

From Cancer to Pathogens: Interactions Between Microbial Population Biology and Medicine

Jake Scott - introducing:

Dmitri Petrov, Pleuni Pennings, Kevin Wood, Oana Carja



Cleveland Clinic

Microbial Population Biology
Gordon Research Conference
10 July 2019

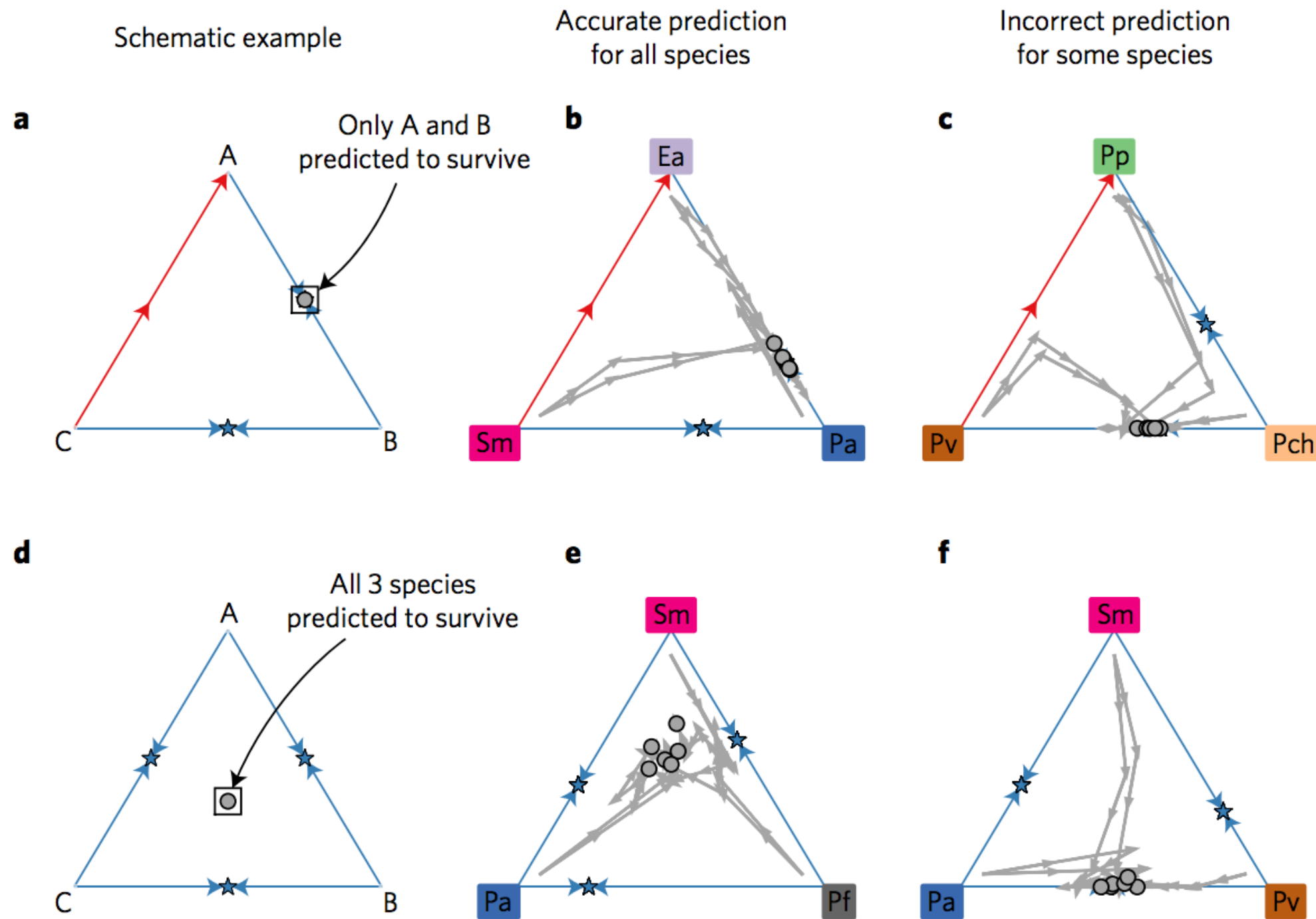
<https://www.lerner.ccf.org/thor/scott/lab/>

scottj10@ccf.org



@CancerConnector

The results of simple co-culture yielded intuition about competition in more complex mixtures in diverse bacteria



