University of Pavia
Dep. of Electrical, Computer and Biomedical Engineering

PREDICTION AND SIMULATION OF MULTI-TARGET THERAPIES FOR TRIPLE NEGATIVE BREAST CANCER THROUGH A NETWORK-BASED DATA INTEGRATION APPROACH

F. Vitali, L.D. Cohen, A. Amato, A. Zambelli, R. Bellazzi

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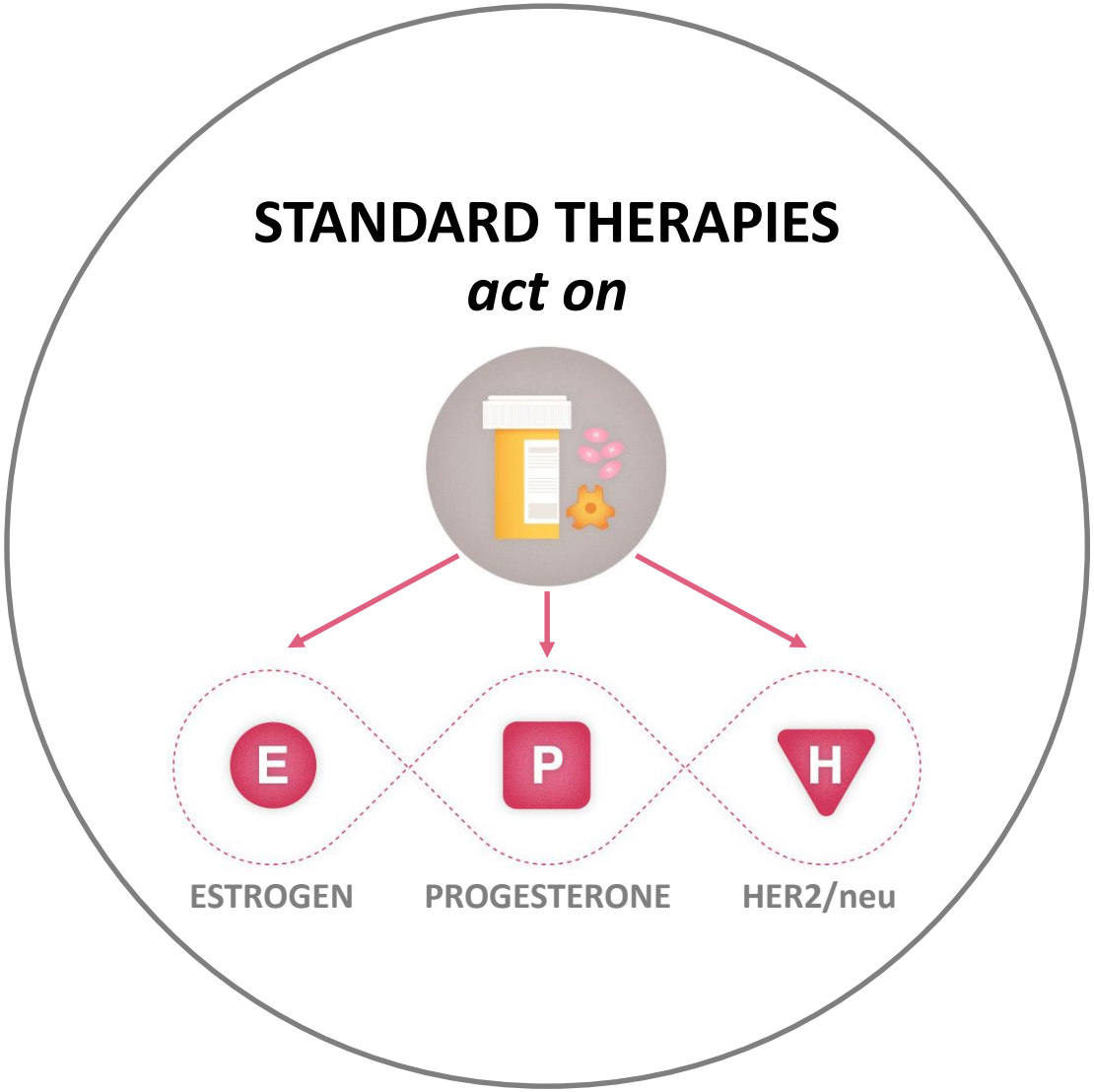
FONDAZIONE SALVATORE MAUGERI CLINICA DEL LAVORO E DELLA RIABILITAZIONE I.R.C.C.S.

Breast Cancer
THERAPIES



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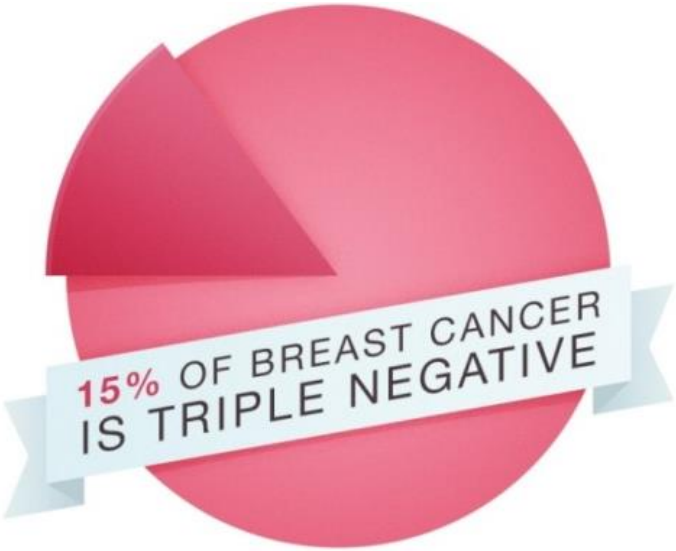
Triple Negative Breast Cancer - TNBC



Triple Negative Breast Cancer - TNBC

BREAST CANCER CELLS

TESTED NEGATIVE

for

STANDARD TREATEMENTS
(HORMONE THERAPY)

