

Derivations of mathematical formulae

Equal f_v integral implies equal effectiveness

Assume exponential growth with a variable growth rate

$$\frac{dN}{dt} = r(t)N \quad (\text{S1})$$

which has the solution

$$N(t) = N_0 \exp \left[\int_0^t r(\xi) d\xi \right] \quad (\text{S2})$$

Let $r(t)$ have period τ s.t. $t = n\tau + \epsilon$ where $n \in [0, 1, 2, \dots]$ and $0 \leq \epsilon < \tau$, then

$$\int_0^t r(\xi) d\xi = n \int_0^\tau r(\xi) d\xi + \int_0^\epsilon r(\xi) d\xi. \quad (\text{S3})$$

Thus for two different rate functions $r_1(t)$ and $r_2(t)$, with the same period, whenever $\epsilon = 0$ that have been normalised such that

$$\int_0^\tau r_1(\xi) d\xi = \int_0^\tau r_2(\xi) d\xi. \quad (\text{S4})$$

We get

$$\int_0^t r_1(\xi) d\xi = n \int_0^\tau r_1(\xi) d\xi = n \int_0^\tau r_2(\xi) d\xi = \int_0^t r_2(\xi) d\xi \quad (\text{S5})$$

and their growth curves (S2) will thus follow the same long term trend

$$N(n\tau) = \exp \left[\int_0^{n\tau} r_1(\xi) d\xi \right] = \exp \left[\int_0^{n\tau} r_2(\xi) d\xi \right] \quad (\text{S6})$$

In our application $r(t)$ is given by $f_v(t)$.

Drug combinations can be more vulnerable to resistance

For simplicity we, treat drug concentrations as constant, which implies that their effect, f_v , is also constant.

This makes it simpler to compare treatments as we can safely ignore the integral (Equation S4). Equal f_v

alone implies equal effect under this assumption. Consider the effects of a 50:50 drug combination, where

both drugs have an equal unknown $\widetilde{\text{IC}}_{50}$ (i.e. mutant IC_{50} divided by native Bcr-Abl1 IC_{50}) for a mutation.

The concentrations C_1 and C_{12} below are given as multiples of the IC_{50} . The equal effect against wildtype normalisation condition implies that

$$f_v = \frac{1}{1 + C_1} = \frac{1}{1 + C_{12} + \frac{1}{4}C_{12}^2}. \quad (\text{S7})$$

From that it follows that the necessary concentration for the monodrug is

$$C_1 = \frac{1}{f_v} - 1 \quad (\text{S8})$$

and the necessary total concentration for the combination

$$C_{12} = \frac{2}{\sqrt{f_v}} - 2. \quad (\text{S9})$$

The combination is more vulnerable to resistance if the mutant grows faster at the drug concentrations specified by the above equation, i.e., if

$$\frac{1}{1 + \frac{(\frac{1}{f_v} - 1)}{\widetilde{\text{IC}}_{50}}} < \frac{1}{1 + \frac{\frac{1}{2}(\frac{2}{\sqrt{f_v}} - 2)}{\widetilde{\text{IC}}_{50}} + \frac{\frac{1}{2}(\frac{2}{\sqrt{f_v}} - 2)}{\widetilde{\text{IC}}_{50}^2} + \frac{\frac{1}{4}(\frac{2}{\sqrt{f_v}} - 2)^2}{\widetilde{\text{IC}}_{50}^3}} \quad (\text{S10})$$

which means

$$\frac{(\frac{1}{f_v} - 1)}{\widetilde{\text{IC}}_{50}} > \frac{(\frac{2}{\sqrt{f_v}} - 2)}{\widetilde{\text{IC}}_{50}} + \frac{(\frac{2}{\sqrt{f_v}} - 2)^2}{4\widetilde{\text{IC}}_{50}^2} \quad (\text{S11})$$

$$\frac{1}{f_v} - 1 > \frac{2}{\sqrt{f_v}} - 2 + \frac{(\frac{2}{\sqrt{f_v}} - 2)^2}{4\widetilde{\text{IC}}_{50}^2} \quad (\text{S12})$$

$$1 + \frac{1}{f_v} > \frac{2}{\sqrt{f_v}} + \frac{\frac{1}{f_v} - \frac{2}{\sqrt{f_v}} + 1}{\widetilde{\text{IC}}_{50}} \quad (\text{S13})$$

$$\widetilde{\text{IC}}_{50} > \frac{1 + \frac{1}{f_v} - \frac{2}{\sqrt{f_v}}}{1 + \frac{1}{f_v} - \frac{2}{\sqrt{f_v}}} \quad (\text{S14})$$

$$\widetilde{\text{IC}}_{50} > 1 \quad (\text{S15})$$

In other words the drug combination is less effective against the mutation than a monodrug therapy assuming it is equally effective against the wildtype so long as $\widetilde{\text{IC}}_{50} > 1$ (i.e., a resistant mutation). The effect is present so long as the mutant is approximately equally resistant towards both drugs, see Figure S1.

