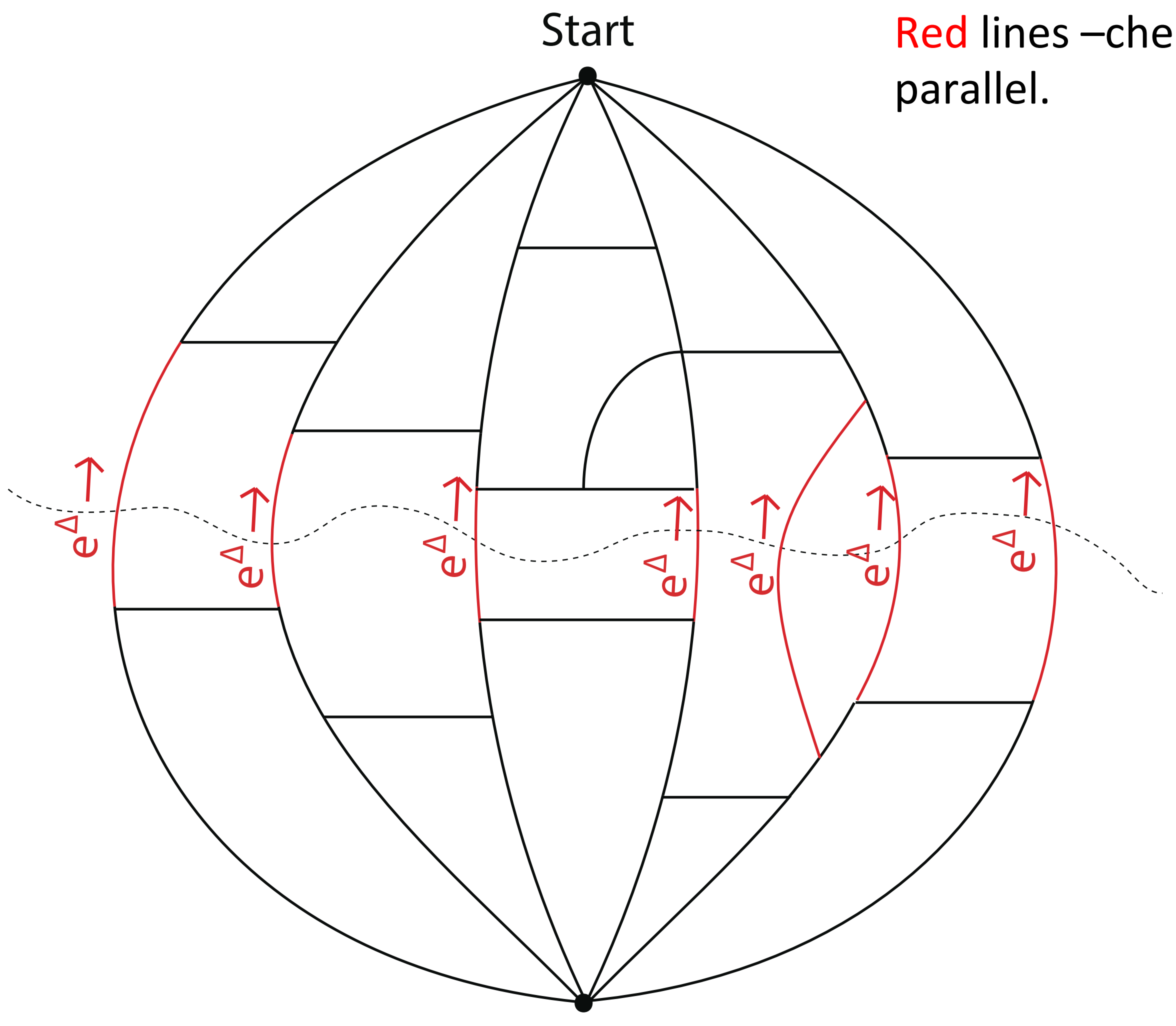


A.M, D.Huse, S.Leibler, PNAS 2012

General Principle



General network



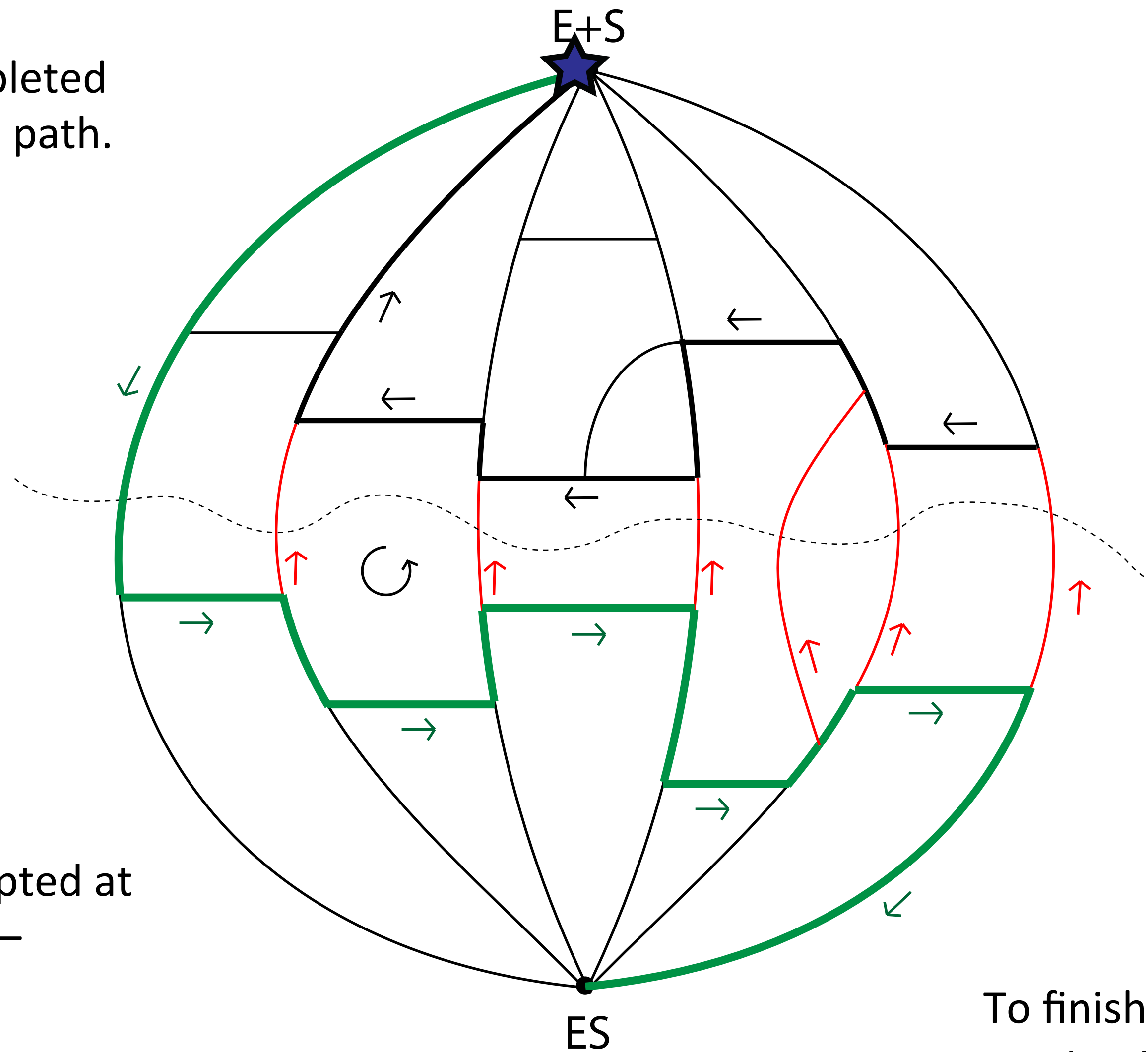
Red lines –checkpoints, in parallel.

