Supplementary Figures

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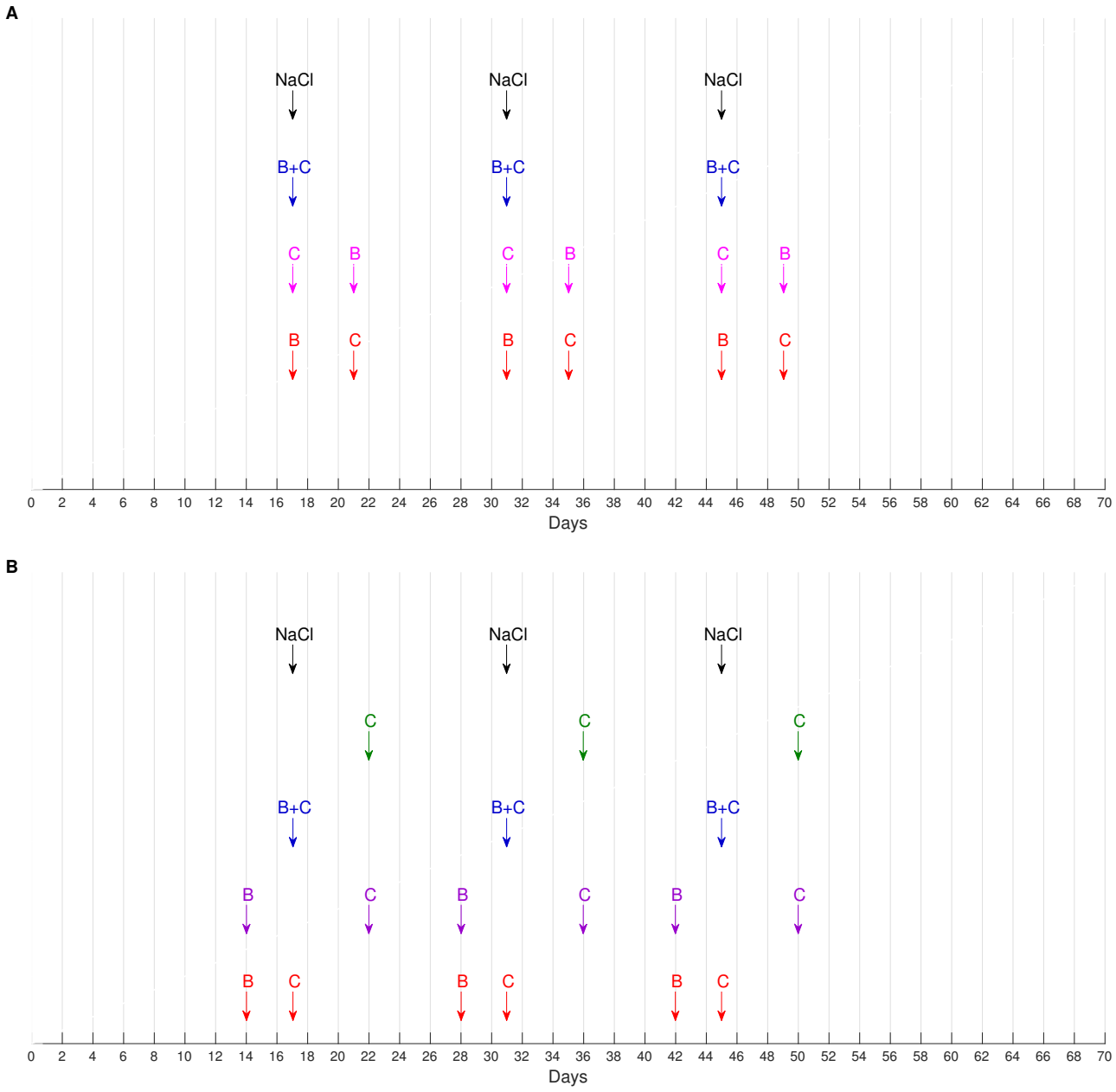
Figure S8: Individual tumor growth simulations

