Frequency-domain derived optimisation of treatment modalities for three tumour growth models

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The Netherlands

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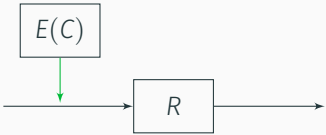
Model analysis in the time domain



Schulthess et al., *CPT Pharmacometrics Syst Pharmacol*, 7, 111–123, 2017

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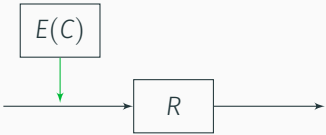

$$\frac{dC}{dt} = -k_e C$$
$$\frac{dR}{dt} = k_{\text{in}} \left(1 + \frac{E_{\max} C}{EC_{50} + C}\right) - k_{\text{out}} R$$

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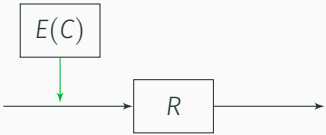

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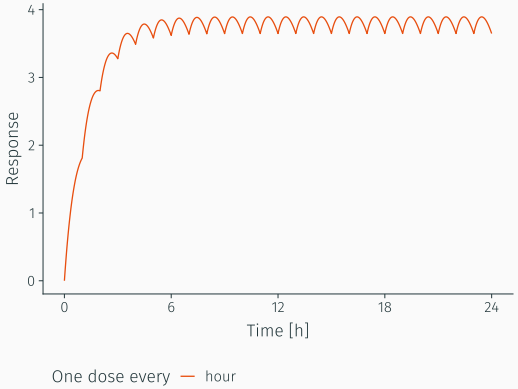

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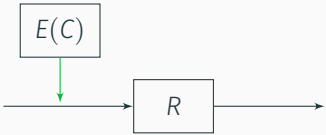

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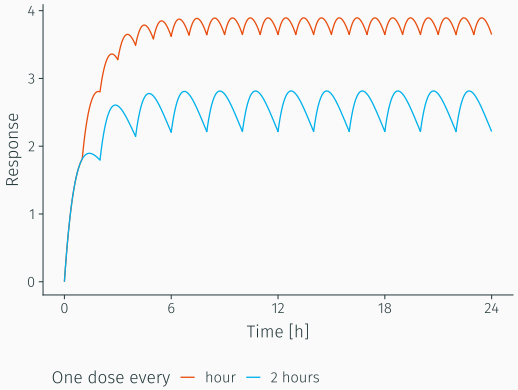

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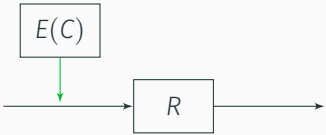

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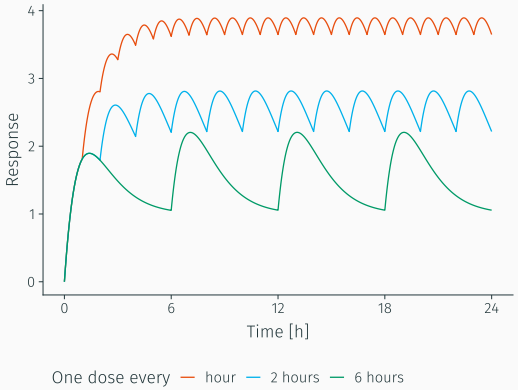

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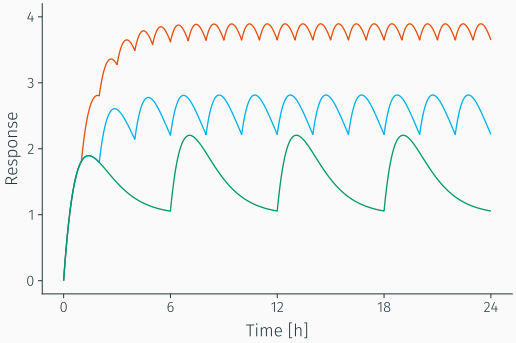
Model analysis in the frequency domain



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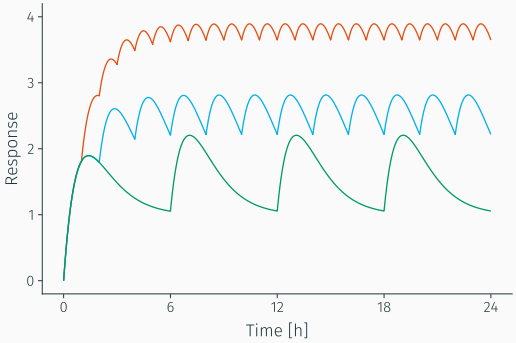

