

Evolution of Robustness and Evolvability

By Dieter Stoker and Stijn Andeweg

25-01-2018

Introduction

Robustness = persistence of a trait/phenotype in a system under perturbations

Evolvability = capacity of a system for phenotypic adaptation to an environment

Robustness promotes evolvability

Main messages

- Evolution of drift robustness in small populations
- Robustness and evolvability are linked and not two separate things
- Empirical adaptive landscapes are exciting
-but many caveats!
- Phenotypic evolvability and phenotypic robustness intrinsically linked in every GPM

Contents

- **A thousand empirical adaptive landscapes and their navigability (Dieter)**
- **Evolution of drift robustness in small populations (Stijn)**
- **Why phenotype robustness promotes phenotype evolvability (Dieter)**
- **Robustness and evolvability of the human signaling network (Stijn)**

A thousand empirical adaptive landscapes and their navigability

José Aguilar-Rodríguez^{1,2†}, Joshua L. Payne^{1,2†} and Andreas Wagner^{1,2,3*}

Aims of the paper

- Showcase high-throughput determination of empirical adaptive landscapes from *in vitro* data
- Determine how easy or hard it is for evolution to navigate these landscapes
- Show that these findings hold for gene expression *in vivo* for yeast
- Conclusion: landscape navigability may have contributed to the enormous success of transcriptional regulation

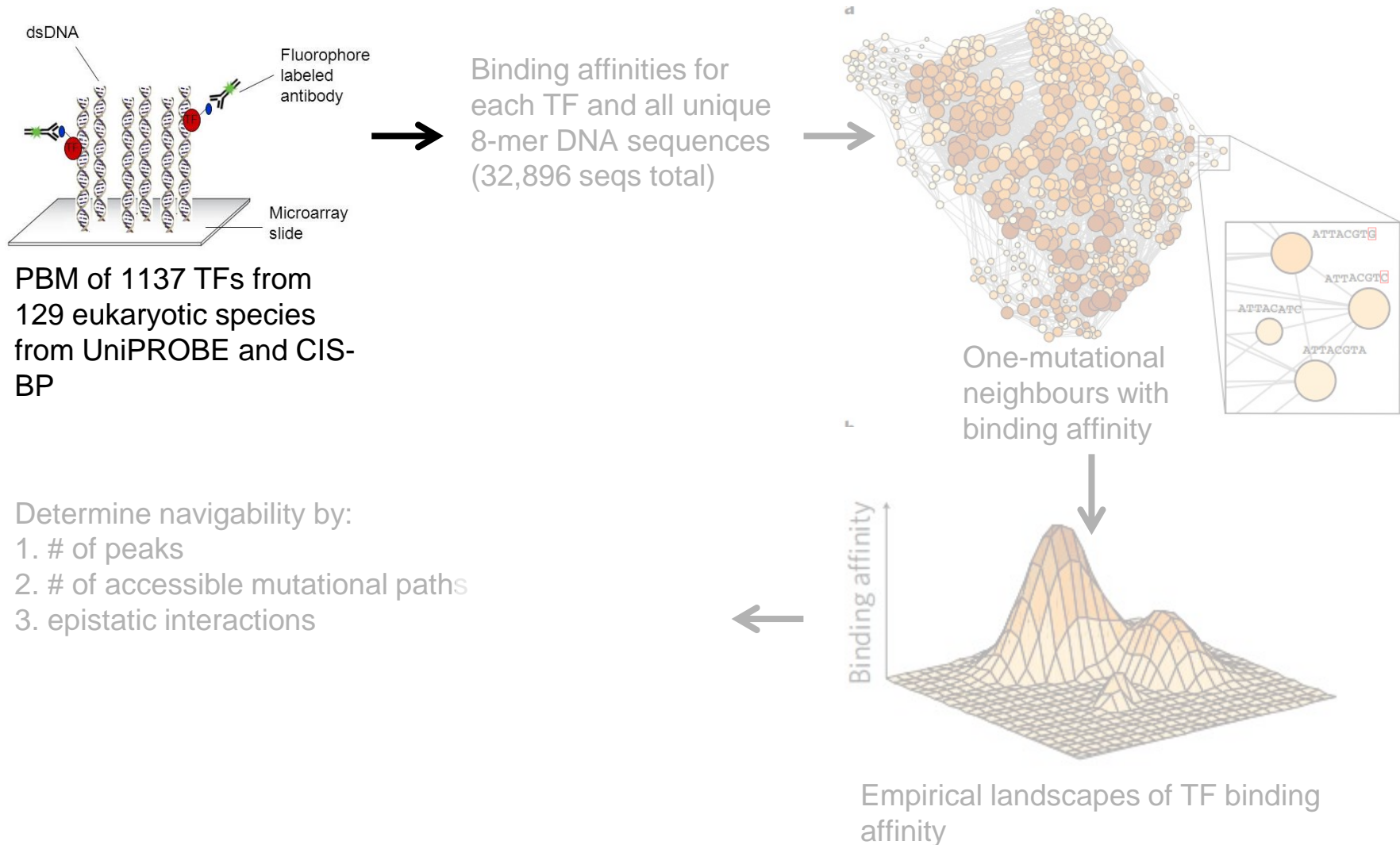
The good

- High throughput visualisation of complete empirical adaptive landscapes
→ how do real adaptive landscapes look?
- Show that many binding peaks have high neutrality around them
 - (*though E vs. Z*)
- Show that *in vitro* measures translate to actual effects *in vivo*

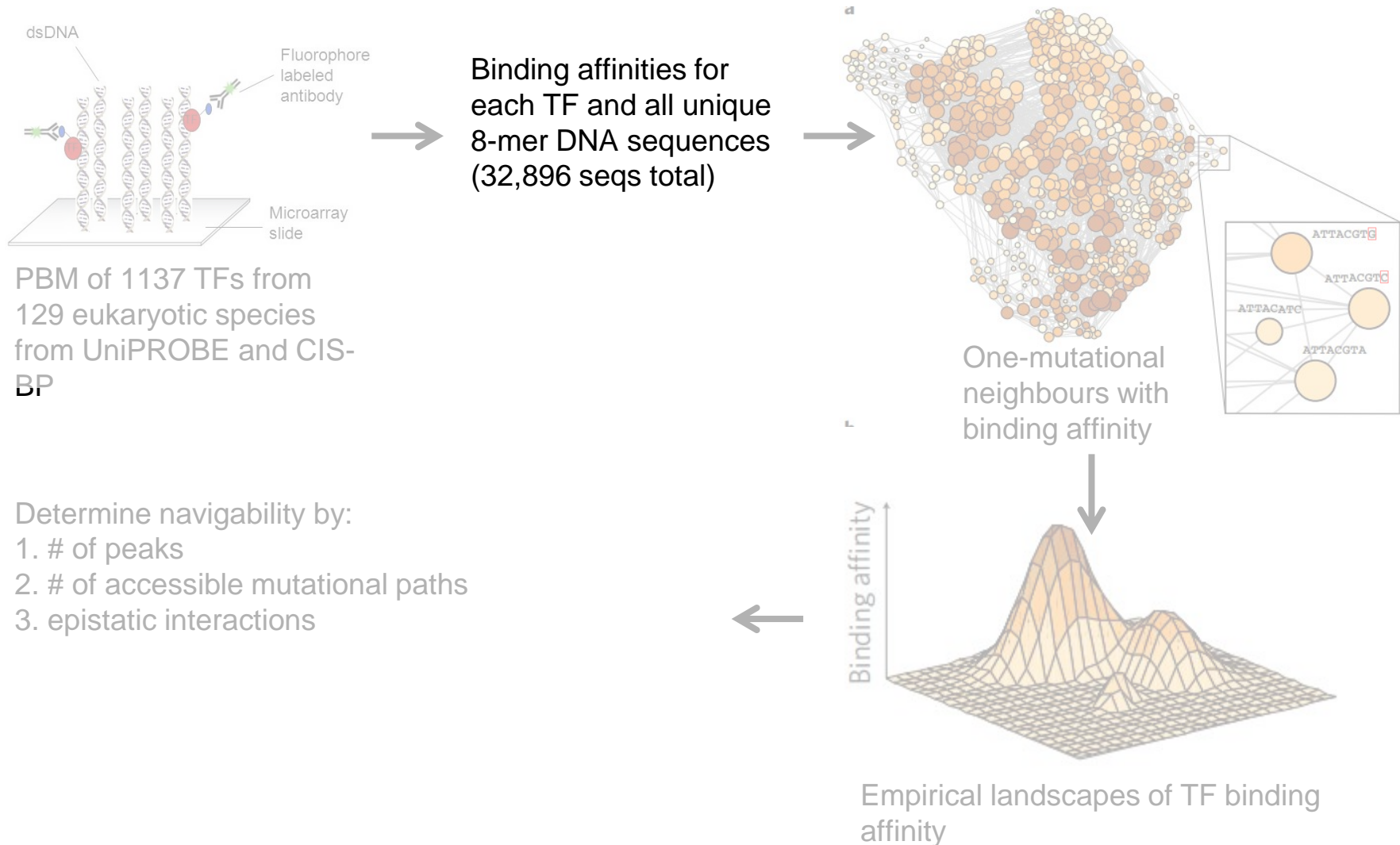
The bad

- Showcase a lack of insight into whether binding affinity can be a related quantitative phenotype of fitness
- Create measures of landscape navigability that don't say that much, or that at least are very uncertain

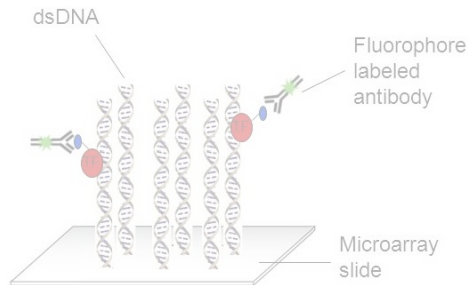
How easily can evolution move through empirical adaptive landscapes of TF binding?



How easily can evolution move through empirical adaptive landscapes of TF binding?

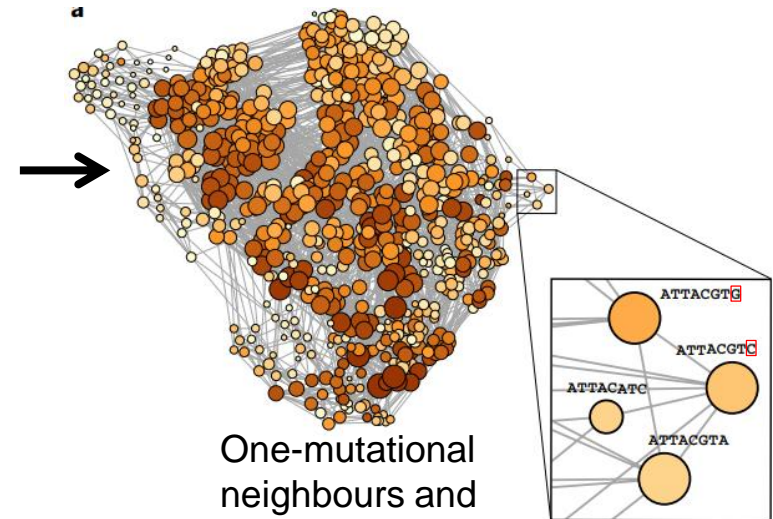


How easily can evolution move through empirical adaptive landscapes of TF binding?



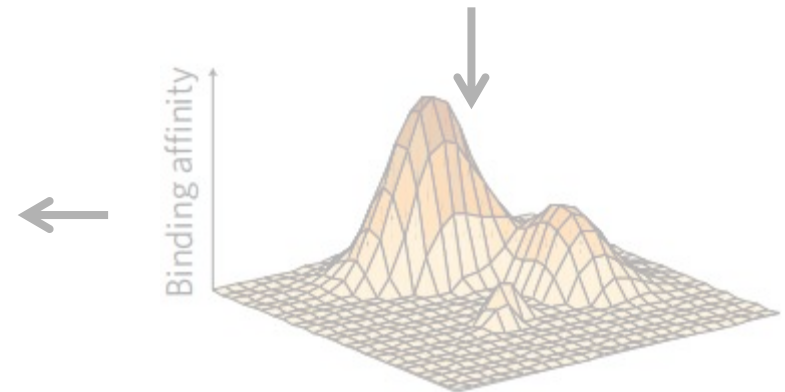
PBM of 1137 TFs from 129 eukaryotic species from UniPROBE and CIS-BP

Binding affinities for each TF and all unique 8-mer DNA sequences (32,896 seqs total)



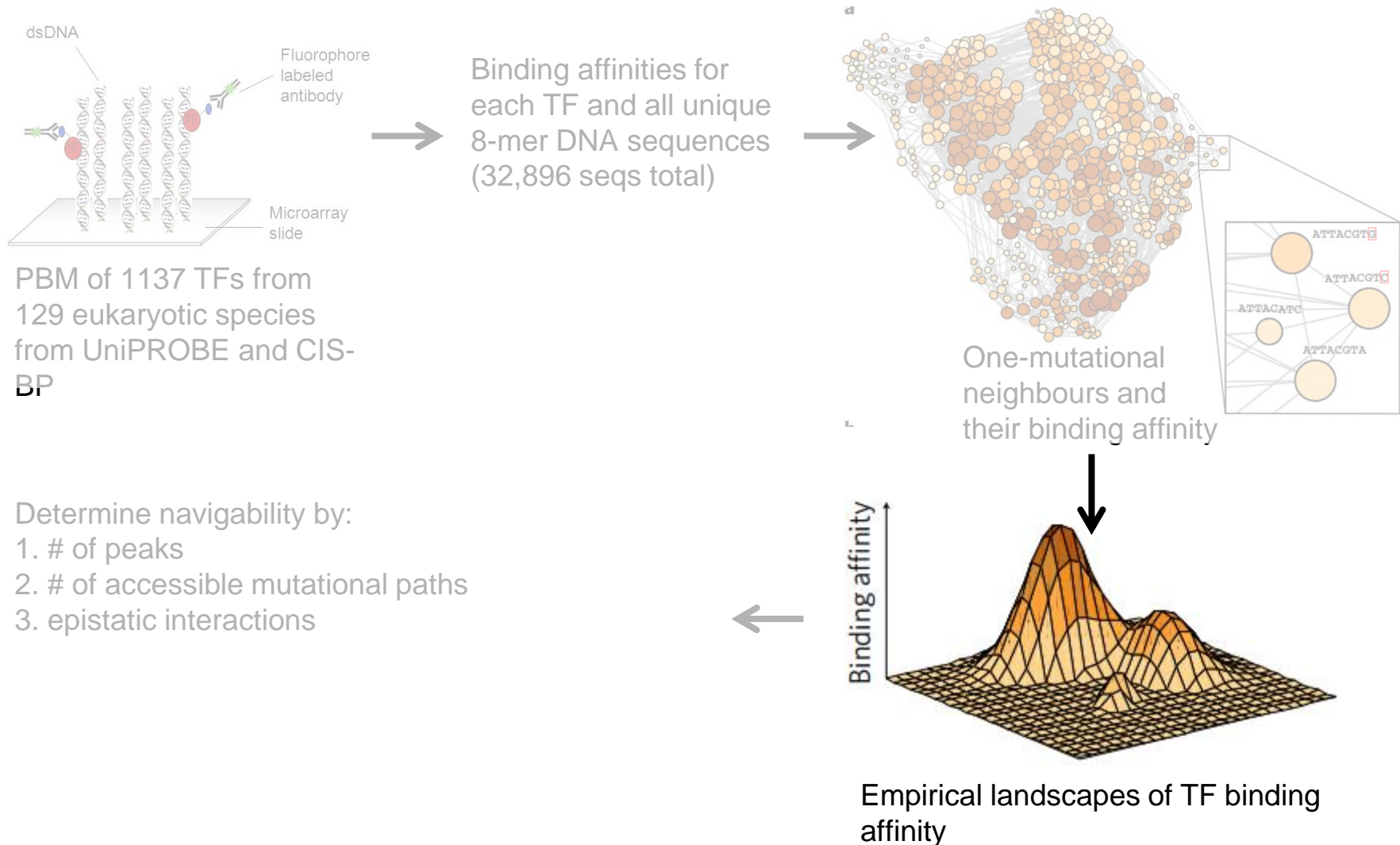
Determine navigability by:

