DEVELOPMENT AND VALIDATION OF A GENERAL APPROACH TO PREDICT AND QUANTIFY THE SYNERGISM OF ANTI-CANCER DRUGS USING EXPERIMENTAL DESIGN AND ARTIFICIAL NEURAL NETWORKS

Pivetta, Tiziana, et al. *Talanta* 115 (2013): 84-93.

Presenter : Soodabeh Zakeri, Vala Khosravi.

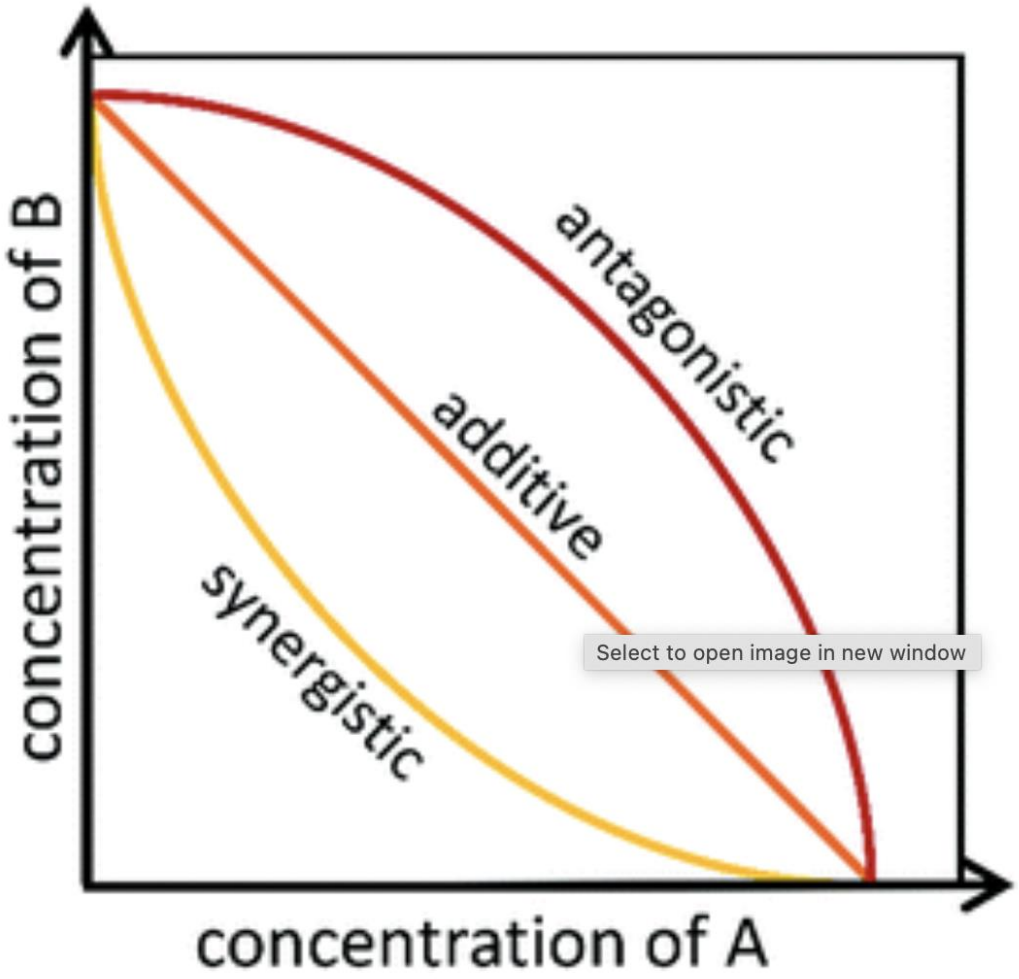
OUTLINE

- Combination therapy meaning
- Background
- Main idea of the paper
- Theoretical aspects of the proposed approach
- Experimental design and neural network
- Validation
- Conclution

BENEFITS OF COMBINATION THERAPY

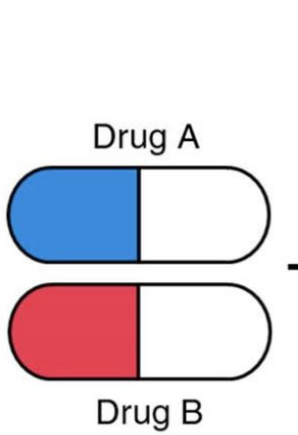
- reduce the development of drug resistance.
- monotherapy usually cannot break down the entire disease pathways and networks
- decrease the dosage
- reduce toxicity