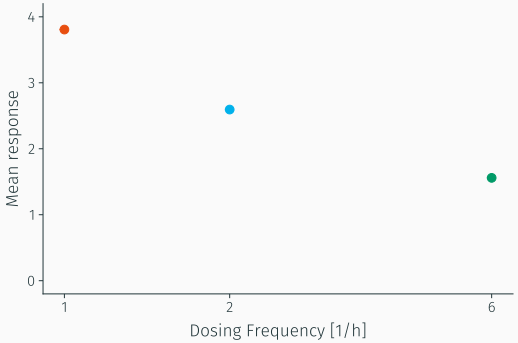

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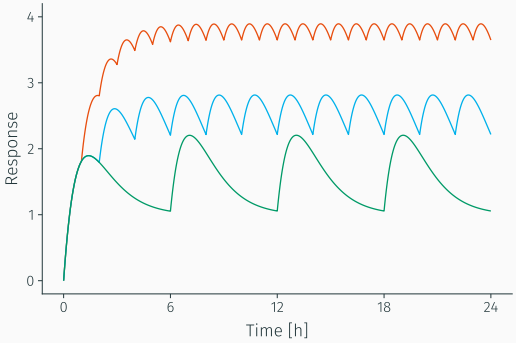

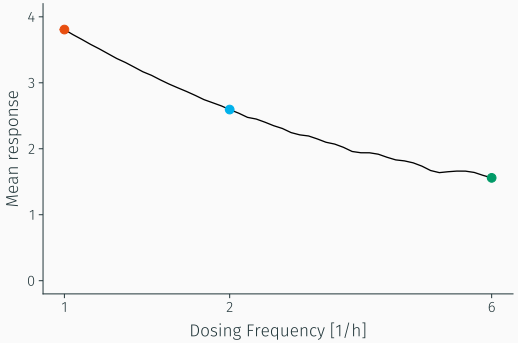

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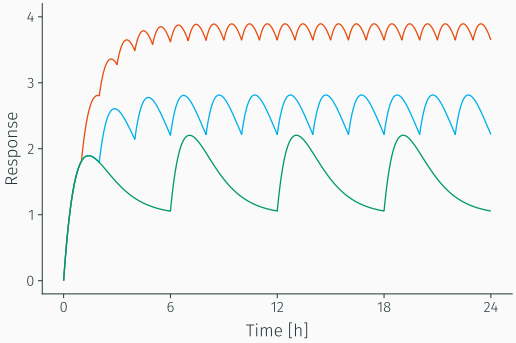

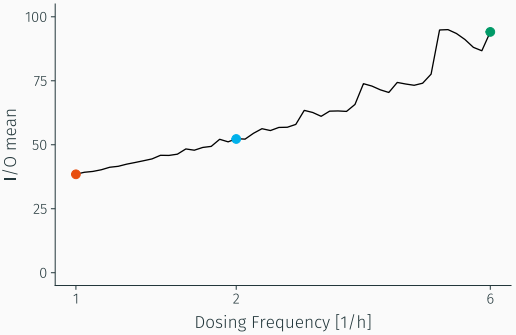

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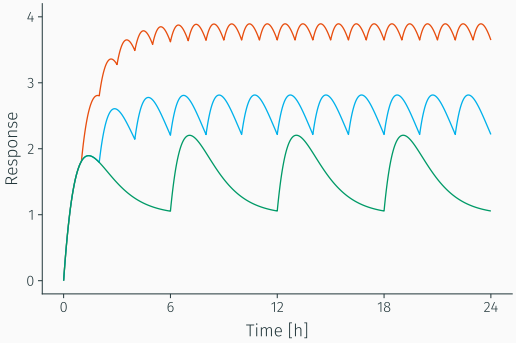

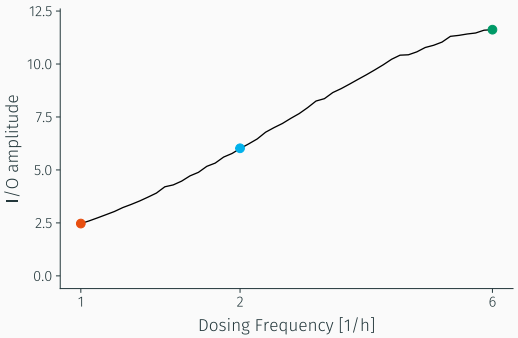

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Frequency-domain response analysis
(FdRA)

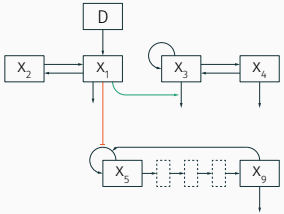
determines & visualises

the response of a dynamic system to periodic inputs.

