

# Introduction to Systems Biology of Cancer

## Lecture 5

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DREAM Challenges



What is Crowd-sourcing?

# Crowd-Sourcing

Term first used in 2006

“The rise of crowd-sourcing”, Wired Magazine  
2006

## Definition

A methodology that uses the voluntary help of large communities to solve problems posed by an organization.

# Crowd-sourcing in History



## 1700s: Breakthroughs In Navigation

The Longitude Act of 1714 was a series of large cash prizes created by the Parliament of the United Kingdom to determine time with the precision required for ocean navigation. The discovery of how to measure longitude accurately was among the important discoveries of the 1600's and 1700's.



## 1800s: Breakthroughs In Chemical Engineering

In the 18th century an engineering prize of 100,000 francs was offered by the French Academy for the production of soda from seawater. Nicholas Leblanc's resulting process became the basis of the modern chemical industry and is considered one of the key chemical engineering inventions of all time.



## 1900s: Breakthroughs In Aviation

In 1919, the \$25,000 Orteig Prize for the first non-stop flight between New York and Paris was won with spectacular results. Between 1905 and 1935, hundreds of aviation prizes stimulated the advancement of aircraft technology.

But more than 300 years before, in 1697...

We are well assured that there is scarcely anything more calculated to rouse noble minds to attempt work conducive to the increase of knowledge than the setting of problems at once difficult and useful, by the solving of which they may attain to personal fame as it were by a specially unique way, and raise for themselves enduring monuments with posterity. For this reason, I . . . propose to the most eminent analysts of this age, some problem, by means of which, as though by a touchstone, they might test their own methods, apply their powers, and share with me anything they discovered, in order that each might thereupon receive his due meed of credit when I publically announced the fact. [Scott 1967a, p. 224]

Johann Bernoulli, crowd-sourcing the problem of the the brachistochrone

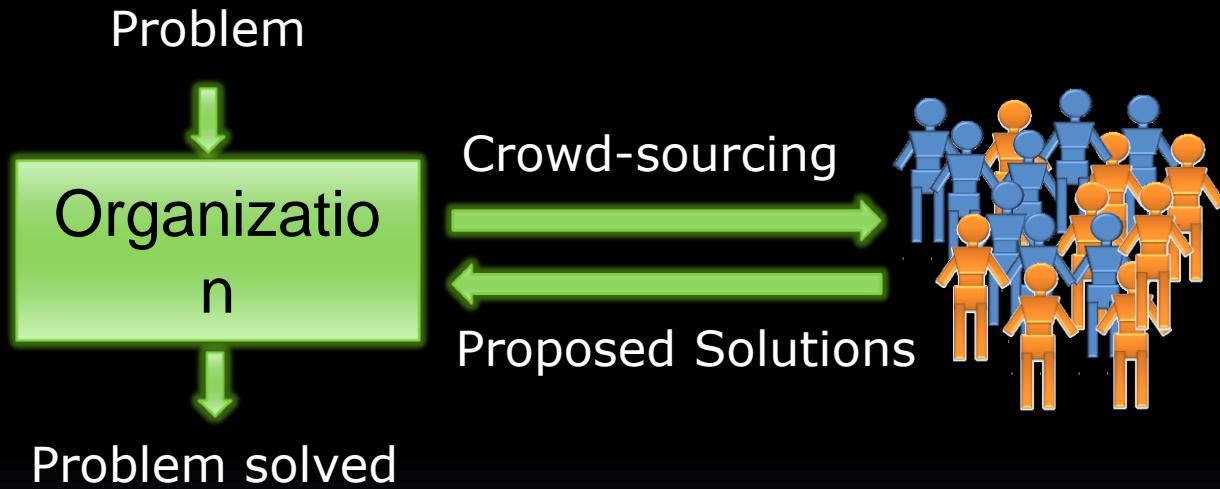
# Crowd-Sourcing

## Definition

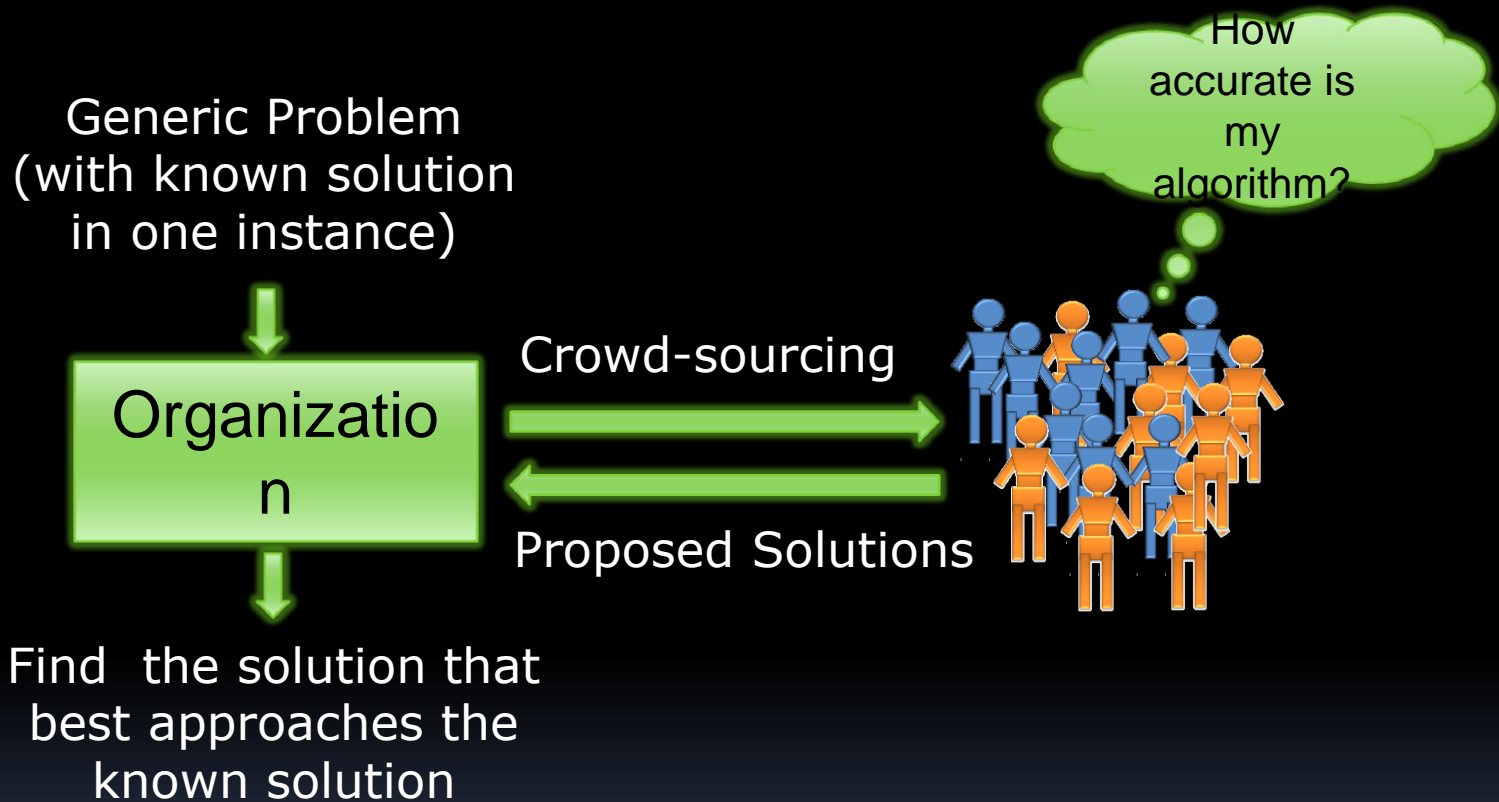
A methodology that uses the voluntary help of large communities to solve problems posed by an organization.



# Crowd-Sourcing



# Crowd-Sourcing for Benchmarking



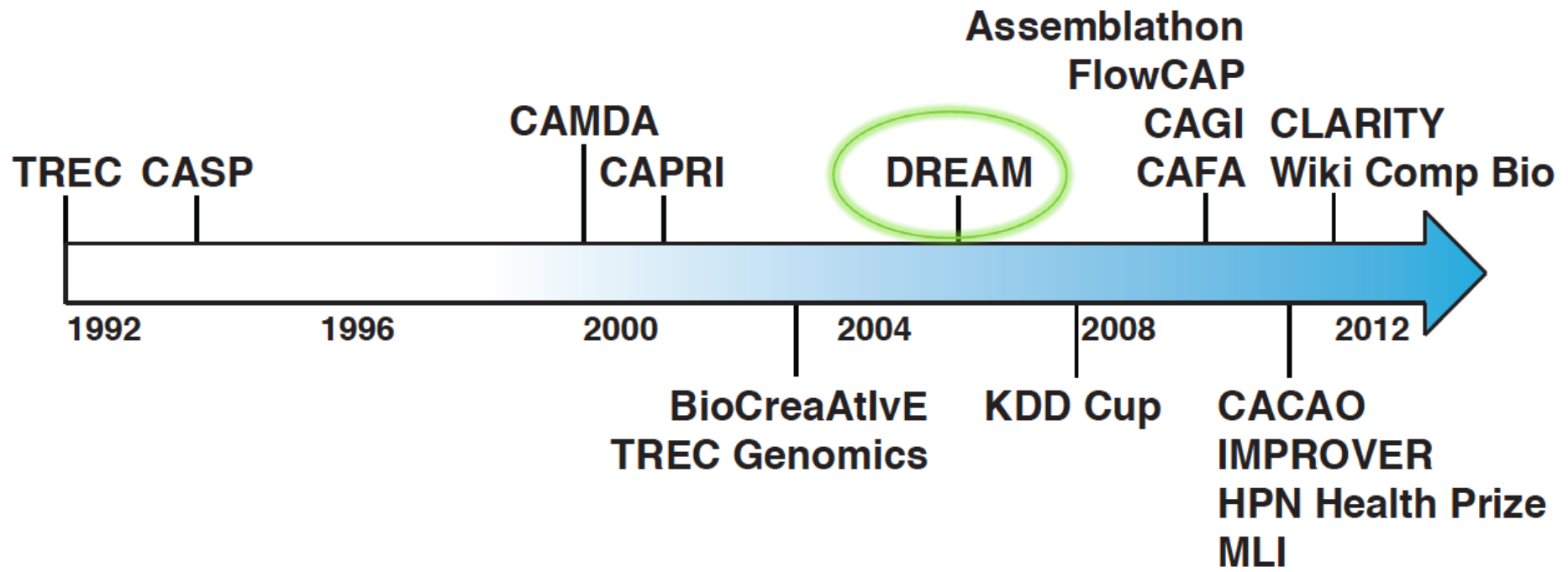


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Johann Bernoulli, crowd-sourcing the problem of the the brachistochrone

# Crowd-sourcing in Computational Biology



# Benefits of crowd-sourcing

- **Performance Evaluation**
  - Unbiased, consistent, and rigorous method assessment

# Difficulties in science validation

- Amgen scientists tried to confirm 53 landmark papers in pre-clinical oncology research: Only 6 (11%) were confirmed.[1]
- Bayer HealthCare reported that only about 25% of published preclinical studies could be validated.[2]
- Poti Gate: Genomics Research at Duke during 2006-2010, lead to the identification of Diagnostic Signatures that spurred clinical trials. The research was later deemed statistically flawed and the clinical trials stopped
- The self-assessment trap: can we all be better than average? [3]

[1] C. Glenn Begley and Lee M. Ellis, Nature 483, 531 (2012)

[2] Prinz,F.,Schlange,T.&Asadullah,K., NatureRev. Drug Discov. 10, 712 (2011).

[3] R. Norel, J.J.Rice, G. Stolovitzky, Mol. Sys. Bio, Oct 11;7:537 (2011)

# Benefits of crowd-sourcing

- **Performance Evaluation**

- Unbiased, consistent, and rigorous method assessment
- Discover the Best Methods
- Determine the solvability of a scientific question

- **Sampling of the space of methods**

- Understand the diversity of methodologies presently being used to solve a problem

# Benefits of crowd-sourcing

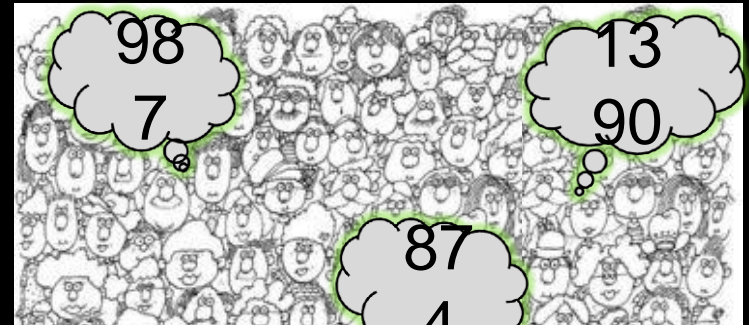
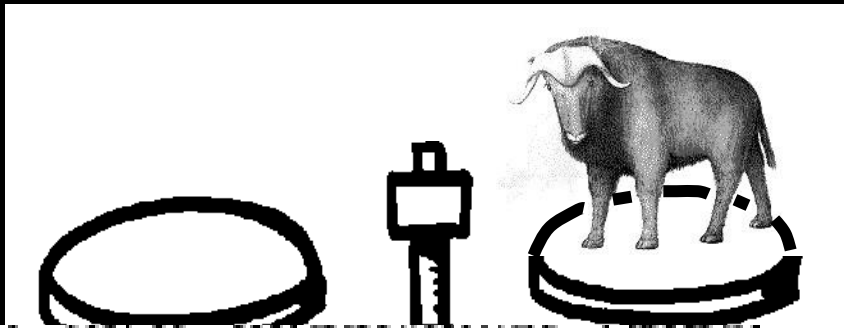
## ■ Acceleration of Research

- The community of participants can do in 4 months what would take 10 years to any group

## ■ Community Building

- Make high quality, well-annotated data accessible.
- Foster community collaborations on fundamental research questions.
- Determine robust solutions through community consensus: “The Wisdom of the Crowds.”

