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_____ *Olivier Lichtarge* _____

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EVOLUTIONARY ACTION

THE CALCULUS OF LIFE

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Rhonald Lua

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THE EVOLUTIONARY ACTION (EA) OF A MUTATION ON FITNESS

$$f'(\gamma) \cdot d\gamma = d\varphi$$

Katsonis and Lichtarge
Genome Research 2014

Evolutionary gradient

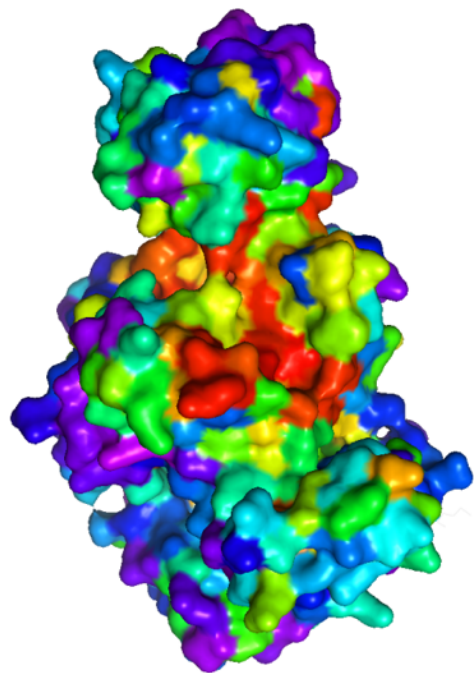
mutation size

Evolutionary Action
of mutation on
fitness

EA MUTATIONAL SCANNING PYRUVATE DECARBOXYLASE (L-PYK)

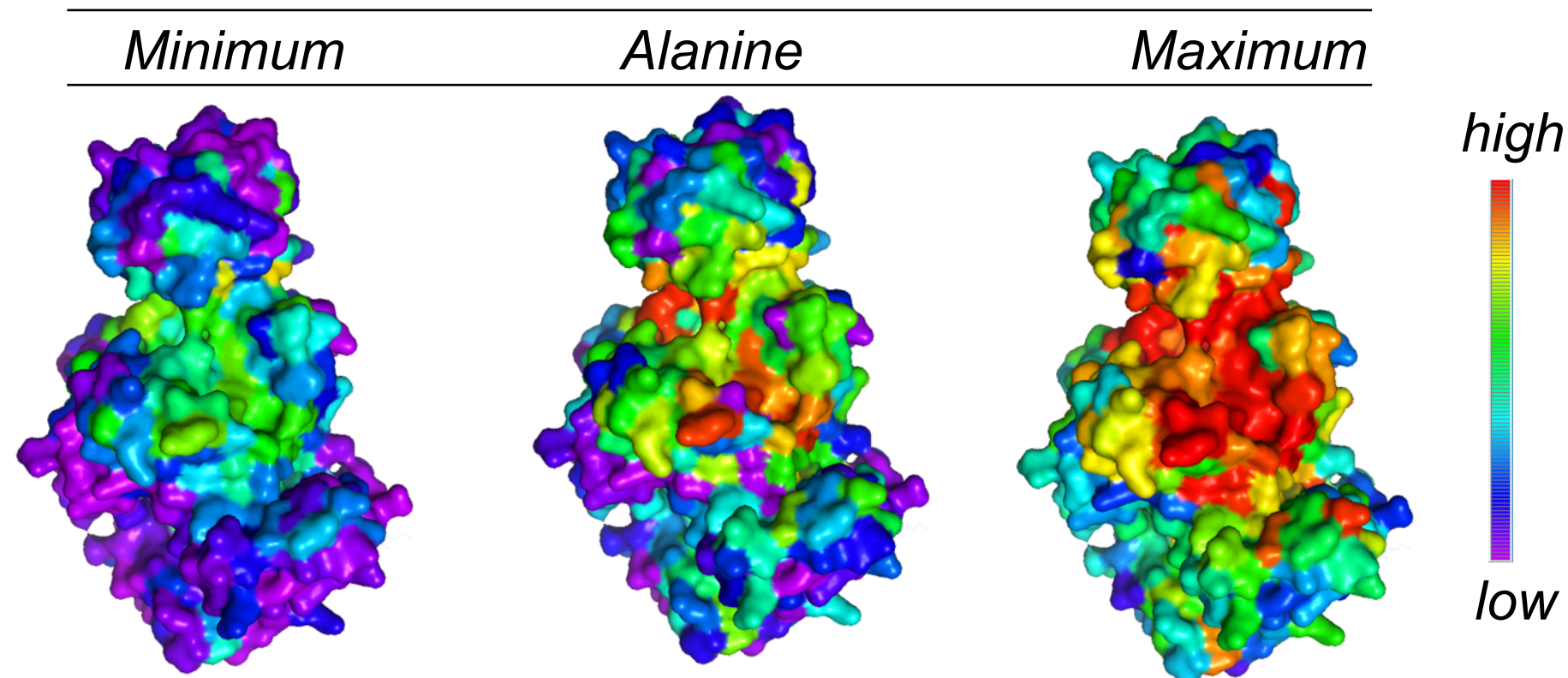
$$f'(\gamma) \cdot d\gamma = d\phi$$

Evolutionary gradient



Length: 543 aa
Structure: 4ip7 Holyoke et al (2013) Biochem
Sequences: 124 from bacteria up to animals