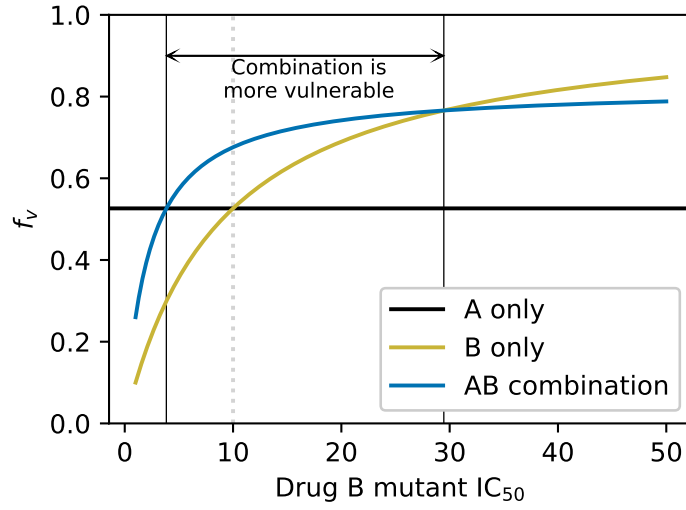


Figure S1: The doses of drug A and B were individually normalised to have the same effect on wildtype cells for each value of the drug B mutant IC_{50} . The growth rate of mutant cells is shown for each drug, calculated according to Equation 1 for A and B and Equation 3 for a drug combination AB, given the concentrations at each point provided by the effect normalisation against wildtype cells. Note the region where the combination has the highest mutant growth rate, implying a greater sensitivity towards the mutation.

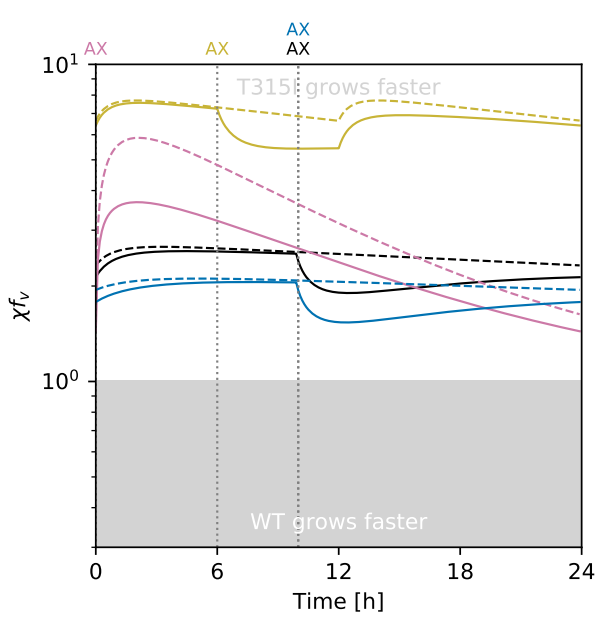
Solutions for Equations 9 and 10

For the exclusive case (Equation 9), letting $a := (IC_{50})_1$ and $b := (IC_{50})_2$ for brevity:

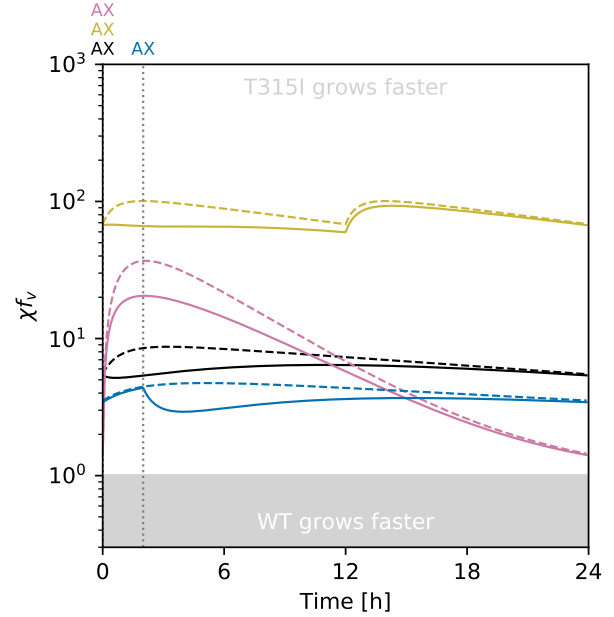
$$C = \frac{1}{\frac{x}{a} + \frac{1-x}{b}} = \frac{ab}{a - ax + bx}. \quad (\text{S16})$$

Similarly for the nonexclusive (Equation 10) case:

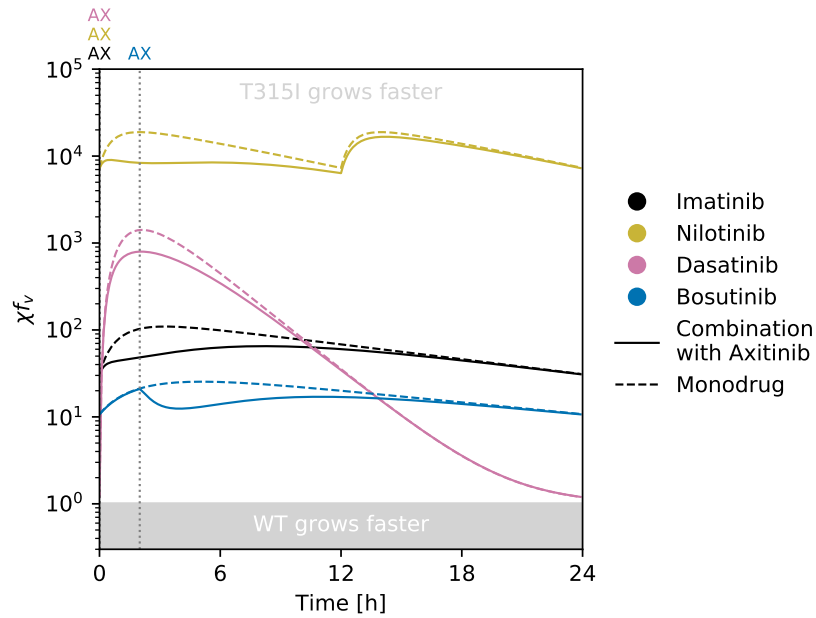
$$C = \frac{a - ax + bx + \sqrt{a^2(x-1)^2 - 6abx(x-1) + b^2x^2}}{2(x-1)x}. \quad (\text{S17})$$



(A) $m = 0.5$



(B) $m = 1$



(C) $m = 2$

Figure S2: Simulations of the effects of axitinib supplementation in a standard TKI treatment. The standard TKI is taken at $t = 0$ for imatinib, dasatinib and bosutinib, and at $t = 0$ and $t = 12$ for nilotinib. Axitinib administration is indicated by the vertical dotted lines and has been optimised to achieve the lowest average χ .