Can n parallel paths, each with a failure rate

$$\eta \sim e^{-\Delta} \text{ be combined to give } \eta \sim e^{-n\Delta}$$

Error correcting kinetic limit

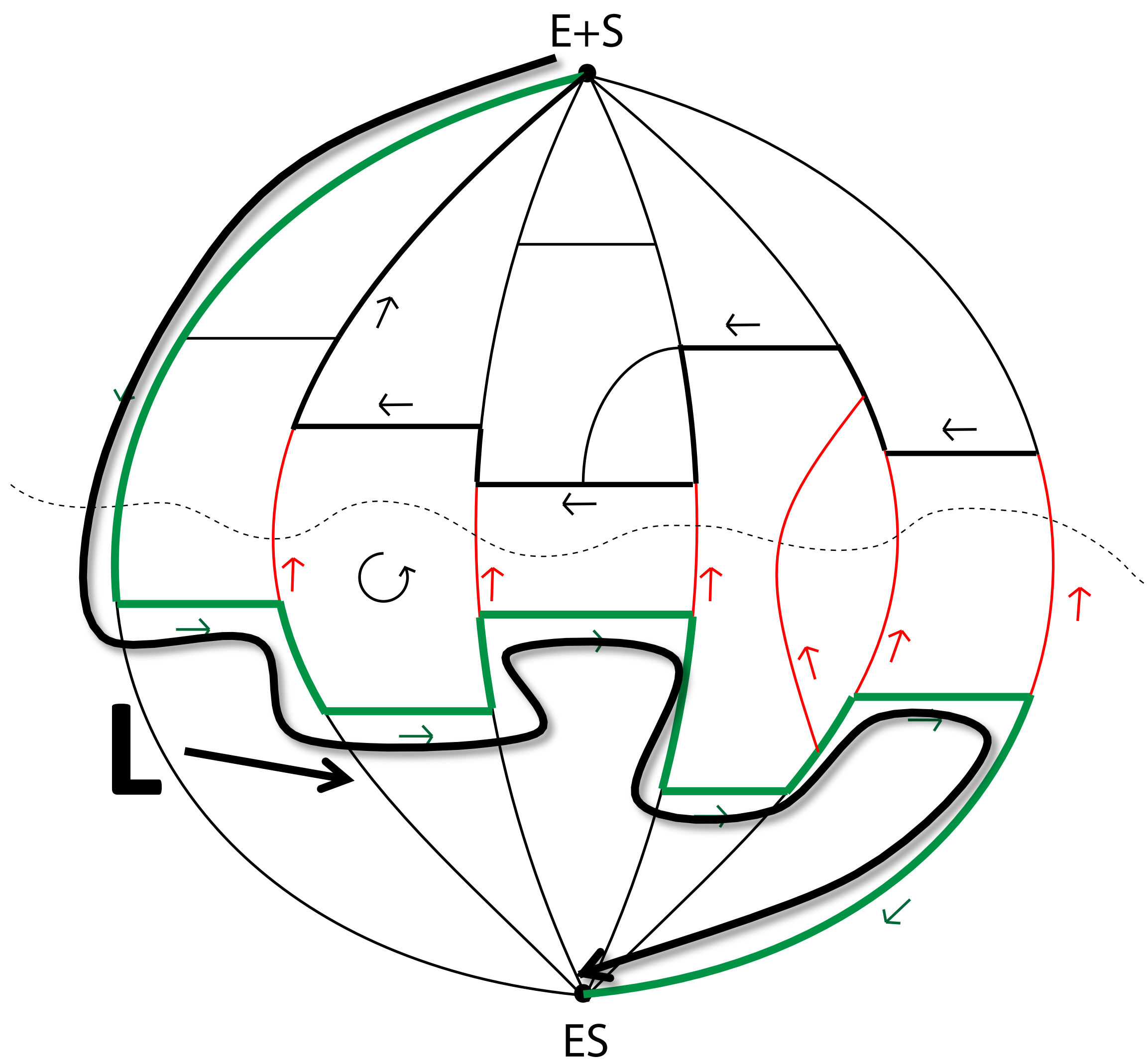
Reaction is completed only along green path.



Reaction interrupted at red checkpoints – '*catastrophe*'

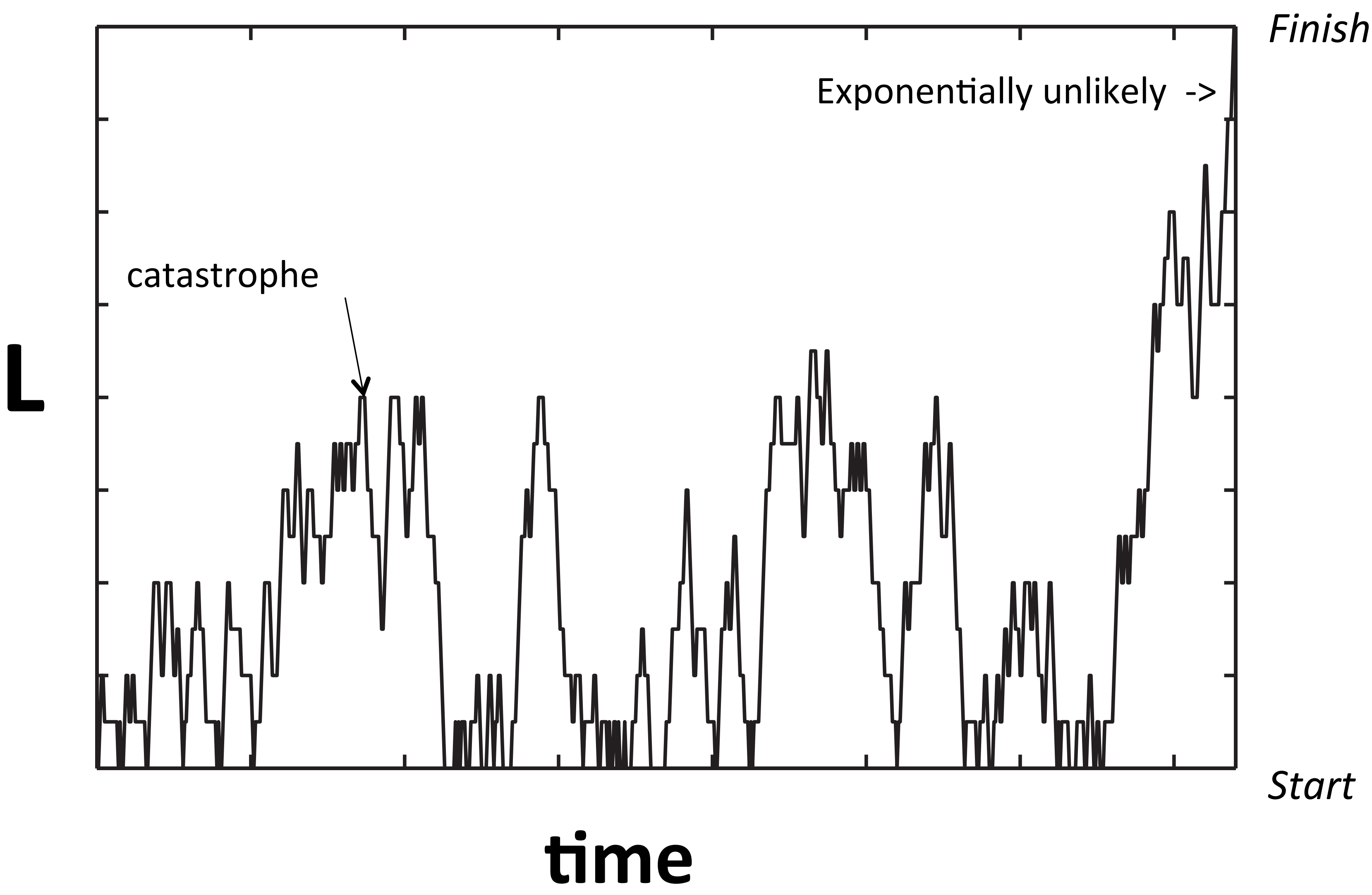
To finish:
must get past *all* red checkpoints.
Exponentially unlikely.