CHEMO-THERAPY

NETWORK BASED APPROACH

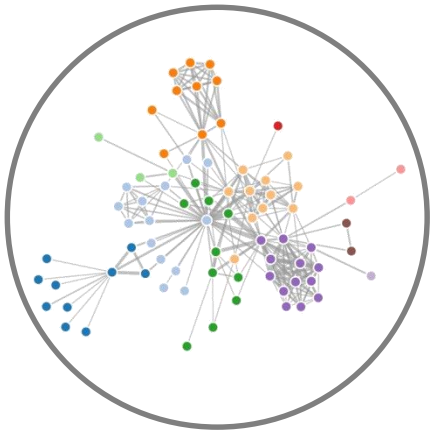
SEARCH FOR NEW THERAPIES

BY EXPLOITING THE PRIOR KNOWLEDGE

DATA SOURCES

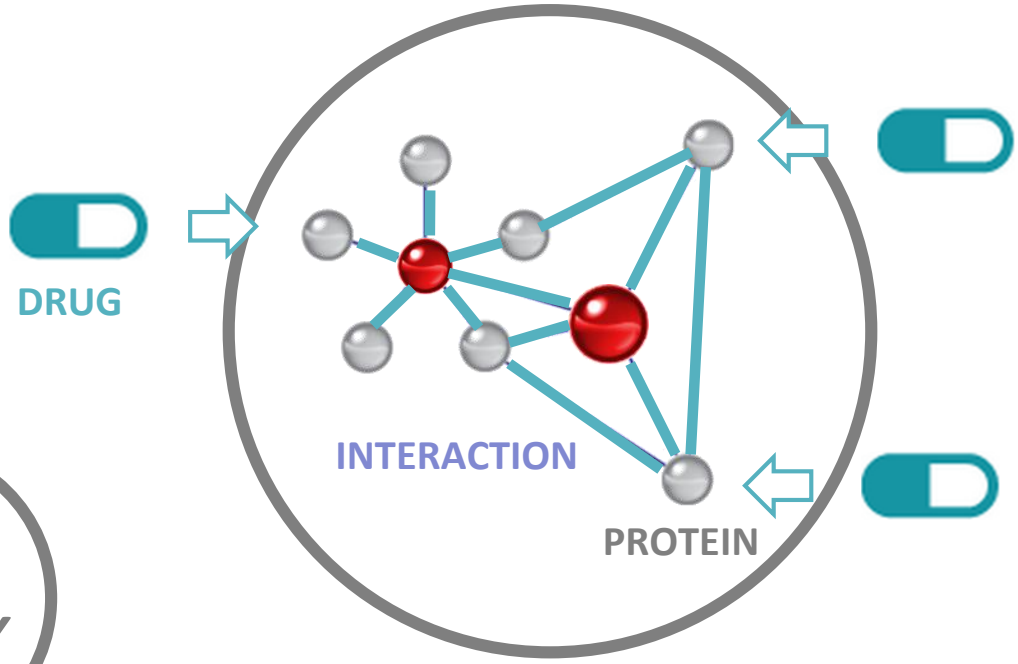
+

INTERACTION NETWORKS



SYNERGISTIC APPROACH

PROTEIN–PROTEIN INTERACTION (PPI) NETWORK



GRAPH THEORY

PIPELINE

Selection of
CANDIDATE TARGET COMBINATIONS

Analysis of
DRUGS

Simulations of
DRUG ACTIONS

Plan
IN-VITRO EXPERIMENTS

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PIPELINE

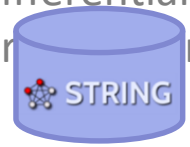
Selection of
CANDIDATE TARGET COMBINATIONS

through
TOPOLOGICAL SCORE OF DRUG SYNERGY (TSDS)

TSDS APPROACH

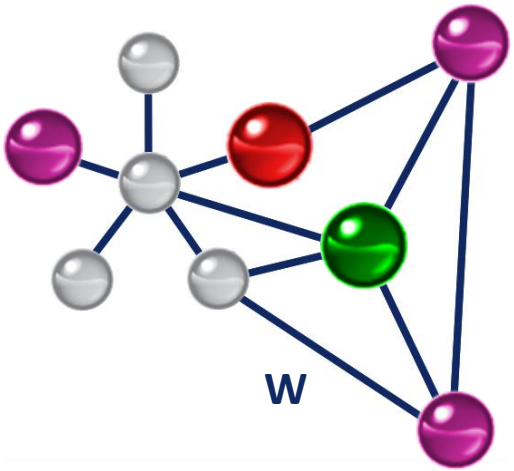
DISEASE PROTEINS

(e.g. mutated or differentially expressed genes)



PPI repository

Experimental evidence



PPI NETWORK

EDGE WEIGHT W

=

LEVEL OF CONFIDENCE

TARGET PROTEINS

CONSTRAINTS:

TOPOLOGICAL FEATURES

and

DRUGGABILITY

TSDS APPROACH

DISEASE PROTEINS

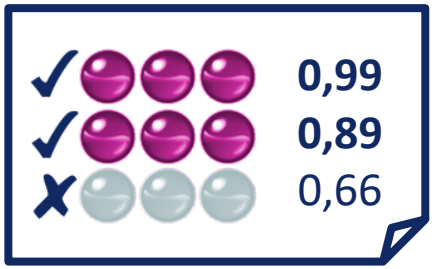
End-points
of
drug effect

TARGET PROTEINS

Sources
of
pharmacological
action

TOPOLOGICAL SCORE OF DRUG SYNERGY

MULTI-TARGET RANKING
based on
DPs RECHABILITY



PERMUTATION-BASED TEST

↓

Significant combinations

F. Vitali et al. , JBI, 2013

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PIPELINE

Selection of
CANDIDATE TARGET COMBINATIONS

Analysis of
DRUGS

Simulations of
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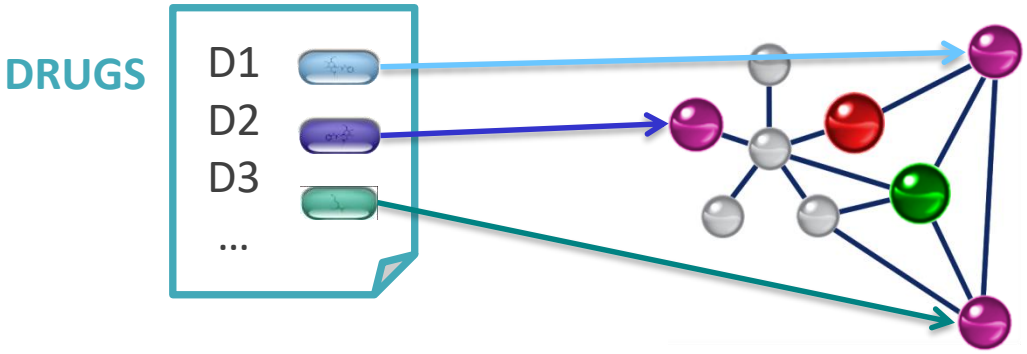
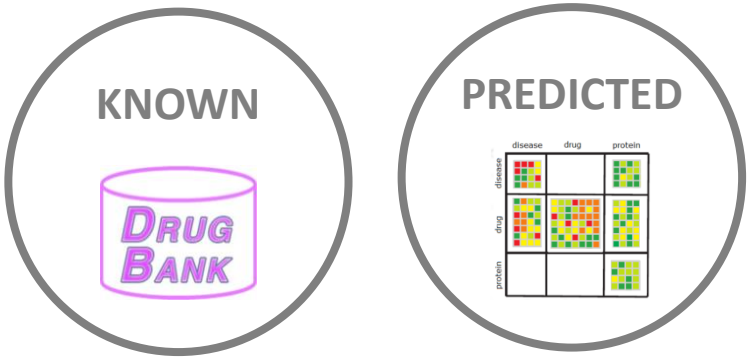
Plan
IN-VITRO EXPERIMENTS

