

## Supplementary Material

### Objective Function for QSP Model Parameter Estimation

Model parameters were estimated using a `FitParameters` in `KroneckerBio` with the constant plus linear error model. Essentially this solves for the parameter values that minimize:

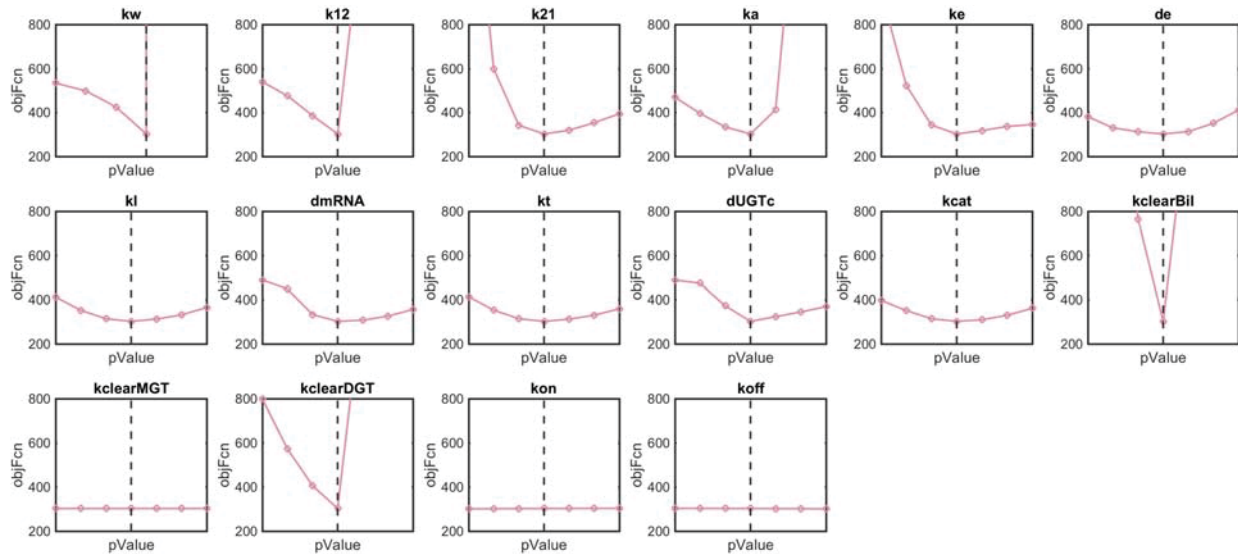
$$ObjFcn(p) = \sum \frac{(x(p, t_i) - x_i)^2}{\sigma(x_i)^2}$$

