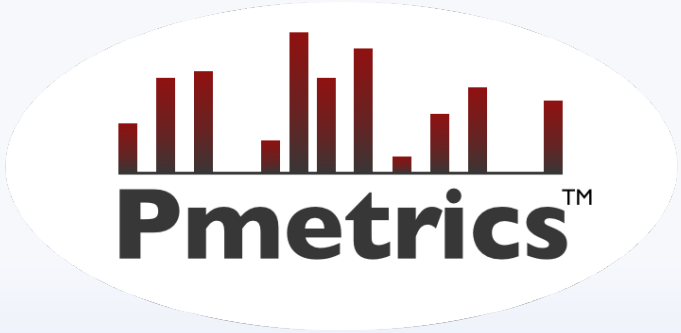

Probability of Target Attainment

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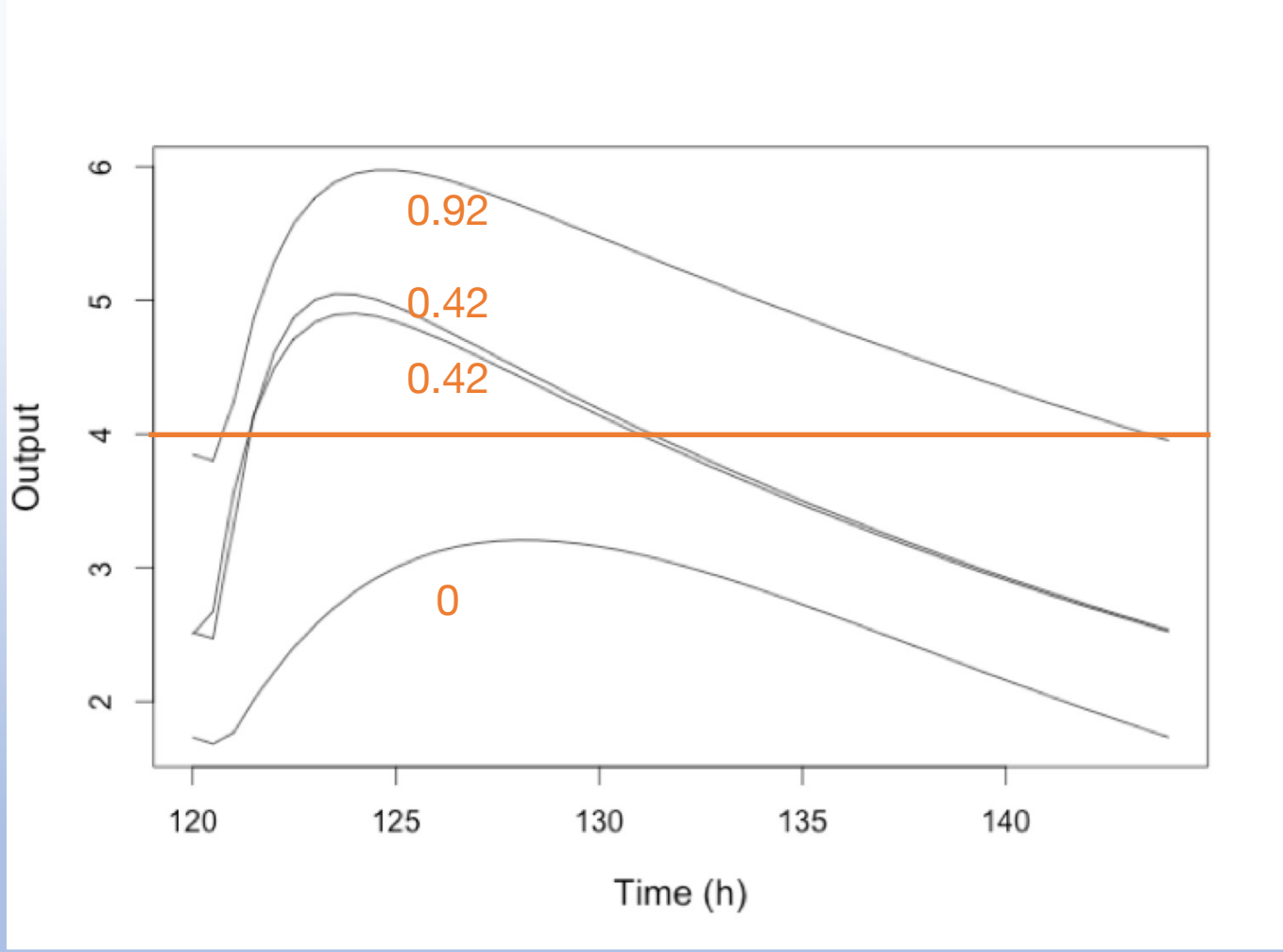
Probability of Target Attainment (PTA)