1. # of peaks
2. # of accessible mutational paths
3. epistatic interactions

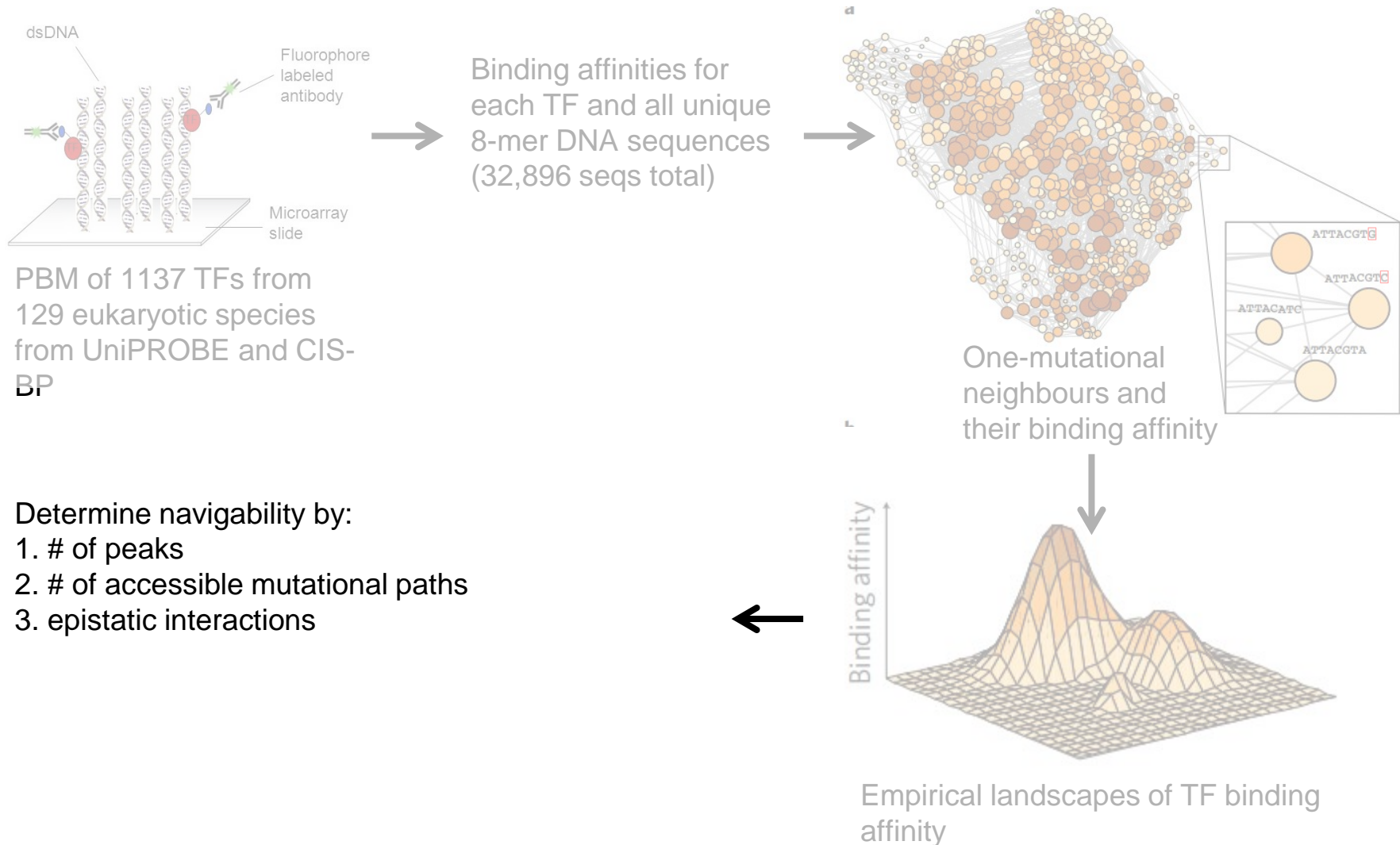


Empirical landscapes of TF binding affinity

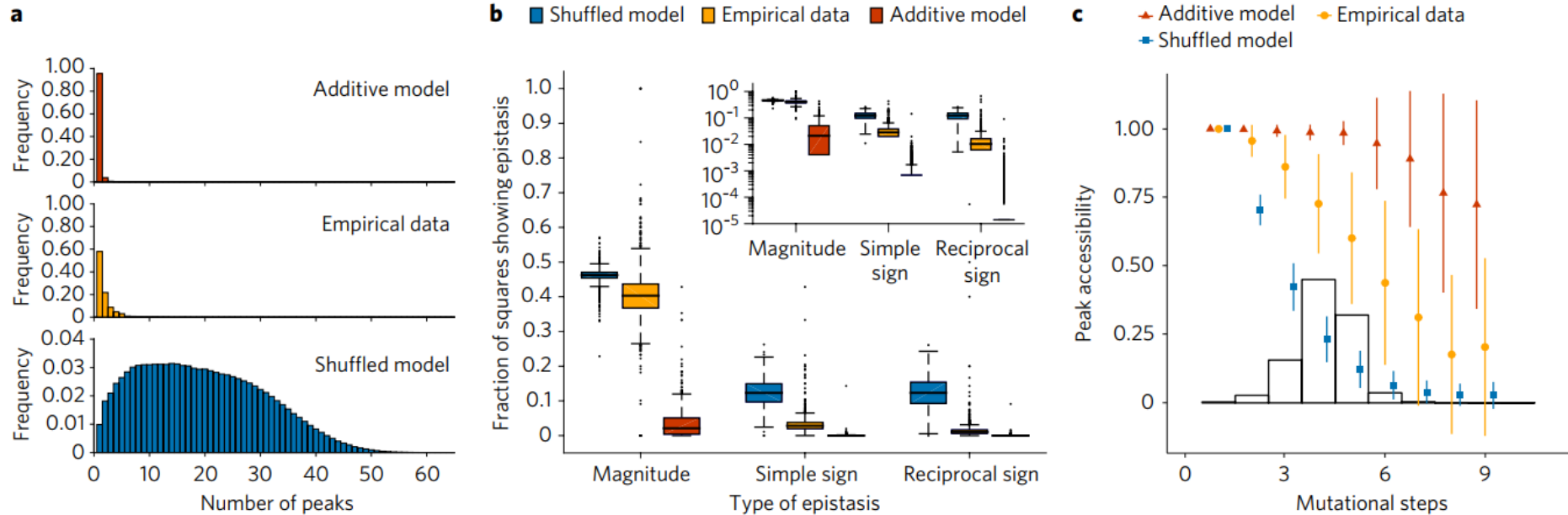
How easily can evolution move through empirical adaptive landscapes of TF binding?



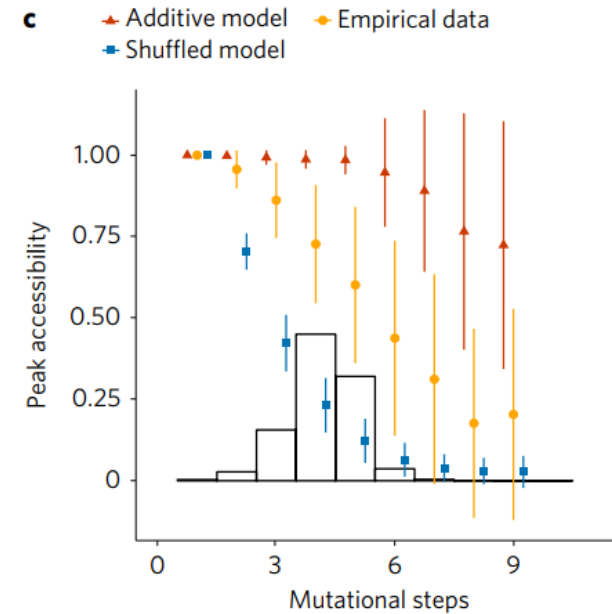
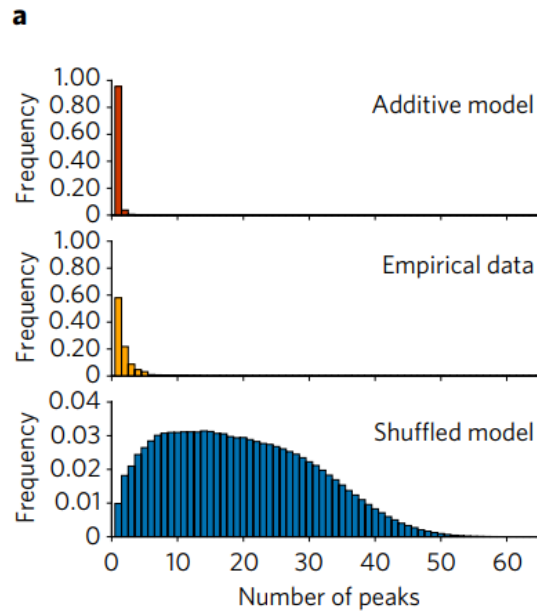
How easily can evolution move through empirical adaptive landscapes of TF binding?



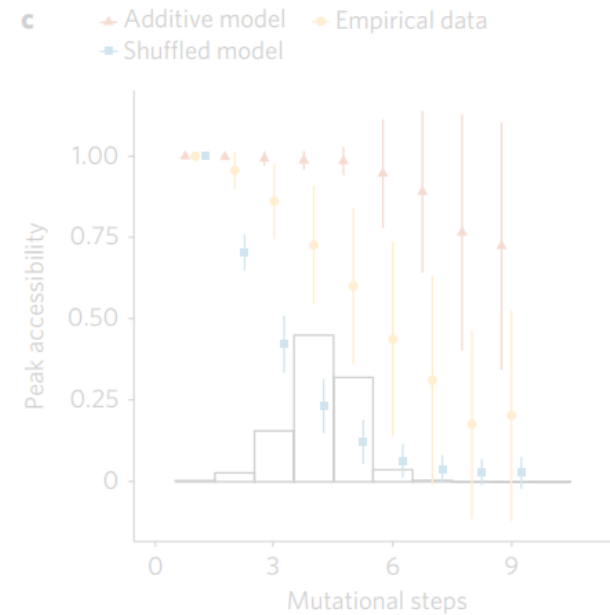
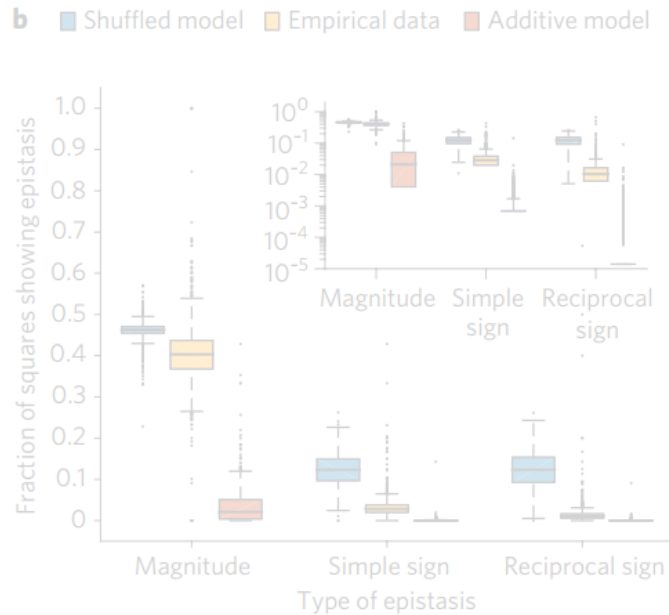
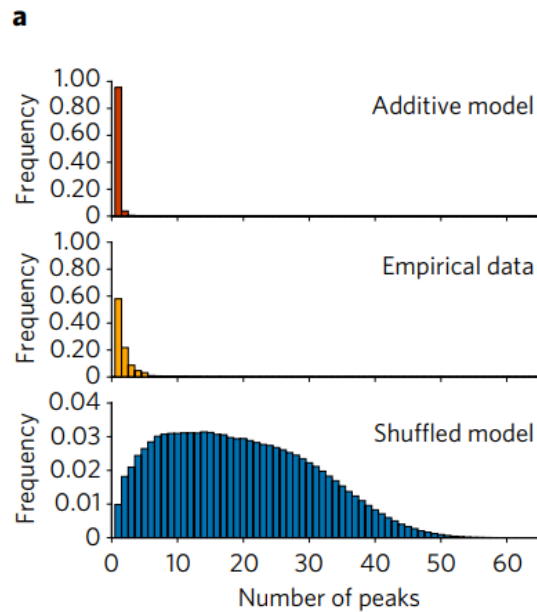
Three measures. Are they valid?



