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# A general pharmacodynamic interaction (GPDI) model

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# Combination therapy – Drug interactions?

Combination therapy is prevalent in many therapeutic areas

- Anti-infectives
- Chemotherapy
- Antiepileptics
- Anaesthesia

What are our current modelling options and their limitations for characterization of pharmacodynamic (PD) drug interactions (DDI)?

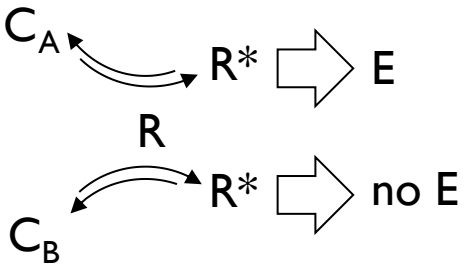
# PD DDI modelling current options

**Mechanistic approaches**

- Receptor theory
  - Competitive interaction models
  - Noncompetitive/uncompetitive models
- Systems biology/pharmacology

**Additivity-based empirical models**

- Loewe Additivity
  - Greco model, …
  - Combination indices
- Bliss Independence
  - Empiric Bliss model(s)




1+1=3?

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# Challenges with current modelling options

**Mechanistic approaches**

- Lack of knowledge to parameterize mechanistic interaction models

**Additivity-based empirical models**

# Greco model

Loewe Additivity

$$1 = \frac{C_A}{EC50_A \times \left(\frac{E}{Emax - E}\right)^{1/H_A}} + \frac{C_B}{EC50_B \times \left(\frac{E}{Emax - E}\right)^{1/H_B}} + \frac{\alpha \times C_A \times C_B}{EC50_A \times EC50_B \times \left(\frac{E}{Emax - E}\right)^{\left(\frac{1}{2H_A} + \frac{1}{2H_B}\right)}}$$

Interaction term

*alpha* = 0 → Loewe Additivity
*alpha* > 0 → Synergy
*alpha* < 0 → Antagonism

W.R. Greco et al. *Cancer Res.*, 50: 5318–27 (1990).

# Challenges with current modelling options

**Mechanistic approaches**

- Lack of knowledge to parameterize mechanistic interaction models

**Additivity-based empirical models**

- Interaction parameters are not quantitatively interpretable
- Single underlying additivity concept
- Mono-dimensional ('symmetric') interactions
- Limitation to two drugs

Greco model

$$1 = \frac{C_A}{EC50_A \times \left(\frac{E}{Emax - E}\right)^{1/H_A}} + \frac{C_B}{EC50_B \times \left(\frac{E}{Emax - E}\right)^{1/H_B}} + \frac{\alpha \times C_A \times C_B}{EC50_A \times EC50_B \times \left(\frac{E}{Emax - E}\right)^{\left(\frac{1}{2H_A} + \frac{1}{2H_B}\right)}}$$

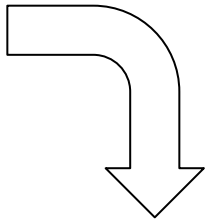
W.R. Greco et al. *Cancer Res.*, 50: 5318–27 (1990).

# Towards a general PD interaction model

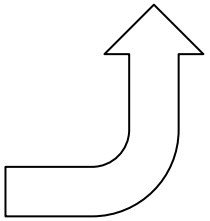
- **Receptor-based mechanistic approaches**
  - Competitive interaction models
  - Noncompetitive/uncompetitive models

- **Additivity-based empirical models**
  - Loewe Additivity
    - Greco model
  - Bliss Independence
    - Empiric Bliss model(s)

Mechanistic elements

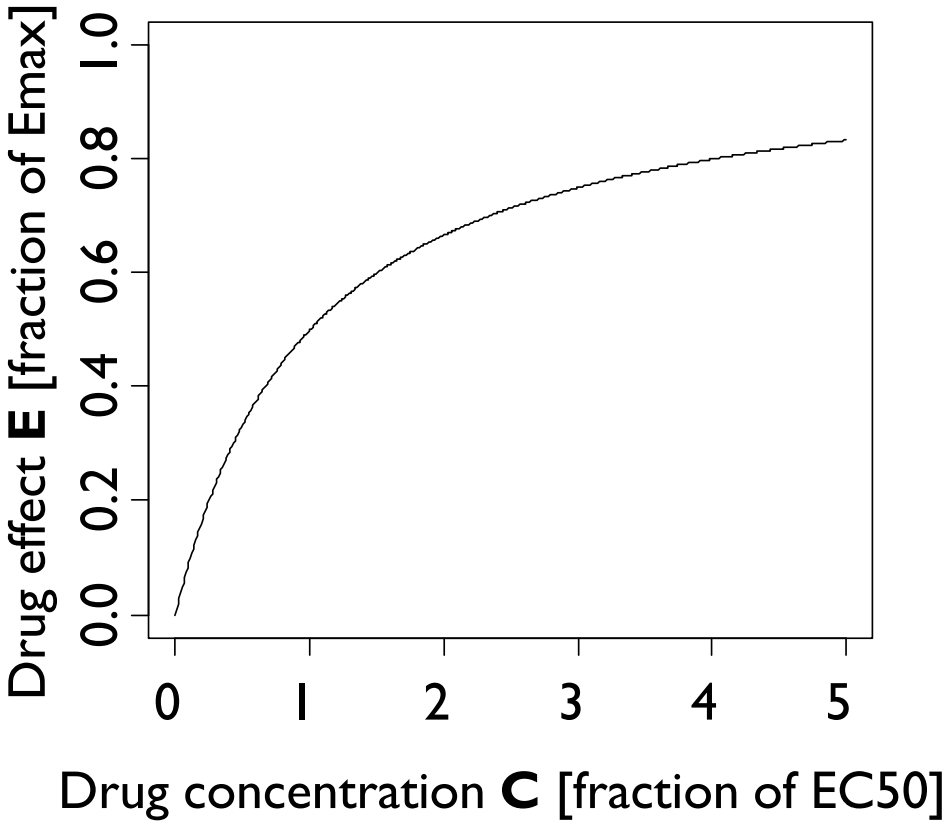


**General PD interaction model**



Basis: additivity criterion

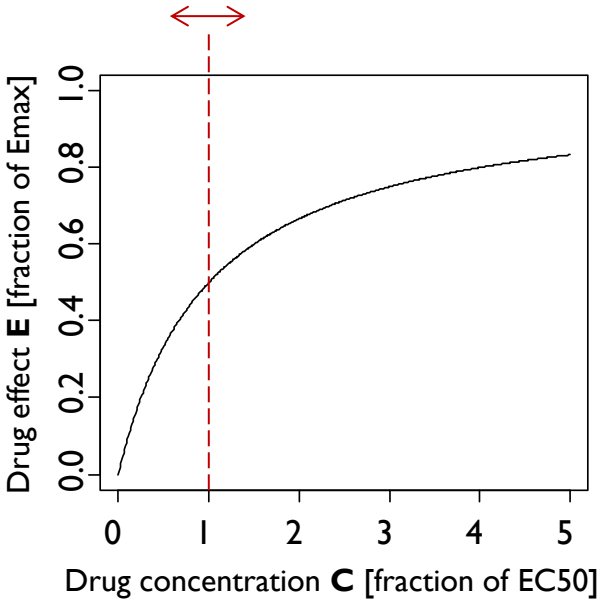
# The Emax model for quantification of drug effects




