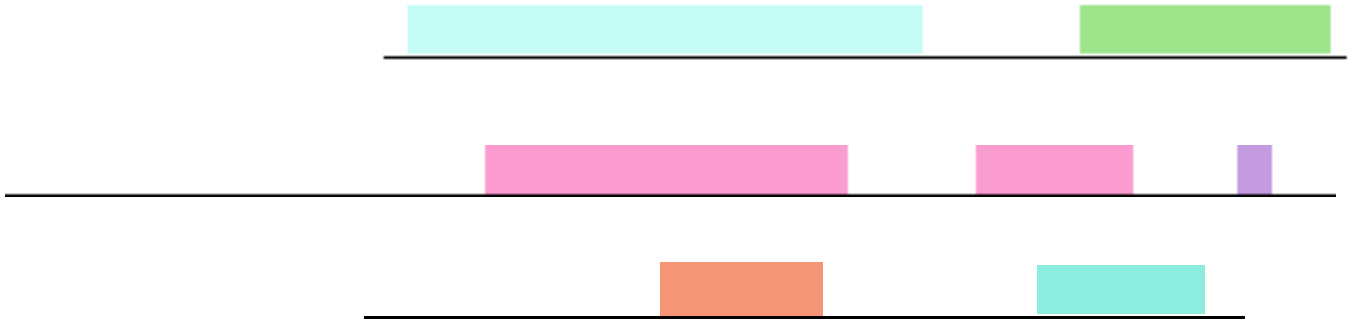
Beyond the *E*-value: stratified statistics for protein domain prediction



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2015-10-15

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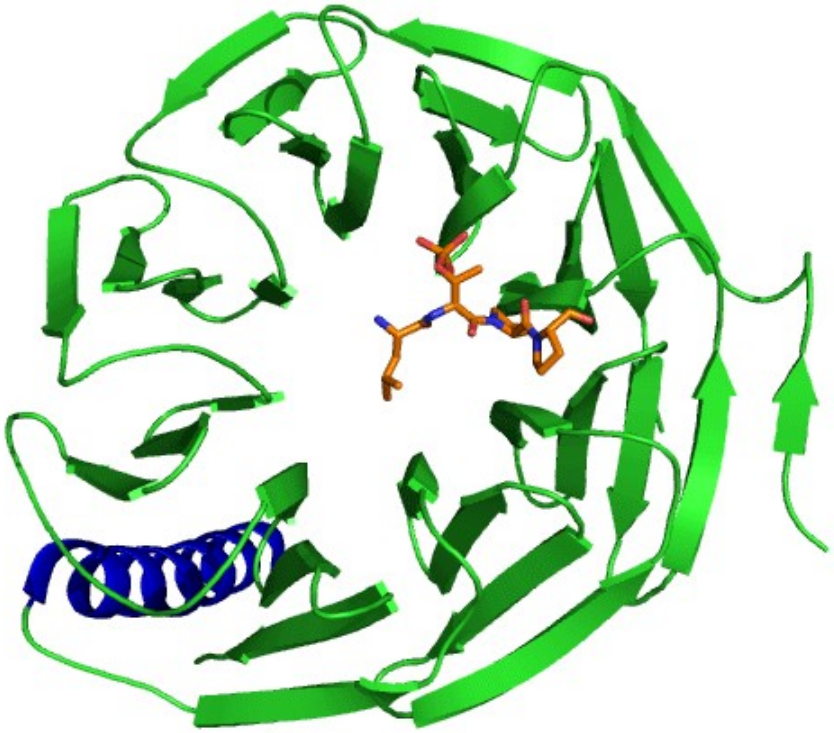
Protein domains



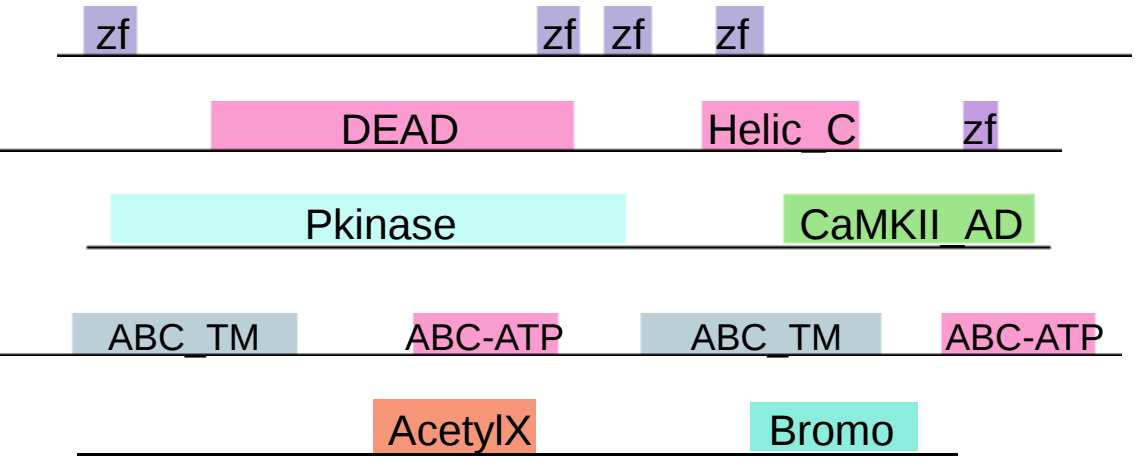
Structure

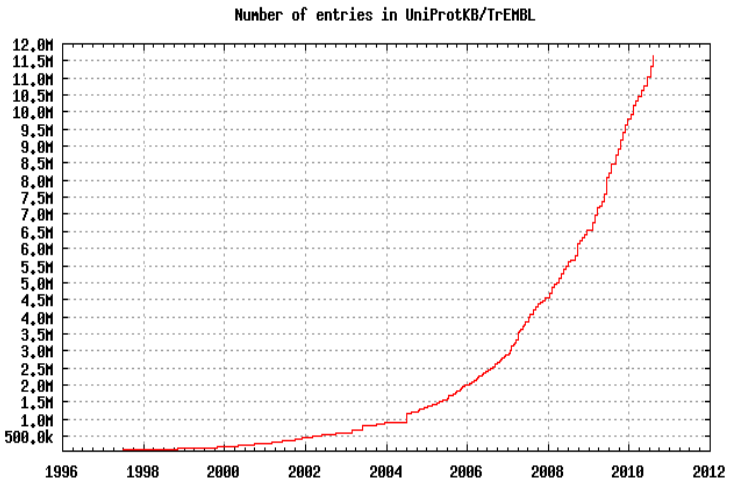
Evolution

Function

Sequence-based domain prediction:

Why predict domains?