Error correcting kinetic limit

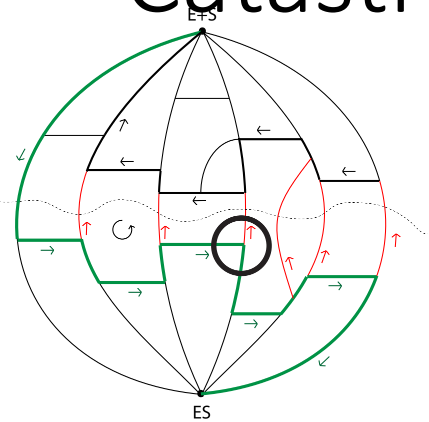


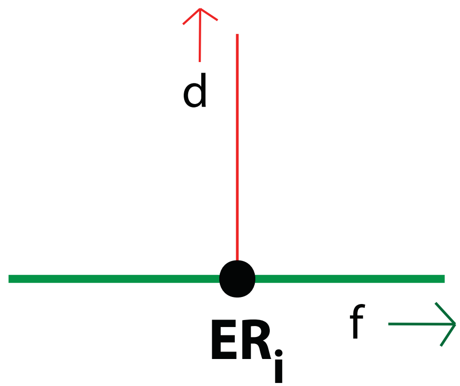
Reaction coordinate
(a measure of reaction progress)

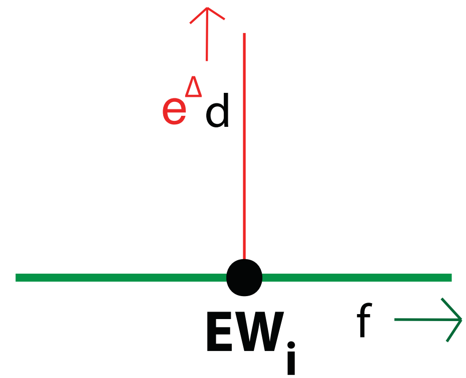
Reaction coordinate & progress



Catastrophes at checkpoints







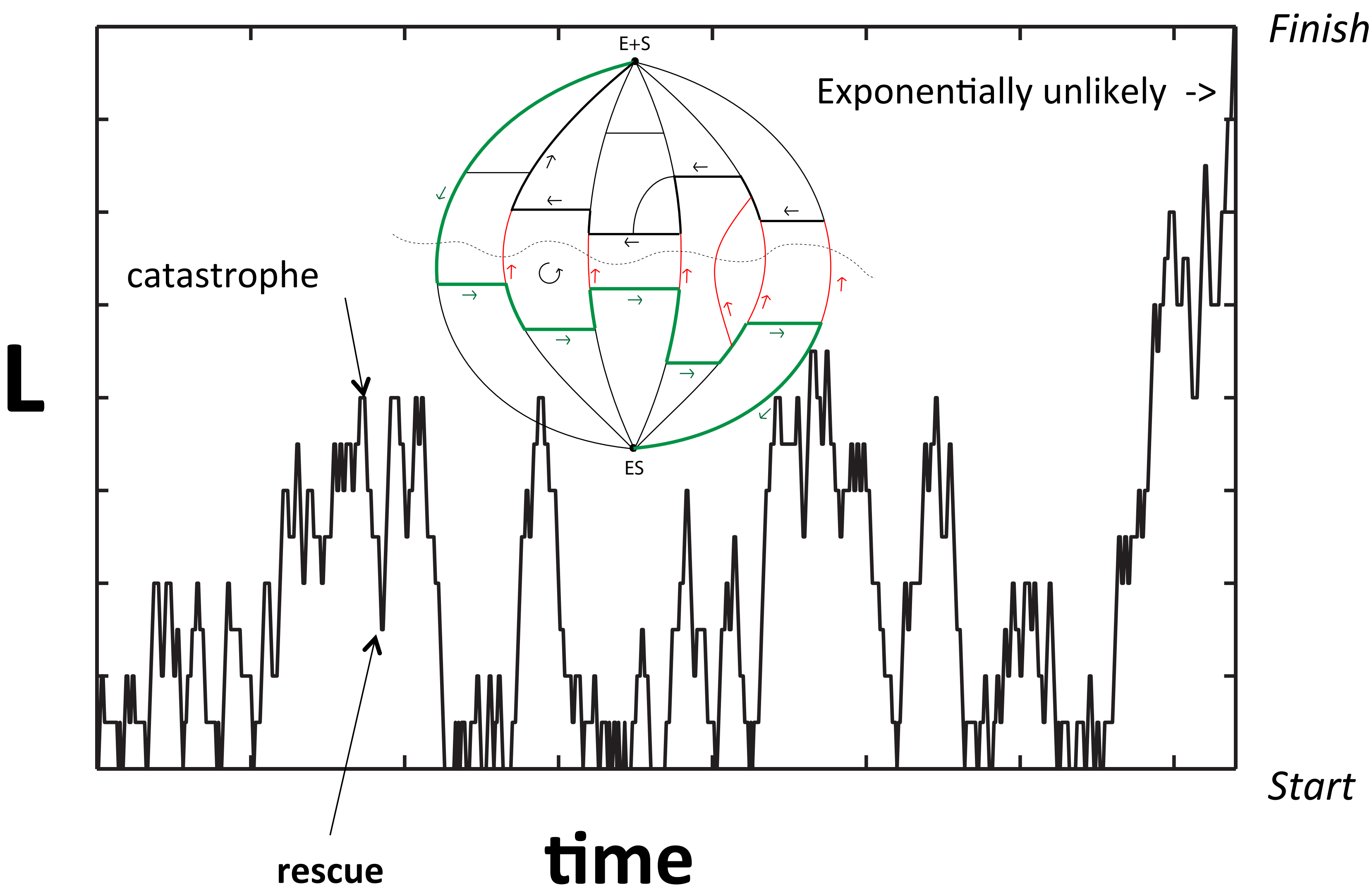
Forward $$p^R_{forw.} = \frac{f}{d+f} \quad > \quad p^W_{forw.} = \frac{f}{e^{\Delta}d+f}$$