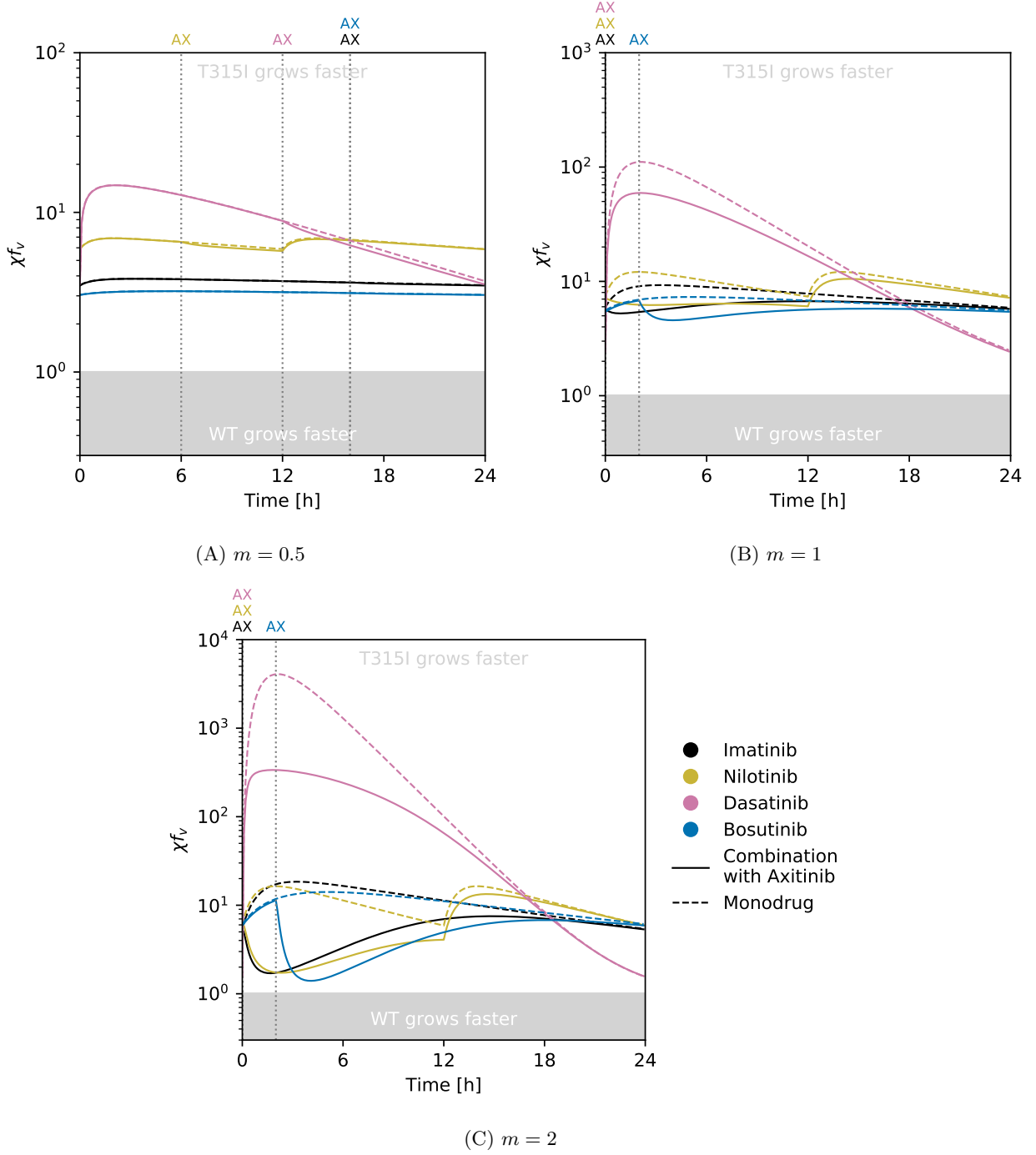
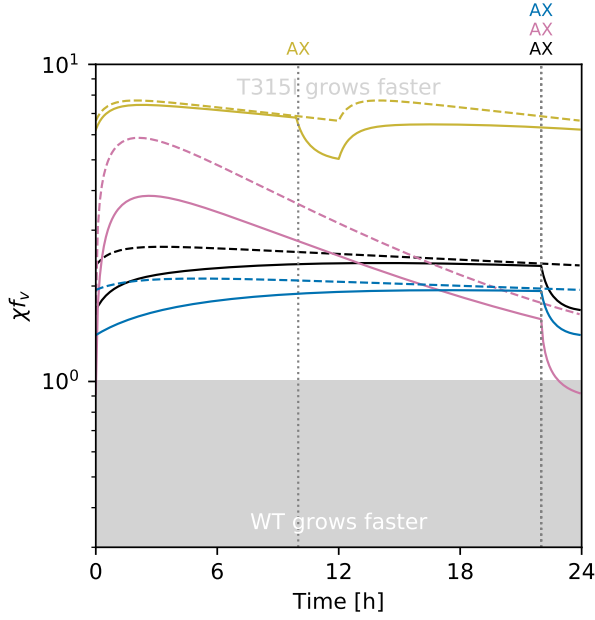
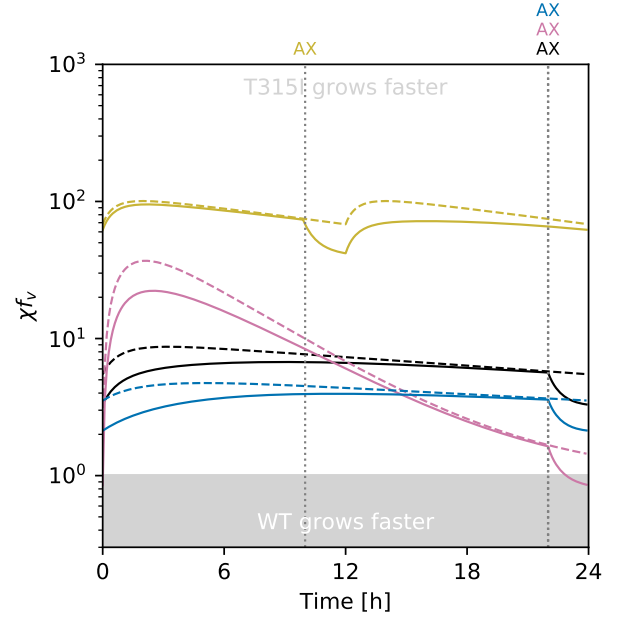