DRUG ANALYSIS

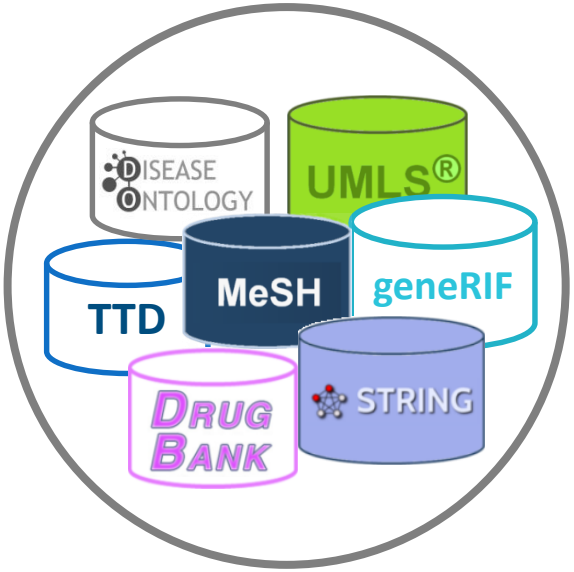


Drug-Target Interactions
DTI



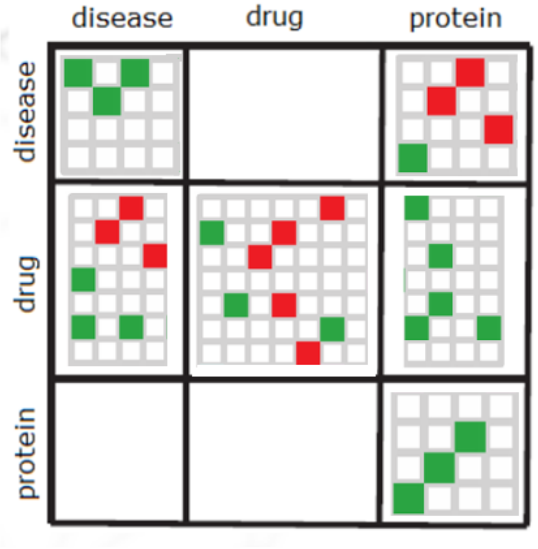
Matrix Tri-factorization

MATRIX TRI-FACTORIZATION



PRIOR KNOWLEGE

Tri-factorization



M. Zitnik et al. , IEEE Transactions on Pattern Analysis and Machine Intelligence , 2014

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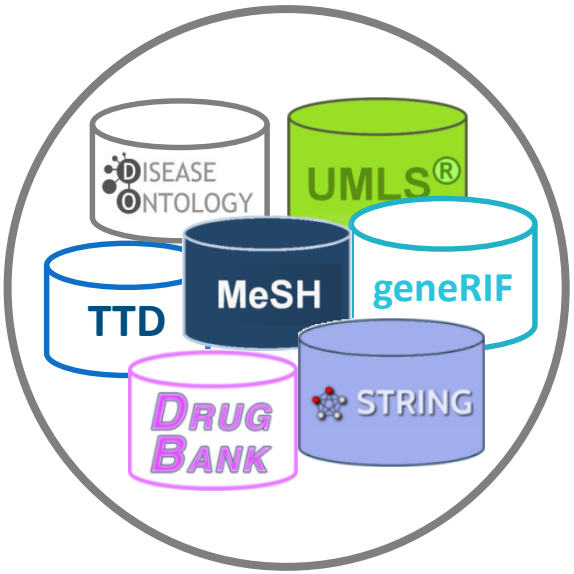
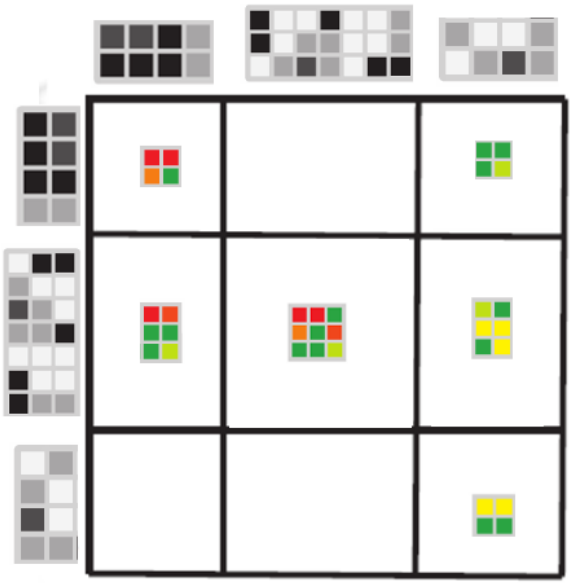
MATRIX TRI-FACTORIZATION



PRIOR KNOWLEGE

Tri-factorization



By resolving an
optimization problem

M. Zitnik et al. , IEEE Transactions on Pattern Analysis and Machine Intelligence , 2014

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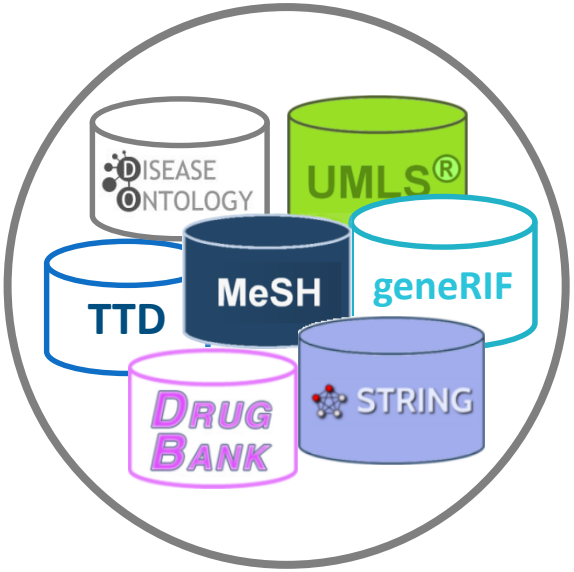
MATRIX TRI-FACTORIZATION



PRIOR KNOWLEGE

DTI Prediction

NOVEL DRUG-TARGET ASSOCIATIONS

M. Zitnik et al. , IEEE Transactions on Pattern Analysis and Machine Intelligence , 2014

PIPELINE

Selection of
CANDIDATE TARGET COMBINATIONS

Analysis of
DRUGS

Simulations of
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Plan
IN-VITRO EXPERIMENTS

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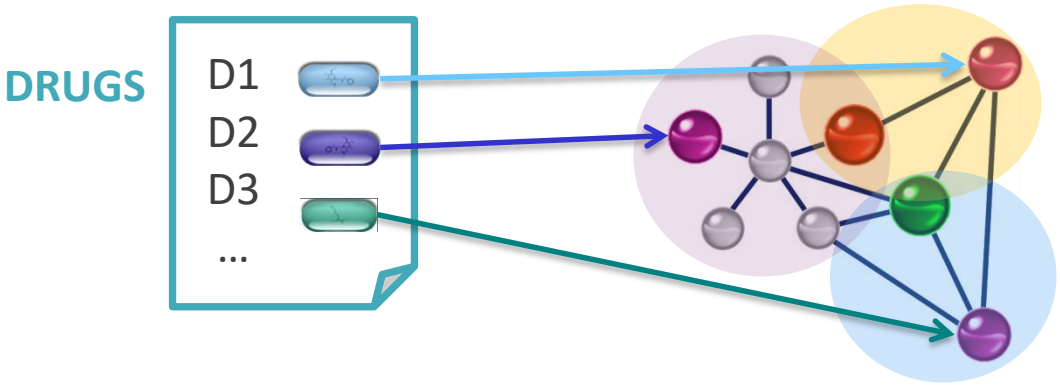
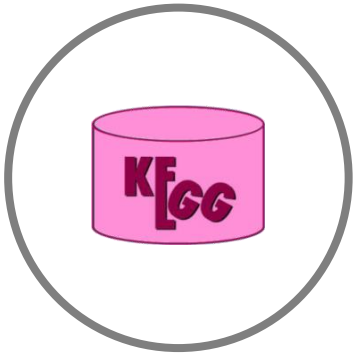
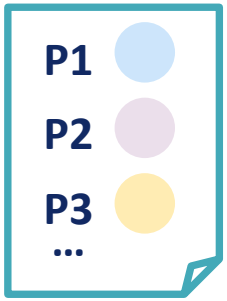
PATHWAY ANALYSIS



