mTADA

Code

This notebook descibes steps used to jointly analyze two traits by `mTADA`.

I. Introduction

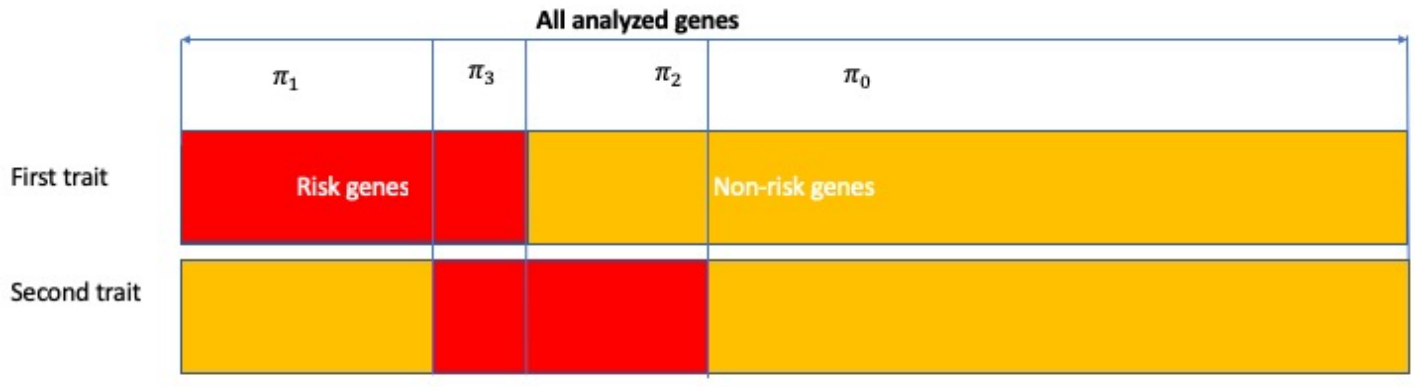
`mTADA` **jointly analyze de novo mutations (DNMs) of two traits to 1) estimate the gene-level genetic overlap of the two traits; 2) report shared and specific risk genes; and 3) identify additional risk genes for each analyzed trait.**

The method requires genetic parameters from single-trait analyses (the third and fourth columns in Table 1 below). Users can obtain single-trait parameters from `extTADA/TADA` methods.

Table 1. `mTADA` **model for one variant category at the** i^{th} **gene**.

Hypothesis	Proportion	First trait	Second trait
H_0	π_0	$x_{i1} \sim Poisson(2N_1\mu_i)$	$x_{i2} \sim Poisson(2N_2\mu_i)$
H_1	π_1	$x_{i1} \sim Poisson(2N_1\gamma_1\mu_i)$; $\gamma_1 \sim Gamma(\bar{\gamma}_1\beta_1, \beta_1)$	$x_{i2} \sim Poisson(2N_2\mu_i)$
H_2	π_2	$x_{i1} \sim Poisson(2N_1\mu_i)$	$x_{i2} \sim Poisson(2N_2\gamma_2\mu_i)$; $\gamma_2 \sim Gamma(\bar{\gamma}_2\beta_2, \beta_2)$
H_3	π_3	$x_{i1} \sim Poisson(2N_1\gamma_1\mu_i)$; $\gamma_1 \sim Gamma(\bar{\gamma}_1\beta_1, \beta_1)$	$x_{i2} \sim Poisson(2N_2\gamma_2\mu_i)$; $\gamma_2 \sim Gamma(\bar{\gamma}_2\beta_2, \beta_2)$

Figure 1. `mTADA` **framework.**



Data for reproducible analyses

Data used in the main manuscript are inside the folder data (data):

1. FullDataSet_DenovoMutations_for_mTADA.txt (data/FullDataSet_DenovoMutations_for_mTADA.txt): all gene-level de novo mutations. These DNMs are used in the main manuscript.
2. SingleTrait_Parameters.txt (data/SingleTrait_Parameters.txt): all single-trait parameters. We used `extTADA` to estimate these parameters from the DNMs above.