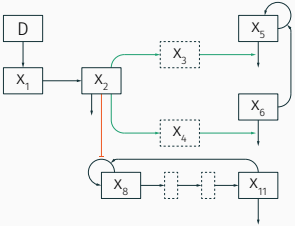
Frequency-domain derived optimisation of treatment modalities for three tumour growth models.

Tumour growth models

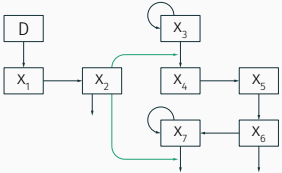
Cell-cycle specific



Metronomic



Acquired resistance



Tumour growth models

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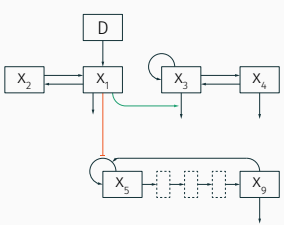

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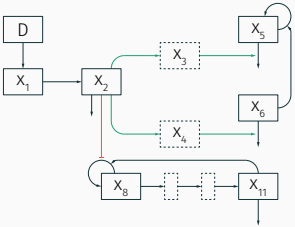
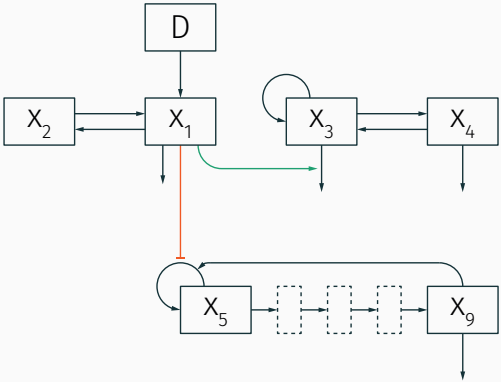


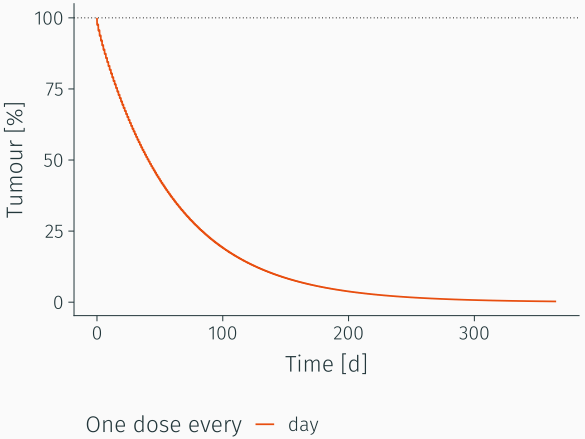
Acquired resistance

Cell-cycle specific tumour growth model



Zhu et al., *J Biomed Inform*, 57, 20–27, 2015

Tumour time course



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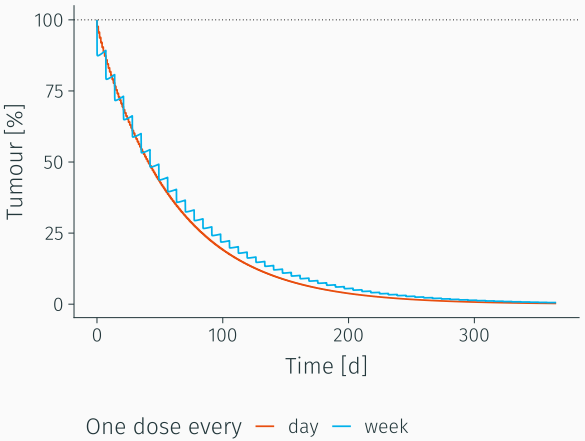