Pathway-Target Interactions
PTI

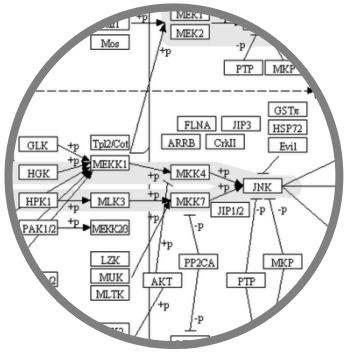


INVOLVED IN DISEASE PROGRESSION

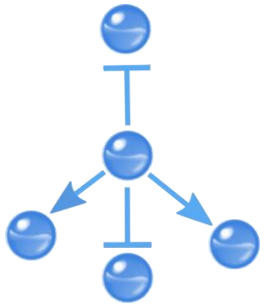


BIOLOGICAL PATHWAYS

PATHWAY MODELS



KEGG PATHWAY

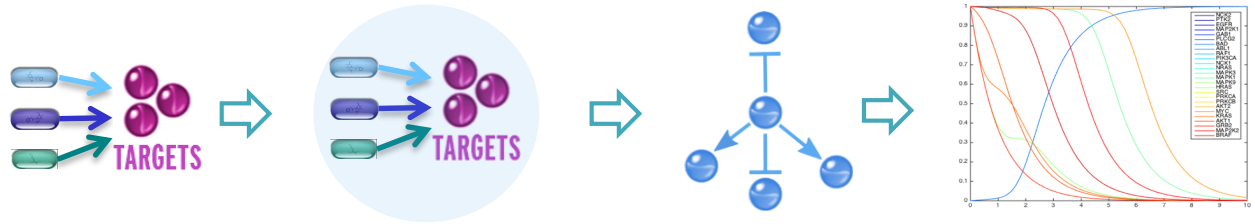


BOOLEAN NETWORK

BOOLEAN RULES

AND	ACTIVATION, EXPRESSION, METHYLATION, PHOSPHORYLATION …	→
NOT	INHIBITION, REPRESSION DEPHOSPHORYLATION, DISSOCIATION, …	⊣

PHARMACOLOGICAL ACTION MODEL



INTERESTING DRUG SELECTION

For each KEGG PATHWAY

BOOLEAN NETWORK

SIMULATONS OF DRUG EFFECTS

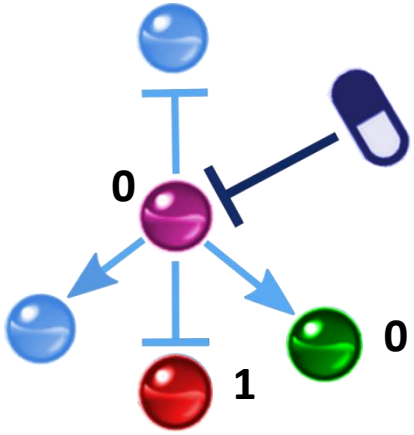
PHARMACOLOGICAL ACTION

TARGETS

	VALUE
ACTIVATION	1
INHIBITION	0

DISEASE GENES

	VALUE
UP	1
DOWN	0



BOOLEAN NETWORK

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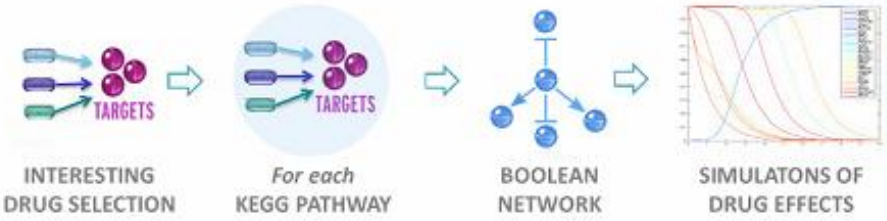
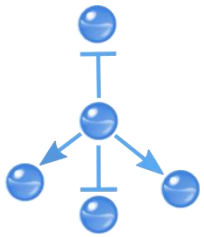
DRUG SIMULATIONS



DRUG ADMINISTRATION SIMULATIONS

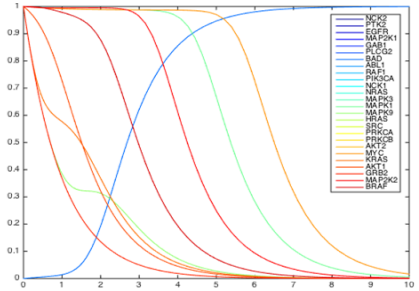
BOOLEAN MODEL

Logical expressions



CONTINUOUS MODEL

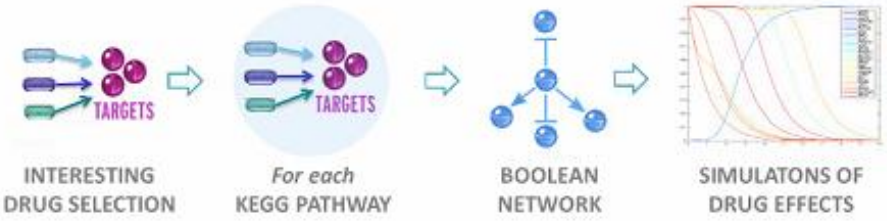
System of ODEs



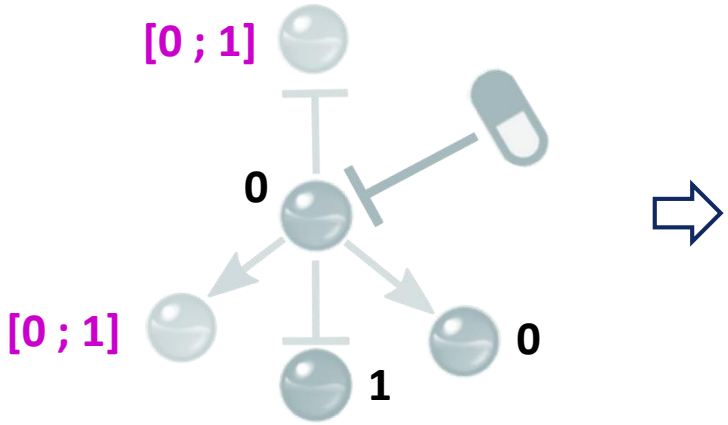
NODE BEHAVIORS

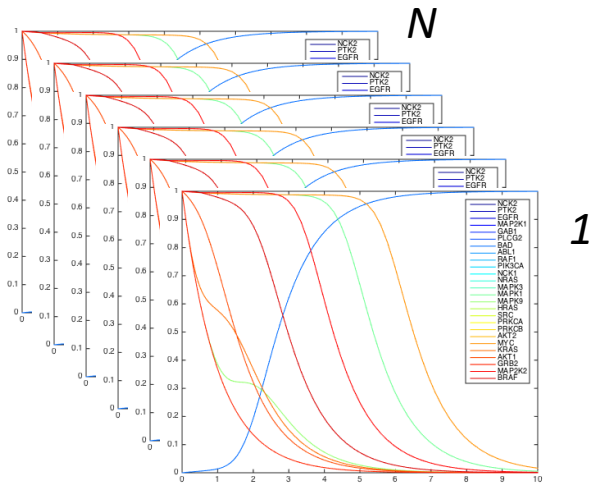
Krumsiek J. et al.., BMC bioinformatics, 2010