Need $f \ll d, e^{\Delta}d$

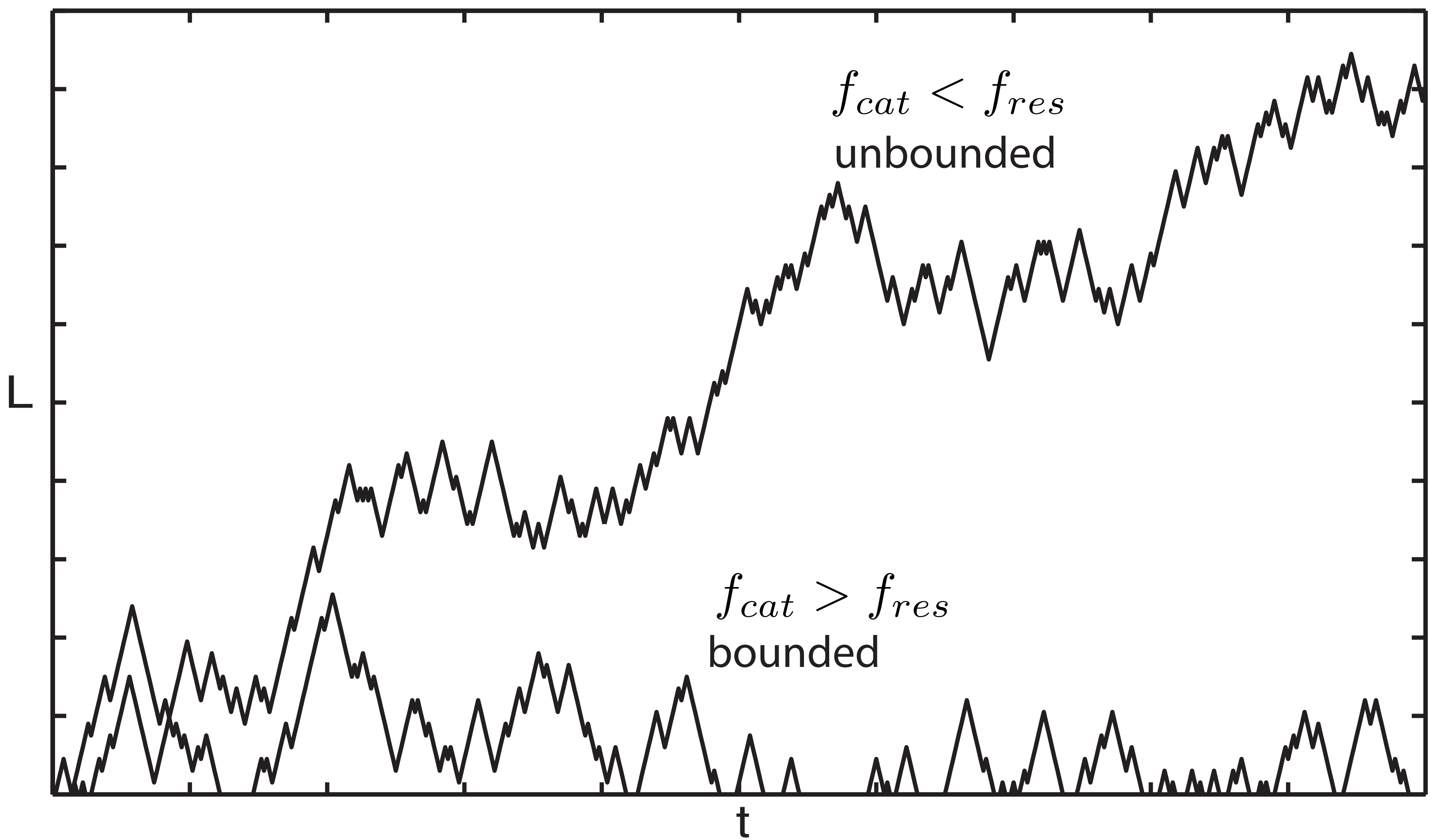
$$\eta \sim \left(\frac{p^W_{forw.}}{p^R_{forw.}}\right)^n \to e^{-n\Delta}$$

Low error rate but very slow completion rate

Catastrophes and rescues



Catastrophes and rescues

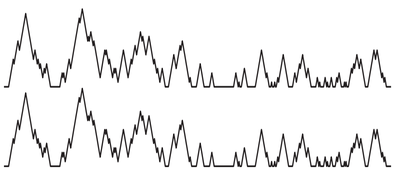


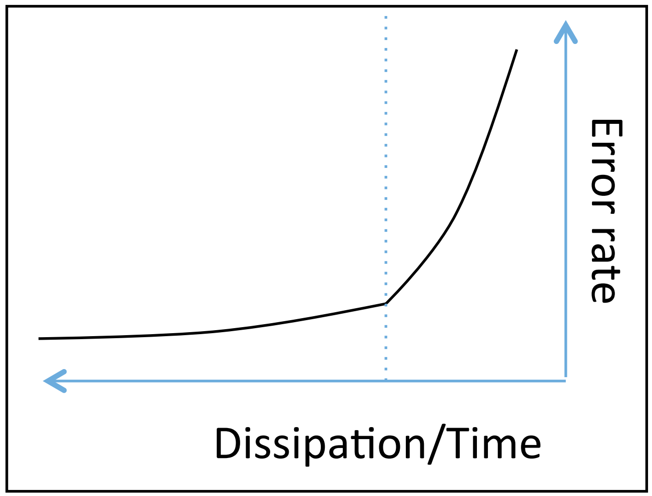
Reaction coordinate & progress

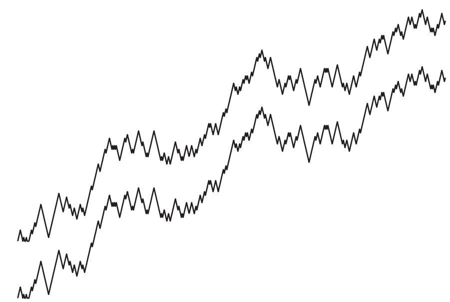
$$p_{res.} \ll p^{R}_{cat.} < p^{W}_{cat.}$$