For new sequences, before experiments start…

Domains may imply functions

Experimental alternatives are unfeasible since protein databases grow exponentially

Representing Domains

```
SNAI_DROME/362-385      YACQ...VCH...KSFSRM...SLLNKHSSS..NC
SNAI_XENLA/232-255      YQCK...SCS...RTFSRM...SLLHKHEET..GC
SNAI_MOUSE/236-259      YQCQ...ACA...RTFSRM...SLLHKHQES..GC
ESCA_DROME/426-449      YSCT...SCS...KTFSRM...SLLTKHSEG..GC
SUHW_DROAN/221-243      HVCG...KCY...KTFRRL...MSLKKHLEF...C
TERM_DROME/323-346      LHCR...RCR...TQFSRR...SKLHIHQKL..RC
ZO20_XENLA/174-196      FMCA...DCG...RCFSVS...SSLKYHQRI...C
EVI1_HUMAN/217-239      IKCK...DCG...QMFSTT...SSLNKHRRF...C
ZO2_XENLA/34-59         YSCA...DCG...KHFSEK...MYLQFHQKNPSEC
EVI1_HUMAN/21-44        YRCE...DCD...QLFESK...AELADHQKF..PC
ZNF10_HUMAN/517-539     YKCN...QCG...IIFSQN...SPFIVHQIA...H
ZNF91_HUMAN/238-260     YKCE...ECG...KAFKQL...STLTTHKII...C
ZFP58_MOUSE/120-142     IKCE...ECG...KAFSTR...STYYRHQKN...H
TRA1_CAEEL/306-331      YKCEF.ADCE...KAFSNA...SDRAKHQNR..TH
ZNF76_HUMAN/345-368     YTCS...TCG...KTYRQT...STLAMHKRS..AH
ZN12_MICSA/106-129      YRCS...QCG...KAFRRT...SDLSSHRRT..QC