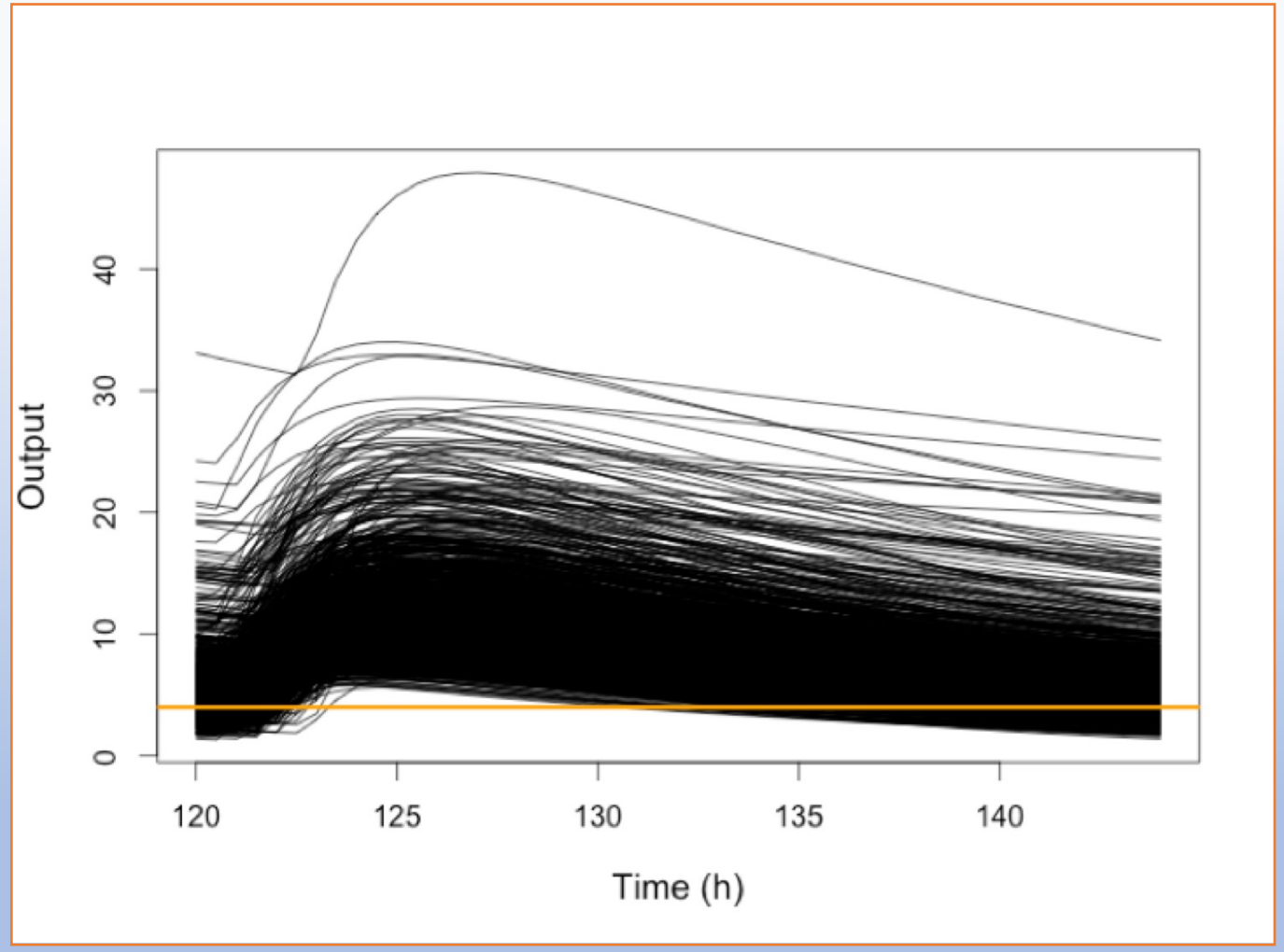
- Simulation technique
- Calculate the proportion of simulated profiles which meet a predefined success threshold for a given dosage regimen
- E.g. AUC:MIC > 10, or %dosage interval (time) > 0.6

