Allometric scaling in oncology disease progression from xenograft tumor growth to human non-small-cell lung cancer

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Objective

- **Derive allometric conversion between published models on mouse and human tumor growth**
  - **Mouse: Xenograft TGI by Simeoni et al.**
  - **Human: NSCLC tumor growth by Wang et al.**

Introduction

- Disease progression model by Y. Wang and colleagues on human tumor growth[1]
  - One-dimensional growth
- Simeoni model[2] for mouse xenograft tumor growth widely used in preclinical experimentation
  - Volume (three-dimensional) growth
- Different dimensions complicate comparison
- An algebraic method is proposed to facilitate extrapolation

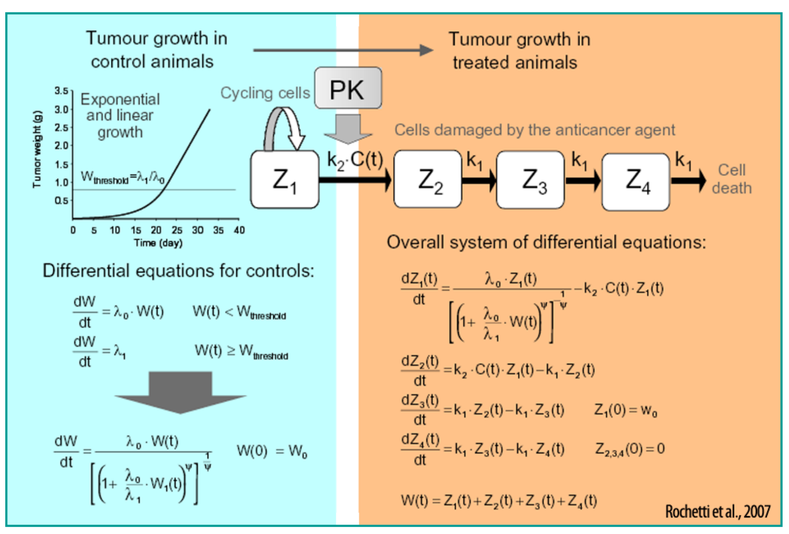
Wang model of human tumor growth

- Non-small-cell lung cancer (NSCLC)
- Clinical parameter for growth: one-dimensional tumor size
- Determined on the basis of CT scans
- 2-year follow-up on tumor size and survival
- Sum of the longest dimensions of individual tumors, reported in centimeters
- Model of linear growth with exponentially decaying drug effect

Mouse xenograft

- Nude mouse pharmacology model, inoculated with human cancer cell lines
- Tumor growth followed over weeks
- Tumor measured in two dimensions at the base of subdermal tumor
- Reported as volume after conversion to cubic mm
- Model developed by Simeoni et al.[2] and compared to clinical doses by Rochetti et al.[3]
- Differential equation system with an exponential followed by a linear growth phase, see Figure 1
  - Transit models applied to describe dying cells

Figure 1. Scheme and Equations of Tumor Growth Inhibition Model[2]



How to extrapolate Simeoni model to predict clinical timecourse?

- Volume versus length
- Empirical versus PK-PD
- Key: use only growth aspect
- Transform linear growth constant into linear part from Simeoni model using algebra (step 1)
- Convert from linear to differential equation system (step 2)
- Allometrically scale exponential part (step 3)

Step 1. Geometrical algebra on number of spheres

$$V(l) = 4/3\,\pi \cdot r^3 = 4/3\,\pi \cdot (shape \cdot l/2)^3$$
$$= \pi/6 \cdot shape^3 \cdot l^3$$

$$V_{n\,spheres} = n \cdot V(l/n) = n\,\pi/6 \cdot (l/n)^3$$
$$= \pi/6 \cdot \left(\frac{1}{n}\right)^2 l^3$$

$$\text{therefore}: shape^3 = \left(\frac{1}{n}\right)^2 \text{ and}$$
$$shape = n^{-2/3}$$

Step 2. Algebraic conversion from linear to differential equation model

$$V(l) = \pi/6 \cdot shape^3 \cdot l^3 = \gamma \cdot l^3, where\ \gamma = \pi/6 \cdot shape^3$$