LOLA1_DROME/794-817     YECR...HCG...KKYRWK...STLRRHENV..EC
ZNF17_HUMAN/435-457     YECN...KCG...KFFRYC...FTLNRHQRV...H
ZG32_XENLA/34-56        FVCV...HCG...KGFRDN...YKLSLHLRI...H
TF3A_BUFAM/104-128      YVCYF.ADCG...QQFRKH...NQLKIHQYI...H
ZG46_XENLA/146-168      YVCT...ECG...TSFRVR...PQLRIHLRT...H
MZF1_HUMAN/412-434      FVCG...DCG...QGFVRS...ARLEEHRRV...H
ZN239_MOUSE/6-28        YKCD...KCG...KGFTRS...SSLLVHHSV...H
ZSC22_HUMAN/352-374     YKCG...ECG...KTFSRS...THLTQHQRV...H
EGR1_HUMAN/396-418      FACD...ICG...RKFARS...DERKRHTKI...H
SUHW_DROAN/349-373      YACK...ICG...KDFTRS...YHLKRHQKYS.SC
CF2_DROME/485-508       YTCP...YCD...KRFTQR...SALTVHTTK..LH
CF2_DROME/401-423       YTCS...YCG...KSFTQS...NTLKQHTRI...H
KRUP_DROME/306-328      YTCE...ICD...GKFSDS...NQLKSHMLV...H
TYY1_HUMAN/383-407      YVCPF.DGCN...KKFAQS...TNLKSHILT...H
ZG52_XENLA/61-83        YTCT...QCN...KQFSHS...AQLRAHIST...H
TTKB_DROME/538-561      YPCP...FCF...KEFTRK...DNMTAHVKI..IH
ZNF76_HUMAN/285-309     YTCPE.PHCG...RGFTSA...TNYKNHVRI...H
SDC1_CAEEL/145-168      YMCQ...VCL...TLFGHT...YNLFMHWRT..SC
SRYC_DROME/358-380      YQCD...ICG...QKFVQK...INLTHHARI...H
SDC1_CAEEL/270-292      YFCH...ICG...TVFIEQ...DNLFKHWRL...H