$$p^{R}_{cat.} < p_{res.} < p^{W}_{cat.}$$

$$p^{R}_{cat.} < p^{W}_{cat.} < p_{res.}$$







$$\eta \sim e^{-n\Delta}, \quad T \sim \Lambda^{n}$$

$$\eta \sim e^{-n\Delta'}, \quad T \sim n\kappa$$

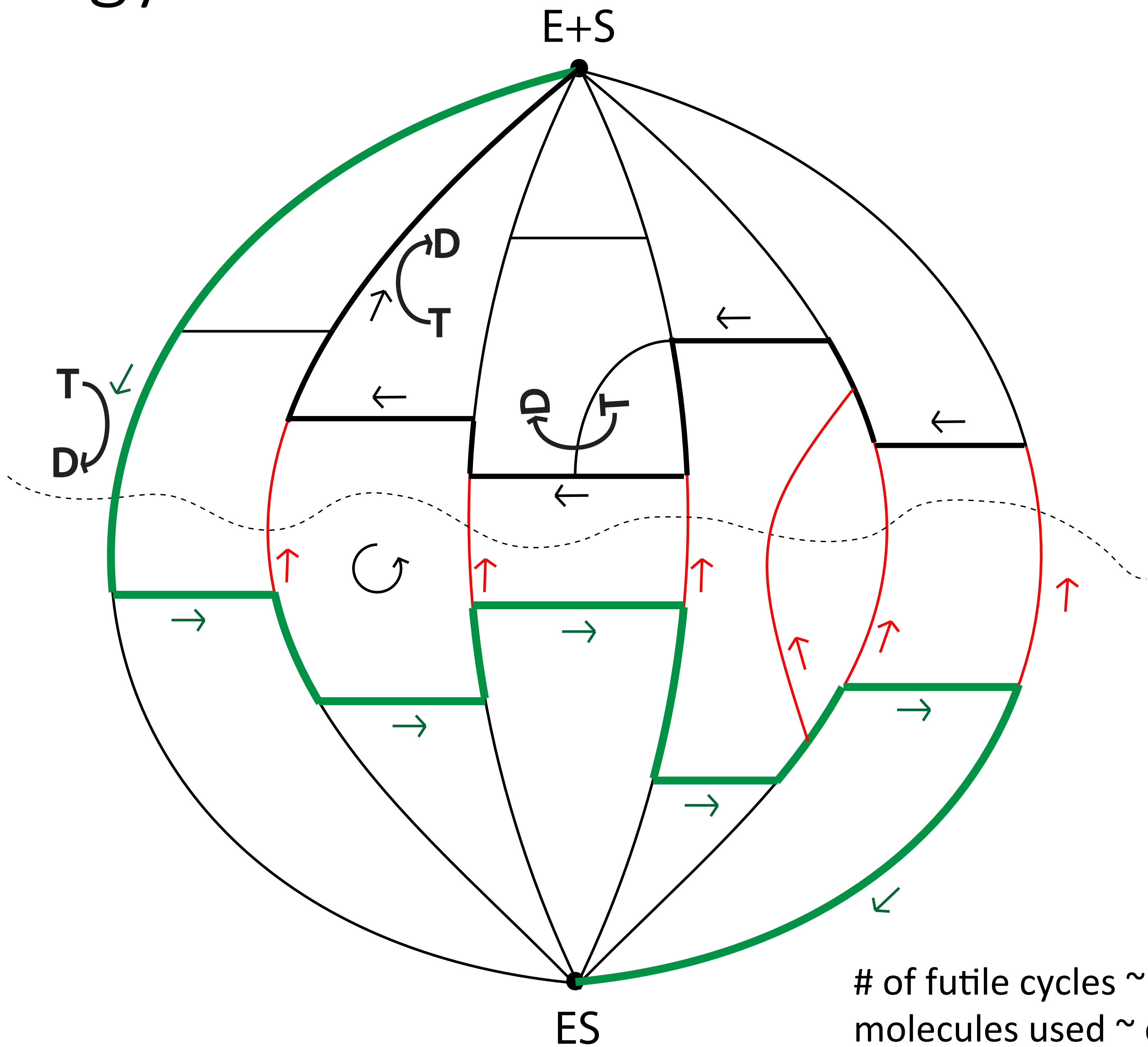
$$\eta \sim e^{-\Delta}, \quad T \sim n\gamma$$