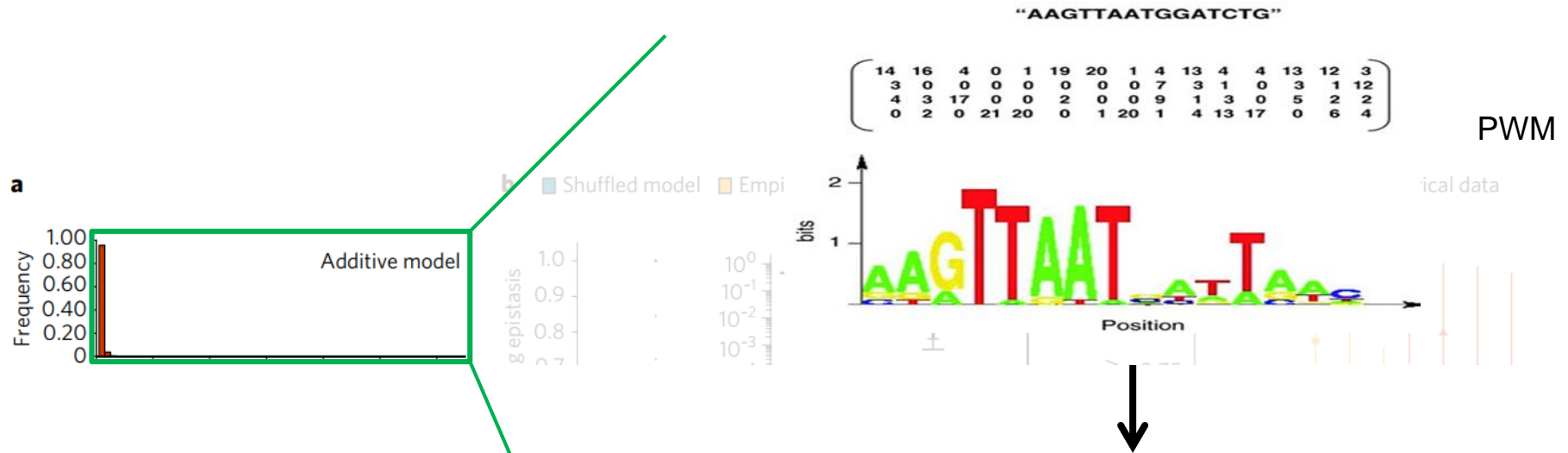
Let's explore two in further detail



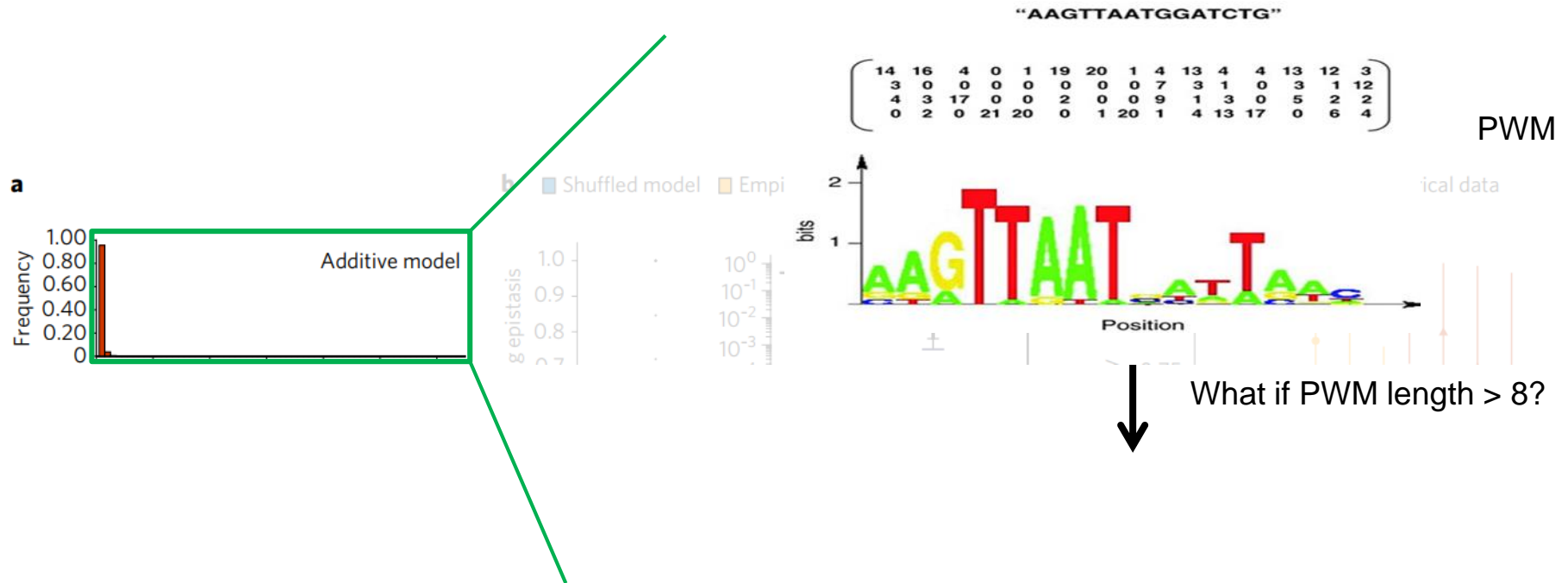
of peaks



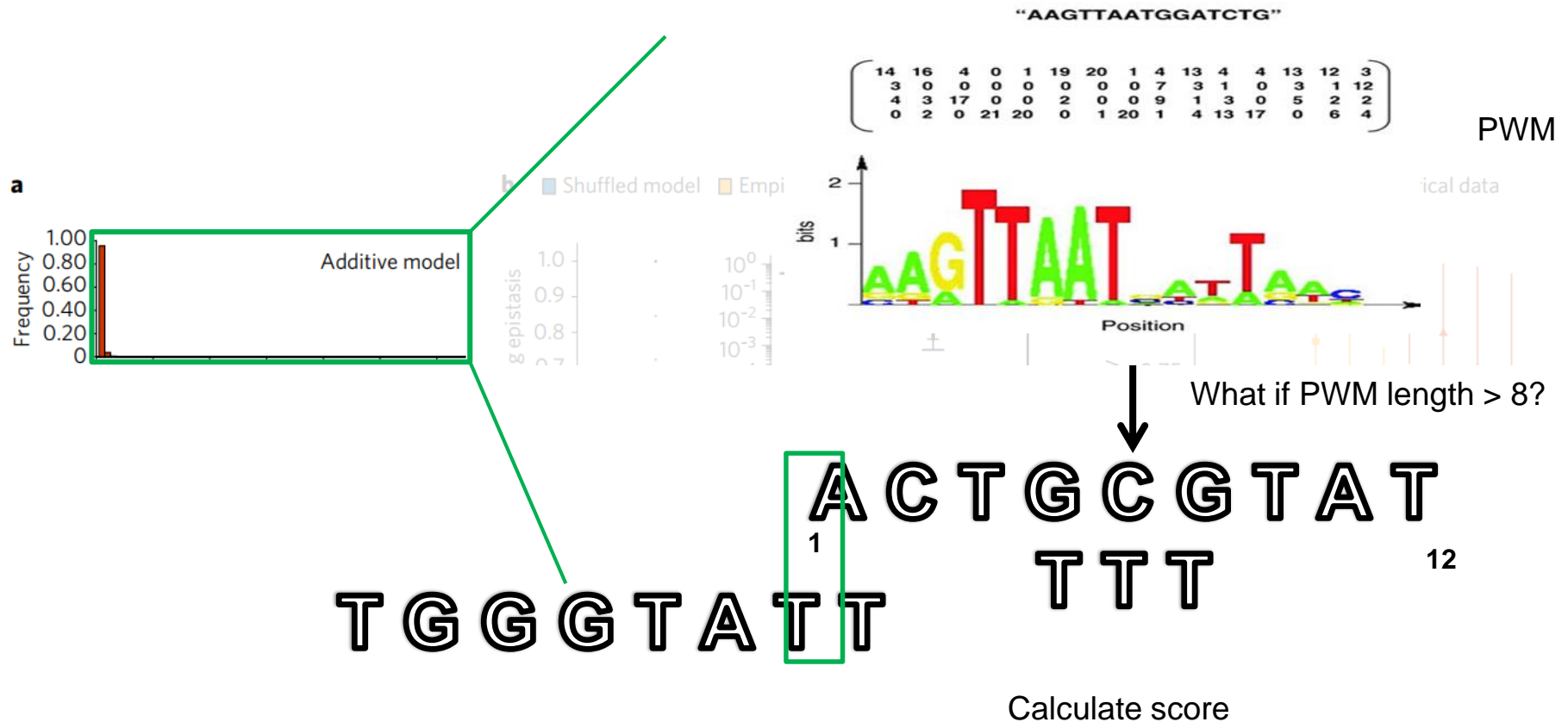
What is the control: additive model



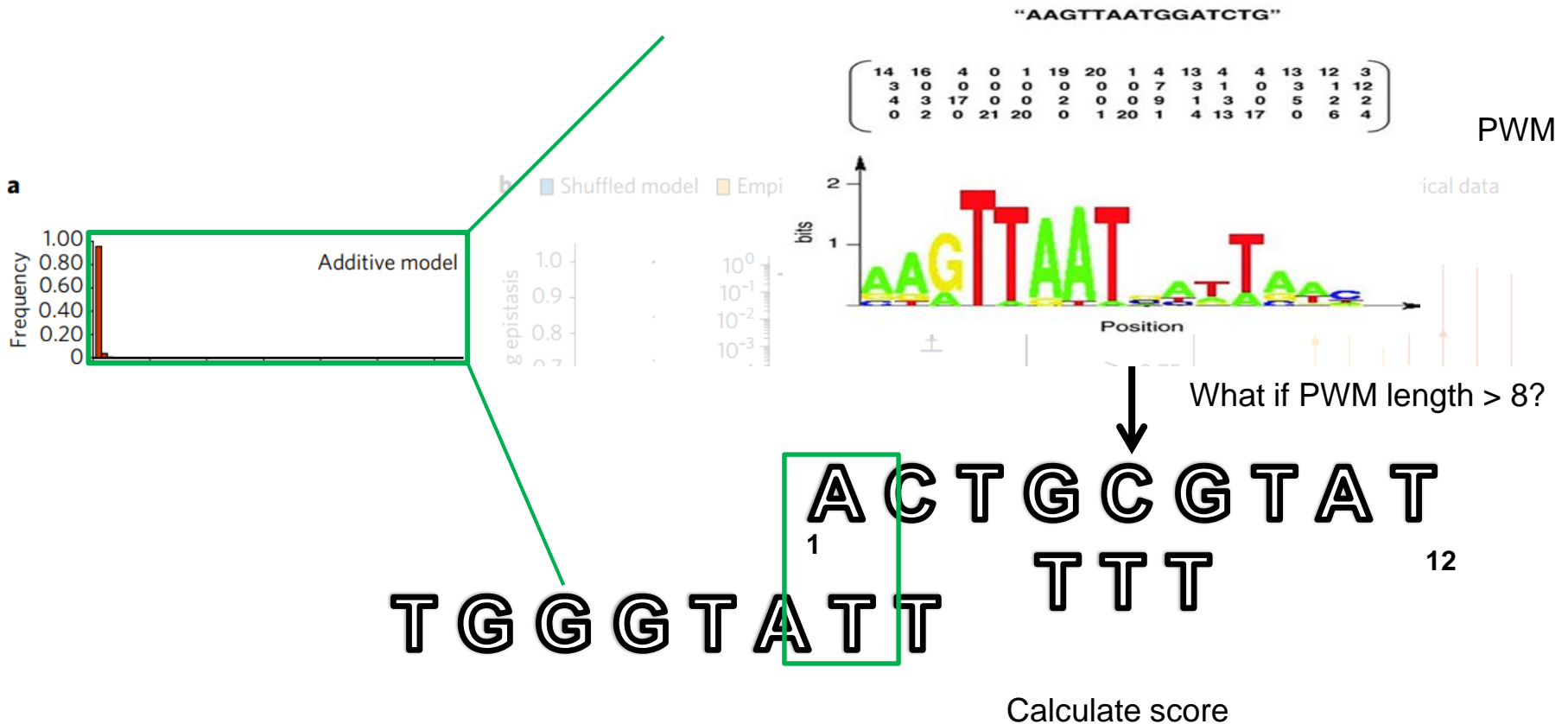
What is the control: additive model



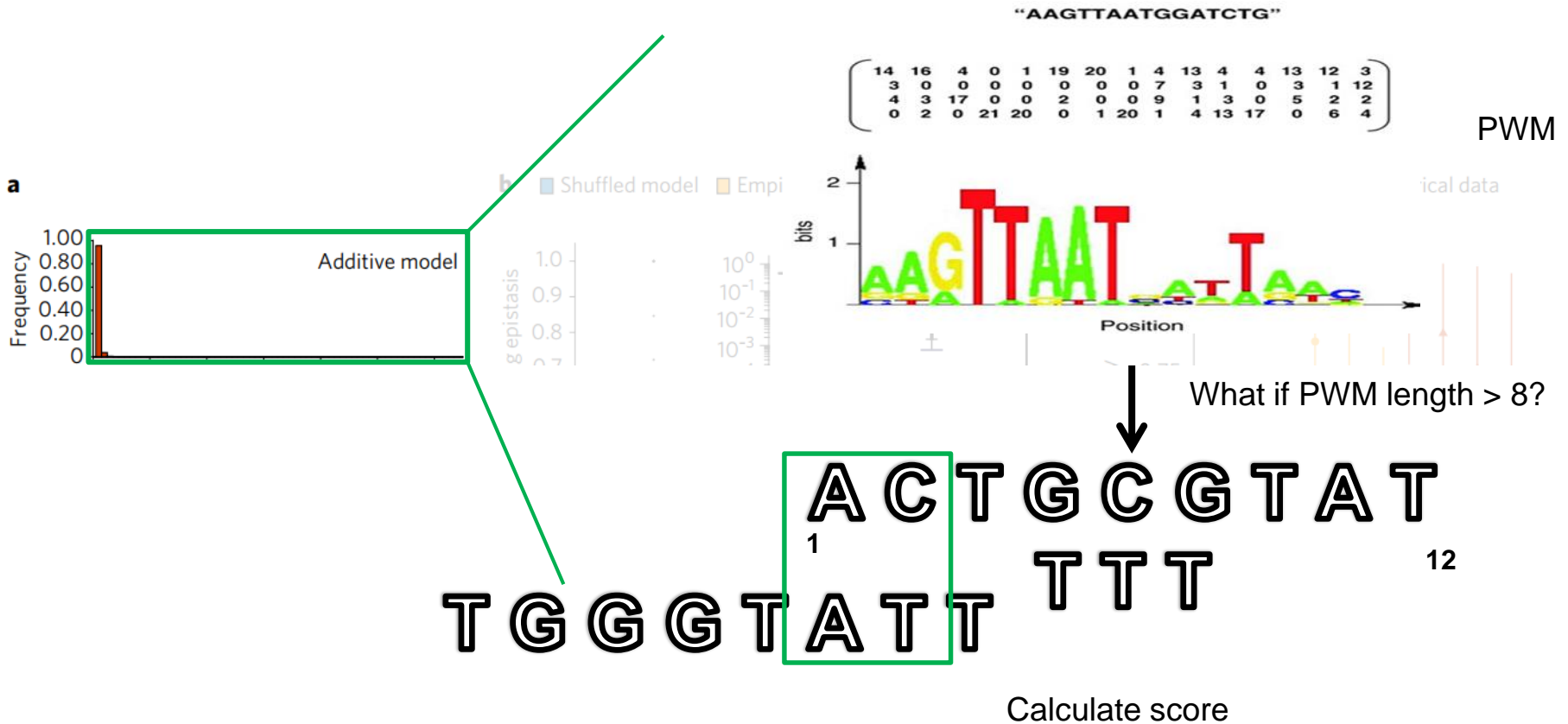
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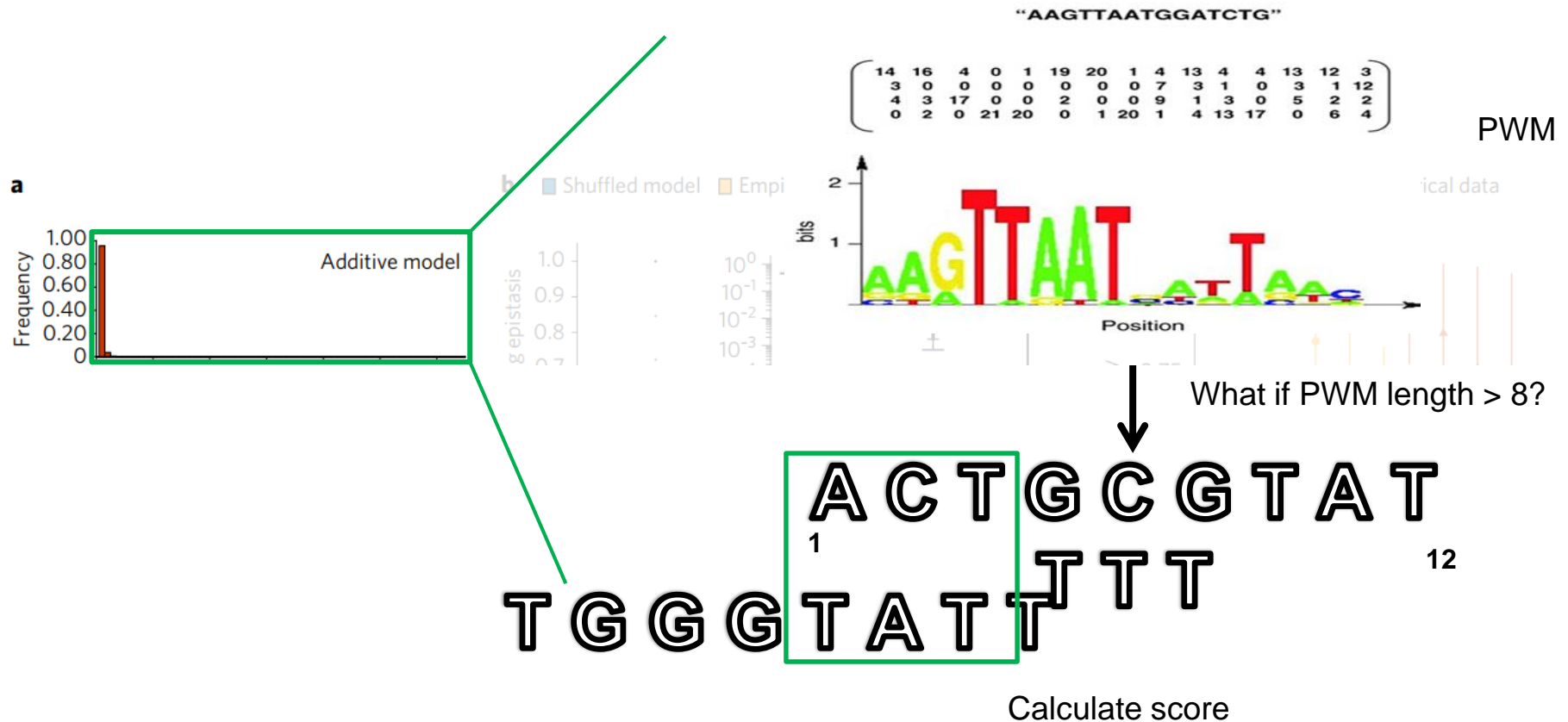
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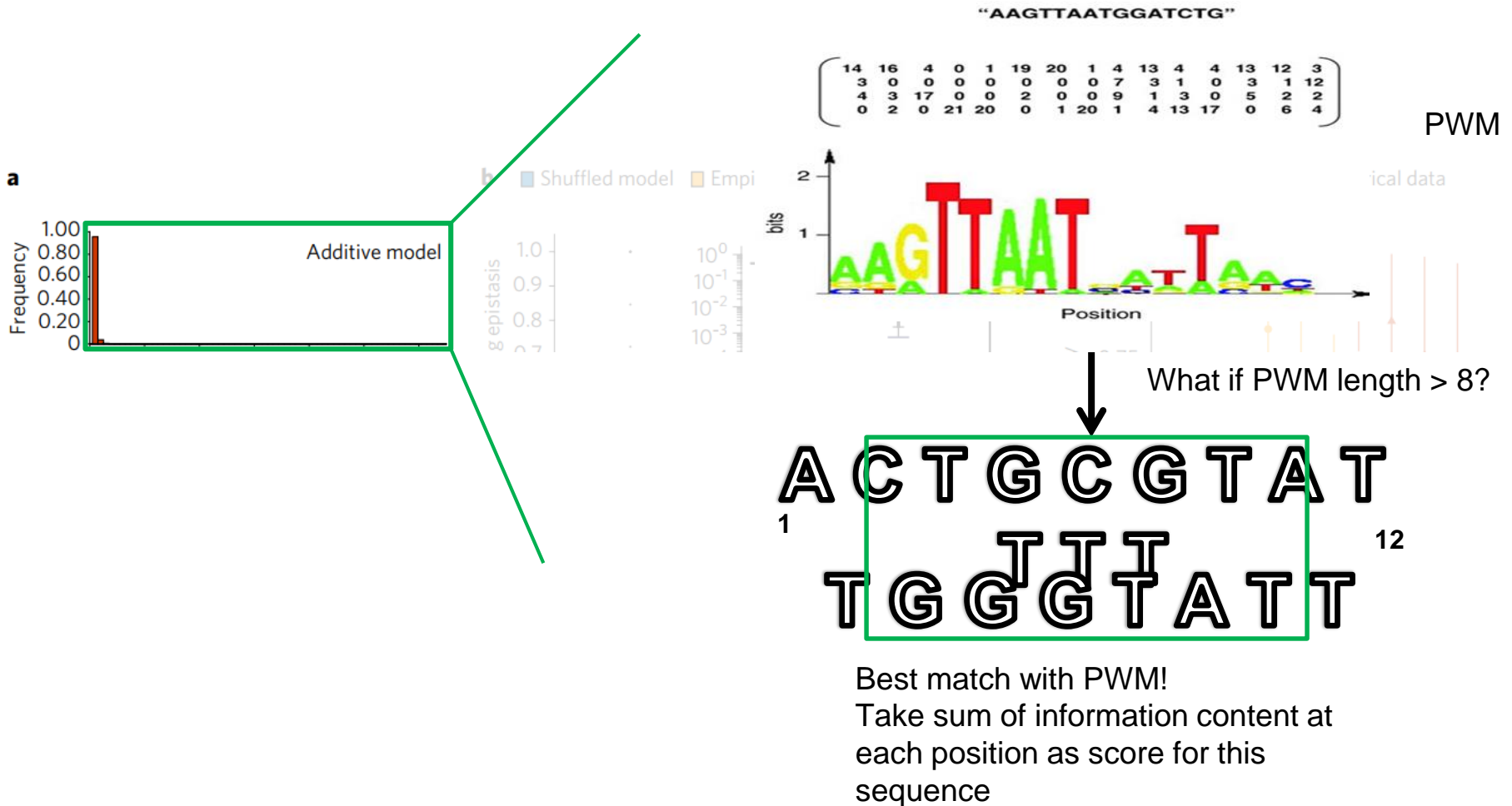
What is the control: additive model