Evolutionary Action scan of mutations on L-PYK fitness

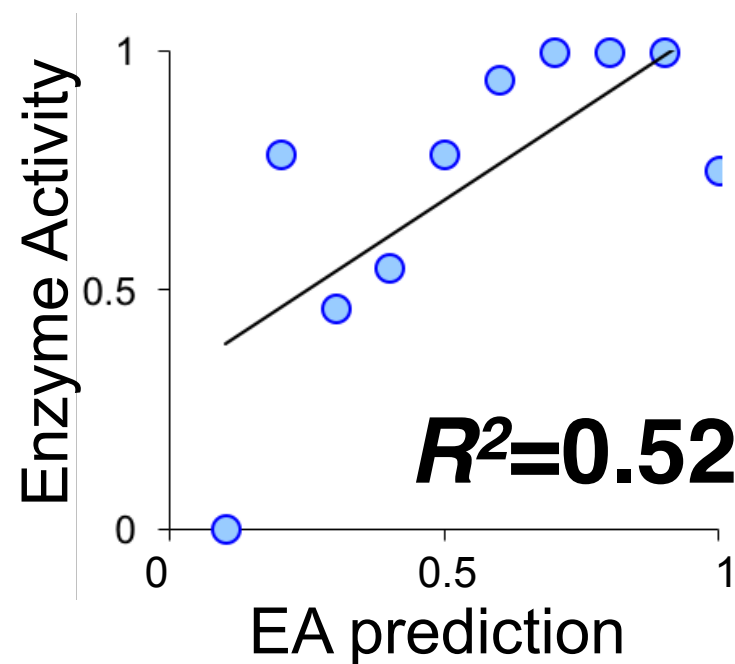


THE EVOLUTIONARY ACTION CORRELATES WITH FUNCTIONAL LOSS DUE TO MUTATIONS IN L-PYK

$$f'(\gamma) \cdot d\gamma = d\phi$$

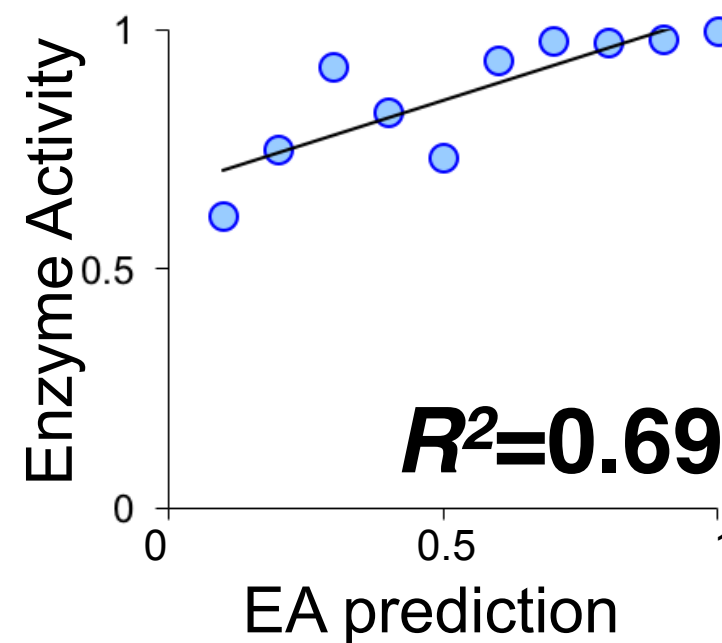
Experiment 1

113 variants in 9 residues



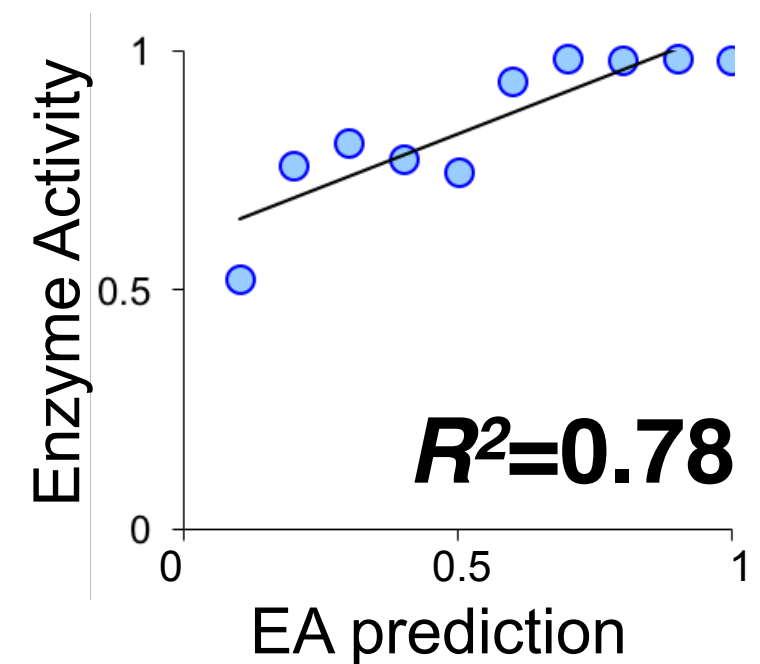
Experiment 2

430 variants in any residues



Experiments 1 and 2

543 variants



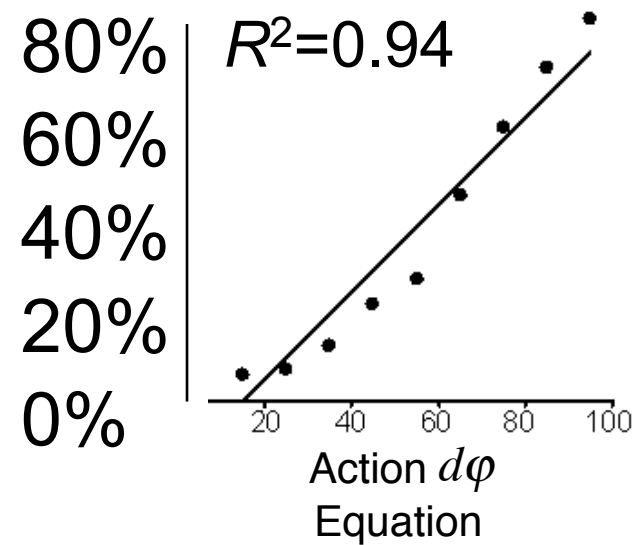
EA CORRELATES WITH FUNCTIONAL LOSS

$$f'(\gamma) \cdot d\gamma = d\phi$$

Lac Repressor

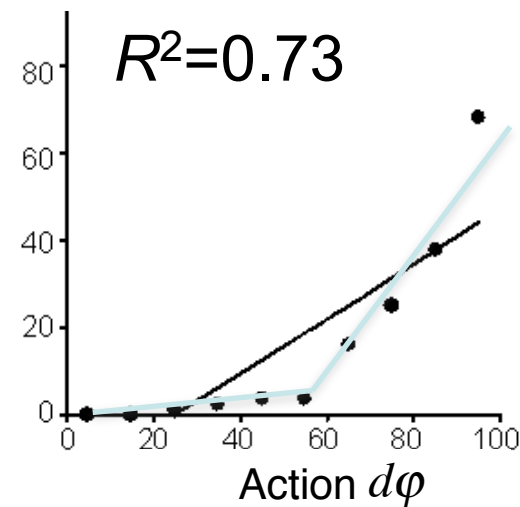
Loss of β -galactosidase repression
in 4041 mutants

