# Error Catastrophe – HIV like melting ice*

G. R. Hart[1] A. L. Ferguson[2]

[1]Department of Physics, University of Illinois at Urbana-Champaign

[2]Department of Materials Science and Engineering, University of Illinois at Urbana-Champaign

**Error catastrophe and phase transition in the empirical fitness Landscape of HIV*
Phys. Rev. E 91, 032705

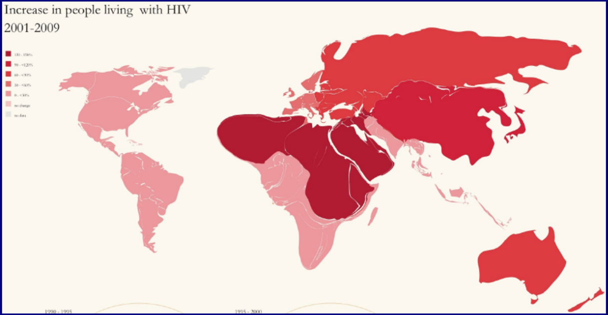
The Hacker Within, Sep 2015

Ferguson Lab

# AIDS

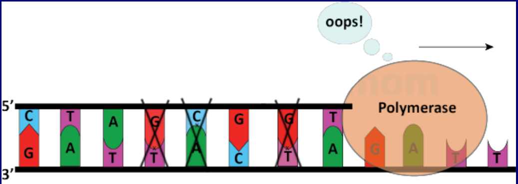

HIV-POSITIVE? WITH HIV TREATMENT,
YOU CAN KEEP THE VIRUS UNDER CONTROL.
This will keep you healthy & reduce the risk of spreading HIV to others.


HIV/AIDS STILL KILLS


Increase in people living with HIV
2001-2009

# HIV

Human Immunodeficiency virus (HIV) is difficult to treat and currently has no cure.



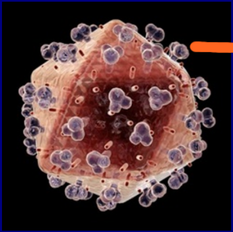

One reason for is the high mutation rate and fast replication rate.

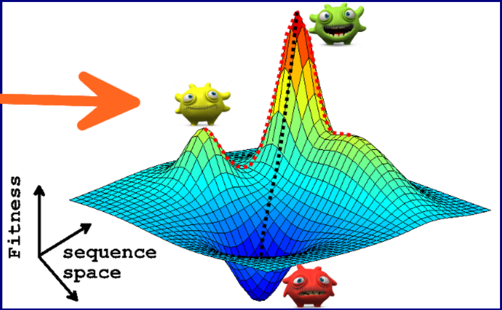


https://yourmomislike.wordpress.com/2012/11/20/your-mom-is-like-an-error-prone-polymerase/

# Fitness Landscape

The virus can be thought of as living on a fitness landscape.



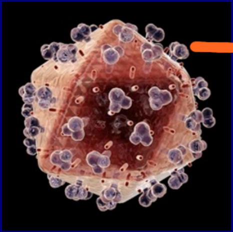


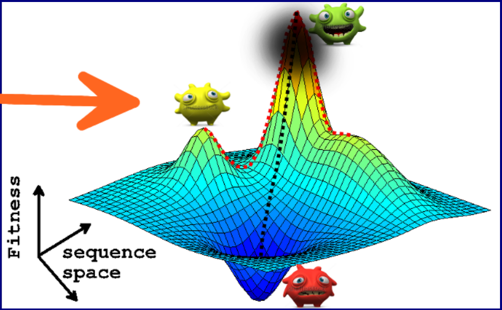



Viruses by Albert Ziganshin from shutterstock.com

# Fitness Landscape

Within a host the viral population lives as a quasispecies.








Viruses by Albert Ziganshin from shutterstock.com

# Statistical Mechanics Analogs

Diversity → Entropy

Fitness → -Energy

Mutation Rate → Temperature

Error Catastrophe → Phase Change



Credit: iStockphoto/Thinkstock

# Fitness Landscape – Potts Model

The infinite range Potts model emerges as the least structured model reproducing the one and two-body mutational probabilities

$$P(\vec{z}) = \frac{1}{Z} e^{-E(\vec{z})}$$

where

$$E(\vec{z}) = \sum_{i=1}^{m} h_i(z_i) + \sum_{i=1}^{m} \sum_{j=i+1}^{m} J_{i,j}(z_i, z_j)$$

The $\{h_i, J_{ij}\}$ are fit to reproduce $P_i^{obs}(A)$ and $P_{i,j}^{obs}(A, B)$

