



Pitt
Medicine

The Carvunis Lab

LI Detector: Measuring Small Fitness Effects in High Throughput

Saurin Parikh

Integrative Systems Biology Program

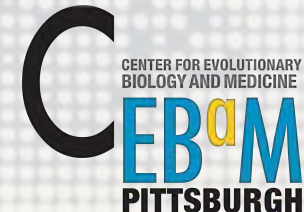
PI: Anne-Ruxandra Carvunis

Department of Computational and Systems Biology

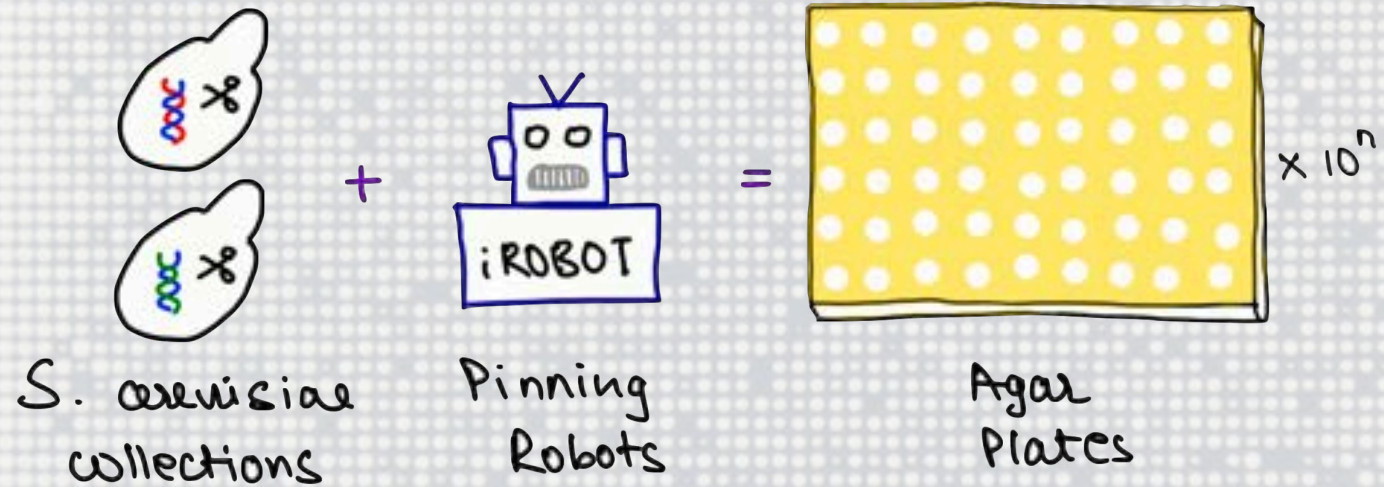
Pittsburgh Center for Evolutionary Biology and Medicine