Community structure follows simple assembly rules in microbial microcosms

Jonathan Friedman^{1*}, Logan M. Higgins^{1,2} and Jeff Gore^{1*}

nature
ecology & evolution

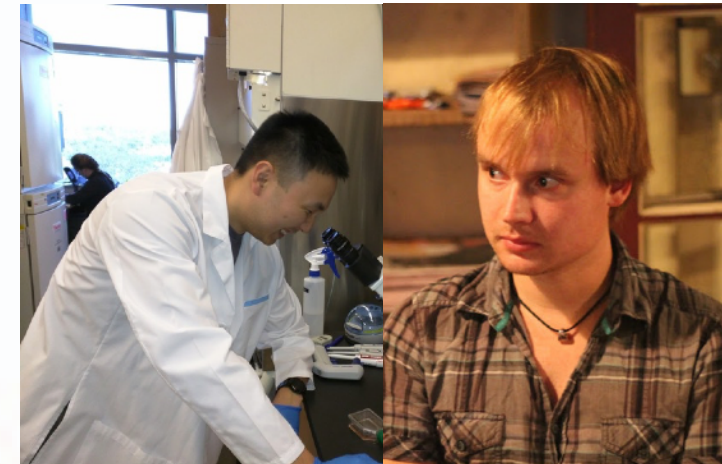
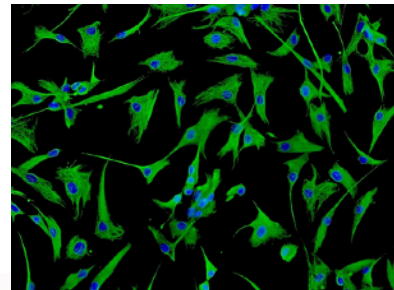
ARTICLES

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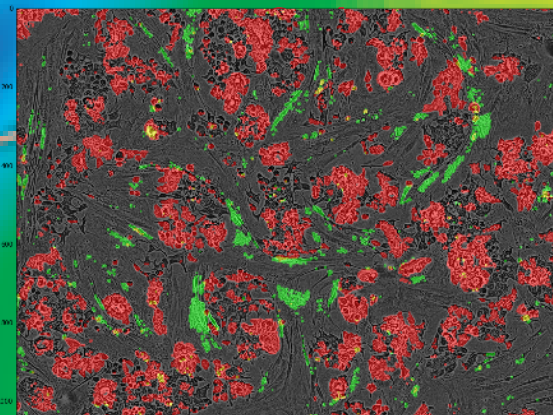
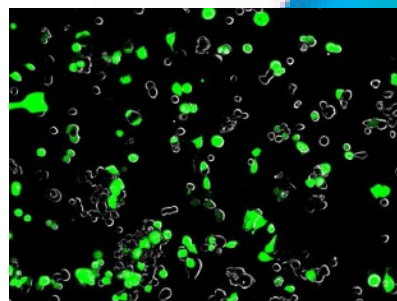
What about a GAME ASSAY to directly measure the effective game cancer cells are playing?