   Note: Users can re-run all these single-trait analyses by following an example here: https://github.com/hoangtn/extTADA (https://github.com/hoangtn/extTADA).

II. Requirements

`mTADA` **is written in** `R`. Other `R` packages are required to run `mTADA`:

- `rstan`: https://mc-stan.org/rstan/ (https://mc-stan.org/rstan/).
- `locfit`: https://cran.r-project.org/web/packages/locfit/index.html (https://cran.r-project.org/web/packages/locfit/index.html).

Software versions were used in our analyses: `R` version 3.5.2, `locfit` version 1.5-9.1, and `rstan` version 2.18.2.

III. An example: joint analysis of DD and EE DNMs.

Only one function `mTADA` (in the **Run** `mTADA` section) is used to obtain results. Therefore, users can go directly to the **Run** `mTADA` section to run `mTADA`. However, some additional steps are described here.

Load the source codes

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```
dataDir <- "./data/"
source("script/mTADA.R")
```

```
locfit 1.5-9.1   2013-03-22
```

Read the data and single-trait parameters

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```
## De novo data
data <- read.table(paste0(dataDir, "FullDataSet_DenovoMutations_for_mTADA.txt"), header
 = TRUE, as.is = TRUE)
## Single-trait parameters
sPar <- read.table(paste0(dataDir, "SingleTrait_Parameters.txt"), as.is = TRUE, header =
TRUE)

trait1 = "DD"
trait2 = "EE"
##Take a quick look at the single-trait parameters of DD and EE
sPar[grep(trait1, sPar[, 1]), ] ##Trait 1
```

	Parameter <chr>	EstimatedValue <dbl>
8	DD_pi[1]	0.02936283
9	DD_hyperGammaMeanDN[1]	22.31762802
10	DD_hyperGammaMeanDN[2]	86.03966530
11	DD_hyperBetaDN[1]	0.82594514
12	DD_hyperBetaDN[2]	0.80689775

5 rows

Hide

```
sPar[grep(trait2, sPar[, 1]), ] ##Trait 2
```

	Parameter <chr>	EstimatedValue <dbl>
18	EE_pi[1]	0.01548789
19	EE_hyperGammaMeanDN[1]	51.08181282
20	EE_hyperGammaMeanDN[2]	65.15189031
21	EE_hyperBetaDN[1]	0.80906448
22	EE_hyperBetaDN[2]	0.80774192

5 rows

Set parameters for two traits.

As described above, `mTADA` needs single-trait parameters:

- the number of trios: *ntrio*;
- the mean and disperson parameters of relative risks: $\bar{\gamma}_j$ and β_j (j=$1, 2$);
- the proportion of risk genes: π_1^S and π_2^S.

All these parameters are shown above.

