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Paralog Screen Modeling GEMINI2

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1 Proposed Model

Person in Charge: Mahdi

1.1 Updated model and aims

On the basis of first version of GEMINI, we aim to pose constrains on the parameters evaluating guide performance (x_{g_i},x_{h_j}) and have the guide pair performance directly dependent on single guides. To achieve this, several models are proposed for the efficacy of guide pairs.

$$D_{g_i,h_j,l} \sim N(x_{g_i} y_{g,l} + x_{h_j} y_{h,l} + f(x_{g_i}, x_{h_j})\, s_{g,h,l}, \tau^{-1}_{g_i,h_j,l}) \tag{1.1}$$

We assume normal distribution for observed data LFC ($D_{g_i,h_j,l}$) from paralog screening. We will use the following annotation:

Table 1.1: Definition of symbols in 1.1

g and h	Genes targeted simultaneously by a guide pair
g_i and h_j	Guide i and guide j targeting gene g and h respectively
l	Cell line l
x_{g_i}	Efficacy of guide i for gene g
x_{h_j}	Efficacy of guide j for gene h
$y_{g,l}$	Effect of gene g in cell line l
$y_{h,l}$	Effect of gene h in cell line l
$s_{g,h,l}$	Combination effect of gene pair g and h in cell line l
$\tau^{-1}_{g_i,h_j,l}$	Variance of LFCs
$D_{g_i,h_j,l}$	Observed LFC for pair (g_i,h_j) in cell line l

The highlighted part is the function we use to model the efficacy of guide pair as a function of (x_{g_i},x_{h_j}). Three choices of the function here are:

1. $\min(x_{g_i}, x_{h_j})$
2. $\max(x_{g_i}, x_{h_j})$
3. $\sqrt{x_{g_i} x_{h_j}}$
4. $x_{g_i} x_{h_j}$

*Note: we will process $\min(x_{g_i}, x_{h_j}) = \frac{x_{g_i}+x_{h_j}-|x_{g_i}-x_{h_j}|}{2}$ and $\max(x_{g_i}, x_{h_j}) = \frac{x_{g_i}+x_{h_j}+|x_{g_i}-x_{h_j}|}{2}$ for further derivation.

We put constrain over parameters for single guide performance (x_{g_i},x_{h_j}): $0 \le x_{g_i} \le 1$; $0 \le x_{h_j} \le 1$.

*Note: we utilize transformation $x_{g_i} = \frac{1}{1+e^{-\lambda z_{g_i}}}$ to apply for corresponding constrain. λ is a positive pre-set parameter for model tuning. The setting ensures the monotonically positive relationship between x_{g_i} and z_{g_i}. All x_{g_i} here could be changed to x_{h_j}.

The problem settings are as illustrated above. The current solution is MLE, more specifically gradient optimization of likelihood function. The utilization of function ①,② and ③ makes it difficult to apply existing software of GLM in which outcome is the LFC, observed variable is a giant sparse matrix of indicators displaying the data structure.

We further introduced a weighting to the constructed likelihood $W_{g_i,h_j,l}$ that is the same dimension with computed LFC and replicate variance.

1.2 MLE MODEL SPECIFICATION

Based on the proposed model in last section with 4 possible link functions $f(x_{g_i}, x_{h_j})$ and constrain over guide effects as well as the assumption of i.i.d, the joint likelihood function to maximize is:

$$\mathscr{L} = \prod_{g_i}\prod_{h_j}\prod_{l}\left(\sqrt{\frac{\tau_{g_i,h_j,l}}{2\pi}}e^{-\frac{\tau_{g_i,h_j,l}\left[D_{g_i,h_j,l}-x_{g_i}y_{g,l}-x_{h_j}y_{h,l}-f(x_{g_i},x_{h_j})s_{g,h,l}\right]^2}{2}}\right) \tag{1.2}$$

