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
  - One-dimensional growth
- Simeoni model for mouse xenograft tumor growth widely used in preclinical experimentation
  - Volume (three-dimensional growth)
- Different dimensions coordinate 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. and compared to clinical doses by Rochetti et al.
- 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

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

\[ V(r) = \frac{4}{3} \pi r^3 \]
\[ V_{\text{base}} = \frac{\pi}{2} \cdot (2r) \cdot (2r) \]
\[ V'_{\text{base}} = \frac{\pi}{2} \cdot (3r) \]

Therefore:
- \( \text{shape} = \frac{3}{2} \)
- \( \text{shape} = \frac{4}{3} \)

Step 2. Algebraic conversion from linear to differential equation model

\[ V(t) = \pi / 6 \cdot \text{shape}^2 \cdot t^3 = \gamma \cdot t^3 \]

Where:\n- \( \gamma = \pi / 6 \cdot \text{shape}^2 \)
- \( V(t) \)
- \( x(t) \)
- \( V(t) = x(t)/\text{shape}^2 \)
- \( \text{shape}^2 = \frac{4}{3} \)

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, lambda to be replaced with rescaled version of the Wang constant (\( \lambda_0 \))
  - Assuming perfect spheres and 5 individual spherical separate tumors as clinical extremes
  - Take the average, that the shapefactor becomes (5 \( \text{shape}/1)+1=0.891 \)
  - The resulting lambda, 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 = 0.25

\[ k_{\text{trans}} = k_{\text{trans}} \text{shape} \]

Sensitivity to shape factor
- Lambda1 appears in 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 growth

Results

Comparison extrapolation to observed
- One drug modeled by Rochetti and Wang: docetaxel
- PK model for man obtained from literature
- Rochetti model and parameters scaled according to steps 1-3, combined with human PK
- See figures 2 and 3
  - The Wang model predicts continuous disease progression
  - Simeoni model allows full regression of tumor
  - Therefore, only compare the models up to \( t + 3 \) months in docetaxel case, until Wang growth overtakes suppression
  - Resulting inhibition relative to placebo at 25 weeks:
    - 55.8% predicted by Wang
    - 55.0% predicted by the scaled Rochetti model

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 lineazension assumption.
  - Alternative approach: Force the Simeoni model to follow Wang growth by recalibration 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 lambda1 consequently becomes important, resulting in a bimodal dose-response curve

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