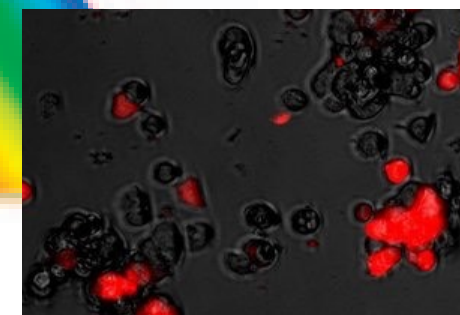
Fibroblasts



AlecS



AlecR



nature
ecology & evolution

ARTICLES

<https://doi.org/10.1038/s41559-018-0768-z>

1.5 years pre-pub on

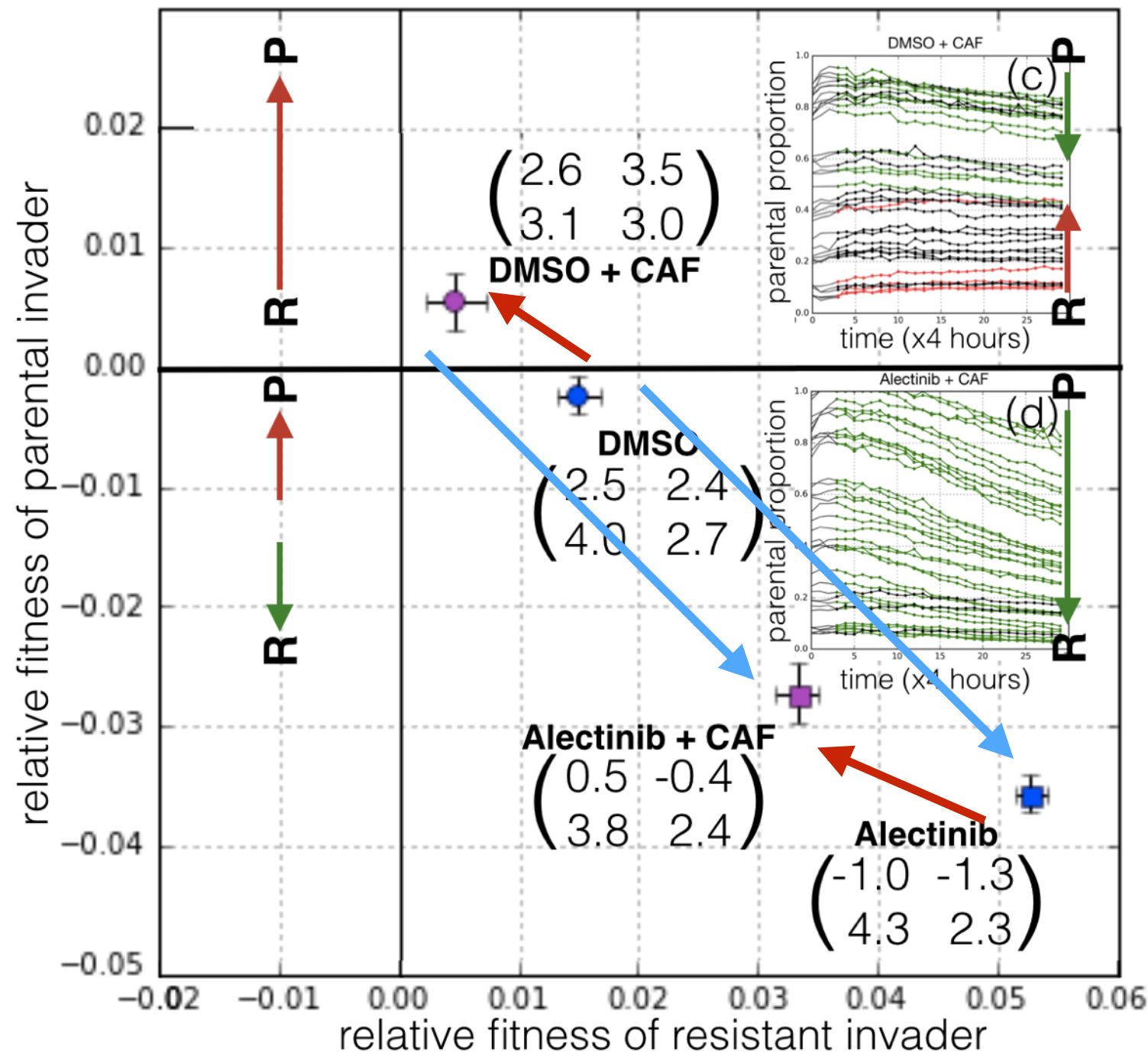
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Fibroblasts and alectinib switch the evolutionary games played by non-small cell lung cancer

Plotting the fitness functions in a game space reveals a *qualitative shift in the game*

$$\begin{array}{c}
 P \quad R \\
 \left(\begin{array}{cc} A & B \\ C & D \end{array} \right) \Rightarrow \left\{ \begin{array}{l} \frac{d}{dt} N_P = N_P \left(A \frac{N_P}{N_T} + B \frac{N_R}{N_T} \right) \\ \frac{d}{dt} N_R = N_R \left(C \frac{N_P}{N_T} + D \frac{N_R}{N_T} \right) \end{array} \right. \\
 \begin{array}{c} \text{parental growth rate} \\ \text{resistant growth rate} \end{array} \\
 \Rightarrow \frac{dp}{dt} = p(1-p) \underbrace{\left((B-D)(1-p) - (C-A)p \right)}_{\text{gain function for } p}
 \end{array}$$

where $N_T = N_P + N_R$ and $p = \frac{N_P}{N_T}$.