DRUG SIMULATIONS



MONTECARLO SIMULATIONS





N simulations
with different initializations

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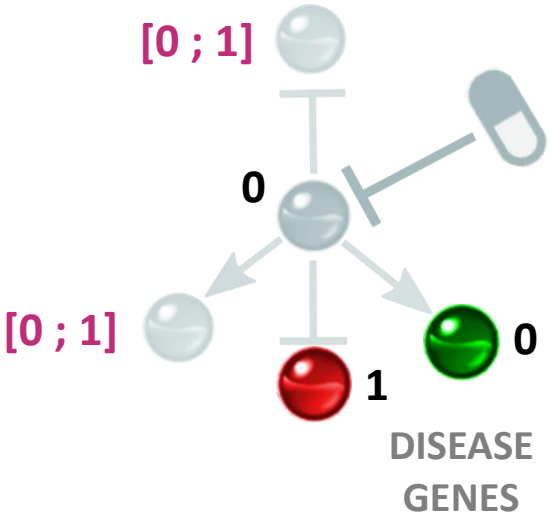
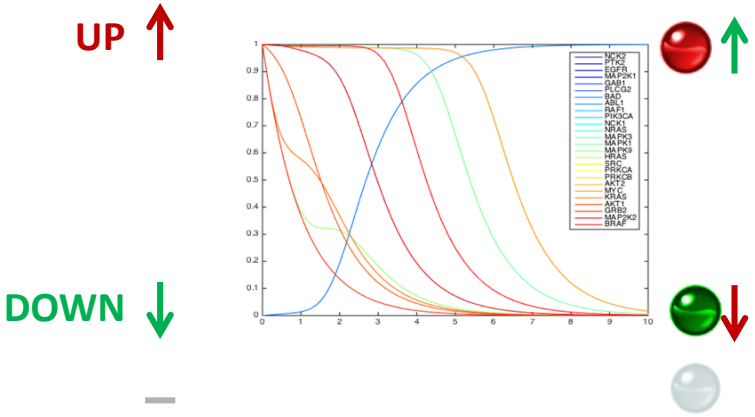
RESULT ANALYSIS





DRUG/DRUG COMBINATION

has to

REGULARIZE as much as possible **Disease Genes**

while

other nodes must **NOT be PERTURBED**

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RESULT ANALYSIS

CONFUSION MATRIX

	$Disease\ Genes$	$\overline{Disease\ Genes}$	
$Regularized\ Genes$	**TP**	**FP**	$Tot\ RG$
$\overline{Regularized\ Genes}$	**FN**	**FN**	$Tot\ \overline{RG}$
	$Tot\ DG$	$Tot\ \overline{DG}$	N

$$Sensitivity = \frac{TP}{Tot\ DG}$$

$$Precision = \frac{TP}{Tot\ PG}$$

AIM: Maximization of regularized disease genes (TP)

Index of **THERAPEUTIC EFFICACY**

$$F\ measure = 2 * \frac{Sensitivity * Precision}{Sensitivity + Precision}$$

PIPELINE

Selection of
CANDIDATE TARGET COMBINATIONS

Analysis of
DRUGS

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DRUG ACTIONS

Plan
IN-VITRO EXPERIMENTS

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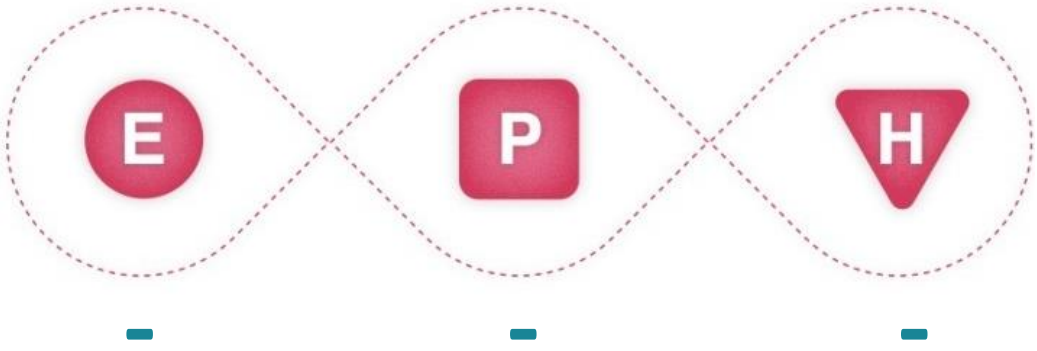
RESULTS - TNBC

BREAST CANCER CELLS

TESTED NEGATIVE

for



RESULTS - TSDS APPROACH

Shah et al., 2012

LETTER

The clonal and mutational evolution spectrum of primary triple-negative breast cancers