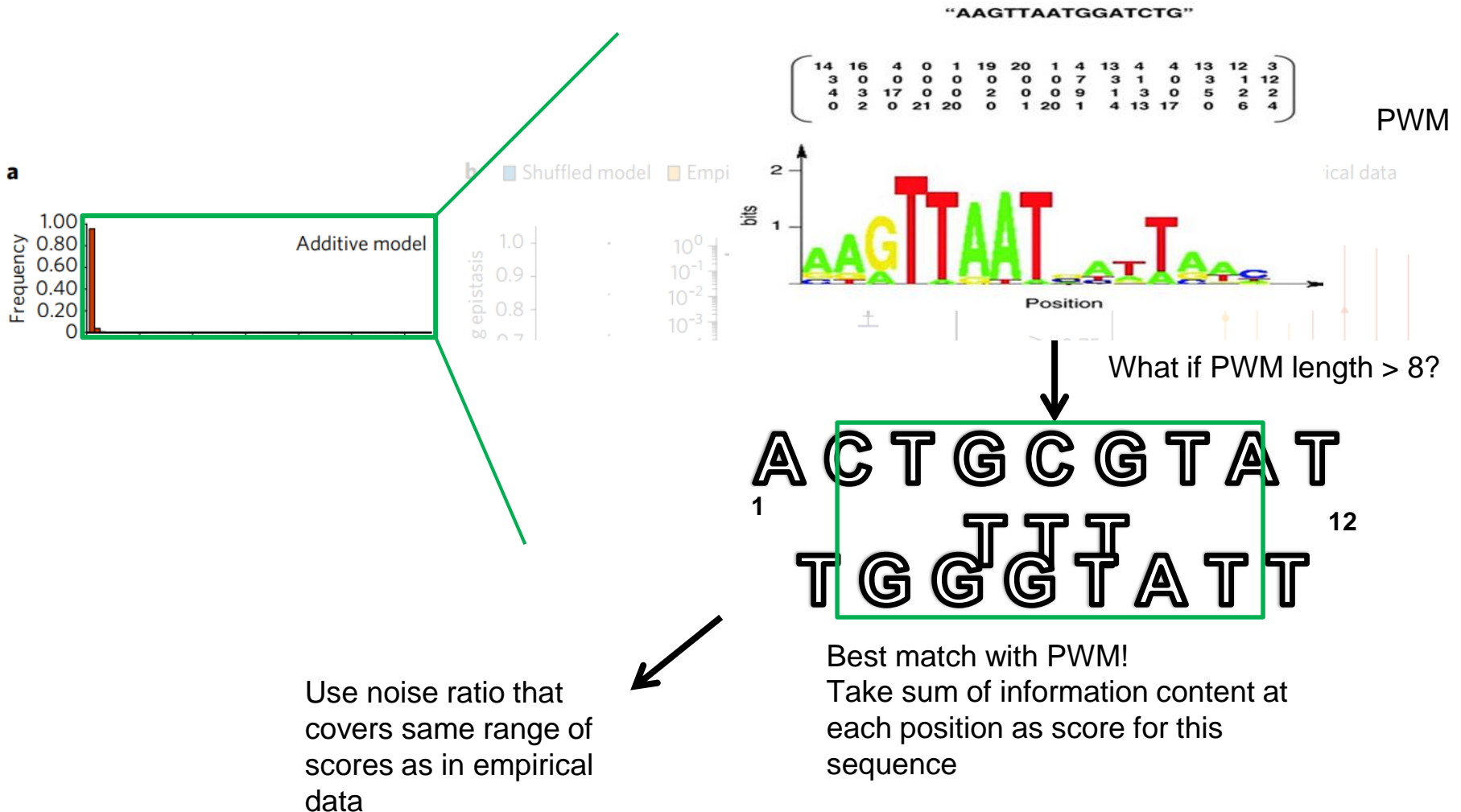
What is the control: additive model



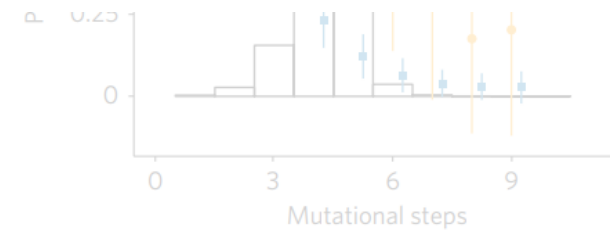
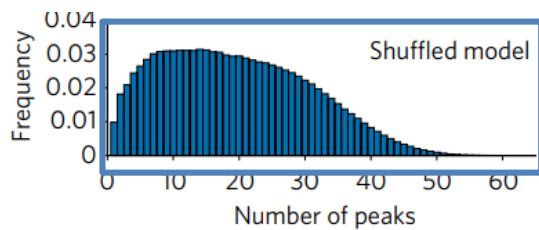
What is the control: additive model



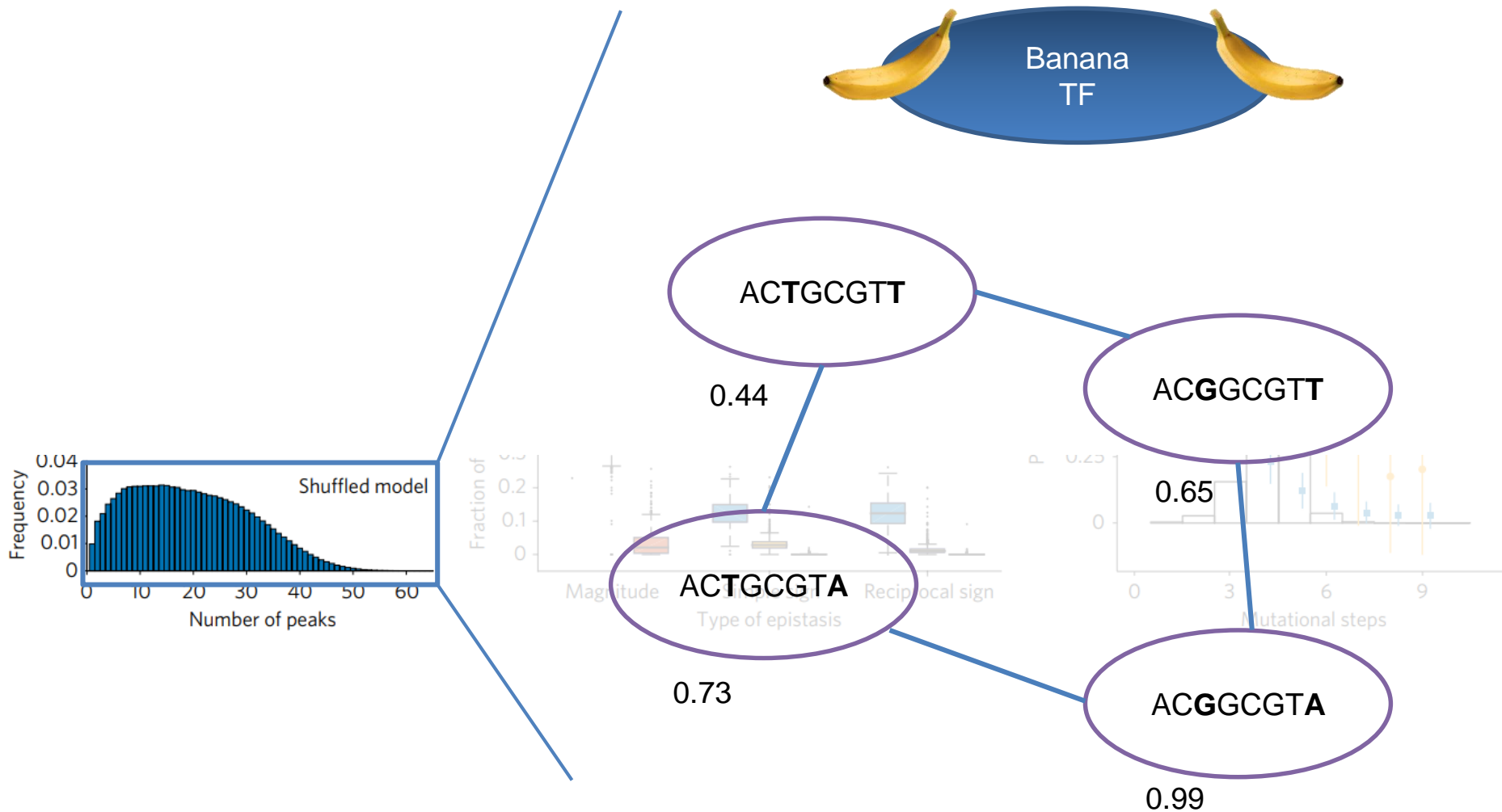
What is the control: additive model



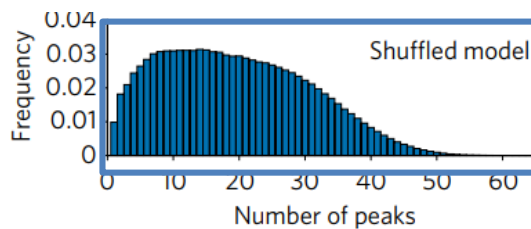
What is the control: shuffled model



What is the control: shuffled model



What is the control: shuffled model



ACTGCGTT

0.44

0.99

ACGGCGTT

0.65

0.44

ACTGCGTA

0.73

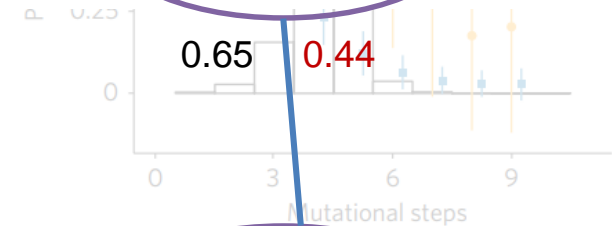
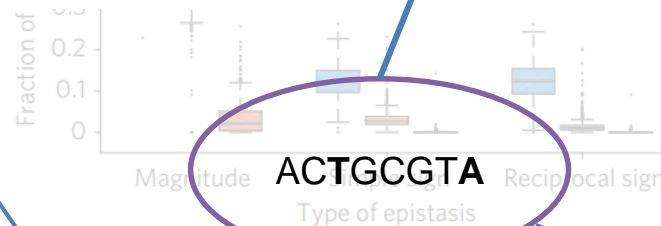
0.65