PTA



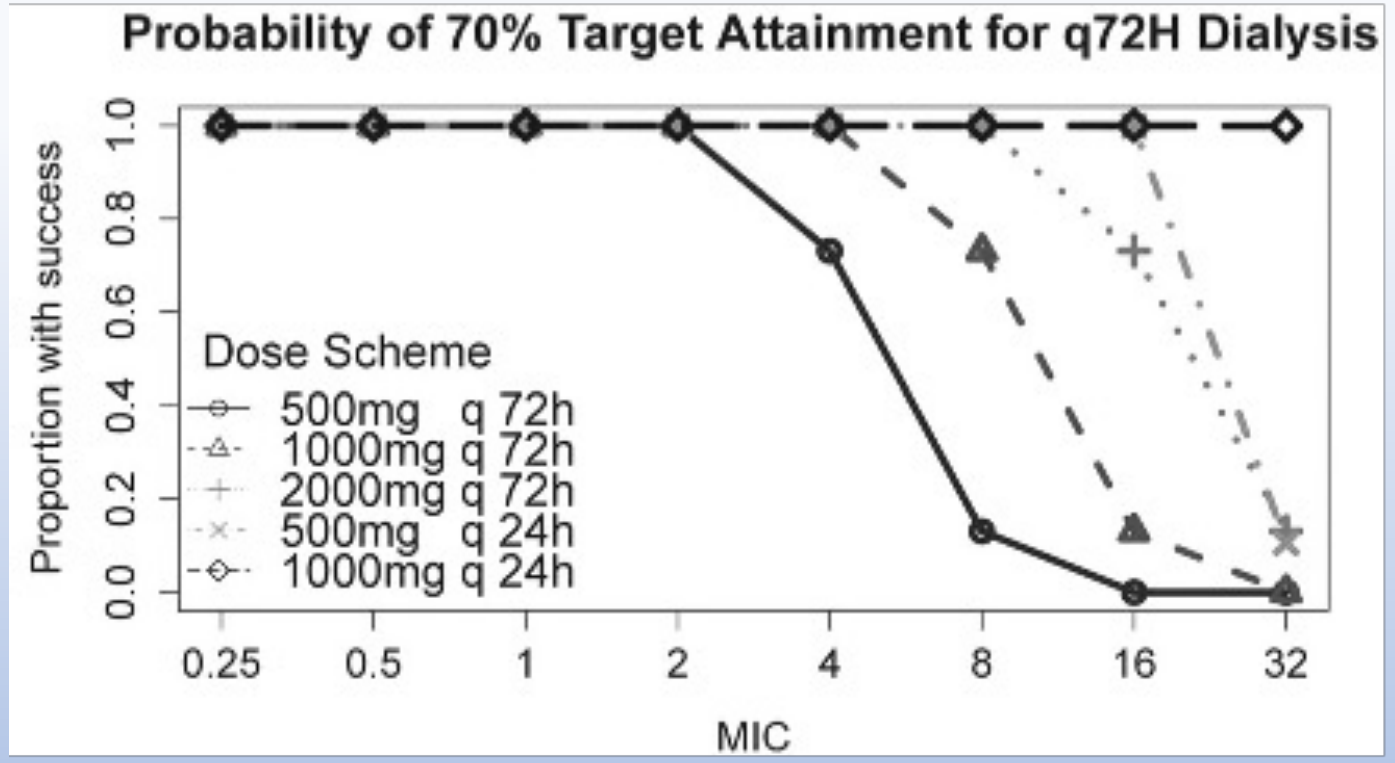
N=4
Mean: 0.44
SD: 0.39
PTA: 25%

PTA



N=1000
Mean: 0.91
SD: 0.14
PTA: 95%

PTA



Loo AS, Neely MN, Anderson EJ, Ghossein C, McLaughlin M, Scheetz MH. Pharmacodynamic target attainment for various ceftazidime dosing schemes in high-flux hemodialysis. Antimicrob Agents Chemother. 2013;57(12):5854–5859.