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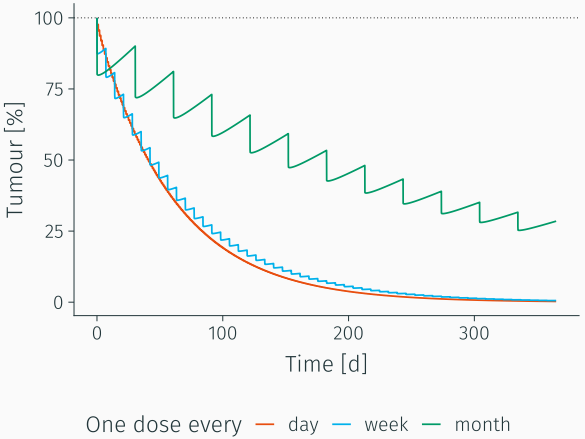

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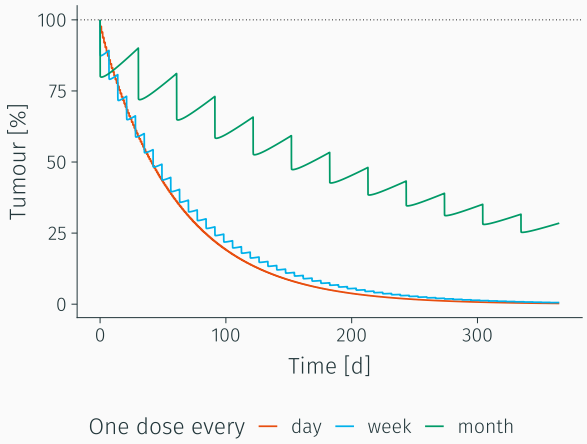

Result #1

- High-frequency dosing leads to best tumour reduction.

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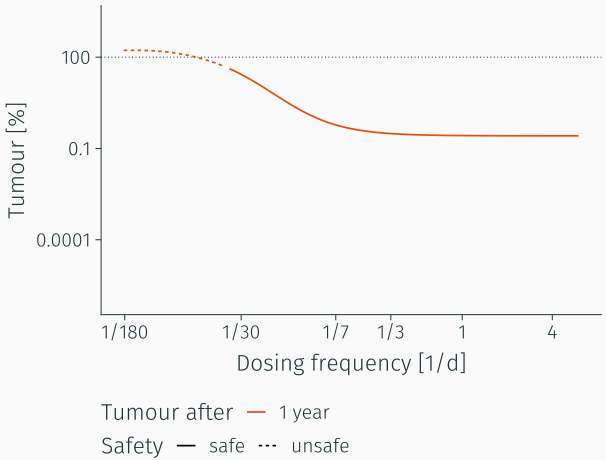
Tumour response to dosing frequency



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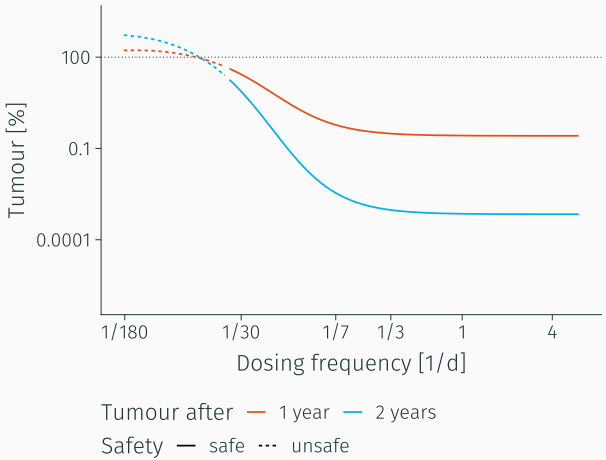

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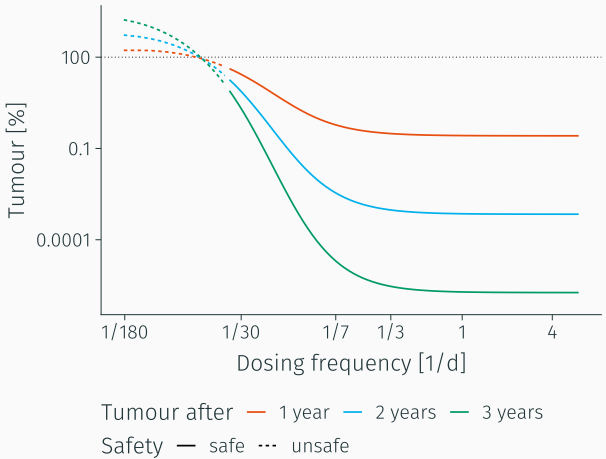