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```
### Trait-1 INFORMATION
ntrio1 = 4293 #family numbers
p1 = 0.02936283 #The proportion of risk genes, this is p1S
meanGamma1 = c(22.31762802,  86.03966530) #Mean Gamma of two categories
beta1 = c(0.82594514, 0.80689775) #Beta values inside the distribution RR ~ Gamma(meanRR
*beta, beta)
dataT1 <- data[, paste0(c("dn_damaging_", "dn_lof_"), trait1)] #De novo data
muDataT1 <- data[, c("mut_damaging", "mut_lof")] #Mutation data of the first trait
########################################
### Trait-2 INFORMATION
ntrio2 = 356
p2 = 0.01548789 #This is p2S
meanGamma2 = c(51.08181282, 65.15189031)
beta2 = c(0.80906448, 0.80774192)
dataT2 <- data[, paste0(c("dn_damaging_", "dn_lof_"), trait2)]
muDataT2 <- muDataT1
```

Run mTADA

In this example, we only use a small number of iterations and two MCMC chains. However, users can change these parameters to obtain more reliable results.

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```
nIteration = 2000 #This should be higher to obtain better results.
nChain = 2 #The number of MCMC chains

##########MAIN ANALYSIS
mTADAresults <- mTADA(geneName = data[, 1],
    #######Trait-1 information
                  ntrio1 = ntrio1, # Trio number of Trait 1
                  p1 = p1, #Risk-gene proportion of Trait 1
                  dataDN1 = data.frame(dataT1), #De novo data of Trait 1
                  mutRate1 = data.frame(muDataT1), # Mutation rates of Trait 1
                  hyperGammaMeanDN1 = c(meanGamma1), # Mean relative risks of Trait 1
                  hyperBetaDN01 = beta1, #NULL, #array(c(1, 1)),
    #######Trait-2 information
                  ntrio2 = ntrio2, # Trio number of Trait 2
                  p2 = p2, #Risk-gene proportion of Trait 2
                  dataDN2 = data.frame(dataT2), # De novo data of Trait 2
                  mutRate2 = data.frame(muDataT2), # Mutation rates of Trait 2
                  hyperGammaMeanDN2 = c(meanGamma2), # Mean relative risks of Trait 2
                  hyperBetaDN02 = beta2, #NULL, #array(c(1, 1)),
    ####Other parameters
                  nIteration = nIteration,
                  useMCMC = TRUE, #If FALSE, it will use the 'Variational Bayes' approac
h.
                  nChain = nChain
                      )
```

```
No information for core numbers (nCore); therefore, nCore = nChain: 2 core(s) is/are use
d

Loading required package: ggplot2
Loading required package: StanHeaders
rstan (Version 2.18.2, GitRev: 2e1f913d3ca3)
For execution on a local, multicore CPU with excess RAM we recommend calling
options(mc.cores = parallel::detectCores()).
To avoid recompilation of unchanged Stan programs, we recommend calling
rstan_options(auto_write = TRUE)
==================
Building the model
=================


=======Use MCMC===========

recompiling to avoid crashing R session
```

```
starting worker pid=11689 on localhost:11216 at 22:36:30.509
starting worker pid=11699 on localhost:11216 at 22:36:30.704

SAMPLING FOR MODEL 'ff6d9758ae6f1964e2f79a593fbb863b' NOW (CHAIN 1).
Chain 1:
Chain 1: Gradient evaluation took 0.06196 seconds
Chain 1: 1000 transitions using 10 leapfrog steps per transition would take 619.6 second
s.
Chain 1: Adjust your expectations accordingly!
Chain 1:
Chain 1:

SAMPLING FOR MODEL 'ff6d9758ae6f1964e2f79a593fbb863b' NOW (CHAIN 2).
Chain 2:
Chain 2: Gradient evaluation took 0.064447 seconds
Chain 2: 1000 transitions using 10 leapfrog steps per transition would take 644.47 secon
ds.
Chain 2: Adjust your expectations accordingly!
Chain 2:
Chain 2:
Chain 2: Iteration:    1 / 2000 [  0%]  (Warmup)
Chain 1: Iteration:    1 / 2000 [  0%]  (Warmup)
Chain 2: Iteration:  200 / 2000 [ 10%]  (Warmup)
Chain 1: Iteration:  200 / 2000 [ 10%]  (Warmup)
Chain 2: Iteration:  400 / 2000 [ 20%]  (Warmup)
Chain 1: Iteration:  400 / 2000 [ 20%]  (Warmup)
Chain 2: Iteration:  600 / 2000 [ 30%]  (Warmup)
Chain 1: Iteration:  600 / 2000 [ 30%]  (Warmup)
Chain 2: Iteration:  800 / 2000 [ 40%]  (Warmup)
Chain 1: Iteration:  800 / 2000 [ 40%]  (Warmup)
Chain 2: Iteration: 1000 / 2000 [ 50%]  (Warmup)
Chain 2: Iteration: 1001 / 2000 [ 50%]  (Sampling)
Chain 1: Iteration: 1000 / 2000 [ 50%]  (Warmup)
Chain 1: Iteration: 1001 / 2000 [ 50%]  (Sampling)
Chain 1: Iteration: 1200 / 2000 [ 60%]  (Sampling)
Chain 2: Iteration: 1200 / 2000 [ 60%]  (Sampling)
Chain 1: Iteration: 1400 / 2000 [ 70%]  (Sampling)
Chain 2: Iteration: 1400 / 2000 [ 70%]  (Sampling)
Chain 1: Iteration: 1600 / 2000 [ 80%]  (Sampling)
Chain 2: Iteration: 1600 / 2000 [ 80%]  (Sampling)
Chain 1: Iteration: 1800 / 2000 [ 90%]  (Sampling)
Chain 2: Iteration: 1800 / 2000 [ 90%]  (Sampling)
Chain 1: Iteration: 2000 / 2000 [100%]  (Sampling)
Chain 1:
Chain 1:  Elapsed Time: 216.836 seconds (Warm-up)
Chain 1:                200.684 seconds (Sampling)
Chain 1:                417.52 seconds (Total)
Chain 1:
Chain 2: Iteration: 2000 / 2000 [100%]  (Sampling)
Chain 2:
Chain 2:  Elapsed Time: 214.078 seconds (Warm-up)
Chain 2:                236.771 seconds (Sampling)
```

```
Chain 2:                450.849 seconds (Total)
Chain 2:
```

```
====
Only pi, alpha and hyper parameters are estimated in this step
The method does not calculate HPDs for hyper betas, just their medians
===
```