Experiment



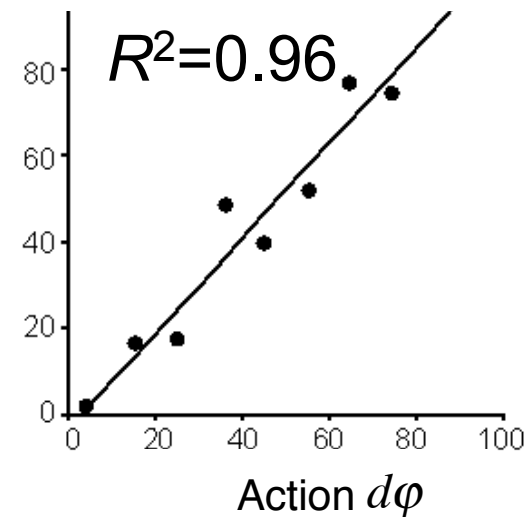
T4 Lysozyme

Loss of plaques
in 2015 mutants



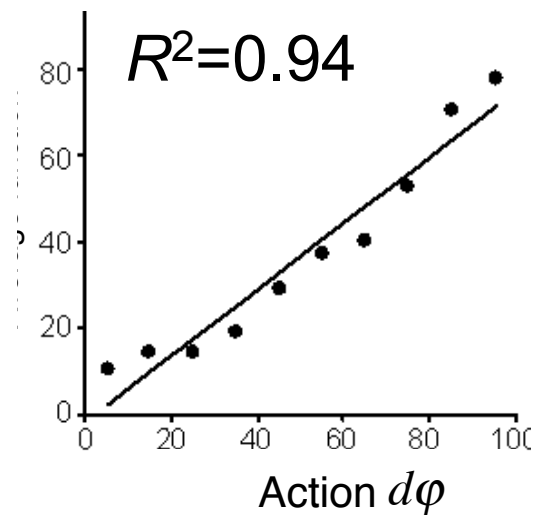
HIV Protease

loss of cleavage
in 336 mutants



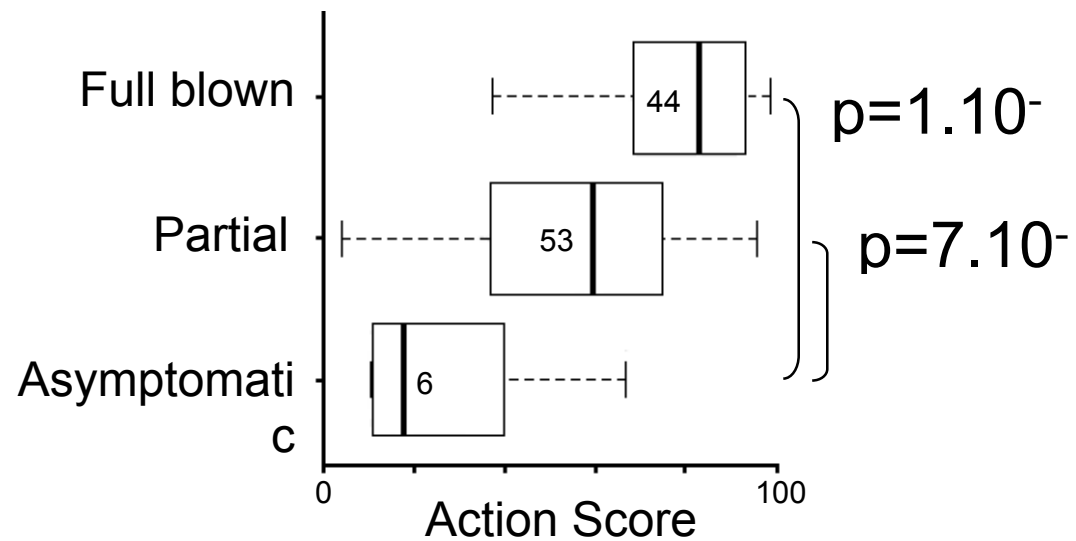
p53

mean loss of transactivation
in 2314 mutants

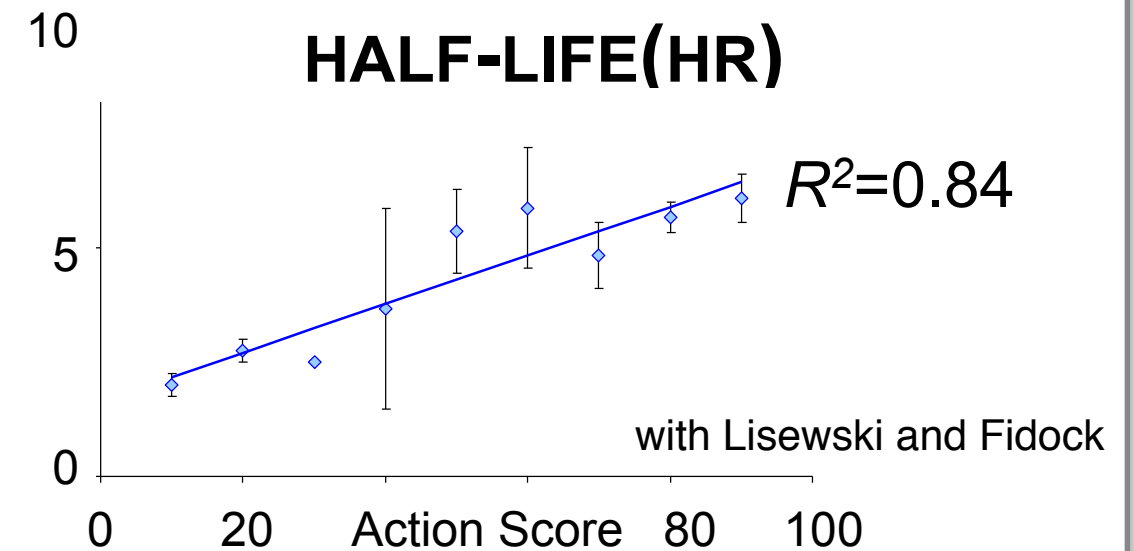


IN PRACTICE, EA IS A MARKER OF MORBIDITY, MORTALITY AND DRUG RESISTANCE

CYSTIC FIBROSIS MORBIDITY



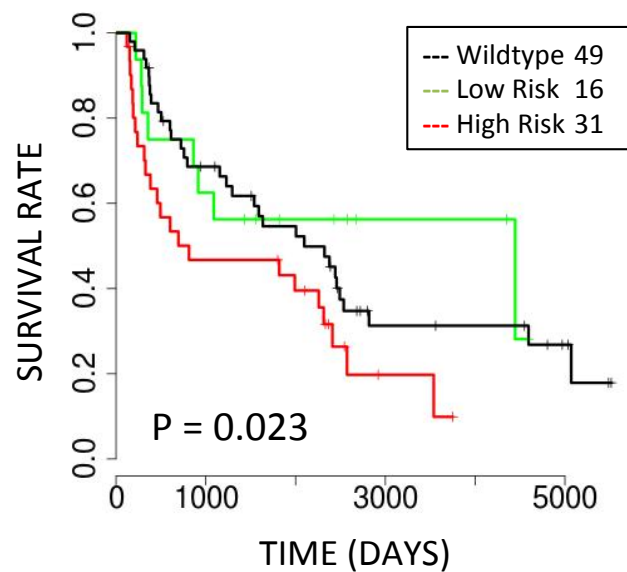
MALARIA CLEARANCE HALF-LIFE(HR)



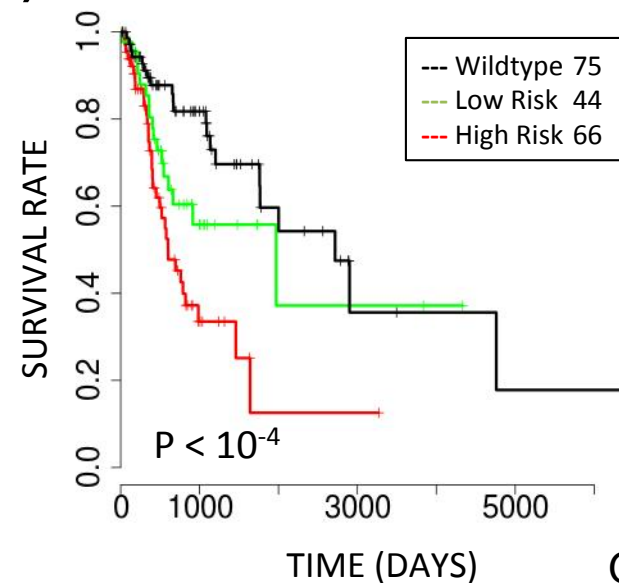
HEAD AND NECK:

a. MORTALITY

MDACC TRAINING COHORT (96)



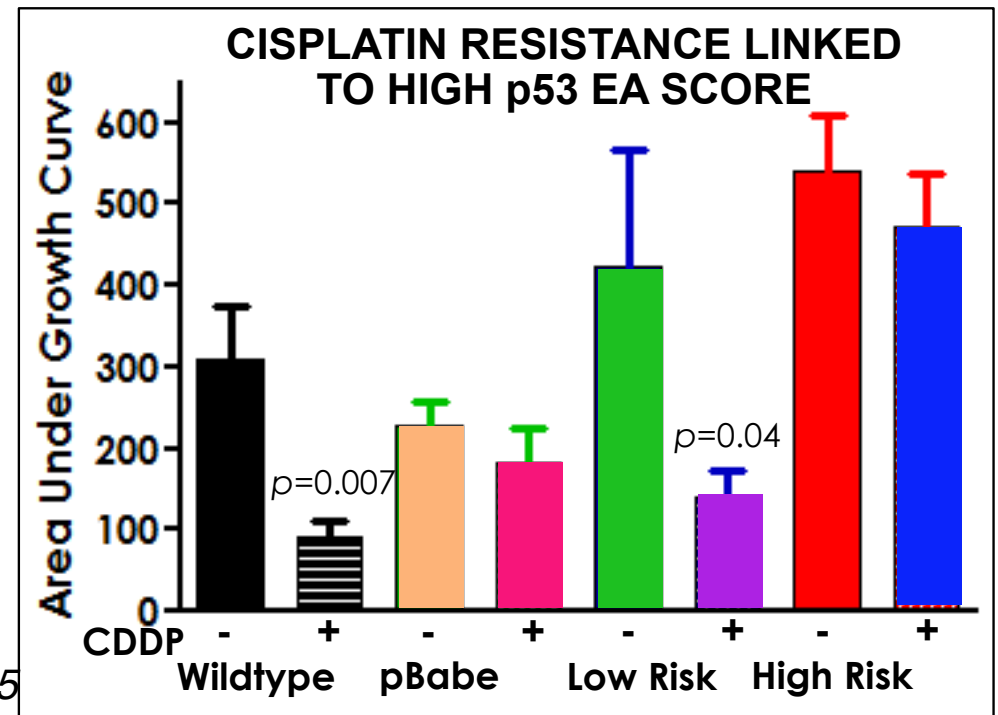
TCGA TESTING COHORT (185)