PM_pta

- Contains all information from a simulation to perform PTA analysis
- class: PMpta, list

```
PM_pta$new(simdata, simlabels, targets,
target.type, success, outeq = 1,  free.fraction
= 1, start, end)
```

Or

```
PM_sim$pta(…)
```

PM_pta$new(): simdata

- A list of simulation outputs. Do not use combine.
- Eg. `simdata <- PM_sim$run(…, combine = F)`

PM_pta$new(): simlabels

- An optional character vector of labels for each simulation in simdata, in order, to be used in plots.
- E.g. `simlabels = c("1200 mg daily", "600 mg bid", "300 mg tie")`
- Default is `simlabels = c("Regimen 1", "Regimen 2", "Regimen 3",…)`

PM_pta$new():targets

- A vector of targets to be compared to exposure
- E.g. `targets=c(0.25, 0.5, 1, 2, 4, 8, 16, 32, 64)` for doubling minimum inhibitory concentrations (MICs) or `targets=4` for a specific concentration which might be a trough

PM_pta$new(): targets

- Can also be a simulated distribution of targets
- Use `makePTAtarget(x)`, where x is a data frame with two columns: targets, frequency

X	Y
0.002	0
0.004	0
0.008	0
0.016	0
0.032	0
0.064	1
0.125	69
0.25	539
0.5	13997
1	68601
2	8445
4	218
8	3
16	0
32	1
64	1
128	1
256	0
512	0

S. aureus vancomycin MIC (Eucast)

PM_pta$new(): target.type

- Specifies which exposure to compare to targets
  - **time**…Will compute the proportion of specified `start` to `end` dosing interval that output is above each target
  - **auc**…Will compute the ratio of AUC for specified `start` to `end` dosing interval to each target
  - **peak**…Will compute the ratio of maximum concentration in specified `start` to `end` dosing interval to each target
  - **min**…Will compute the ratio of minimum concentration in specified `start` to `end` dosing interval to each target
  - **n**…Will compute the ratio of concentration at time n to each target; n must be a simulated time point within the specified `start` to `end` dosing interval

PM_pta$new(): success

- Single value that defines the threshold *proportion* (`target.type="time"`) or *ratio* (all other target.types) to be defined as success
- e.g. `success=10` for AUC:target ≥ 10, or `success=0.8` for 80% of dosing interval above target

PM_pta$new(): outeq

- Define the output equation values to use for the PTA

PM_pta$new():free.fraction

- Multiply output values by this amount prior to PTA
- Useful to simulate free, active fraction of total concentration

PM_pta$new(): start and end

- **start**…The beginning of the interval whose cocentrations will be used to calculate the PTA
- **end**…The end of the interval

PM_pta structure

- **results**…data frame with the following columns:
  - simnum - regimen
  - id - simulated subject (1 to nsim)
  - target - targets
  - pdi - ratio/proportion, as specified by `target.type`
- **outcome**…data frame with the following columns
  - simnum
  - target (if `targets` are discrete)
  - prop.success
  - pdi.mean

Summarize PM_pta

- When targets are discrete:

$pta

	simnum	target	prop.success	pdi.mean	pdi.sd
1	1	0.25	1.000	27.8001331	25.3544073
2	1	0.50	1.000	13.9000666	12.6772037
3	1	1.00	1.000	6.9500333	6.3386018
4	1	2.00	0.956	3.4750166	3.1693009
5	1	4.00	0.647	1.7375083	1.5846505
6	1	8.00	0.251	0.8687542	0.7923252
7	1	16.00	0.063	0.4343771	0.3961626
8	1	32.00	0.009	0.2171885	0.1980813
9	2	0.25	1.000	55.6002668	50.7088175
10	2	0.50	1.000	27.8001334	25.3544088
11	2	1.00	1.000	13.9000667	12.6772044

$pdi

	target	simnum	lowerCI	median	upperCI
1	0.25	1	6.87164250	20.6004900	90.4035400
2	0.25	2	13.74328490	41.2009800	180.8070790
3	0.25	3	10.71711530	27.3798100	121.3775870
4	0.25	4	21.43423050	54.7596200	242.7551350
5	0.50	1	3.43582125	10.3002450	45.2017700
6	0.50	2	6.87164245	20.6004900	90.4035395
7	0.50	3	5.35855765	13.6899050	60.6887935
8	0.50	4	10.71711525	27.3798100	121.3775675
9	1.00	1	1.71791063	5.1501225	22.6008850
10	1.00	2	3.43582123	10.3002450	45.2017697
11	1.00	3	2.67927883	6.8449525	30.3443967
12	1.00	4	5.35855763	13.6899050	60.6887837