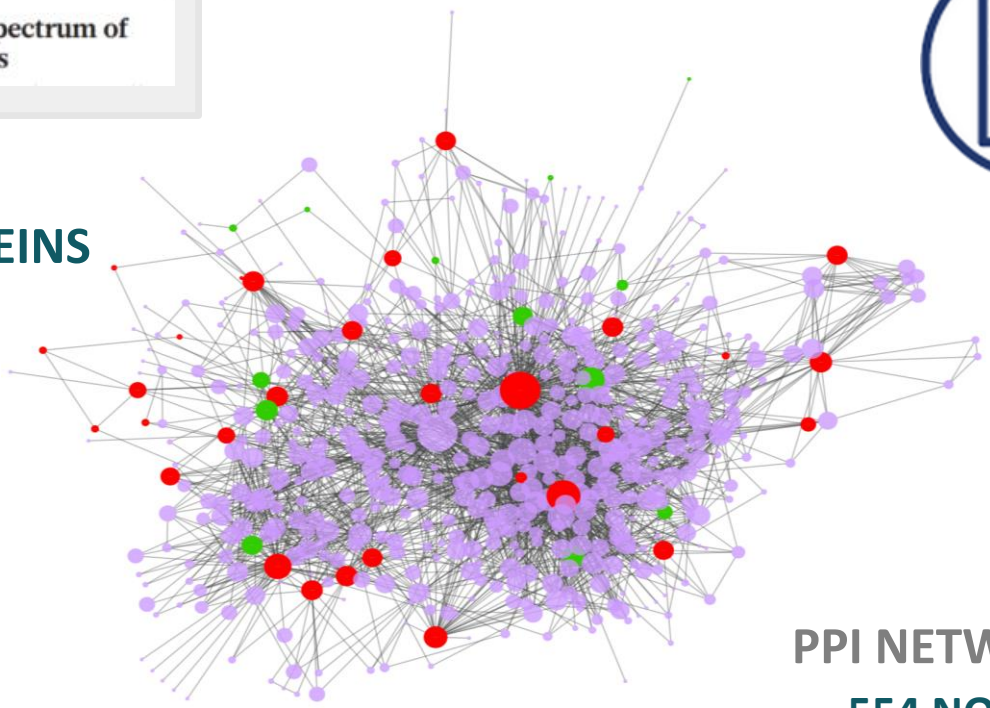
32 TARGET PROTEINS

43 DISEASE PROTEINS

involved in the genetic changes

STRING

PPI repository

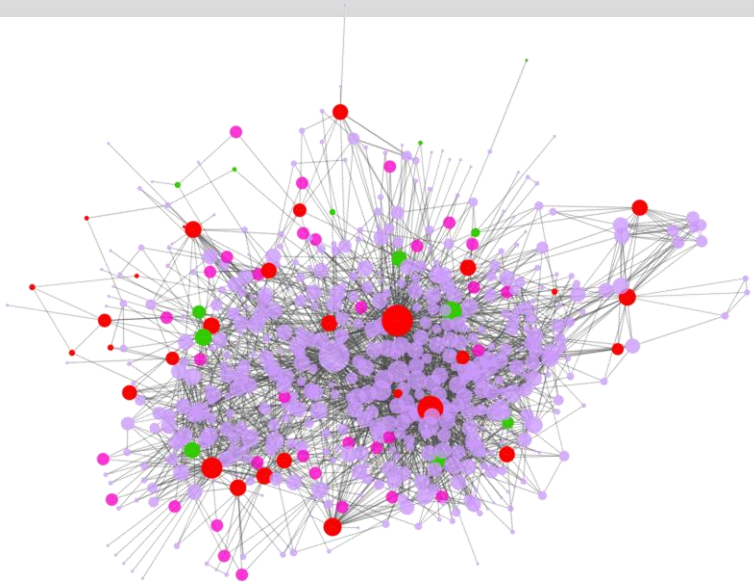


PPI NETWORK

554 NODES

2602 EDGES

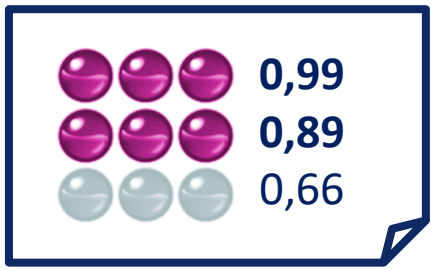
RESULTS - TSDS APPROACH



32 TARGET PROTEINS

TOPOLOGICAL SCORE OF DRUG SYNERGY

MULTI-TARGET RANKING



134 combinations of
16 different proteins

↓

None are currently used in ongoing clinical trials

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RESULTS - DRUG AND PATHWAY ANALYSIS

IMATINIB PATHWAY ANALYSIS

KEGG

MAPK signaling pathway
Jak-STAT signaling
Toll-like receptor signaling
ErbB signaling
Phosphatidylinositol signaling
...

20 BIOLOGICAL PATHWAYS
related to
Targets and TNBC

↓

BOOLEAN MODELS

RESULTS - DRUG AND PATHWAY ANALYSIS

IMATINIB PATHWAY ANALYSIS

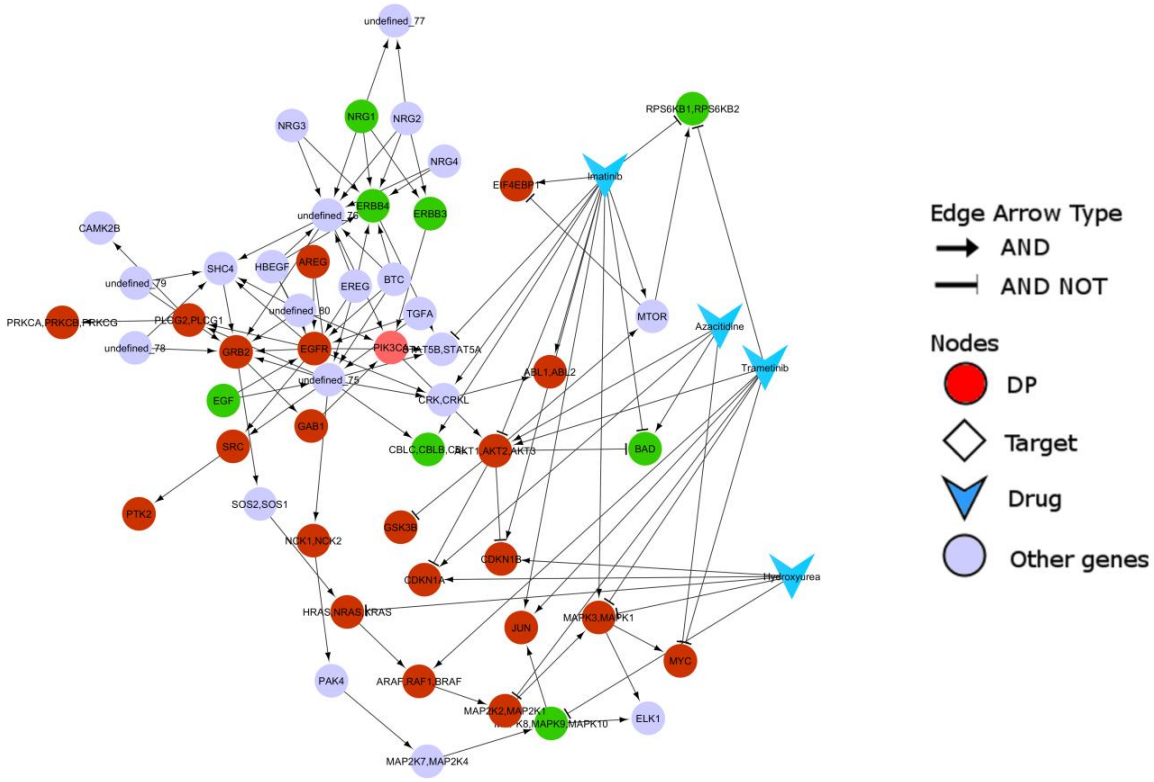
ELECTIVE DRUG FOR

- Chronic myeloid leukemia
- Gastro-intestinal stromal tumors

REPOSITIONING?

RESULTS - PATHWAY ANALYSIS

MAPK signaling pathway – BOOLEN NETWORK



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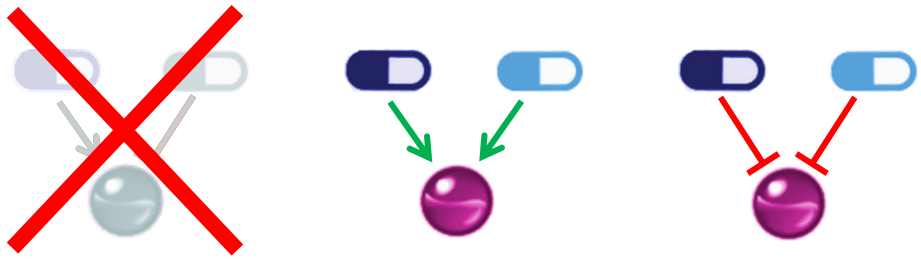
RESULTS - PATHWAY ANALYSIS