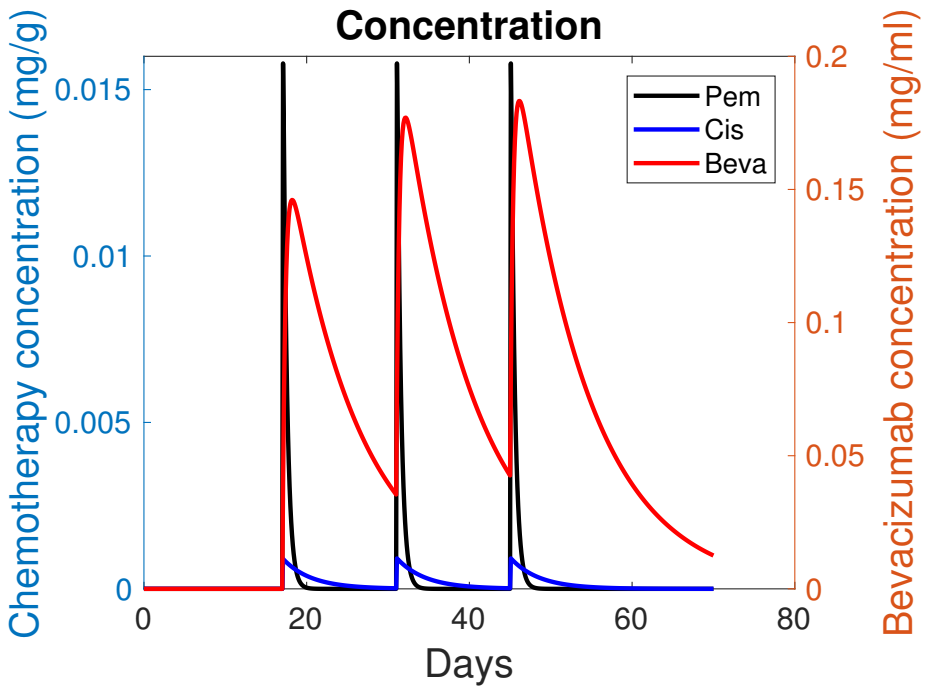
Figure S1: Design of experiments -1 and -2



Arrows indicate administration time.
A- Experiment-1 : Black arrows: Control group. Blue arrows: Concomitant group (”Beva + Chemo”). Magenta arrows: Reversed group with cytotoxics administered 4 days before bevacizumab (”Chemo then Beva 4 days”). Red arrows: Sequential group with bevacizumab administered 4 days before cytotoxics (”Beva then Chemo 4 days”).