We further substitute all x_{g_i} and x_{h_j} to $x_{g_i} = \frac{1}{1+e^{-\lambda z_{g_i}}}$ for applying the constrain. Then the likelihood will become:

$$\mathscr{L} = \prod_{g_i}\prod_{h_j}\prod_{l}\left(\sqrt{\frac{\tau_{g_i,h_j,l}}{2\pi}}e^{-\frac{\tau_{g_i,h_j,l}\left[D_{g_i,h_j,l}-\frac{y_{g,l}}{1+e^{-\lambda z_{g_i}}}-\frac{y_{h,l}}{1+e^{-\lambda z_{h_j}}}-f(\frac{1}{1+e^{-\lambda z_{g_i}}},\frac{1}{1+e^{-\lambda z_{h_j}}})s_{g,h,l}\right]^2}{2}}\right) \tag{1.3}$$

The next step will be deriving out the log likelihood for transforming product into sum for better optimization and avoid the operation of exponential. The weighting on log likelihood will be added in this step as well. The weighted log likelihood will be:

$$\ell = \sum_{g_i}\sum_{h_j}\sum_{l}\left(\frac{W_{g_i,h_j,l}}{2}\ln\left(\frac{\tau_{g_i,h_j,l}}{2\pi}\right) - \frac{\tau_{g_i,h_j,l}\cdot W_{g_i,h_j,l}\left[D_{g_i,h_j,l}-\frac{y_{g,l}}{1+e^{-\lambda z_{g_i}}}-\frac{y_{h,l}}{1+e^{-\lambda z_{h_j}}}-f\left(\frac{1}{1+e^{-\lambda z_{g_i}}},\frac{1}{1+e^{-\lambda z_{h_j}}}\right)s_{g,h,l}\right]^2}{2}\right) \tag{1.4}$$

From 1.4, we start to derive the gradient for optimization in the following sections in terms of different parameters, which will be the input for gradient optimization algorithm for quicker convergence.

2 GRADIENT IN TERMS OF TERM Z

Person in Charge: Mahdi and Ruitong

We have obtained the weighted log likelihood to optimize in last section and from the function 1.4, we will derive the gradient for all Z terms (z_{g_i} and z_{h_j}). The following derivative is all written for term z_{g_i} but again the same derivative applied to z_{h_j}.

2.1 LINK FUNCTION MINIMUM

First, for minimum link function, we have:

$$\begin{aligned}\frac{\partial \ell(z_{g_i})}{\partial z_{g_i}} = &\sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} W_{g_i,h_j,l}\Big[D_{g_i,h_j,l} - \frac{y_{g,l}}{1+e^{-\lambda z_{g_i}}} - \frac{y_{h,l}}{1+e^{-\lambda z_{h_j}}} - \min(\frac{1}{1+e^{-\lambda z_{g_i}}}, \frac{1}{1+e^{-\lambda z_{h_j}}}) s_{g,h,l}\Big] \cdot \\ &\Big[\frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^2}\big(y_{g,l} + \frac{(1-\mathrm{sign}(z_{g_i} - z_{h_j}))s_{g,h,l}}{2}\big)\Big]\end{aligned} \tag{2.1}$$

We could re-write the gradient to try for closed-form solution of global-maximum.

$$\frac{\partial \ell(z_{g_i})}{\partial z_{g_i}} = \frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^2} \cdot A - \frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^3} \cdot B \tag{2.2}$$

where:

$$\begin{aligned}A &= \sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} W_{g_i,h_j,l}\Big[D_{g_i,h_j,l} - \frac{y_{h,l}}{1+e^{-\lambda z_{h_j}}} - \min(\frac{1}{1+e^{-\lambda z_{g_i}}}, \frac{1}{1+e^{-\lambda z_{h_j}}}) s_{g,h,l}\Big]\Big[y_{g,l} + \frac{(1-\mathrm{sign}(x_{g_i} - x_{h_j}))s_{g,h,l}}{2}\Big] \\ &= \sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} W_{g_i,h_j,l}\Big[D_{g_i,h_j,l} - y_{h,l}\cdot x_{h_j} - \min(x_{g_i}, x_{h_j}) s_{g,h,l}\Big]\Big[y_{g,l} + \frac{(1-\mathrm{sign}(x_{g_i} - x_{h_j}))s_{g,h,l}}{2}\Big]\end{aligned}$$