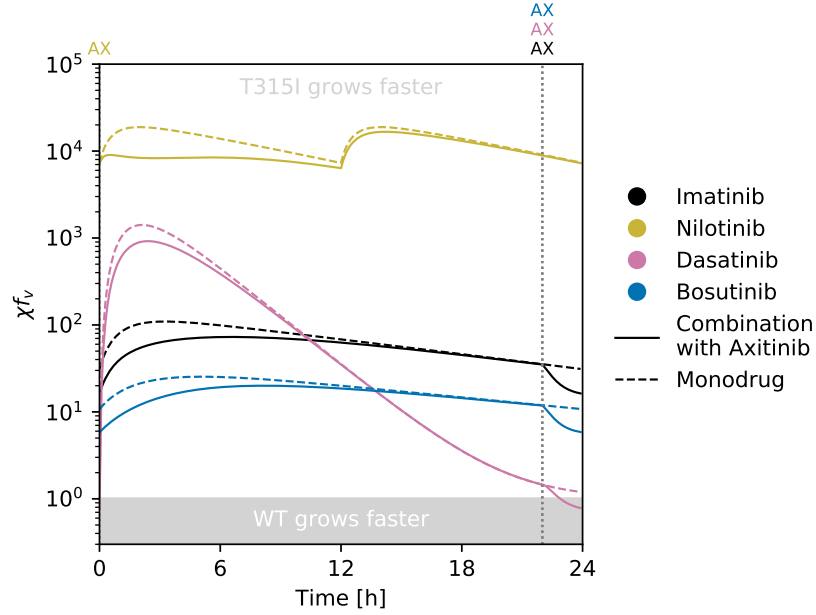
Figure S3: Simulations of the effects of axitinib supplementation in a standard TKI treatment. The standard TKI is taken at $t = 0$ for imatinib, dasatinib and bosutinib, and at $t = 0$ and $t = 12$ for nilotinib. Axitinib administration is indicated by the vertical dotted lines and has been optimised to achieve the lowest average χ . Treatment effects have been normalised such that imatinib, nilotinib, dasatinib and bosutinib cause a 90% growth reduction and axitinib causes a 5% growth reduction.



(A) $m = 0.5$

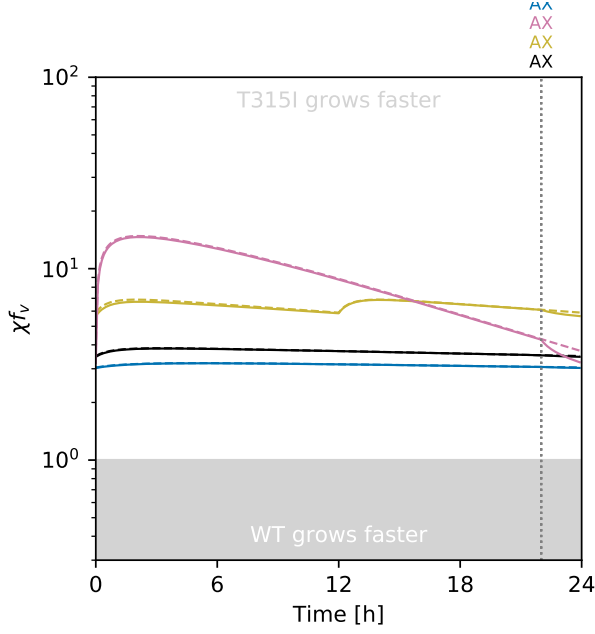


(B) $m = 1$

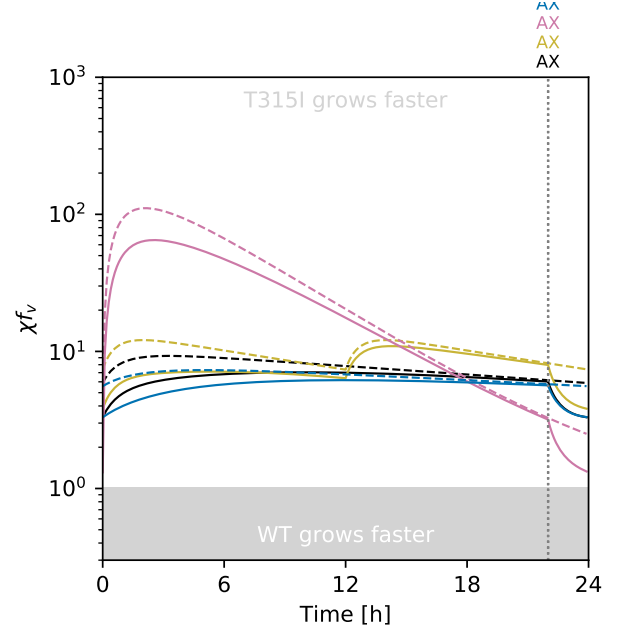


(C) $m = 2$

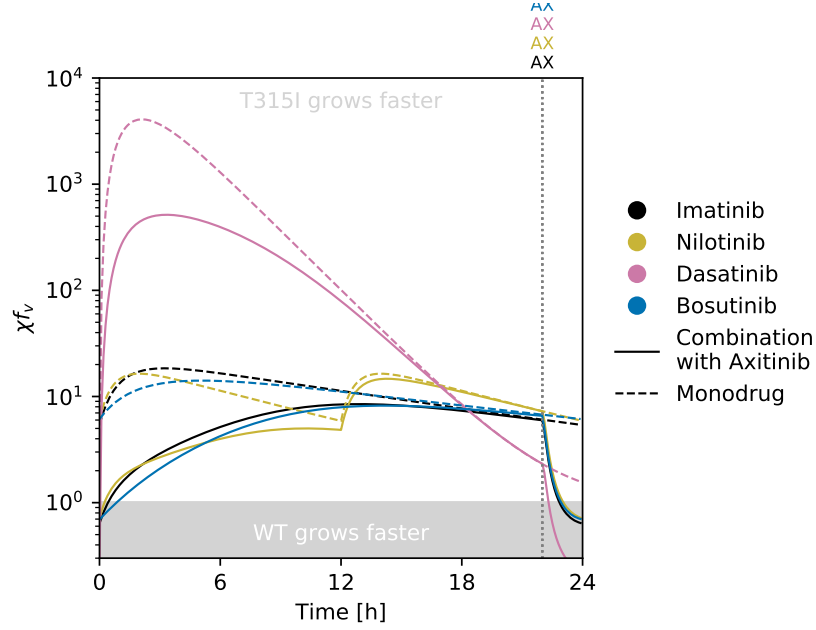
Figure S4: Simulations of the effects of axitinib supplementation in a standard TKI treatment. The standard TKI is taken at $t = 0$ for imatinib, dasatinib and bosutinib, and at $t = 0$ and $t = 12$ for nilotinib. Axitinib administration is indicated by the vertical dotted lines and has been optimised to achieve the instantaneous χ .