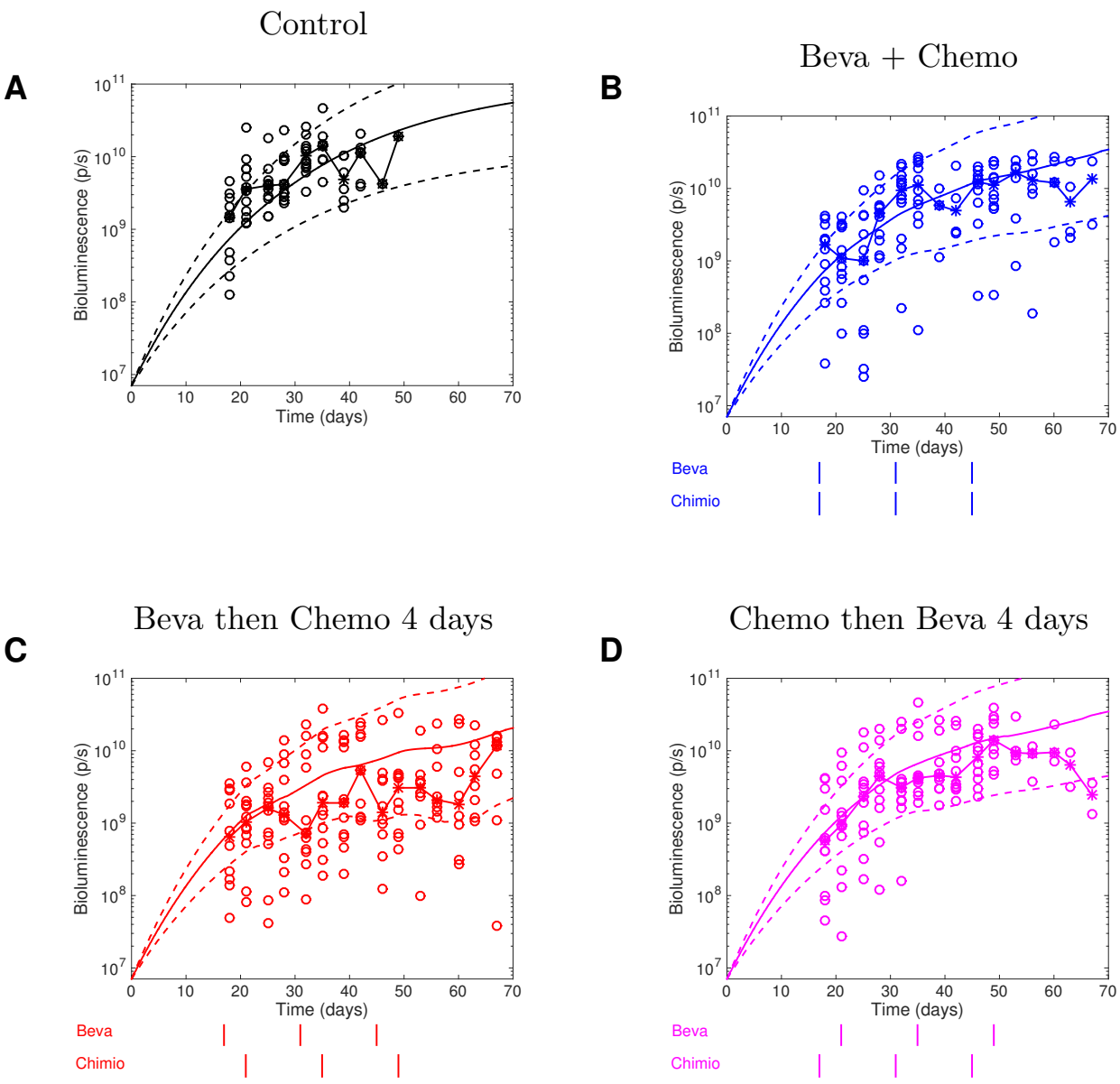
B- Experiment-2 : Black arrows: Control group. Green arrows: Cytotoxics only group (Chemo). Blue arrows: Concomitant group (”Beva + Chemo”). Purple arrows: Aberrant sequential group with bevacizumab administered 8 days before cytotoxics (”Beva then Chemo 8 days”). Red arrows: Optimized sequential group with bevacizumab administered 3 days before cytotoxics (”Beva then Chemo 3 days”)

Figure S2: Pharmacokinetic profiles



Pharmacokinetics profile of bevacizumab (red line), pemetrexed (black line) and cisplatin (blue line) for 3 treatment cycles (intra-peritoneal injections of 20, 100 and 3 mg/kg for bevacizumab, pemetrexed and cisplatin respectively).

Figure S3: Visual predictive checks of the Monolix fit



Visual predictive checks of the initial Monolix fit shows lack of descriptive power, especially for the “Beva then Chemo 4 days” group.
Circles: experimental data. Stars with broken lines: median data. Solid lines: tumor growth simulated curves using median parameter values, dashed lines: 95% intervals for inter-animal variability, generated from the simulation of 1000 virtual animals with parameters distributed according to the distribution estimated by the mixed-effects fit.