Get results

mTADA's output includes:

1. data: main gene-level results (posterior probabilities for the four models as described in the main manuscript: PP0, PP1, PP2 and PP3).
2. probModel: a vector of $\pi_j, (j = 0..3)$ in Table 1.
3. pars: the estimated value and credible interval of π_3 (described as p12 in the our code).
4. mcmcData: MCMC sampling results for π_3.

The most important information is from data. **Users can use this information to obtain top prioritized genes for downstream analyses (e.g., top shared/specific genes, top genes for each trait)**. However, we will also take a quick look at all these information.

Results for downstream analyses (gene-level posteior probabilities of four models)

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```
fData <- mTADAresults$data ## Full analysis results of the two-trait analysis.
head(fData)
```

	geneN... <fctr>	dn_damaging_... <int>	dn_lof_DD <int>	dn_damaging_EE <int>	dn_lof_EE <int>	NO <dbl>	BOTH <dbl>	
1	A1BG	0	0	0	0	0.9784946	0.0028550015	0
2	A1BG-AS1	0	0	0	0	0.9647405	0.0060271817	0
3	A1CF	0	0	0	0	0.9893911	0.0006431995	0
4	A2M	0	0	1	0	0.7714102	0.0024827978	0
5	A2M-AS1	0	0	0	0	0.9637469	0.0062617028	0
6	A2ML1	0	0	0	0	0.9919857	0.0002078256	0

6 rows | 1-9 of 9 columns

Genes with PP3 > 0.8 (Posterior probabilities of Model 3)

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```
fData[fData$BOTH > 0.8, ]
```

	geneN... <fctr>	dn_damaging_... <int>	dn_lof_DD <int>	dn_damaging_EE <int>	dn_lof_EE <int>	NO <dbl>	BOT <db
2348	CACNA1A	5	0	2	0	3.093126e-04	0.99335
3201	CHD2	0	6	0	1	4.581862e-10	0.93658
6254	GABBR2	2	0	2	0	2.498878e-03	0.95234
6265	GABRB3	2	0	2	0	9.156252e-04	0.97993
6610	GNAO1	4	1	2	0	1.589460e-08	0.99839
7165	HECW2	5	1	1	0	1.920582e-06	0.89109
7426	HNRNPU	0	7	0	1	8.711099e-13	0.93592
8283	KCNQ2	9	0	2	0	3.222422e-13	0.99820
8284	KCNQ3	3	0	1	0	4.281558e-03	0.91256
10146	MLL	1	26	1	0	1.470790e-48	0.86655

1-10 of 14 rows | 1-8 of 9 columns Previous **1** 2 Next

Genes with PP1 > 0.8 (Posterior probabilities of Model 1)