TRA1_CAEEL/276-300      NKCEY.PGCG...KEYSRL...ENLKTHRRT...H
ESCA_DROME/370-392      CKCN...LCG...KAFSRP...WLLQGHIRT...H
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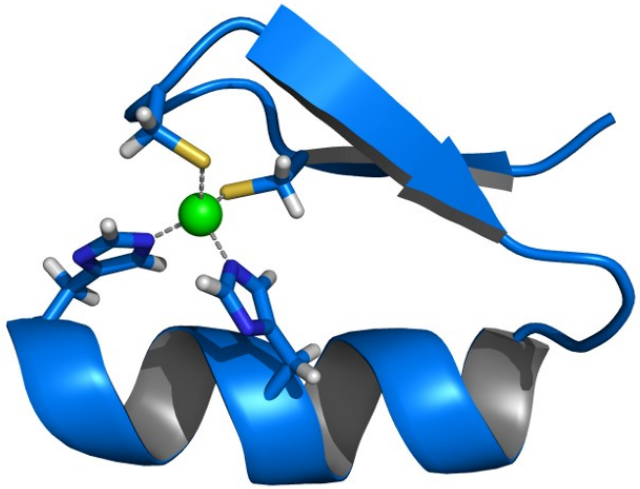
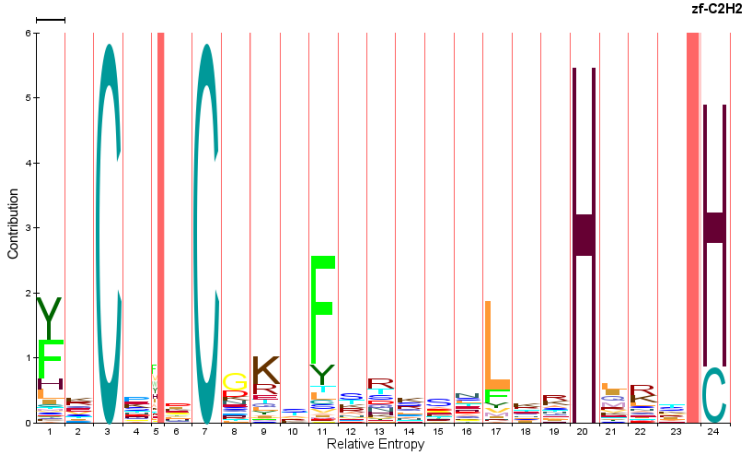
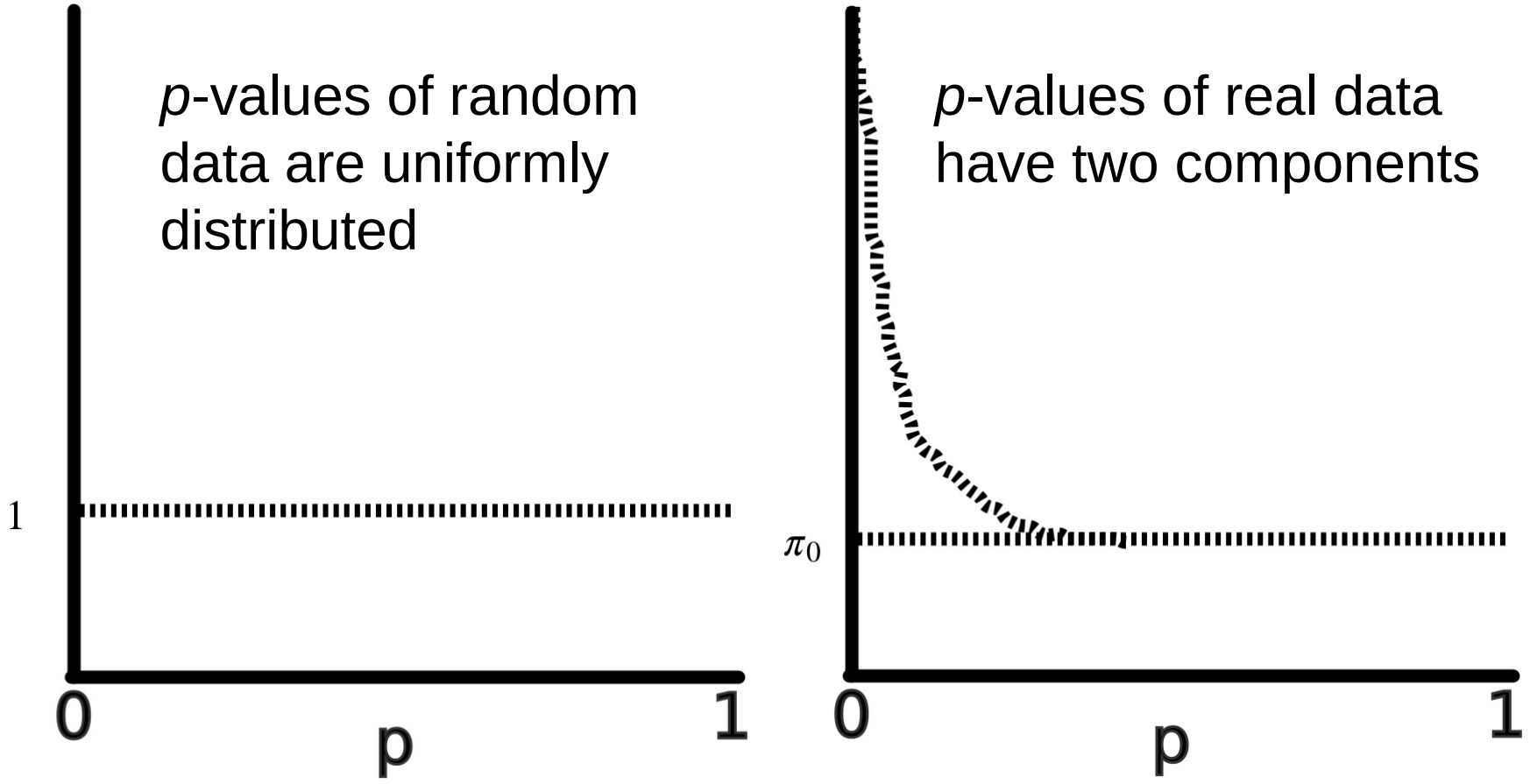


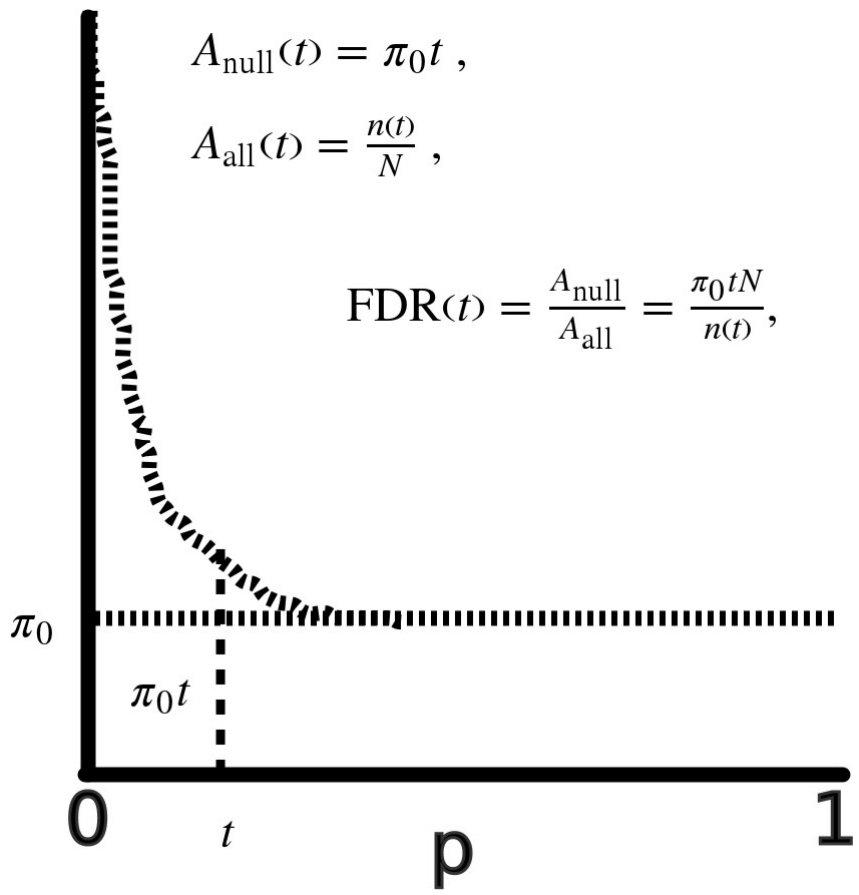


Computing *q*-values



Step 1: estimate π_0 (proportion of data that is false)

Computing *q*-values



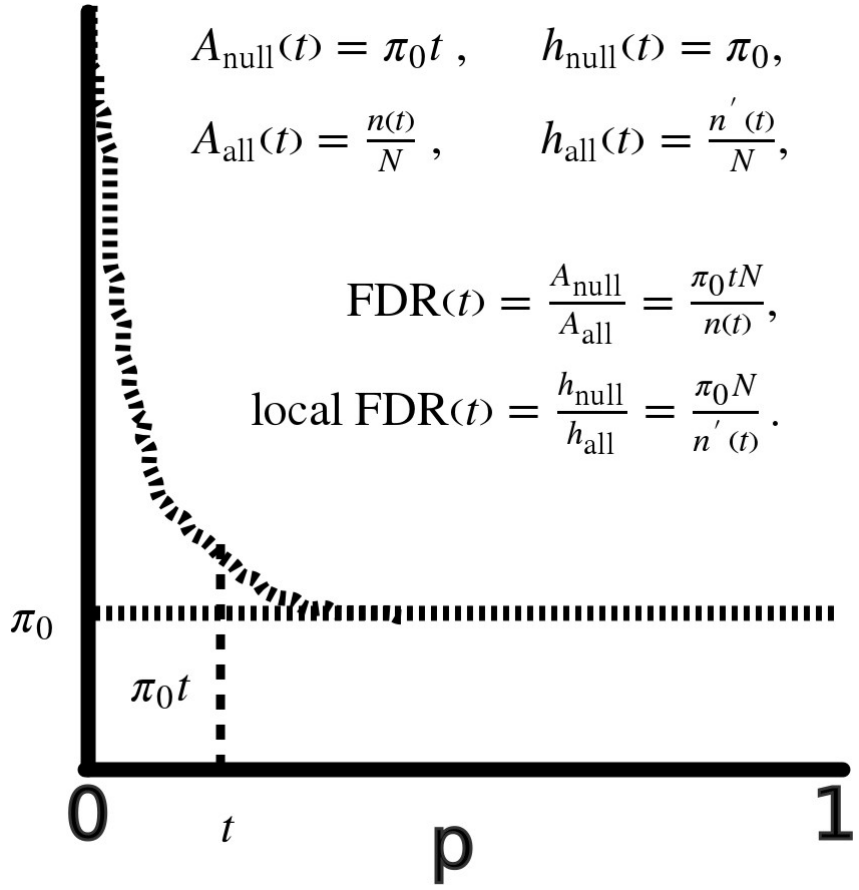
Step 2: Directly estimate FDR(*t*) for all thresholds *t*

- *N* = # tests
- *n(t)* = # sig tests

Step 3: Ensure monotonicity

$q(p) = \min_{t;p \le t} \text{FDR}(t)$

The local FDR



Local FDR = Posterior Error Probability

FDR = average local FDR of significant predictions

Local FDRs are optimal for stratified problems

Goal: Find thresholds t_i for each stratum (family) *i* that maximize predictions

$$\sum_i n_i\left(t_i\right),$$

constraining the combined *FDR* across strata to *Q:*

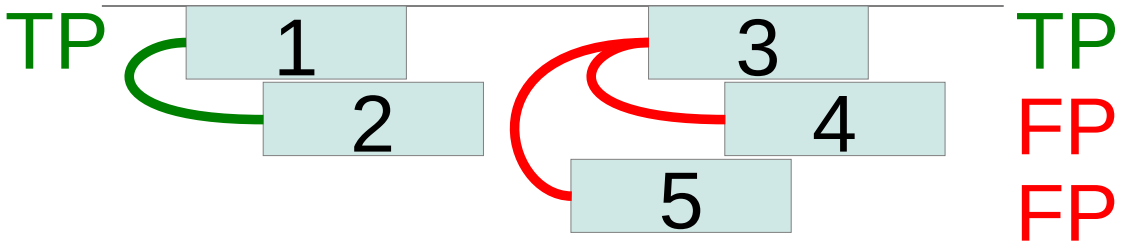
$$\frac{\sum_i \pi_{0,i} t_i N_i}{\sum_i n_i\left(t_i\right)} \leq Q\,.$$

Necessary condition of solution:
Equal per-stratum *local FDR* thresholds!

