How Anti-cancer Targeted Therapies Used in Combination Interact: Analysis with a Semi-Mechanistic Model of Minimal Signalling Networks

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Introduction

- **Targeted agents:**
  - Specific inhibitors of signalling pathways used in oncology to counteract tumour proliferation and angiogenesis.
  - Efficient and safe alternative or complement to cytotoxic chemotherapies [1].
- **Cross-talks between signalling cascades:** Over-activation of one pathway after the blockade of another one by a targeted agent.
- **Rationale to combine several targeted agents:** to block several pathways at once and avoid cross-talks.

Objectives

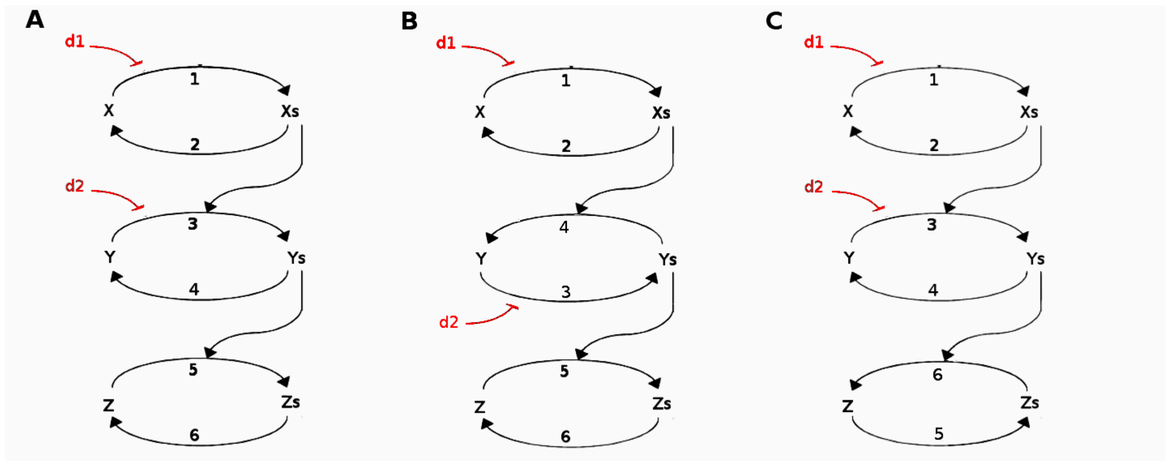
- **Explore response surfaces to a combination of targeted therapies in minimal signalling networks using a semi-mechanistic pharmacodynamic model.**
- **Apply a minimal model to data simulated from a complex signalling network.**

Methods

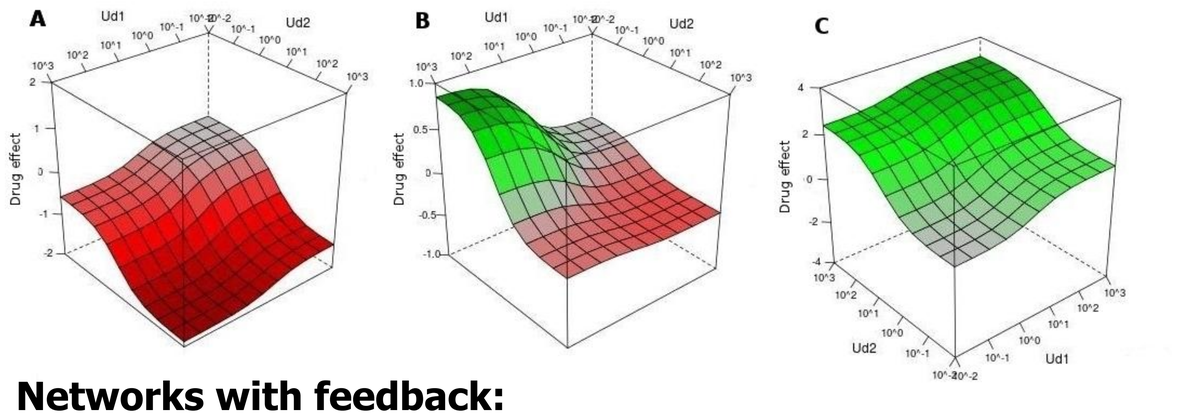
- **Minimal signalling networks:**
  - Interaction of 3 enzymes X, Y and Z (in either inactive or active state) on either serial or parallel pathway, with or without feedback loops.
  - 2 drugs D1 and D2, given as continuous infusions, inhibit the activations of X and Y respectively.
  - Response surfaces computed for each network: Ud1, Ud2, Zs.
    - Ud1 and Ud2: normalized drug concentrations.
    - Response: fraction of enzyme Z activated (Zs) at steady state.
- **Signalling network kinetics:**
  - System of 6 ordinary differential equations for each network.
  - 14 parameters.
  - Linear kinetics for activation and deactivation.
  - Drug inhibition described by Hill equations.
  - Enzyme catalysis described by saturable effect equations.
- **Application to complex signalling networks:**
  - Model describing Erb4-PI3K-AKT/Ras-Raf-ERK pathways [2].
  - Combination of Raf inhibitor (D1) and PI3K inhibitor (D2).
  - Simulation of ERK activation in response to different concentrations of both D1 and D2.
  - Parameter estimation using a minimal model in NONMEM 7.