Lowest error,
Highest time

Low error,
Low time

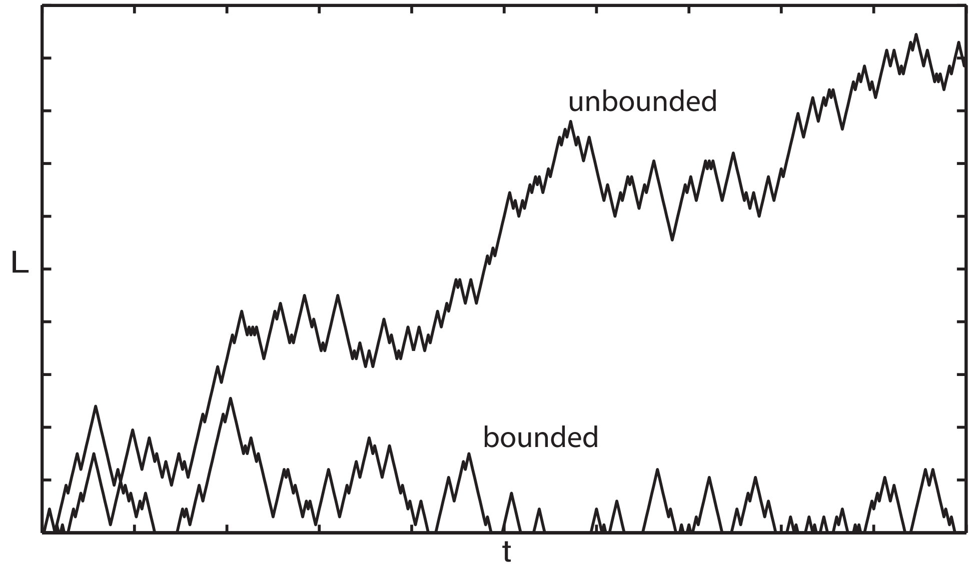
High error,
Low time

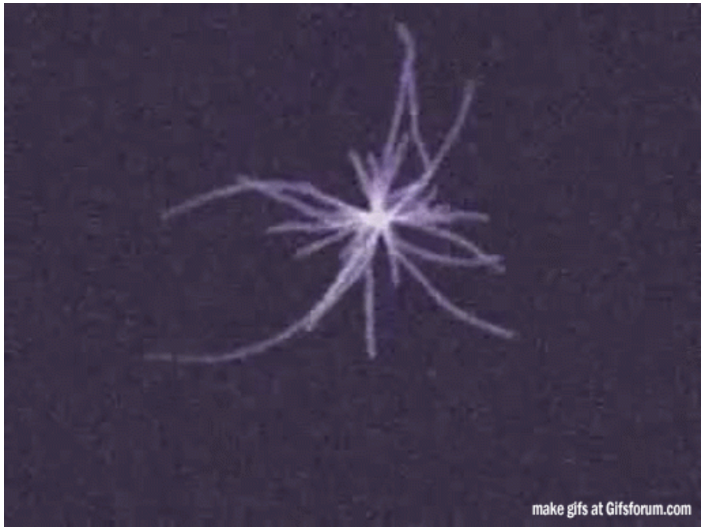
Energy vs Error Rate tradeoff



# of futile cycles ~ # of ATP molecules used ~ dissipation

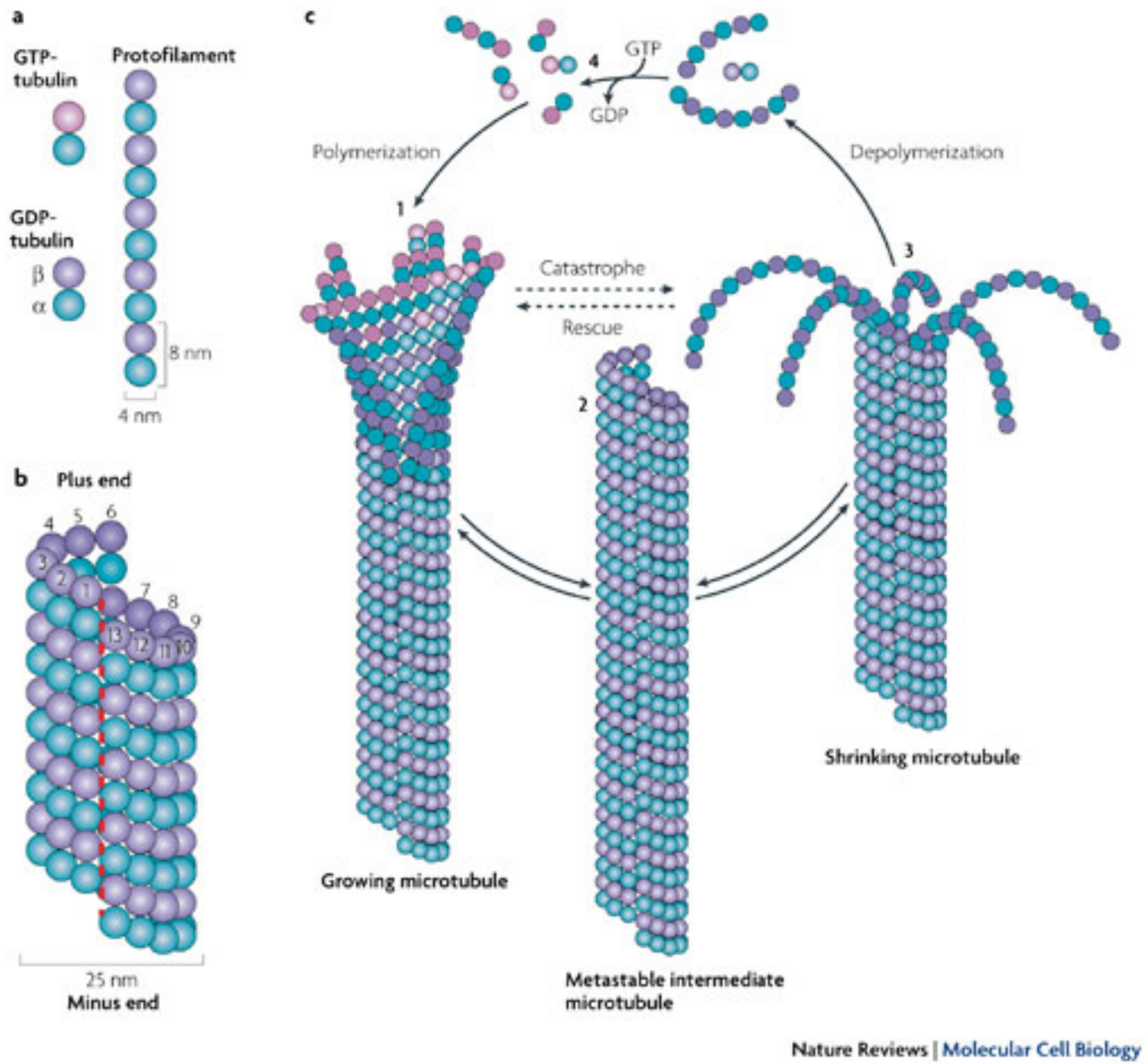
Dynamic instability of microtubules



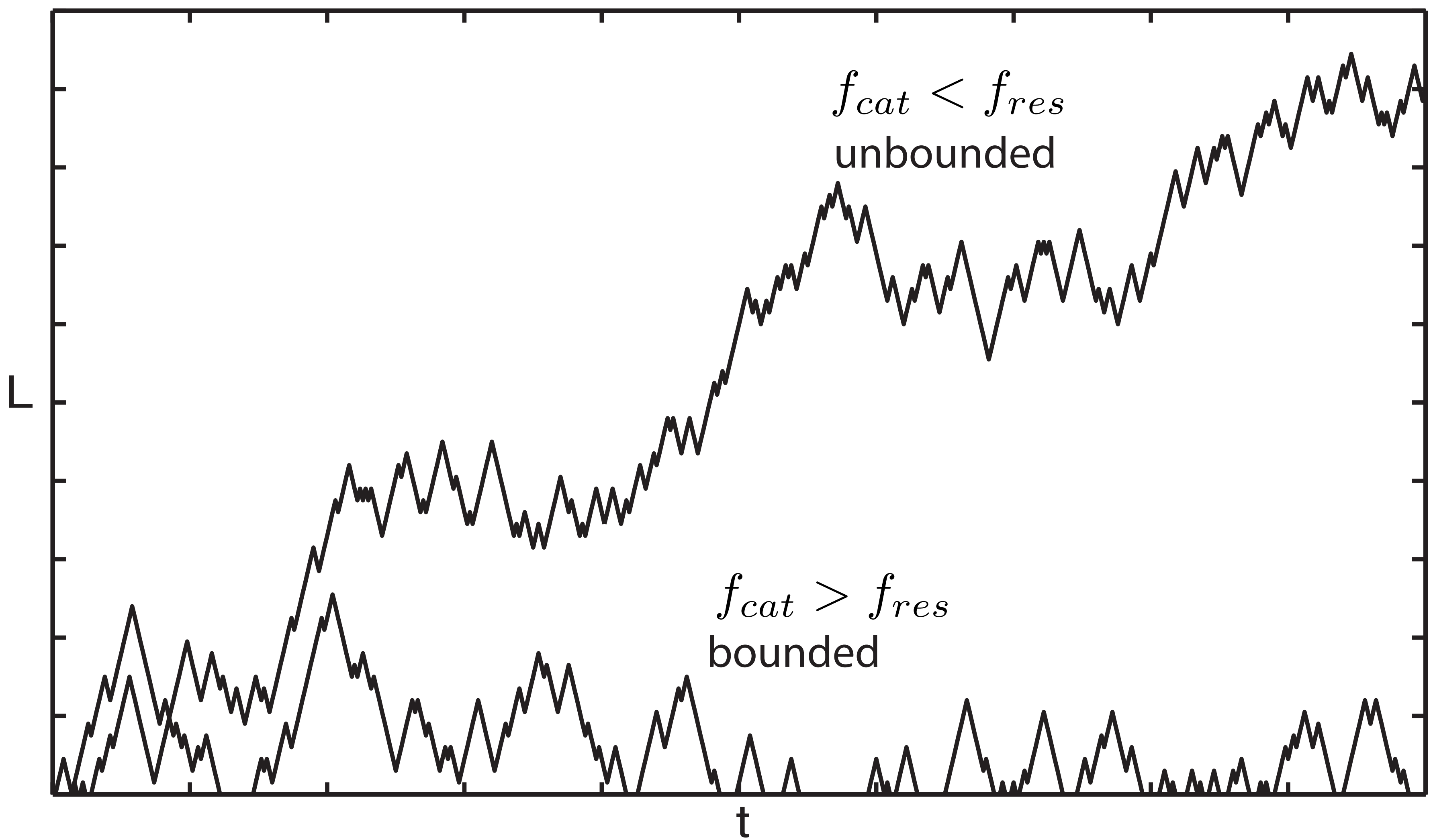


Tim Mitchison (HMS)

