Getting Real: Merging Bioinformatics Standards and Crypto-State-of-the-Art

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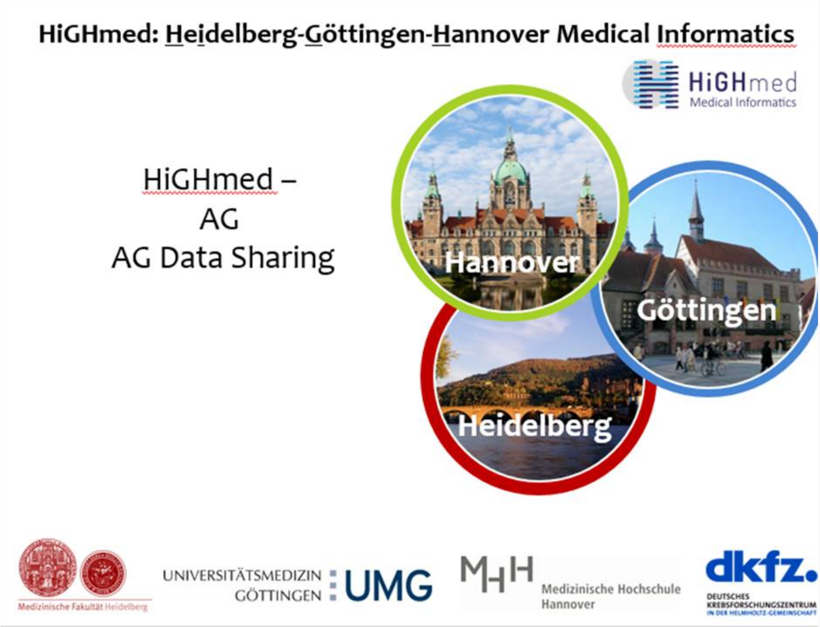
Embedded into real practice . . .



HiGHmed: Heidelberg-Göttingen-Hannover Medical Informatics

HiGHmed
Medical Informatics

HiGHmed –
AG
AG Data Sharing

Medizinische Fakultät Heidelberg

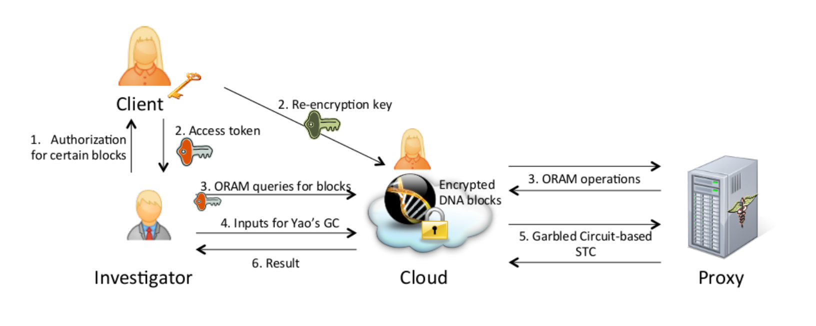
UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

MHH Medizinische Hochschule Hannover

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Examples (1): Oblivious RAM (ORAM)

write several times; shuffle data chunks; hide query $\Rightarrow$ protect queries

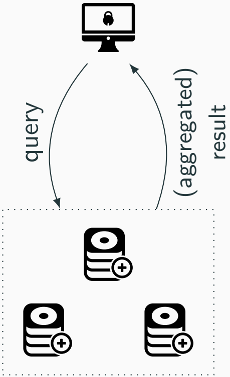


- pattern matching $\surd$
- DNA fingerprint(s) $\equiv$ description vector$\surd$
- Bayesian learning/updates $\surd$

Karvelas, Peter, Katzenbeisser, Tews, Hamacher *"Privacy Preserving Whole Genome Sequence Processing through Proxy-Aided ORAM"* Workshop on Privacy in the Electronic Society (WPES2014):1-10

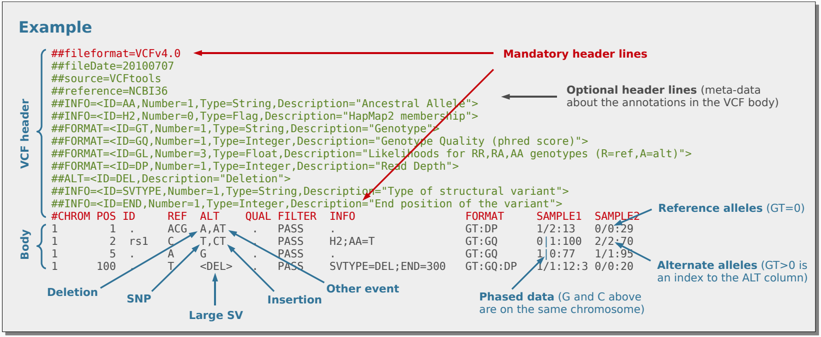
Examples (2): Privacy-Preserving VCF Queries

- Genomic data is sensitive data
- Medical treatment and research profits from access to large genomic datasets
- Trivially aggregating multiple genomic databases . . .
    - allows for more detailed analysis
    - but risks privacy of each dataset and entry
    - might not be desirable by the database provider
- **Solution:** Secure Multi-Party Computation (SMPC) for private aggregation and database queries