Results

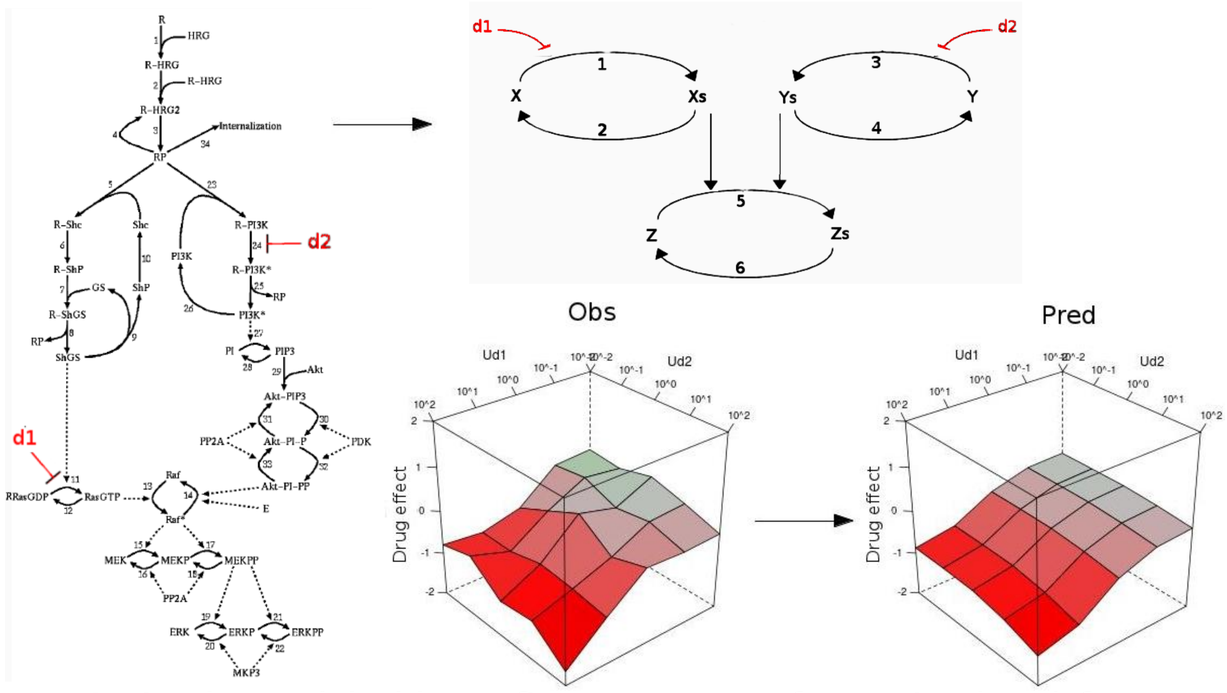
- **Networks without feedback:**
  - 32 different minimal networks including 16 non coherent networks (opposite overall effect of D1 and D2).
  - Each network generates different response surfaces (e.g networks A,B,C).



  - Amplitude of response stronger for serial than parallel networks.



- **Networks with feedback:**
  - 128 different minimal networks.
  - Sensitivity analysis to feedback strength:
    - **Positive feedback** enhances the amplitude and sigmoidicity of the response. A strong positive feedback leads to an all-or-none response as previously shown in [2].
    - **Negative feedback** lowers the overall sensitivity of the response. A strong negative feedback increases the delay to reach steady state and leads to no response from the network for the strongest feedbacks.
- **Application to simulated data:**
  - Best fit obtained with a parallel network in accordance with Hatakeyama's model structure. Our model discriminates between serial and parallel pathways.



  - A simple model able to fit response surfaces simulated from a more complicated model.
  - Goodness-of-fit plots does not invalidate our model.

Conclusions and Perspectives

- Even in a minimal setting (only 3 enzymes), the pathway structure may result in non-trivial response. It is therefore determinant to understand the signalling network and to identify potential cross-talks in order to optimize how targeted agents should be combined.
- Models including the pharmacokinetics of the targeted agents in combination and non-linear reaction kinetics will be investigated.
- Successful application to simulated data suggests the feasability to lump complex signalling pathway with limited loss of information.

References

[1] T. Bagnyukova, Chemotherapy and signalling: How can targeted therapies supercharge cytotoxic agents ? , Cancer. Biol. Ther. 2010 November 1; 10(9): 839:853.68(5) .
[2] M. Hatakeyama, S. Kimura, T. Naka, A computational model on the modulation of mitogen-activated protein kinase (MAPK) and Akt pathways in heregulin-induced ErbB signalling Biochem. J. (2003) 373, 451–463.
[3] J.E. Ferell Jr and E.M. Machleder. The biochemical basis of an all-or-none cell fate switch in xenopus oocytes. Science, 280(5365) :895-898, 1998.