**Table S1:** Bilirubin production rate in Healthy Human Subjects, a 4 1/2 year old CN1 subject, and in Gunn rats.

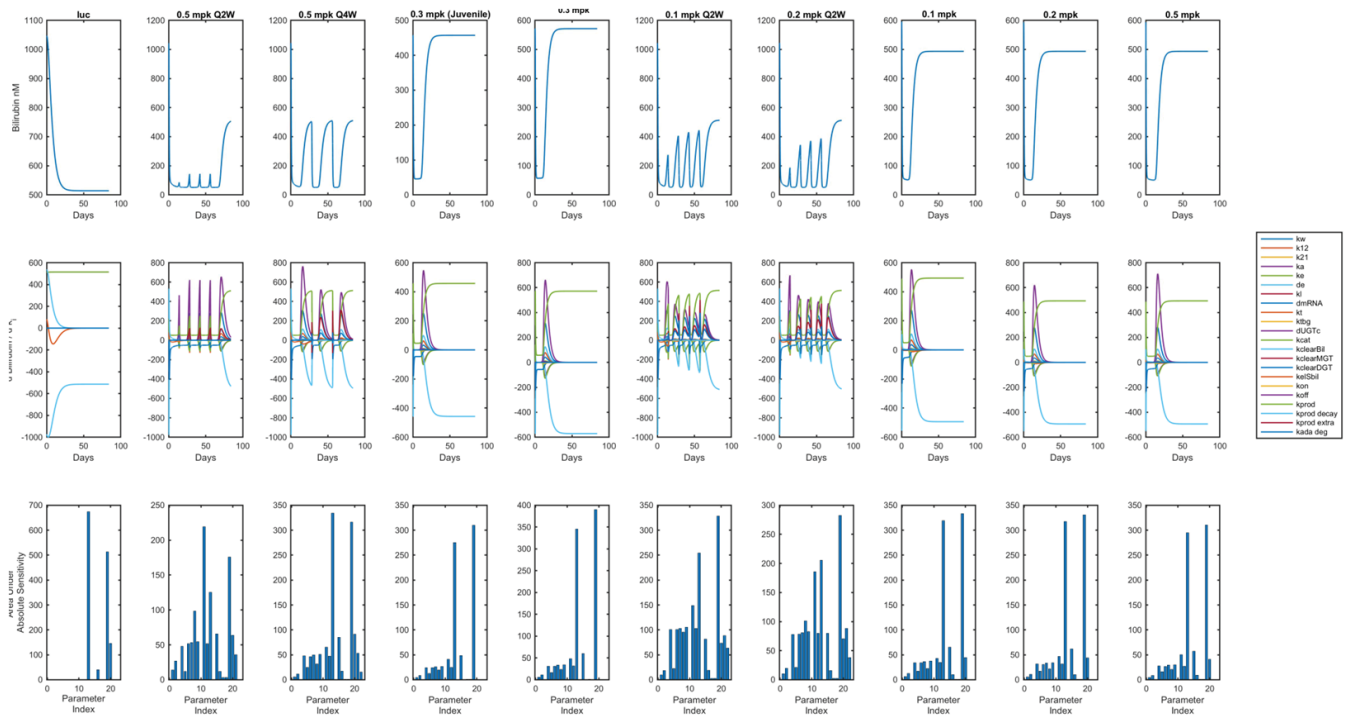
<b>Population</b>	<b>Bilirubin Production (mg/kg/day)</b>	<b>Elimination Half-Life (hour)</b>	<b>Reference</b>
Healthy Adult	3.8	0.45	Berk 1969
4 ½ y.o CN1 (Case Study)	3	156	Schmid 1963
Gunn Rat	3.25	55	Calvert 1978

## Supplementary Figures:

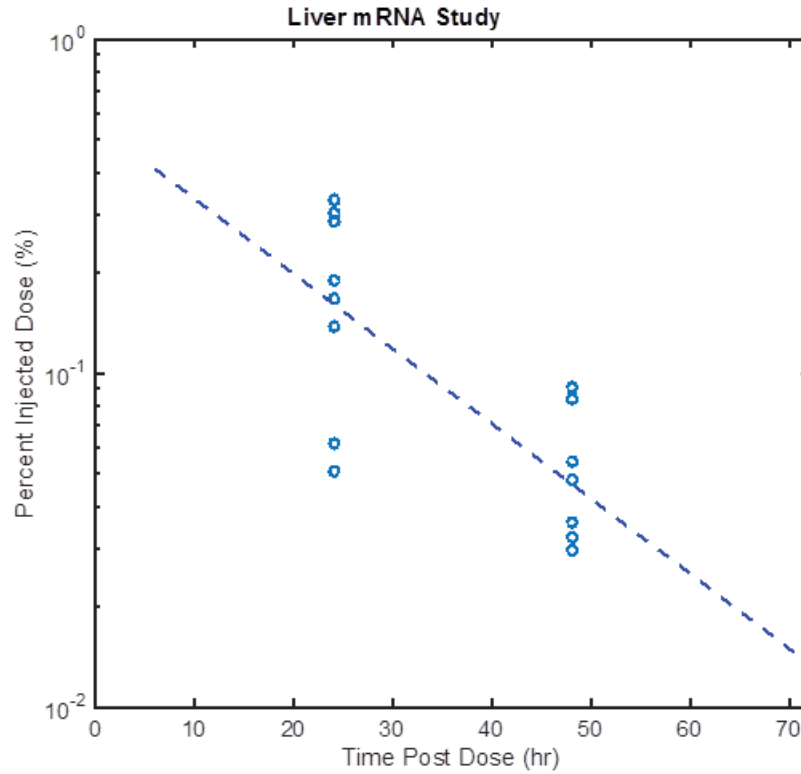
**Figure S1:** Visualizing the model-parameter objective function through a parameter scan 10-fold up and down from the best fit parameter values (dotted line). The objective function (y-axis) is the sum of squared error of the model parameterization weighted by the standard deviation at each time point. This function is evaluated at a range of parameter values from 10 lower (left-limit) nominal (dotted vertical line) and 10 fold higher (right-limit).