# The Wisdom of the Crowds



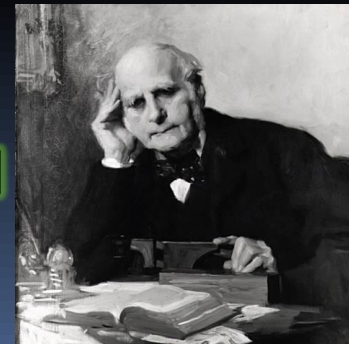
This result is, I think, more creditable to the trustworthiness of a democratic judgment than might have been expected.



Real Weight

Mean

1198 lb ~ 1197lb



*VOX POPULI.*

IN these democratic days, any investigation into the trustworthiness and peculiarities of popular judgments is of interest. The material about to be discussed refers to a small matter, but is much to the point.

*NATURE*

[MARCH 7, 1907]



# ENTER THE



## DIALOGUE FOR REVERSE ENGINEERING ASSESMENT AND METHODS



# Partnership with Sage Bionetworks



Synapse

Feb 2013

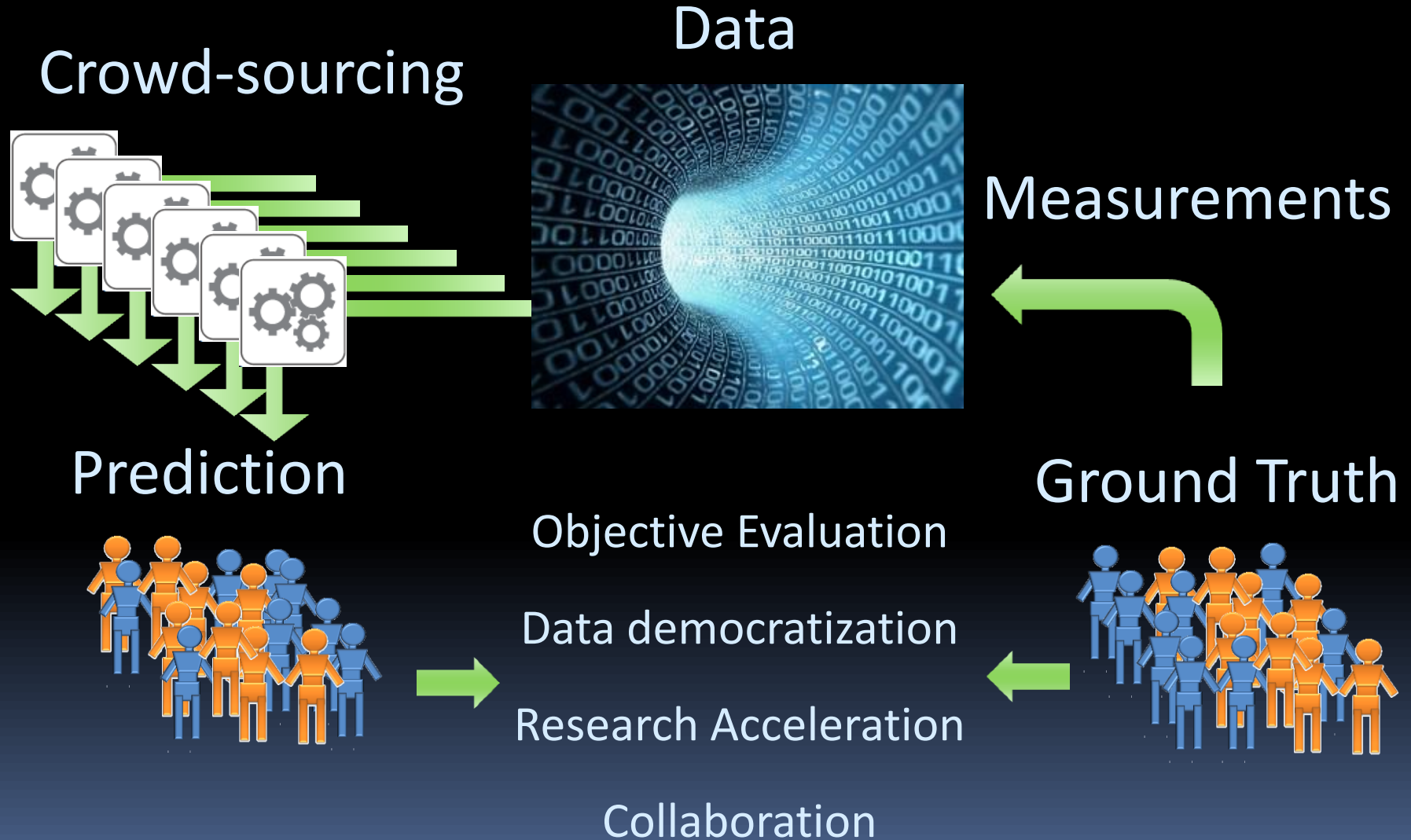


DREAM Challenges

# Mission of DREAM Challenges

- Our mission is
  - to contribute to the solution of important biomedical problems
  - to foster collaboration between research groups
  - to democratize data
  - to accelerate research
  - to objectively assess algorithm performance
- Problems we do challenges on:
  - Transcriptional and signaling networks,
  - Predictions of response to perturbations,
  - Translational research (tox, RA, AD, ALS, AML, ...)

# Structure of a DREAM Challenge



# Beyond a Challenge

Data



Best Methods



Diagnosis  
Prognosis  
Treatment

Measurements



Patient

# Recent DREAM Challenges

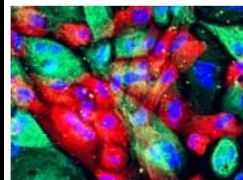
<http://dreamchallenges.org/>



## DREAM 9.5 - DREAM Olfaction Prediction Challenge

December 2014 - March 2015 (Pre-Registration Open)

This challenge's focus is to map the chemical properties of odors to predict a give subject's behavioral responses.



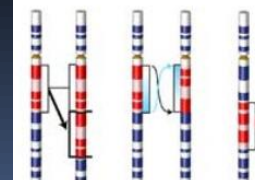
## DREAM 9.5 Prostate Cancer DREAM Challenge

February - June 2015 (Pre-Registration Open)

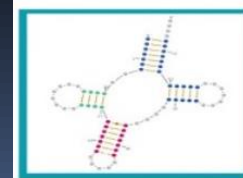
This challenge will focus on predicting survival for prostate cancer patients based on patients' clinical variables.

# Upcoming DREAM Challenges: Registration Open

<http://dreamchallenges.org/upcoming-challenges/>



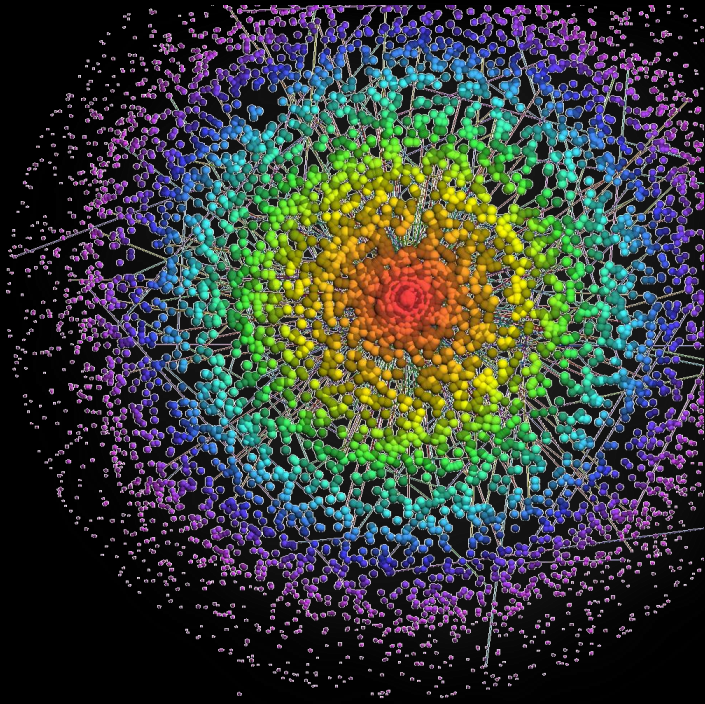
## DREAM 9.5 - ICGC-TCGA DREAM Somatic Mutation Calling Tumor Heterogeneity Challenge (SMC-Het)



## DREAM 9.5 - ICGC-TCGA DREAM Somatic Mutation Calling RNA Challenge (SMC-RNA)

TBD Winter 2014-2015 (Pre-Registration Open)





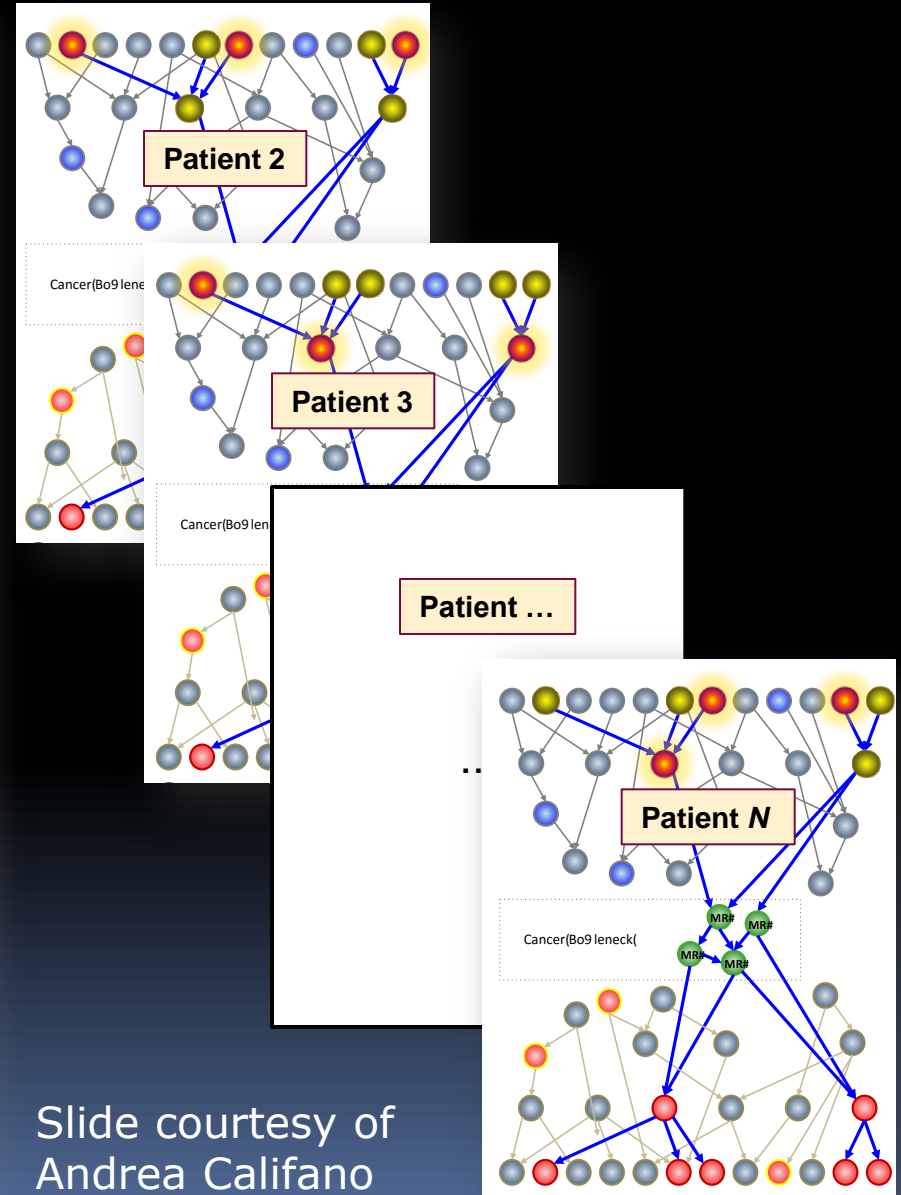
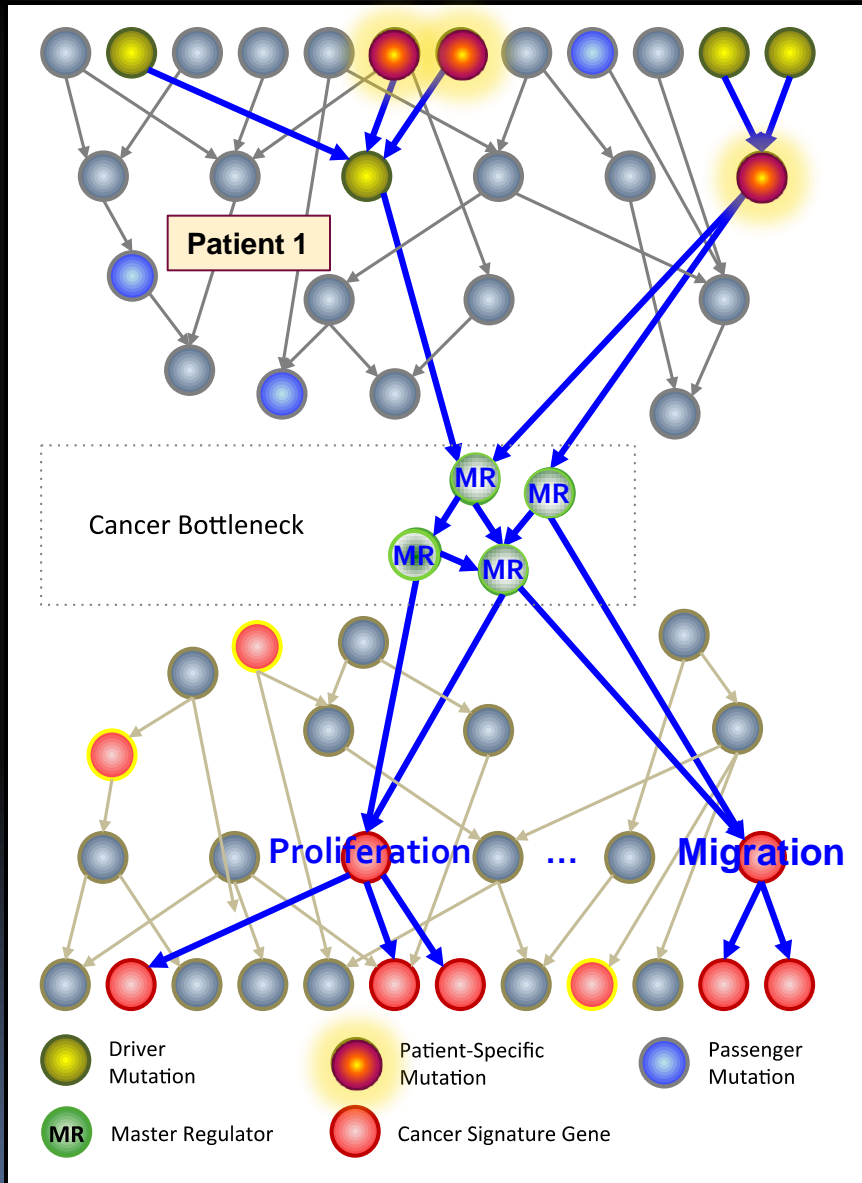
# Network Inference



