# Detecting Bliss Synergy in in -vivo Combination Studies with a Tumor Kinetic Model

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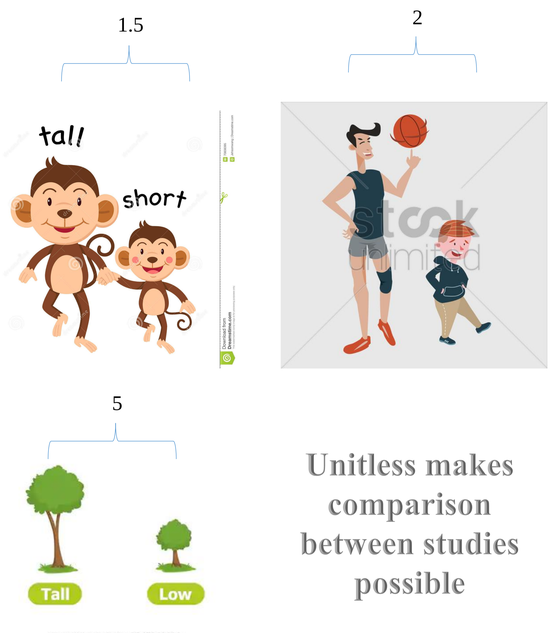
## Abstract

Linear models are generally reliable methods for analyzing tumor growth in-vivo, with drug effectiveness being represented by the steepness of the regression slope. With immunotherapy, however, not all tumor growth follows a linear pattern, even after log transformation. Tumor kinetics models are mechanistic models that describe tumor proliferation and tumor killing macroscopically, through a set of differential equations. In drug combination studies, although an additional drug-drug interaction term can be added to such models, however, the drug interactions suggested by tumor kinetics models cannot be translated directly into synergistic effects. We have developed a novel statistical approach that simultaneously models tumor growth in control, monotherapy, and combination therapy groups. This approach makes it possible to test for synergistic effects directly and to compare such effects among different studies.

## Motivating Examples




## Introduction and Objectives

History:

- Tumor growth data are often fitted to a linear model with fixed or random effects
- Tumor growth does not always follow a linear pattern before or after log transformation
- Tumor growth under treatment can be described using a set of differential equations
- Significant interaction term in kinetic model does not directly imply synergy

Issues:

- Two stage modeling
- The interaction term is time and dose dependent

Solution:

- A tumor kinetics model framework based on Bliss independence theory

## Methods

### Untreated Group Model

In-vivo tumor growth follows exponential growth in the early phases of development

$$\frac{dW(t)}{dt} = \lambda W(t)$$

### Single Drug Group Model

The monotherapy tumor growth model is written used system of differential equations.

$$\frac{dx_1(t)}{dt} = (\lambda - k_2)x_1(t)$$

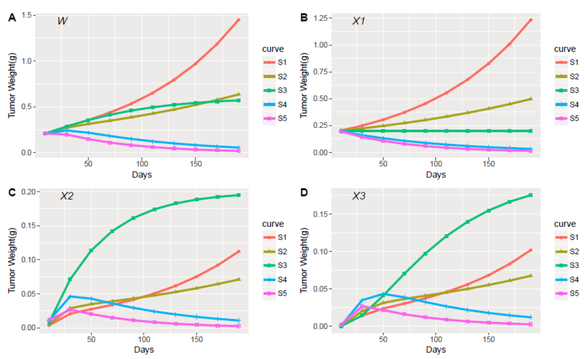
$$\frac{dx_2(t)}{dt} = k_2 x_1(t) - k_1 x_2(t)$$

$$\frac{dx_3(t)}{dt} = k_1[x_2(t) - x_3(t)]$$

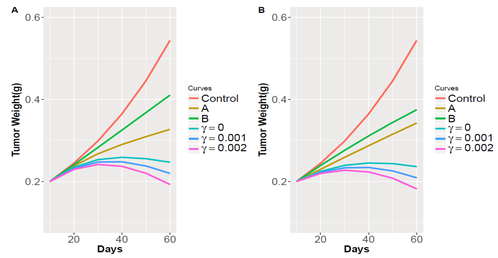
$$\mathrm{W}(t) = x_1(t) + x_2(t) + x_3(t)$$

### Combination Group Model

$$y_j(t) = 1 - \frac{W_j(t)}{W_0(t)}, j = A, B, and\ AB$$




## Simulations and Results




$$W_j(t) = w(10) + \alpha_j(t-10) + \beta_j(t-10)^2, j = A, B$$

$$I(t) = \gamma(t-10)$$

Parameters of Differential Equations in Simulations 1 through 6

| Simulation | 1 (No) | 2 (Weak) | 3(Strong) | 4(No) | 5(Weak) | 6(Strong) |
|---|---|---|---|---|---|---|
| $\lambda$ | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| $k_{2,A}$ | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| $k_{1,A}$ | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| $k_{2,B}$ | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| $k_{1,B}$ | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| $\sigma$ | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| $W(0)$ | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| $\gamma$ | 0 | 0.001 | 0.002 | 0 | 0.001 | 0.002 |
| N | 10 | 10 | 10 | 20 | 20 | 20 |

$\gamma$; synergy parameter; $k_{1,A}$, killing rate, drug A; $k_{1,B}$, killing rate, drug B; $k_{2,A}$, drug efficacy parameter, drug A; $k_{2,B}$, drug efficacy parameter, drug B; $\lambda$, proliferating cell growth rate; $\sigma$, common variance; $W(0)$, initial tumor weight.