$$B = \sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} \cdot W_{g_i,h_j,l} \cdot y_{g,l} \cdot \Big[y_{g,l} + \frac{(1-\mathrm{sign}(x_{g_i} - x_{h_j}))s_{g,h,l}}{2}\Big]$$

It is noteworthy that in A and B we do not have operation for terms z_{g_i} and z_{h_j} other than the sign of difference. We then again rewrite the derivative to transform from z_{g_i} back to x_{g_i} and calculate when the gradient can be set to zero. That will lead to:

$$\lambda(1-x_{g_i})x_{g_i}(A-x_{g_i}B)=0 \tag{2.3}$$

The solution will be:

$$x_{g_i}=\begin{cases} 1 \\ 0 \\ \frac{A}{B} \end{cases}$$

....

2.2 Link function maximum

Similarly, for maximum link function, we have:

$$\frac{\partial \ell(z_{g_i})}{\partial z_{g_i}} = \sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}\Big[D_{g_i,h_j,l}-\frac{y_{g,l}}{1+e^{-\lambda z_{g_i}}}-\frac{y_{h,l}}{1+e^{-\lambda z_{h_j}}}-\max(\frac{1}{1+e^{-\lambda z_{g_i}}},\frac{1}{1+e^{-\lambda z_{h_j}}})s_{g,h,l}\Big]\cdot \\ \Big[\frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^2}\big(y_{g,l}+\frac{(1+\mathrm{sign}(z_{g_i}-z_{h_j}))s_{g,h,l}}{2}\big)\Big] \tag{2.4}$$

We could re-write the gradient to try for closed-form solution of global-maximum.

$$\frac{\partial \ell(z_{g_i})}{\partial z_{g_i}} = \frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^2}\cdot A-\frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^3}\cdot B \tag{2.5}$$

where:

$$A=\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}\Big[D_{g_i,h_j,l}-\frac{y_{h,l}}{1+e^{-\lambda z_{h_j}}}-\max(\frac{1}{1+e^{-\lambda z_{g_i}}},\frac{1}{1+e^{-\lambda z_{h_j}}})s_{g,h,l}\Big]\Big[y_{g,l}+\frac{(1+\mathrm{sign}(x_{g_i}-x_{h_j}))s_{g,h,l}}{2}\Big] \\ =\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}\Big[D_{g_i,h_j,l}-y_{h,l}\cdot x_{h_j}-\max(x_{g_i},x_{h_j})s_{g,h,l}\Big]\Big[y_{g,l}+\frac{(1+\mathrm{sign}(x_{g_i}-x_{h_j}))s_{g,h,l}}{2}\Big]$$

$$B=\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}\cdot W_{g_i,h_j,l}\cdot y_{g,l}\cdot\Big[y_{g,l}+\frac{(1+\mathrm{sign}(x_{g_i}-x_{h_j}))s_{g,h,l}}{2}\Big]$$

It is noteworthy that in A and B we do not have operation for terms z_{g_i} and z_{h_j} other than the sign of difference. We then again rewrite the derivative to transform from z_{g_i} back to x_{g_i} and calculate when the gradient can be set to zero. That will lead to:

$$\lambda(1-x_{g_i})x_{g_i}(A-x_{g_i}B)=0 \tag{2.6}$$

The solution will be:

$$x_{g_i}=\begin{cases}1\\0\\\frac{A}{B}\end{cases}$$

. . . .

