Pitt Medicine

The Carvunis Lab

LI Detector: Measuring Small Fitness Effects in High Throughput

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INTEGRATIVE SYSTEMS BIOLOGY

CENTER FOR EVOLUTIONARY BIOLOGY AND MEDICINE
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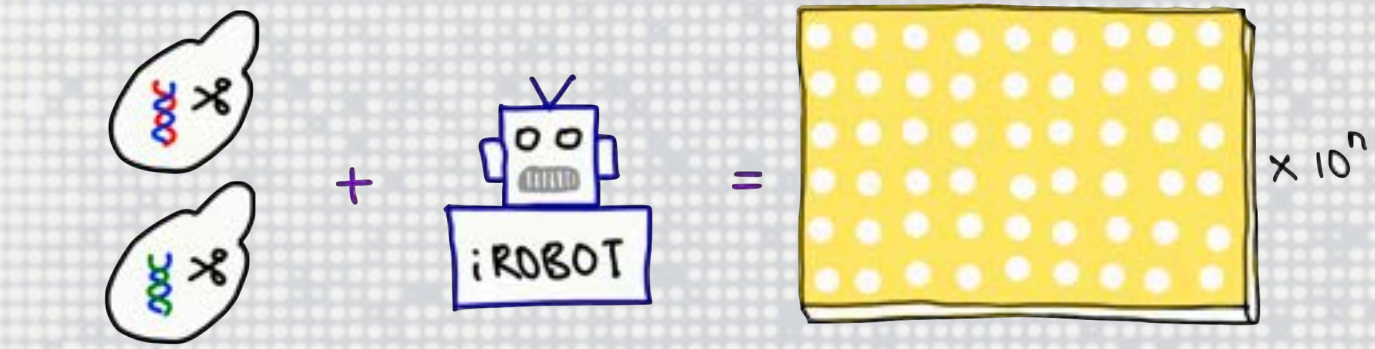
Colony-based high-throughput screens (CBHTS)



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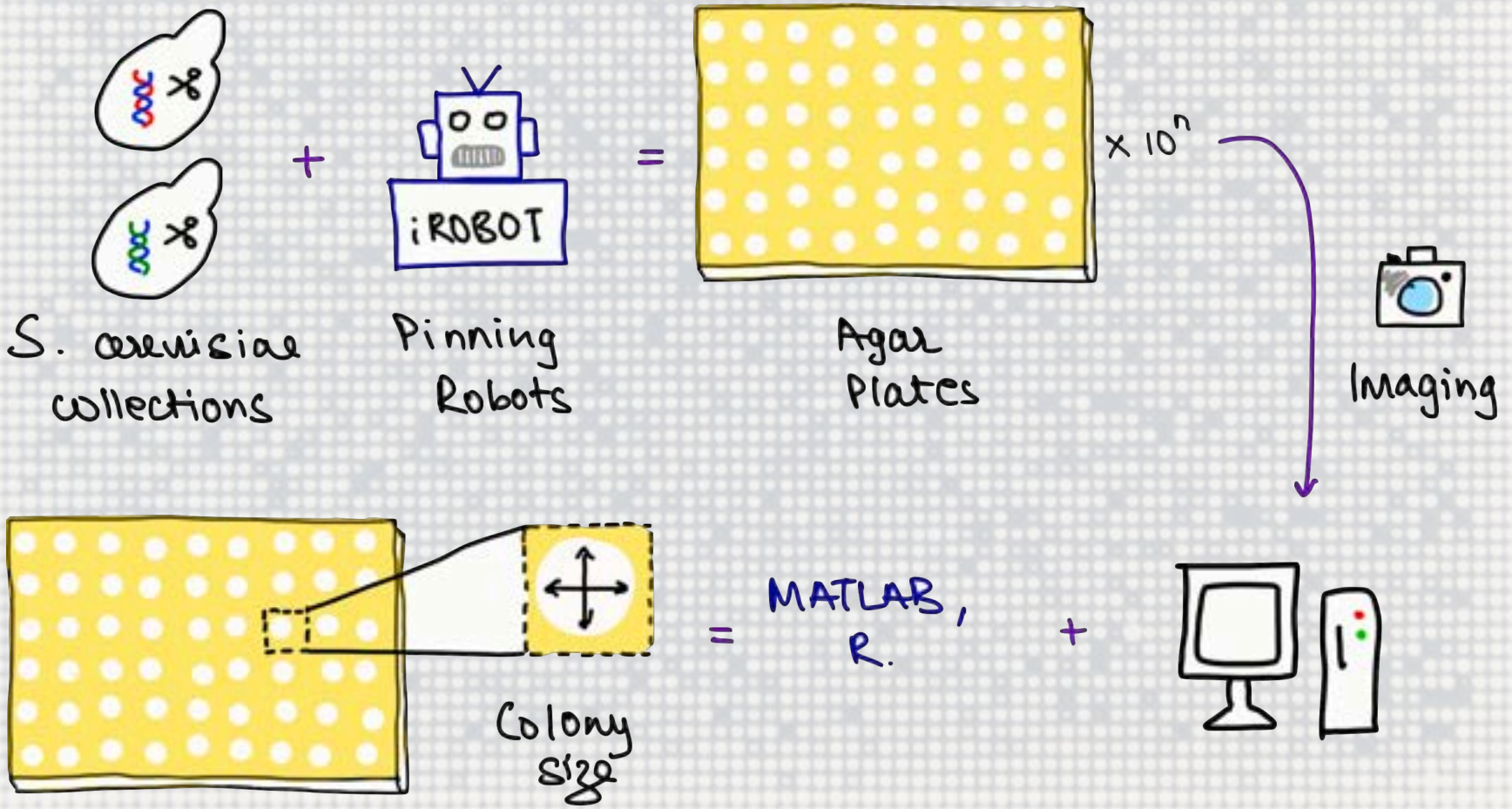