(A) $m = 0.5$



(B) $m = 1$



(C) $m = 2$

Figure S5: Simulations of the effects of axitinib supplementation in a standard TKI treatment. The standard TKI is taken at $t = 0$ for imatinib, dasatinib and bosutinib, and at $t = 0$ and $t = 12$ for nilotinib. Axitinib administration is indicated by the vertical dotted lines and has been optimised to achieve the lowest instantaneous χ . Treatment effects have been normalised such that imatinib, nilotinib, dasatinib and bosutinib cause a 90% growth reduction and axitinib causes a 5% growth reduction.

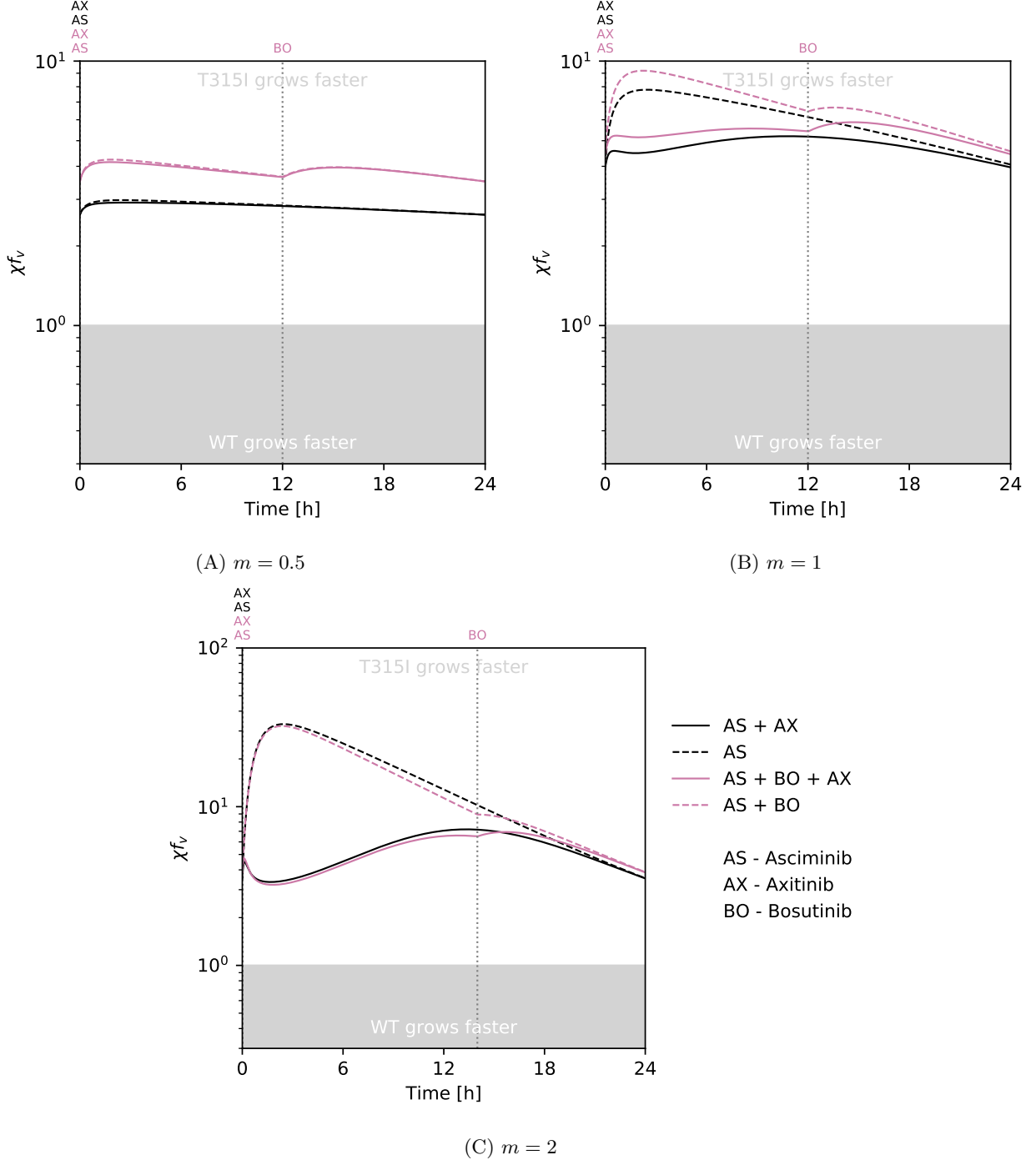
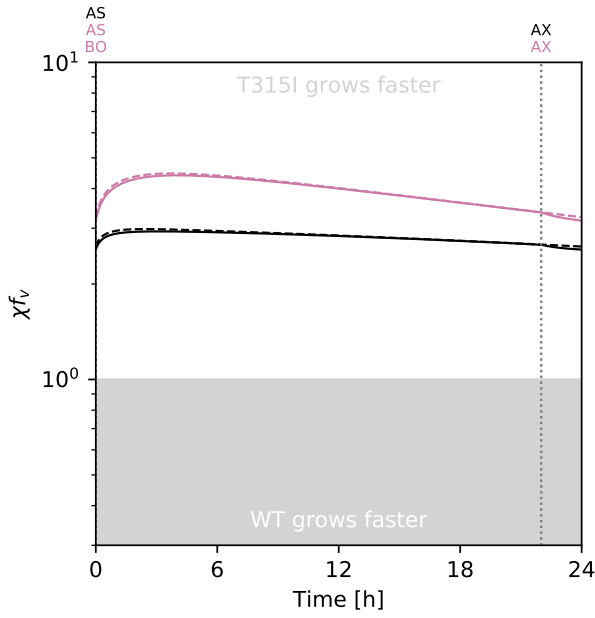
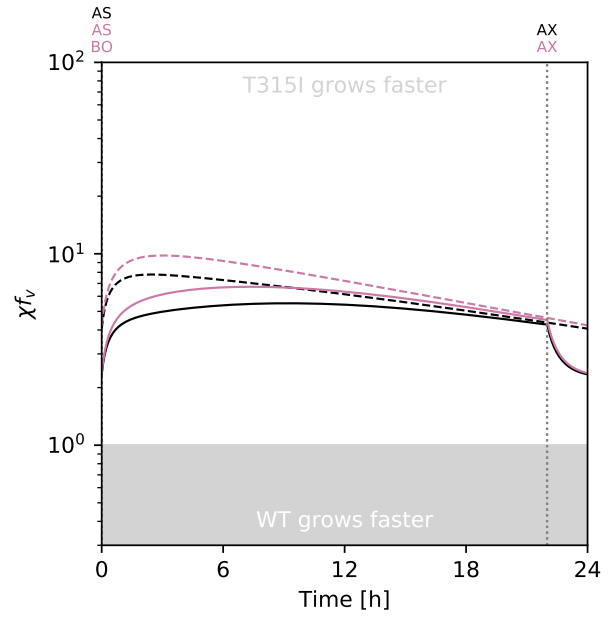


