Web-based Supplementary Materials for "Experimental Designs for Multi-drug Combination Studies Using Signaling Networks", by Hengzhen Huang, Hong-Bin Fang and Ming T. Tan

Web Appendix A.

Let

$$\begin{aligned}
\lambda &= \left[\sigma_f^2 \mathbf{V}_f^e(\boldsymbol{\phi}) + \sigma_\epsilon^2 \mathbf{W}_e\right]^{-1} \sigma_f^2 \mathbf{r}(\mathbf{x}_0) \text{ and} \\
\lambda_0 &= \mathbf{z}(\mathbf{x}_0)^\top \boldsymbol{\theta} - \lambda^\top \mathbf{Z}_e \boldsymbol{\theta}.
\end{aligned}$$

Then $\hat{Y}_e(\mathbf{x}_0)$ in Eq.(20) can be re-written as

$$\hat{Y}_e(\mathbf{x}_0) = \lambda_0 + \lambda^\top \mathbf{Y}_e.$$

Hence

$$\begin{aligned}
\text{MSE} &= E\left[Y_e(\mathbf{x}_0) - \hat{Y}_e(\mathbf{x}_0)\right]^2 \\
&= E\left[\mathbf{z}(\mathbf{x}_0)^\top \boldsymbol{\theta} + f(\mathbf{x}_0) - \lambda_0 - \lambda^\top \mathbf{Y}_e\right]^2 \\
&= E\left[\mathbf{z}(\mathbf{x}_0)^\top \boldsymbol{\theta} + f(\mathbf{x}_0) - \lambda_0 - \lambda^\top \mathbf{Y}_e + \lambda^\top \mathbf{Z}_e \boldsymbol{\theta} - \lambda^\top \mathbf{Z}_e \boldsymbol{\theta}\right]^2 \\
&= E\left[\mathbf{z}(\mathbf{x}_0)^\top \boldsymbol{\theta} - \lambda_0 - \lambda^\top \mathbf{Z}_e \boldsymbol{\theta}\right]^2 + E\left[f(\mathbf{x}_0) - \lambda^\top \mathbf{Y}_e + \lambda^\top \mathbf{Z}_e \boldsymbol{\theta}\right]^2 \\
&+ 2E\left[(\mathbf{z}(\mathbf{x}_0)^\top \boldsymbol{\theta} - \lambda_0 - \lambda^\top \mathbf{Z}_e \boldsymbol{\theta})(f(\mathbf{x}_0) - \lambda^\top \mathbf{Y}_e + \lambda^\top \mathbf{Z}_e \boldsymbol{\theta})\right] \\
&= \left[\mathbf{z}(\mathbf{x}_0)^\top \boldsymbol{\theta} - \lambda_0 - \lambda^\top \mathbf{Z}_e \boldsymbol{\theta}\right]^2 + E\left[f(\mathbf{x}_0) - \lambda^\top (\mathbf{Y}_e - \mathbf{Z}_e \boldsymbol{\theta})\right]^2 \\
&= \left[\mathbf{z}(\mathbf{x}_0)^\top \boldsymbol{\theta} - \lambda_0 - \lambda^\top \mathbf{Z}_e \boldsymbol{\theta}\right]^2 \\
&+ \sigma_f^2 + \lambda^\top \left[\sigma_f^2 \mathbf{V}_f^e(\boldsymbol{\phi}) + \sigma_\epsilon^2 \mathbf{W}_e\right] \lambda - 2\lambda^\top \sigma_f^2 \mathbf{r}(\mathbf{x}_0).
\end{aligned}$$

By direct substitution the MSE is

$$\begin{aligned}
\text{MSE} &= \sigma_f^2 - \sigma_f^2 \mathbf{r}(\mathbf{x}_0)^\top [\sigma_f^2 \mathbf{V}_f^e(\boldsymbol{\phi}) + \sigma_\epsilon^2 \mathbf{W}_e]^{-1} \sigma_f^2 \mathbf{r}(\mathbf{x}_0) \\
&= \sigma_f^2 - \sigma_f^2 \mathbf{r}(\mathbf{x}_0)^\top [\mathbf{V}_f^e(\boldsymbol{\phi}) + (\sigma_\epsilon^2/\sigma_f^2) \mathbf{W}_e]^{-1} \mathbf{r}(\mathbf{x}_0).
\end{aligned}$$

Web Appendix B.

In the numerical experiment of Fang et al. (2016), 10 single drugs, denoted by $A_1, \ldots, A_{10}$, were considered and their single drug curves are known as

$$
\begin{aligned}
y(x_1) &= 10 - 15\log(x_1), & y(x_2) &= 10 - 15\log(0.8465x_2),\\
y(x_3) &= 10 - 15\log(0.7165x_3), & y(x_4) &= 10 - 15\log(0.6065x_4),\\
y(x_5) &= 10 - 15\log(0.5134x_5), & y(x_6) &= 10 - 15\log(0.4346x_6),\\
y(x_7) &= 10 - 15\log(0.3679x_7), & y(x_8) &= 10 - 15\log(0.3114x_8),\\
y(x_9) &= 10 - 15\log(0.2636x_9), & y(x_{10}) &= 10 - 15\log(0.2231x_{10}),
\end{aligned}
$$

where $x_1, \ldots, x_{10}$ are dose-levels of $A_1, \ldots, A_{10}$, respectively.

Web Table 1.

Data generated from single drug curves

Dose-level	$y(x_1)$	$y(x_2)$	$y(x_3)$	$y(x_4)$	$y(x_5)$	$y(x_6)$	$y(x_7)$	$y(x_8)$	$y(x_9)$	$y(x_{10})$
0.01	79.08	81.58	84.08	86.58	89.08	91.58	94.08	96.58	99.08	99.99
0.15	38.46	40.96	43.46	45.96	48.46	50.96	53.46	55.96	58.46	60.96
0.29	28.57	31.07	33.57	36.07	38.57	41.07	43.57	46.07	48.57	51.07
0.43	22.66	25.16	27.66	30.16	32.66	35.16	37.66	40.16	42.67	45.16
0.57	18.43	20.93	23.43	25.93	28.43	30.93	33.43	35.93	38.43	40.93
0.71	15.14	17.64	20.14	22.64	25.14	27.64	30.14	32.64	35.14	37.64
0.85	12.44	14.94	17.44	19.94	22.44	24.94	27.44	29.94	32.44	34.94
0.99	10.15	12.65	15.15	17.65	20.15	22.65	25.15	27.65	30.15	32.65