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CBHTS have been used to identify…

Gene – gene interactions

RESEARCH ARTICLE

Global Mapping of the Yeast Genetic Interaction Network

RESEARCH ARTICLE

The Genetic Landscape of a Cell

RESEARCH ARTICLE

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

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

CellPress

Volume 126, Issue 1, 11 August 2006, Pages 611-625

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

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, Maithreyan Srinivasan, Pascale Pochart, Alia Qureshi-Emili, Ying Li, Brian Godwin, Diana Conover, Theodore Kalbfleisch, Govindan Vijayadamodar, Meijia Yang, Mark Johnston, Stanley Fields & Jonathan M. Rothberg

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But their use in evolutionary biology has been limited!

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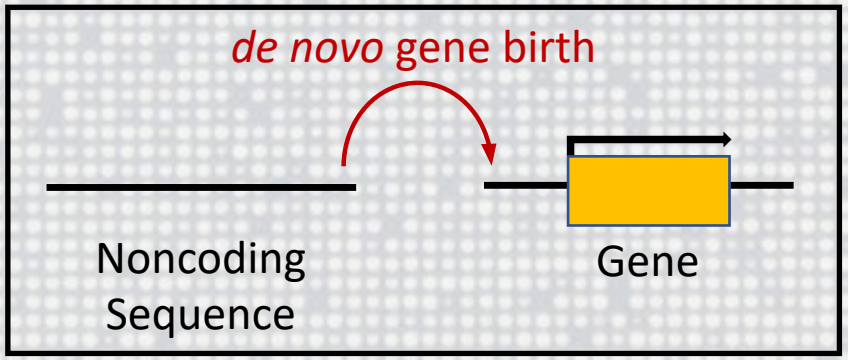
CBHTS can reveal evolutionary phenomena



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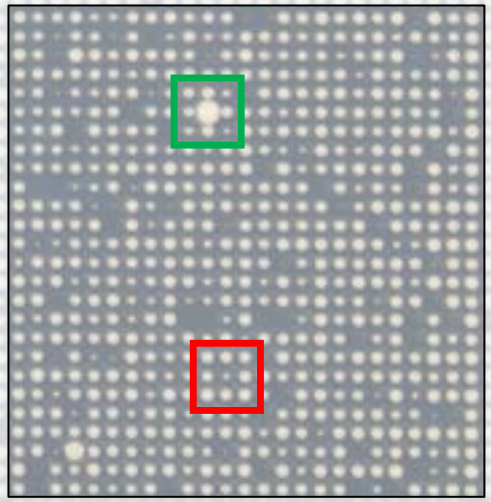
CBHTS can reveal evolutionary phenomena

Saccharomyces



Overexpression → Adaptive

Deletion → Deleterious

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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

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Assumptions

1.