ACGGCGTA

0.99

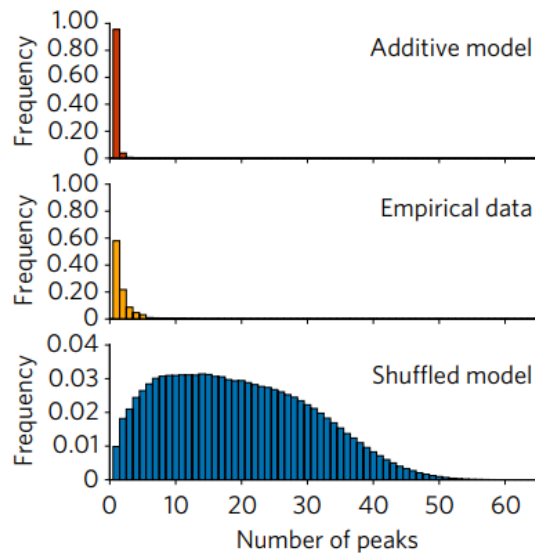
0.73

Do this 1000 times
per TF

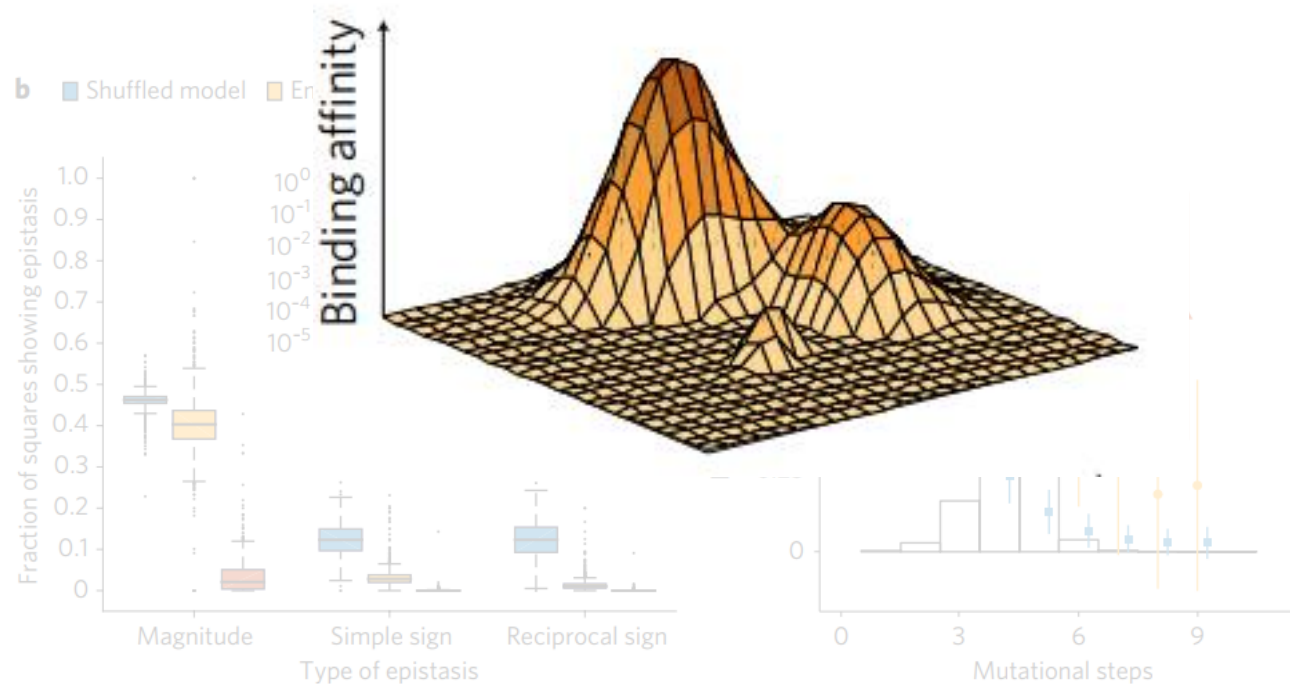


Empirical landscape nicely in between

a

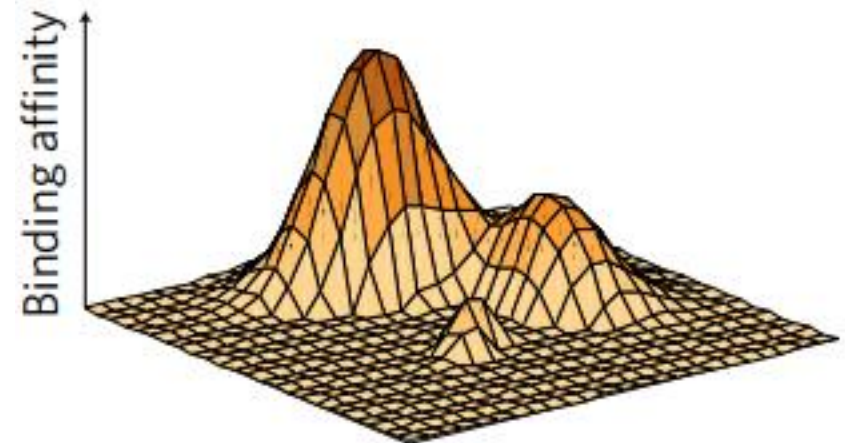
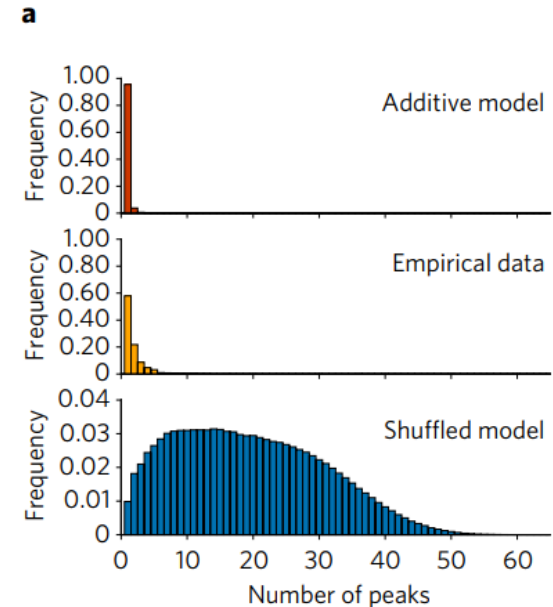


b



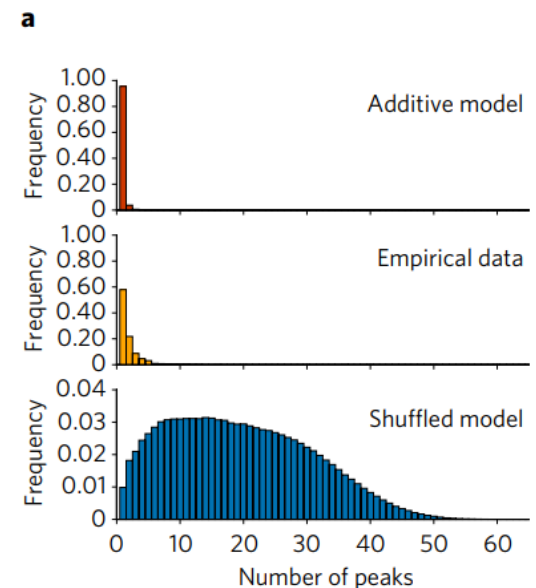
But...

- Binding affinity \neq fitness
- Global optimum \neq optimum
- Different binding affinities might be wanted!

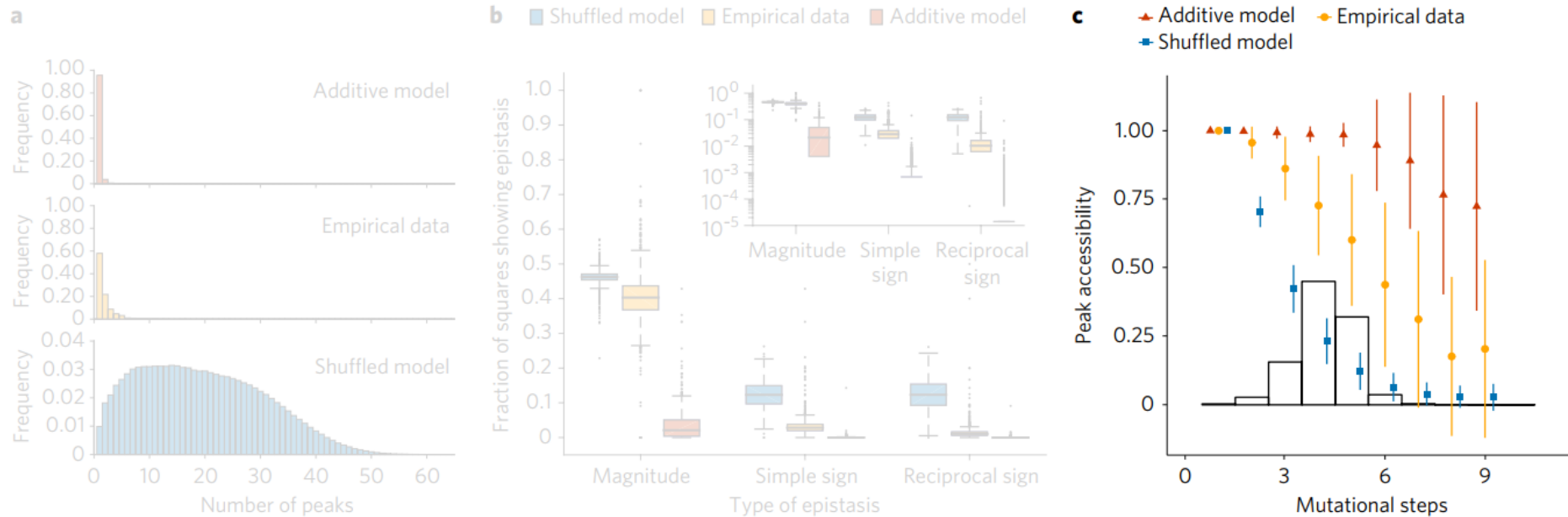


So, measure 1:

- Incorrect assumption that higher binding affinity is optimal for all TFs.
 - Different levels of binding could well be actively selected for!
- Binding affinity is not a good fitness, and therefore a very situation than RNA landscape

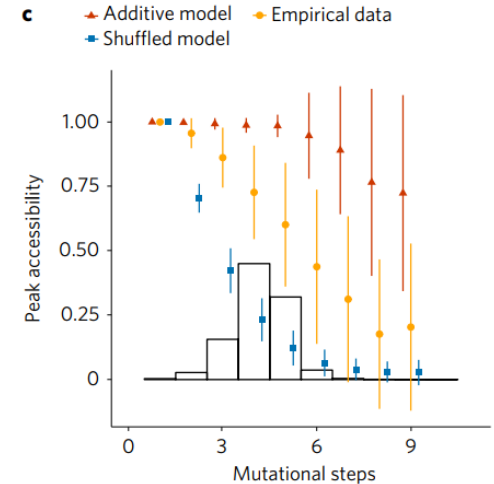


of mutational steps



Two problems

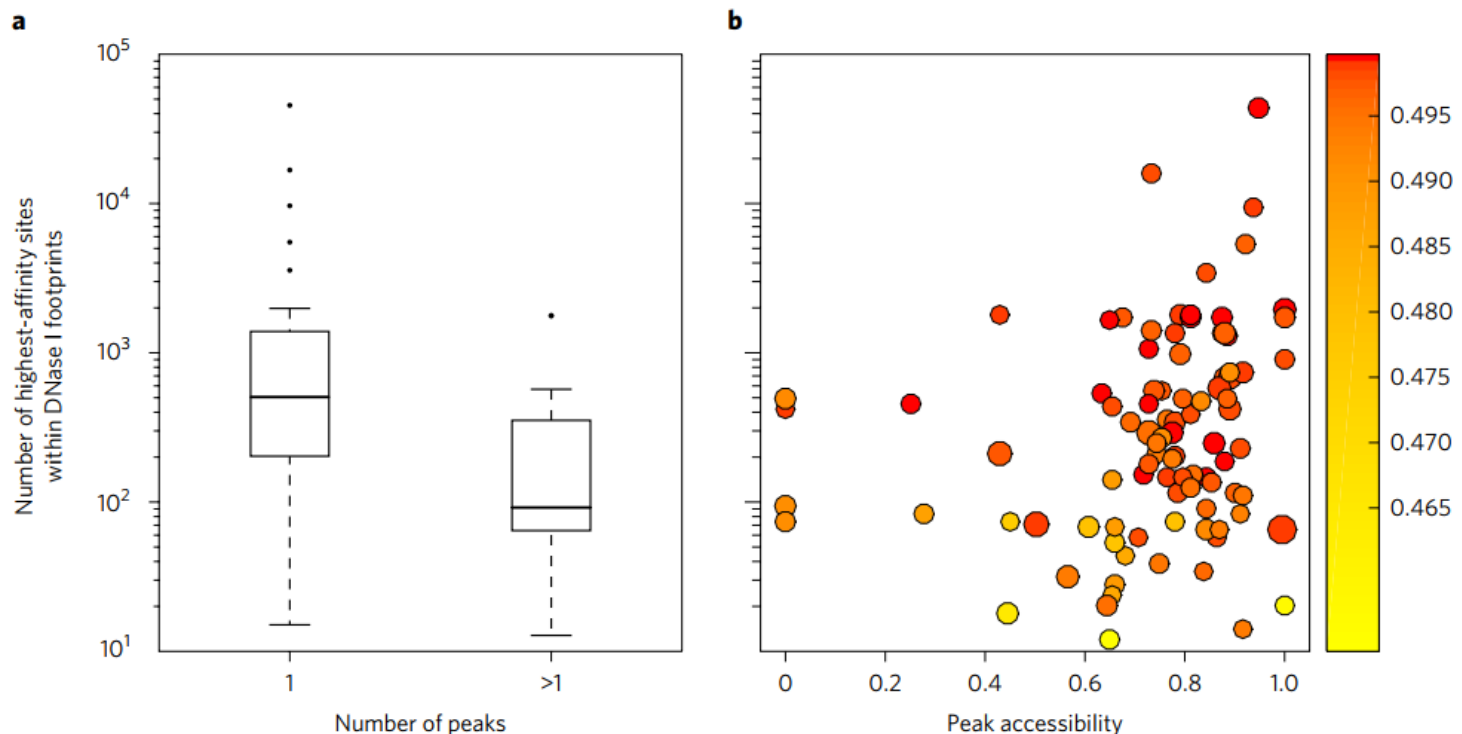
- Peak accessibility refers to the global peak
- Require paths to have steps with binding affinity rising monotonically.
 - assume slight decrease in binding affinity is not possible, while it may well be over the info threshold relative to protein production/fitness



Global optimum thinking continued

in vivo

- Aim to prove that landscapes with more peaks are more difficult for evolution to navigate
- Data shown is in mouse heart tissue.

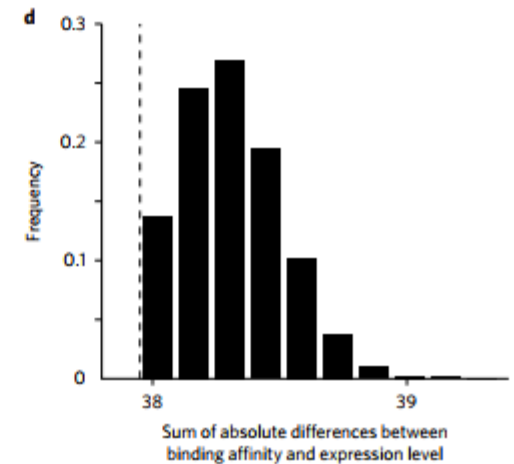
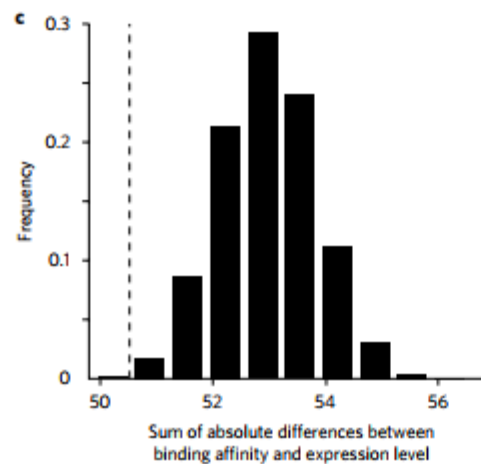
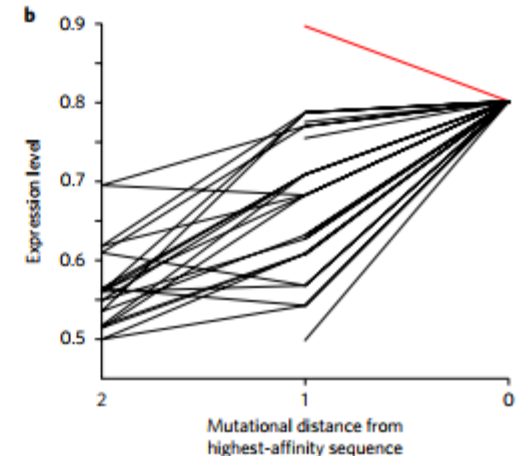
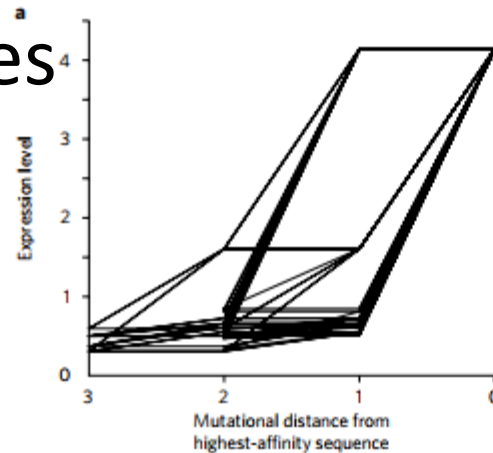
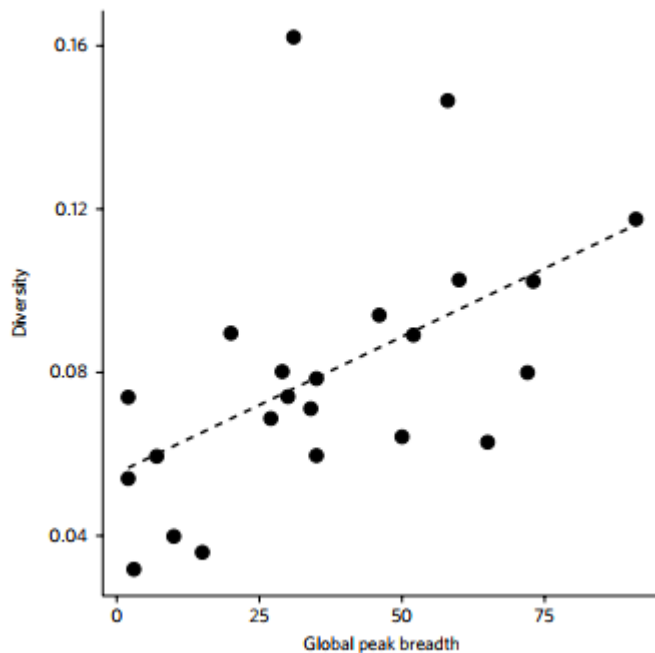


So...

- This figure doesn't say much about navigability.

Further

- Affinity correlates with gene exp.