Empirical FDR tests

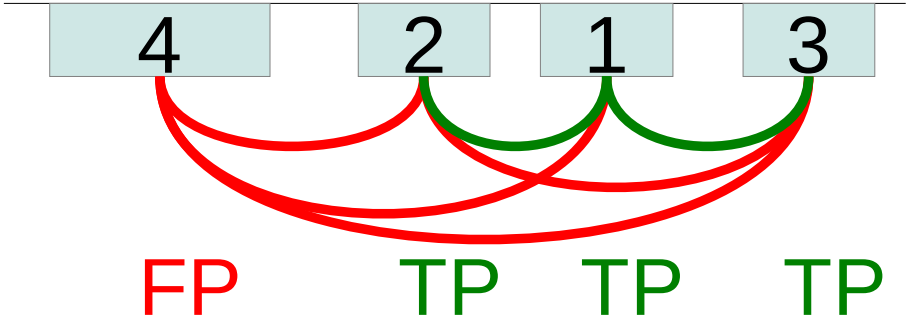
A

Clan Overlap



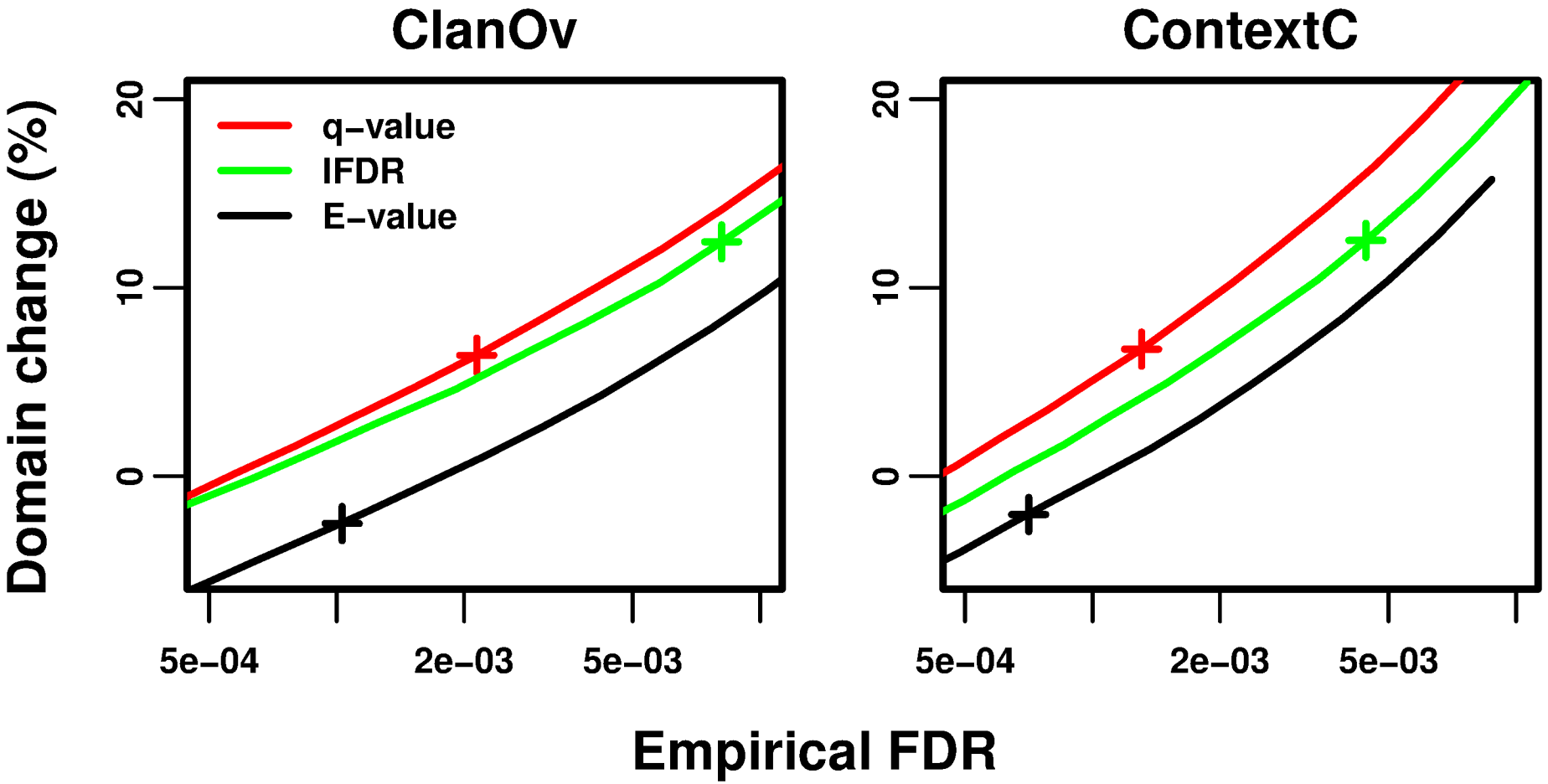
B

Context Coherence

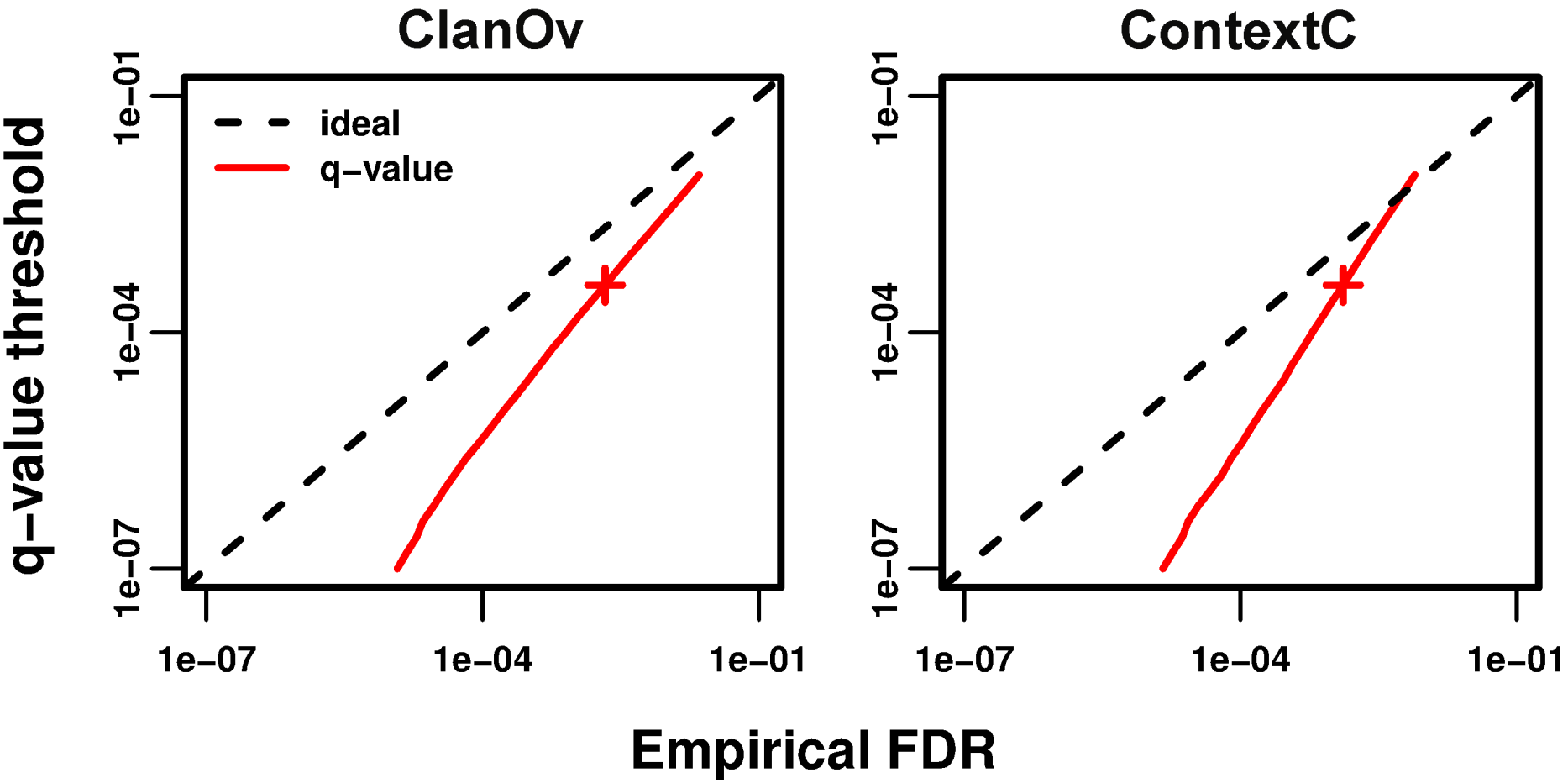


FDR Tests adapted from:
Mistry, *et al*. Nucl Acids Res. 2013;41: e121–e121.