2.3 Link function square root

Then, when we moved to link function square root, we will have the corresponding first derivative as:

$$\begin{aligned}\frac{\partial\ell(z_{g_i})}{\partial z_{g_i}}&=\lambda\sqrt{x_{g_i}}(1-x_{g_i})\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}\Big[D_{g_i,h_j,l}-x_{g_i}y_{g,l}-x_{h_j}y_{h,l}-\sqrt{x_{g_i}x_{h_j}}s_{g,h,l}\Big]\cdot\Big[\sqrt{x_{g_i}}y_{g,l}+\frac{s_{g,h,l}\sqrt{x_{h_j}}}{2}\Big]\\&=\lambda\sqrt{x_{g_i}}(1-x_{g_i})\Big(\sqrt{x_{g_i}}A-x_{g_i}\sqrt{x_{g_i}}B-x_{g_i}C+D\Big)\end{aligned} \tag{2.7}$$

While we have:

$$A=\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}\big(D_{g_i,h_j,l}y_{g,l}-x_{h_j}y_{g,l}y_{h,l}-\frac{s^2_{g,h,l}x_{h,j}}{2}\big)$$

$$B=\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}y^2_{g,l}$$

$$C=\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}\big(\frac{3s_{g,h,l}y_{g,l}\sqrt{x_{h,j}}}{2}\big)$$

$$D=\sum_{h_j}\sum_{l}\tau_{g_i,h_j,l}W_{g_i,h_j,l}\big(\frac{D_{g_i,h_j,l}s_{g,h,l}\sqrt{x_{h_j}}}{2}-\frac{s_{g,h,l}x^{\frac{3}{2}}_{h,j}y_{h,l}}{2}\big)$$

Then we will have x_{g_i} with solution 1,0 and the root of polynomial equation $\sqrt{x_{g_i}}A - x_{g_i}\sqrt{x_{g_i}}B - x_{g_i}C + D = 0$ when setting the gradient equal to zero. We intend to use polyroot in R for solving the polynomial, but we only keep roots ranging from 0 to 1. We choose the final solution out of pool (0,1,square of selected roots) that gives out maximum cost as the new update for x_{g_i}.

. . . .

2.4 Link function product

Lastly, for the link function, we will have the corresponding first derivative for guide effect as:

$$\begin{aligned}\frac{\partial \ell(z_{g_i})}{\partial z_{g_i}} &= \sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} W_{g_i,h_j,l}\left[D_{g_i,h_j,l} - x_{g_i} y_{g,l} - x_{h_j} y_{h,l} - x_{g_i} x_{h_j} s_{g,h,l}\right] \cdot \left[y_{g,l}\frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^2} + s_{g,h,l} x_{h_j}\frac{\lambda e^{-\lambda z_{g_i}}}{(1+e^{-\lambda z_{g_i}})^2}\right] \\ &= \lambda x_{g_i}(1-x_{g_i})\sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} W_{g_i,h_j,l}\left[D_{g_i,h_j,l} - x_{g_i} y_{g,l} - x_{h_j} y_{h,l} - x_{g_i} x_{h_j} s_{g,h,l}\right] \cdot \left[y_{g,l} + s_{g,h,l} x_{h_j}\right]\end{aligned} \tag{2.8}$$

While we have:

$$A = \sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} W_{g_i,h_j,l} \cdot \left(D_{g_i,h_j,l} - x_{h_j} y_{h,l}\right) \cdot \left(y_{g,l} + s_{g,h,l} x_{h_j}\right)$$

$$B = \sum_{h_j}\sum_{l} \tau_{g_i,h_j,l} W_{g_i,h_j,l} \cdot \left(y_{g,l} + s_{g,h,l} x_{h_j}\right)^2$$