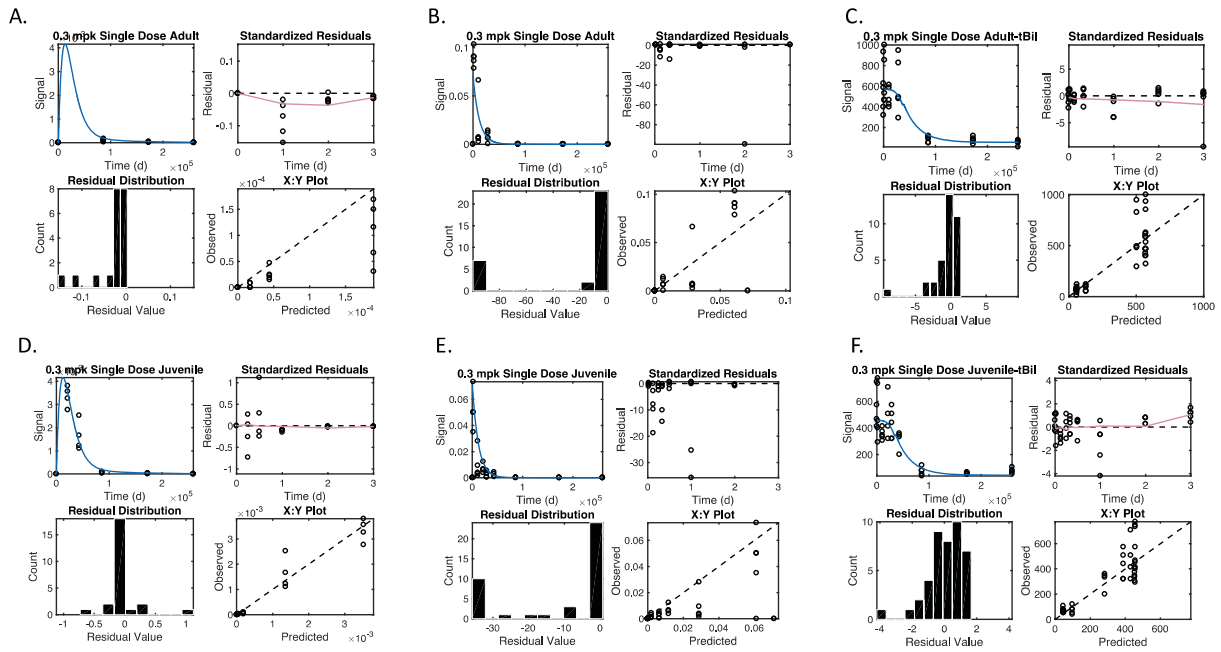
**Figure S2:** Sensitivities were calculated for all model parameters for all dose regimen shown in Figures 2-4 in the main text. The top row shows Total Bilirubin for each dose regimen. The middle row shows the sensitivity of total bilirubin to each model parameter. The legend on the far right lists the parameter names. The row on the bottom shows the area under the absolute sensitivity curves for each parameter. The parameters are in the same order as in the middle row.



