Modelling and simulation applied to personalised medicine

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Objective

- To develop an efficient methodology to identify the best drug combinations to be administered to patients with acute myeloid leukemia based on ex-vivo response vs exposure experiments
  - Not for dose-selection (so far)
  - Compute subject's specific descriptors to correlate with clinical outcome

Studied Population & Methodology

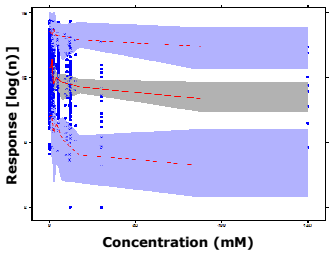
- Seventy adult patients diagnosed with de novo AML
- Marrow samples were collected at diagnosis, sent to the laboratory, and incubated for 48 hours in well plates containing single drugs [Cytabarine (cyt), Idarubicin (ida)] or combinations of the two drugs
  - Cyt (μM) = 0, 0.039, 0.156, 0.625, 2.5 & 10
  - Ida (μM) = 0, 0.0039, 0.0156, 0.0625, 0.25 & 1
  - Cyt & Ida = 0.039/0.0039, 0.156/0.0156, 0.625/0.0625 2.5/0.25, 10/1
- Annexin V-FITC was used to quantify the drug-induced apoptosis
- Response measured was number of malignant cells alive

Strategy for Data Analysis & Results

Workflow

- PD modelling of data from monotherapy
  - Population approach with NONMEM 7.2
  - All model parameters associated to inter-patient variability
  - No covariate effects were explored
  - PD model used to describe response vs exposure
  - Steady-state conditions were assumed

$$E = E_0 \times \left[1 - I_{MAX} \times \frac{C^n}{C^n + IC_{50}^n}\right]$$

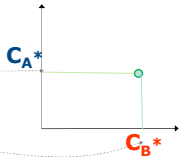


Drug	E_0 (n)	I_{MAX} (-)	IC_{50} (μM)	γ (-)	SD [log(n)]
Cyt	42600 (178)	0.996 (1.1)	5.34 (192)	1 (70)	0.23 (55)
Ida	41900 (178)	1*	0.11 (157)	1.8 (62)	0.31 (54)

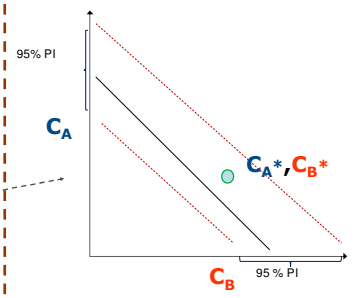
Inter-patient variability expressed as CV in parenthesis; *, not significantly different from 1; RSE were omitted for clarity

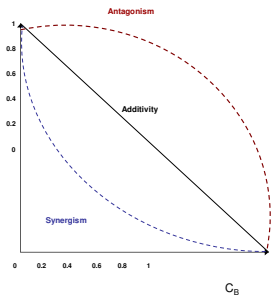
- Select a set of effect magnitudes
  - 20, 40, 60, & 80% decrease in malignant cells with respect to baseline
  - Identify for each subject the corresponding concentration pair
  - Non-modelling step using raw data from drug combination

0	$[A]_1$	$[A]_2$	....	$[A]_n$
$[B]_1$	$[A]_1/[B]_1$	$[A]_2/[B]_1$	....	$[A]_n/[B]_1$
$[B]_2$	$[A]_1/[B]_2$	$[A]_2/[B]_2$	....	$[A]_n/[B]_1$
....	....	....	....	
$[B]_n$	$[A]_1/[B]_n$	$[A]_2/[B]_n$	....	$[A]_n/[B]_n$



- For each drug get access to the variance-covariance matrix for each individual set of PD parameters obtained from the popPD analysis in monotherapy
- Create (simulate) for each patient 1000 sets of PD parameters
- Calculate the concentration (C) that elicits a response equal to the response to the combination for each set of simulated parameters & pre-defined effect magnitude & studied drug
  - Calculate the 95% PI of CA and CB
  - Generate the isobologram
  - Calculate the combination index
    - Using the 2.5th percentile of each C
  - Allows characterization of the interaction
  - Additional descriptor to correlate with clinical response

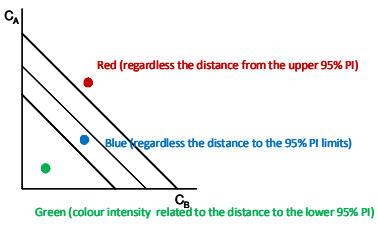




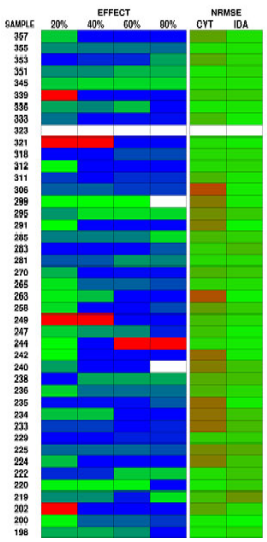
Combination Index (CI)= $\frac{C_A^*}{C_A} + \frac{C_B^*}{C_B}$

CI > 1 Synergism
CI =1 Additivity
CI < 1 Antagonism

- Summarize the isolobologram using color maps to better interpret results and decision making about the choice of the drug combination



NRMSE
Normalised root mean square error



Set of individual paremeter estimates (EBEs)

```
$PROB Citarabine
$INPUT ID CONC DV SBF CATE
$DATA cytarabine48.dta IGNORE=#IGNORE=(ID.NE.##ID##)
$PRED
E0=THETA(1)*EXP(ETA(1))
IMAX=1
IC50=THETA(2)*EXP(ETA(2))
GAM=THETA(3)*EXP(ETA(3))
AA=CONC**GAM
BB=IC50**GAM
IPRED=LOG(E0*(1-IMAX*AA/(AA+BB)))

W=THETA(4)*EXP(ETA(4))
Y=IPRED+W*EPS(1)
```

Original data

Population model

```
$THETA ##THETA1## FIX    ; E0
$THETA ##THETA2## FIX    ; EC50
$THETA ##THETA3## FIX    ; GAM
$THETA ##THETA4## FIX    ; Additive error
$OMEGA BLOCK(5)
##ETC11##
##ETC21## ##ETC22##
##ETC31## ##ETC32## ##ETC33##
$OMEGA ##ETC44##

$SIGMA 1 FIX    ; SD additive error in log scales

$SIMULATION (##ID##) ONLY SUBPROBLEMS=1000
$TABLE ID E0 IMAX IC50 GAM NOHEADER NOAPPEND
       FIRSTONLY NOPRINT FILE=parameters.tab
```

Variance-Covariance matrix of individual model parameters

Conclusions

- We present an efficient methodology to characterize the type of drug interaction for individualize treatments
- Modelling is limited to data obtained from monotherapy avoiding the use of PD models for drug interactions and estimating interaction parameters