The solution will again be:

$$x_{g_i} = \begin{cases} 1 \\ 0 \\ \frac{A}{B} \end{cases}$$

3 Gradient in terms of term Y

Person in Charge: Mahdi and Ruitong

Similarly, We will annotate x_{g_i} here as the original form instead of the one with exponential transformation for easy presentation. In that way, we will re-write the log likelihood as:

$$\ell(y_{g,l}) = \sum_i \sum_{h_j} \left(- \frac{\tau_{g_i,h_j,l} W_{g_i,h_j,l} \left[D_{g_i,h_j,l} - x_{g_i} \cdot y_{g,l} - x_{h_j} \cdot y_{h,l} - f(x_{g_i}, x_{h_j}) s_{g,h,l} \right]^2}{2} \right) \tag{3.1}$$

We could then easily have:

$$\frac{\partial \ell(y_{g,l})}{\partial y_{g,l}} = \sum_i \sum_{h_j} \tau_{g_i,h_j,l} W_{g_i,h_j,l} \left[D_{g_i,h_j,l} - x_{g_i} \cdot y_{g,l} - x_{h_j} \cdot y_{h,l} - f(x_{g_i}, x_{h_j}) s_{g,h,l} \right] x_{g_i} \tag{3.2}$$

Then,we will have the closed form solution as:

$$y_{g,l} = \frac{A}{B} \tag{3.3}$$

where:

$$A = \sum_i \sum_{h_j} \tau_{g_i,h_j,l} W_{g_i,h_j,l} \left[D_{g_i,h_j,l} - x_{h_j} \cdot y_{h,l} - f(x_{g_i}, x_{h_j}) s_{g,h,l} \right] x_{g_i}$$

$$B = \sum_i \sum_{h_j} x_{g_i}^2 \tau_{g_i,h_j,l} W_{g_i,h_j,l}$$

It is noteworthy that B is always positive. When penalization on Y is added to the maximized cost function, we will have a μ added in B term.

4 Gradient in terms of term S

Person in Charge: Mahdi and Ruitong

Here, we have the weighted log likelihood contributed by term $s_{g,h,l}$ only.

$$\ell(s_{g,h,l}) = \sum_i \sum_j \left(-\frac{\tau_{g_i,h_j,l} W_{g_i,h_j,l} \left[D_{g_i,h_j,l} - x_{g_i} \cdot y_{g,l} - x_{h_j} \cdot y_{h,l} - f(x_{g_i}, x_{h_j}) s_{g,h,l} \right]^2}{2} \right) \tag{4.1}$$

Further, we will write the gradient as shown below:

$$\frac{\partial \ell(s_{g,h,l})}{\partial s_{g,h,l}} = \sum_i \sum_j \tau_{g_i,h_j,l} W_{g_i,h_j,l} \left[D_{g_i,h_j,l} - x_{g_i} \cdot y_{g,l} - x_{h_j} \cdot y_{h,l} - f(x_{g_i}, x_{h_j}) s_{g,h,l} \right] \cdot f(x_{g_i}, x_{h_j}) \tag{4.2}$$

Then, the closed form of solution can be written below as:

$$s_{g,h,l} = \frac{A}{B} \tag{4.3}$$

where:

$$A = \sum_i \sum_j \tau_{g_i,h_j,l} W_{g_i,h_j,l} \left[D_{g_i,h_j,l} - x_{g_i} \cdot y_{g,l} - x_{h_j} \cdot y_{h,l} \right] \cdot f(x_{g_i}, x_{h_j})$$

$$B = \sum_i \sum_j \tau_{g_i,h_j,l} W_{g_i,h_j,l} \cdot f(x_{g_i}, x_{h_j})^2$$

When penalization on Y is added to the maximized cost function, we will have a γ added in B term.