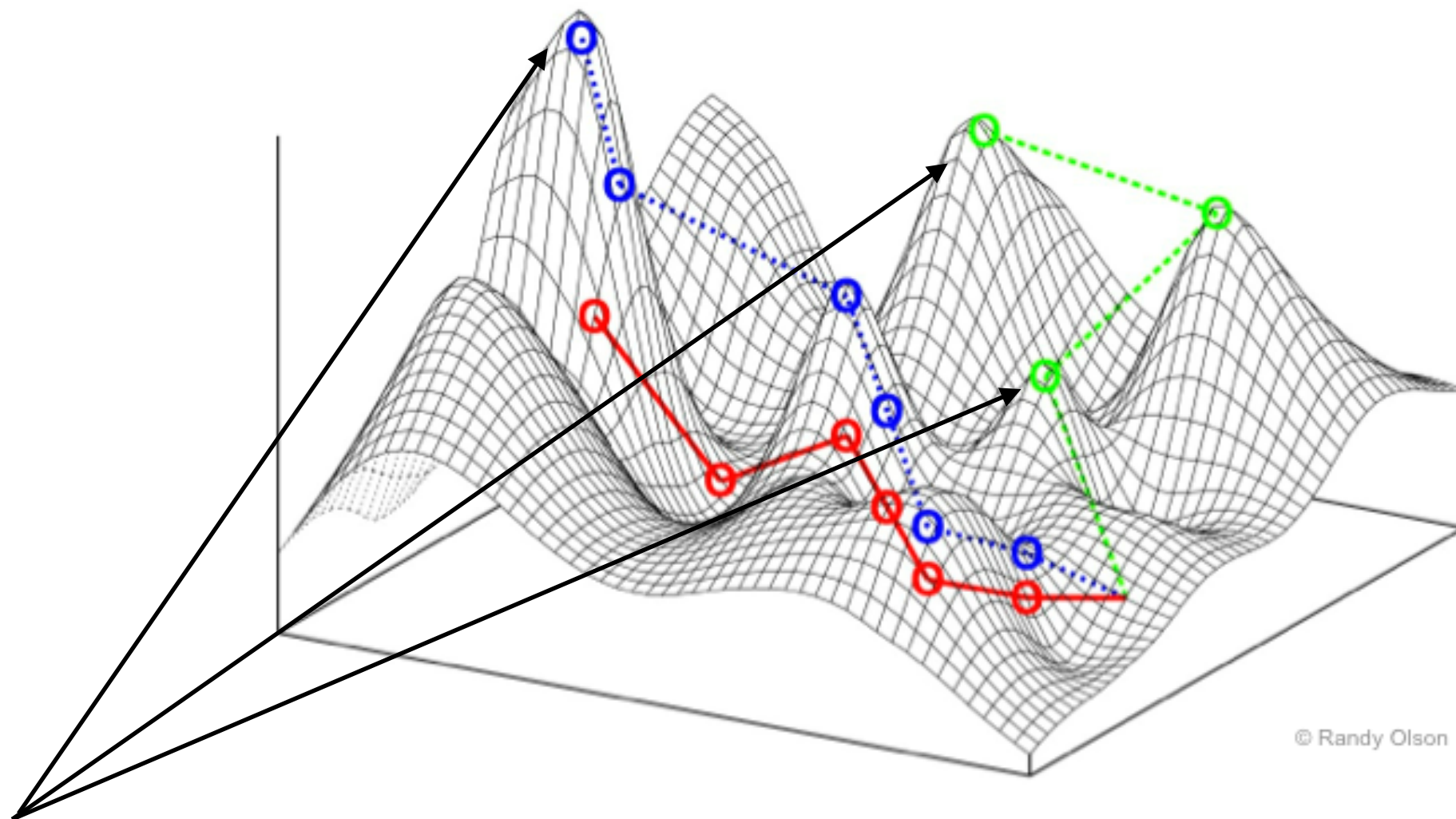


Adding CAFs shifts the game up/left

Adding alectinib shifts the game down/right

Can we think of drugs in this new way to steer evolution rationally?