# Inference of Causal Networks in Biology

- Networks provide a mechanistic understanding of biological processes
- Many of the methods to infer networks use ad-hoc assumptions that may not hold in practice
- Benchmarking methods for gene regulatory network inference is necessary to understand the strength and weaknesses of network inference algorithms.

# Using networks to causally interpret cancer data



Slide courtesy of  
Andrea Califano



- An analysis of regulatory network inference
- A system to study animal dispersal
- Zinc-finger nuclease protein delivery
- A membrane-protein backbone structure pipeline
- Resources to probe microRNA function

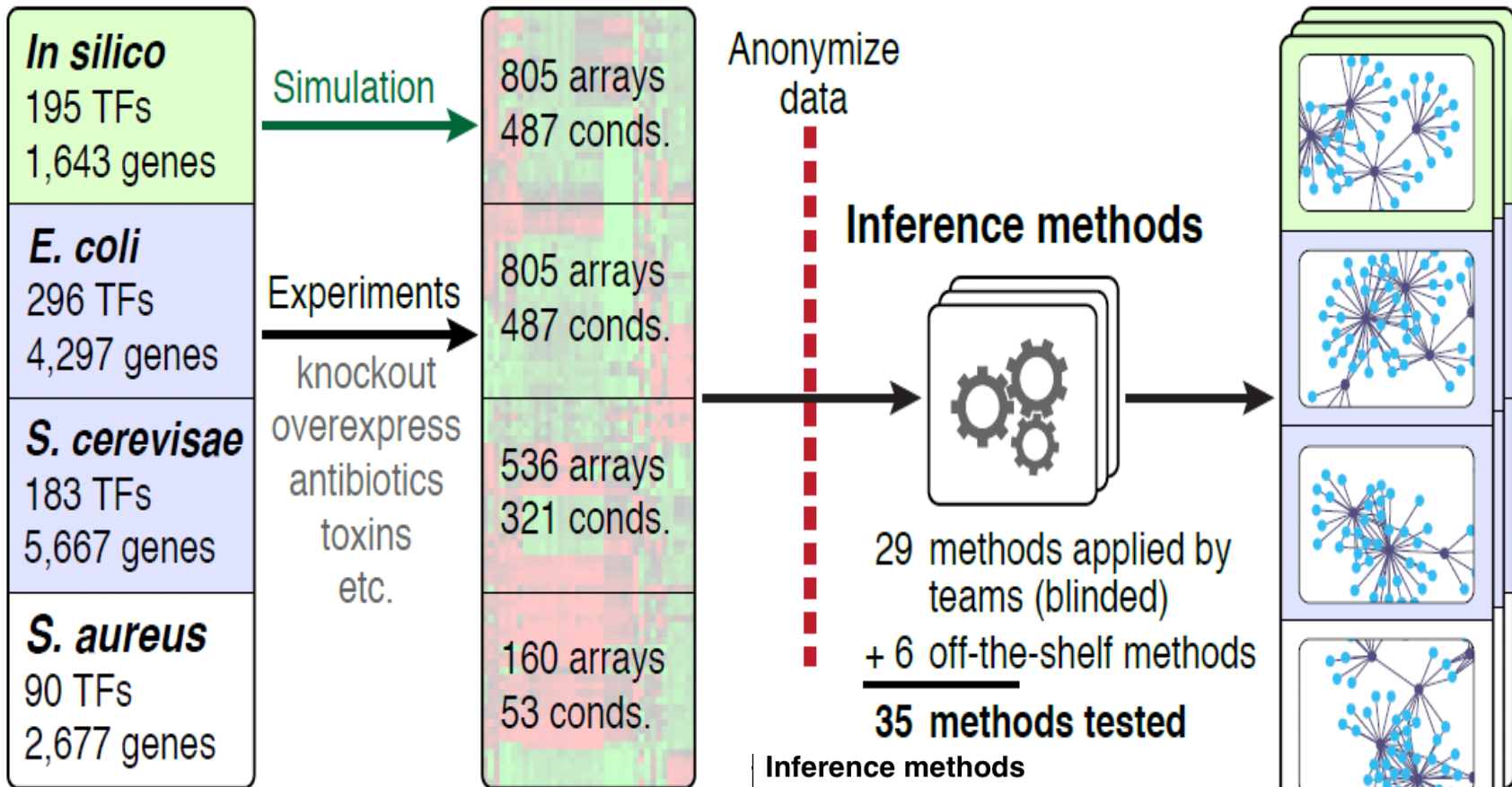
**DREAM 5**

## Wisdom of crowds for robust gene network inference

Daniel Marbach<sup>1,2,11</sup>, James C Costello<sup>3-5,11</sup>, Robert Küffner<sup>6,11</sup>, Nicole M Vega<sup>3-5</sup>, Robert J Prill<sup>7</sup>,  
Diogo M Camacho<sup>3-5,10</sup>, Kyle R Allison<sup>3-5</sup>, The DREAM5 Consortium<sup>8</sup>, Manolis Kellis<sup>1,2</sup>, James J Collins<sup>3-5,9</sup> &  
Gustavo Stolovitzky<sup>7</sup>

# DREAM5 network inference challenge

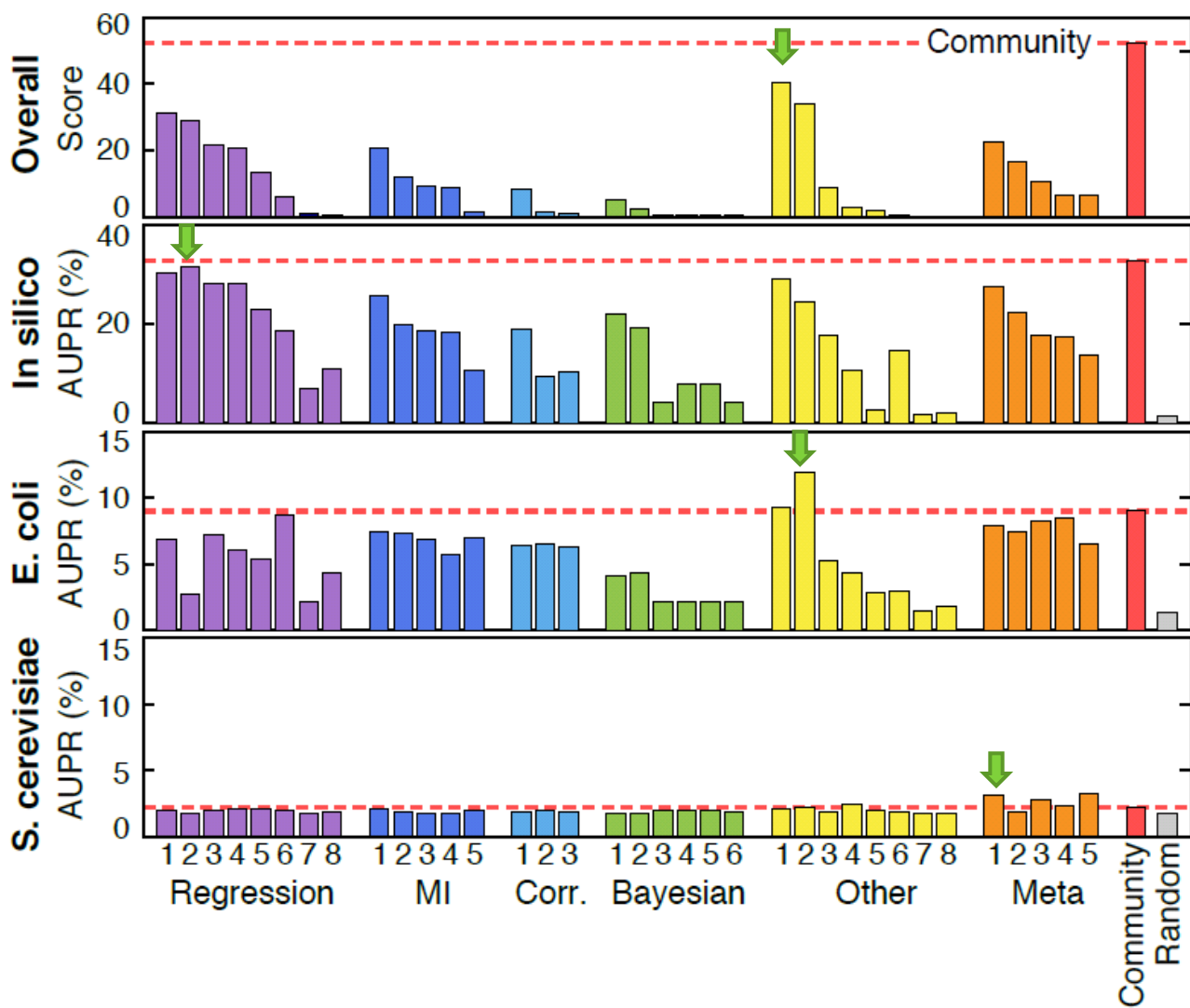
(1) Target network      (2) Microarray compendia      (3) Inferred networks