$$E = \frac{Emax \times C^H}{EC50^H + C^H}$$

# GPDI model implementation on EC50

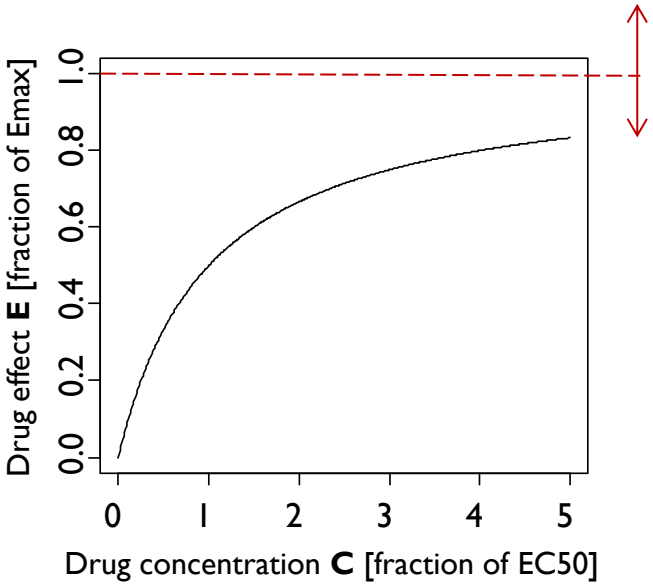
- $$E_A = \frac{Emax_A \times {C_A}^{H_A}}{\left(EC50_A \times \left(1+\frac{Int_{AB} \times C_B}{EC50_{INT,AB}+C_B}\right)\right)^{H_A} + {C_A}^{H_A}}$$
- $$E_B = \frac{Emax_B \times {C_B}^{H_B}}{\left(EC50_B \times \left(1+\frac{Int_{BA} \times C_A}{EC50_{INT,BA}+C_A}\right)\right)^{H_B} + {C_B}^{H_B}}$$




- 4 parameter interaction model
  - $Int_{AB}$, $Int_{BA}$ (-1 < Int < *Inf*) (0: Additivity, <0: Synergy, >0: Antagonism)
  - $EC50_{INT,AB}$ , $EC50_{INT,BA}$
- Simplifications:
  - $Int_{AB} = Int_{BA}$ (joint INT parameter)
  - $EC50_{Int,AB} = EC50_B$ and $EC50_{Int,BA} = EC50_A$

# GPDI model implementation on Emax

- $E_A = \frac{Emax_A \times \left(1 + \frac{Int_{AB} \times C_B}{EC50_{INT,AB} + C_B}\right) \times {C_A}^{H_A}}{{EC50_A}^{H_A} + {C_A}^{H_A}}$
- $E_B = \frac{Emax_B \times \left(1 + \frac{Int_{BA} \times C_A}{EC50_{INT,BA} + C_A}\right) \times {C_B}^{H_B}}{{EC50_B}^{H_B} + {C_B}^{H_B}}$




- 4 parameter interaction model
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  - $EC50_{INT,AB}$ , $EC50_{INT,BA}$
- Simplifications:
  - $Int_{AB} = Int_{BA}$ (joint INT parameter)
  - $EC50_{Int,AB} = EC50_B$ and $EC50_{Int,BA} = EC50_A$

# The GPDI model is compatible with several additivity criteria

$$E_A = \frac{Emax_A \times {C_A}^{H_A}}{\left(EC50_A \times \left(1 + \frac{Int_{AB} \times C_B}{EC50_{INT_AB} + C_B}\right)\right)^{H_A} + {C_A}^{H_A}}$$

$$E_B = \frac{Emax_B \times {C_B}^{H_B}}{\left(EC50_B \times \left(1 + \frac{Int_{BA} \times C_A}{EC50_{INT_BA} + C_A}\right)\right)^{H_B} + {C_B}^{H_B}}$$

- Loewe Additivity
- Bliss Independence
- Effect summation
- Highest single agent
- …

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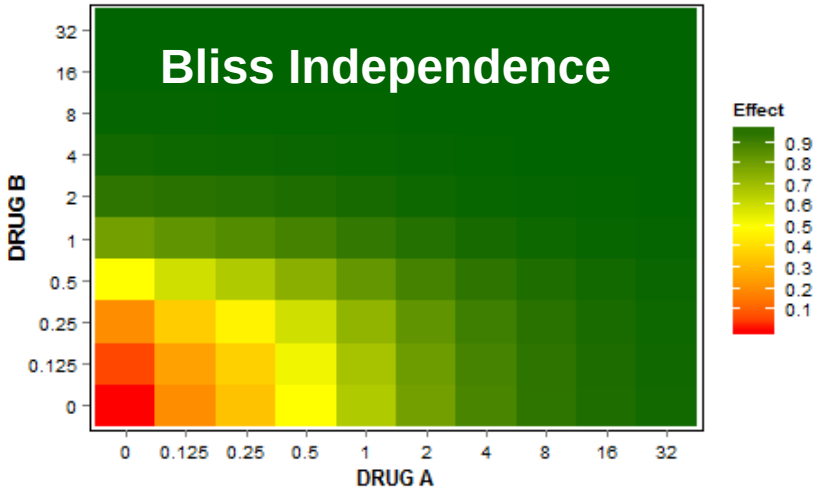
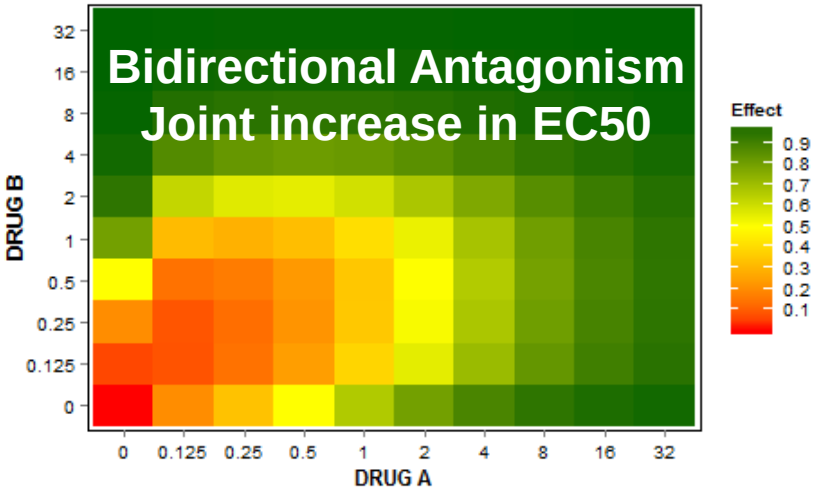
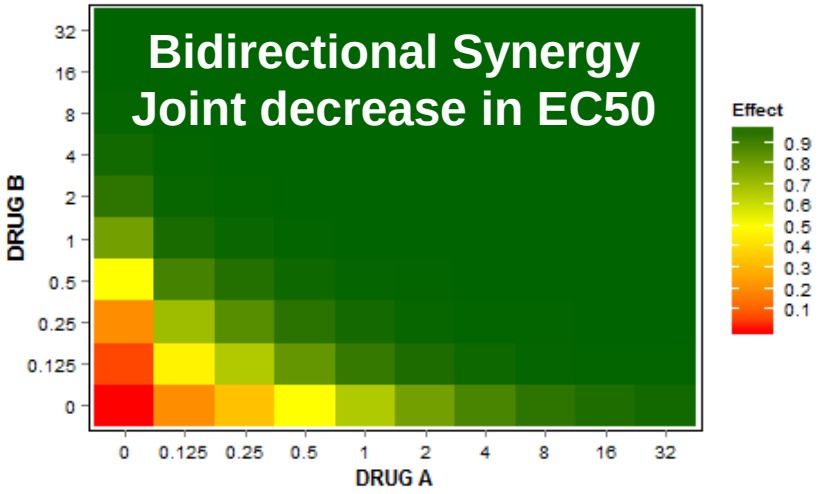
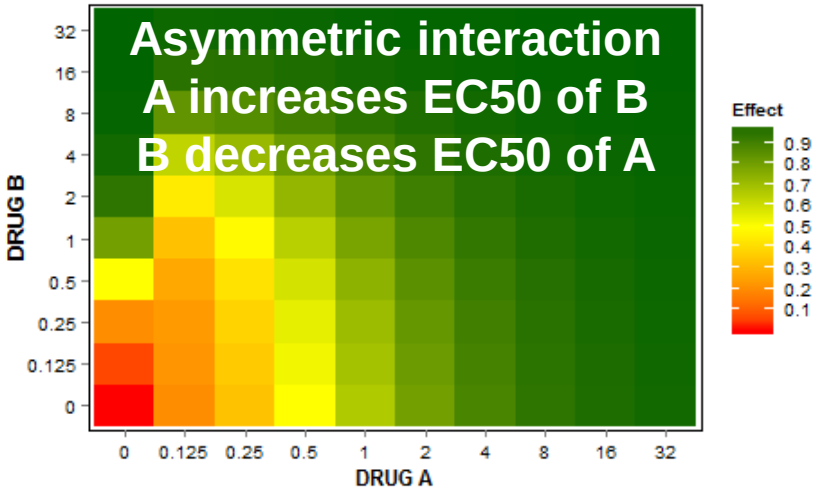
# GPDI Model on EC50 Two Drugs