Key questions:



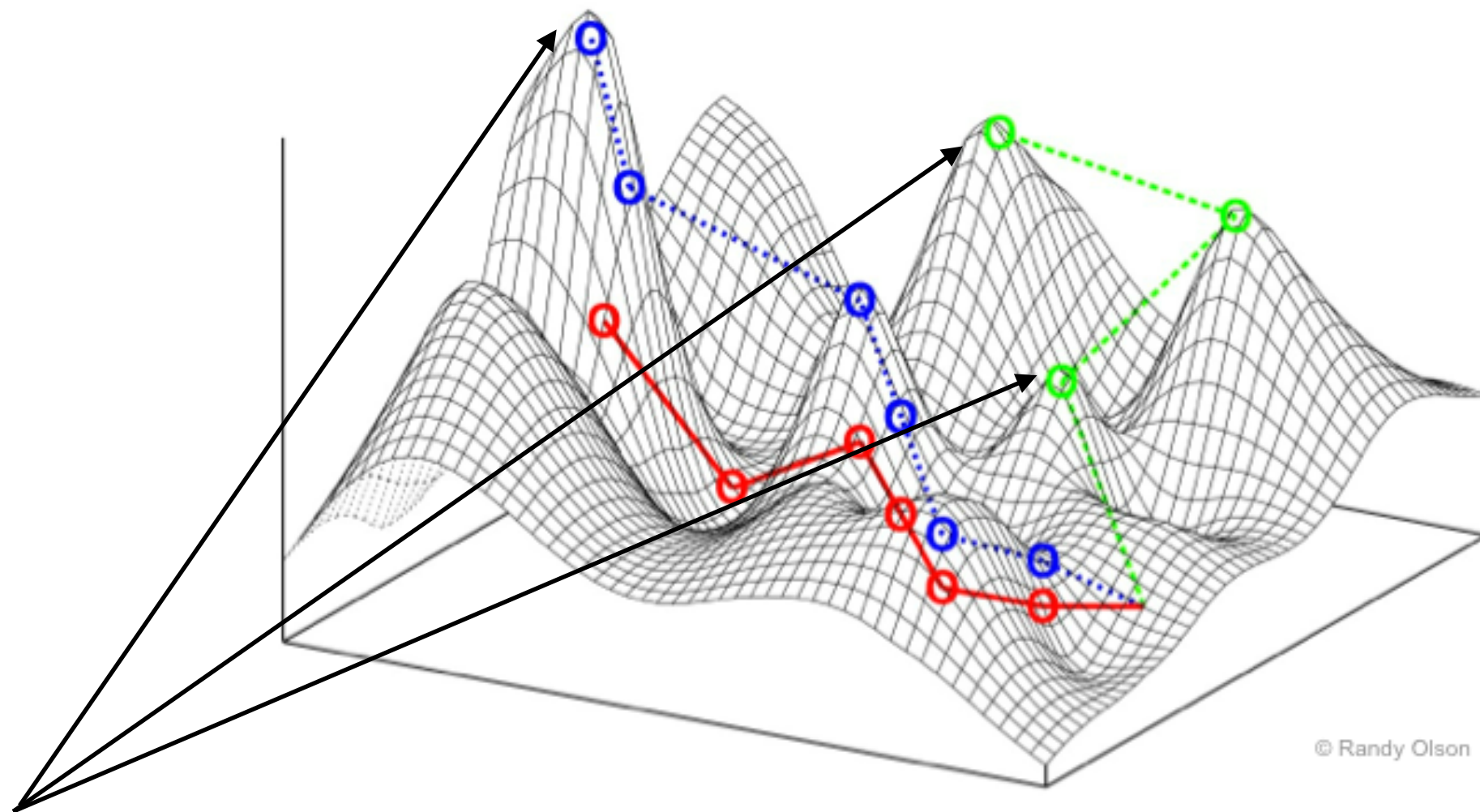
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1. Where will evolution drive a disease?
(and what are the evolutionary
consequences - e.g. CS)