Terrapon, *et al*. BMC Bioinformatics. 2012;13: 67.
Ochoa, *et al*.. BMC Bioinformatics. 2011;12: 90.

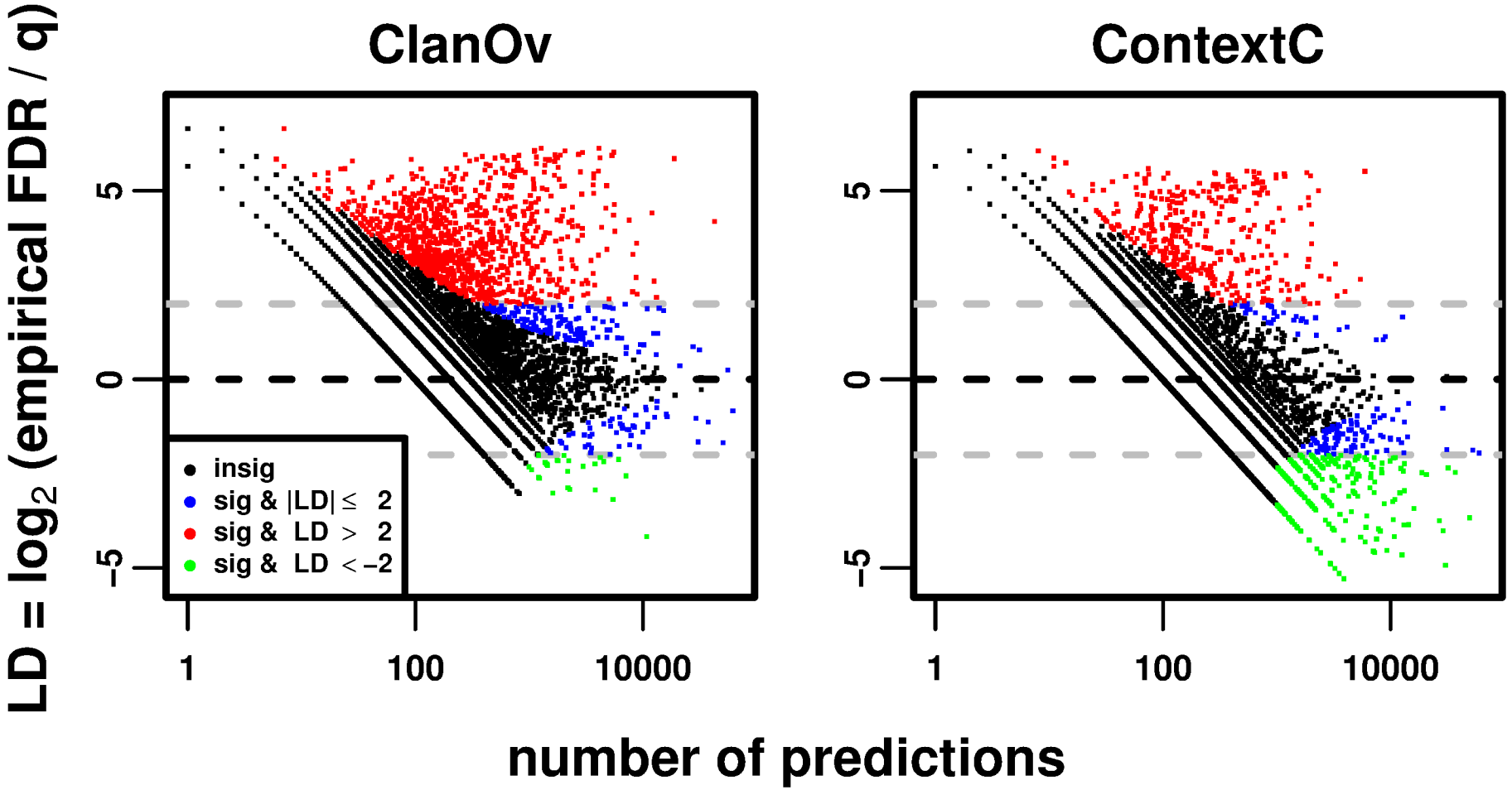
Stratified statistics improve upon *E*-values



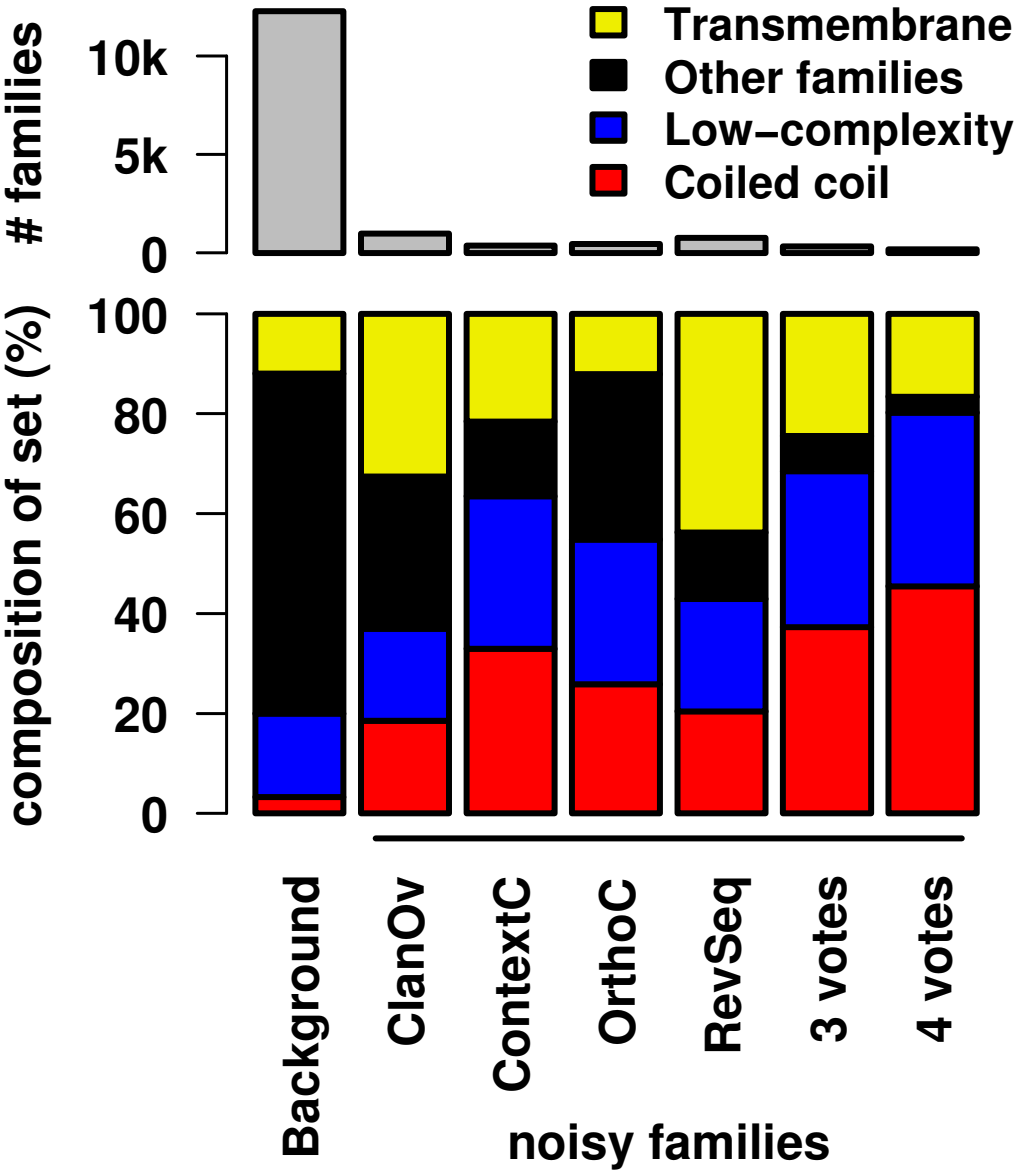
Disagreement between *q*-values and empirical FDRs



Measuring noise per domain family

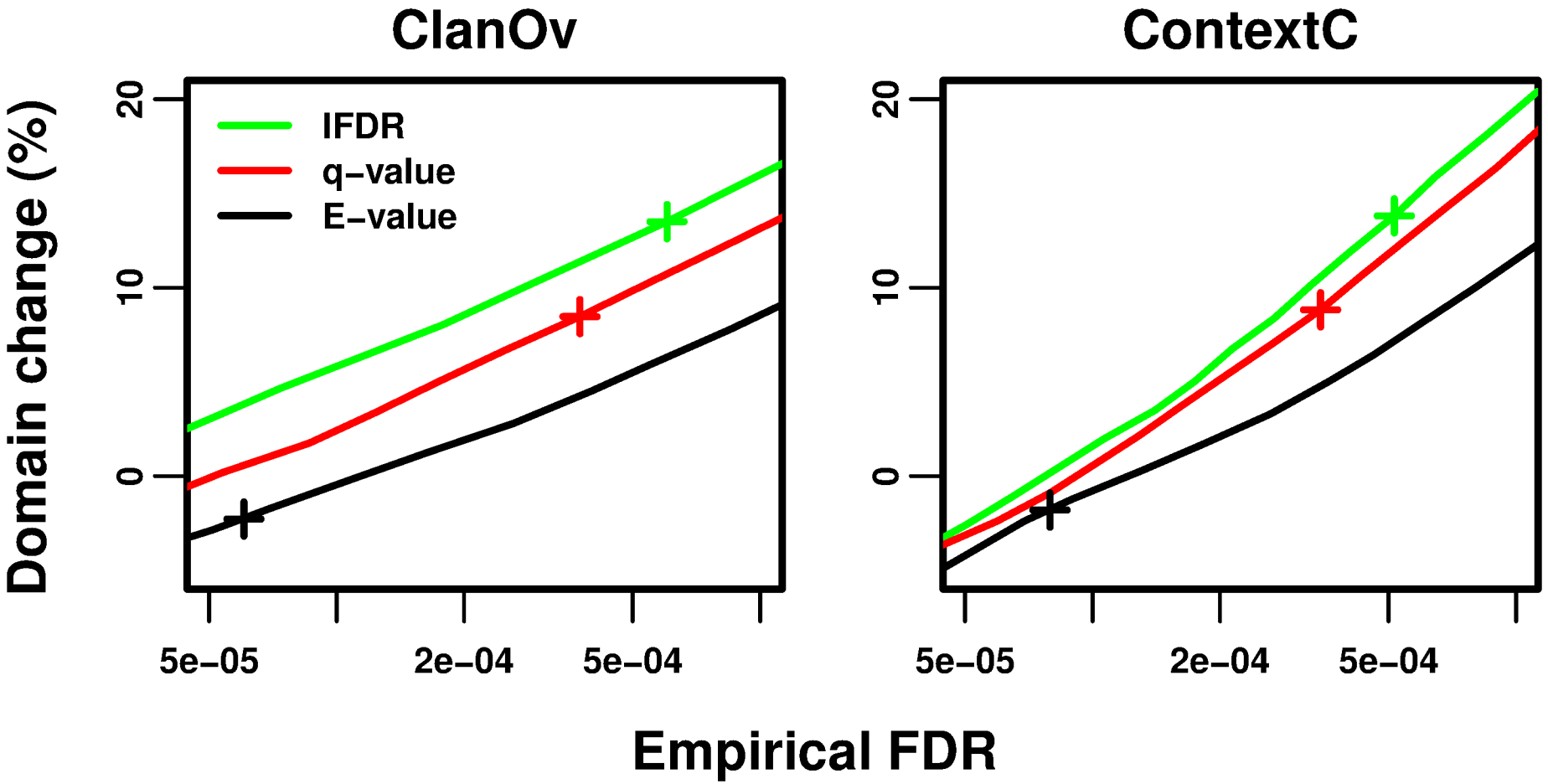


Structural classes enriched in noise

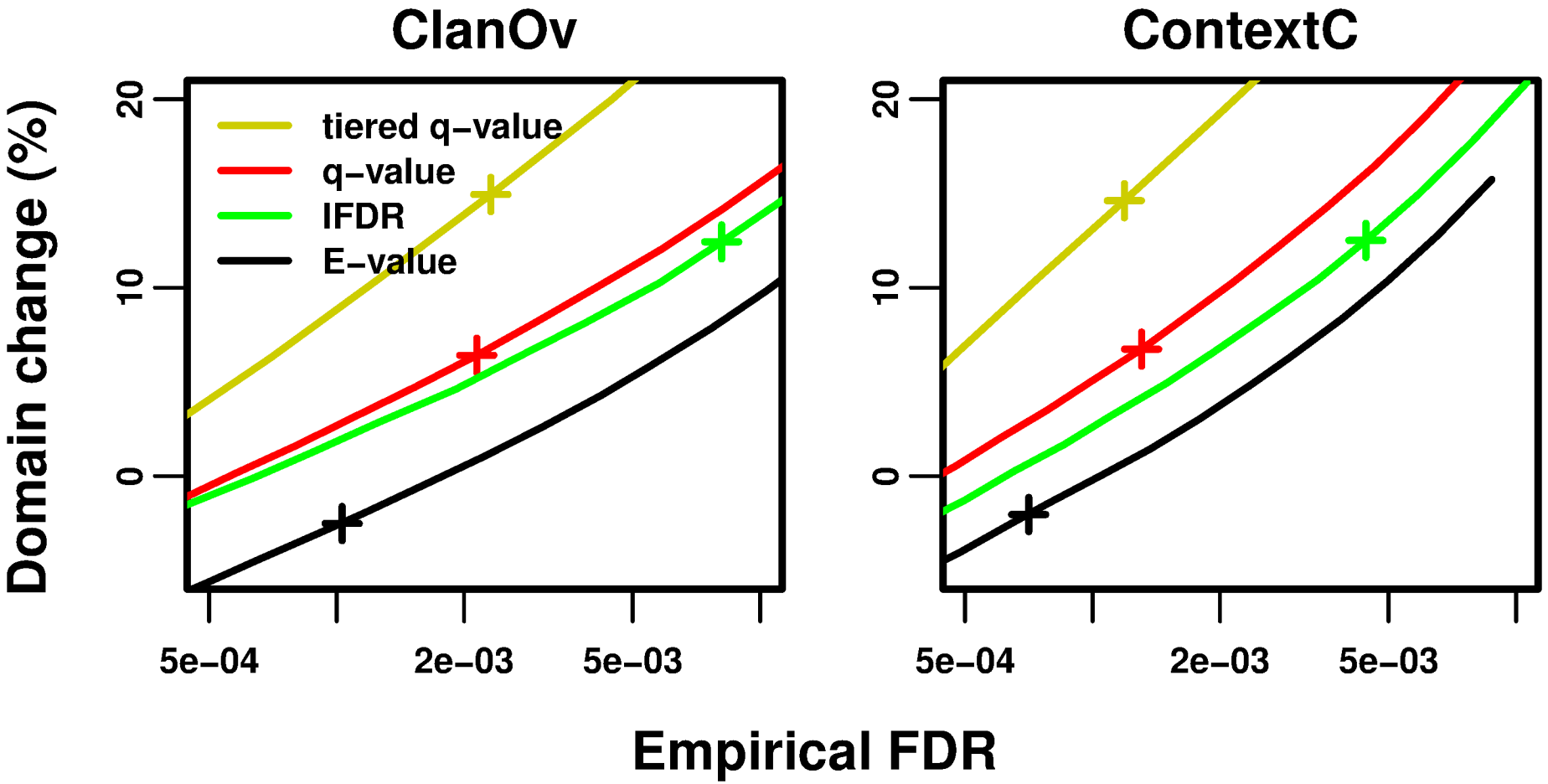


Similar findings:
- Rackham *et al*. JMB 403, 480–493 (2010).
- Wong, *et al.* PLoS Comput Biol 6, e1000867 (2010).