POLYPHARMACOLOGY = multiple drugs acting on different targets



NO OPPOSITE DRUG-TARGET INTERACTIONS

DRUG ADMINISTRATION SIMULATIONS

1. Imatinib
2. Imatinib + Vemurafenib
3. Imatinib + Flucytosine
4. Imatinib + Vemurafenib + Flucytosine

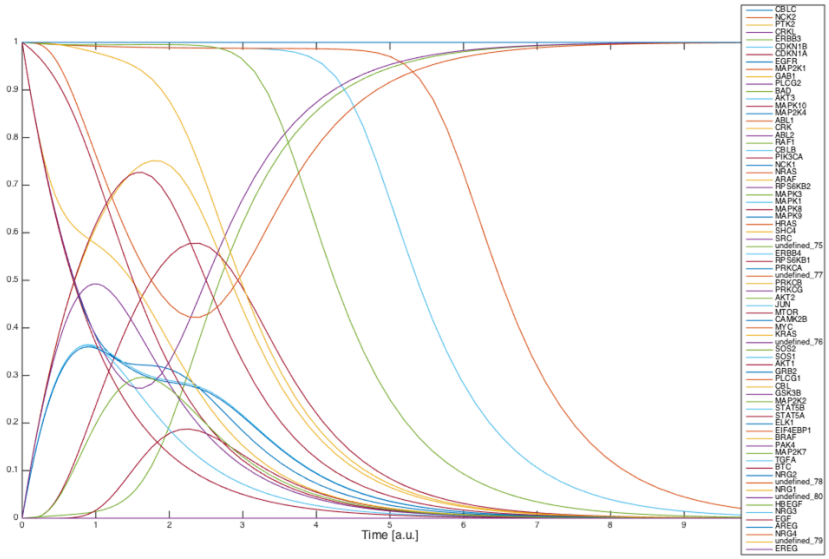
RESULTS – MONTECARLO SIMULATIONS

for each **DRUG:**

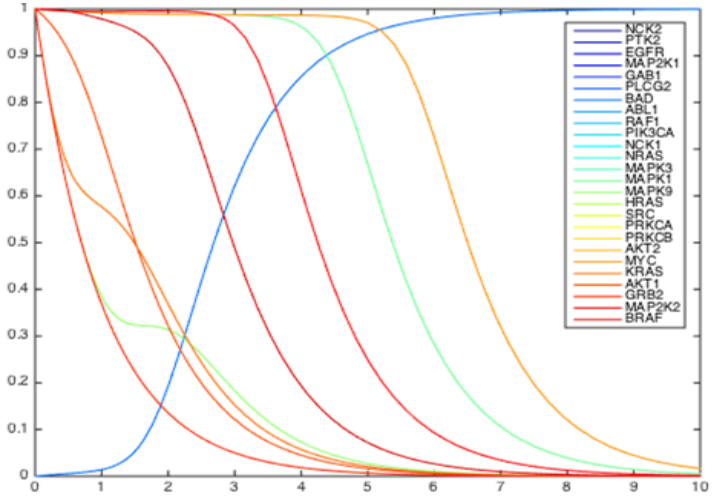
for each **PATHWAY:**

MONTECARLO SIMULATIONS by applying Odefy

Example: Imatinib – MAPK pathway



ALL NODE BEHAVIOURS



DISEASE NODE BEHAVIOURS

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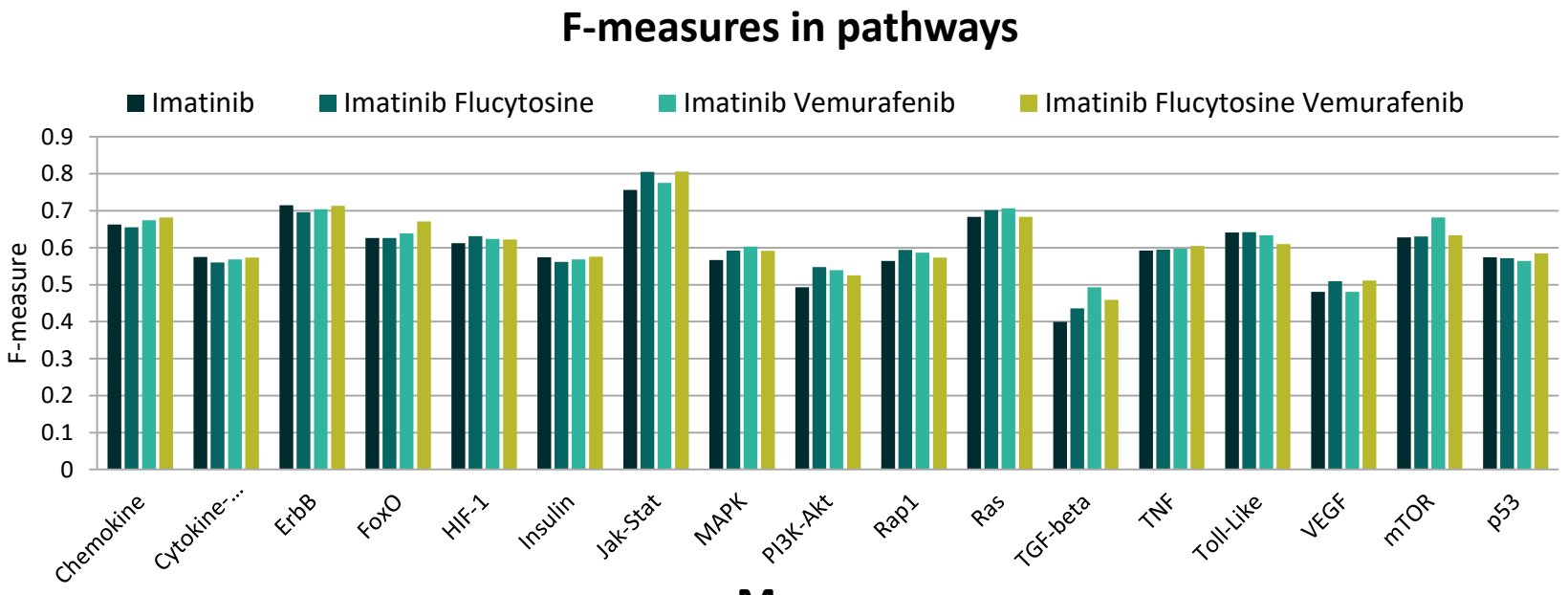
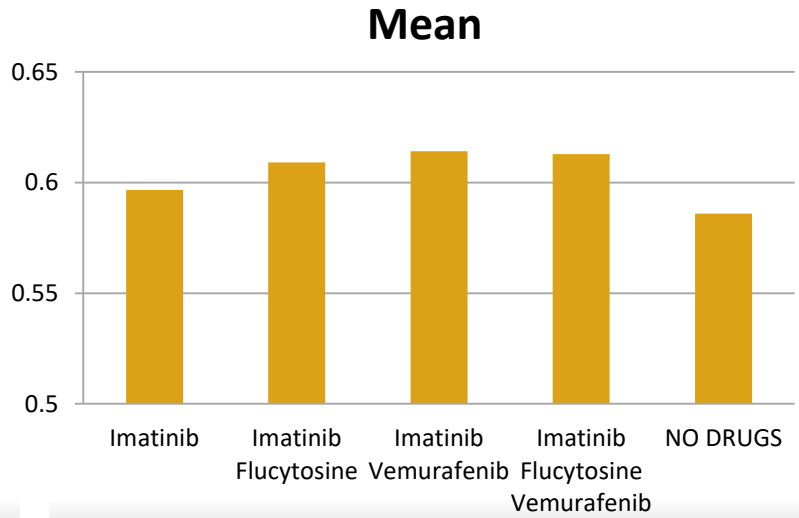
RESULTS – MONTECARLO SIMULATIONS