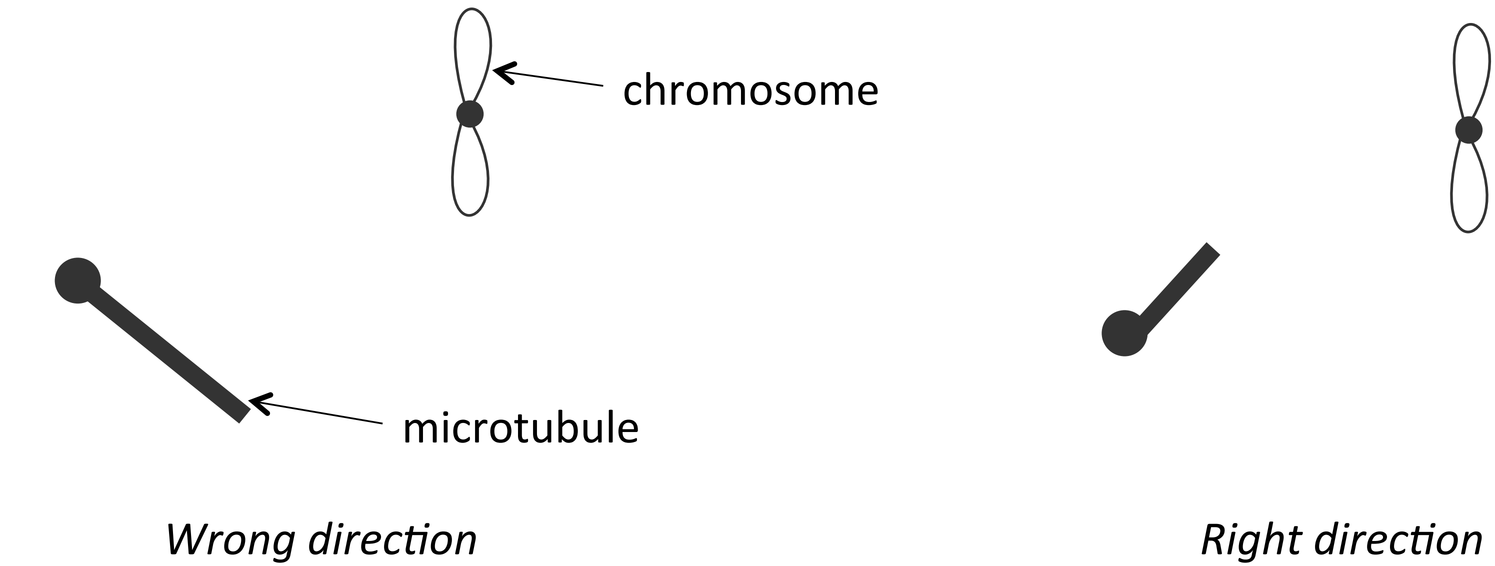
Non-equilibrium growth of microtubules



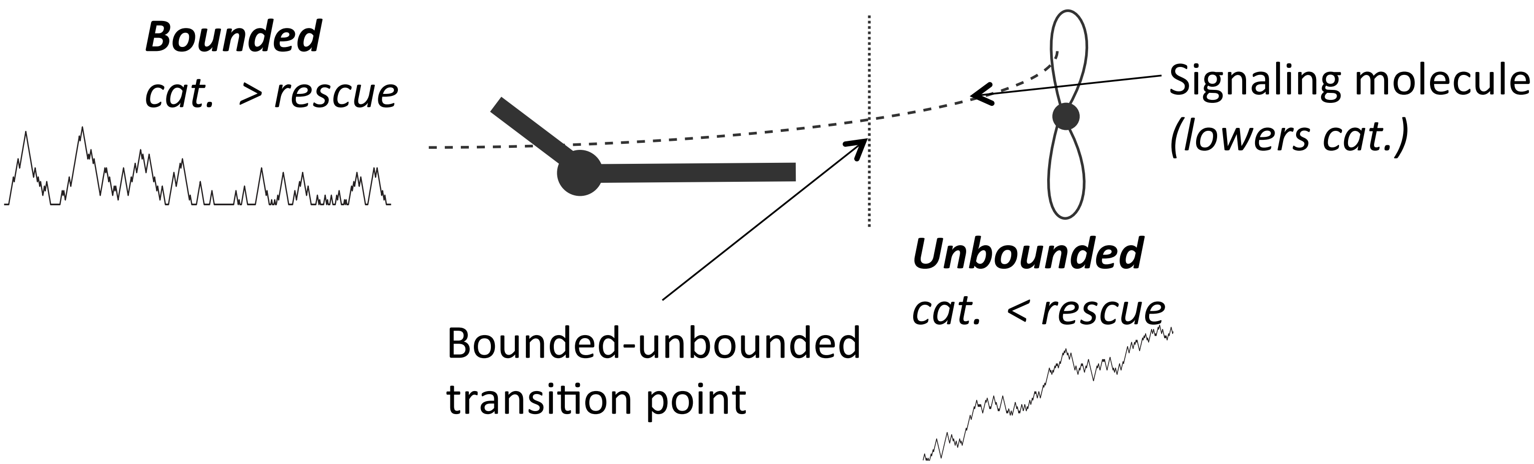
Microtubule growth regimes



Microtubule growth as a search strategy



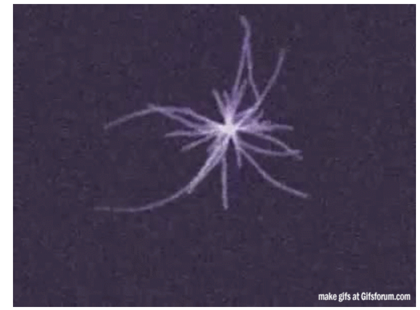
Proposal: Set <catastrophe rate> ~ <rescue rate>



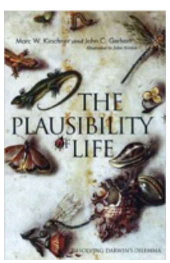
Microtubules and foraging

Foraging ants

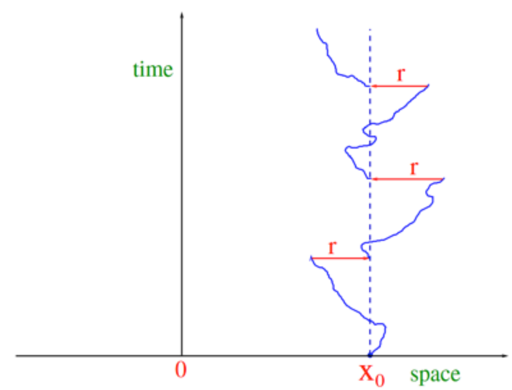
Microtubules



When should you return home and try again?



Kirschner/Gerhart



Diffusion with Stochastic Resetting

Martin R. Evans[1,2] and Satya N. Majumdar[2]
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[2]*Univ. Paris-Sud, CNRS, LPTMS, UMR 8626, Orsay F-01405, France*
(Received 14 February 2011; published 18 April 2011)

Algorithms that get stuck

Algorithmica (1996) 16: 543–547

Algorithmica

A Method for Obtaining Randomized Algorithms with Small Tail Probabilities

H. Alt,[1] L. Guibas,[2] K. Mehlhorn,[3], R. Karp,[4] and A. Wigderson[5]

Abstract. We study strategies for converting randomized algorithms of the Las Vegas type into randomized algorithms with small tail probabilities.