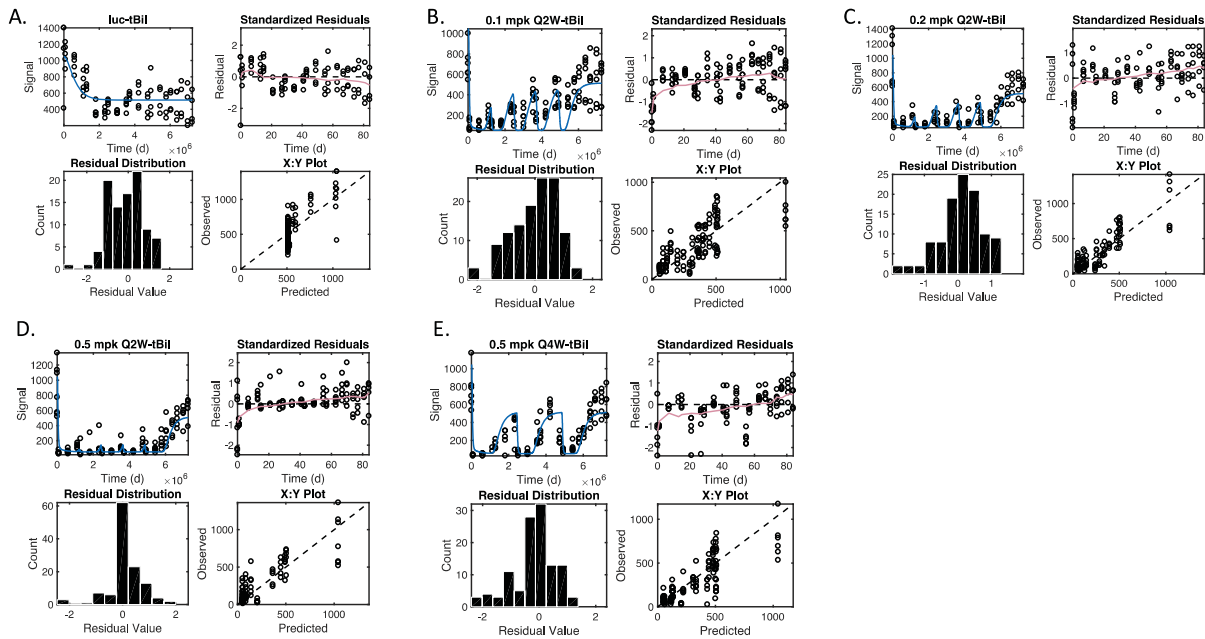
**Figure S3:** Estimating Half-Life of liver mRNA from liver mRNA vs time data in Gunn rats. hUGT1A1-modRNA was measured in the livers of Gunn rats at 24, 48, and 72 hours after dosing. Linear regression was performed to the log transformed data to get a slope. The best fit line is shown as a dashed line. The cytoplasmic half-life of hUGT1A1-modRNA was measured in vivo in Gunn Rat livers to be 13.4 hour [18.4 – 10.4] mean and 95% CI.



**Figure S4:** Diagnostic plots for model fits of the single 0.3 mg/kg dose PK/PD study in Gunn rats. Both adult (A-C) and juvenile (D-F) Gunn rat data was analyzed. The model time-series prediction (blue line) is overlaid with all replicate data values (upper left of each dose group (A-F)). The standardized residuals for each data value with respect to model prediction is plotted through time (top right of each dose group), with the residual moving average plotted in pink along with a histogram of all residuals (bottom left of each dose group). The model predictions vs observed data (x-y) plot is also provided (bottom right of each dose group).



**Figure S5:** Diagnostic plots for model predictions to the multi-dose PD study in Gunn rats. The model time-series prediction (blue line) is overlaid with all replicate data values (upper left of each dose group (A-E)). The standardized residuals for each data value with respect to model prediction is plotted through time (top right of each dose group), with the residual moving average plotted in pink along with a histogram of all residuals (bottom left of each dose group). The model predictions vs observed data (x-y) plot is also provided (bottom right of each dose group).



**Figure S6:** Predicted human plasma drug levels (left column) and total bilirubin (right column) simulations of Q4W doses (0.1, 0.3, and 0.5 mg/kg) with 20% parameter variation applied. A 20% parameter variation also captured the variability seen in the rat studies (data now shown). Shaded regions denote the bounds in which 95% of model predictions are contained after applying the parameter variation.