2. How fast will it go?

3. Can we *control* these things?

GP maps in yeast and cancer



1. Where will evolution drive a disease?

Dmitri Petrov, PhD
Stanford

**Development of a Comprehensive
Genotype-to-Fitness Map
of Adaptation-Driving Mutations in Yeast**

Venkataram et al., 2016, *Cell* 167, 1–12
September 22, 2016 © 2016 Elsevier Inc.
<http://dx.doi.org/10.1016/j.cell.2016.08.002>

**Mapping the in vivo fitness landscape of lung
adenocarcinoma tumor suppression in mice**

Zoë N. Rogers^{1,8}, Christopher D. McFarland^{2,8}, Ian P. Winters¹, Jose A. Seoane^{1,3,4}, Jennifer J. Brady¹,
Stephanie Yoon⁵, Christina Curtis^{1,3,4,6}, Dmitri A. Petrov^{2*} and Monte M. Winslow^{1,4,6,7*}

nature
genetics

BRIEF COMMUNICATION

<https://doi.org/10.1038/s41588-018-0083-2>

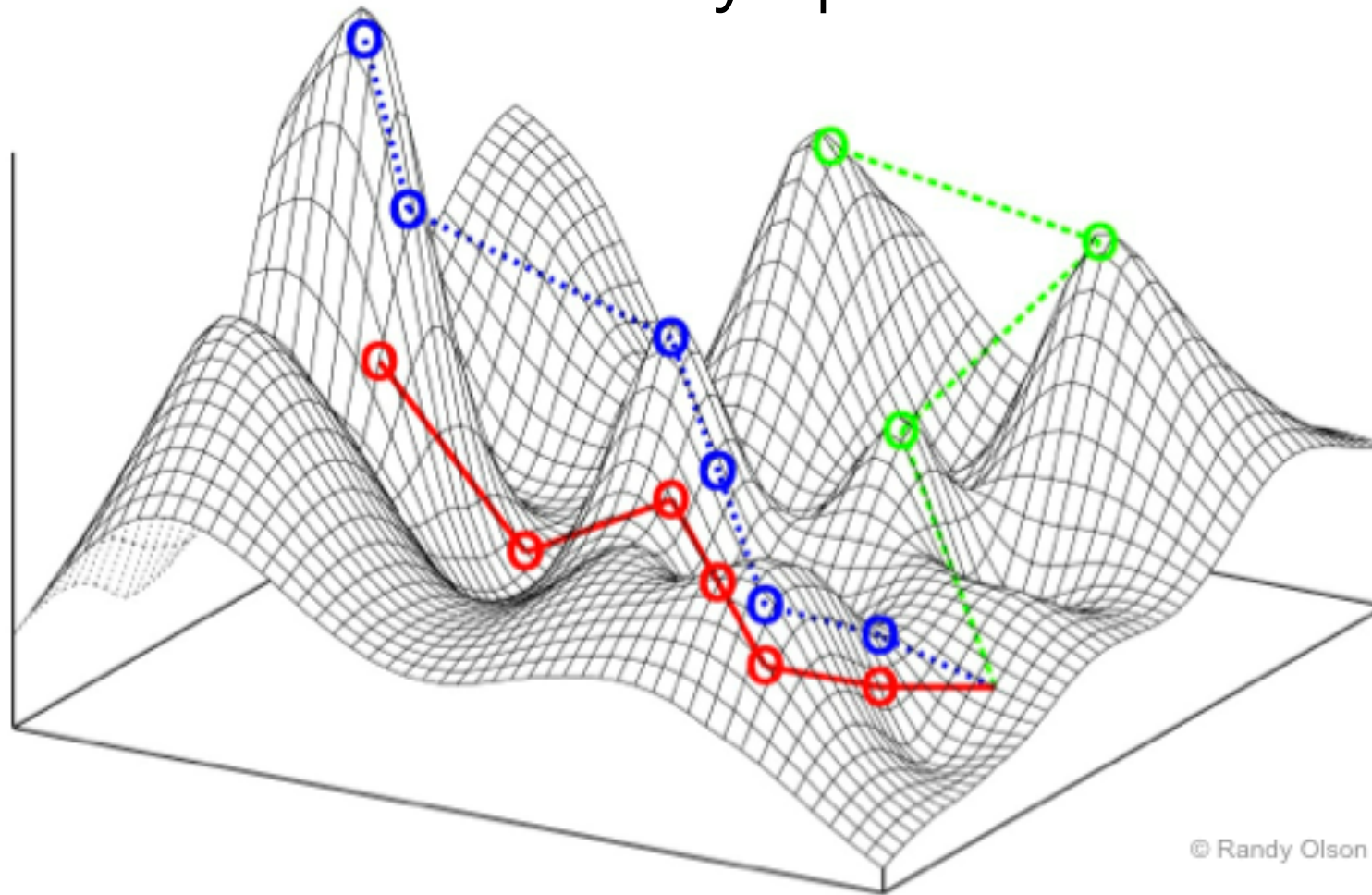
**Single Nucleotide Mapping of the Locally Accessible Trait Space in
Yeast Reveals Pareto Fronts that Constrain Initial Adaptation**

Yuping Li, Dmitri A. Petrov*, Gavin Sherlock*



bioRxiv
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Key questions:



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Pleuni Pennings, PhD
SFSU

2. How fast will it go? and in what order?

<https://abetterscientist.wordpress.com/2019/02/01/sequential-evolution-of-hiv-drug-resistance-against-two-drug-treatments/>

Challenging conventional wisdom on the evolution of resistance to multi-drug HIV treatment: Lessons from data and modeling.