# GPDI Model Three Drugs

Bidirectional interactions between three drugs A, B and C:

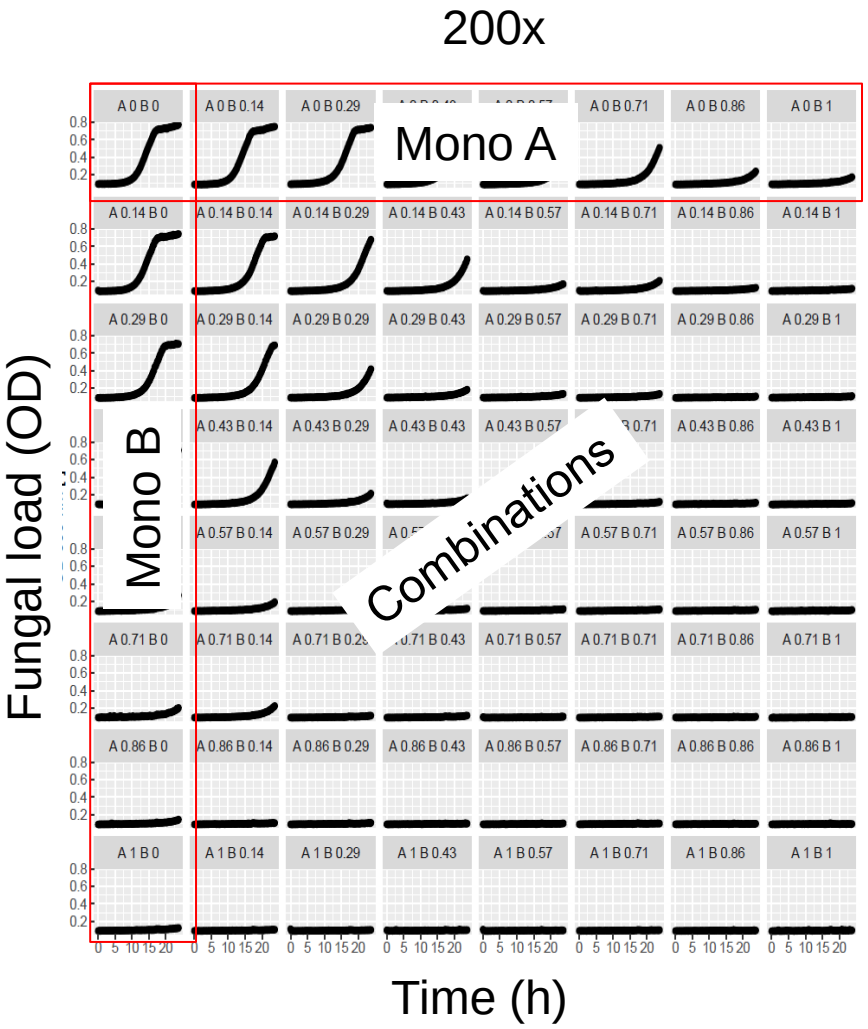
- $$E_A = \frac{Emax_A \times C_A^{H_A}}{\left(EC50_A \times \left(1+\frac{INT_{AB} \times C_B}{EC50_{INT,AB}+C_B}\right) \times \left(1+\frac{INT_{AC} \times C_C}{EC50_{INT,AC}+C_C}\right)\right)^{H_A} + C_A^{H_A}}$$

Drug C modulates interaction between A and B:

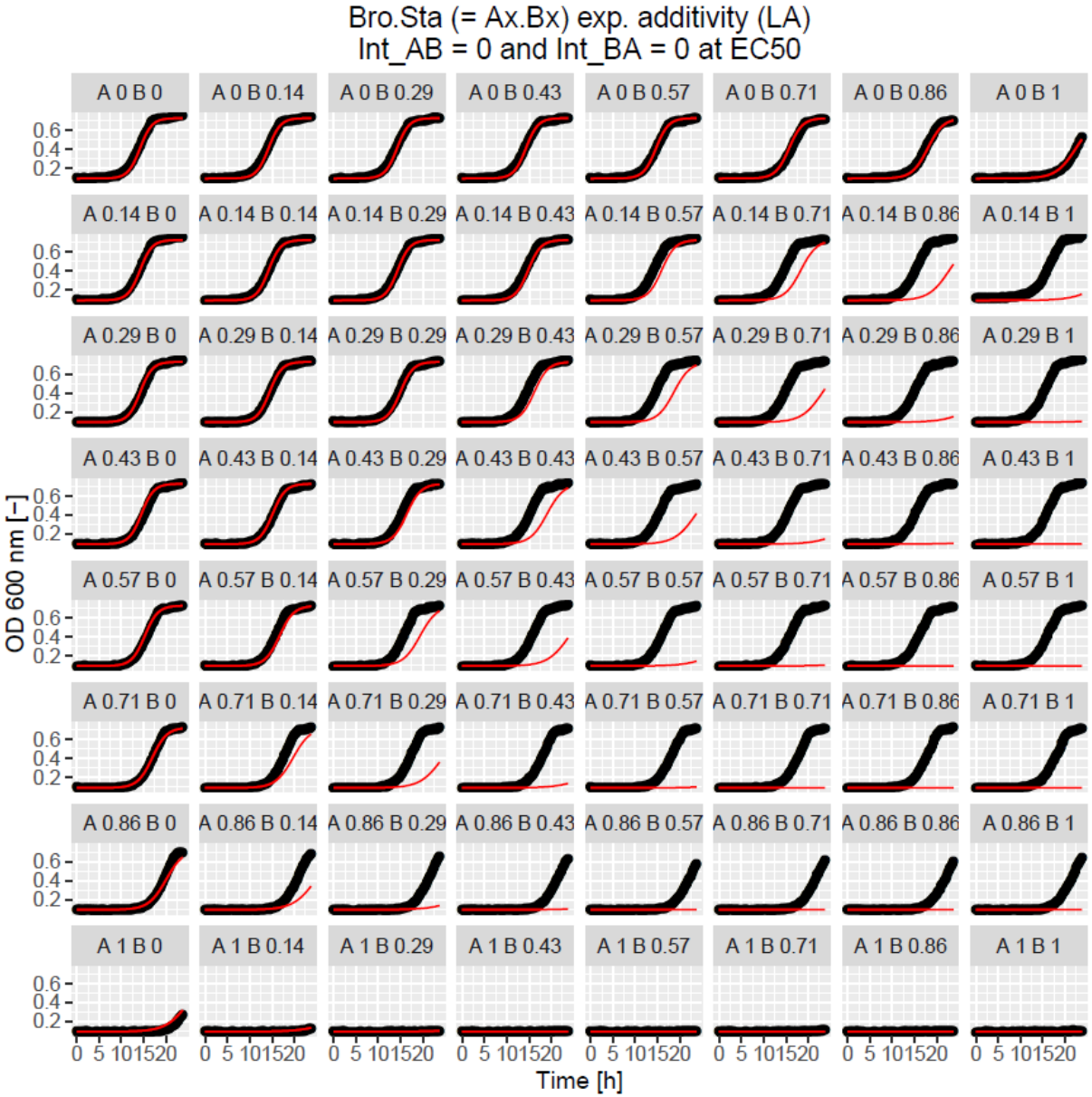
- $$E_A = \frac{Emax_A \times C_A^{H_A}}{\left(EC50_A \times \left(1+\frac{INT_{AB} \times \left(1+\frac{INT_{AB|C} \times C_C}{EC50_{INT,AB|C}+C_C}\right) \times C_B}{EC50_{INT,AB}+C_B}\right) \times \left(1+\frac{INT_{AC} \times C_C}{EC50_{INT,AC}+C_C}\right)\right)^{H_A} + C_A^{H_A}}$$