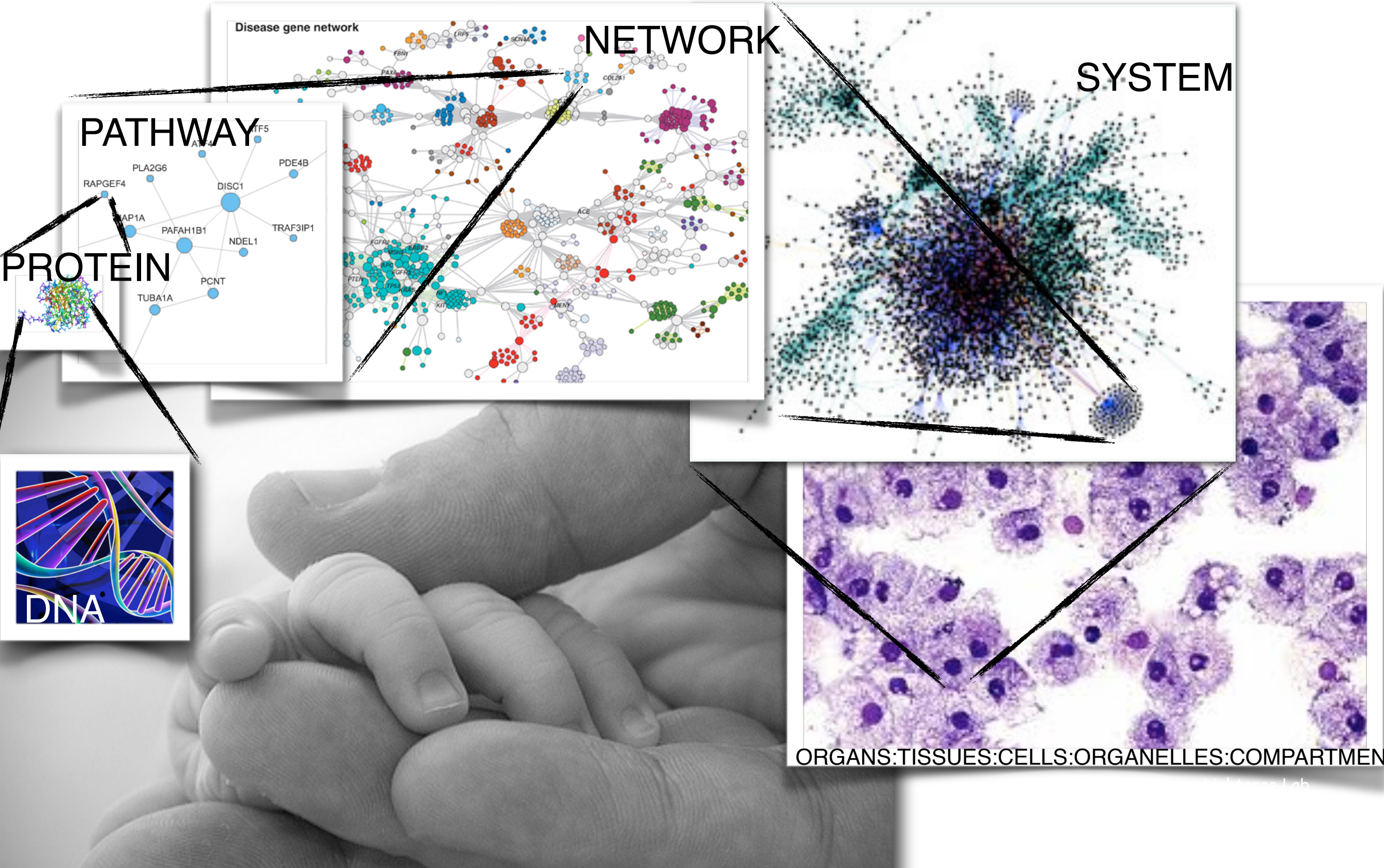
Neskey et al and Jeff Myers *Cancer Res* 2015

Osman et al
Cancer Res 2015

b. DRUG RESISTANCE MARKER

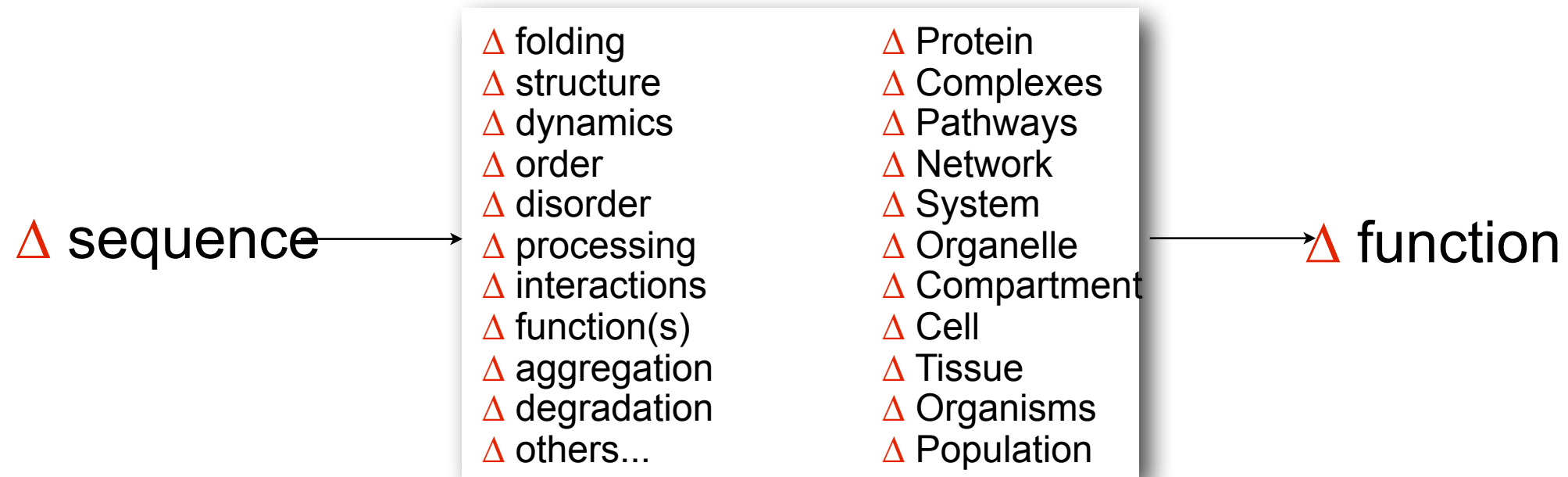


HOW DOES IT ALL WORK?