University of Pittsburgh School of Medicine

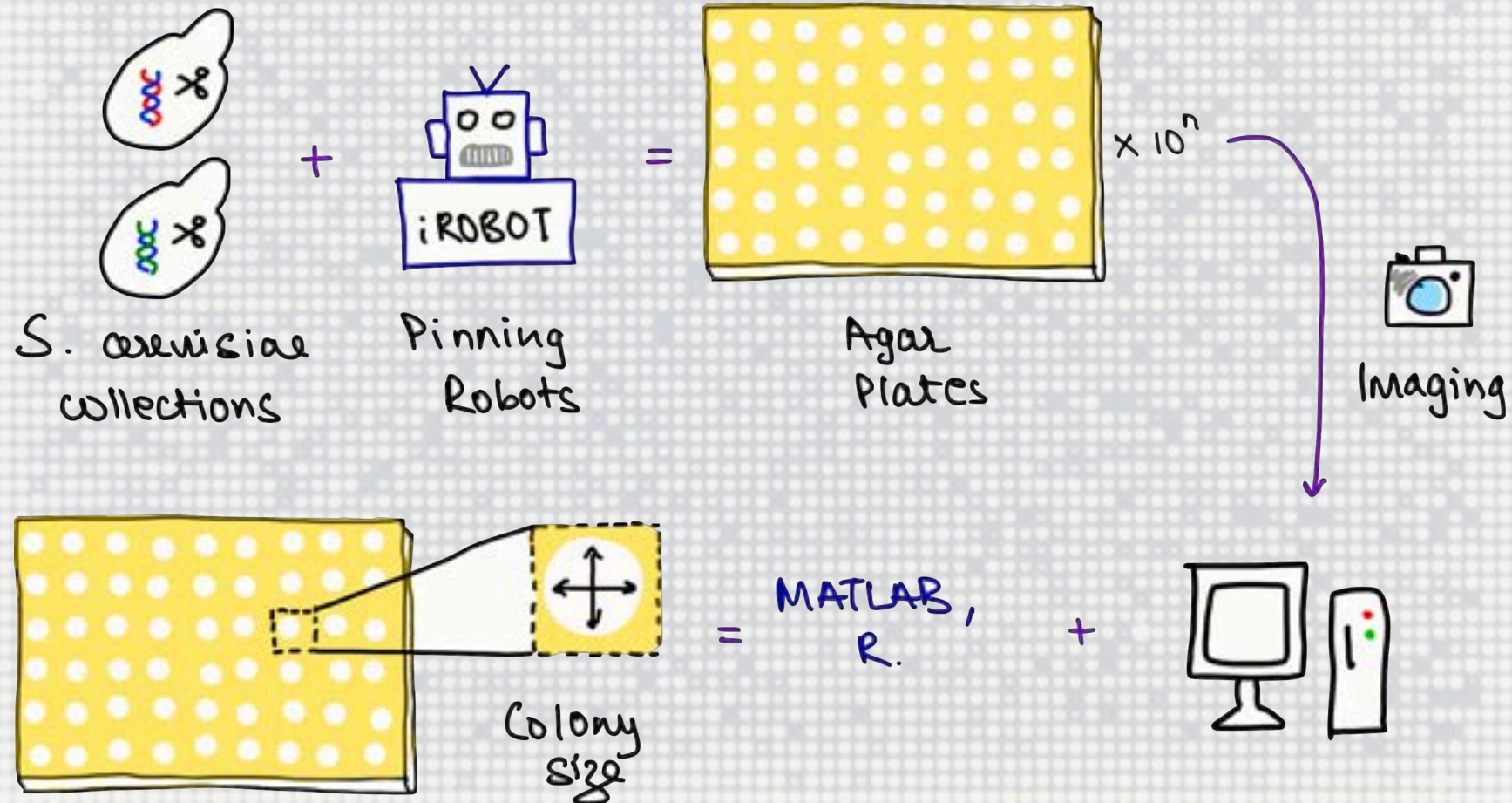
INTEGRATIVE SYSTEMS BIOLOGY



Colony-based high-throughput screens (CBHTS)



Colony-based high-throughput screens (CBHTS)



CBHTS have been used to identify...

Gene – gene interactions

RESEARCH ARTICLE

Global Mapping of the Yeast Genetic Interaction Network

Amy Hin Yan Tong^{1,2,3}, Guillaume Lesage^{1,2}, Gary D. Bader⁴, Huiming Ding¹, Hong Xu^{1,2}, Xiaofeng Xin^{1,2}, James Young¹, Gab...

*** These authors contributed equally to this work.
• See all authors and affiliations

Science 06 Feb 2008
Vol. 320, Issue 5839, pp. 808-813
DOI: 10.1126/science.1159137

RESEARCH ARTICLE

The Genetic Landscape of a Cell

Michael Costanzo^{1,2,3}, Anastasia Baryshnikova^{1,2,3}, Jeremy Bellay², Yongil Kim², Eric D. Spear⁴, Carolyn S. Sevier⁴, Huiming...