# Application of the GPDI Model

- Dataset:
  Cokol et al. Mol Syst Biol, 7: 544 (2011).
  - Target organism:
    *S. cerevisiae BY4741*
  - 200 combinations of anti-fungal and non-antifungal drugs.
- Inhibition of growth model
- GPDI model
  - Loewe additivity
  - Bliss Independence
- Comparison to Greco model



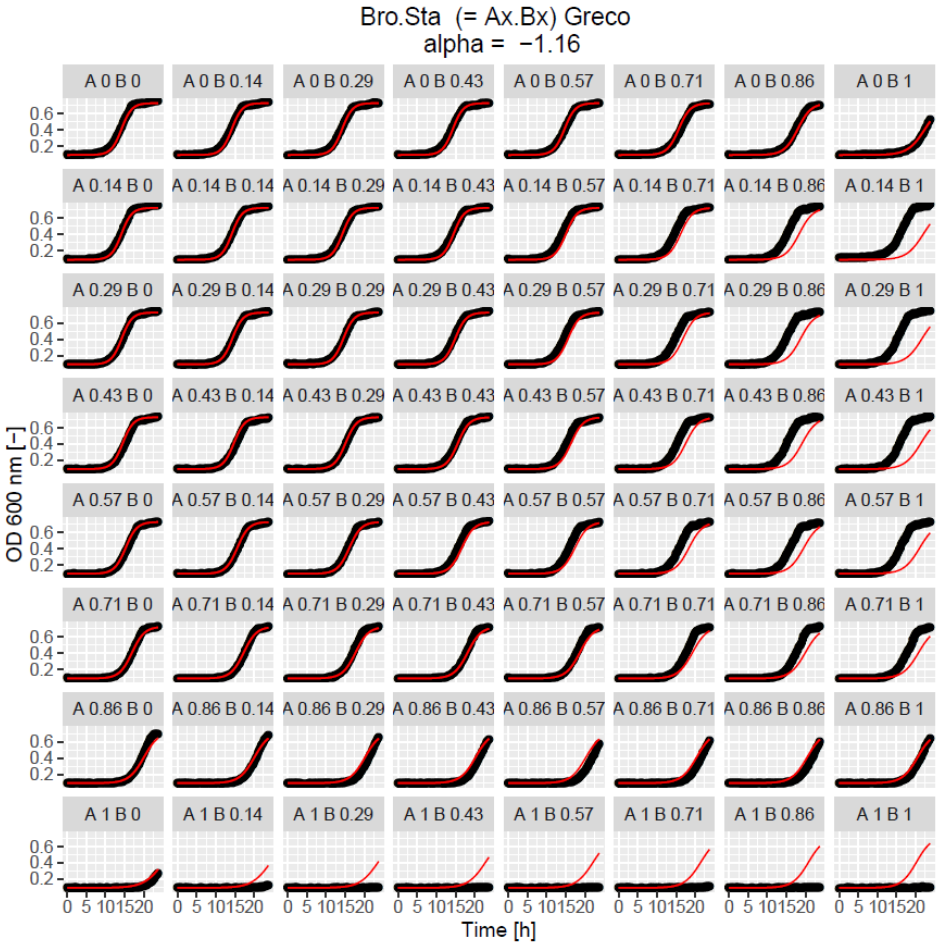
# Ind. Prediction of Loewe Additivity

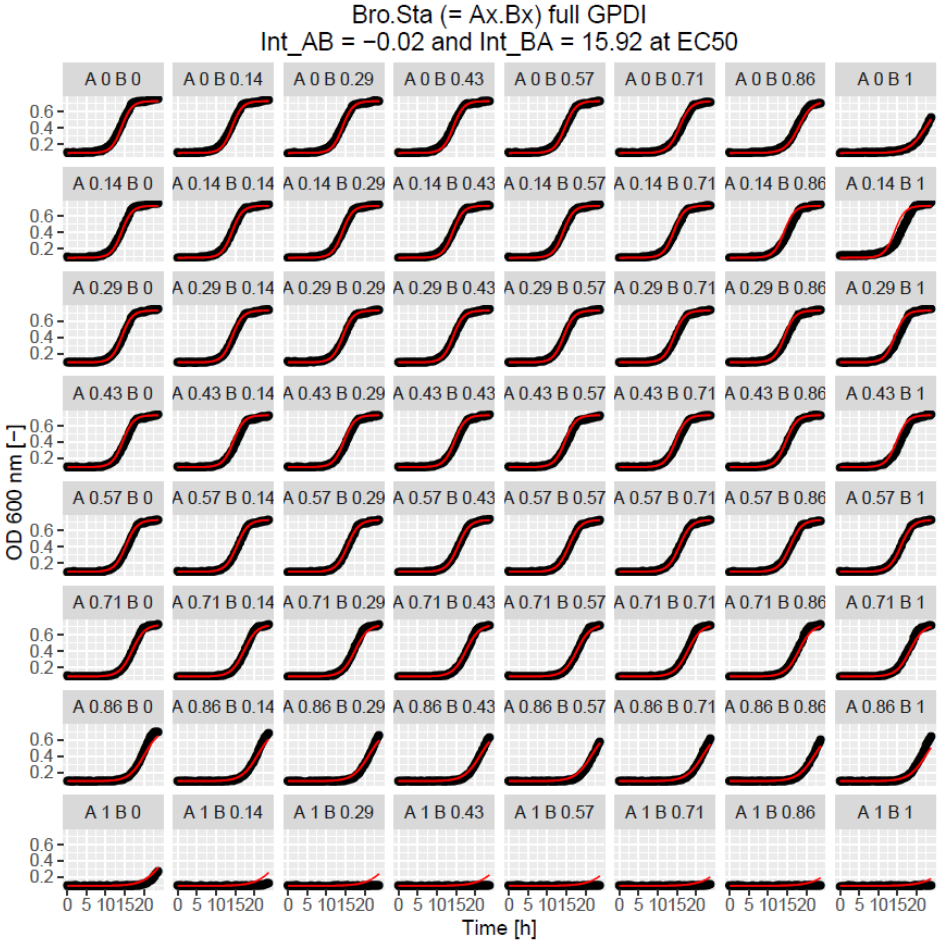



- Observation
- Prediction

Ax Bx (fold MIC)