pta = probability of target attainment

pdi = pharmacodynamic index

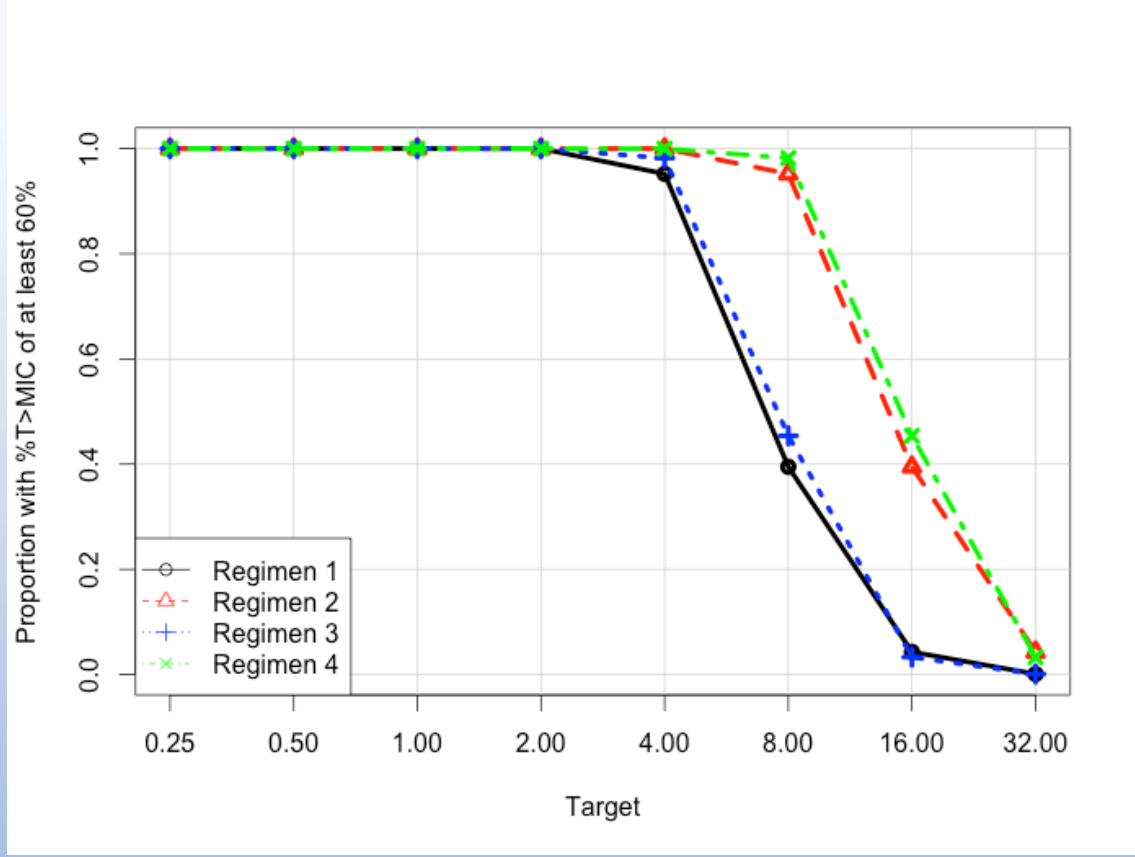
target.type="min", success=1

Summarize PM_pta

- When targets are continuous:

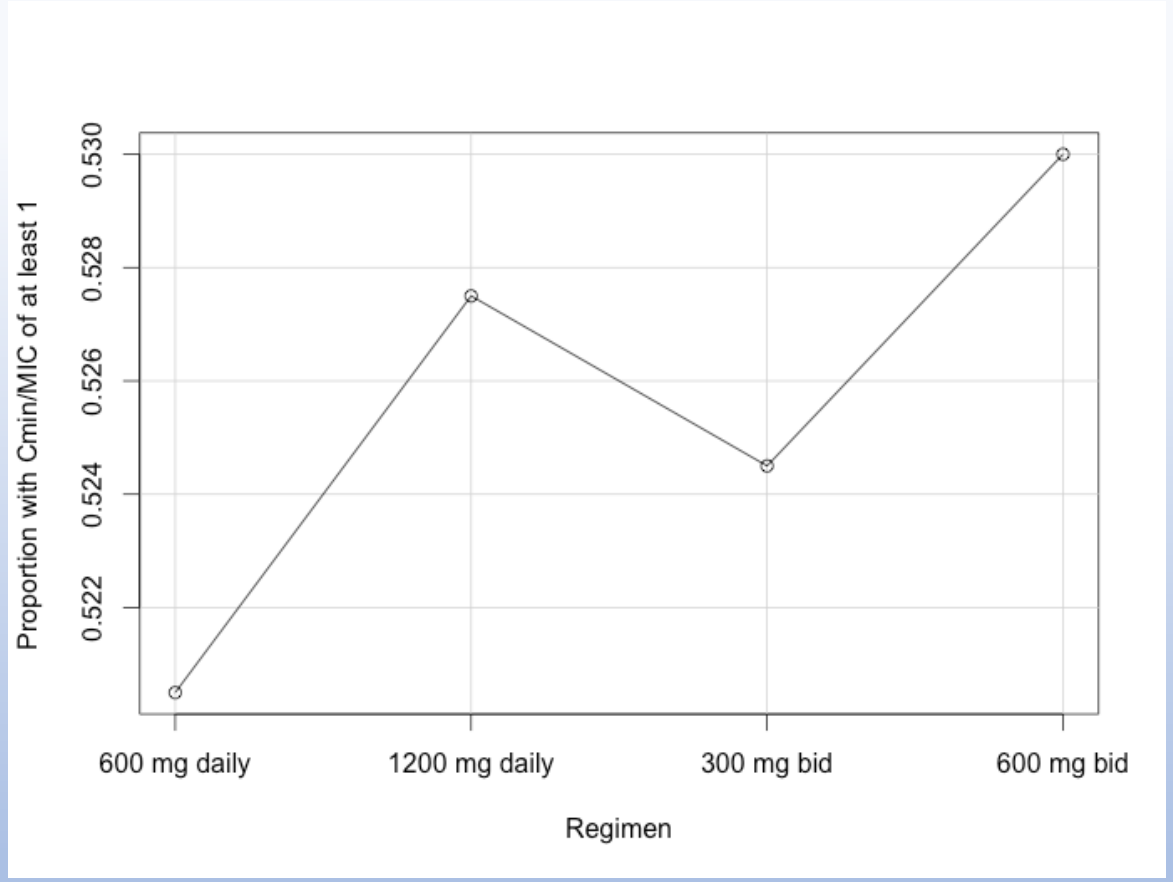
```
$pta
  simnum prop.success  pdi.mean   pdi.sd
1      1       0.5205  83.66498 210.8501
2      2       0.5275 164.57114 421.4380
3      3       0.5245 105.44602 235.1845
4      4       0.5300 208.13321 470.3897

$pdi
  simnum lowerCI   median   upperCI
1      1   0.016 2.172168  586.0183
2      2   0.016 4.000000 1172.0363
3      3   0.016 2.907910  689.3476
4      4   0.016 4.000000 1378.6958
```

PM_pta$plot()



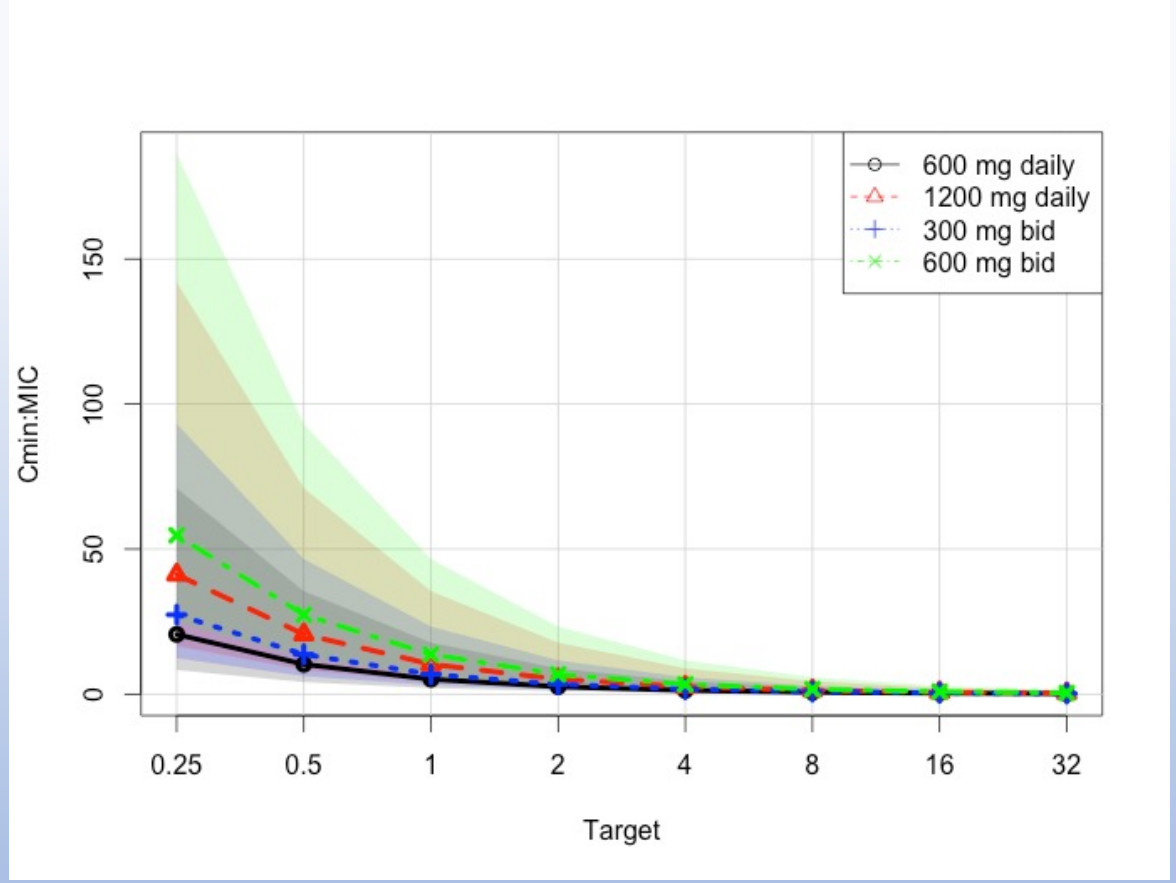

```
pta1$plot(,ylab="Proportion with %T>MIC of at least 60%", grid=T,legend = list(x = "bottomleft"))
```