Alison Feder, Kristin Harper, Pleuni Pennings

June 2019

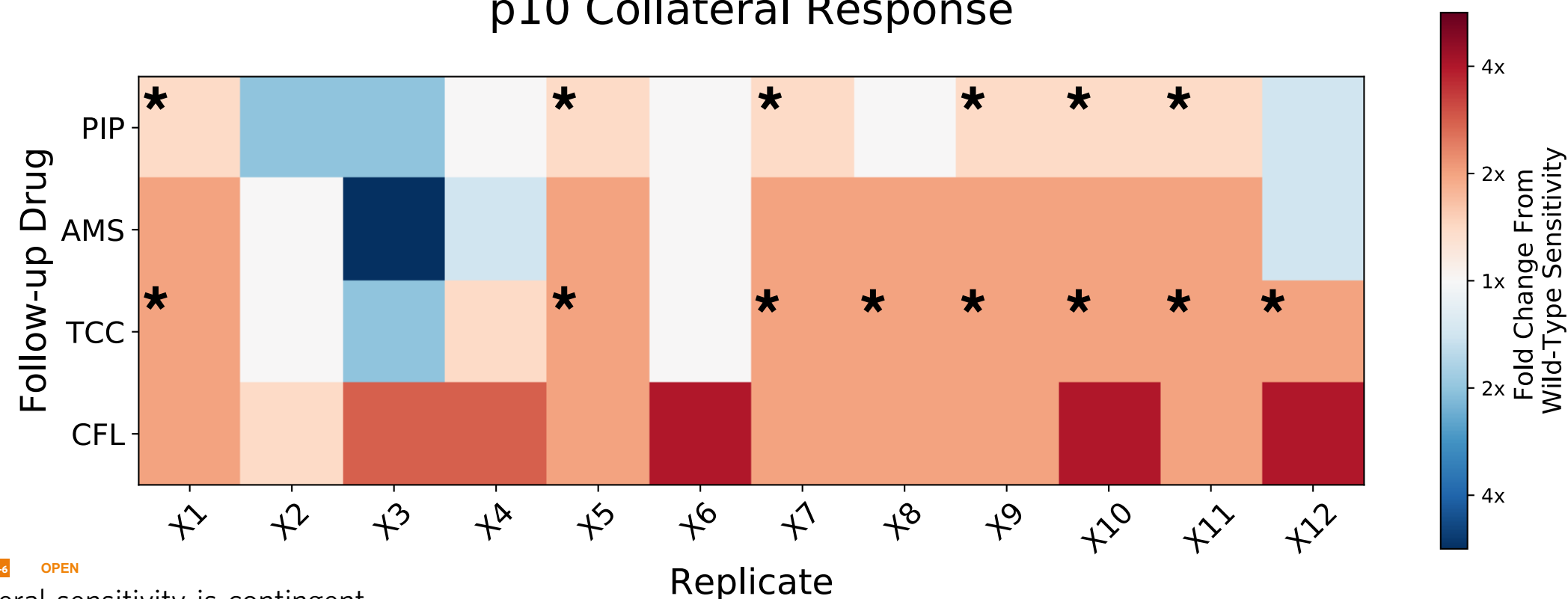
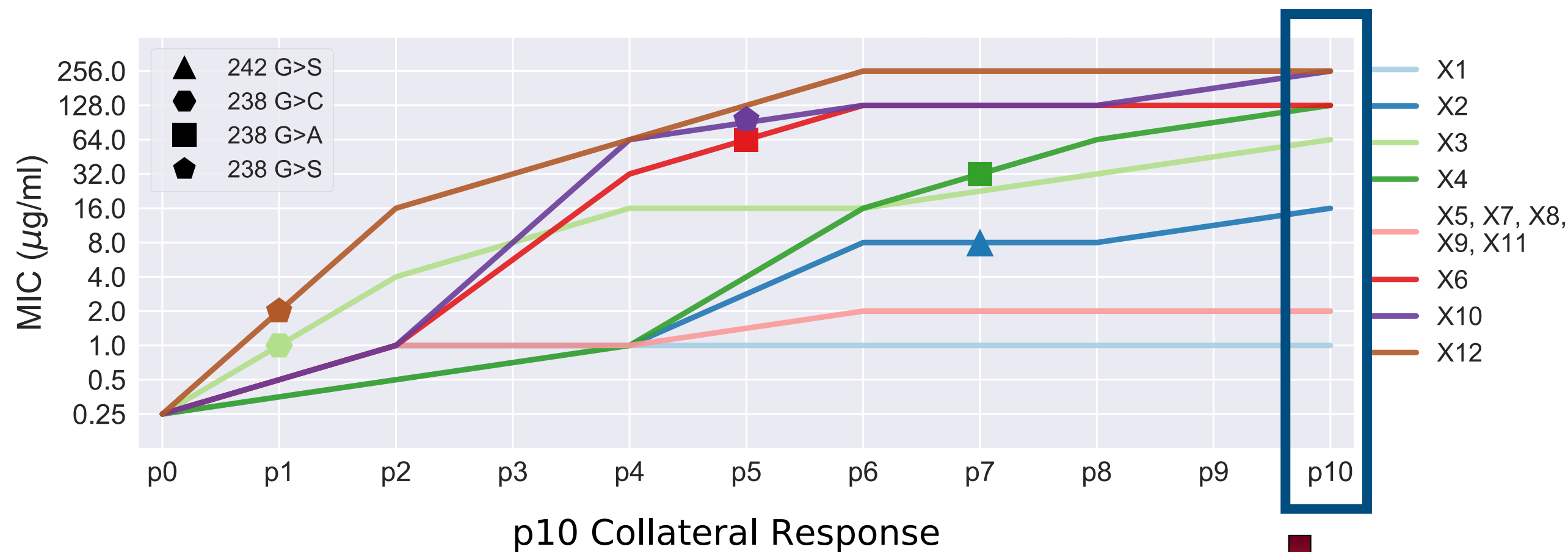
Imperfect drug penetration leads to spatial monotherapy and rapid evolution of multidrug resistance

Stefany Moreno-Gamez^{a,b,1}, Alison L. Hill^{a,1}, Daniel I. S. Rosenbloom^{a,c}, Dmitri A. Petrov^d, Martin A. Nowak^a, and Pleuni S. Pennings^{d,e,f,2}

www.pnas.org/cgi/doi/10.1073/pnas.1424184112



in vitro: evolution under cefotaxime is not repeatable,
and collateral sensitivity varies with genetic divergence