# Individual predictions using Greco (left) or GPDI model (right)

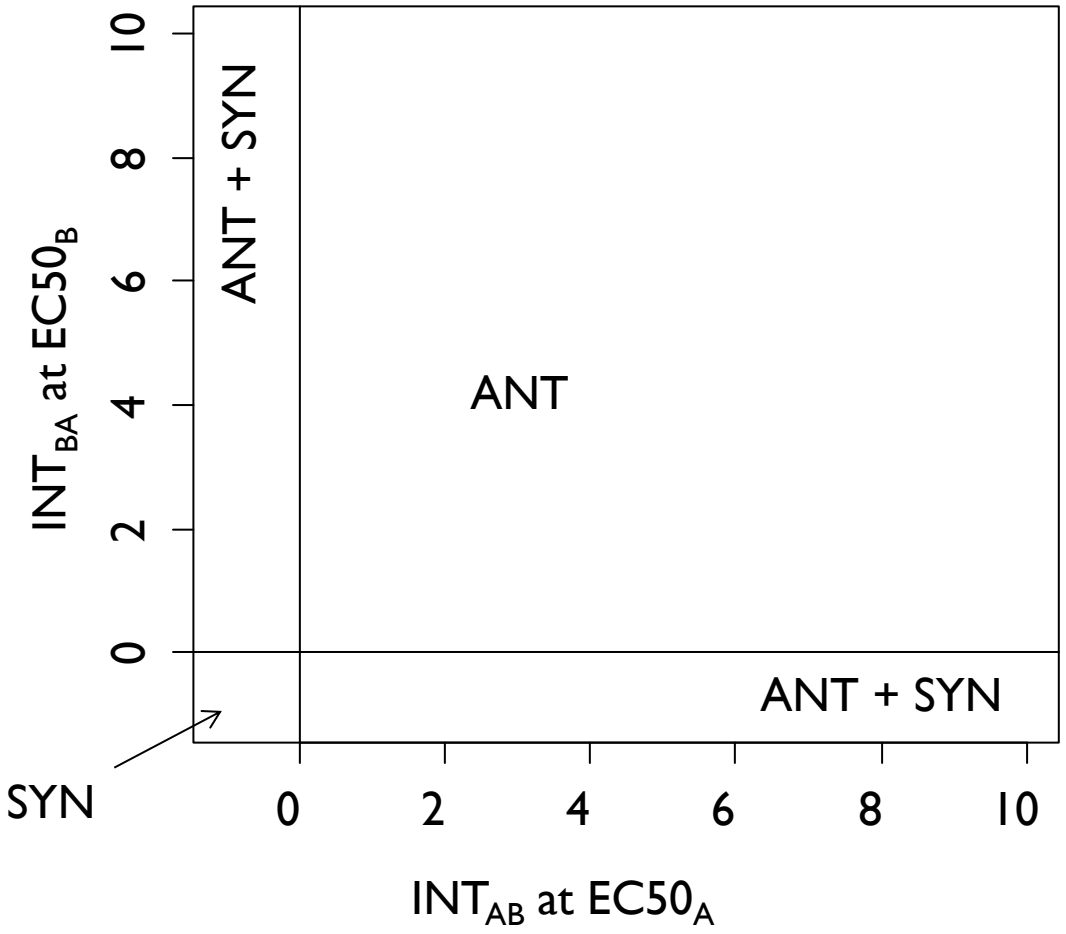



- Observation
- Prediction

Ax Bx (fold MIC)

# INT values at EC50



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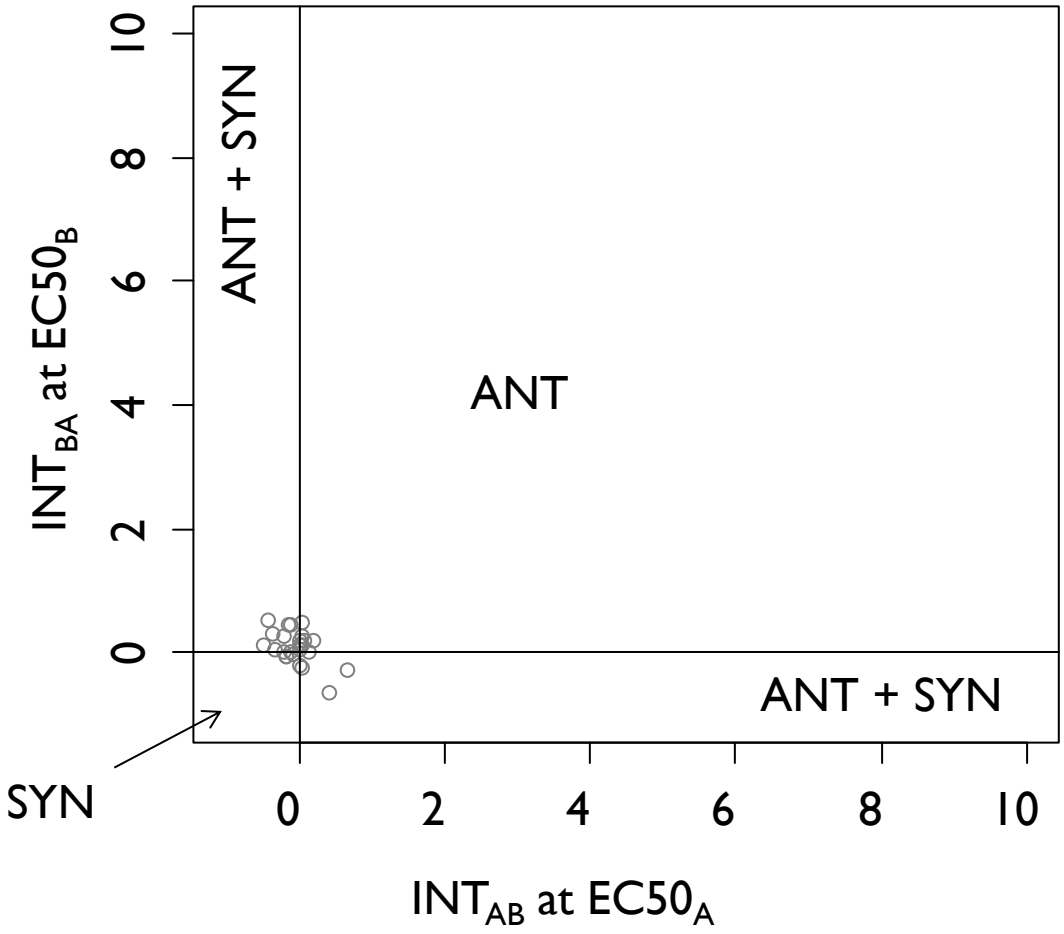
# INT values at EC50 of sham combinations