Information Processing Letters 47 (1993) 173–180
Elsevier

27 September 1993

Optimal speedup of Las Vegas algorithms *

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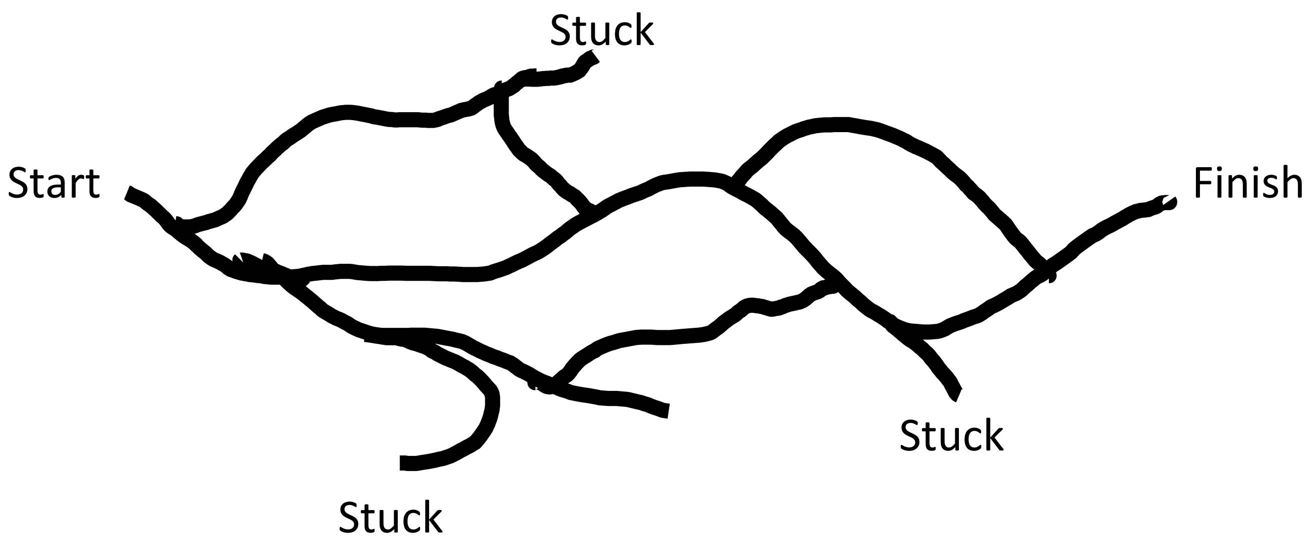
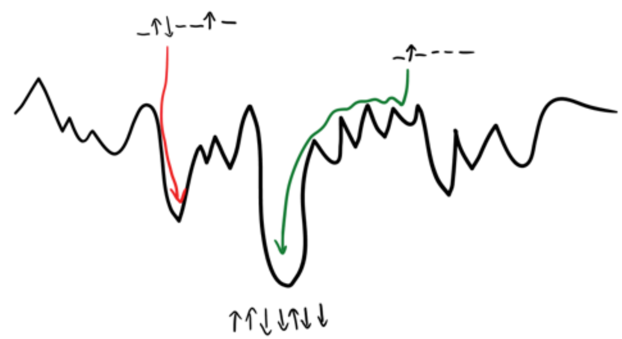
Algorithms that get stuck

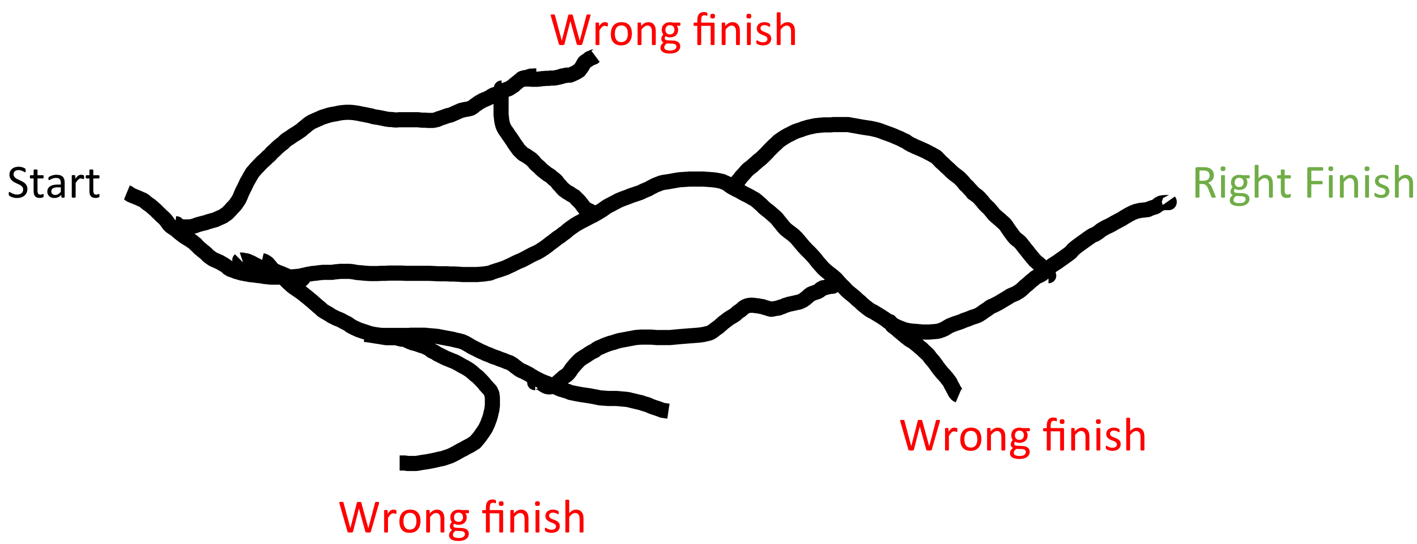


Restarts cut tail of first passage time distribution

Example:
Simulated annealing
on a glassy landscape



Duality: Errors vs (first passage) Time



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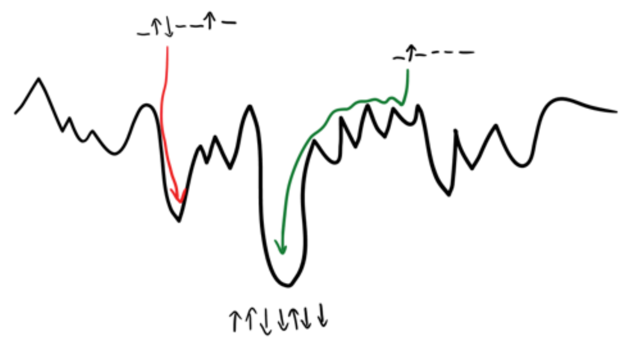
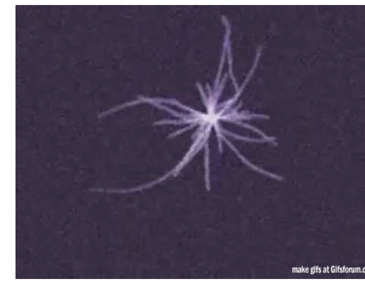
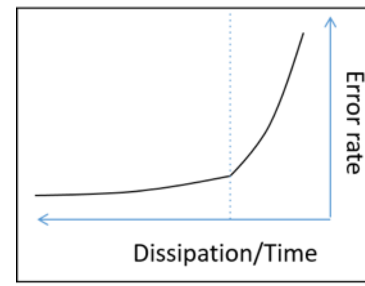


Summary

Proofreading = Dynamic instability in chemical space
(catastrophes and rescues)



Happy medium in error-energy tradeoff



Happy medium in returns home (search, stochastic algorithms..)