Science 22 Jan 2010
Vol. 327, Issue 5954, pp. 429-437
DOI: 10.1126/science.1188823

RESEARCH ARTICLE

A global genetic interaction network maps a wiring diagram of cellular function

Michael Costanzo^{1,2}, Benjamin VanderSluis^{2,3,4}, Elizabeth M. Koch^{2,3}, Anastasia Baryshnikova^{1,2}, Carlos Pons^{1,2,3}, Guohang T...

Science 23 Sep 2016
Vol. 353, Issue 6306, eaaf1420
DOI: 10.1126/science.aaf1420

Gene – environment interactions

Integration of chemical-genetic and genetic interaction data links bioactive compounds to cellular target pathways

Ainslie B Parsons, Renée L Brost, Huiming Ding, Zhijian Li, Chaoying Zhang, Bilal Sheikh, Grant W Brown, Patricia M Kane, Timothy R Hughes & Charles Boone

Nature Biotechnology 22, 62–69 (2004) | Download Citation ±

Cell

Volume 126, Issue 3, 11 August 2006, Pages 611–625

CellPress

Resource

Exploring the Mode-of-Action of Bioactive Compounds by Chemical-Genetic Profiling in Yeast

Ainslie B. Parsons^{1,2,3,4,11}, Andres Lopez^{1,2,11}, Inmar E. Givoni^{1,2,4,11}, David E. Williams⁵, Christopher A. Gray⁵, Justin Porter⁵, Gordon Chua¹, Michelle Sopko^{1,2}, Renée L. Brost¹, Cheuk-Hoi Ho^{1,2}, Jiyi Wang⁶, Troy Ketela⁷, Charles Brenner⁸, Julie A. Brill⁹, G. Esteban Fernandez⁸, Todd C. Lorenz⁸, Gregory S. Payne⁸, Satoru Ishihara¹⁰ ... Charles Boone^{1,2,3,4,8}

Protein – protein interactions

A comprehensive analysis of protein–protein interactions in *Saccharomyces cerevisiae*

Peter Uetz, Loic Giot, Gerard Cagney, Traci A. Mansfield, Richard S. Judson, James R. Knight, Daniel Lockshon, Vaibhav Narayan, Mithreyan Srinivasan, Pascale Pochart, Alia Qureshi-Emili, Ying Li, Brian Godwin, Diana Conover, Theodore Kalbfleisch, Govindan Vijayadmodar, Meijia Yang, Mark Johnston, Stanley Fields & Jonathan M. Rothberg

Nature 403, 623–627 (2000) | Download Citation ±



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•** These authors contributed equally to this work.
• See all authors and affiliations

Science 304 Feb 20 2009
Vol. 304, Issue 5694, pp. 974-979
DOI: 10.1126/science.1165191

RESEARCH ARTICLE

The Gen

Michael Costanzo^{1,2}, Benjamin VanderSluis^{1,2,3}, Elizabeth M. Koch^{1,2}, Anastasia Baryshnikova⁴, Carlos Pons^{1,2,3}, Guohang T...

Science 22 Jan 2010
Vol. 327, Issue 5954, pp. 429-431
DOI: 10.1126/science.1188823

RESEARCH ARTICLE

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Michael Costanzo^{1,2}, Benjamin VanderSluis^{1,2,3}, Elizabeth M. Koch^{1,2}, Anastasia Baryshnikova⁴, Carlos Pons^{1,2,3}, Guohang T...

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Science 23 Sep 2010
Vol. 330, Issue 6006, pp. 1429-1435
DOI: 10.1126/science.1194209