SYNERGISTIC, ADDITIVE AND ANTAGONISTIC



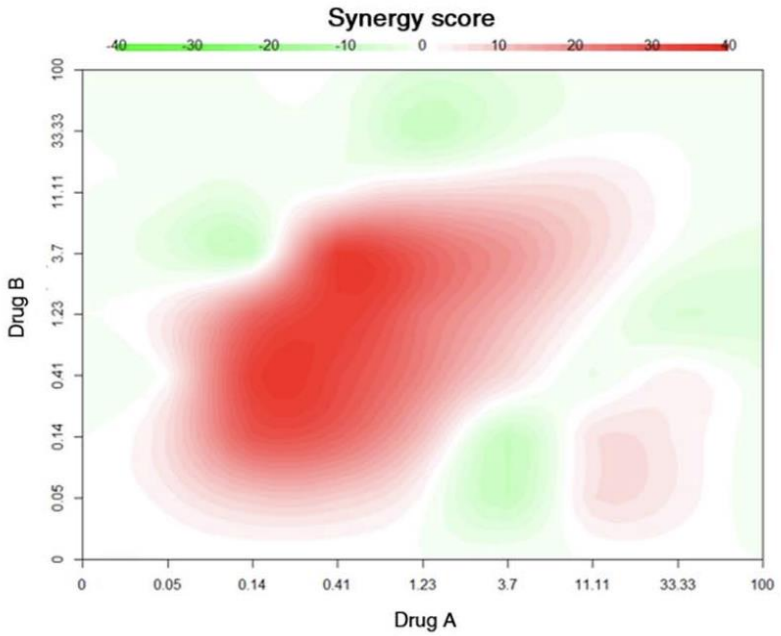
CLASSIFICATION AND REGRESSION TASK IN DRUG COMBINATION PREDICTION

$E_{A,B} < E_A + E_B$
$E_{A,B} = E_A + E_B$
$E_{A,B} > E_A + E_B$



Classification task

Regression task



Loewe
Bliss
HSA
ZIP
…

LOEWE ADDITIVITY MODEL

$$\frac{d_1}{D_1\,(\text{when } E_1 = E_{\text{Loewe}})} + \frac{d_2}{D_2\,(\text{when } E_2 = E_{\text{Loewe}})} = 1$$

$$S_{\text{Loewe}} = \text{CI} = \frac{d_1}{D_1} + \frac{d_2}{D_2}$$

BACKGROUND

Study	Published Year	Algorithms	Category Of Methods	Input
Julkunen et al. Leveraging multiway interactions for systematic prediction of pre-clinical drug combination effects.	2020	Combo FM	Classic ML methods	Fingerprints, cell lines' gene expression, drugs' concentrations
Gayvert et al. A computational approach for identifying synergistic drug combinations .	2017	Random Forest	Classic ML methods	Single drug dose response
Ianevski et al. Prediction of drug combination effects with a minimal set of experiments.	2019	DECREASE	Classic ML methods	Dose–response matrix
Jiang et al. Deep graph embedding for prioritizing synergistic anticancer drug combinations	2020	GCN	Deep learning methods	PPIs, DTIs

IMPORTANT PHRASES

- **Cytotoxicity :** Cytotoxicity is the degree to which a substance can cause damage to a cell.

❖In this presentation, the number of dead cells for the drug i is indicated by a_i

- **enzymatic inhibition :** Certain enzyme inhibitors **may slow tumor formation within weeks** and could lead to treatments that retard or prevent recurrences of cancers
- **CC50 :** the dose of the drug which inhibits 50% of cell proliferation

DRUG COMBINATION DATA SET

Experiments!

CI HAS LIMITED !!!

- CI is based on the assumption that the action of the drugs is due only to the inhibition of enzyme kinetics
- addition to enzymatic inhibition, drug-receptor and non-specific interactions are also involved.
- Cisplatin (CDDP) is an example of drug that does not act directly on enzyme kinetics.