Federation of genomic databases

Variant Call Format (VCF)



Example

```
##fileformat=VCFv4.0
##fileDate=20100707
##source=VCFtools
##reference=NCBI36
##INFO=<ID=AA,Number=1,Type=String,Description="Ancestral Allele">
##INFO=<ID=H2,Number=0,Type=Flag,Description="HapMap2 membership">
##FORMAT=<ID=GT,Number=1,Type=String,Description="Genotype">
##FORMAT=<ID=GQ,Number=1,Type=Integer,Description="Genotype Quality (phred score)">
##FORMAT=<ID=GL,Number=3,Type=Float,Description="Likelihoods for RR,RA,AA genotypes (R=ref,A=alt)">
##FORMAT=<ID=DP,Number=1,Type=Integer,Description="Read Depth">
##ALT=<ID=DEL,Description="Deletion">
##INFO=<ID=SVTYPE,Number=1,Type=String,Description="Type of structural variant">
##INFO=<ID=END,Number=1,Type=Integer,Description="End position of the variant">
#CHROM POS ID     REF  ALT    QUAL FILTER  INFO                 FORMAT     SAMPLE1   SAMPLE2
1        1 .      ACG  A,AT    .   PASS    .                    GT:DP      1/2:13    0/0:29
1        2 rs1    C    T,CT    .   PASS    H2;AA=T              GT:GQ      0|1:100   2/2:70
1        5 .      A    G       .   PASS    .                    GT:GQ      1|0:77    1/1:95
1      100 .      T    <DEL>   .   PASS    SVTYPE=DEL;END=300   GT:GQ:DP   1/1:12:3  0/0:20
```

VCF header
Body
Mandatory header lines
Optional header lines (meta-data about the annotations in the VCF body)
Reference alleles (GT=0)
Alternate alleles (GT>0 is an index to the ALT column)
Deletion
SNP
Large SV
Insertion
Other event
Phased data (G and C above are on the same chromosome)

Figure 1: VCF format example – from vcftools website.

Beacon Project

Beacon Network

Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.

Beacon Network (GA4GH Project) established to evaluate eagerness of institutions world-wide to engage in distributed variant query service.

“Do you have a genome with mutation X in your database?”

“Yes” / **“No”**

Beacon Privacy Issues

Recent work (Thenen, N., Ayday, E., C. Ercument; bioRxiv; 200147; Sep. 2017) strongest challenge to privacy of Beacon networks yet

- Need only 5 queries to re-identify member in 65-individuals beacon (95 % confidence)
  - even when single-nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) $< 5\%$ are hidden
  - exploiting linkage disequilibrium
  - and high-order Markov chains

Our work mitigates this risk by

- hiding which beacon contributed to total
- incurring a threshold on `count`-queries
- enabling a reverse follow-up scenario

Variant Query Format

- Compression/Encoding of variant data into $(\kappa = 32, \psi = 16)$ bit (key, value) space
- Key holds the position in a reference genome $(\log_2(3.2 \cdot 10^9) \approx 31.6 < 32)$
- Small value space must incur variant information loss
- But domain-specific knowledge makes a virtue of this necessity to let similar variants match
- Allow same key multiple times to store e.g. diploid variations or upper and lower length of deletion/copy number variation (CNV)/inversion

VQF Translation

Variant	Stored Information	#Values
SNP/SNV	Alternative nucleotide.	4
Deletion/CNV /Inversion	Up and down rounded logarithm (base $b = 2$) of length, up to log-length s. Plus frameshift bit for deletions.	$s = 16$
Insertion	Up to $s_{\text{ins}} = 7$ inserted nucleotides and a frameshift bit.	$2 \cdot 4^{s_{\text{ins}}=7}$
Other	Only flag as *other* variation. Captures more complex variations.	1

Privacy-Preserving Genomic Queries

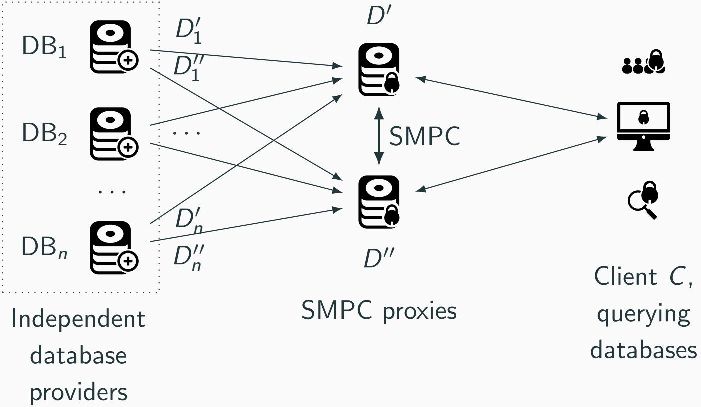
Supported queries are of the form:

SELECT f(*) FROM Variants
WHERE ((loc$_1$, var$_1$), ..., (loc$_m$, var$_m$)) IN Genome
AND cancer = X AND ... AND age$_{\mathrm{min}}$ $\leq$ age $\leq$ age$_{\mathrm{max}}$

f(*) can be an arbitrary function (e.g., aggregation, threshold).