Figure S4: Monolix fit vs median data

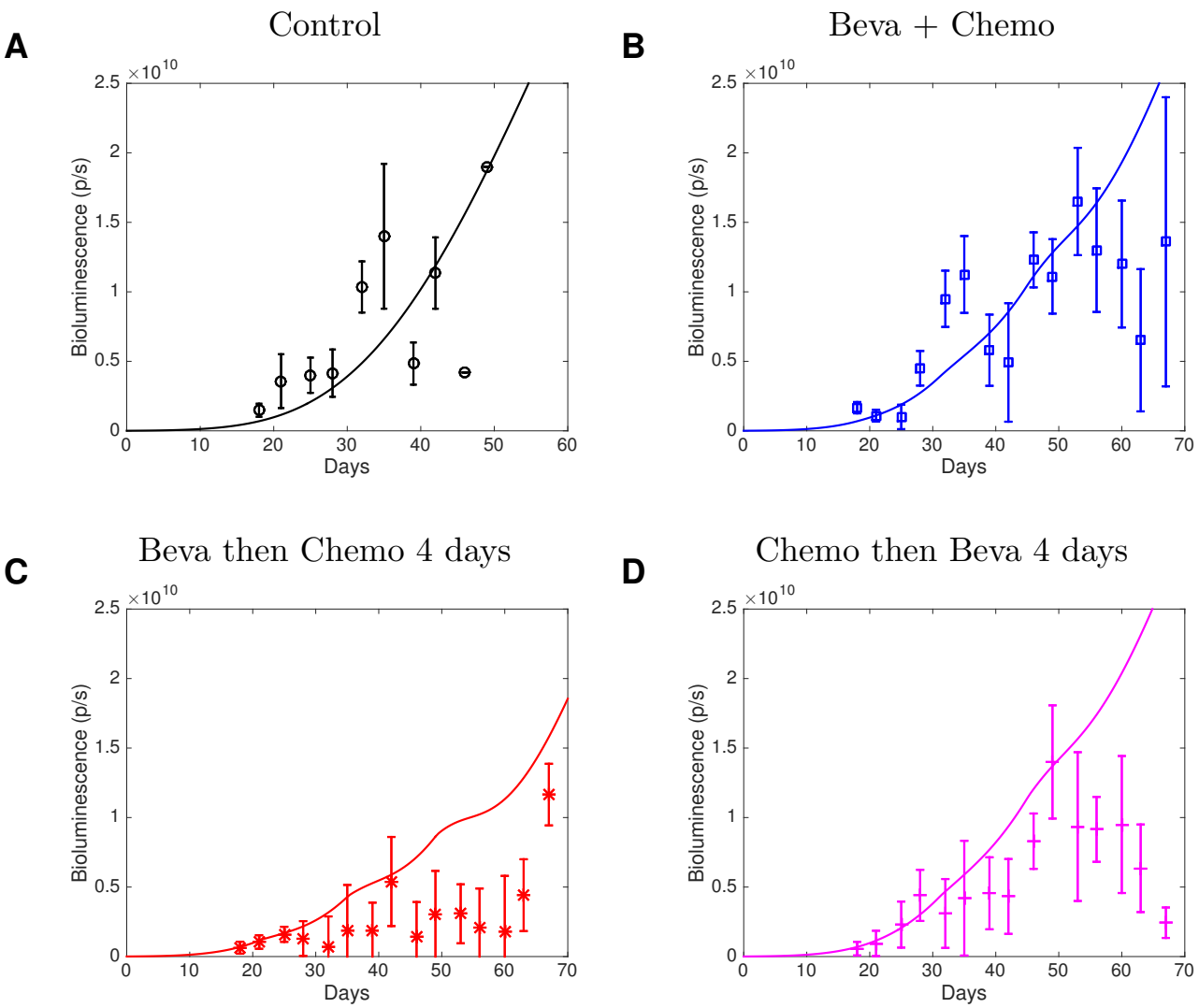
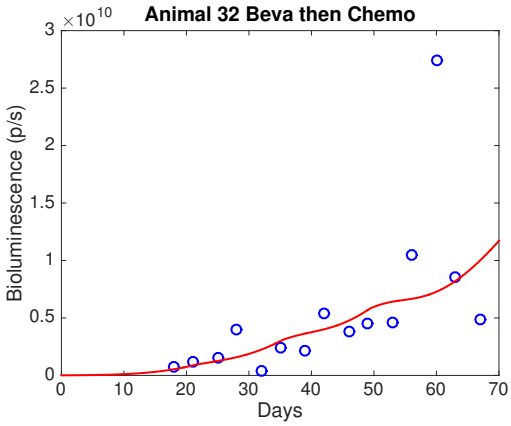


Figure S5: Individual fits of the animal that had the most important contribution to the likelihood