THEORETICAL ASPECTS OF THE PROPOSED APPROACH

NON-ALGEBRAIC ADDITIVE EFFECT

$$NAAE = \sum_{i=1}^{n} a_i + \sum_{k=2}^{n} \left[(-1)^{k-1} \cdot \frac{C_{n,k}\{a_1, a_2, \ldots, a_n\}}{100^{k-1}} \right]$$

$$NAAE = \sum_{i=1}^{n} a_i - \frac{1}{100}\left[\sum_{i \neq j} a_i a_j\right] + \frac{1}{100^2}\left[\sum_{i \neq j \neq l} a_i a_j a_l\right] - \ldots$$
$$+(-1)^{k-1} \cdot \frac{1}{100^{n-1}}\left[\prod a_i\right]$$

For 2 drugs : $$NAAE = a_1 + a_2 - \frac{a_1 a_2}{100}$$

For 3 drugs : $$NAAE = a_1 + a_2 + a_3 - \frac{a_1 a_2 + a_1 a_3 + a_2 a_3}{100} + \frac{a_1 a_2 a_3}{100^2}$$

NET MULTI-DRUG EFFECT INDEX

$$NMDEI = E_{exp.} - NAAE$$

EXPERIMENTAL DESIGN INPUT

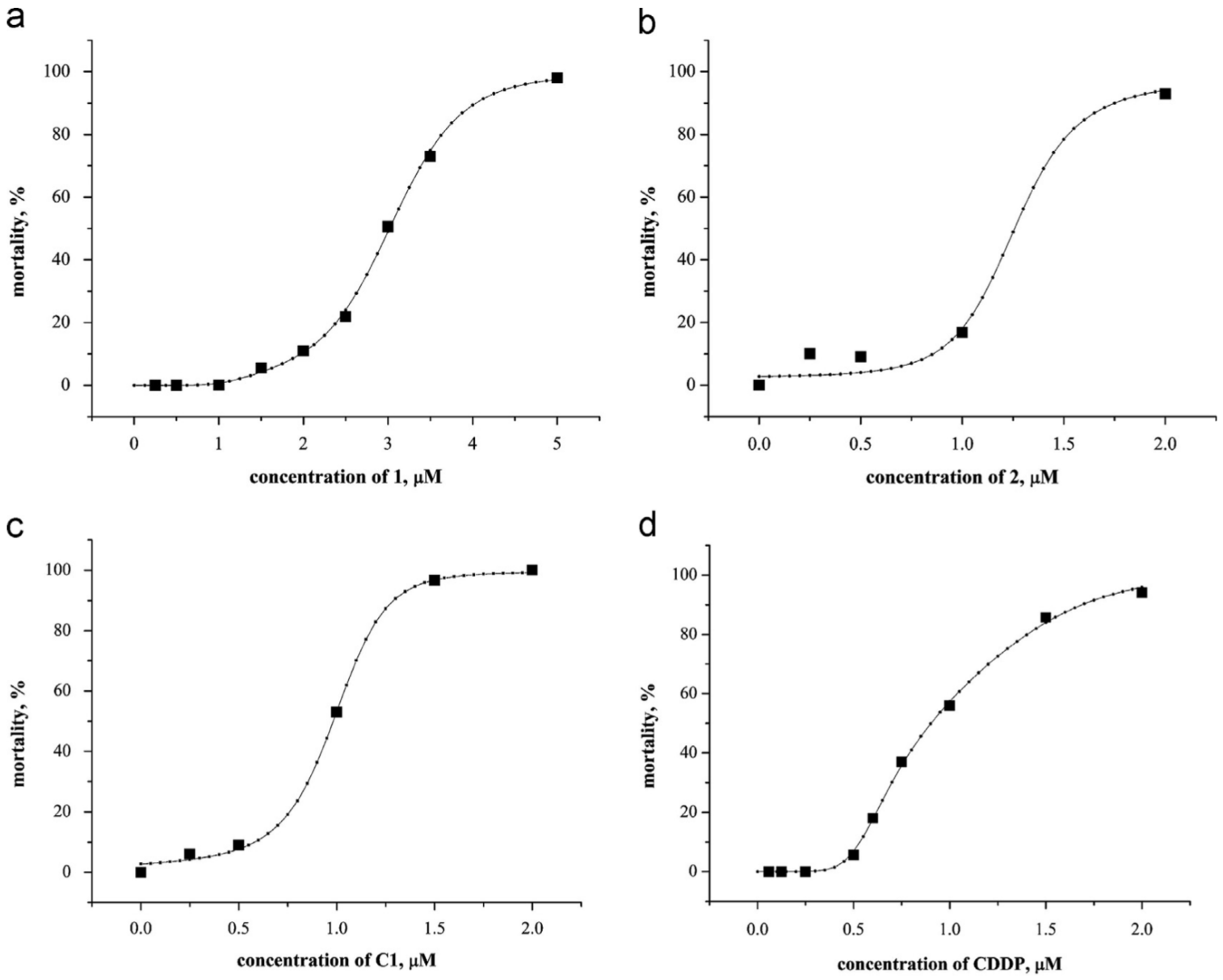
- **DRUGS**
  - **CDDP :** Cisplatin is a chemotherapy medication used to treat a number of cancers
  - **(1)** Cu(1,10-orthophenanthroline) (H2O)2(ClO4)2,
  - **(2)** [Cu(1,10-orthophenanthroline)2(H2O)](ClO4)2
  - **(C1)** [Cu(1,10-orthophenanthroline)2(imidazolidine-2-thione)] (ClO4)2