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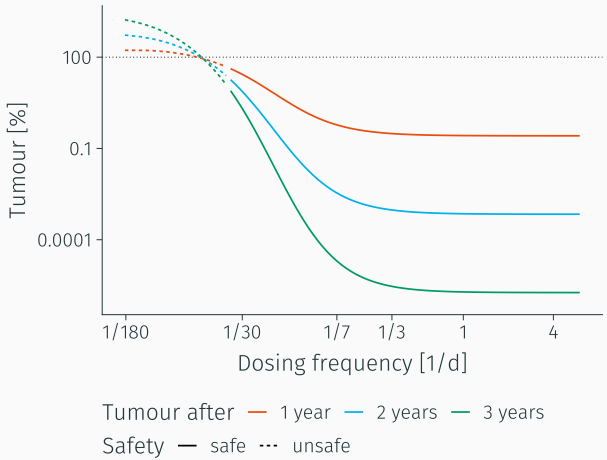
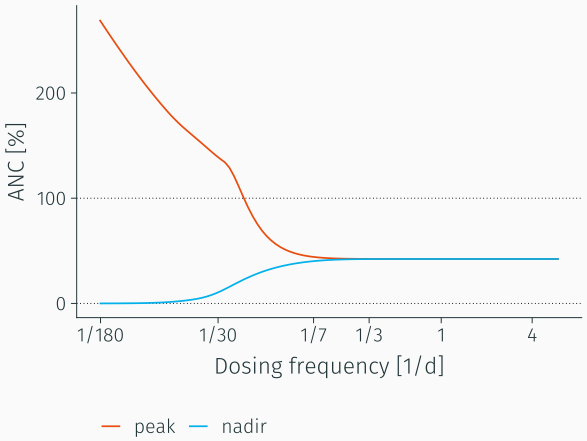


Result #2

- High-frequency dosing does not improve tumour reduction.
- Mid-frequency dosing sufficient.
- Low-frequency dosing predicted to be ineffective & unsafe.

Zhu et al., *J Biomed Inform*, 57, 20–27, 2015

ANC response to dosing frequency



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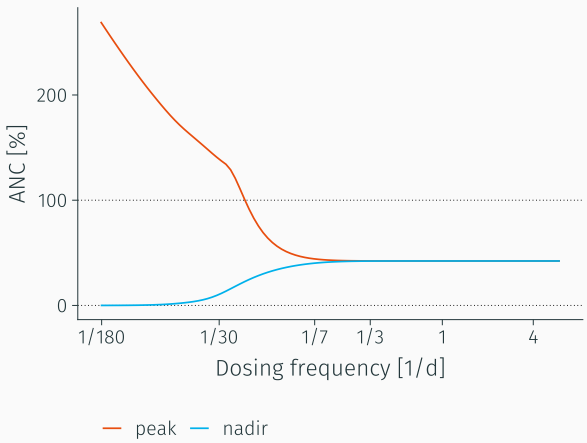

Result #3

- Mid-frequency dosing leads to rebound.
- Mid-frequency dosing avoids neutropenia.

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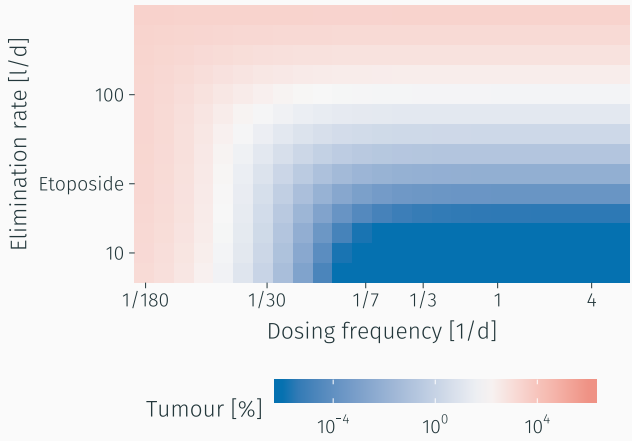
Tumour response to dosing frequency and elimination rate



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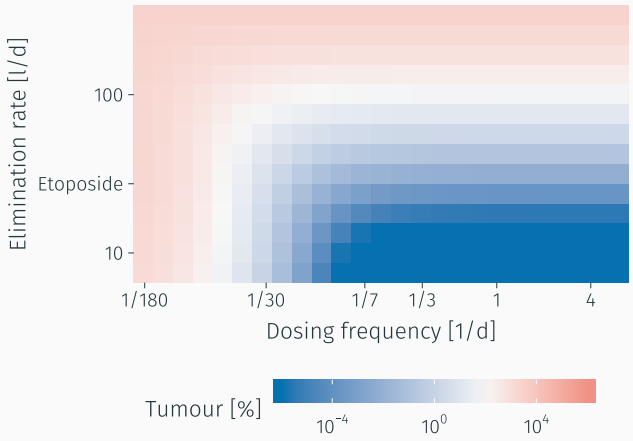

Result #4

- Reduced elimination rate improves tumour reduction.