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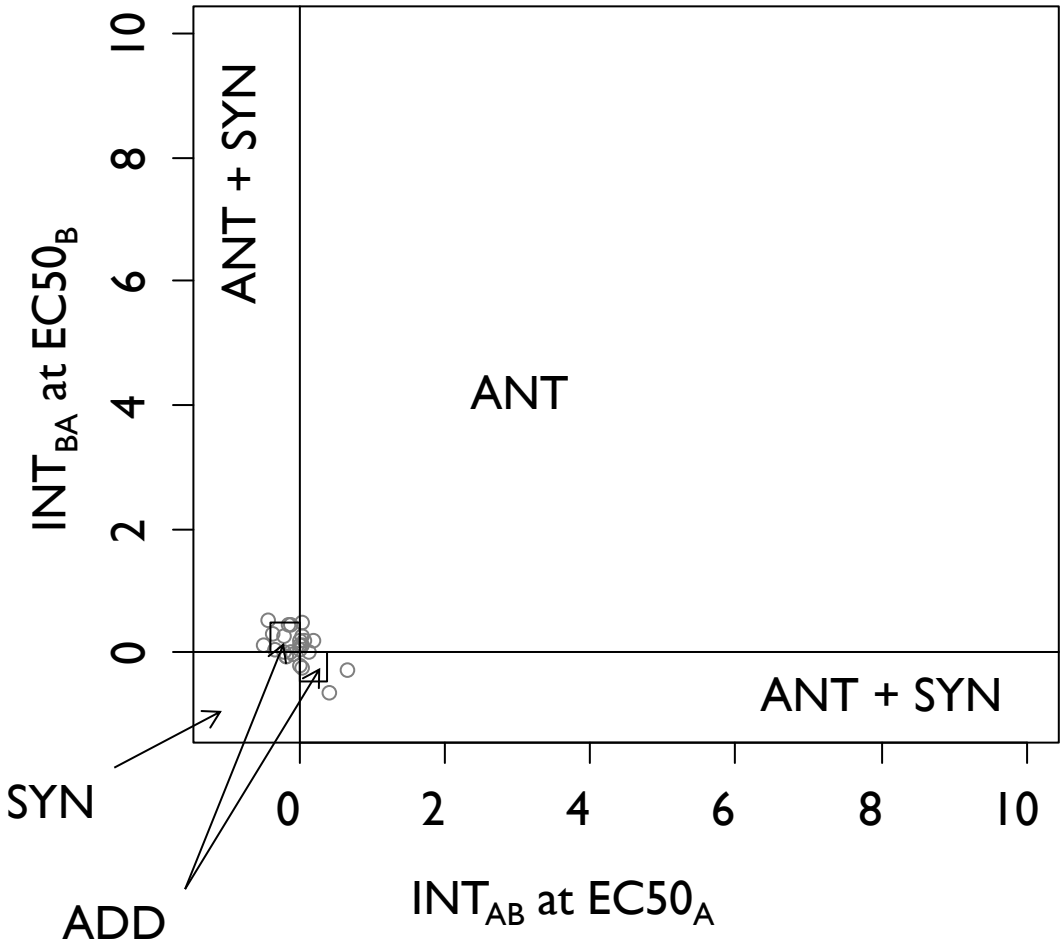
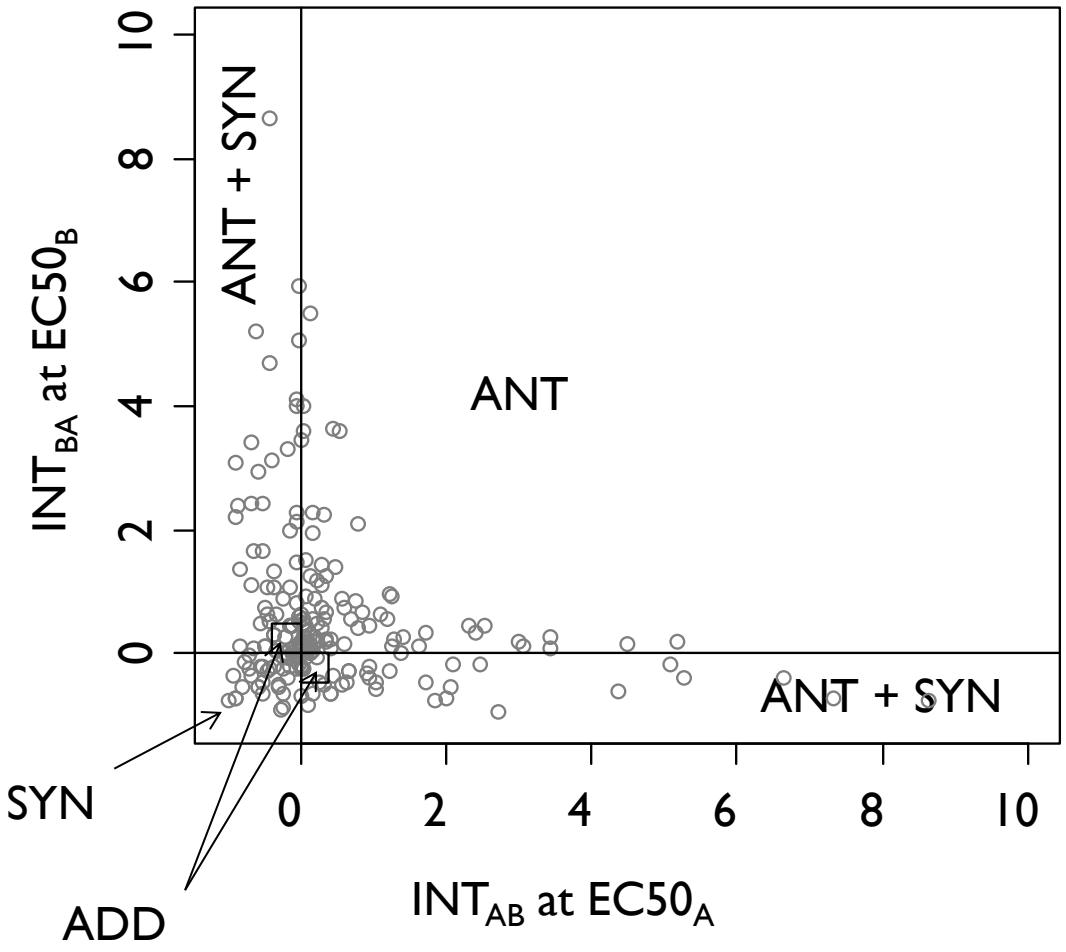
# INT values at EC50 of sham combinations