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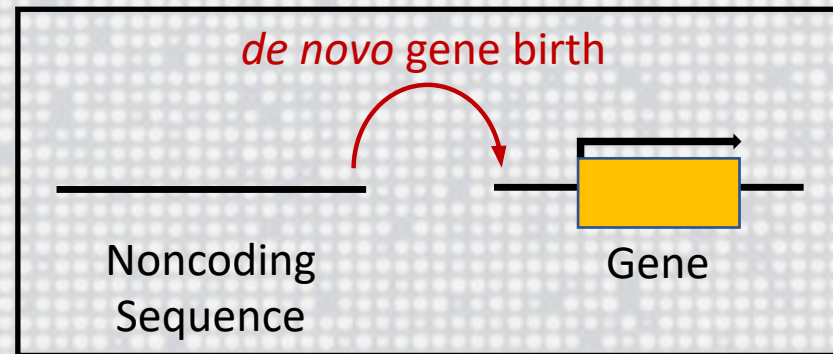
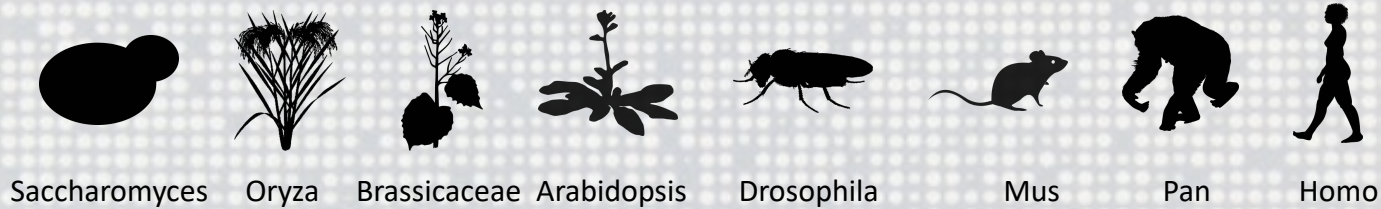
right, Daniel
L, Ying Li,
Yang, Mark

But their use in evolutionary biology has been limited!



@saur1n

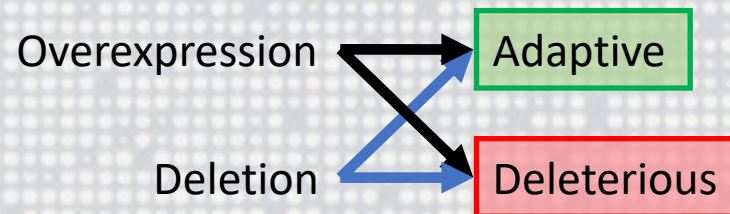
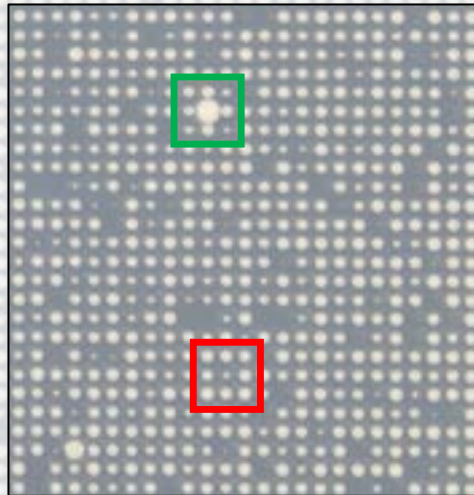
CBHTS can reveal evolutionary phenomena



CBHTS can reveal evolutionary phenomena



Saccharomyces



Correcting for spatial bias ends up ignoring small fitness effects

“The environment can rarely be maintained constant across plates”

- Zackrisson et al. 2016



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Correcting for spatial bias ends up ignoring small fitness effects

Existing Methods For Spatial Bias Correction

Collins et al. 2006, Wagih et al. 2013, Young et al. 2013, Bean et al. 2014, Zackrisson et al. 2016

Assumptions

1.