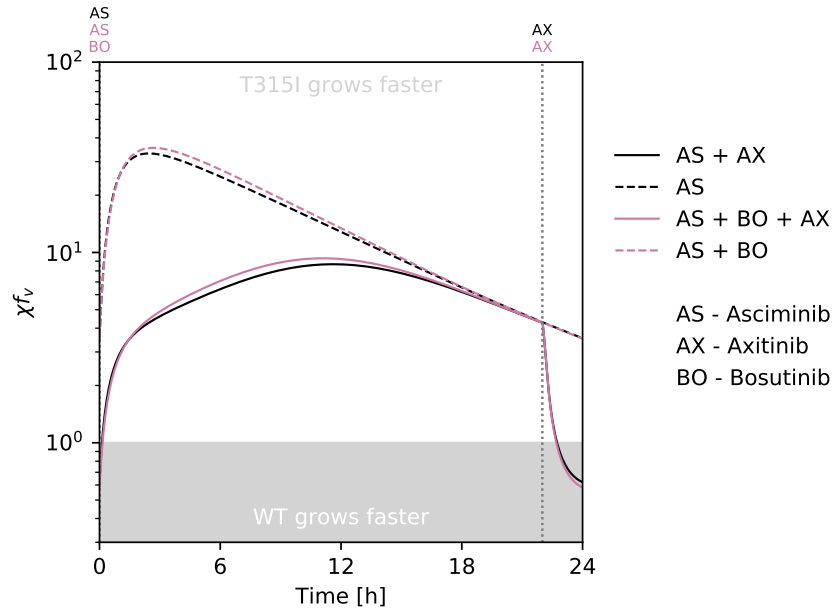
Figure S6: The effects of added axitinib to supplement a bosutinib and asciminib combination. Drug doses are normalised such that bosutinib–asciminib achieves 90% growth reduction together and axitinib achieves 5% growth reduction. Axitinib and asciminib (simultaneous is optimal) are administered at $t = 0$, bosutinib administration is indicated by the dotted vertical lines. All administration timings were optimised for minimum average χ .



