Constrained randomization

The basic idea is pretty simple. We generate a large number of possible randomization lists based on the requirements of the study design. For each randomization, we evaluate whether the balancing criteria have been met; by selecting only the subset of randomizations that pass this test, we create a sample of eligible randomizations. With this list of possible randomizations is in hand, we randomly select one, which becomes the actual randomization. Because we have limited the final selection only to possible randomizations that have been vetted for balance (or whatever criteria we require), we are guaranteed to satisfy the pre-specified criteria.

Simulated data

I am using a single simulated data set to illustrate the constrained randomization process. Using the `simstudy` package, creating this data set is a two-step process of *defining* the data and then *generating* the data.

Defining the data

There will be a total of 200 nursing homes in 3 (rather than 4) networks. Just as in the real data, racial/ethnic composition will differ by network (because they are based in different parts of the country). And the networks are different sizes. The proportions of African-American/Latinx residents are generated using the `beta` distribution, which ranges from 0 to 1. In `simstudy`, the beta distribution is parameterized with a mean (specified in the `formula` argument) and dispersion (specified in the `variance` argument. See this for more details on the *beta* distribution.

```
library(simstudy)
library(data.table)

def <- defData(varname = "network", formula = "0.3;0.5;0.2",
  dist = "categorical", id = "site")

defC <- defCondition(condition = "network == 1",
  formula = "0.25", variance = 10, dist = "beta")
defC <- defCondition(defC, condition = "network == 2",
  formula = "0.3", variance = 7.5, dist = "beta")
defC <- defCondition(defC, condition = "network == 3",
  formula = "0.35", variance = 5, dist = "beta")
```

Generating the data

```
set.seed(2323761)

dd <- genData(200, def, id = "site")
dd <- addCondition(defC, dd, newvar = "prop")

dd[, stratum := cut(prop, breaks = c(0, .25, .4, 1),
  include.lowest = TRUE, labels = c(1, 2, 3))]

dd
```

```
##       site  prop network stratum
##   1:     1 0.340       2       2
##   2:     2 0.181       2       1
##   3:     3 0.163       2       1
##   4:     4 0.099       3       1
##   5:     5 0.178       2       1
##  ---
## 196:   196 0.500       2       3
## 197:   197 0.080       3       1
## 198:   198 0.479       3       3
## 199:   199 0.071       2       1
## 200:   200 0.428       2       3
```

Randomization

Now that we have a data set in hand, we can go ahead an randomize. I am using the `simstudy` function `trtAssign`, which allows us to specify the strata as well as the the ratio of controls to intervention facilities. In this case, we have a limit in the number of sites at which we can implement the intervention. In this simulation, I assume that we'll randomize 150 sites to control, and 50 to the intervention, a 3:1 ratio.

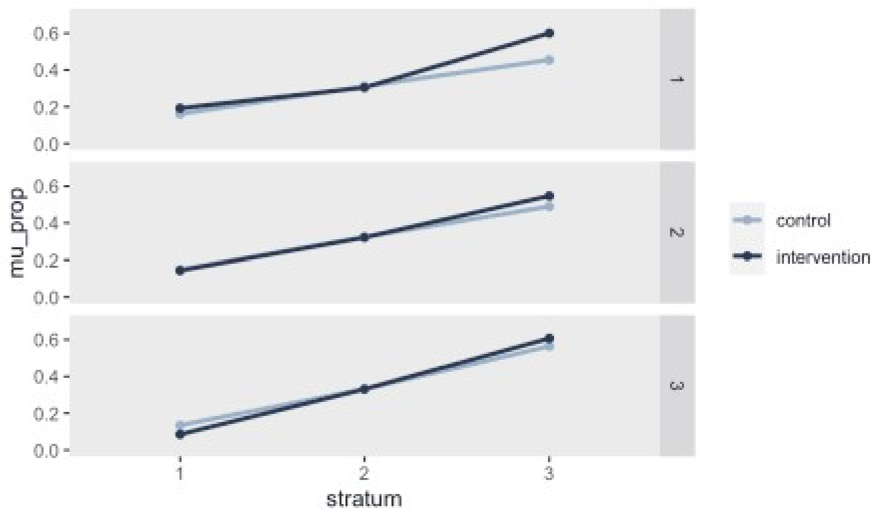
```
dr <- trtAssign(dd, nTrt = 2, balanced = TRUE, strata = c("network",
"stratum"),
  ratio = c(3, 1), grpName = "rx")
```

We want to inspect an average proportion of African-American/Latinx residents within each strata (without adjusting for nursing home size, which is ignored here). First, we create a data table that includes the difference in average proportions between the facilities randomized to the intervention and those randomized to control:

```
dx <- dr[, .(mu_prop = mean(prop)), keyby = c("network", "stratum",
"rx")]
dc <- dcast(dx, network + stratum ~ rx, value.var = "mu_prop")
dc[, dif := abs(`1` - `0`)]
```

Looking at both the table and the figure, Stratum 3 (>40%) in Network 1 jumps out as having the largest discrepancy, about 15 percentage points:

```
##    network stratum    0     1     dif
## 1:       1       1 0.16 0.192 0.03062
## 2:       1       2 0.31 0.305 0.00641
## 3:       1       3 0.45 0.600 0.14568
## 4:       2       1 0.15 0.143 0.00394
## 5:       2       2 0.32 0.321 0.00310
## 6:       2       3 0.49 0.547 0.05738
## 7:       3       1 0.13 0.085 0.04948
## 8:       3       2 0.33 0.331 0.00029
## 9:       3       3 0.56 0.607 0.04284
```



