Drug response model

Idea

Disentangle the independent effect and the synergistic effect of the drug combinations in our model.

We want to predict the effect of a drug combination given the estimated independent effect (effect of the two drugs under the assumption that their effects are independent).

Several synergy scores already provide some estimation of the independent effect. They make use of simple models and consider each drug independently. We will instead train an independent effect predictor on all drugs jointly, with less assumptions about the shape of the independent effect.

- Note: the single drug responses are *easier* to obtain as one needs $O(n)$ experiments for n drugs, whereas $O(n^2)$ experiments are needed for drug synergies.
- One could test all drugs alone before moving to drug combination experiments, or train the single response model and the synergy model jointly if both types of experiments are performed in parallel.

Drug Response Matrix

- For a given pairs (A, B) of drugs, we have: $Y^{A,B} = (y_m^{i,j})$ the drug response matrix $\in \mathcal{R}^{k \times k}$. ($m$ stands for measured)
- Each coefficient (i, j) in the matrix Y corresponds to the relative inhibition ($y_m^{i,j} =$ pourcentage of cells that have died) when drug A has been applied with concentration c_i and drug B has been applied with concentration c_j.
- Usually, $c_0 = 0$, such that the first column and the first row of the matrix correspond to the single drug responses, for drug A and drug B respectively.
- We denote $Y^D \in \mathcal{R}^k$ the single drug response of drug D.

- The size of the matrix k may vary. (3×3 to 10×10)

Features

- Each drug D is associated with a feature representation h_D.
- In advanced models which make use of GNNs, this feature representation h_D will be learnt using the Protein-protein interactions and Drug-Protein interactions within the cell.
- Each experiment is performed on a given cell line/cell type l.

Model

For a given drug response experiment (A, B, c_A, c_B, l), we want to predict the response $y_m^{c_A,c_B}$.

Naive approach

$\hat{y}_m^{c_A,c_B} = F_\phi(h_A, h_B, c_A, c_B, l)$. Several variations are possible:

- Compute embeddings and take the dot product
  $F_\phi(h_A, h_B, c_A, c_B, l) = \langle g_\theta(h_A, c_A, l) | g_\theta(h_B, c_B, l) \rangle$
- Compute embeddings and feed in an MLP
  $F_\phi(h_A, h_B, c_A, c_B, l) = f_\mu[g_\theta(h_A, c_A, l), g_\theta(h_B, c_B, l)]$

Taking advantage of the single drug responses

We want to model the independent effect by predicting the whole drug response matrix given the single drug responses, without any information about the identity of the drugs:
$I_\theta(c_A, c_b, Y^A, Y^B)$

- $\hat{y}_m^{c_A,c_B} = I_\theta(c_A, c_b, Y^A, Y^B) + f_\mu(h_A, h_B, c_A, c_B,)$

f_μ only predicts the synergy.

If one trains a model I_θ on all pairs of single drug responses, **it allows I_θ to learn the expected response to drug combinations without knowing the identity of the drugs**. Some drugs are synergistic, others are antagonist, our model will capture the average response of the cell (given single drug responses).

Having a better estimate of the independent effect would allow f_μ to better capture the synergistic effect (and only the synergistic effect).

Link with known synergy scores:

- If $I_\theta(c_A, c_b, Y^A, Y^B) = y_m^{c_A} + y_m^{c_B} - y_m^{c_A} * y_m^{c_B}$ this is equivalent to predicting BLISS score with f_μ ($y_m^{c_D}$ is the measured response for drug D at concentration c_D)
- If $I_\theta(c_A, c_b, Y^A, Y^B) = g_A + g_B - g_A * g_B$ with $g_D = MLE(\text{logistic}, Y^D)|_{c_D}$ this is equivalent to predicting ZIP score with f_μ. $MLE(\text{logistic}, Y^D)$ refers to the logistic function fitted on data Y^D, and $|_{c_D}$ refers to evaluating the function at c_D. MLE stands for *maximum likelihood estimator*.

Compared to previous scores, we make less assumptions about the shape of the idenpendent effect, and learn it from data.

- Issues: the dimension of Y^D might vary from one drug to the other (we should check on the dataset we currently use). If the dimension varies, we can use transformers.
- Note: do not forget to normalize all drug responses s.t. response=100 (or 1) when concentration is 0.

Variations

f_μ predicts the proportion of additional cells that will die after the independent effect has been *applied*:

- $\hat{y}_m^{c_A, c_B} = I_\theta + f_\mu - I_\theta * f_\mu$

Learn the algebra?

- $\hat{y}_m^{c_A, c_B} = F_\phi[I_\theta(c_A, c_b, Y^A, Y^B), f_\mu(h_A, h_B, c_A, c_B,)]$. Enfore $F_\phi(., 0) = Id$ and partial derivative w.r.t second variable strictly positive

Getting a score for active Learning

For our model to be compatible with active learning, we need to predict one score per drug pair.

- predict f_μ for each element of the matrix and average. Use the posterior distribution of this average in the acquisition function
- Compute the posterior distribution of f_μ for each element of the matrix. Design an acquisition function that can handle this. *e.g.* : $score^{A,B} = max_{i,j}(\hat{\mu}_{i,j}^{A,B} + \hat{\sigma}_{i,j}^{A,B})$
- Take into account the concentrations of the drug in the score. *e.g.*
  $score^{A,B} = max_{i,j}[\hat{\mu}_{i,j}^{A,B} + \hat{\sigma}_{i,j}^{A,B} - \lambda(c_i + c_j)]$ or
  $score^{A,B} = max_{(c_i+c_j)<C_{\max}}[\hat{\mu}_{i,j}^{A,B} + \hat{\sigma}_{i,j}^{A,B}]$