Parameters of Differential Equations in Simulation 7 through 12

| Simulations | 7(No) | 8(Weak) | 9(Strong) | 10(NO) | 11(Weak) | 12(Strong) |
|---|---|---|---|---|---|---|
| $\lambda$ | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| $\alpha_A$ | 3E-3 | 3E-3 | 3E-3 | 3E-3 | 3E-3 | 3E-3 |
| $\beta_A$ | -3E-6 | -3E-6 | -3E-6 | -3E-6 | -3E-6 | -3E-6 |
| $\alpha_B$ | 4E-3 | 4E-3 | 4E-3 | 4E-3 | 4E-3 | 4E-3 |
| $\beta_B$ | -1E-5 | -1E-5 | -1E-5 | -1E-5 | -1E-5 | -1E-5 |
| $\sigma$ | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| $W(0)$ | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| $\gamma$ | 0 | 0.001 | 0.002 | 0 | 0.001 | 0.002 |
| N | 10 | 10 | 10 | 20 | 20 | 20 |

$\gamma$; synergy parameter; $\lambda$, proliferating cell growth rate; $\sigma$ and $\beta$, parameters of quadratic growth function; $\sigma$, common variance; $W(0)$, initial tumor weight.

Mean of 1000 Parameter Estimations for Simulations 1 through 6

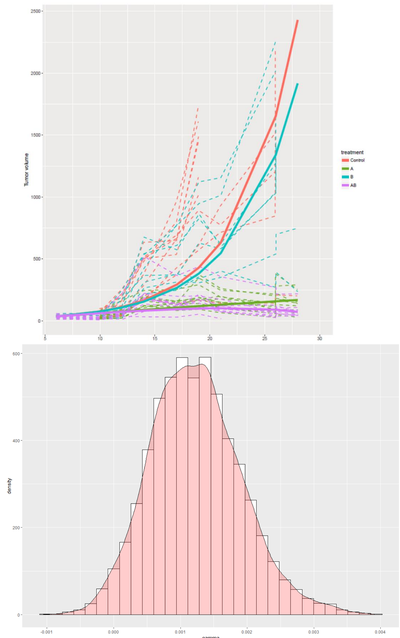
| Simulation | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| $\lambda$ | 0.02 | 0.02 | 0.0199 | 0.02 | 0.02 | 0.02 |
| $k_{2,A}$ | 0.0152 | 0.0151 | 0.015 | 0.0152 | 0.0151 | 0.015 |
| $k_{1,A}$ | 0.1049 | 0.1069 | 0.1066 | 0.1026 | 0.1036 | 0.1038 |
| $k_{2,B}$ | 0.0146 | 0.0146 | 0.0144 | 0.0148 | 0.0147 | 0.0146 |
| $k_{1,B}$ | 0.0231 | 0.0222 | 0.0232 | 0.0219 | 0.0219 | 0.0223 |
| $\sigma$ | 0.0983 | 0.0989 | 0.099 | 0.0992 | 0.0995 | 0.0995 |
| $W(0)$ | 0.2002 | 0.2003 | 0.2003 | 0.2002 | 0.2002 | 0.2002 |
| $\gamma$ | 0 | 0.001 | 0.002 | 0 | 0.001 | 0.002 |
| Synergistic | 5.20% | 61.50% | 99.70% | 5.30% | 88.70% | 100% |

Mean of 1000 Parameter Estimations for Simulations 7 through 12

| Simulation | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|
| $\lambda$ | 0.0202 | 0.0202 | 0.0202 | 0.0202 | 0.0202 | 0.0202 |
| $k_{2,A}$ | 0.013 | 0.013 | 0.0132 | 0.013 | 0.013 | 0.0133 |
| $k_{1,A}$ | 0.1253 | 0.1247 | 0.1191 | 0.1265 | 0.1251 | 0.1192 |
| $k_{2,B}$ | 0.0109 | 0.0108 | 0.0106 | 0.011 | 0.0109 | 0.0106 |
| $k_{1,B}$ | 0.0975 | 0.0984 | 0.1022 | 0.0956 | 0.0969 | 0.1036 |
| $\sigma$ | 0.0992 | 0.0991 | 0.0993 | 0.0998 | 0.0999 | 0.1 |
| $W(0)$ | 0.1977 | 0.1977 | 0.1977 | 0.1977 | 0.1977 | 0.1977 |
| $\gamma$ | 1e-04 | 0.0011 | 0.0021 | 1e-04 | 0.0011 | 0.002 |
| Synergistic | 5.60% | 54.00% | 99.30% | 7.50% | 75.20% | 100% |

$\gamma$; synergy parameter; $k_{1,A}$, killing rate, drug A; $k_{1,B}$, killing rate, drug B; $k_{2,A}$, drug efficacy parameter, drug A; $k_{2,B}$, drug efficacy parameter, drug B; $\lambda$, proliferating cell growth rate; $\sigma$, common variance; $W(0)$, initial tumor weight.

## Example




## Conclusion

- We report a novel statistical method that directly tests synergistic effects using tumor-growth data generated in vivo.
- Synergistic effect is evaluated simply by testing whether the synergy index parameters are statistically significant
- The model has potential to include drug-concentration data from a pharmacokinetic analysis

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