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```
fData[fData$FIRST > 0.8, ]
```

	geneN... <fctr>	dn_damaging_... <int>	dn_lof_DD <int>	dn_damaging_EE <int>	dn_lof_EE <int>	NO <dbl>	BC <c
347	ADNP	1	19	0	0	4.080469e-37	0.19885
681	ANKRD11	0	32	0	0	2.294720e-60	0.13711
1001	ARID1B	0	30	0	0	1.702385e-56	0.14473
1002	ARID2	0	3	0	0	2.191889e-03	0.17291
1153	ASXL1	0	4	0	0	1.843811e-05	0.17086
1155	ASXL3	0	14	0	0	2.520815e-25	0.19831
1317	AUTS2	0	4	0	0	1.133047e-05	0.18285
1450	BCL11A	2	3	0	0	7.452502e-07	0.18902
1630	BRPF1	0	4	0	0	7.108166e-05	0.13126
2355	CACNA1E	2	2	0	0	4.906898e-02	0.08806

1-10 of 69 rows | 1-8 of 9 columns Previous **1** 2 3 4 5 6 7 Next

Genes with PP2 > 0.8 (Posterior probabilities of Model 2)

Hide

```
fData[fData$SECOND > 0.8, ]
```

	geneN…	dn_damaging_…	dn_lof_DD	dn_damaging_EE	dn_lof_EE	NO	BOT
	<fctr>	<int>	<int>	<int>	<int>	<dbl>	<db
14671	SCN1A	2	0	4	4	2.031812e-12	0.11970

1 row | 1-8 of 9 columns

Use mTADA's results for single-trait analyses.

We can obtain single-trait results by summing PP1 and PP3 (Trait 1) or PP2 and PP3 (Trait 2).

Trait 1

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```
fData[, 'pTrait1'] <- fData[, 'BOTH'] + fData[, 'FIRST']
fData1 <- fData[fData$pTrait1 > 0.8, ]
head(fData1[, c(1:5, 10)])
```

	geneNa…	dn_damaging_DD	dn_lof_DD	dn_damaging_EE	dn_lof_EE	pTrait1
	<fctr>	<int>	<int>	<int>	<int>	<dbl>
347	ADNP	1	19	0	0	1.0000000
447	AHDC1	0	8	0	0	1.0000000
681	ANKRD11	0	32	0	0	1.0000000
1000	ARID1A	1	2	0	0	0.9149582
1001	ARID1B	0	30	0	0	1.0000000
1002	ARID2	0	3	0	0	0.9977940

6 rows

Trait 2

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```
fData[, 'pTrait2'] <- fData[, 'BOTH'] + fData[, 'SECOND']
fData2 <- fData[fData$pTrait2 > 0.8, ]
head(fData2[, c(1:5, 11)])
```

	geneNa…	dn_damaging_DD	dn_lof_DD	dn_damaging_EE	dn_lof_EE	pTrait2
	<fctr>	<int>	<int>	<int>	<int>	<dbl>
2348	CACNA1A	5	0	2	0	0.9957813
3201	CHD2	0	6	0	1	0.9365805
6254	GABBR2	2	0	2	0	0.9958140
6265	GABRB3	2	0	2	0	0.9975110

	geneNa… <fctr>	dn_damaging_DD <int>	dn_lof_DD <int>	dn_damaging_EE <int>	dn_lof_EE <int>	pTrait2 <dbl>
6610	GNAO1	4	1	2	0	0.9983942
7165	HECW2	5	1	1	0	0.8910935

6 rows

Other information

Some additional information can be obtained from mTADA's results.

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```
pCI <- mTADAresults$pars ## Genetic parameters
piValue <- mTADAresults$probModel ## Posterior probabilities of genes for four models
mcmcResult <- mTADAresults$mcmcData ##MCMC results
```

The proportions of risk genes

piValue is a vector of π values. In the result below, pNO, pFIRST, pSECOND, and pBOTH are π_0, π_1, π_2 and π_3 respectively in **Table 1**.

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```
piValue
```

```
       pNO     pFIRST    pSECOND      pBOTH
0.96185829 0.02265382 0.00877888 0.00670901
```

Estimated information of π_3.

Credible-interval information is from pCI.

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```
pCI ## Mode: estimated values; CI: credible interval with low (l) and upper (u) values
```

```
                      Mode          lCI         uCI
p12              0.00670901  0.003715159  0.01033473
gammaMeanDN1[1] 22.87837653 19.965979478 25.56982137
```

To check the convergent information of π_3, we can visualize MCMC results.