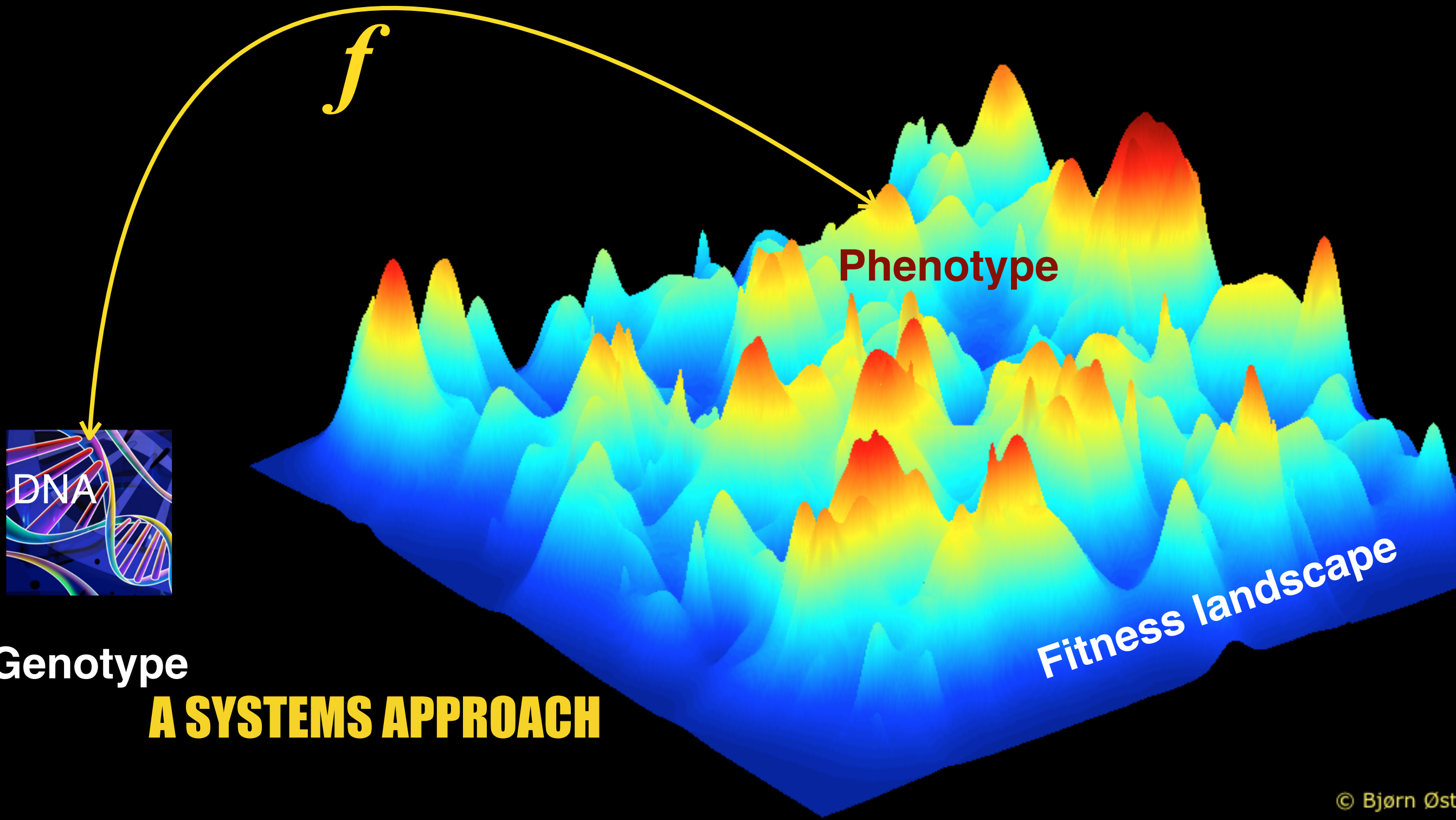
MUTATIONS PERTURB MYRIAD FEATURES



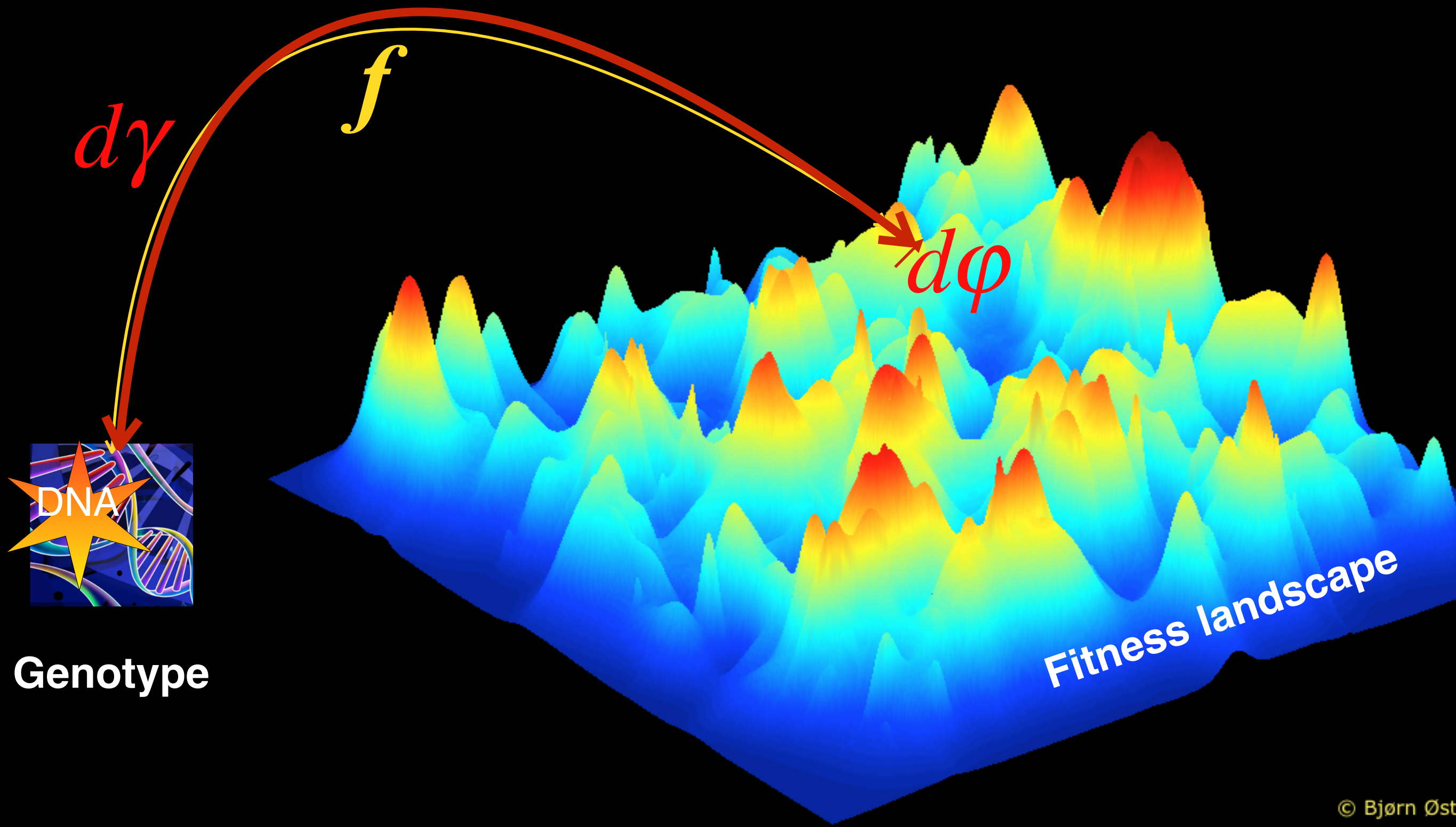
An ill-posed problem?

IS THERE A BETTER REPRESENTATION?

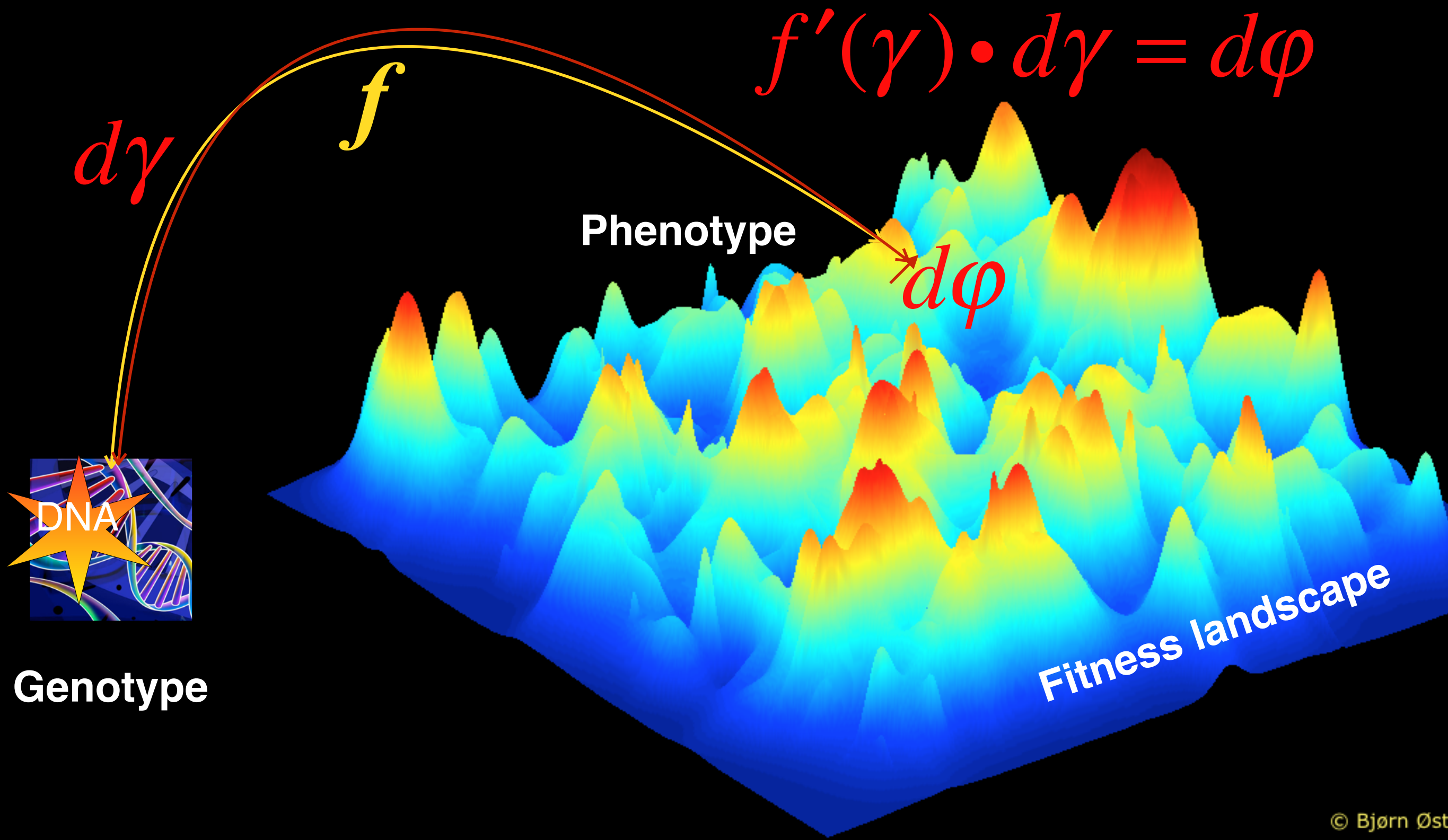
THE EVOLUTIONARY FUNCTION MAPS GENOTYPE TO PHENOTYPE