Correcting for spatial bias ends up ignoring small fitness effects

Existing Methods For Spatial Bias Correction

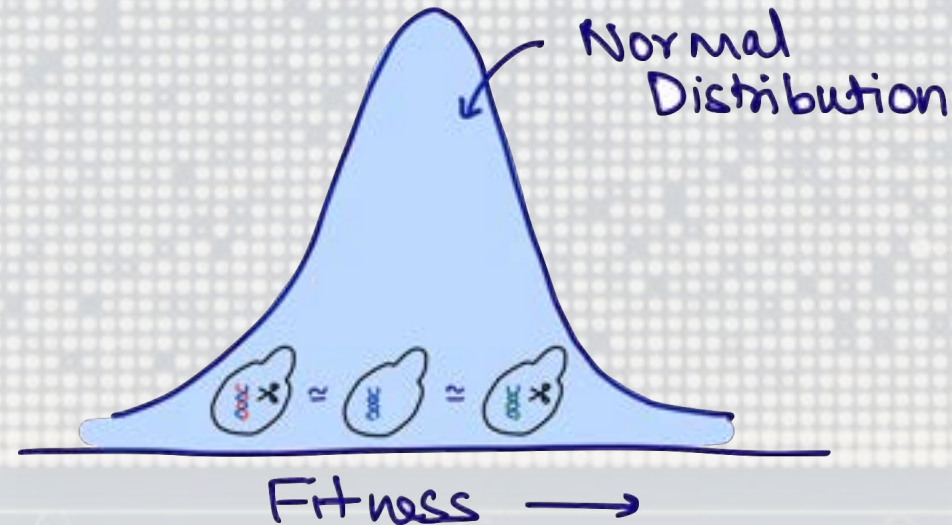
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Assumptions

1.



2.



LI Detector reveals the truth!



LI Detector reveals the truth!

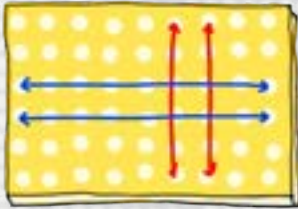


$$\text{Relative Fitness} = \frac{\text{Colony size}}{\text{Reference colony size}}$$

LI Detector reveals the truth!



$$\text{Relative Fitness} = \frac{\text{Colony size}}{\text{Reference colony size}}$$



Row / Column



Agar Surface

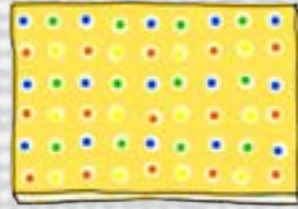
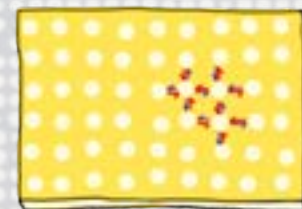


Plate History

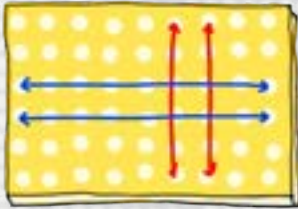


Neighbor Colony

LI Detector reveals the truth!



$$\text{Relative Fitness} = \frac{\text{Colony size}}{\text{Reference colony size}}$$



Row / Column



Agar Surface

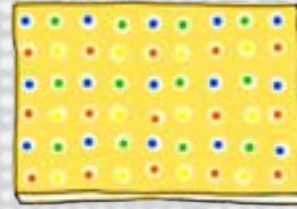
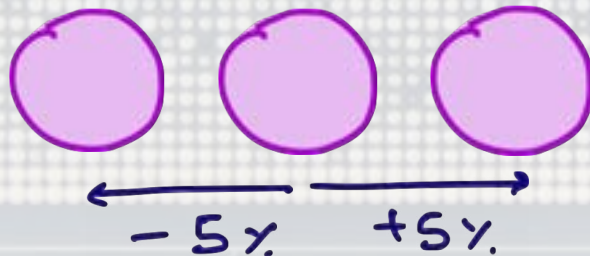


Plate History



Neighbor Colony



5 % Fitness effects
70 % sensitivity
95 % specificity



@saur1n

LI Detector can expand the use of CBHTS

1. Relative fitness makes across plates comparisons more accurate
2. No limits on the number of mutants in a screen
3. Specifically designed to detect both adaptive and deleterious fitness



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2. No limits on the number of mutants in a screen
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Endless possible experimental setups!!



@saur1n

Thank You!

The Carvunis Lab

Carvunis Lab

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Nelson Coelho

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Summer'19

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