Conclusion

Result #1

- High-frequency dosing leads to best tumour reduction.

Conclusion

Result #1

- High-frequency dosing leads to best tumour reduction.

Result #2

- Mid-frequency dosing sufficient, effective & safe.

Conclusion

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Zhu et al., *J Biomed Inform*, 57, 20–27, 2015

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Conclusion

- Mid-frequency dosing with a reduced elimination rate is optimal.

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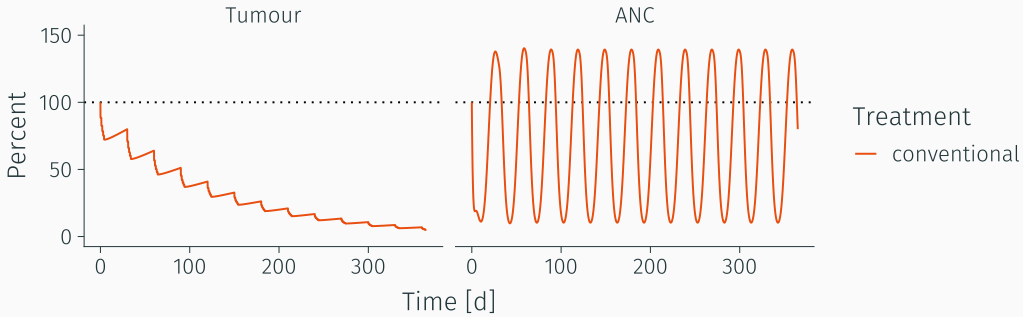

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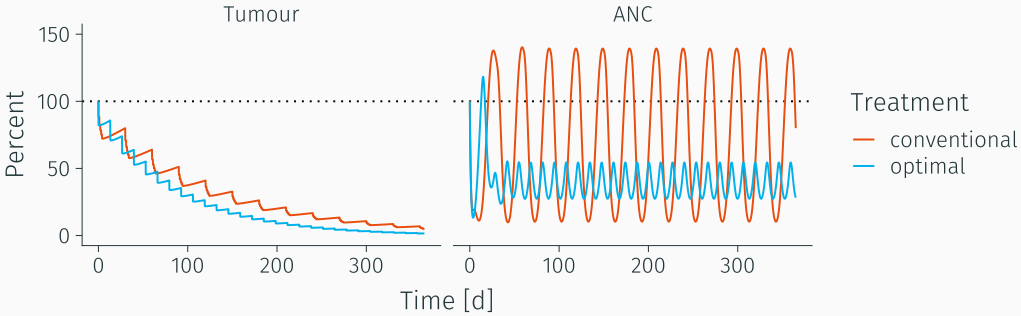

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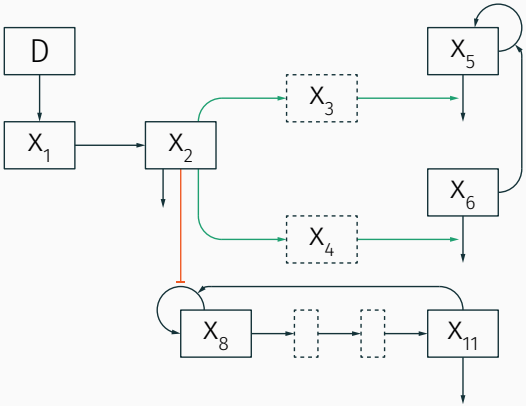
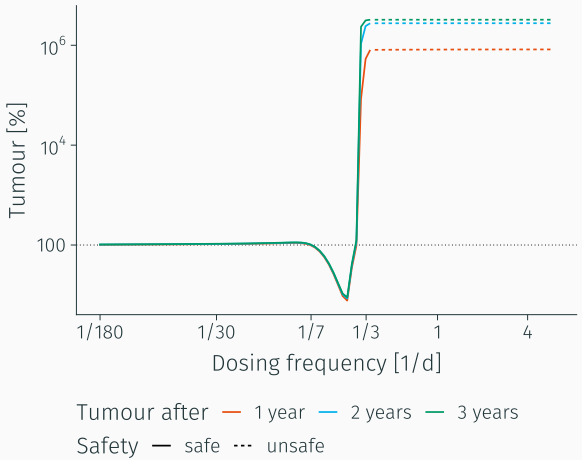
Metronomic chemotherapy model