MUTATIONS PERTURB THIS MAPPING



PROVIDED EVOLUTION IS DIFFERENTIABLE THE ACTION OF A MUTATION DEPENDS SIMPLY ON f'



AN EQUATION FOR THE EVOLUTIONARY ACTION (EA) OF A MUTATION ON FITNESS

$$f'(\gamma) \cdot d\gamma = d\varphi$$

Evolutionary gradient

mutation size

Evolutionary Action
(EA) of mutation on
fitness

NEED ONLY TO COMPUTE ITS FACTORS

THE EVOLUTIONARY GRADIENT IS A RATIO OF VARIATIONS

$$f'(\gamma) \sim \frac{\Delta\varphi}{\Delta\gamma}$$

Evolutionary gradient

Evolutionary Trace (ET)



Lichtarge et al *J Mol Biol* 1996

THESE VARIATIONS ARE IN THE SEQUENCE (GENOTYPE) AND IN THE RESULTING CHANGE IN FITNESS (PHENOTYPE)

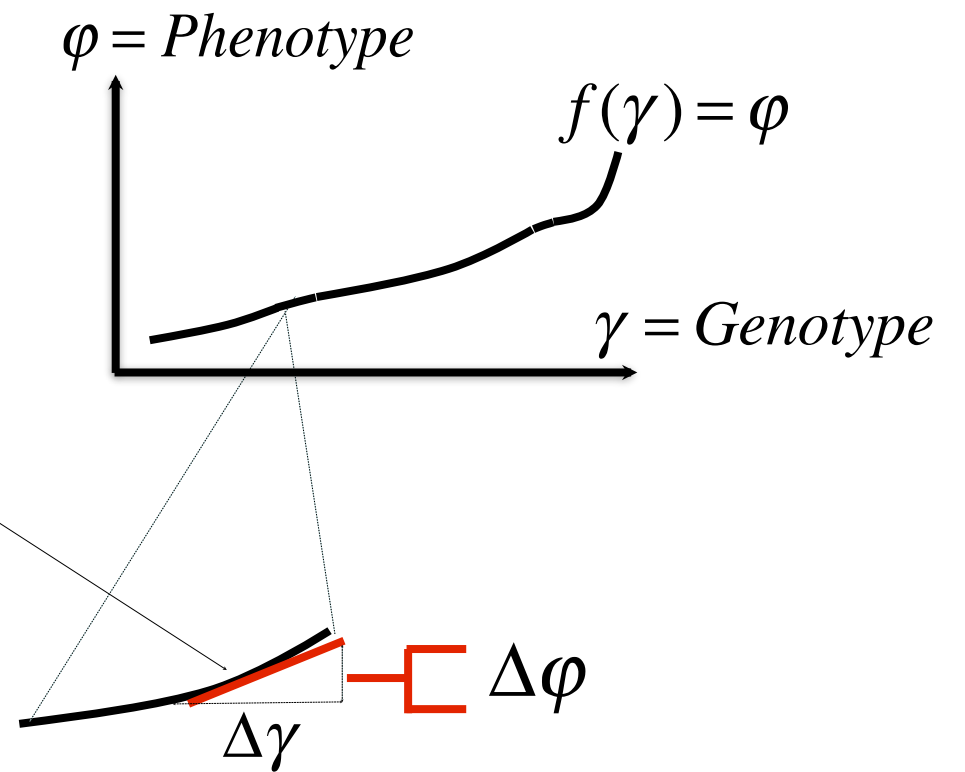
$$f'(\gamma) \sim \frac{\Delta\phi}{\Delta\gamma}$$

Evolutionary gradient

Evolutionary Trace (ET)

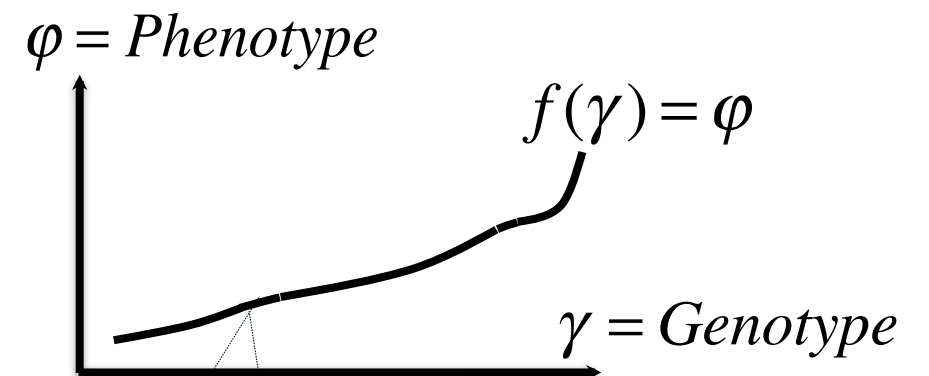


Lichtarge et al *J Mol Biol* 1996



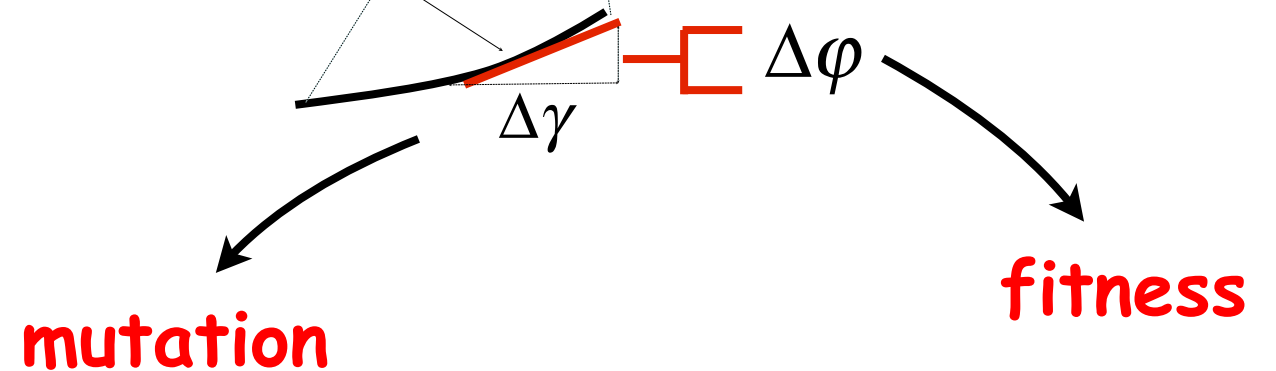
THIS RATIO IS *FITNESS VARIATION:MUTATIONAL VARIATION*

$$f'(\gamma) \sim \frac{\Delta\phi}{\Delta\gamma}$$



Evolutionary gradient

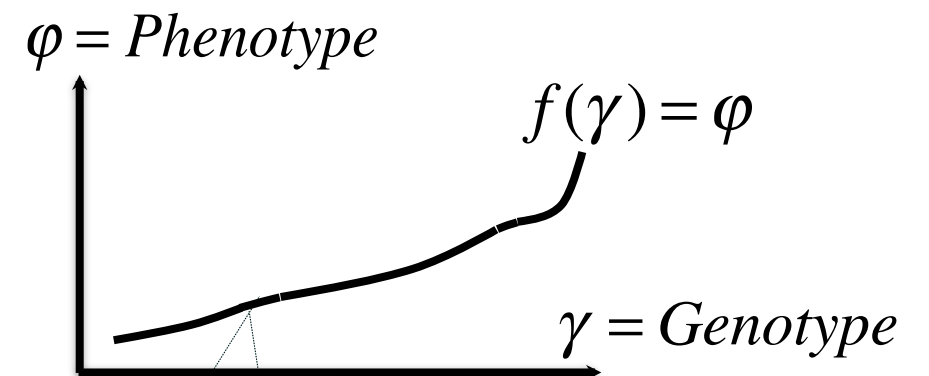
Evolutionary Trace (ET)