Conclusions and Comparison

- RNA landscapes
 - actual fitness
 - here a proxy that is much less black-and-white, but that is treated as if it is.
- Require mutational paths that are strictly neutral or positive, while especially in binding affinity, many could be over the info threshold
- Neutrality around the peak
 - might allow for innovation
 - but E-score vs. Z-score

ARTICLE

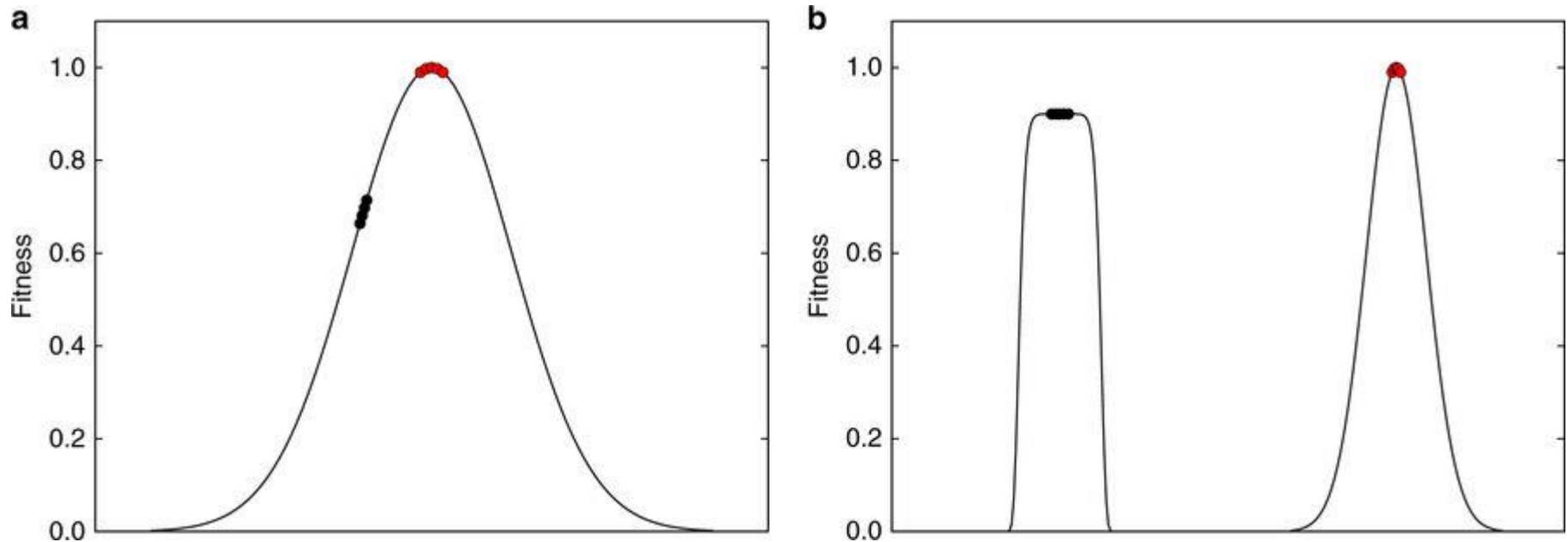
DOI: 10.1038/s41467-017-01003-7

OPEN

Evolution of drift robustness in small populations

Thomas LaBar^{1,2,3} & Christoph Adami^{1,2,3,4}

Evolution of drift robustness in small populations



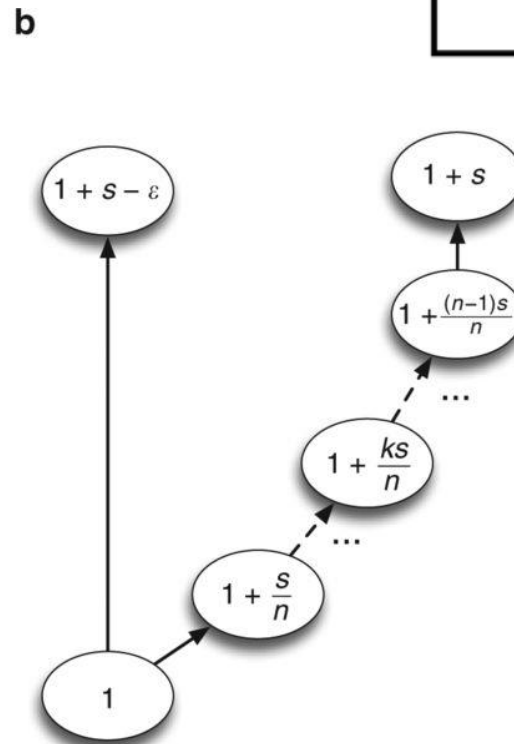
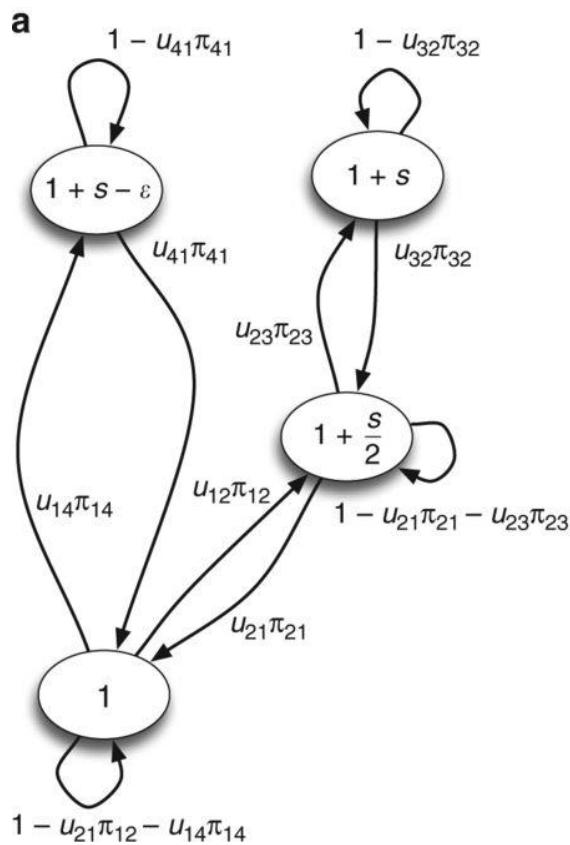
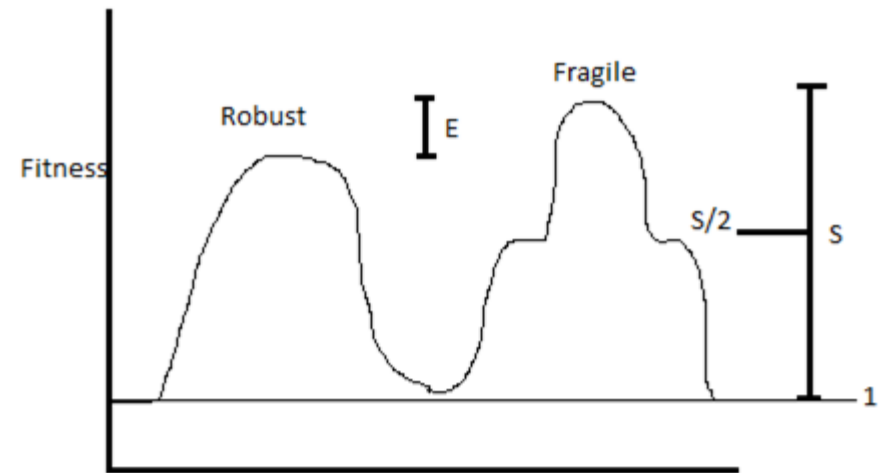
Hypothesis: small populations evolve towards lower but robuster fitness peak.

Small pop. -> weakened purifying selection

Methods

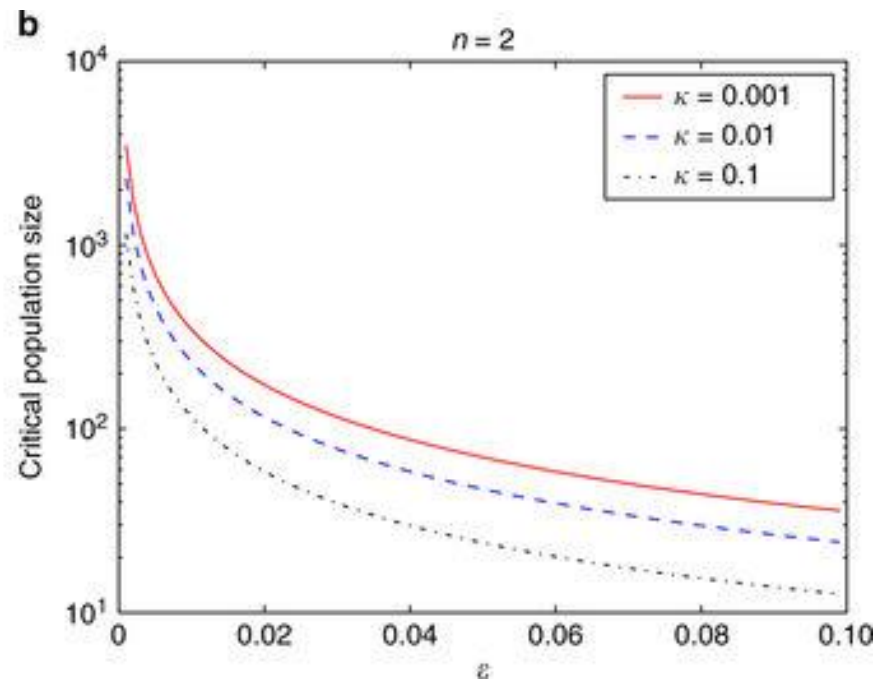
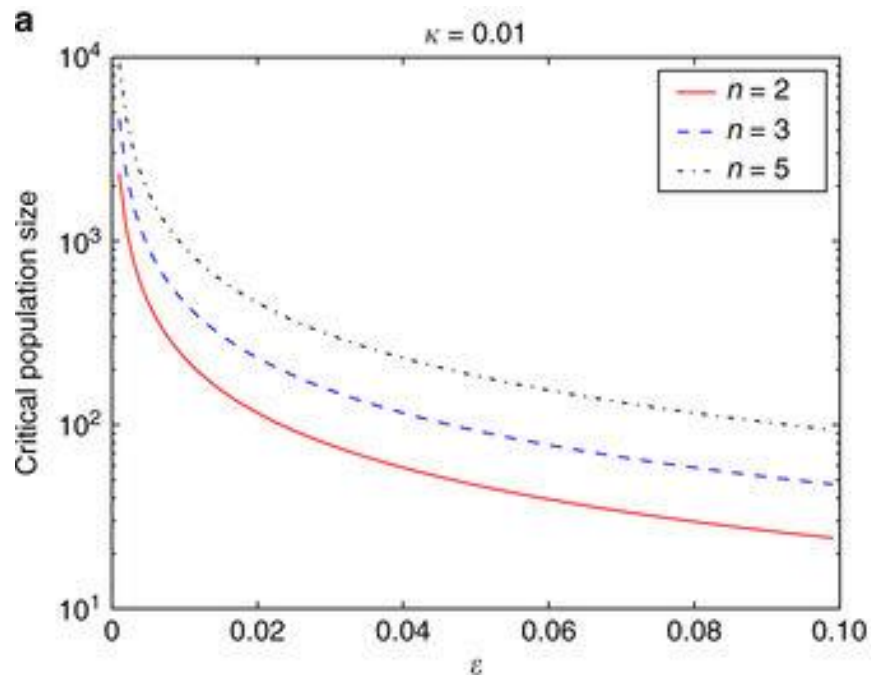
- Mathematical model (Markov model, Two-peak 2D fitness landscape)
- Avida system (complex fitness landscape)

Mathematical model



Mathematical model: Results

Shift from robust to fragile top at: $N_{\text{crit}} = 1 + (n - 1) \frac{\log \kappa^{-1}}{2\epsilon}$

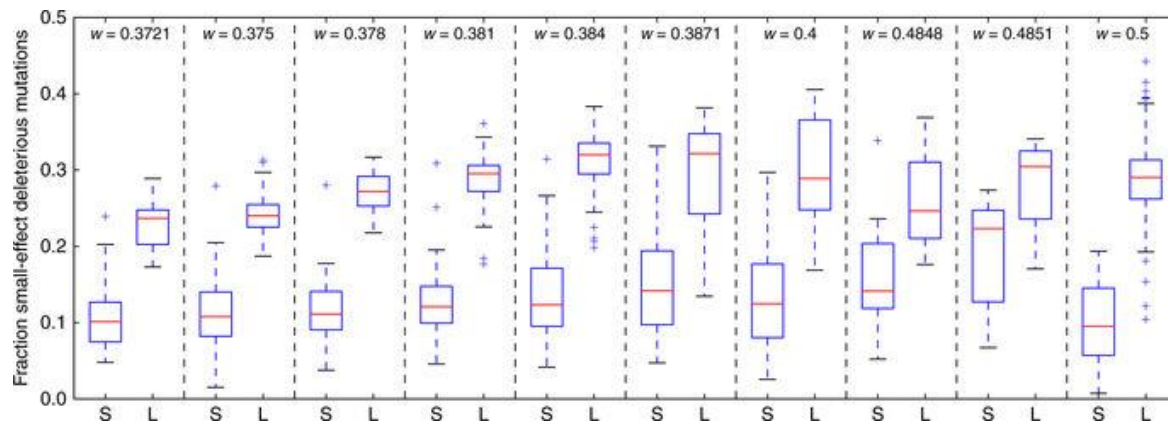


Assumptions mathematical model

- monomorphic population
- evolution as transition from one genotype to the other
- only two fitness peaks
- 2D

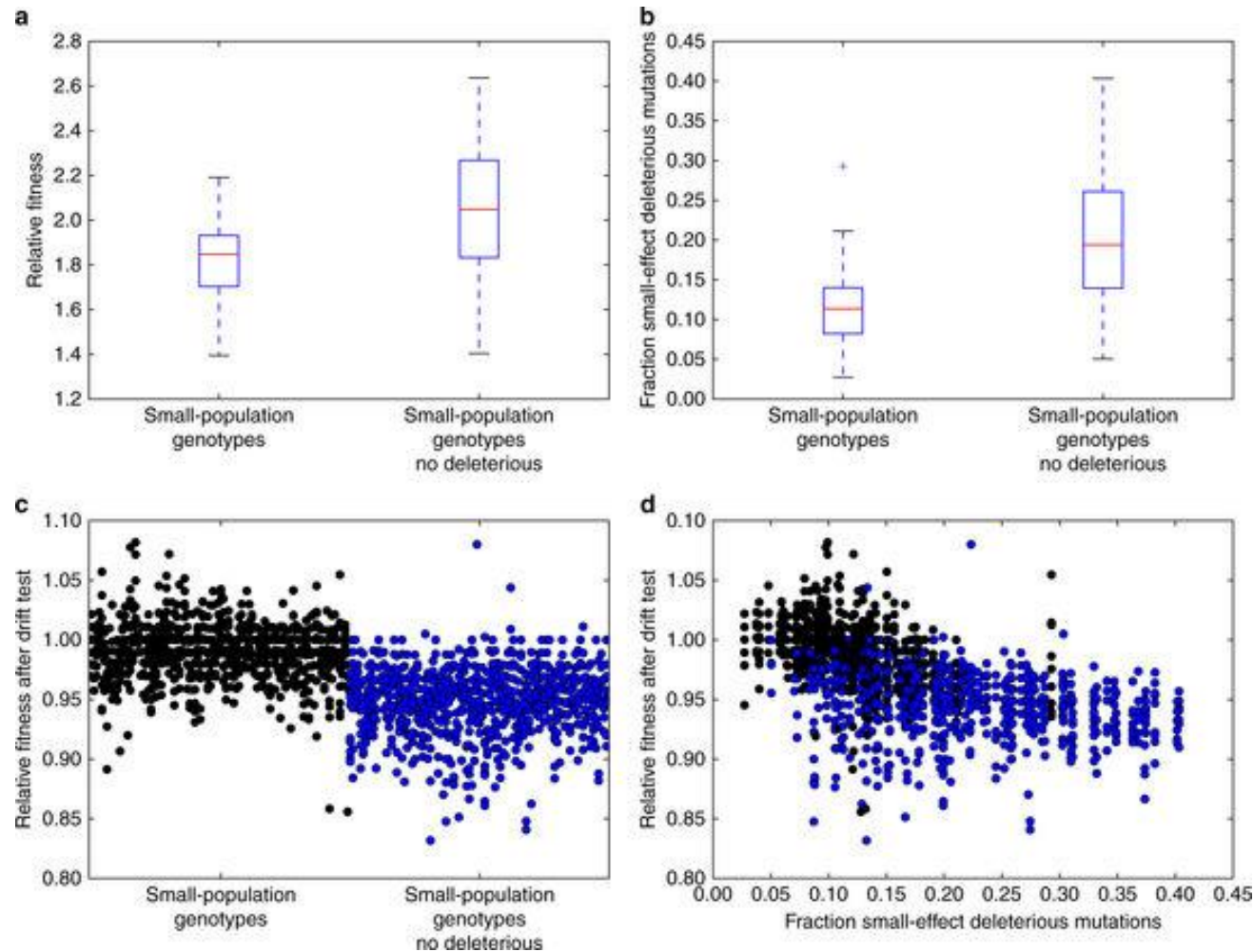
Avida model

- self-replicating avidians
- Distribution of Fitness Effect/Drift test



Less small-effect deleterious mutations in small population

Less small-effect deleterious mutations and lower fitness in small population



Discussion

- extended mathematical model: rising slope s/n , slope going down ks/n , slope going up $(n-1)s/n$
- avidian offspring replace random avidian in population
- When avidians at carrying capacity no empty space