We assume $P(\vec{z}) \propto f(\vec{z})$

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# Fitness Landscape – Parameter Inference

We fit the $\{h_i, J_{ij}\}$ to the MSA using Bayesian Inference:

$$\begin{aligned} L(model/data) = P(model/data) &= \frac{P(data/model)P(model)}{P(data)} \\ &\propto P(data/model)P(model) \\ &= P(model) \prod_{\{\vec{z}\}} P_{model}(\vec{z})^{P_{obs}(\vec{z})M} \end{aligned}$$

where $P(model) = \prod_i e^{-\gamma_1 h_i^2} \prod_{i,j} e^{-\gamma_2 J_{ij}^2}$

We perform Newton descent with analytic gradients

- Synthesize an initial estimate of $\{h_i, J_{ij}\}$
- Evaluate $\{P_i, P_{ij}\}$ by MC sampling the current Hamiltonian
- Refine $\{P_i, P_{ij}\}$ towards $\{P_i^{obs}, P_{ij}^{obs}\}$ by stepping $\{h_i, J_{ij}\}$

MPI, OMP, and GPU parallel implementations

# Partition Function – Thermodynamic properties

In principle if we have the Hamiltonian we have the partition function

$$Z(T) = \sum_{\vec{z}} e^{-E(\vec{z})/T}$$

The partition function gives us thermodynamics as a function of T

$$F(T) = -T \ln(Z(T)) \qquad S(T) = \frac{U(T) - F(T)}{T}$$

$$U(T) = \frac{\partial \ln(Z(T))}{\partial \beta} \qquad C_v(T) = \frac{\partial U}{\partial T} = \frac{1}{T^2} \frac{\partial^2 \ln(Z(T))}{\partial \beta^2}$$

# Partition Function – Thermodynamic properties

In principle if we have the Hamiltonian we have the partition function

$$Z(T) = \sum_{\vec{z}} e^{-E(\vec{z})/T} = \sum_{E} g(E) e^{-E/T}$$

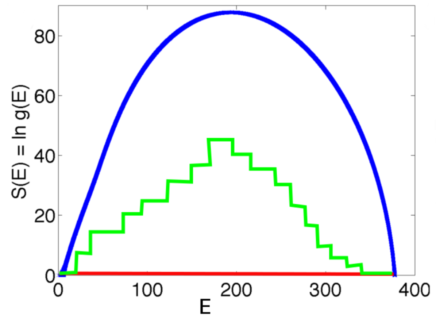
The partition function gives us thermodynamics as a function of T

$$F(T) = -T \ln(Z(T)) \qquad S(T) = \frac{U(T) - F(T)}{T}$$

$$U(T) = \frac{\partial \ln(Z(T))}{\partial \beta} \qquad C_v(T) = \frac{\partial U}{\partial T} = \frac{1}{T^2} \frac{\partial^2 \ln(Z(T))}{\partial \beta^2}$$

# Partition Function – Wang-Landau Algorithm

$$Z(T) = \sum_{\vec{z}} e^{-E(\vec{z})/T} = \sum_{E} g(E) e^{-E/T}$$




Wang-Landau sampling

- Random walk in energy space.
- Accept spin flip based on $P(E_1 \to E_2) = \min(g(E_1)/g(E_2), 1)$.
- After attempted spin flip increase $g(E_{current})$ by a factor $f$.
- Every iteration decrease $f$ towards 1.