Targets are continuous



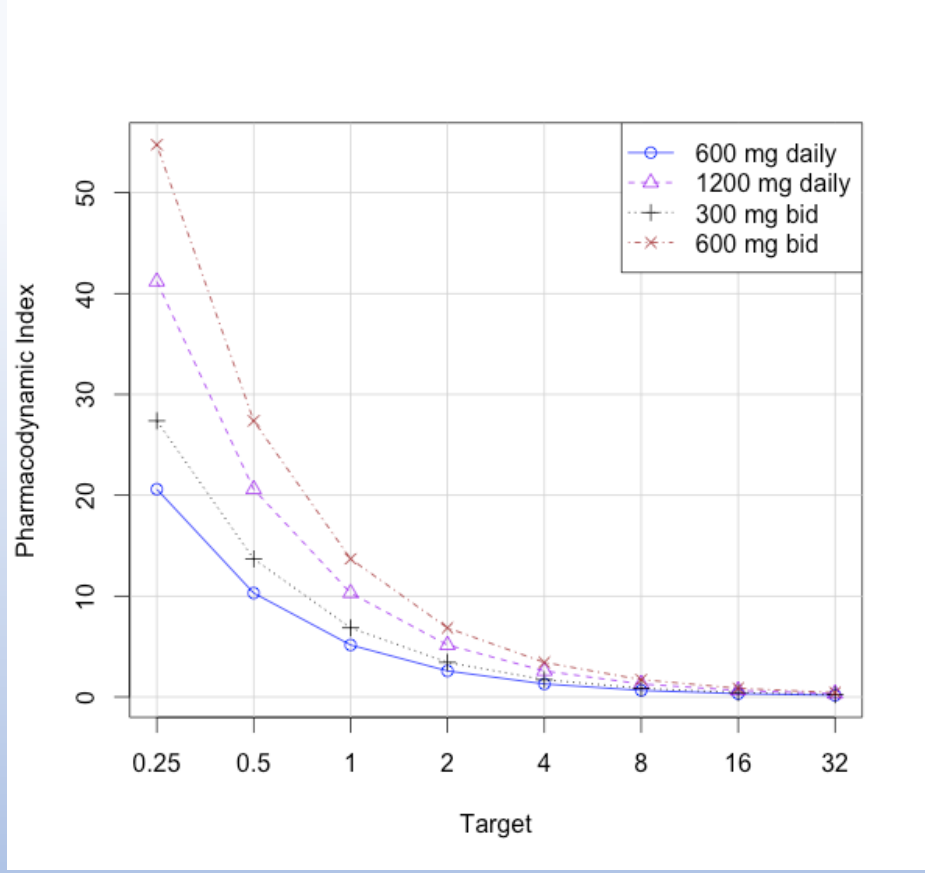

```
pta2$plot(grid = T, ylab = "Proportion with Cmin/MIC of at least 1")
```