Houy & Le Grand, *Journal of Theoretical Biology*, 446, 71–78, 2018

Tumour response to dosing frequency



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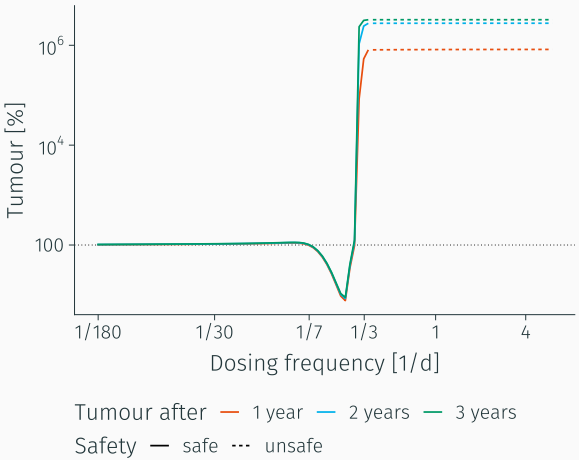
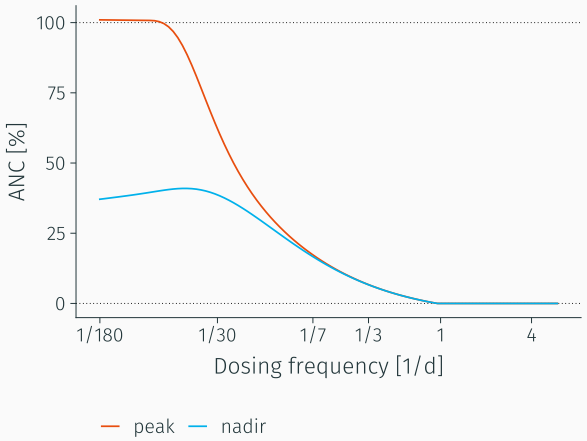


Result #1

- Mid-frequency dosing leads to tumour reduction.

Houy & Le Grand, *Journal of Theoretical Biology*, 446, 71–78, 2018

ANC response to dosing frequency



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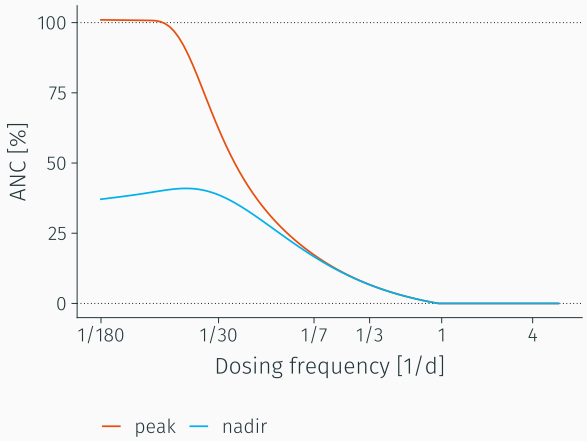
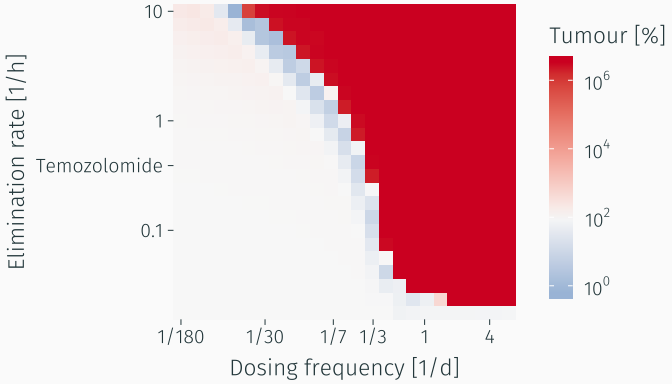


Result #2

- Low-frequency dosing leads to rebound.
- Low- and mid-frequency dosing avoids neutropenia.