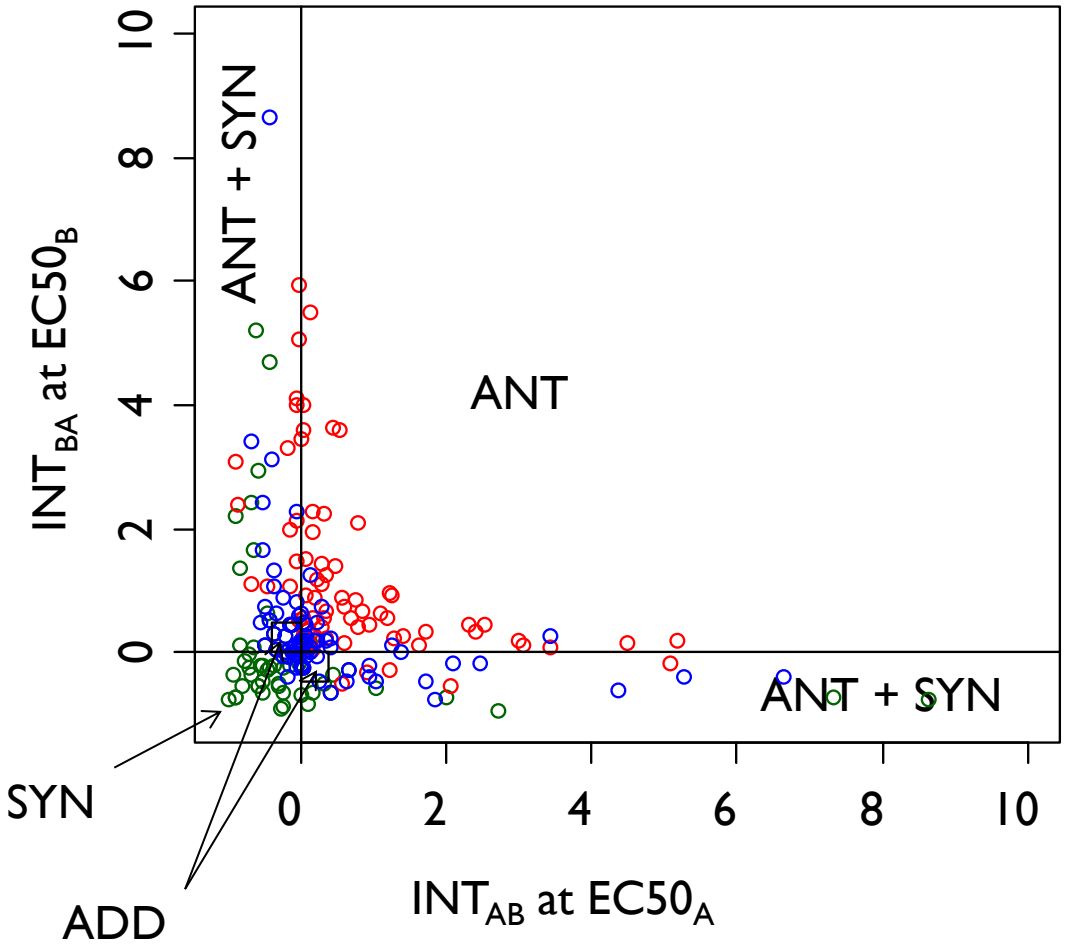


# 188/200 PD DDI supported estimation of full GPDI model*




* i.e. significant separate INT value for each drug vs. joint INT parameter

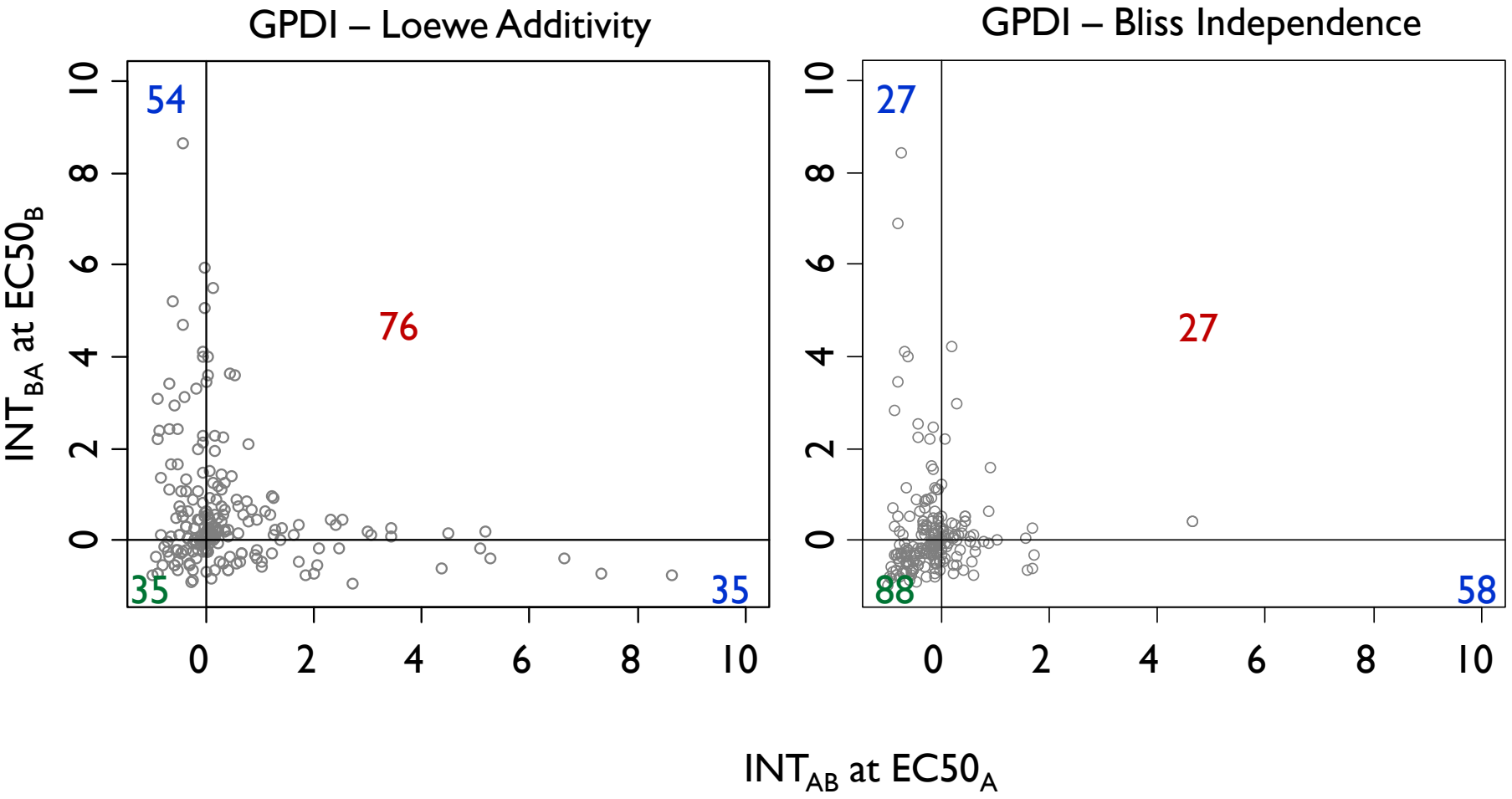
# PD DDI are often misclassified by conventional analyses!




Result of Greco analysis:

- Antagonism
- Additivity
- Synergy

# The choice of additivity criterion affects the determined interaction



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# Conclusions

- The GPDI model combined elements from mechanism-based interaction models with empirical additivity concepts.
- Advantages of the GPDI model over conventional approaches are:
  - interpretable parameters
  - Applicability for > 2 interacting drugs
  - Compatibility with multiple additivity criteria
  - More-dimensional interactions
  - Scalability to adapt to complexity of the data
  - Applicability in both concentration-effect and longitudinal modelling

# GPDI model application studies at PAGE 2016

*In vitro* and *in vivo* (acute mouse infection model) drug effects of rifampicin, isoniazid, ethambutol and pyrazinamide against *M. tuberculosis*

II-50

Abstract II-50

## Pre-clinical Susceptibility Characterization and Pharmacodynamic Interaction Assessment Using the Multistate Tuberculosis Pharmacometric Model

Oskar Clewe[1], Sebastian G. Wicha[1], Corné de Vogel[2], Jurriaan E. M. de Steenwinkel[2], Ulrika S. H. Simonsson[1]

1. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. 2. Department of Medical Microbiology and Infectious Diseases, Erasmus Medical Center, Rotterdam, The Netherlands.

### Objectives

For diseases such as tuberculosis, where a combination of drugs are needed to effectively combat the bacterial infestation, the possibility of both positive and negative pharmacodynamic drug interactions exist. This information could be provided from a pre-clinical setting in which cost and ethical implications are minor. This work aimed at characterizing the susceptibility of *Mycobacterium tuberculosis (M. tuberculosis)* to rifampicin (RIF), isoniazid (INH) and ethambutol (ETH) and assessing the pharmacodynamic interactions of duo combinations of the three drugs using *in vitro* time kill data.

### Methods

*In vitro* time kill experiments were performed with *M. tuberculosis* genotype strain Beijing 1585 using both single and duo combination series of RIF, INH and ETH concentrations. Viability, defined as colony forming units (cfu), was assessed at day 1, 2, 3 and 6 after drug exposure. The Multistate Tuberculosis Pharmacometric (MTP) model framework [1] and the general pharmacodynamic

For the effect on the F bacteria; RIF was found to act synergistic on both INH and ETH, INH was found to exert agonistic effect on RIF and showed no significant deviation from an additive effect when combined with ETH, ETH was found to act synergistic on RIF but showed no deviation from a additive effect when combined with INH. For the effect on the S state bacteria all three drugs was found to act antagonistic on one another when studied in duo combinations.