Monolix fit | **Adapted fit**

Animal 8 Beva then Chemo 4 days



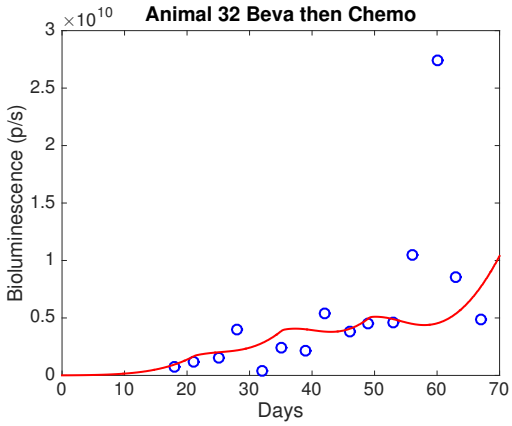


Figure S6: Adapted fit vs median data

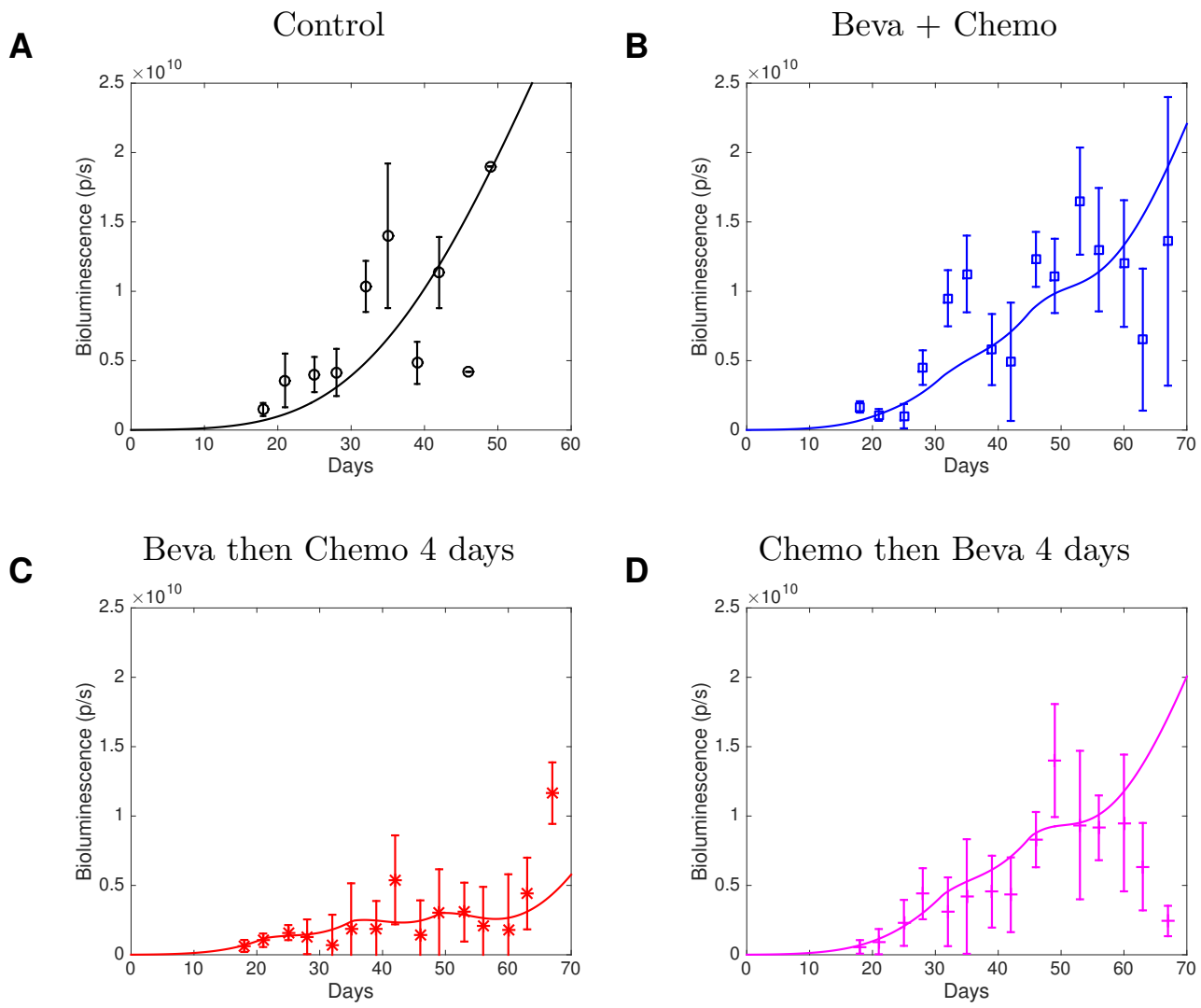
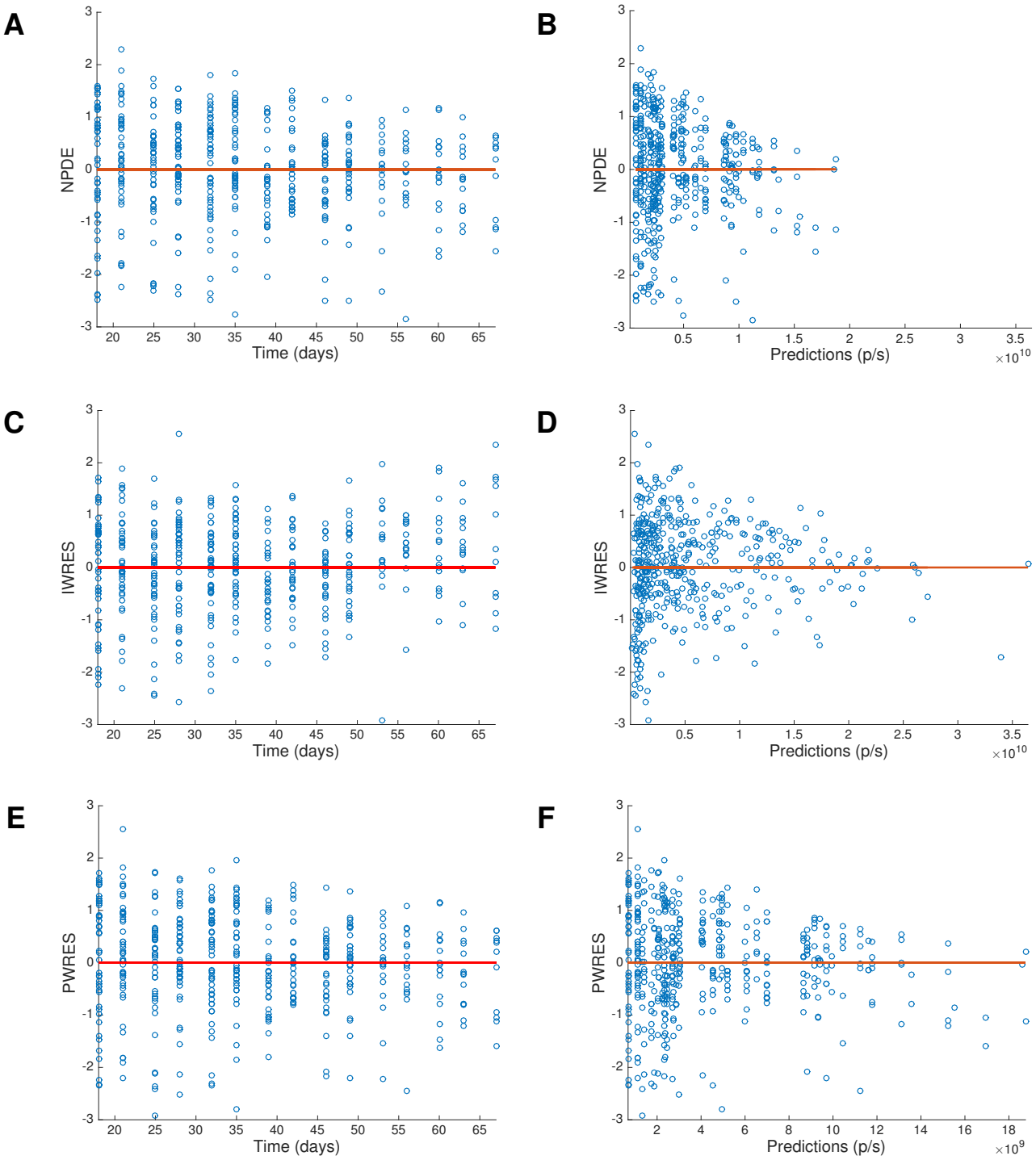
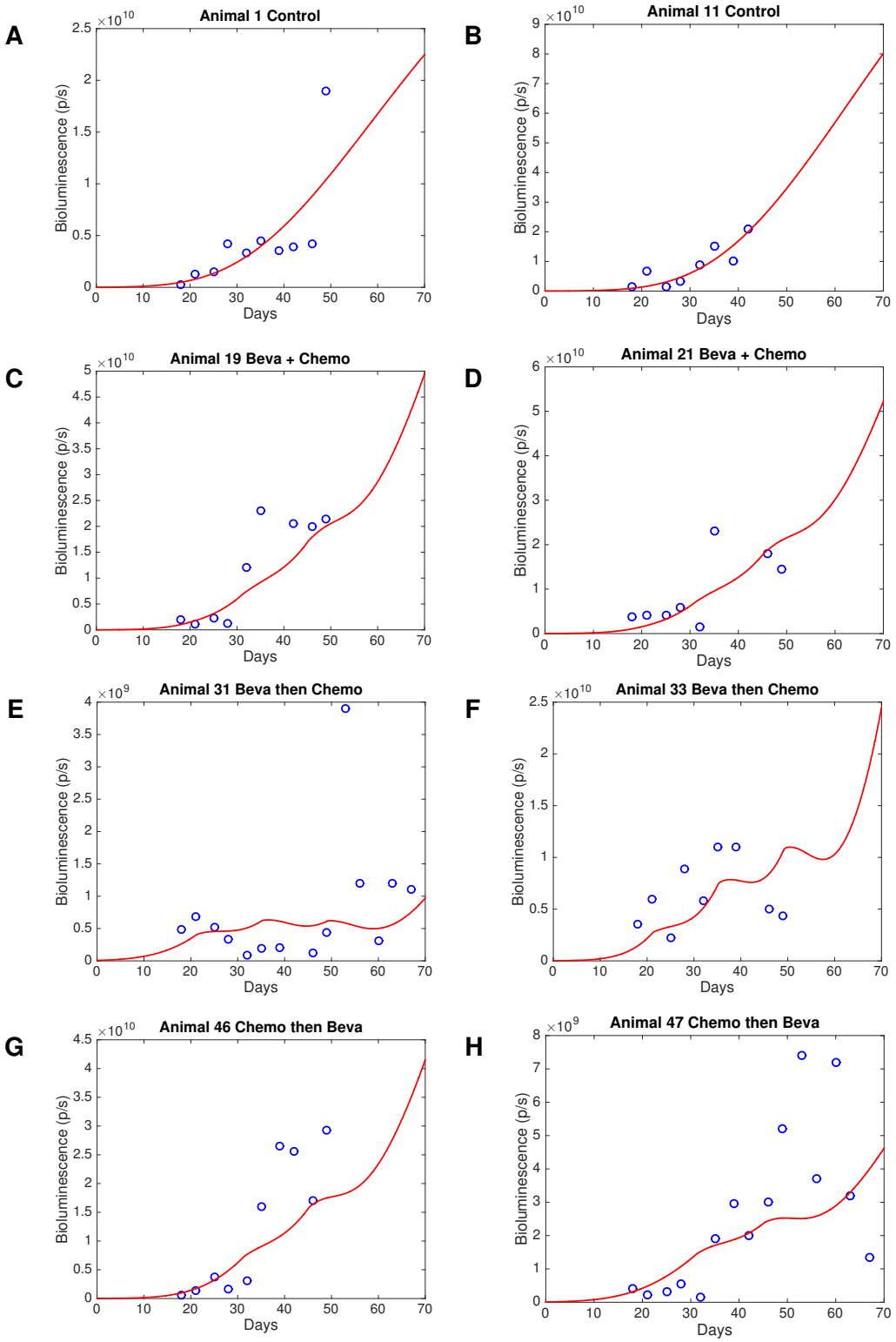


Figure S7: Residual analysis for experiment-1 population analysis



A- Normalized Predictions Distribution Errors (NPDE) *vs.* time
B- Normalized Predictions Distribution Errors (NPDE) *vs.* predictions
C- Individual Weighted Residuals (IWRES) *vs.* time
D- Individual Weighted Residuals (IWRES)*vs.* predictions
E- Population Weighted Residuals (PWRES) *vs.* time
F- Population Weighted Residuals (PWRES) *vs.* predictions
Plots were generated using residuals exported from Monolix.

Figure S8: Individual tumor growth simulations



Individual tumor growth simulations of random subjects from experiment-1.
Blue circles: experimental data. Red lines: simulated tumor growth curves