- **CELL LINES**
- The CCRF-CEM (acute T-lymphoblastic leukemia) human cell line was purchased from the American Type Culture Collection (ATCC-LGC; Milan, Italy).

SET UP OF THE EXPERIMENTAL DESIGN

	# of combination	# of CDDP solutions	#of other drug solution alone	training set	validating set	test set
60 solution 1 and CDDP	42	9	9	25	24	11
44 solution 2 and CDDP	34	6	4	18	16	10
46 solution C1 and CDDP	34	7	5	21	19	6

TRAINING AND VERIFICATION OF THE ARTIFICIAL NEURAL NETWORK



CALCULATED
(--) AND EXPERIMENTAL
(■) DOSE–RESPONSE DATA

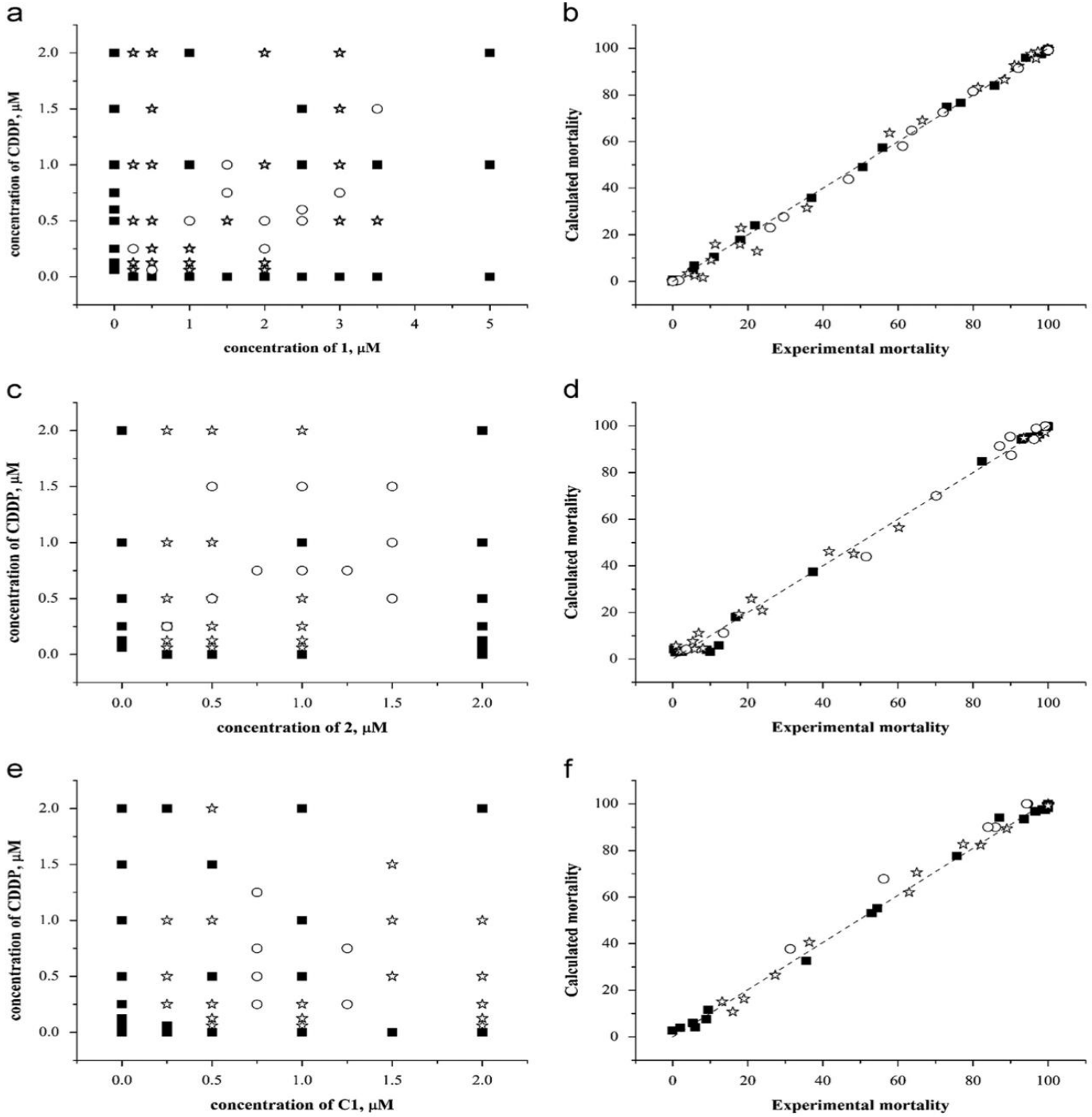
ROOT MEAN SQUARE ERROR

$$RMSE = \sqrt{\frac{\sum_{p=1}^{N}\sum_{k=1}^{M}(o_{pk} - o^{*}_{pk})^2}{N \times M}}$$

N the number of experiments used for training,
M the number of response variables,
, $\mathbf{o_{pk}}$, and $\mathbf{o^{*}_{pk}}$ are, the estimated and the actual output value