## Inference methods

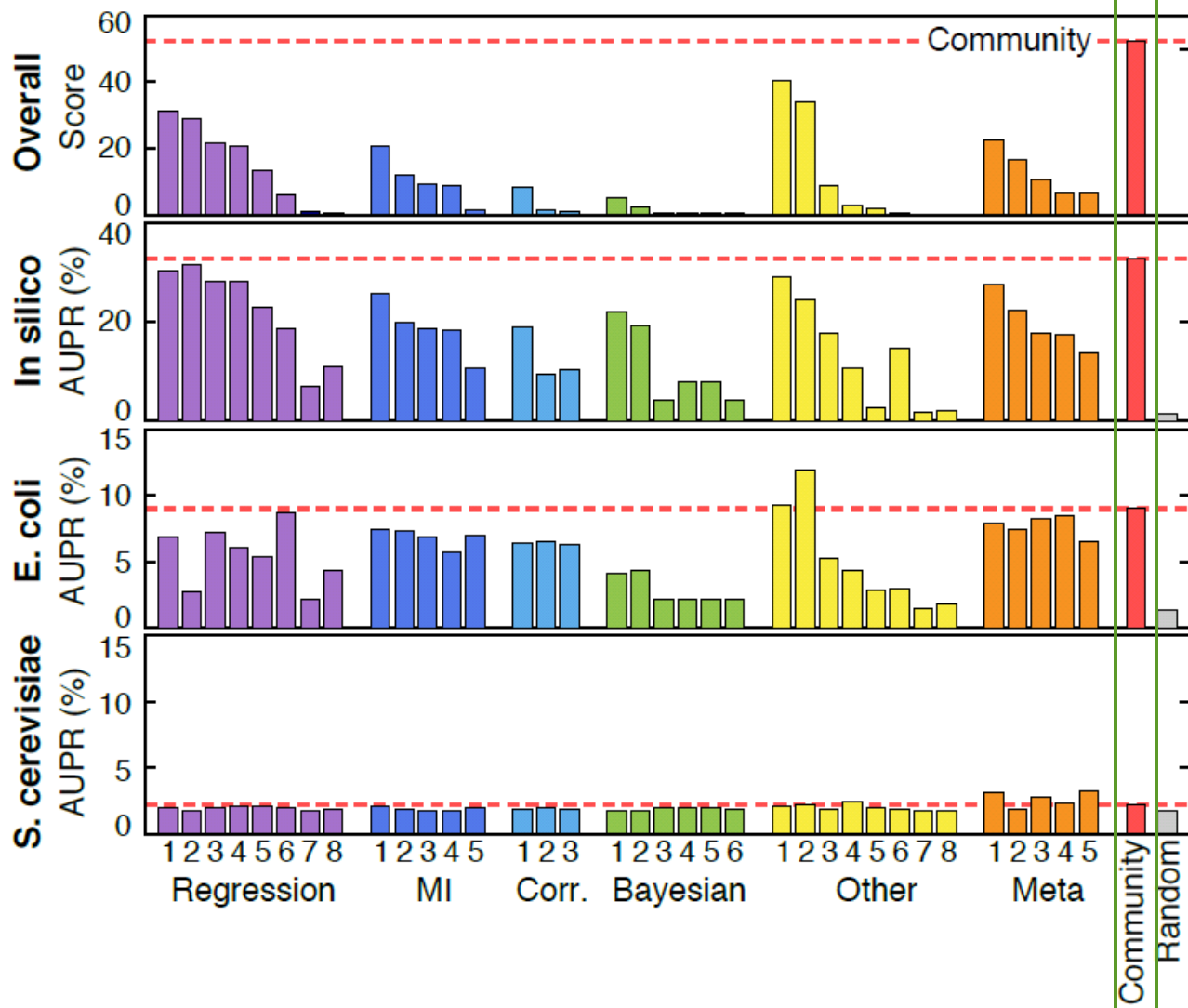
- Regression
- Mutual information
- Correlation
- Bayesian networks
- Other
- Meta
- Community

# Different methods are best performers for different networks

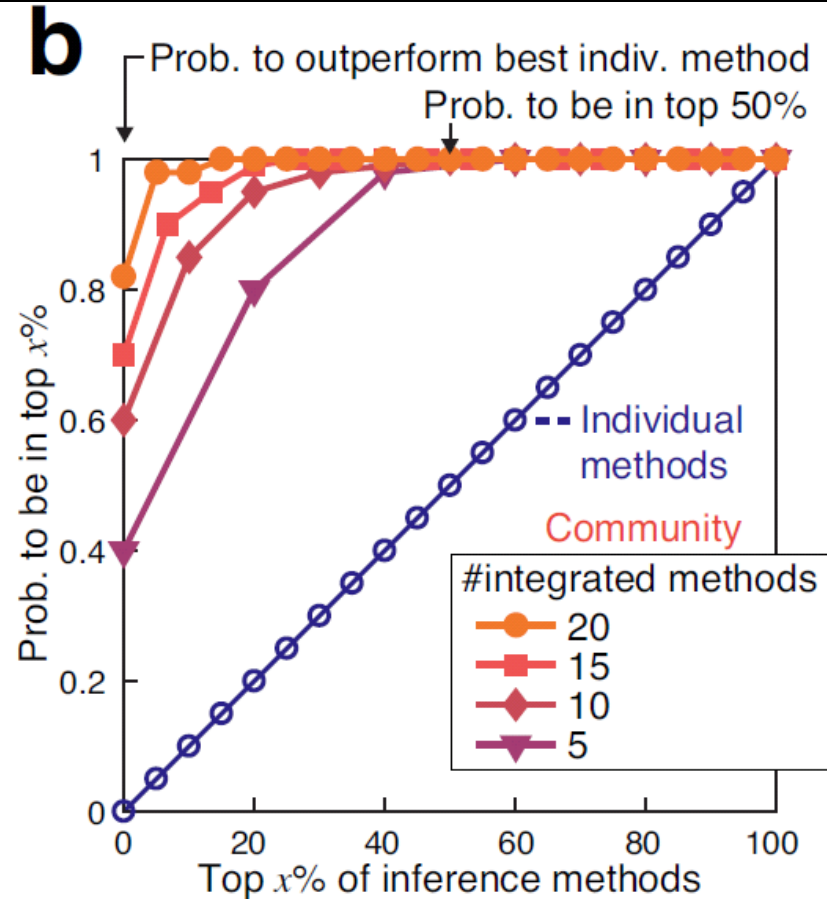
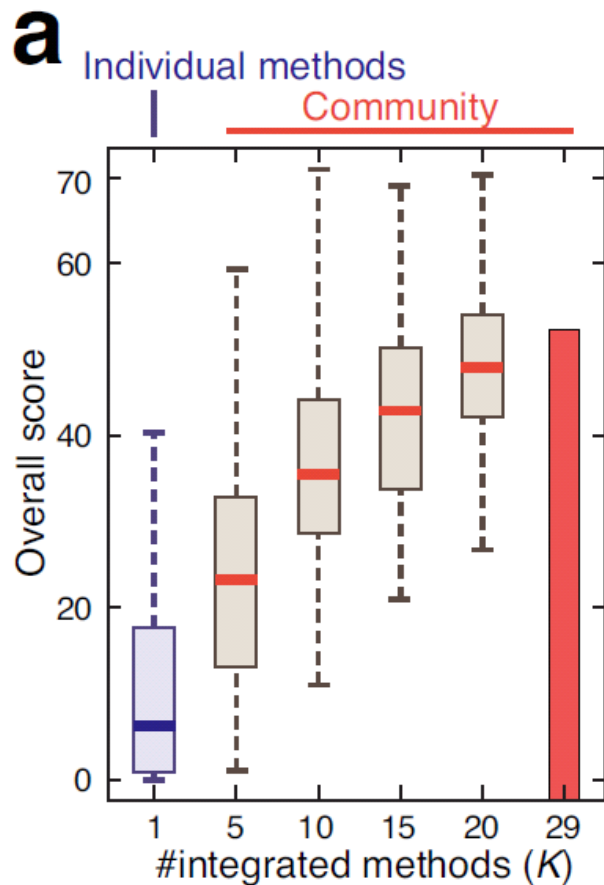




