

## A minimal PKPD model to evaluate synergic effects of combined non small cell lung cancer therapies

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### Organisation

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## SCOPE OF THE METHOD

<b>The Method relates to</b>	Human health
<b>The Method is situated in</b>	Regulatory use - Routine production, Translational - Applied Research
<b>Type of method</b>	In silico

## DESCRIPTION

### Method keywords

Antiangiogenic therapy  
Immunotherapy  
Radiotherapy  
Variability  
Synergy modelling  
Anomalous diffusion  
Fractal kinetics

### Scientific area keywords

Mathematical modelling  
Lung cancer  
Mouse data  
Multiple therapy

### Method description

This is a mathematical compartmental formulation of dose-effect synergy modelling for multiple therapies in Non Small Cell Lung Cancer (NSCLC): antiangiogenic, immuno- and radiotherapy. The model formulates the dose-effect relationship in a unified context, with tumor proliferating rates and necrotic tissue volume progression as a function of therapy management profiles. The model accounts for inter- and intra-response variability by

using surface model response terms. Slow acting peripheral compartments such as fat and muscle for drug distribution are not modelled. This minimal Pharmacokinetic-Pharmacodynamic (PKPD) model is evaluated with reported data in mice from literature and demonstrates physiological value. Furthermore, the model can be used to study therapy management protocols and is an aiding tool in the clinical decision making process. Although developed with data from mice studies, the model is scalable to NSCLC patients.

### **Lab equipment**

No

### **Method status**

Published in peer reviewed journal

## **PROS, CONS & FUTURE POTENTIAL**

### **Advantages**

The proposed PKPD model is minimal and simple which provides a good overview of essential features necessary to be introduced, such as effect sites, isobole surface models of interaction, degree of synergy among drugs and patient response to treatment (i.e., drug resistance). The model is directly scalable to diagnosed/treated NSCLC patients.

### **Challenges**

The toxicity and risk of Radiation Pneumonitis (RP) affecting the healthy tissue in proximity of tumor volume voxel during RT treatment are not included in this model. Tissues with heterogeneous density have non-homogeneous drug distribution, hence drug trapping occurs. This can be modelled in PK compartmental formulation by adding a memory term, able to characterize long tail dynamics of drug release. The challenge to accommodate this in our model is the multi-scale pathway.

### **Modifications**

When available, the numerical values introduced in the model parameters were assumed from literature. However, several parameters were not available, so the study introduced variability to assess their effect. The results suggest this is a fairly sensible model to be further calibrated on experimental data.

### **Future & Other applications**

Such a minimal PKPD model once calibrated for the patient at hand, hence addressing the personalised medicine concept, can be used for evaluating various combination therapies. The model is successfully used to predict RP incidence in NSCLC treated with SBRT in patients. In view of time, cost and patient-related risks associated with unique emergency situations (e.g., pandemic outbreak), their relevance in regulatory decision-making on dose modification becomes crucial.

## **REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION**

### **References**

Ionescu C. M., Ghita M., Copot D., Derom E. and Verellen D. A Minimal PKPD Interaction Model for Evaluating Synergy Effects of Combined NSCLC Therapies. J. Clin. Med. 2020, 9, 1832; doi:10.3390/jcm9061832

### **Links**

## A Minimal PKPD Interaction Model for Evaluating Synergy Effects of Combined NSC...

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