Lichtarge et al *J Mol Biol* 1996

THE MAGNITUDE OF SEQUENCE AND FITNESS VARIATIONS CAN BE READ FROM EVOLUTION IN THE SAME WAY AS ET

$$f'(\gamma) \sim \frac{\Delta\phi}{\Delta\gamma}$$



Evolutionary gradient

Evolutionary Trace (ET)



Lichtarge et al *J Mol Biol* 1996

mutation

variation

E

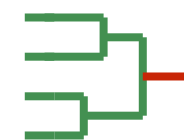
KERTFTGHKKLM
KERTFTGHKRLM
KERTFTVHKRLM
KERTFTGHKKLM
VERTFTGHKSQM
VERTDTGHKRQM
VERTFTGMKRQM

S

ASR.YTGVKKNM
ASR.YTGVKKNV
ASR.YTGHKKNM
ASR.YTGHKKNM

fitness assay

divergence



THE EVOLUTIONARY GRADIENT (ET) IS USEFUL

Application/Test	Protein	Collaborator	References
Predict Binding site	Gα transducin	<i>Bourne</i>	<i>Lichtarge PNAS</i> 1996
Separate function	Nuclear Transport	<i>Moore</i>	<i>Cushman J. Mol. Biol.</i> 2004
	Steroid receptors	<i>Smith</i>	<i>Raviscioni Proteins</i> 2006
	Ku	<i>Bertuch</i>	<i>Ribes-Zamora Nat Struc Molec Biol</i> 2007
	RecA - LexA	<i>Herman</i>	<i>Adikesavan PLoS Genetics</i> 2011
Swap function	RGS	<i>Wensel</i>	<i>Sowa PNAS</i> 2000
<i>Biol</i> 2001			<i>Sowa Nat Struct</i>
	Proneural proteins	<i>Hassan</i>	<i>Quan Development</i> 2004
	Nuclear Receptors	<i>Cooney</i>	<i>Raviscioni J. Mol Biol.</i> 2005
Redesign function	GPCRs	<i>Wensel</i>	<i>Yang Mol Endocrinol</i> 2002
2003			<i>Lin J Biol Chem.</i>
<i>Chem.</i> 2006		<i>Lefkowitz</i>	<i>Madabushi J Biol Chem.</i> 2004
			<i>Shenoy J Biol</i>
		<i>Bouvier</i>	<i>Kobayashi Traffic</i> 2009
		<i>Hansen</i>	<i>Bonde Biochem Pharmacol</i> 2010
Build inhibitors	Nuclear Receptors	<i>Cooney</i>	<i>Gu J. Biol. Chem.</i> 2005
	GRK	<i>Clark</i>	<i>Baameur Mol Pharm</i> 2010
	Cohesin	<i>Pati</i>	
Assess gene variations HPD		<i>Bodamer</i>	<i>Item Mol Gen Metab</i> 2007
	RRM2B	<i>Shinawi</i>	<i>Shaibani Arch Neurol.</i> 2009
	TP53	<i>Myers</i>	
	CAGI		
Predict protein function	Structural Proteome		<i>Kristensen Prot Sci</i> 2006
			<i>Ward PloS One</i> 2009
			<i>Erdir J Mol Biol</i> 2010
			<i>Kristensen BMC bioinf</i> 2008
			<i>Ward Bioinformatics</i> 2009
			<i>Venner PLoS One</i> 2011

THE EVOLUTIONARY ACTION EQUATION IS COMPUTABLE

$$f'(\gamma) \cdot d\gamma = d\phi$$

Katsonis and Lichtarge
Genome Research 2014

Evolutionary gradient

mutation size

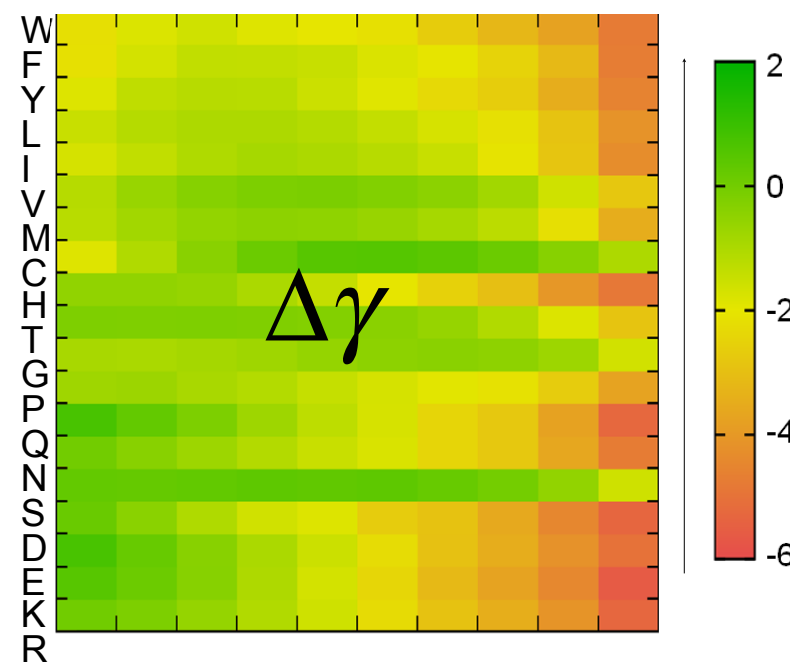
Evolutionary Action of
mutation on fitness

Evolutionary Trace (ET)



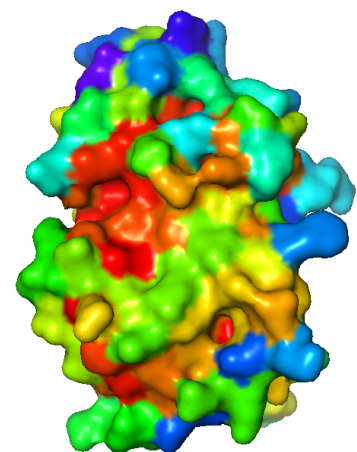
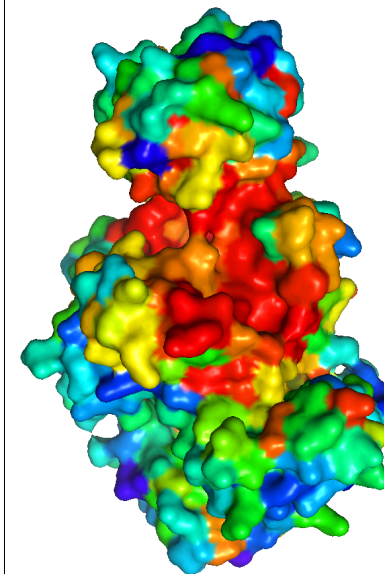
Lichtarge et al *J Mol Biol* 1996