# But the community prediction is always among the 3 best: it's robust

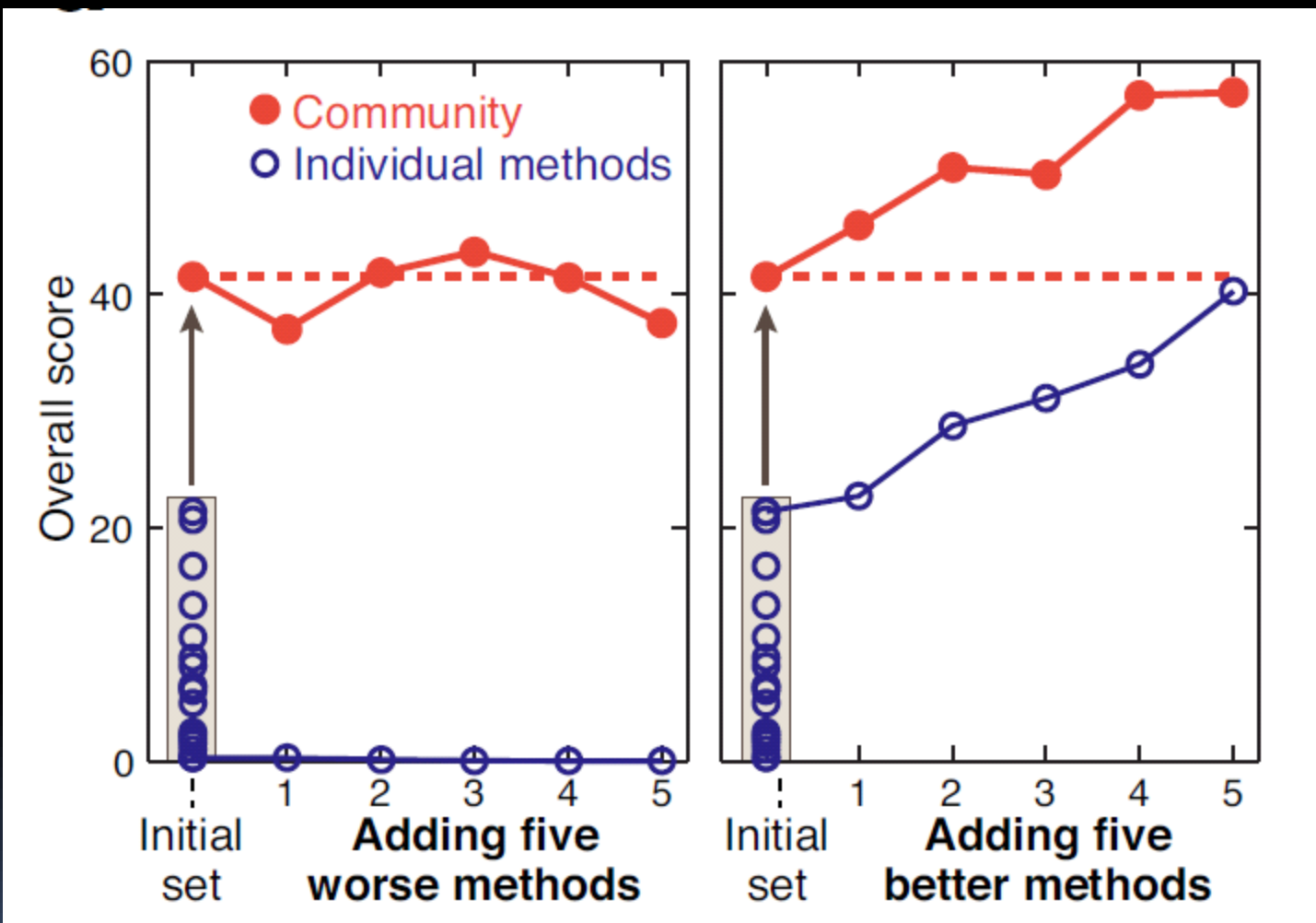


# Wisdom of Crowds: Aggregation is robust and often better than the best





# Wisdom of Crowds (cntd)



# Staphylococcus Aureus community network

## 1084 genes ; 1688 edges; GO enriched modules

### b *S. aureus* community network

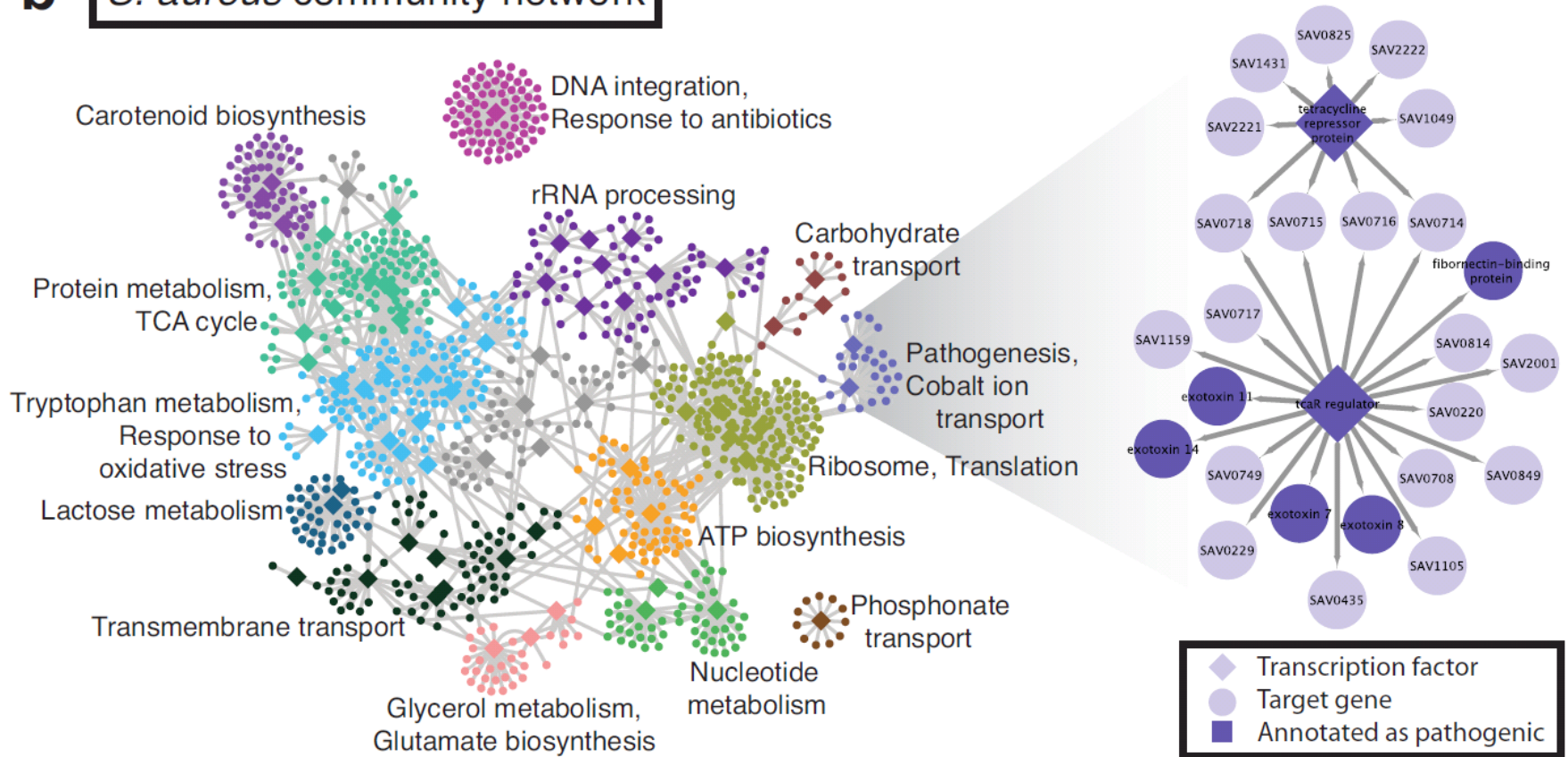


Figure 4. *E. coli* and *S. aureus* community networks



# The NCI-DREAM7 Challenges

75 teams, 46 cities, 3 continents

\_computational  
BIOLOGY

ANALYSIS

**NATURE BIOTECHNOLOGY**

Received 19 February; accepted 25 September; published online 17 November 2014; doi:10.1038/nbt.3052

## The challenge of predicting synergistic and antagonistic compound-pair activity from individual compound perturbations

Mukesh Bansal<sup>1,2,\*,#</sup>, Jichen Yang<sup>8,\*</sup>, Charles Karan<sup>3,\*</sup>, Michael P. Menden<sup>9</sup>, James C. Costello<sup>10,†</sup>, Hao Tang<sup>8</sup>, Guanghua Xiao<sup>8</sup>, Yajuan Li<sup>11</sup>, Jeffrey Allen<sup>8,11</sup>, Rui Zhong<sup>8</sup>, Beibei Chen<sup>8</sup>, Minsoo Kim<sup>8,12</sup>, Tao Wang<sup>8</sup>, Laura M. Heiser<sup>13</sup>, Ronald Realubit<sup>3</sup>, Michela Mattioli<sup>14</sup>, Mariano J. Alvarez<sup>1,2</sup>, Yao Shen<sup>1,2</sup>, NCI-DREAM community<sup>15</sup>, Daniel Gallahan<sup>16</sup>, Dinah Singer<sup>16</sup>, Julio Saez-Rodriguez<sup>9</sup>, Yang Xie<sup>8,12,#</sup>, Gustavo Stolovitzky<sup>17,#</sup>, Andrea Califano

# Synergistic Combinations

## Recent Examples

- CHK1 inhibitors with DNA damaging agents
- PARP inhibitor in combination with PI3K inhibitor
- Trastuzumab and Lapatanib

## Endpoints of synergistic activity are

- reducing or delaying the development of resistance to treatment
- improving overall survival
- lowering toxicity by decreasing individual compound dose

## A drug could sensitize cells to other compound by

- regulating its absorption and distribution
- inhibiting compound degradation
- inhibiting pathways that induce resistance
- reducing the other compound's toxicity

# Why an NCI-DREAM Synergy Prediction Challenge?

- In-vitro screening of all-against-all combinations for a diversity of libraries is becoming more common
- This imposes serious limits to the size of the libraries
- In silico methods to predict compound synergy may effectively complement high-throughput synergy screens
- The NCI-DREAM synergy prediction challenge aims at predicting compound synergy from molecular profiles of single compound activity

# The NCI-DREAM Synergy Prediction Challenge

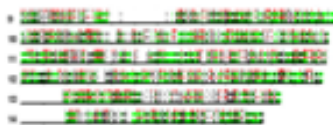
Task: Predict the order of 91 compound pairs from the most synergistic to the most antagonistic

**INPUT DATA (no training set)**

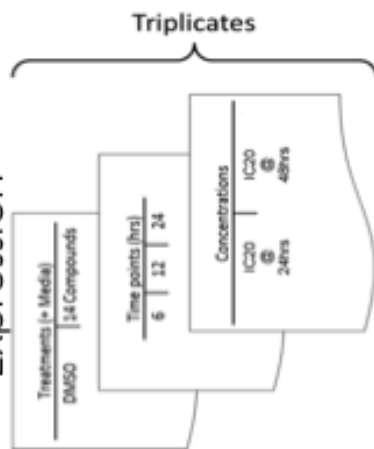
LY3, a Diffuse large B-cell lymphoma (DLBL) cell line

Drug	IC20 at 24h (μM)	IC20 at 48h (μM)
Aclacinomycin A	0.105	0.036
Blebbistatin	100	10
Camptothecin	0.31	0.01
Cycloheximide	5	0.264
Doxorubicin hydrochloride	0.101	0.03
Etoposide	0.811	0.812
Geldanamycin	0.032	0.001
H-7, Dihydrochloride	20.2	12.4
Methotrexate	100	100
Mitomycin C	2.56	0.553
Monastrol	100	50
Rapamycin	22	13.8
Trichostatin A	0.143	0.114
Vincristine	0.01	0.005

Mutations



Expression



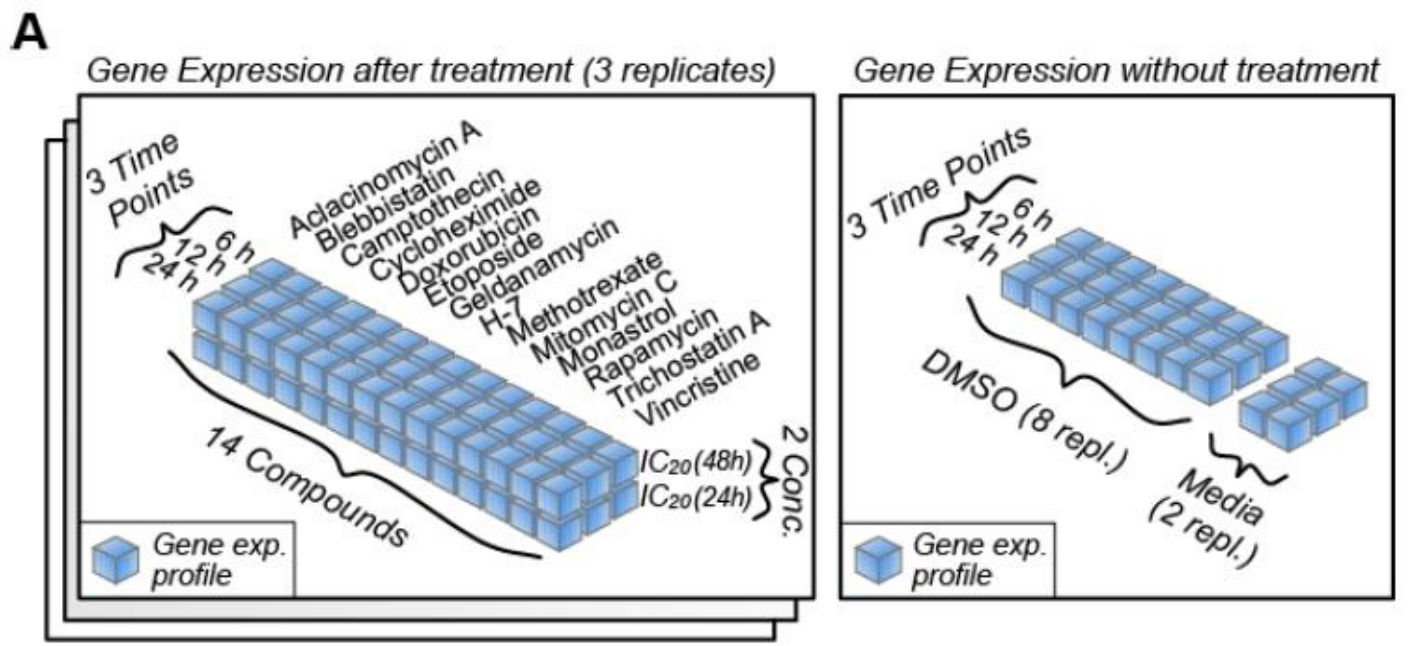
Genes

**PREDICTIONS**

Rank	Combination
1	Aclacinomycin A & Cycloheximide
2	Blebbistatin & Etoposide
3	Etoposide & Methotrexate
4	Mitomycin C & Monastrol
5	Mitomycin C & Rapamycin
...	...
90	Monastrol & Rapamycin
91	Vincristine & Trichostatin A



# The Data

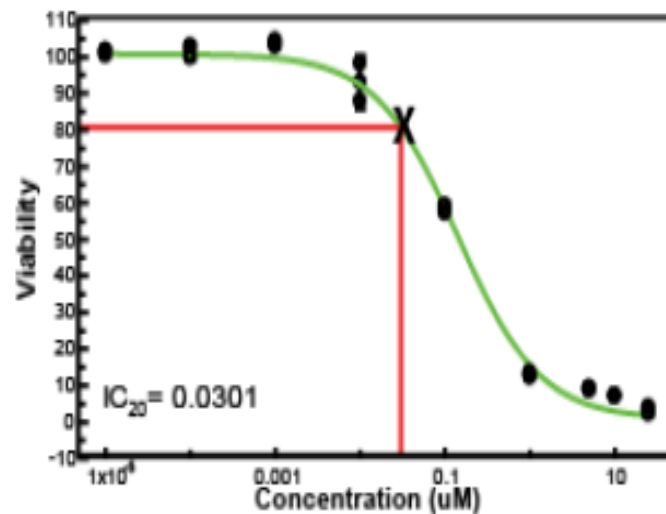


Cell line (OCI-LY3)



Copy number variation (CNV)

Single Nucleotide Polymorphism (SNP)





# Synergy and Antagonism define in terms of Bliss Independence

V = viability; fraction of surviving cells in the cell culture

I = inhibition; fraction of dead cells in the cell culture

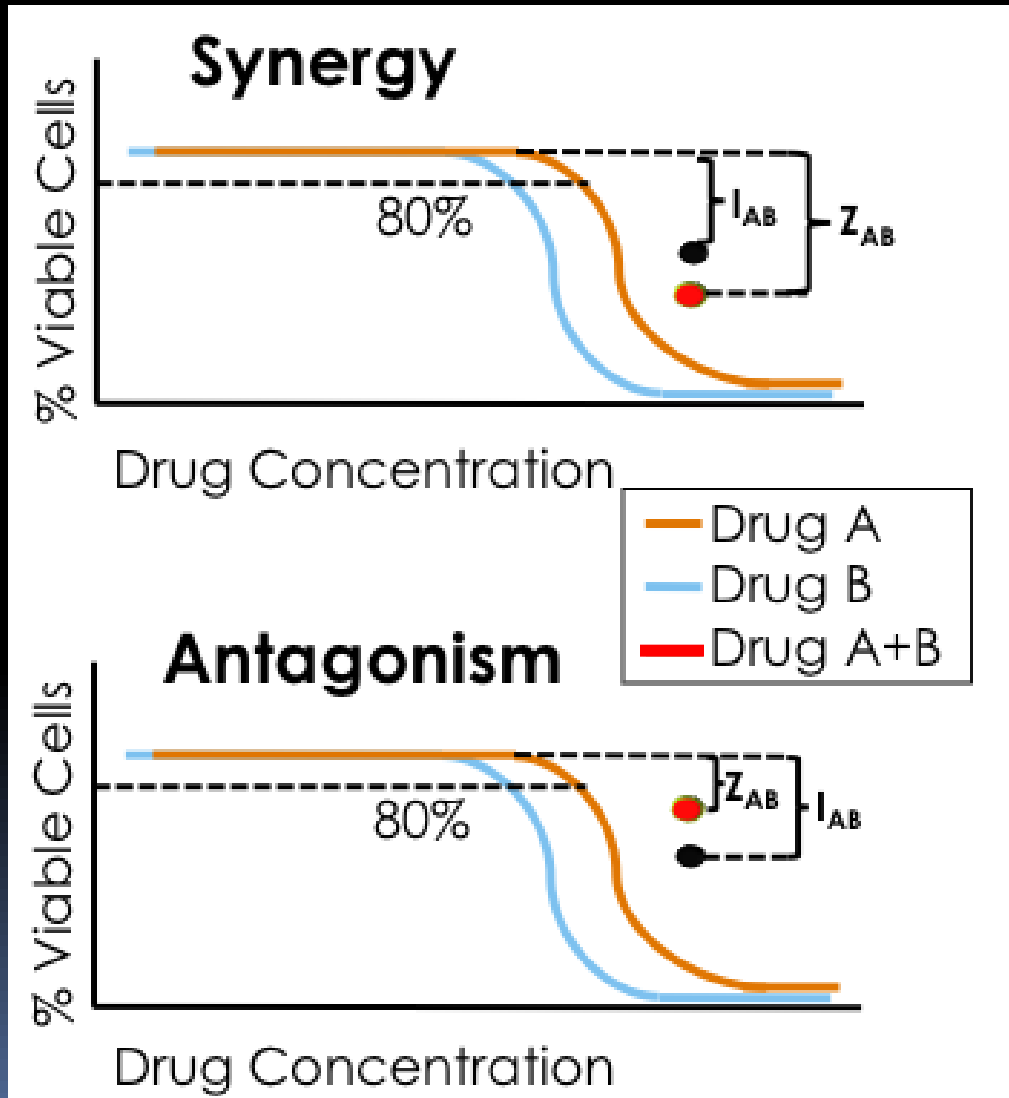
## Bliss Independence:

If cells are treated with Drug A and Drug B simultaneously and A and B act independently, then

$$V_{AB} = V_A \cdot V_B$$

$$I_{AB} = 1 - V_{AB} = I_A + (1 - I_A) \cdot I_B$$

# Synergy and Antagonism define in terms of Bliss Independence



Drug A and B were both given at their respective  $IC_{20}$

Therefore, if they were independent, their joint inhibitions would be

$$I_{AB} = 0.2 + 0.2 - 0.04 = 0.36$$

Call the inhibition by A and B administered at  $IC_{20}$ ,  $Z_{AB}$

The Excess over Bliss is defined as

$$EoB = Z_{AB} - I_{AB}$$

A&B synergistic  $\rightarrow EoB > 0$

A&B antagonistic  $\rightarrow EoB < 0$

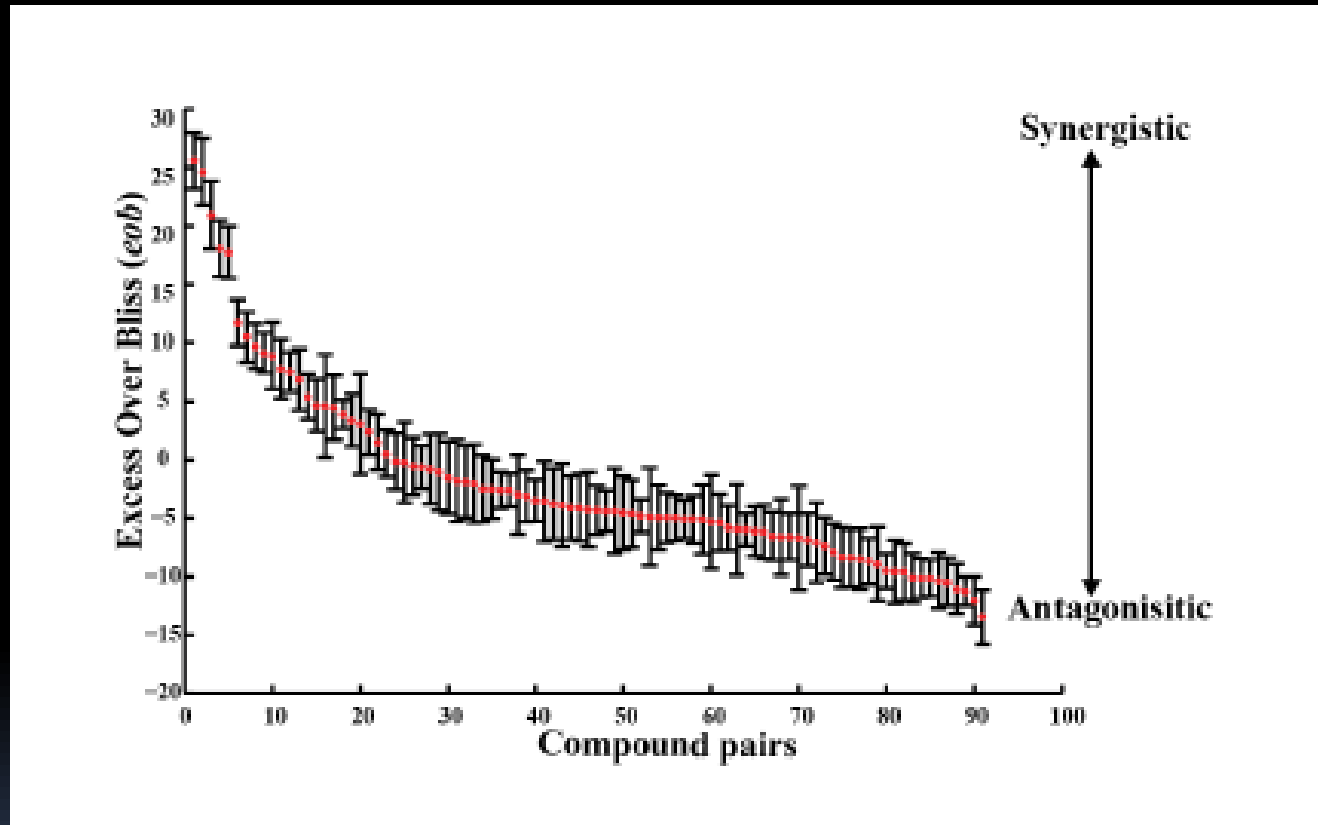


# Scoring the submissions: Concordance index

Actual order	Predicted order	Pairwise order	Score
<u>Cell combo 1</u>	<u>Cell combo 1</u>	<u>    </u> <u>    </u>	Right: +1
<u>Cell combo 2</u>	<u>Cell combo 3</u>	<u>    </u> <u>    </u>	Right: +1
<u>Cell combo 3</u>	<u>Cell combo 2</u>	<u>    </u> <u>    </u>	Wrong: 0

$$\text{C-index} = (1 + 1 + 0) / 3 = 2/3$$

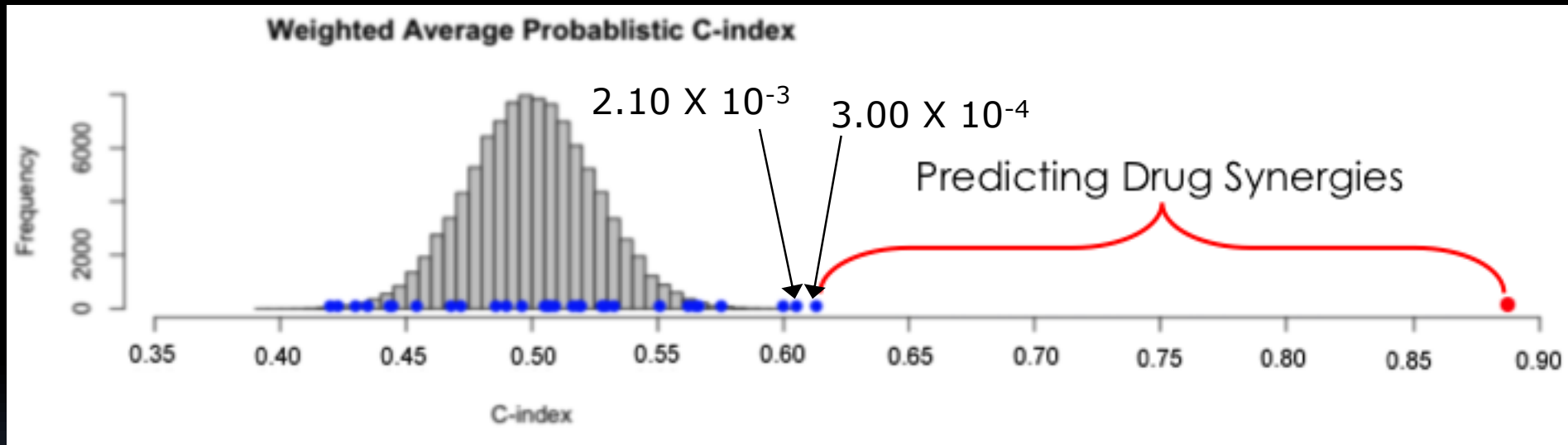
# Scoring with (probabilistic) concordance index due to a noisy Gold Standard



The concordance index is the proportion of pairs of cell lines whose EoB order was correctly predicted.

# Results – 31 Submissions

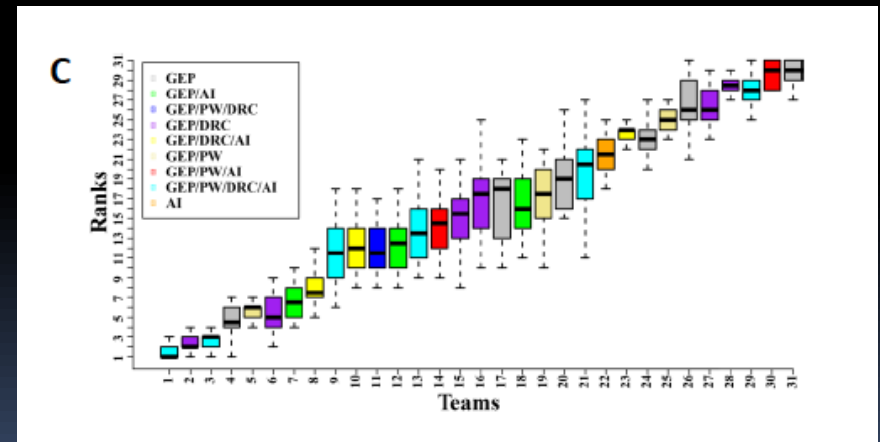
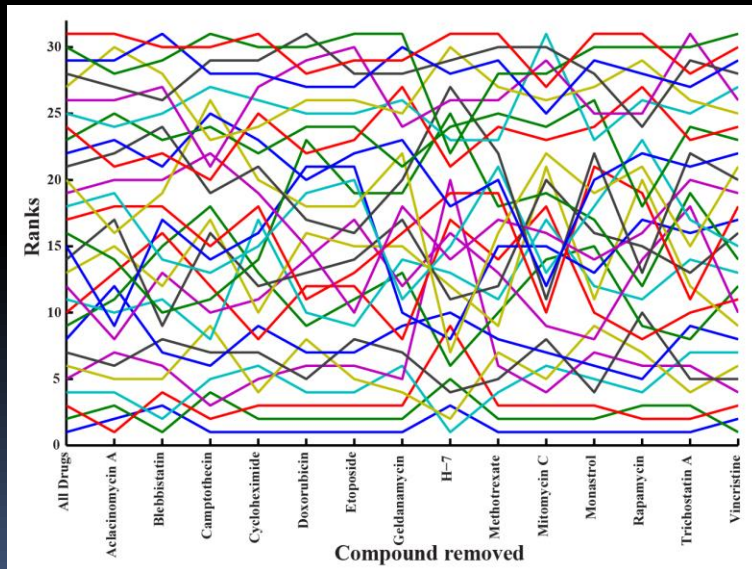
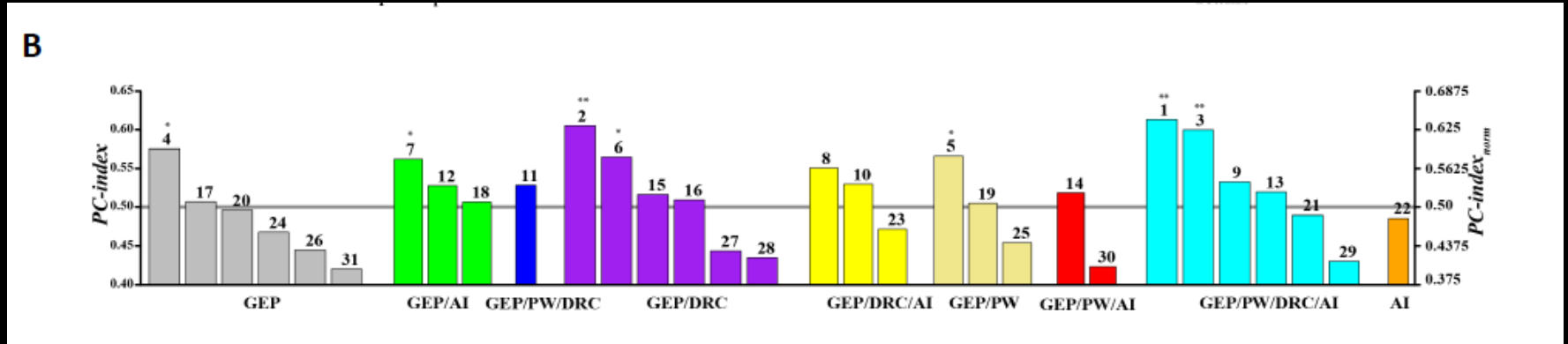
## PLENTY OF ROOM FOR IMPROVEMENT



Only 3 methods were statistically significant at  $FDR < 0.05$ .