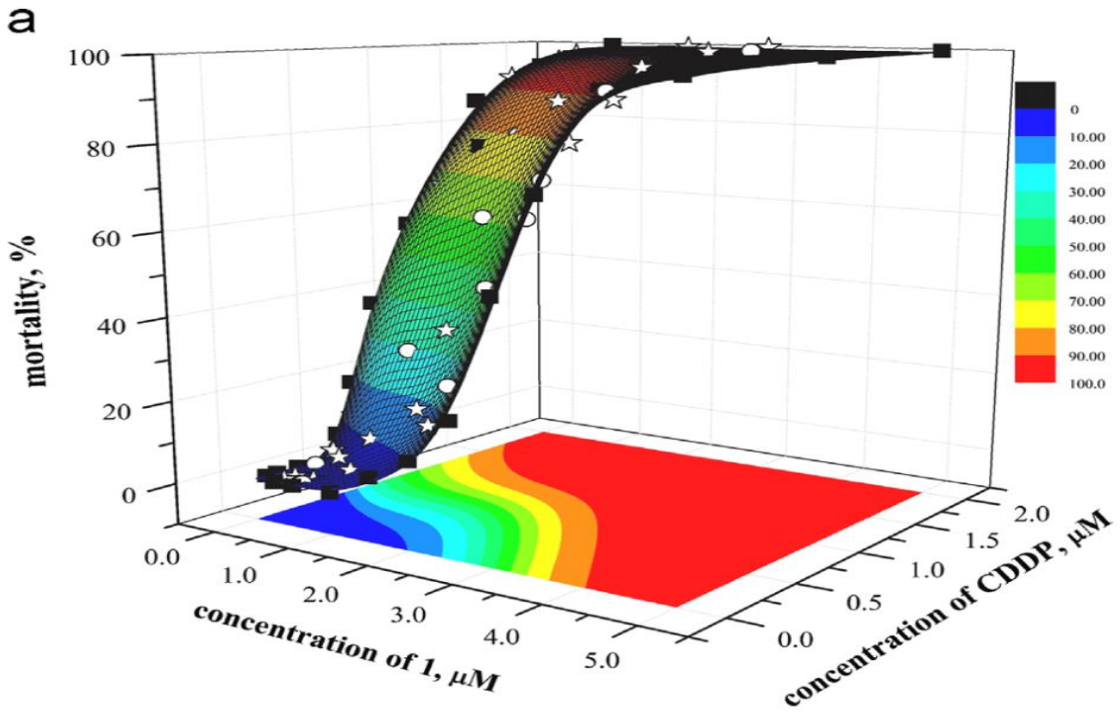
EXPERIMENTAL DESIGN

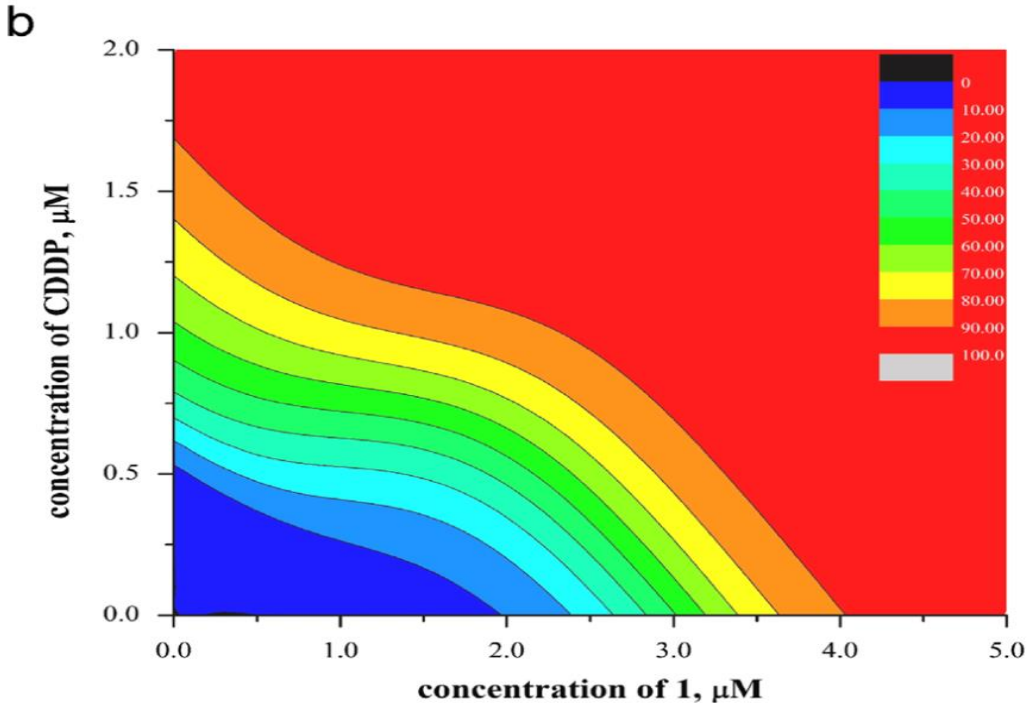
■ TRAINING SET,
☆ VALIDATION SET