Substitution log-odds



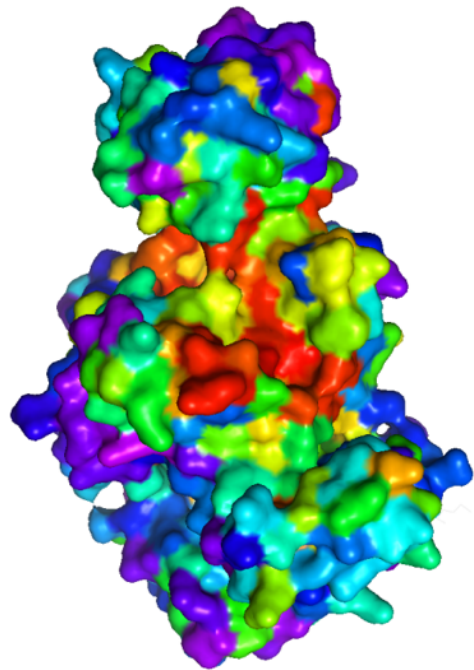
Pyruvate
decarboxylase

SUMO
ligase



EA MUTATIONAL SCANNING PYRUVATE DECARBOXYLASE (L-PYK)

ET

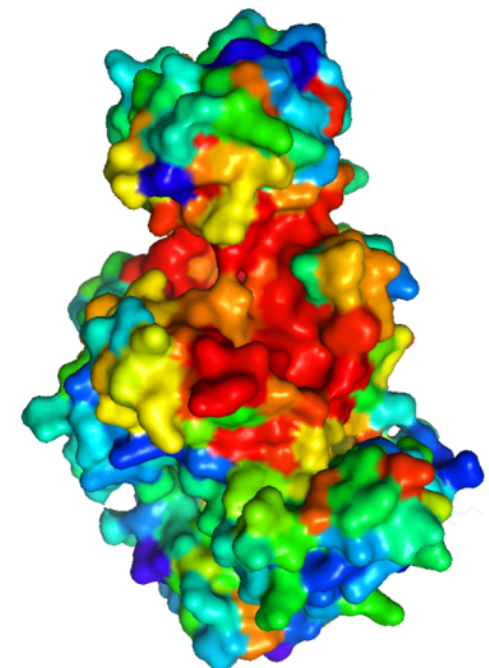
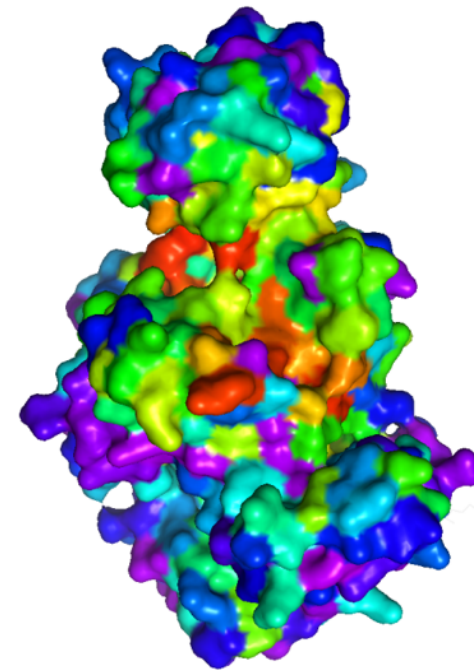
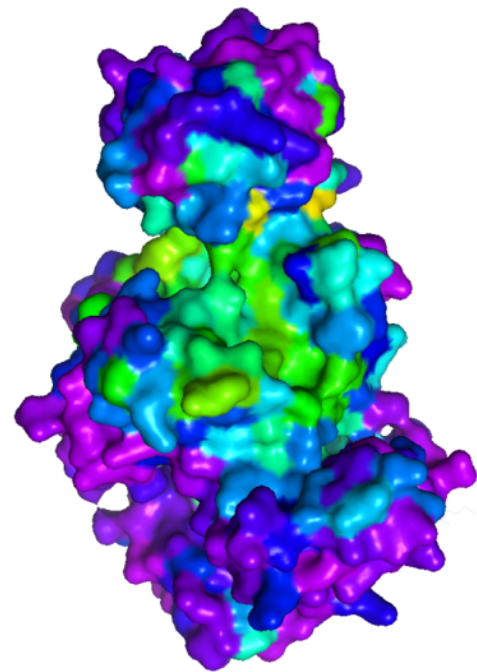


EA SCAN

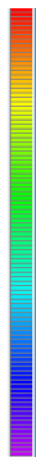
Minimum

Alanine

Maximum

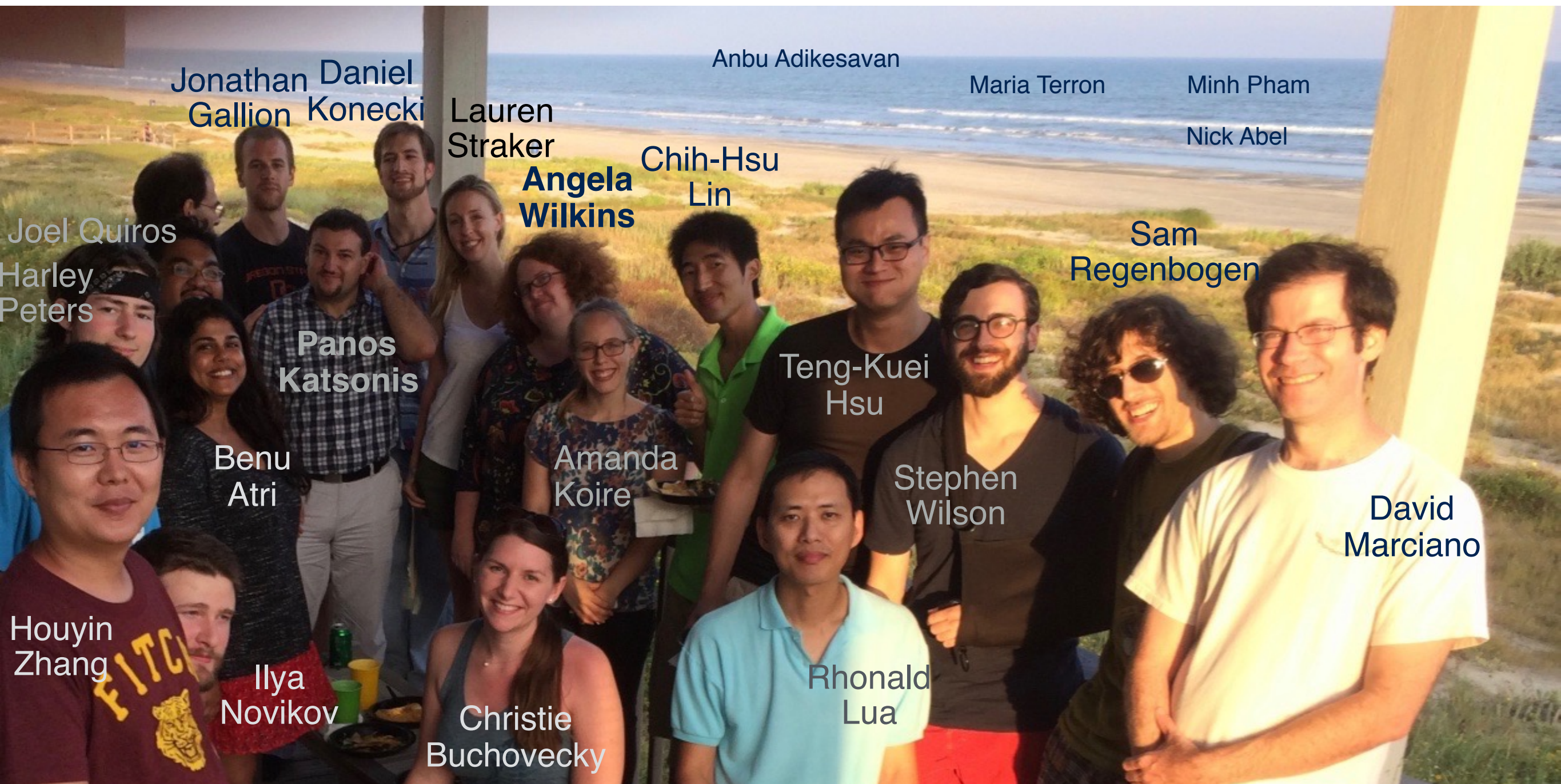


high



low

Length: 543 aa
Structure: 4ip7 Holyoke et al (2013) Biochem
Sequences: 124 from bacteria up to animals



Jonathan Daniel
Gallion Konecki

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Straker

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Wilkins

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Lin

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