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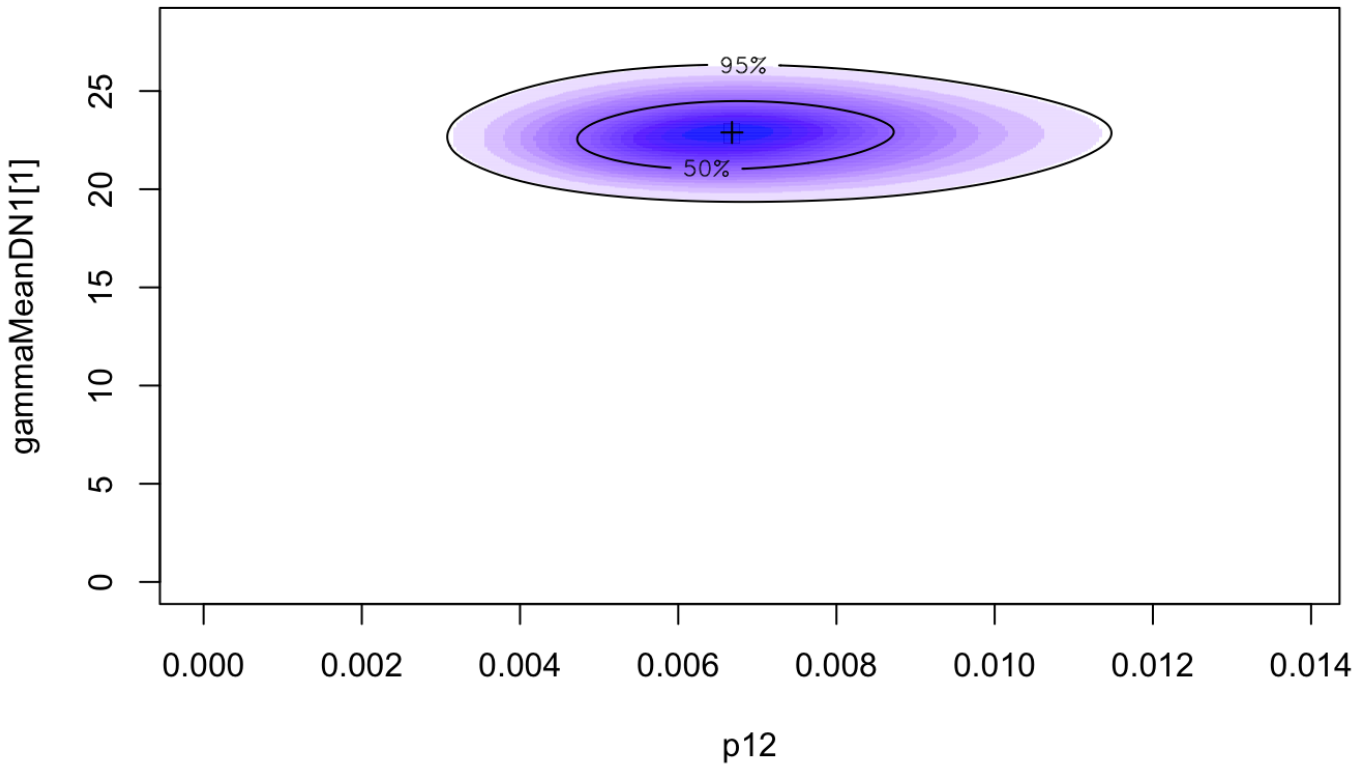
```
## p12 is pi3 in the model
plotParHeatmap1(mcmcResult = mcmcResult, pars = c('p12', 'gammaMeanDN1[1]'))
```



Citation

mTADA**: a framework for identifying risk genes from de novo mutations in multiple traits.** Hoang T. Nguyen, Amanda Dobbyn, Ruth C. Brown, Brien P. Riley, Joseph Buxbaum, Dalila Pinto, Shaun M Purcell, Patrick F Sullivan8, Xin He, Eli A. Stahl.