Houy & Le Grand, *Journal of Theoretical Biology*, 446, 71–78, 2018

Tumour response to dosing frequency and elimination rate



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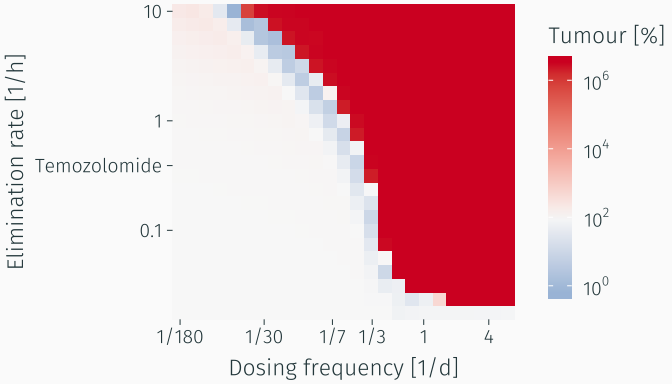
Tumour response to dosing frequency and elimination rate



Result #3

- Increased elimination rate improves tumour reduction.

Conclusion

Result #1

- Mid-frequency dosing leads to tumour reduction.

Conclusion

Result #1

- Mid-frequency dosing leads to tumour reduction.

Result #2

- Low- to mid-frequency dosing leads to rebound & avoids neutropenia.

Conclusion

Result #1

- Mid-frequency dosing leads to tumour reduction.

Result #2

- Low- to mid-frequency dosing leads to rebound & avoids neutropenia.

Result #3

- Increased elimination rate improves tumour reduction.

Conclusion

Result #1

- Mid-frequency dosing leads to tumour reduction.

Result #2

- Low- to mid-frequency dosing leads to rebound & avoids neutropenia.

Result #3

- Increased elimination rate improves tumour reduction.

Conclusion

- Low- to mid-frequency dosing with an increaced elimination rate is optimal.

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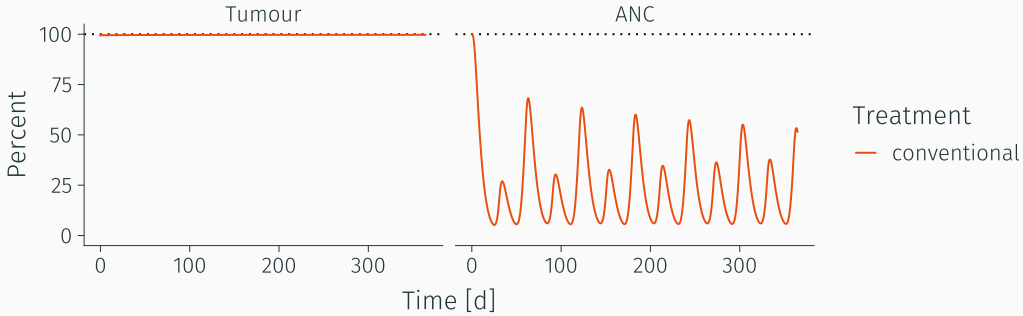

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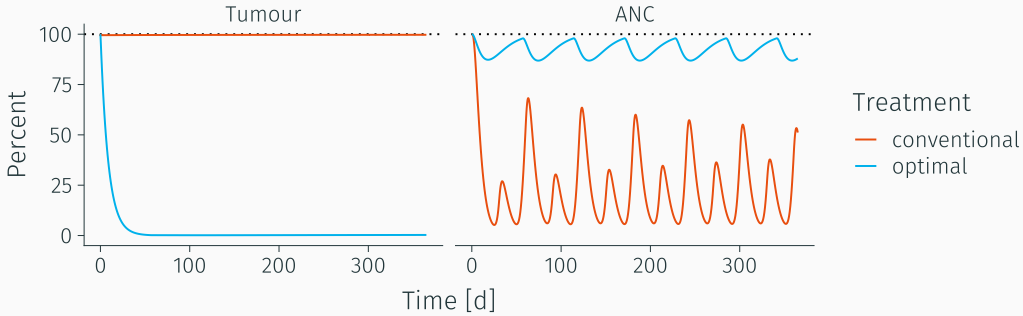
Conclusion

- Low- to mid-frequency dosing with an increaced elimination rate is optimal.



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Summary & outlook

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Numerical FdRA...

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- confirmed the conventional treatment regimen for the cell-cycle specific model.

Summary & outlook

Numerical FdRA...

- confirmed the conventional treatment regimen for the cell-cycle specific model.
- suggested a new treatment regimen for the metronomic chemotherapy model.

Summary & outlook

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