Length/Wang:
$x0 = base$
$x1 = base + \Delta l$
$\Delta x = x1 - x0 = \Delta l$

Volume/TGI:
$V0 = \gamma \cdot base^3$
$V1 = \gamma \cdot (base + \Delta l)^3$
$\Delta V = V1 - V0 = \gamma \cdot \left[(base + \Delta l)^3 - base^3\right]$

$$\frac{\Delta V}{\gamma} = (base + \Delta l)^3 - base^3 = (b + \Delta l) \cdot \left(b^2 + 2b\Delta l + \Delta l^2\right) - b^3$$
$$= b^3 + 2b^2\Delta l + b\Delta l^2 + \Delta l b^2 + 2b\Delta l^2 + \Delta l^3 - b^3 = 3\Delta l b^2 + 3b\Delta l^2 + \Delta l^3$$
$$= 3\Delta l b^2 \left(1 + \frac{\Delta l}{b} + \frac{\Delta l^2}{3b^2}\right)$$
$$\Delta V = \gamma 3\Delta l b^2 \left(1 + \frac{\Delta l}{b} + \frac{\Delta l^2}{3b^2}\right) \approx \gamma 3\Delta l b^2$$

Step 2: lambda 1

- The 1-dimensional growth in Wang model is linear with time
- Corresponds with the linear phase of the Simeoni model
- In the Simeoni model, lambda1 to be replaced with rescaled version of the Wang constant (ΔV)
- Assuming perfect spheres and 5 individual spherical separate tumors as clinical extremes
- Take the average, than the shapefactor becomes $(5^{-2/3}+1)/2 = 0.691$
- The resulting lamda1, 0.638 g/day, seems sufficiently close to the Simeoni estimate with 0.331 g/day for the model to stay valid

Step 3: Allometric conversion of transit and exponential growth rate

- No clinical information available
- Allometric conversion as fall-back position
- Standard factor for rates is -0.25

$$k_{1,human} = k_{1,mouse} \bullet \left(\frac{BW_{man}}{BW_{mouse}}\right)^{-0.25}$$
$$l_{0,human} = l_{0,mouse} \bullet \left(\frac{BW_{man}}{BW_{mouse}}\right)^{-0.25}$$

Sensitivity to shape factor

- Lambda1 appears in a term without any multiplication
- The shapefactor therefore scales the absolute amplitude of volume predictions
- The shapefactor does not influence the predictions relative to baseline or placebo, or predictions in the 1-dimensional unit of length that Wang uses
- It is recommended to present results either in 1-dimensional length or emphasize the relative effect on growthn

Results

Comparison extrapolation to observed

- One drug modeled by Rochetti and Wang: docetaxel
- PK model for man obtained from literature[4]
- Rochetti model and parameters scaled according to steps 1-3, combined with human PK
- See figures 2 and 3
- The Wang model predicts continous disease progression
- Simeoni model allows full regression of tumor
- Therefore, only compare the models up to +- 6 months in docetaxel case, until Wang growth overtakes suppression
- Resulting inhibition relative to placebo at 25 weeks:
  - 55.6 % predicted by Wang
  - 55.0% predicted by the scaled Rochetti model

Figure 2. Predicted tumor size according to Y. Wang[1] and after scaling of Simeoni[3] model as described in steps 1-3 for docetaxel. The tumor size is shown in 1-dimensional units as defined in[1].