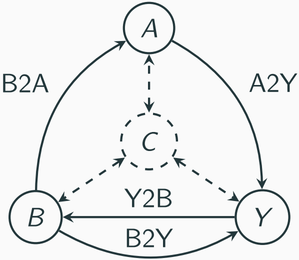
D. Demmler, K. Hamacher, T. Schneider, S. Stammler.
Privacy-Preserving Whole-Genome Variant Queries 16th Int. Conf. Cryptology And Network Security (CANS) accepted, 2017.

Schematic Overview



The ABY Framework

- ABY (Demmler, D., Schneider, T., Zohner, M. (NDSS'2015)) is a C++ framework for secure two-party computation
- 3 supported protocols:
  - Arithmetic sharing: $+$ secret-sharing
  - Boolean sharing (GMW): $\oplus$ secret-sharing
  - Yao's garbled circuits
- Open source on github: `http://encrypto.de/code/ABY`



Benchmarks

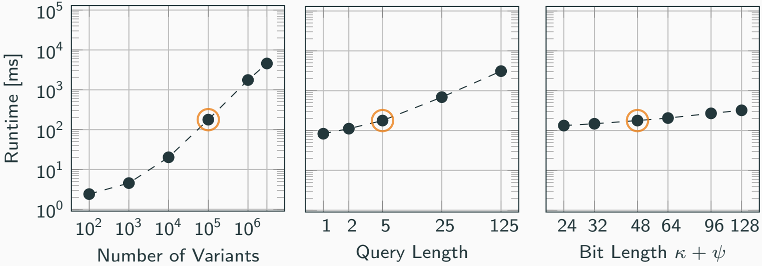


Figure 2: Online runtime in ms.

A typical query from 100 000 variants on 5 positions with $\kappa = 32$ and $\psi = 16$ needs 178 ms runtime and 11 MiB communication in the online phase. (Setup phase: 3.4 s, 733 MiB)

Summary & Acknowledgements

- Trust not essential: computational trust
  vs. social/legal construct
- work in security / protocol design / cryptography
  mature and applicable
- loss of (computational) efficiency $\surd$
  but trade-off might be worth it
- framework(s) do exist;
  but you <u>need</u> experts in crypto & bioinfo
  "Anyone, from the most clueless amateur to the best cryptographer, can create an algorithm that he himself can't break." — Bruce Schneier

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CRISP
Center for Research
in Security and Privacy

CYSEC
Cybersecurity
TU Darmstadt

Bundesministerium
für Bildung
und Forschung

HiGHmed
Medical Informatics

DFG

HESSEN
Hessisches
Ministerium für
Wissenschaft
und Kunst

FCI
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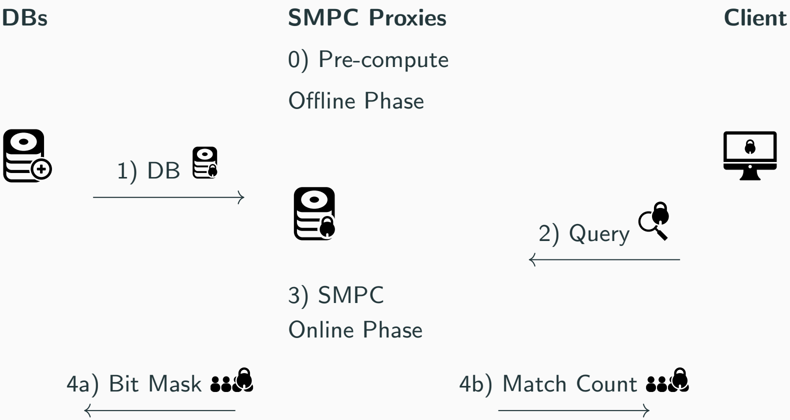
Protocol

Protocol Phases



DBs

SMPC Proxies

Client

0) Pre-compute

Offline Phase

1) DB

2) Query

3) SMPC

Online Phase

4a) Bit Mask

4b) Match Count

Circuit Design

- GMW protocol for inherent secret-sharing
- Efficient SIMD operations
- Variant matching: array of equality gates combined with OR tree
- Auxiliary information: combined with AND tree

Homomorphic Encryption (HE)

Starting with

C. Gentry. *"Fully Homomorphic Encryption Using Ideal Lattices"* 41$^{\mathrm{st}}$ ACM Symposium on Theory of Computing (STOC), 2009

$$\begin{tikzcd}
A, B \arrow[r, "+"] \arrow[d, "\mathrm{Enc}"] & A + B \\
\mathrm{Enc}(A), \mathrm{Enc}(B) \arrow[r, "\oplus"] & \mathrm{Enc}(A + B) \arrow[u, "\mathrm{Dec}"']
\end{tikzcd}$$

Several framworks, e.g., Damgård, et.al., *"Efficient and secure comparison for online-auctions"*, ACSIP2007, Lecture Notes in Computer Science (4586)