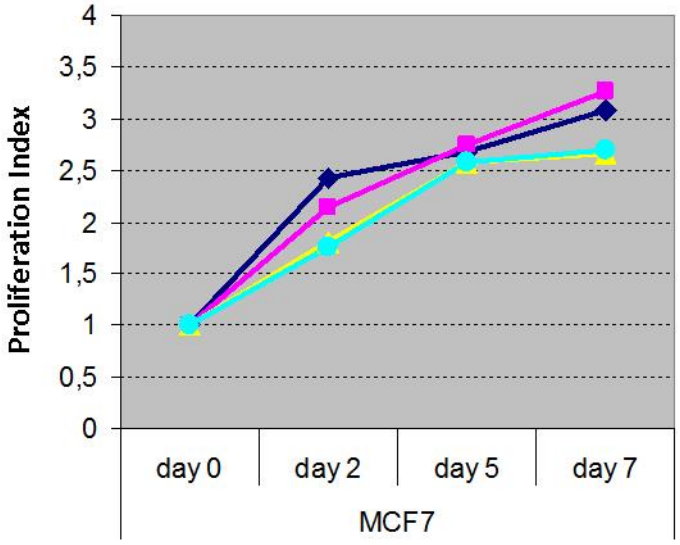




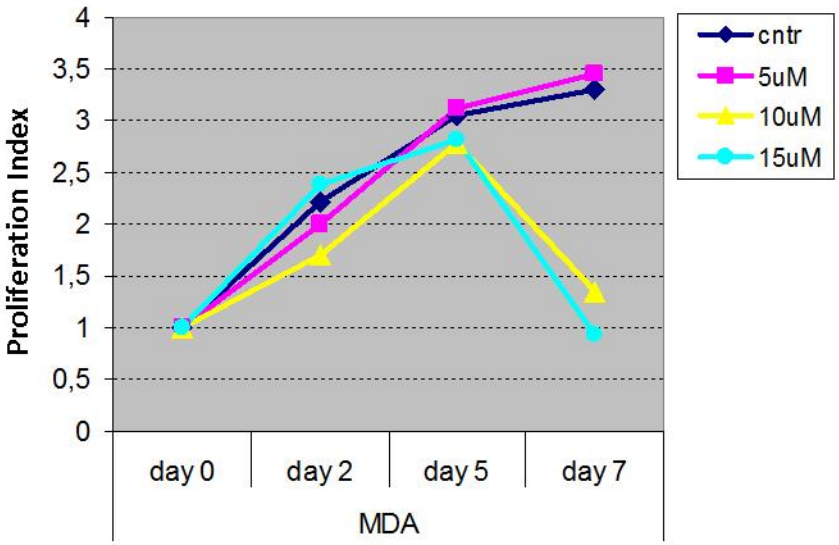
IN VITRO RESULTS

MTT assay – Evaluation of cell viability

2-5-7 days of treatment with different concentration of Imatinib



Luminal subtype



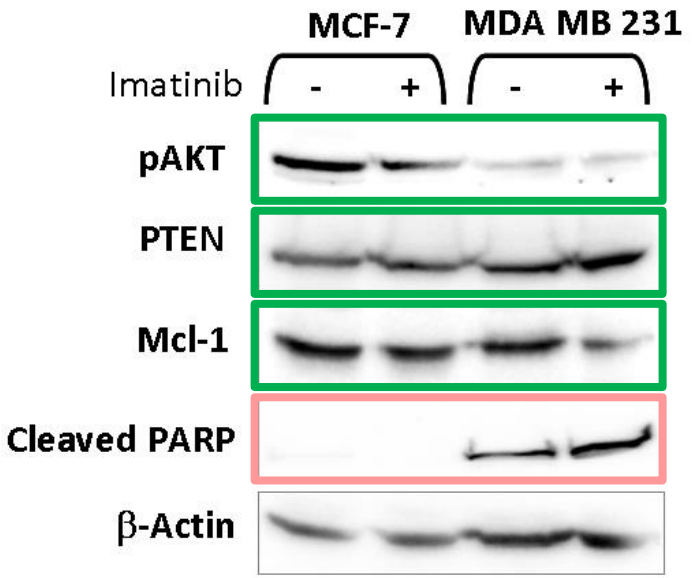
TNBC subtype

BMS bioinformatics mathematical modeling and synthetic biology

IN VITRO RESULTS

Western Blot assay – Disease gene evaluation

One week treatment with 10µ Imatinib



Luminal vs TNBC

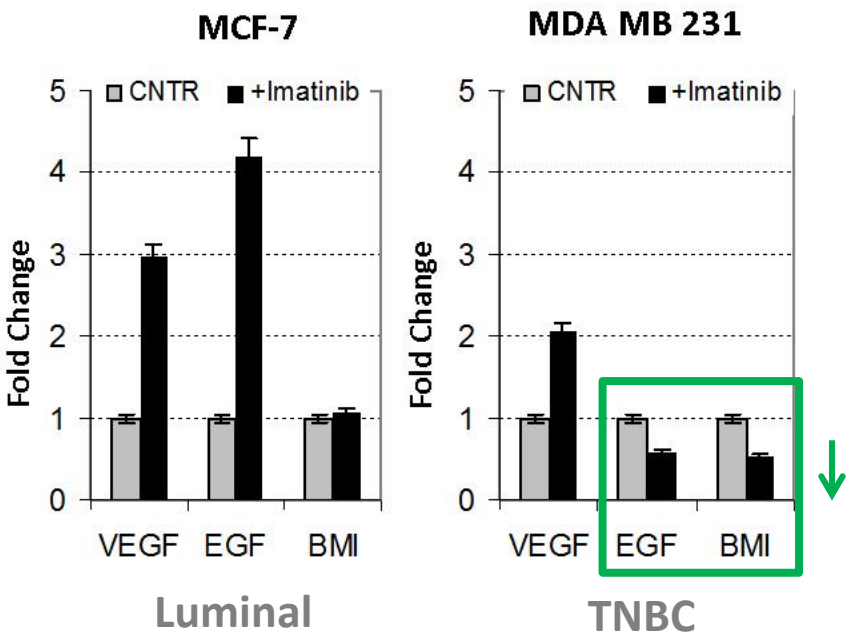
Survival Decrease

DNA Damage

IN VITRO RESULTS

Gene expression assay – Disease gene evaluation

One week treatment with 10µ Imatinib



Genes involved in TNBC PROGRESSION

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IN-VITRO EXPERIMENTS ON GOING of drug combinations

CONCLUSIONS

- The application to breast cancer
  - highlights **potential targets and drugs**
  - enables the selection of top candidate pathways and potential **drug combinations** in a variety of multifactorial diseases

- The developed approach can easily be applied to other complex diseases
  - Network construction based on a list of mutated proteins in patient's specific proteomic or genomic background – precision medicine

ON GOING

- Combinations of different drugs

- Future works:
  - Bayesian networks instead of Boolean graphs