Constraining the randomization

We want to do better and ensure that the maximum difference within a stratum falls below some specified threshold, say a 3 percentage point difference. All we need to do is repeatedly randomize and then check balance. I've written a function `randomize` that will be called repeatedly. Here I generate 1000 randomization lists, but in some cases I might need to generate many more, particularly if it is difficult to achieve targeted balance in any particular randomization.

```
randomize <- function(dd) {

  dr <- trtAssign(dd, nTrt = 2, strata = c("network", "stratum"),
balanced = TRUE,
    ratio = c(3, 1), grpName = "rx")

  dx <- dr[, .(mu_prop = mean(prop)), keyby = c("network", "stratum",
"rx")]
  dx <- dcast(dx, network + stratum ~ rx, value.var = "mu_prop")
  dx[, dif := abs(`1` - `0`)]

  list(is_candidate = all(dx$dif < 0.03), randomization = dr[,.(site,
rx)],
    balance = dx)

}

rand_list <- lapply(1:1000, function(x) randomize(dd))
```

Here is one randomization that fails to meet the criteria as 5 of the 9 strata exceed the 3 percentage point threshold:

```
## [[1]]
## [[1]]$is_candidate
## [1] FALSE
##
## [[1]]$randomization
##      site rx
##   1:    1  0
##   2:    2  1
##   3:    3  0
##   4:    4  1
##   5:    5  0
##  ---
## 196:  196  0
## 197:  197  1
## 198:  198  0
## 199:  199  0
## 200:  200  0
##
## [[1]]$balance
##    network stratum    0     1    dif
## 1:       1       1 0.16 0.207 0.0503
## 2:       1       2 0.30 0.334 0.0330
## 3:       1       3 0.45 0.600 0.1457
## 4:       2       1 0.15 0.138 0.0107
## 5:       2       2 0.32 0.330 0.0078
## 6:       2       3 0.50 0.514 0.0142
## 7:       3       1 0.13 0.085 0.0493
## 8:       3       2 0.34 0.311 0.0239
## 9:       3       3 0.55 0.647 0.0950
```

Here is another that passes, as all differences are below the 3 percentage point threshold:

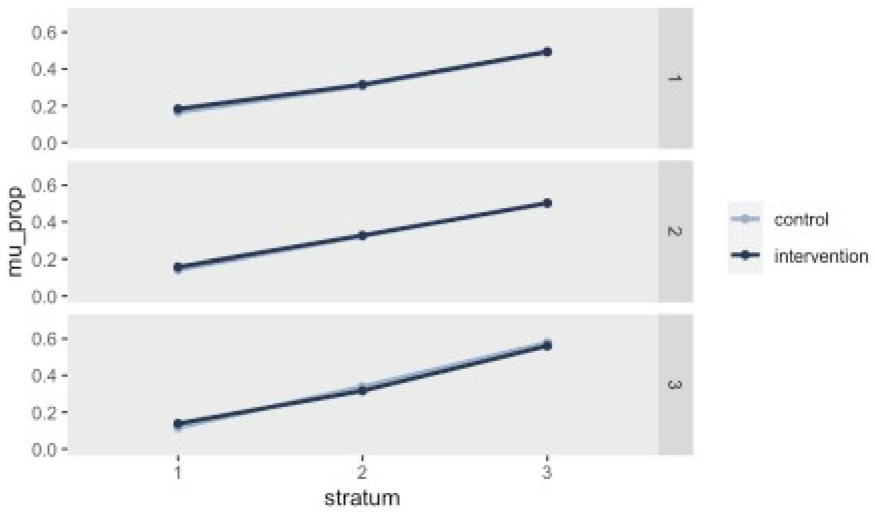
```
## [[1]]
## [[1]]$is_candidate
## [1] TRUE
##
## [[1]]$randomization
##      site rx
##   1:    1  1
##   2:    2  0
##   3:    3  1
##   4:    4  0
##   5:    5  1
##  ---
## 196:  196  1
## 197:  197  0
## 198:  198  1
## 199:  199  1
## 200:  200  0
##
## [[1]]$balance
##    network stratum    0    1    dif
## 1:       1       1 0.16 0.18 0.0168
## 2:       1       2 0.31 0.31 0.0039
## 3:       1       3 0.49 0.49 0.0041
## 4:       2       1 0.15 0.14 0.0144
## 5:       2       2 0.32 0.33 0.0064
## 6:       2       3 0.50 0.52 0.0196
## 7:       3       1 0.12 0.12 0.0095
## 8:        3        2 0.34 0.31 0.0239
## 9:        3        3 0.57 0.58 0.0134
```

All that remains is to identify all the randomization sets that met the criteria (in this case there are only 6, suggesting we should probably generate at least 100,000 randomizations to ensure we have enough to pick from).

```
candidate_indices <- sapply(rand_list, function(x) x[["is_candidate"]])
candidates <- rand_list[candidate_indices]
(n_candidates <- length(candidates))
## [1] 6
selected <- sample(x = n_candidates, size = 1)
ds <- candidates[[selected]][["randomization"]]

ds <- merge(dd, ds, by = "site")
dx <- ds[, .(mu_prop = mean(prop)), keyby = c("network", "stratum",
"rx")]
```

And looking at the plot confirms that we have a randomization scheme that is balanced based on our target:



Of course, the selection criteria could be based on any combination of factors. We may have multiple means that we want to balance, or we might want the two arms to be similar with respect to the standard deviation of a measure. These additional criteria may require more randomization schemes to be generated just because balance is that much more difficult to achieve, but all that really costs is computing time, not programming effort.