(A) $m = 0.5$



(B) $m = 1$



(C) $m = 2$

Figure S7: The effects of added axitinib to supplement a bosutinib and asciminib combination. Drug doses are normalised such that bosutinib–asciminib achieves 90% growth reduction together and axitinib achieves 5% growth reduction. Bosutinib and asciminib are administered at $t = 0$, axitinib administration is indicated by the dotted vertical lines. All administration timings were optimised for minimum instantaneous χ .

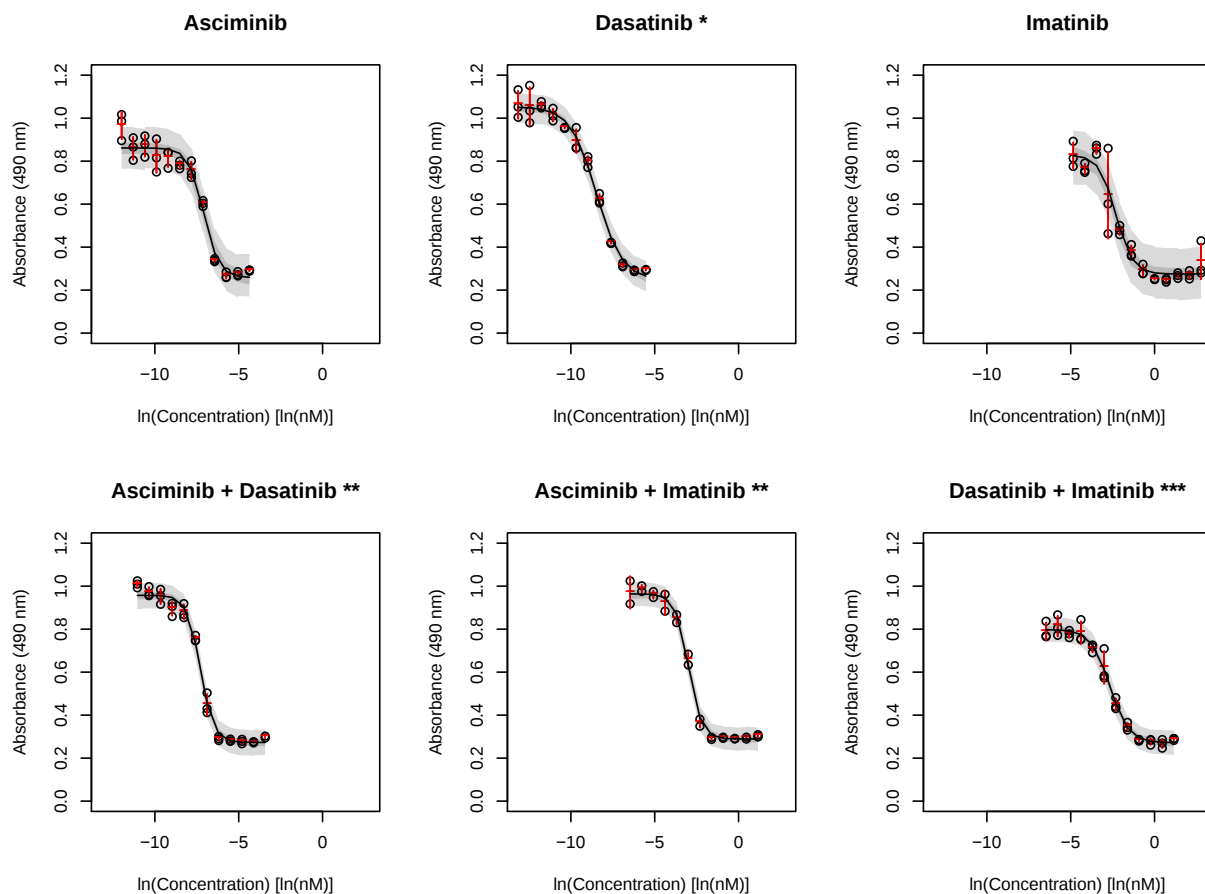


Figure S8: Dose response curves of KCL-22 cells cultured in the presence of a range of inhibitors. 490 nm absorbance using the Celltiter MTS assay correlates linearly with the number of viable cells. The red crosses indicate mean $\pm$ standard deviation of MTS assay results. The black line shows the mean, the light grey shaded region shows the 89% compatibility interval for posterior predictive simulations and the dark grey shaded region shows the 89% compatibility interval for the mean for the predicted dose response curve. Asterisks (*, ** and ***) indicate experiment batches, and incubation times varies slightly between them.