5 Gradient In terms of Variance

Person in Charge: Mahdi and Ruitong

Since all four terms in full log likelihood function contains the variance term $\tau_{g_i,h_j,l}$, we do not repeatedly list out the log likelihood here, we will directly display the contribution of each $\tau_{g_i,h_j,l}$ for the log likelihood.

$$\ell(\tau_{g_i,h_j,l}) = \left(\frac{W_{g_i,h_j,l}}{2} \ln\left(\frac{\tau_{g_i,h_j,l}}{2\pi}\right) - \frac{\tau_{g_i,h_j,l} W_{g_i,h_j,l} \left[D_{g_i,h_j,l} - x_{g_i} \cdot y_{g,l} - x_{h_j} \cdot y_{h,l} - f(x_{g_i}, x_{h_j}) s_{g,h,l} \right]^2}{2} \right) \tag{5.1}$$

The gradient is as shown below:

$$\frac{\partial \ell(\tau_{g_i,h_j,l})}{\partial \tau_{g_i,h_j,l}} = \left(\frac{1}{2\tau_{g_i,h_j,l}} - \frac{\left[D_{g_i,h_j,l} - x_{g_i} \cdot y_{g,l} - x_{h_j} \cdot y_{h,l} - f(x_{g_i}, x_{h_j}) s_{g,h,l} \right]^2}{2} \right) \tag{5.2}$$

We can easily find out that the closed form update for $\tau_{g_i,h_j,l}$) will be $\frac{1}{A}$ where A is highlighted in magenta color. A small noise of 0.05 is added to A to avoid large number of τ.

6 Model Initialization and Optimization

Person in Charge: Mahdi and Ruitong

6.1 Initiation

This section will document the ways of initializing this model.

Table 6.1: Parameter Initialization

x_{g_i}	1-a (some noise to add)
$y_{g,l}$	Median of LFC (gene g - NC pairs) in cell line l
$s_{g,h,l}$	Median$(D_{g,h,l})$ - $y_{g,l}$ - $y_{h,l}$
$\tau_{g_i,h_j,l}$	$\frac{1}{2*\beta_{prior}}$

Here, we have $\beta_{prior} = \kappa(\sigma^2_{g_i,h_j,p} + \sigma^2_{g_i,h_j,l})$ where κ determines the skewness of the prior (default is 0.5); $\sigma^2_{g_i,h_j,p}$ is the empirical variance of (g_i, h_j) pair, calculated using pDNA's replicates; and $\sigma^2_{g_i,h_j,l}$ is the empirical variance of (g_i, h_j) pair, calculated using sample l's replicates.

We further have the weights $W_{g_i,h_j,l}$ calculated as shown below:

$$\begin{aligned} W_{g_i,h_j,l} &= \min(W_{g_i,l}, W_{h_j,l}) \\ &= \min(\frac{1}{1+|D_{g_i,h_j,l} - y_{g,l}|^3}, \frac{1}{1+|D_{g_i,h_j,l} - y_{h,l}|^3}) \end{aligned}$$

6.2 Optimization

We updated the parameters in the order of x_{g_i}, x_{h_j}, $y_{g,l}$, $s_{g,h,l}$ and finally $\tau_{g_i,h_j,l}$. For single gene effect y and double gene effect with one gene in the pair belonging to negative control genes s, we set the values to zero after each round of updating. The cost function we are finally maximizing is:

$$\begin{aligned} \ell = &\sum_{g_i}\sum_{h_j}\sum_{l}\left(\frac{W_{g_i,h_j,l}}{2}\ln\left(\frac{\tau_{g_i,h_j,l}}{2\pi}\right) - \frac{\tau_{g_i,h_j,l}\cdot W_{g_i,h_j,l}\left[D_{g_i,h_j,l} - x_{g_i}\cdot y_{g,l} - x_{h_j}\cdot y_{h,l} - f(x_{g_i}, x_{h_j})s_{g,h,l}\right]^2}{2}\right) \\ &- \frac{\mu}{2}\sum_{g}\sum_{l} y^2_{g,l} - \frac{\gamma}{2}\sum_{g}\sum_{h}\sum_{l} s^2_{g,h,l} \end{aligned} \tag{6.1}$$