2.

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LI Detector reveals the truth!

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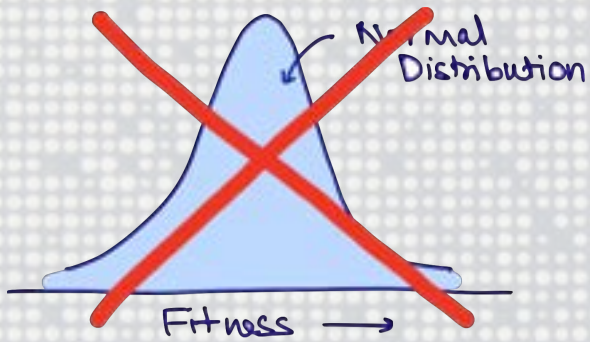

$$\text{Relative Fitness} = \frac{\text{Colony size}}{\text{Reference colony size}}$$

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LI Detector reveals the truth!

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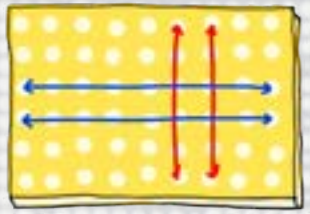

Row / Column


Agar Surface

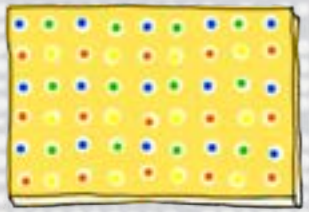
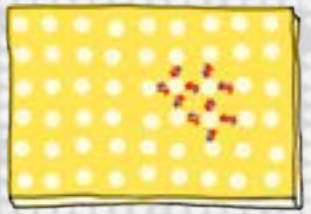


Plate History


Neighbor Colony

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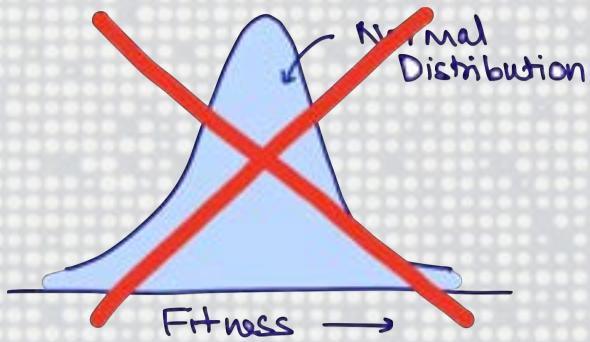
LI Detector reveals the truth!



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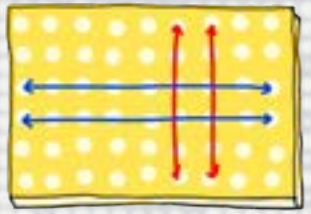
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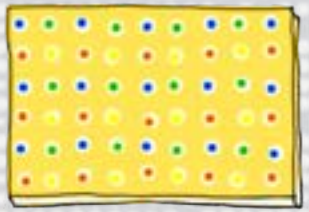
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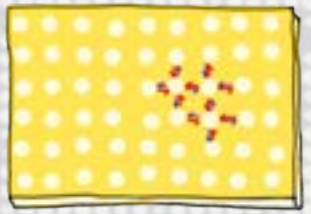
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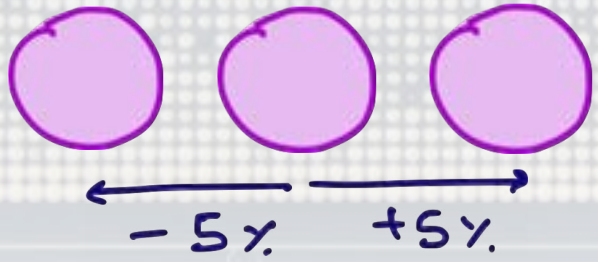

5 % Fitness effects
70 % sensitivity
95 % specificity

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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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Endless possible experimental setups!!

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Thank You!

The Carvunis Lab

Carvunis Lab

Anne-Ruxandra Carvunis
Nelson Coelho
Aaron Wacholder
Branden Van Oss
Carly Houghton
John Iannotta
Kate McCourt
Omer Acar

Summer'19

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