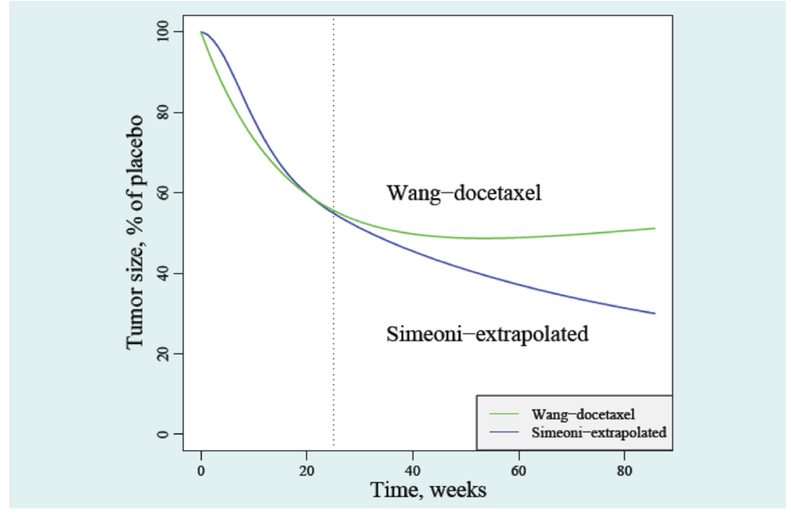
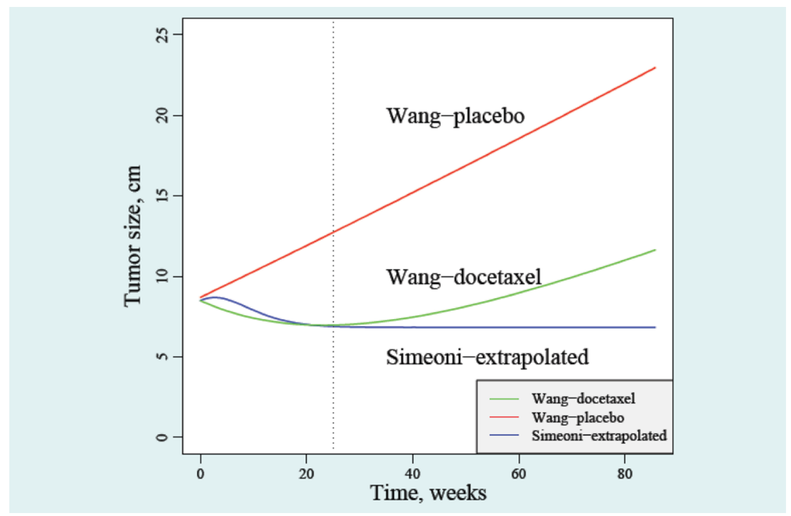


Figure 3. Predicted tumor size according to Y. Wang[1] and after scaling of Simeoni[3] model as described in steps 1-3 for docetaxel. The tumor size is shown relative to the placebo predictions of[1].



Discussion

- Check of extrapolation of Simeoni model with clinical results performed for one compound only
- While result is encouraging, database with substantially more compounds warranted before wider application
- Simeoni model assumes a *linear* growth phase as the limit
- Wang model assumes a *cubic* growth phase
- The derivation in steps 1-3 assumes a growth close to the original tumor size
- Ineffective treatments would result in larger growing tumors and would therefore violate the linearization assumption.
- Alternative approach: Force the Simeoni model to follow Wang growth by recalculation of lambda1 as a continuous function of tumor size
  - The growth equation becomes a second-order differential equation.
  - Sensitivity of the Simeoni fit to this particular property is yet unknown
- More effective treatments would switch the Simeoni model to the exponential growth phase
  - The allometric conversion of lambda0 consequently becomes important, resulting in a biphasic dose-response curve (not shown)

Further steps

- Future work might entail e.g.:
- Including predictions of other compounds
- Application to other models of clinical tumor growth
- Evaluation of Gompertz type of models for xenograft tumor growth

Conclusions

- **Conversion of Simeoni model to Y. Wang's growth parameters possible**
- **1-compound check positive: docetaxel mouse extrapolation in excellent agreement to Wang model (55.0 versus 55.6 %)**
- **Limitation 1: Conversion only valid when close to baseline volume**
- **Limitation 2: After half a year, docetaxel response started to be overtaken by linear growth according to Wang but not according to Simeoni model**

References

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3. Rocchetti M., Simeoni M., Pesenti E., De Nicolao G., and Poggesi I. (2007) Predicting the active doses in humans from animal studies: a novel approach in oncology. Eur. J. Cancer 43, 1862-1868.
4. Bosch T., Huitema A., Doodeman V., Jansen R., Witteveen E., Smit W., Jansen R., van Herpen C., Soesan M., Beijnen J., and Schellens J. (2006). Pharmacogenetic Screening of CYP3A and ABCB1 in Relation to Population Pharmacokinetics of Docetaxel Clin. Cancer Res. 12, 5786-5793

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