○ TEST SET



RESPONSE SURFACE WITH EXPERIMENTAL DATA

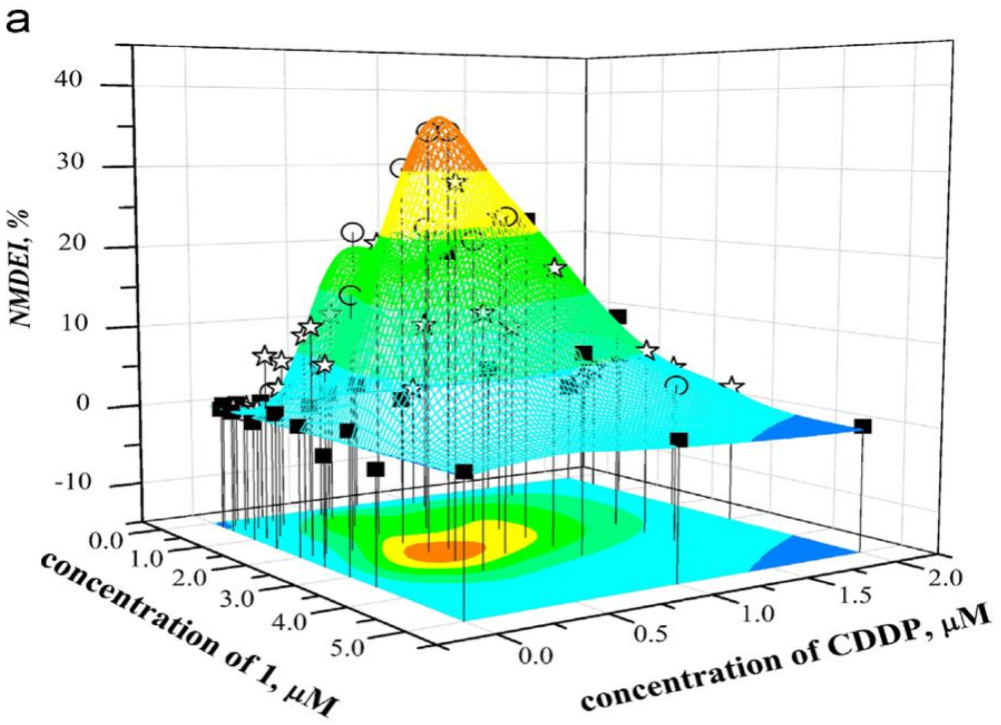
■ TRAINING SET,
☆ VALIDATION SET
○ TEST SET