PDI plot

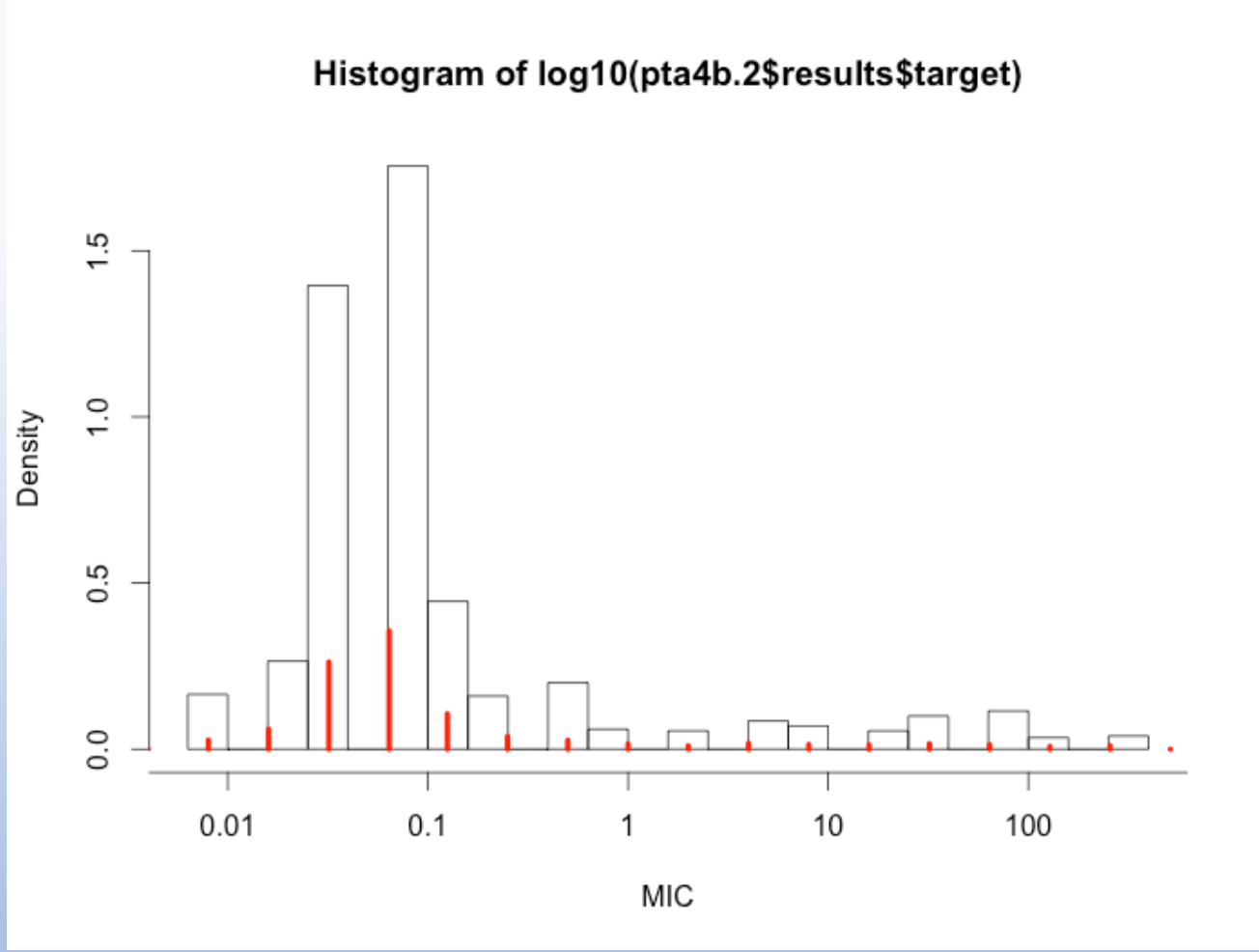



```
Pta2$plot(plot.type = "pdi", ylab = "Cmin:MIC", grid = T)
```

PDI plot




```
pta2$plot(plot.type = "pdi", ci = 0, grid = T, col = c("blue", "purple", "black", "brown"), lwd = 1)
```




```
hist(log10(pta4b.2$results$target),breaks=20,freq=F,xlab="MIC",xaxt="n")
axis(side=1,at=pretty(log10(pta4b.2$results$target)),labels=10**pretty(log10(pta4b.2$results$target)))
lines(x=log10(mic1$mic),y=mic1$n/sum(mic1$n),type="h",col="red",lwd=4)
```