ARTICLE

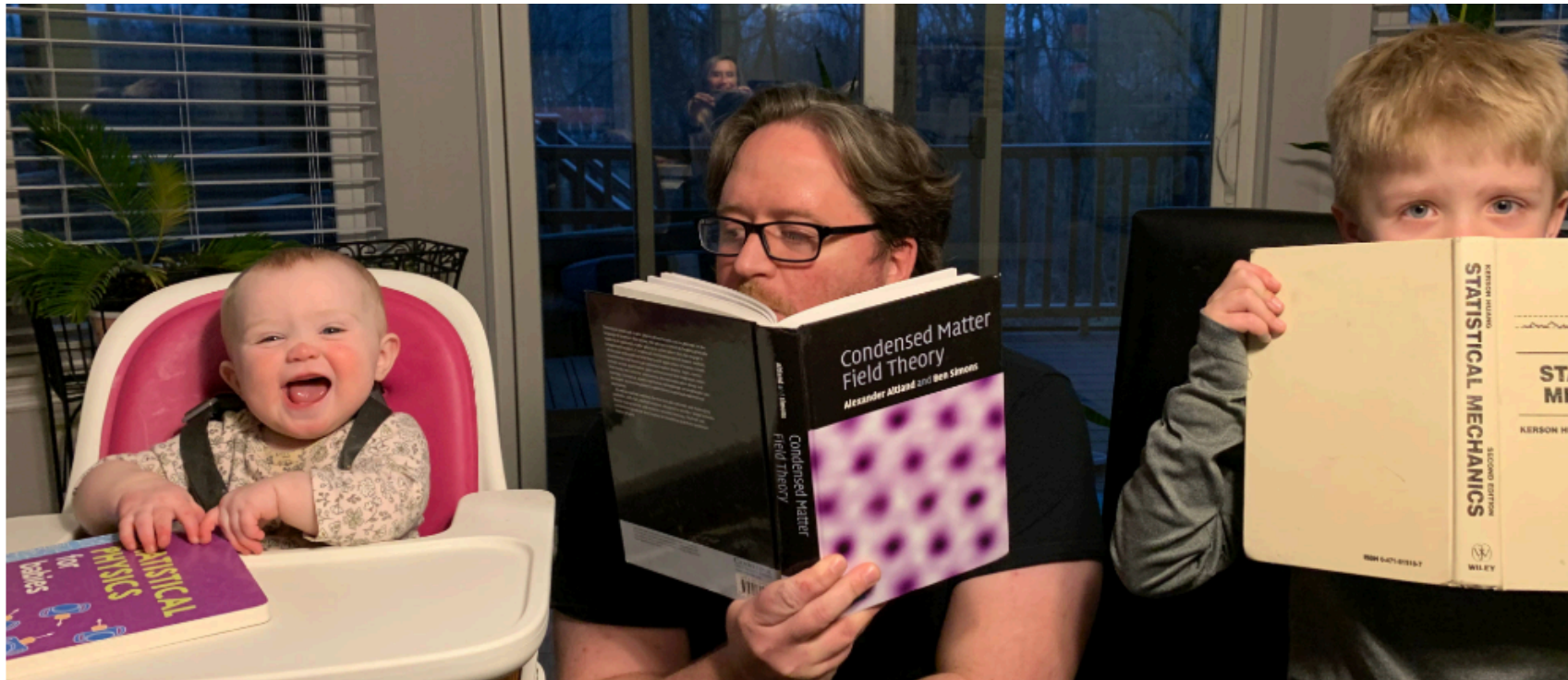
<https://doi.org/10.1038/s41467-018-08098-6>

OPEN

Antibiotic collateral sensitivity is contingent
on the repeatability of evolution

Daniel Nichol^{1,2,12}, Joseph Rutter³, Christopher Bryant⁴, Andrea M. Hujer^{3,4}, Sai Lek⁵, Mark D. Adams⁵,
Peter Jeavons¹, Alexander R.A. Anderson², Robert A. Bonomo^{3,4,6,7,8,9} & Jacob G. Scott^{7,10,11}





Kevin Wood, PhD UMichigan

PHYSICAL REVIEW LETTERS **120**, 238102 (2018)

Antibiotics can be used to contain drug-resistant bacteria by maintaining sufficiently large sensitive populations

Elsa Hansen, Jason Karslake, Robert J. Woods, Andrew F. Read,  Kevin B. Wood

doi: <https://doi.org/10.1101/638924>

Tuning Spatial Profiles of Selection Pressure to Modulate the Evolution of Drug Resistance

Maxwell G. De Jong¹ and Kevin B. Wood^{1,2,*}



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Pervasive and diverse collateral sensitivity profiles inform optimal strategies to limit antibiotic resistance

Jeff Maltas,  Kevin B. Wood

doi: <https://doi.org/10.1101/24107>

How can heterogeneity be maintained?

Are there other ways to move through genotype space?



Oana Carja, PhD
Carnegie Mellon

Theoretical Population Biology

Volume 86, June 2013, Pages 29-42

Evolution with stochastic fitnesses: A role for recombination

Oana Carja^a  , Uri Liberman^b, Marcus W. Feldman^a

Evolutionary Rescue Through Partly Heritable Phenotypic Variability

GENETICS | **INVESTIGATION** Oana Carja^{*.1} and Joshua B. Plotkin[†]

Genetics, Vol. 211, 977–988 March 2019