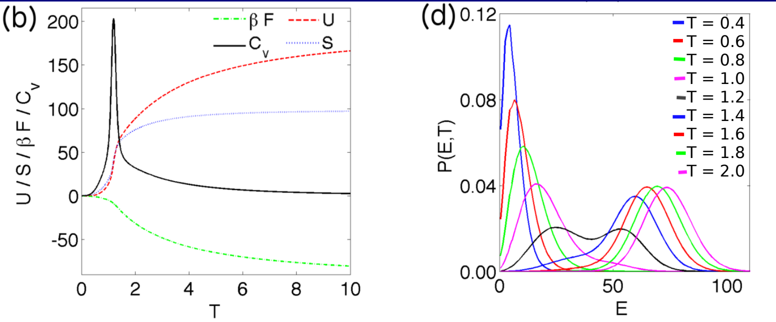


F. Wang and D. P. Landau, Phys. Rev. Lett. **86** (10) 2050, 2001

D. P. Landau, Shan-Ho Tsai, and M. Exler, Am. J. Phys. **72** (10), 2004

# Phase Transition and Error Catastrophe

Ice: low energy & low entropy
Water: high energy & high entropy




G. R. Hart and A. L. Ferguson, Phys. Rev. E **91** 032705, 2015

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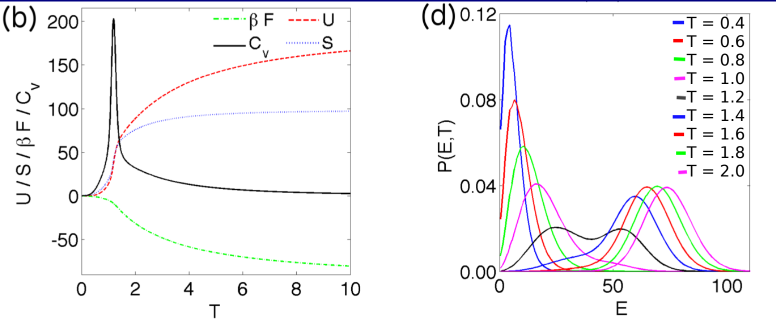
# Phase Transition and Error Catastrophe

Ice: low energy & low entropy → high fitness & low diversity
Water: high energy & high entropy → low fitness & high diversity



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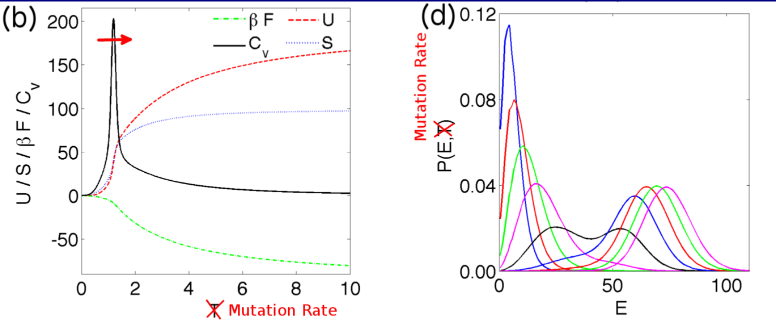
# Phase Transition and Error Catastrophe

Error Catastrophe – raising the mutation rate leads to accumulation of lethal mutations and population collapse.




1. Mutagenic drugs could push the protein past the transition



G. R. Hart and A. L. Ferguson, Phys. Rev. E **91** 032705, 2015

# Partition Function – Wang-Landau Algorithm

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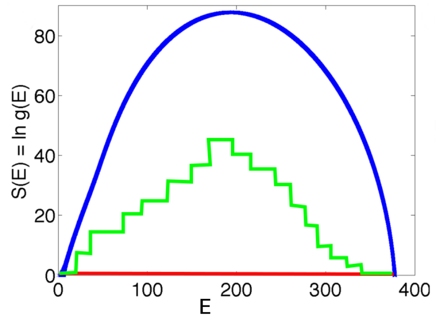


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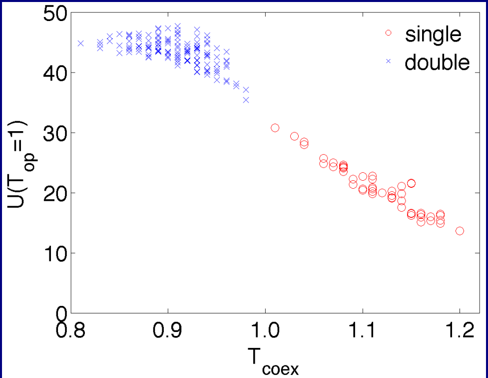
# Triggering Error Catastrophe

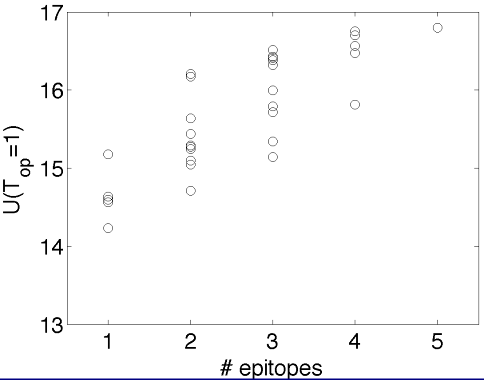
2. Can targeting pairs of residues induce the transition?




Yes

# Triggering Error Catastrophe

3. Can immune responses induce the transition?




No



G. R. Hart and A. L. Ferguson, Phys. Rev. E **91** 032705, 2015

# Thank You

Greg Hart
grhart2@illinois.edu

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