# No methods class over performed the others

PW: Pathway info; DRC: Drug Response Curve; PW: Pathway info



Resampling shows robustness of best performers to removal of each drug

# No methods class over performed the others

## *Similarity of differential expression Hypothesis*

- 10/31 teams hypothesized that compounds with higher transcriptional profile similarity were more likely to be synergistic.
- 8/31 hypothesized the opposite
- 13/31 hypothesized a mixture or more complex hypothesis

## *Genetic Profiles*

- 2/31 teams used LY3 genetic profiles

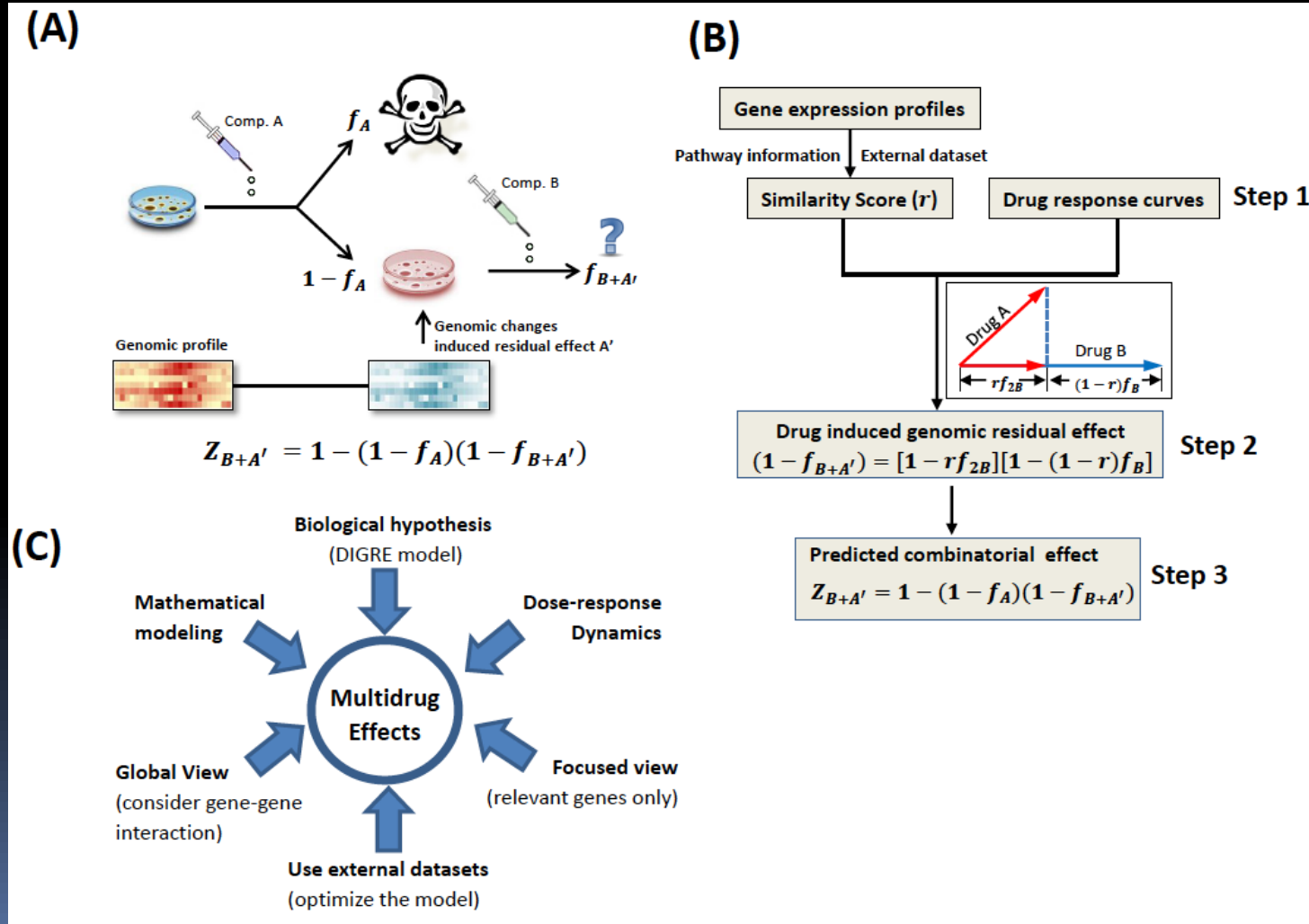
## *Use of additional information*

- 12/31 teams relied only on provided information
- 19/31 used additional information such as pathway knowledge



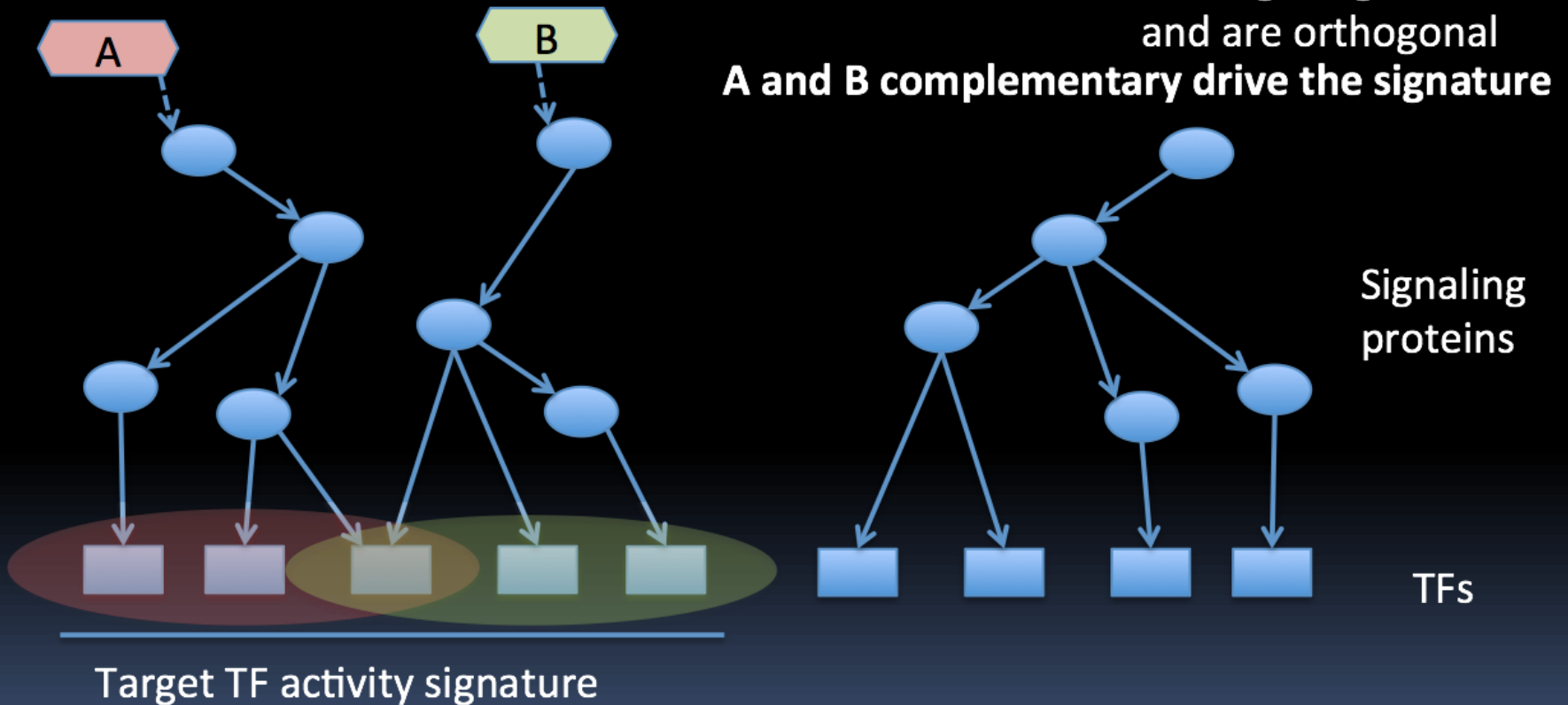
# NCI / DREAM Synergy Challenge Best Performer

**UTSW-MC:** University of Texas Southwestern Medical Center- Dallas, TX, Jichen Yang, Hao Tang, Rui Zhang, Jeffery Allen, Min Kim, Beibei Chen, Tao Wang, Guanghua Xiao, Yang Xie

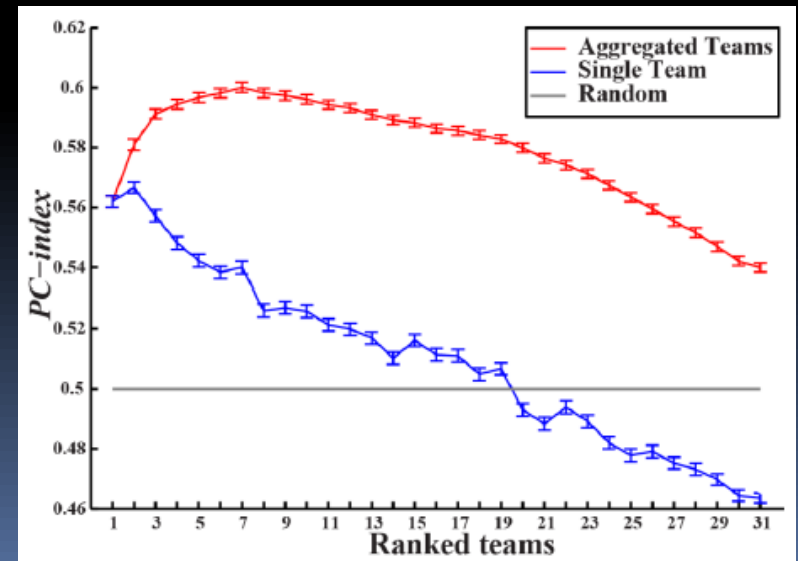
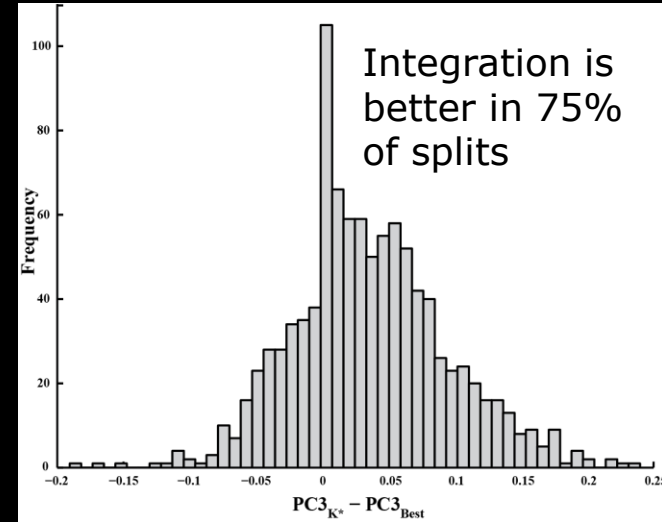
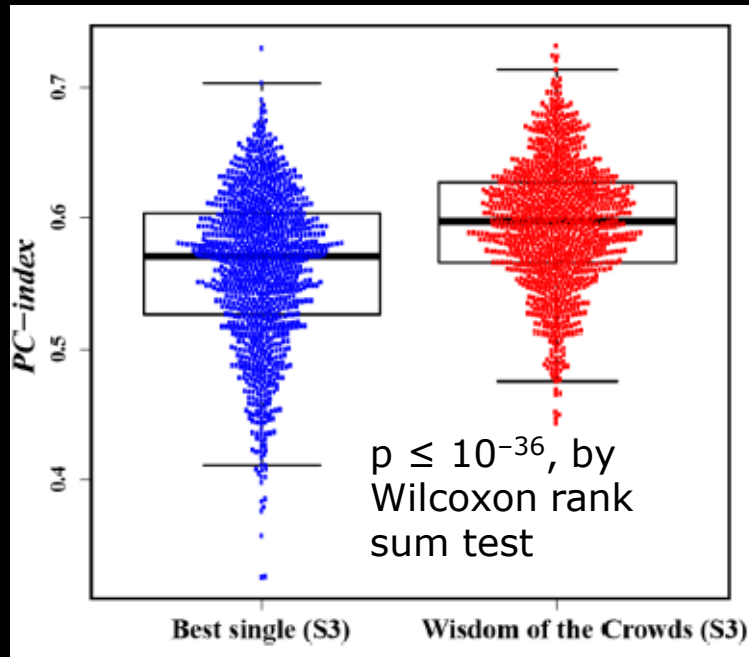