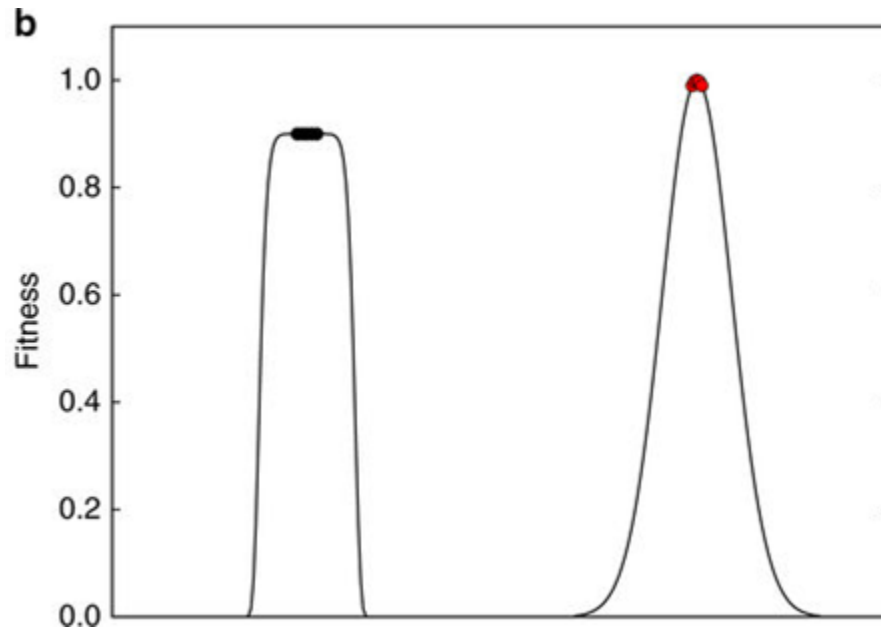
Comparison

small populations -> evolution of drift
robustness?

Similar to: “Survival of the Flattest”?
compared to small population

Conclusion

Small population tend to evolve toward a more drift robust state with a lower fitness.



Why Phenotype Robustness Promotes Phenotype Evolvability

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Accepted: December 7, 2017

Aims of the paper

- Show that Phenotype Evolvability (PE) is an increasing function of Phenotype Robustness (PR) \rightarrow general for any GPM
- Large neutral networks are responsible for differences between random and bio
- New measure for PE

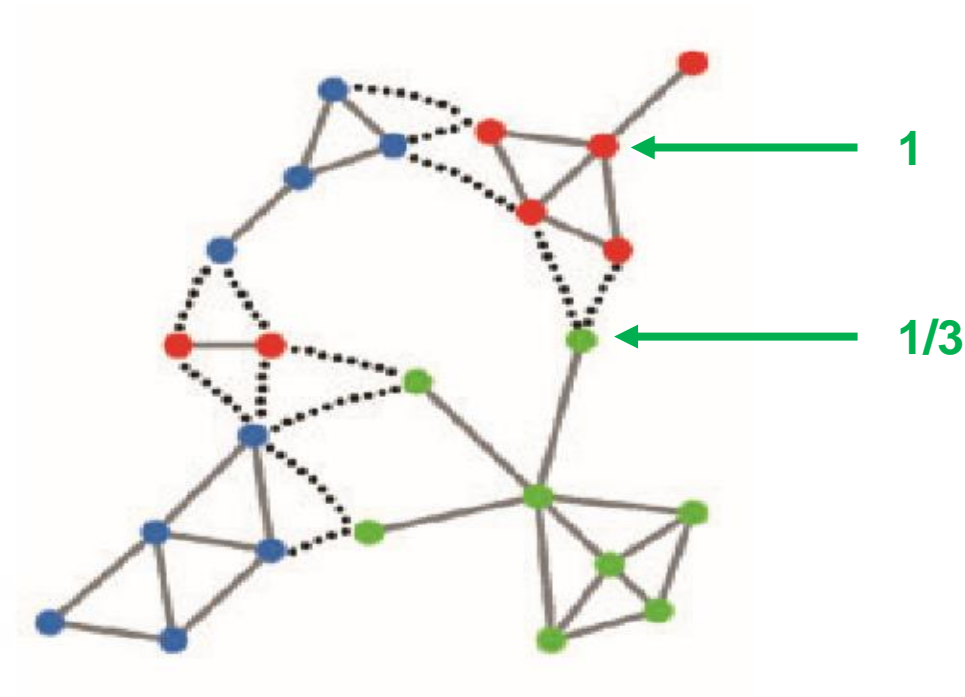
The good

- Stress importance of large neutrality in TFBS networks
- Introduce a new measure for phenotype evolvability

The bad

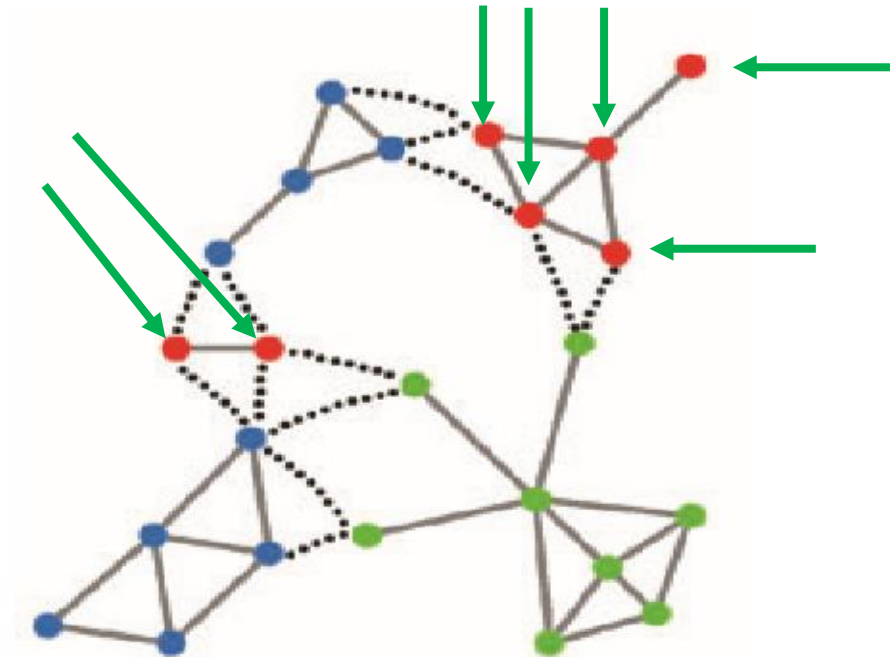
- Strange control
- Not very new to us

Definitions



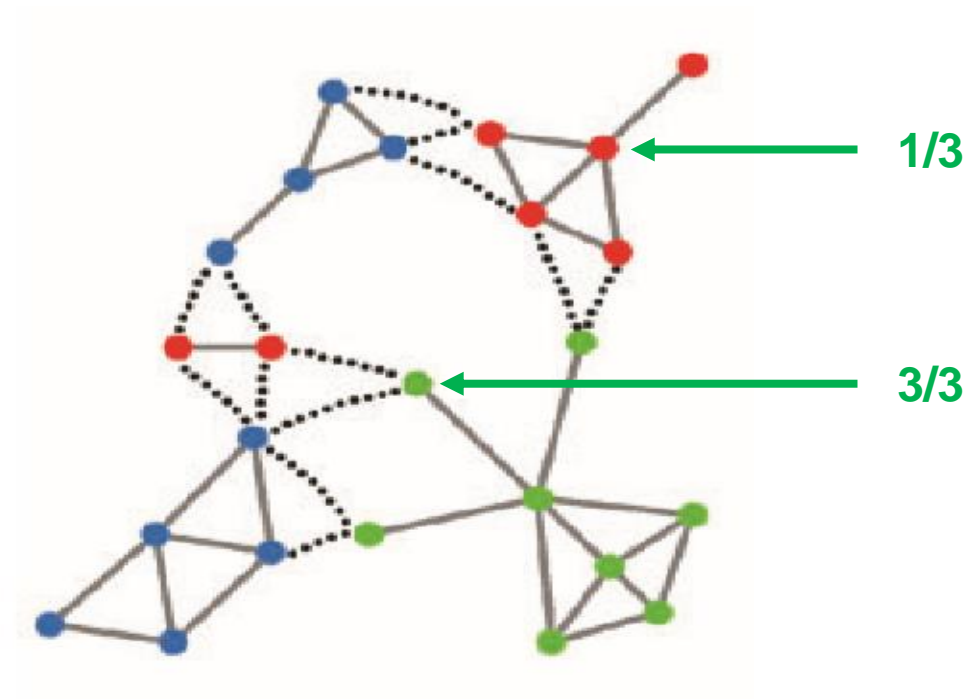
- **GR** = genotype robustness = prob. with which random mutation does not change phenotype

Definitions



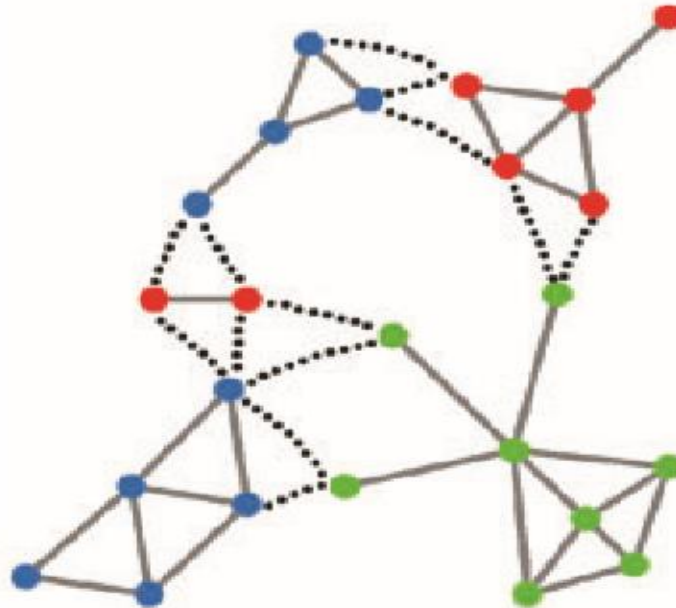
- **PR** = **p**henotype **r**obustness = mean genotype robustness of all genotypes with a specific phenotype

Definitions



- **GE** = genotype **e**volvability = fraction of all phenotypes reachable by one mutation from a given genotype

Definitions



1 for all
phenotypes
in this
schema

- **PE** = **p**henotype **e**volvability = traction of all phenotypes reachable by one mutation from any genotype exhibiting a given phenotype.
-compare **PE'**

What they did

$$E(PR_i) \approx g_i/G, \quad (1)$$

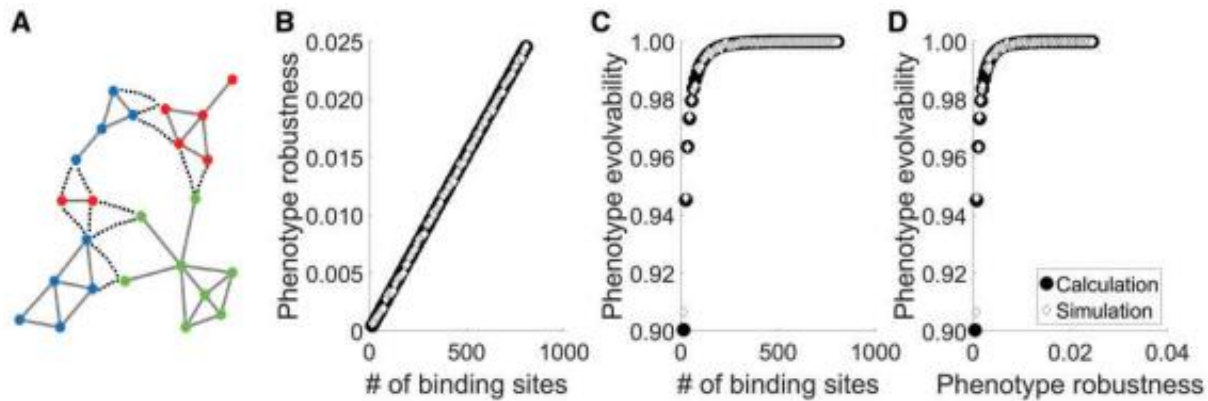
whereas the corresponding expected PE is

$$E(PE_i) \approx 1 - \sum_{j \neq i} e^{-mg_j g_i/G} / (K - 1). \quad (2)$$

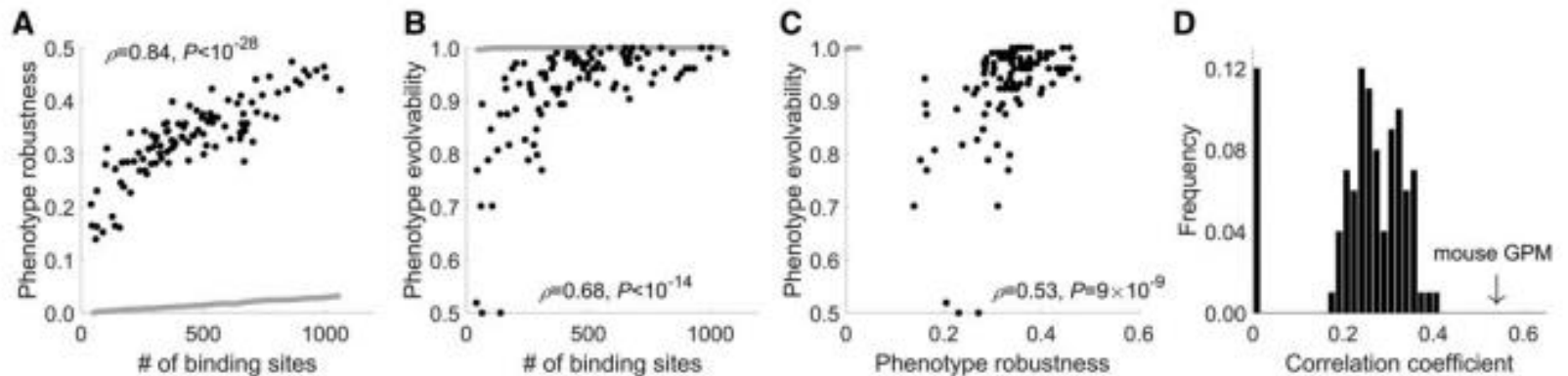
Hence,

$$\underline{E(PE_i)} \approx 1 - \sum_{j \neq i} e^{-mg_j \underline{E(PR_i)}} / (K - 1). \quad (3)$$