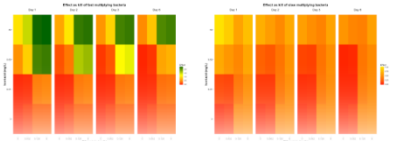


Figure 2 Heat map displaying drug effect by interaction between INH and RIF scaled by the largest drug effect found in mono exposure. To the left is the effect on fast multiplying bacteria and to the right is the effect on slow multiplying bacteria.

II-44

## Assessment of Pharmacodynamic Interactions in the Mouse using the Multistate Tuberculosis Pharmacometric Model and the General Pharmacodynamic Interaction Model

Chunli Chen[1], Sebastian G.Wicha[1], Gerjo J. de Knegt[2], Fatima Ortega-Muro[3], Laura Alameda[3], Veronica Sousa[3], Jurriaan E.M. de Steenwinkel[2], Ulrika SH Simonsson[1]

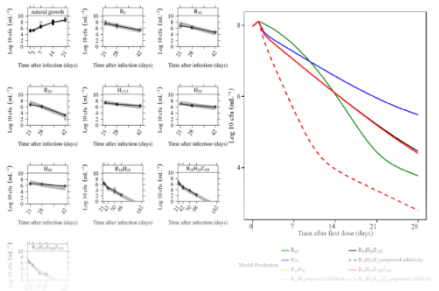
1. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden 2. Erasmus MC, Department of Medical Microbiology & Infectious Diseases, Rotterdam, the Netherlands 3. Diseases of Developing World Medicines Development Campus, GlaxoSmithKline, Tres Cantos, Madrid, Spain

### Objectives

The aim of this study was to gain insight into possible pharmacodynamic (PD) interactions between drugs when given to treat drug susceptible tuberculosis in an chronic tuberculosis mouse model using the Multistate Tuberculosis Pharmacometric (MTP) model [1] and the General Pharmacodynamic Interaction (GPDI) model [2] based on the Bliss Independence criterion.

### Methods

Pharmacokinetic (PK) models for rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) were developed using sparse PK data from separate infected BALB/c mice, combined with rich PK data from healthy BALB/c mice [3]. Infected BALB/c mice randomized to monotherapy received either 4 weeks of RIF (5, 10 or 20 mg/kg) or INH (12.5, 25 or 50 mg/kg) or EMB (50, 100 or 200 mg/kg) or PZA (75, 150 or 300 mg/kg). The PD biomarker colony forming unit (cfu) was assessed after 1, 2 and 4 weeks treatment



# Acknowledgements

PMx research group at Uppsala University

- Elin Svensson
- Anders Kristofferson

PreDiCT-TB consortium

The research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (www.imi.europe.eu) under *grant agreement* n° 115337, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

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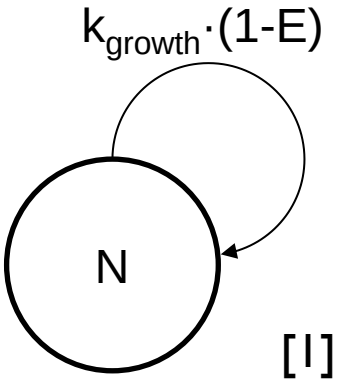
# Appendix

# Implementation of Combined Effects on Inhibition of Growth

GPDI within Bliss Independence:

$$E = E_A + E_B - E_A \times E_B$$

- $$E_A = \frac{Emax_A \times {C_A}^{H_A}}{\left(EC50_A \times \left(1+\frac{Int_{AB} \times C_B}{EC50_{INT,AB}+C_B}\right)\right)^{H_A}+{C_A}^{H_A}}$$
- $$E_B = \frac{Emax_B \times {C_B}^{H_B}}{\left(EC50_B \times \left(1+\frac{Int_{BA} \times C_A}{EC50_{INT,BA}+C_A}\right)\right)^{H_B}+{C_B}^{H_B}}$$



[1]

GPDI within Loewe additivity:

$$1 = \frac{C_A}{EC50_A^* \times (\frac{E}{Emax_A - E})^{1/H_A}} + \frac{C_B}{EC50_B^* \times (\frac{E}{Emax_B - E})^{1/H_B}}$$

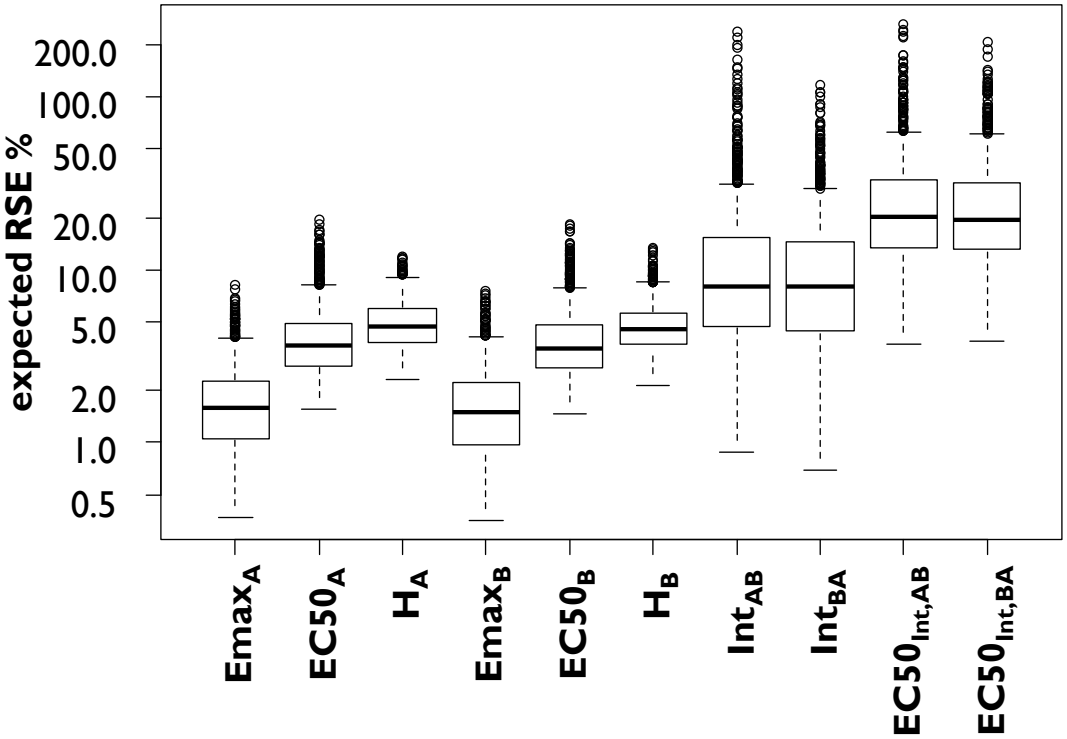
$$EC50_A^* = EC50_A \times \left(1 + \frac{Int_{AB} \times C_B}{EC50_{INT,AB} + C_B}\right)$$

$$EC50_B^* = EC50_B \times \left(1 + \frac{Int_{BA} \times C_A}{EC50_{INT,BA} + C_A}\right)$$

[1] W.J. Jusko, *J. Pharm. Sci.* 60 (1971).

# The full GPDI Model is identifiable on standard checkerboard designs

**8x8 checkerboard**

- 1000 scenarios assessed
- n=3 replicates per scenario
- max. growth: 10 $\log_{10}$ CFU/mL
- $\sigma_{add}$ = 0.3 $\log_{10}$ CFU/mL

| | |
|---|---|
| Emax | $\in \{0.5, 1\}$ |
| EC50 | $\in \{0.5, 2\}$ |
| H | $\in \{1, 4\}$ |
| Int | $\in \{-0.9, -0.2\} \cup \{2, 20\}$ |
| EC50_Int | $\in \{0.1, 1\}$ |