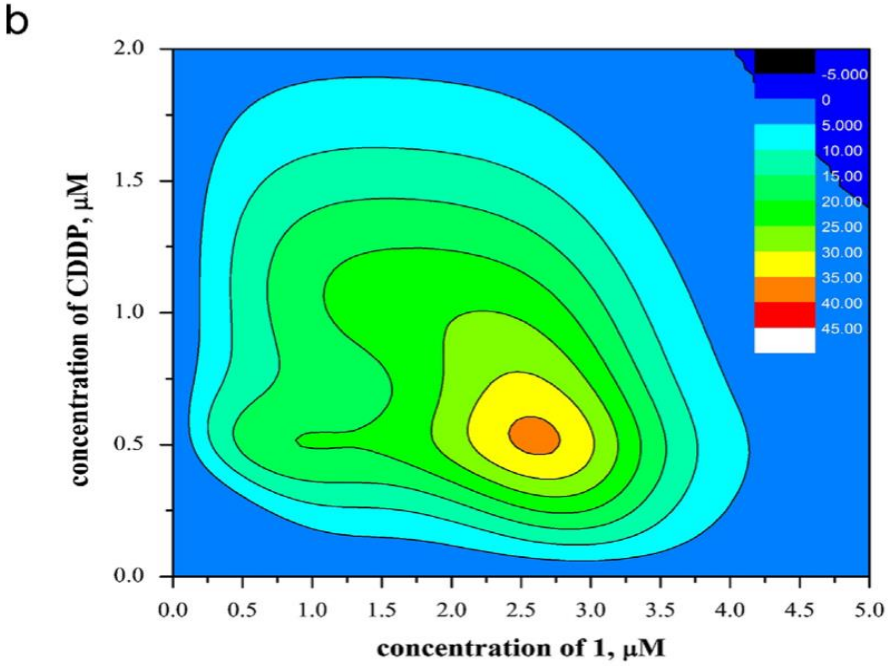




NMDEI SURFACE WITH EXPERIMENTAL DATA

■ TRAINING SET,
☆ VALIDATION SET
○ TEST SET





COMPARISON WITH IB AND CI METHODS

System	Solution	Conc. of drug$_1$ (μM)	Conc. of CDDP (μM)	Experimental cytotoxicity (%)	*NMDEI (%)*[a]	*CIC.I.*[b]
CDDP	***a***		1.0	50		
1-CDDP	***b***	3.00	–	50	–	–
	c	1.88	0.60	50	25	1.28
	d	1.88	–	9	–	–
	e	–	0.60	18	–	–
	f	2.63	0.55	74	36	1.23
	g	2.63		29	–	–
	h		0.55	12	–	–
2-CDDP	***i***	1.25		50	–	–
	j	0.75	0.80	50	29	1.50
	k	0.75		7	–	–
	l	1.05	0.85	82	44	0.98
	m	1.05		20	–	–
	n		0.85	19	–	–
C1-CDDP	***o***	0.98	–	50	–	–
	p	0.50	0.45	50	16	1.40
	q	–	0.45	28	–	–
	r	0.50	–	8	–	–
	s	0.87	0.45	83	33	0.88
	t	0.87		32	–	–
	u		0.45	28	–	–
PAC-CDDP[c]	***aa***	0.01	–	88	–	–
	ab		1.0	82	–	–
	ac	0.01	1.0	97	−1	0.602
	ad	0.002	–	43	–	–
	ae	–	0.2	30	–	–
	af	0.002	0.2	70	10	0.815

CONCLUSIONS

- The predicted combinations that presented the highest synergistic effect were actually prepared and experimentally tested. In all cases, the data predicted by the network were experimentally confirmed.

THANK YOU FOR YOUR ATTENTION