- Mistry, *et al*. Nucl Acids Res. 41: e121–e121 (2013).

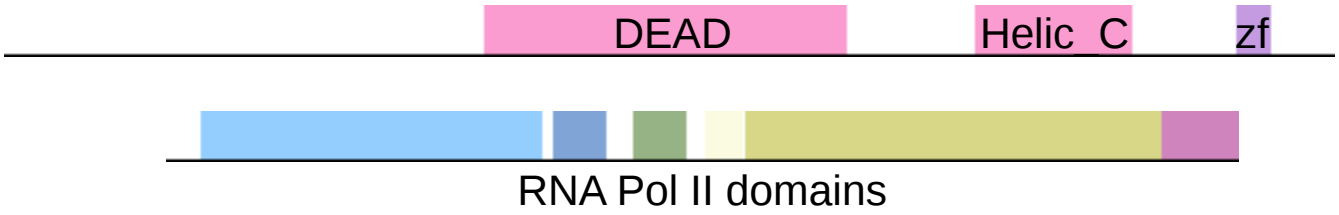
Local FDR outperforms *q*-values in families with correct stats



Tiered *q*-values borrows strength from repeating domains



Domain Prediction Using Context: dPUC



Background

- Domains co-occur in limited combinations

Idea

- Score domains in combination

Future work

- Use *q*-values or local FDRs to improve dPUC

http://compbio.cs.princeton.edu/dpuc/
Ochoa, *et al*. BMC Bioinformatics 12, 90 (2011).

Conclusions

Local FDRs are optimal for stratified problems

But *q*-values are more robust to imperfect *p*-values

For domains, repetitive families have inacurate *p*-values

Our FDR-based easy-to-calculate statistics improve domain prediction compared to using *E*-values

Future work:

- Developing methods that combine these statistics with domain context
- Improve *p*-values by improving the standard null model for protein sequences

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Funding: NIH, NSF

Software:

DOM STRAT <STATS>

https://github.com/alexviiia/DomStratStats

dPUC2

http://compbio.cs.princeton.edu/dpuc