# SynGen method for predicting synergy

Califano lab



# The wisdom of the crowds: Aggregate is robust



S1

Split for ordering the teams according to performance

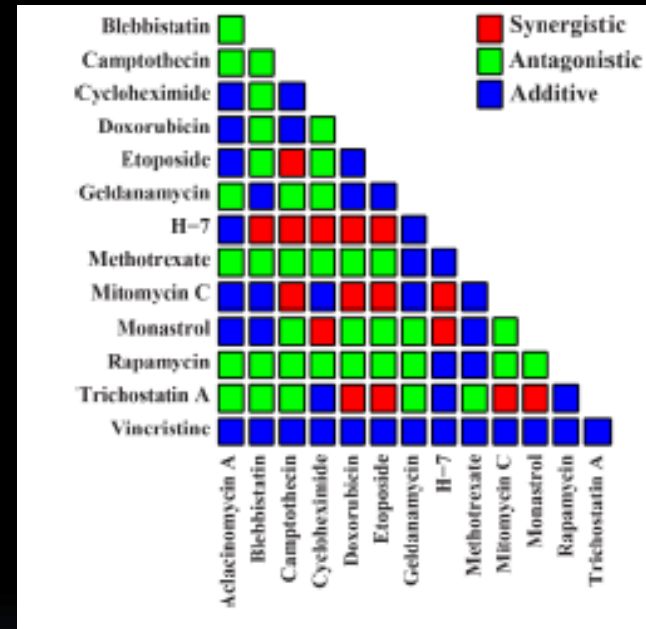
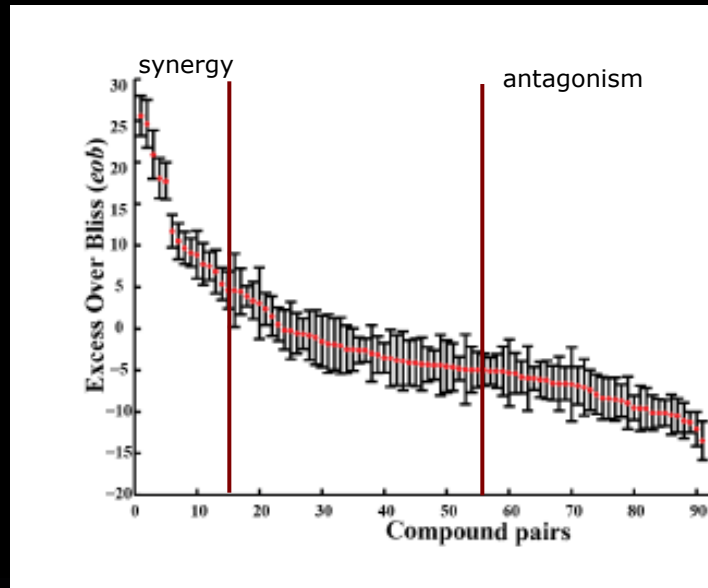
S2

Split for choosing the best numbers to aggregate

S3

Split to evaluate performance

# Scoring with Classification in Synergistic and Antagonistic

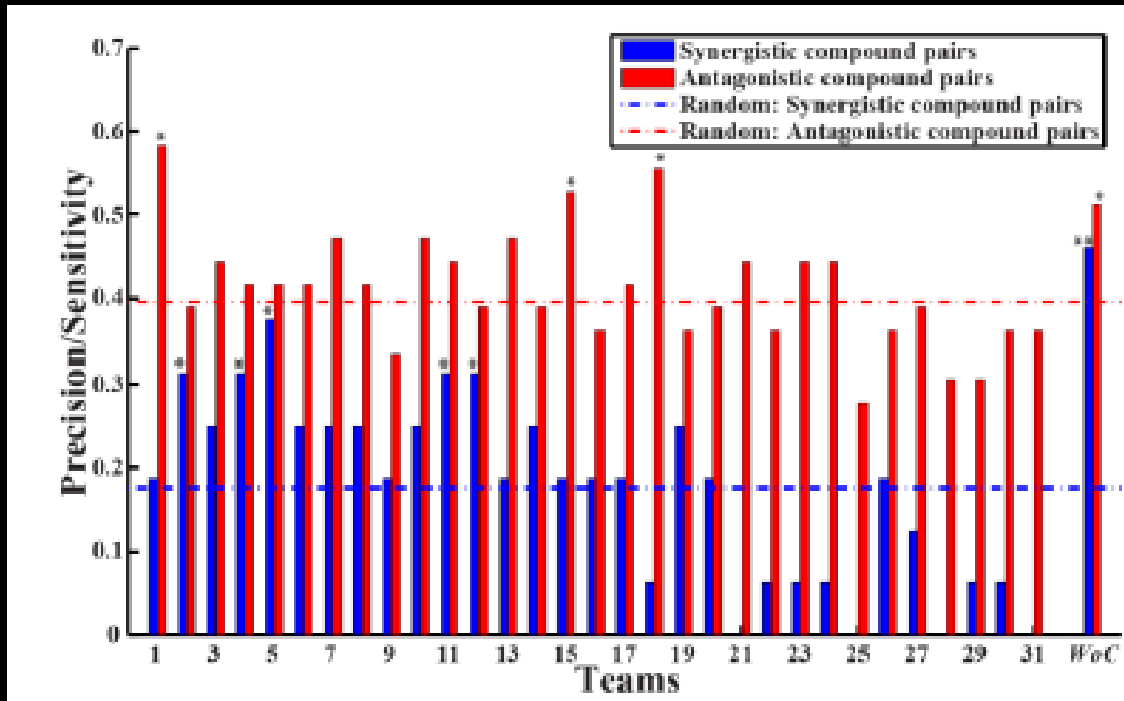


There are 16 synergistic and 36 antagonistic pairs.

Compounds exhibiting poly-pharmacology, such as H-7 and Mitomycin C, were enriched in synergistic pairs.

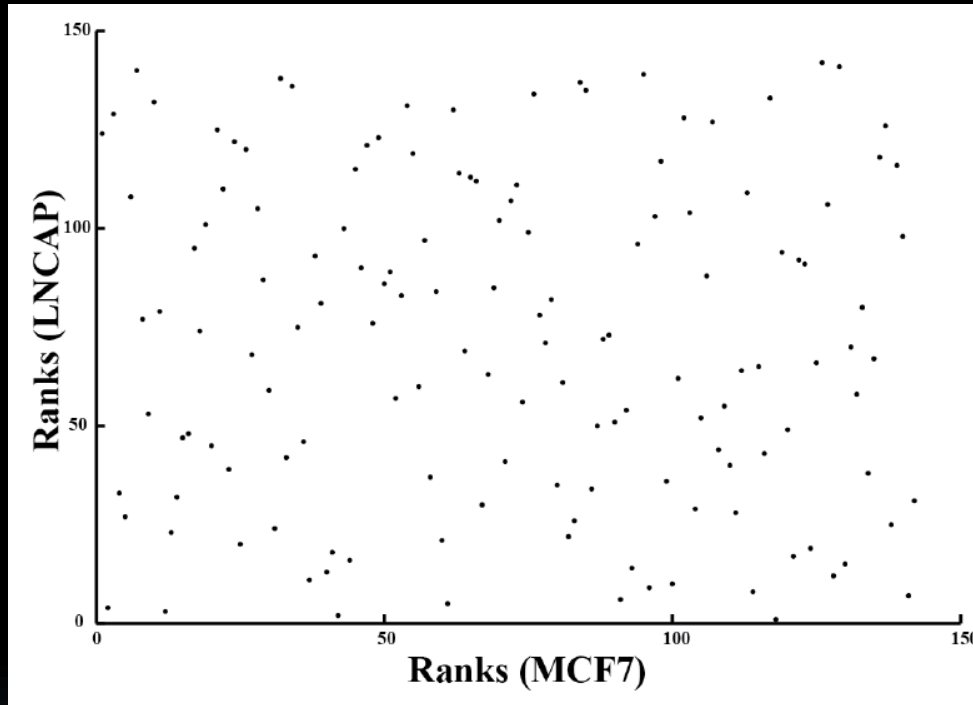
Compounds with more targeted mechanisms, such as Rapamycin and Blebbistatin, were least synergistic.

# Sensitivity Analysis



DIGRE was the best at predicting antagonism, but its prediction of synergy was non-statistically significant. However, it never misclassified a synergistic interaction as antagonistic or vice-versa.

# Synergy is context dependent



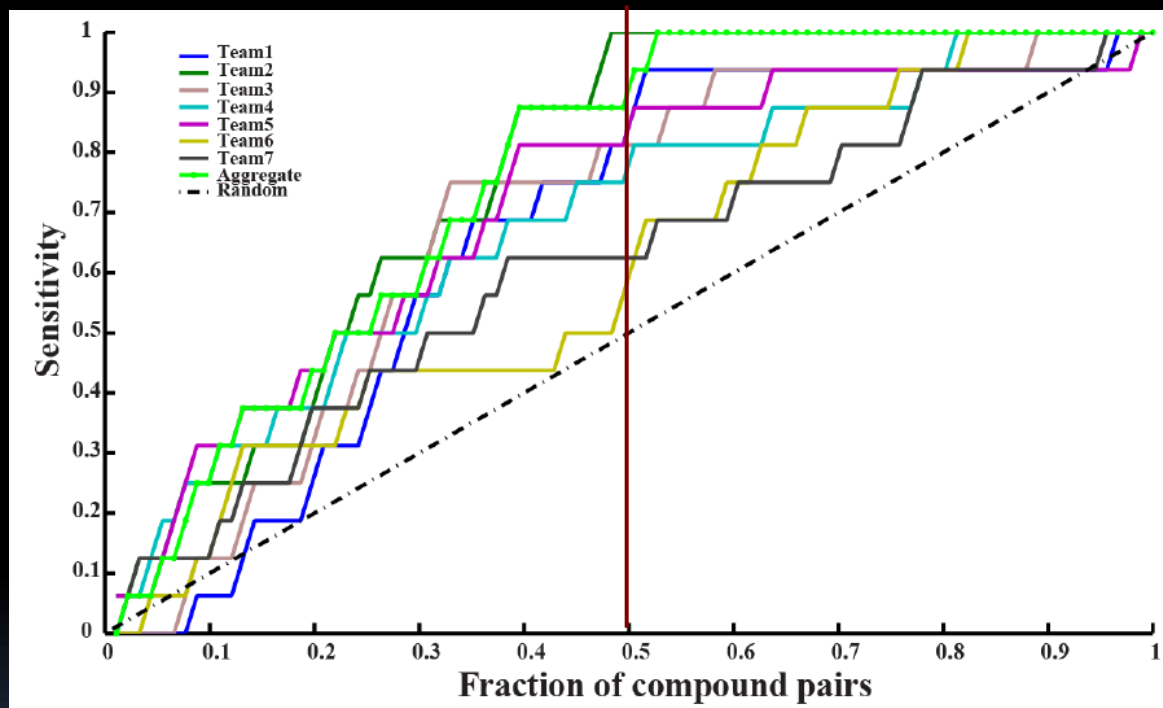
142 compound pairs

Spearman corr=-0.06

When the same pairs are tried in MCF7 and LNCaP, the synergy and antagonism is not preserved

Genetics and regulatory architecture of the context will become increasingly relevant to generalize results across multiple contexts.

Top performing team could already produce significant reduction in screening.



The top team at predicting synergy would have allowed the screening of only  $\frac{1}{2}$  the compounds without losing any synergistic pair



# Conclusions

- >3 months, ~90 researchers → > 23 person-years!
- Prediction is possible without a training set
- Synergy and Antagonism are context dependent; therefore prediction is more important as screens cannot be generalized from one cell to other
- Synergy and antagonism need alternative hypothesis: methods that are good at predicting one seem to be bad at predicting the other.
- We developed new metrics for synergy assessment: the probabilistic C-index
- Top performing team could already produced significant reduction in screening.
- there is an ample room for both algorithm and evaluation metric improvements
- DREAM challenges can provide a valuable mechanism to accelerate the development of predictive models for combination therapy

# Conclusions

- **Challenges**

- Challenges are becoming a powerful method for doing science
- Data sets multiply their impact by becoming accessible to a wide segment of the community
- A rigorous assessment can be attained by blinding participants from test data sets
- We can tap on the Wisdom of the Crowds.



# Acknowledgements

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  - Chris Bare
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  - Kely Norel
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  - Pablo Meyer Rojas
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  - Thomas Cokelaer
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  - Michael Menden
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- **OHSU**
  - Joe Gray
  - Adam Margolin
  - Mehmet Gonen
  - Laura Heiser
- **Prize4Life**
  - Neta Zach
- **NCI**
  - Dinah Singer
  - Dan Gallahan
- **ISMMS**
  - Eli Stahl
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