What they did

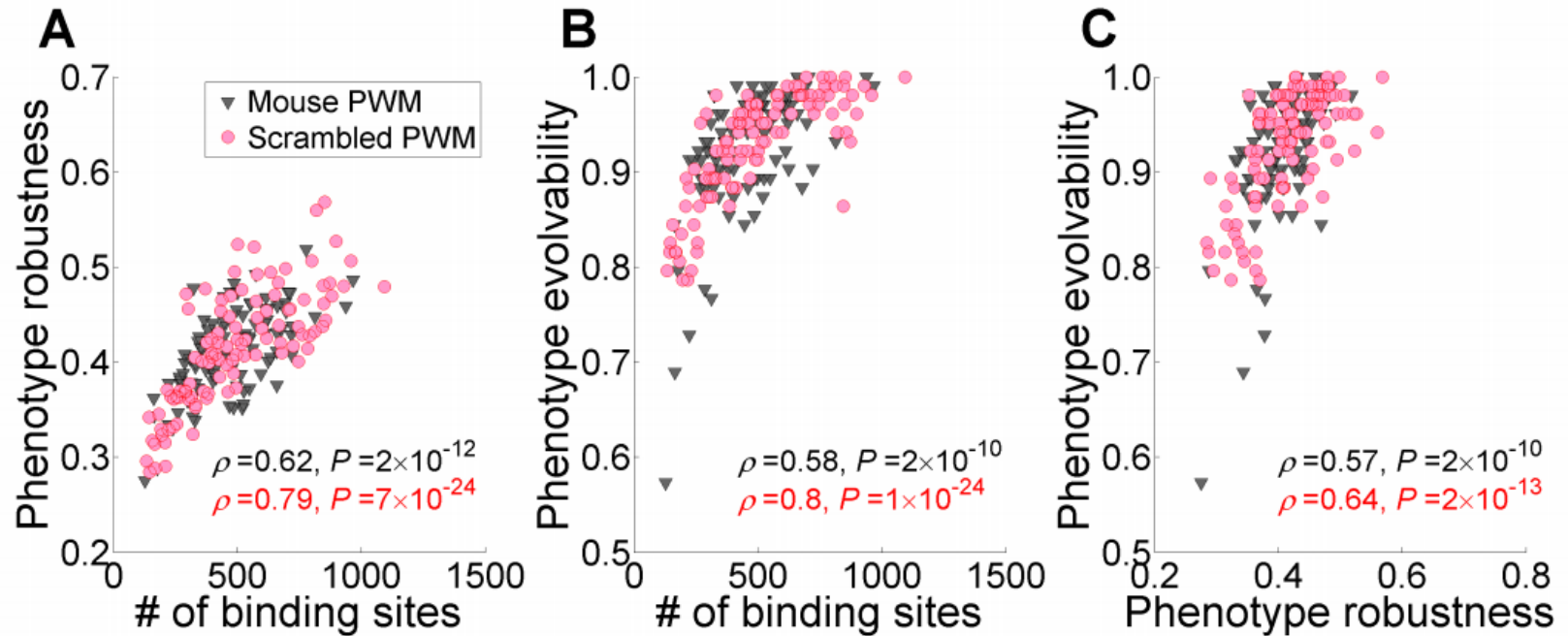


What they did



- Grey line = random shuffled control
→ strange control

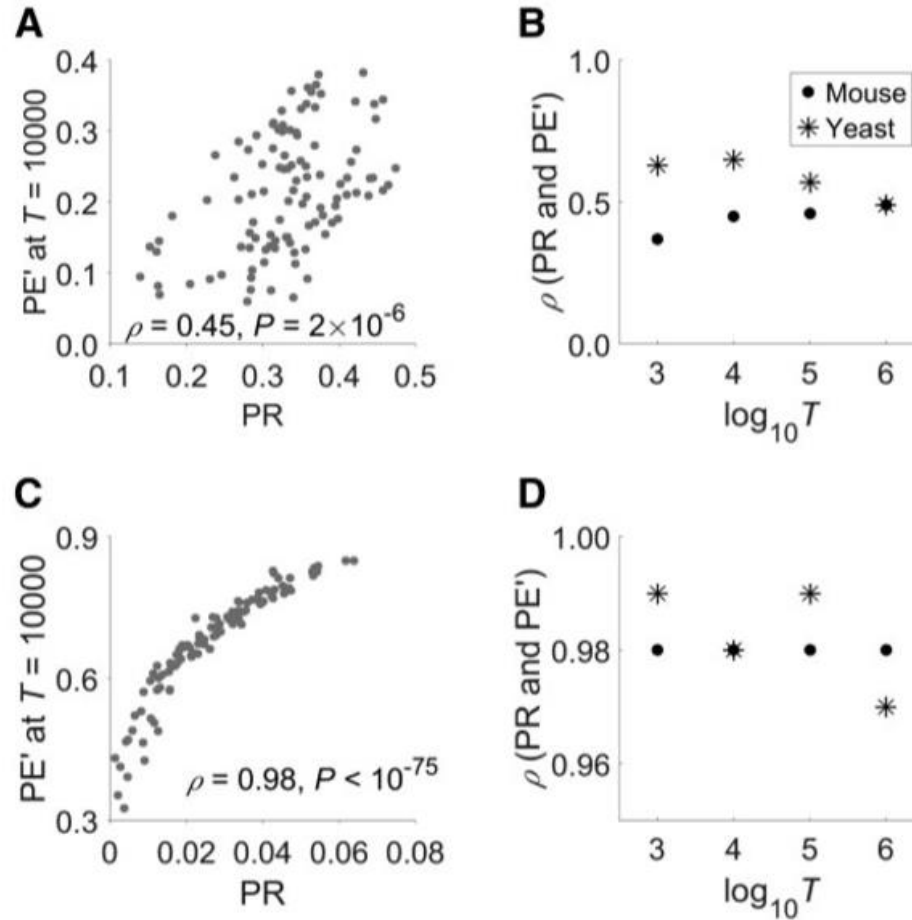
What they did



Better measure than PE

- Population genetic simulations
- Haploid adult population
- All phenotypes but one lethal
- Go to equilibrium diversity
- Then: different optimal phenotype
- See whether reached within certain time
→ **PE'**

Better measure than PE



Discussion and Comparison

- Strange to have constant # of TFBS in total genome, constant # TFs, but differing # of binding sites per TF
- Only SNPs
 - importance of mut. operators
- Control in figure 2 is ill-informed by empirical knowledge
- Switches of environment only at pop. genotypic equilibrium
- Nice that $PE \sim PR$ is general property of GPM



Robustness and Evolvability of the Human Signaling Network

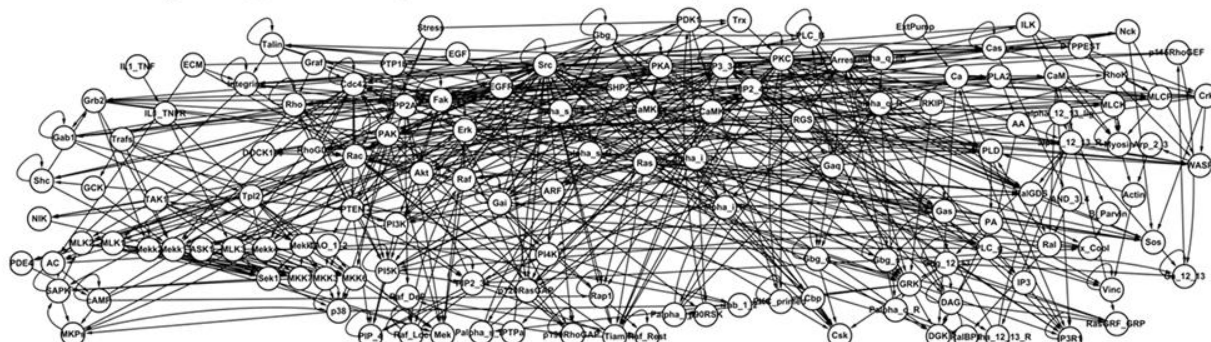
Junil Kim^{1,3}, Drieke Vandamme^{2,3}, Jeong-Rae Kim^{1,3}, Amaya Garcia Munoz², Walter Kolch^{2,4,5}, Kwang-Hyun Cho^{1*}

1 Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Yuseong-gu, Daejeon, Republic of Korea, **2** Systems Biology Ireland, University College Dublin, Dublin, Ireland, **3** Department of Mathematics, University of Seoul, Seoul, Republic of Korea, **4** Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland, **5** School of Medicine and Medical Science, University College Dublin, Dublin, Ireland

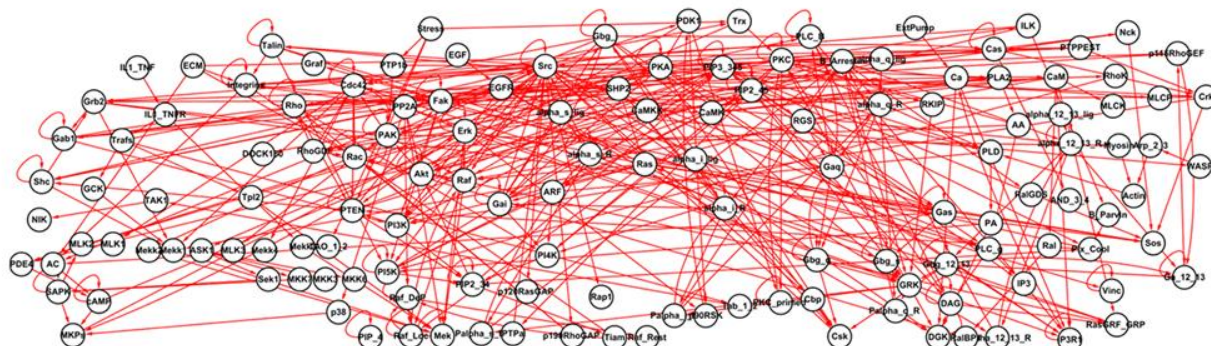
Human Signaling Network: biochemical intracellular signal transduction networks
adapted from: Helikar T, 2008

Consists of: tyrosine kinases, G protein-coupled receptors and integrins

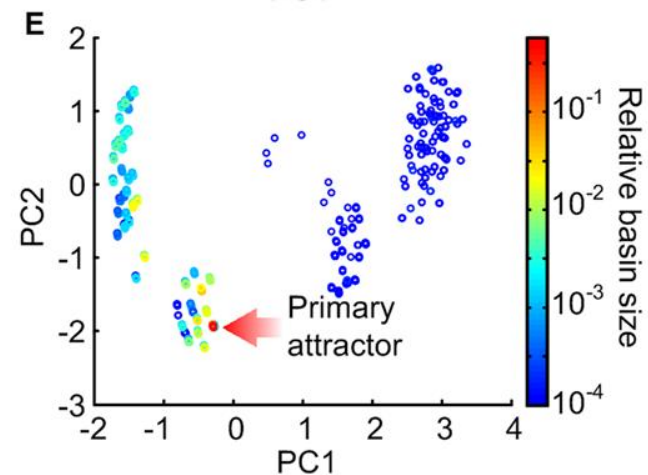
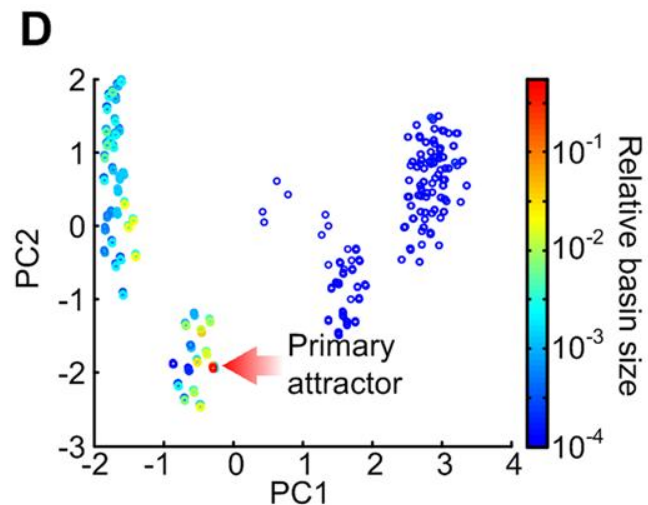
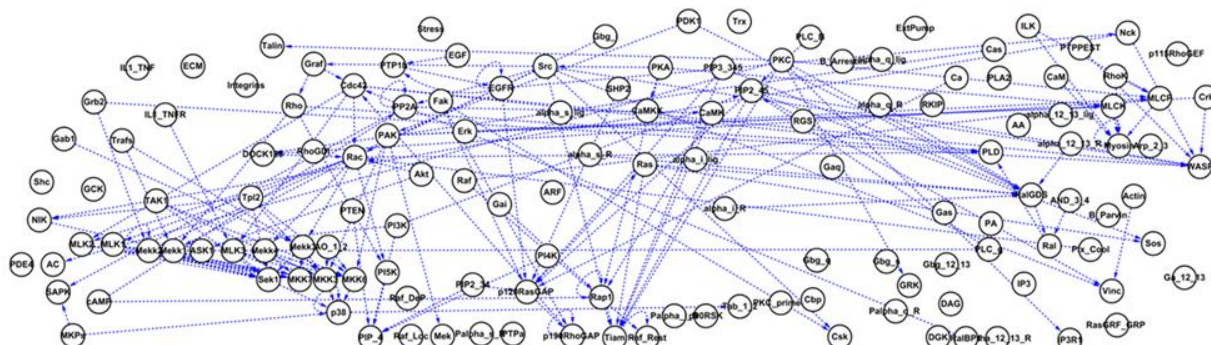
A Human signaling network (Number of links: 575)



B Evolvable core sub-network (Number of links: 408)



C Robust neighbor sub-network (Number of links: 167)

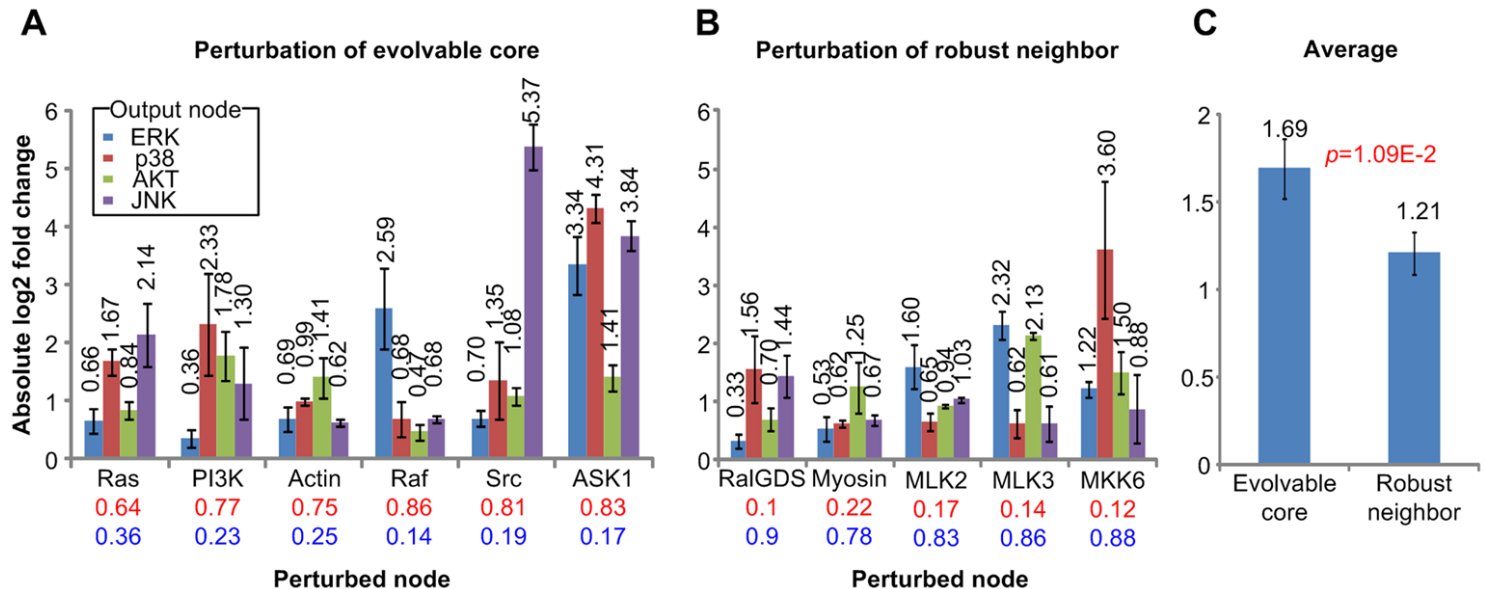


→ Evolvable core links
→ Robust neighbor links

Their definition of evolvability

Evolvable core: deletion of one node causing the attractor to change.

Robust neighborhood: deletion of one node does not change the attractor.



Paper conclusion

- Splitting out evolvability and robustness as two different things is misguided
- Their definition of evolvability actually means 'critical for normal network function'
- Drug targets:
 - Approved: big bombs
 - Experimental: more precise
 - not evo vs. robust!

Take home messages

- Empirical adaptive landscapes:
 - Possible, but difficult to wrangle
- Smaller populations can pick broader fitness peaks
- PE increases with PR.
 - PE' might be better measure
 - Mind your control
- Bogus network analyses by people who murder concepts for fun do get published