kWIP: The k-mer Weighted Inner Product

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21 August 2015

Disclaimer

DRAFT

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`DRAFT`

Or as Norman says, `kWIP` is Kevin's Work In Progress

Collaboration

- This work is a collaborative effort
  - Norman Warthmann
  - Cheng Soon Ong
  - Chris Webers

Overview

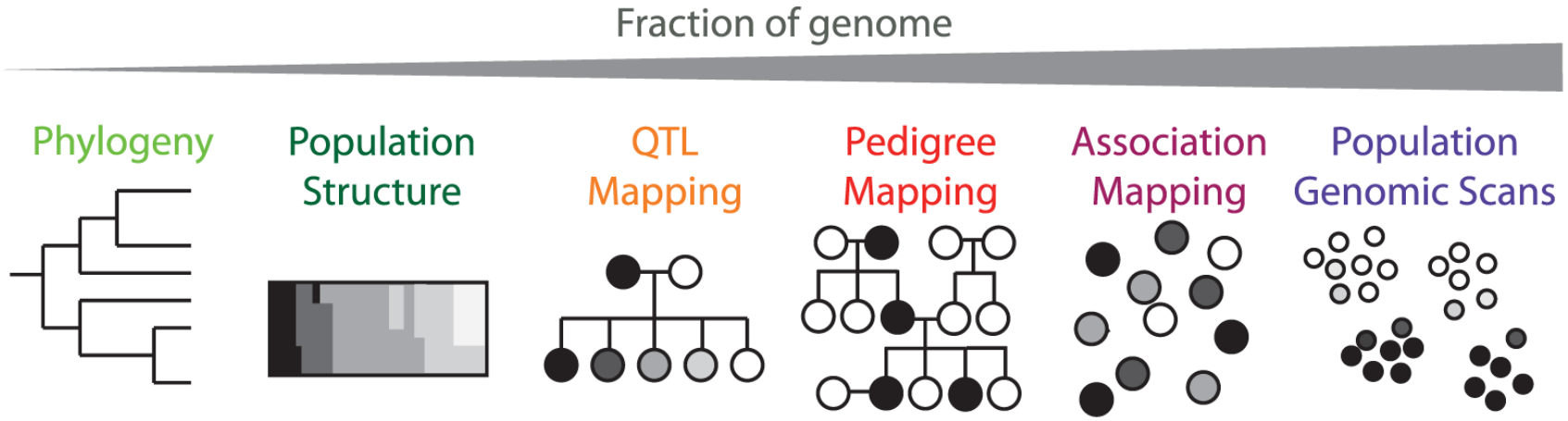
- Motivation
- Technological overview
- Early results and plans
- Demonstration

Large-scale population genomics

- Moving from 100s to 1000s and 10000s of samples *per PhD!*

Large-scale population genomics

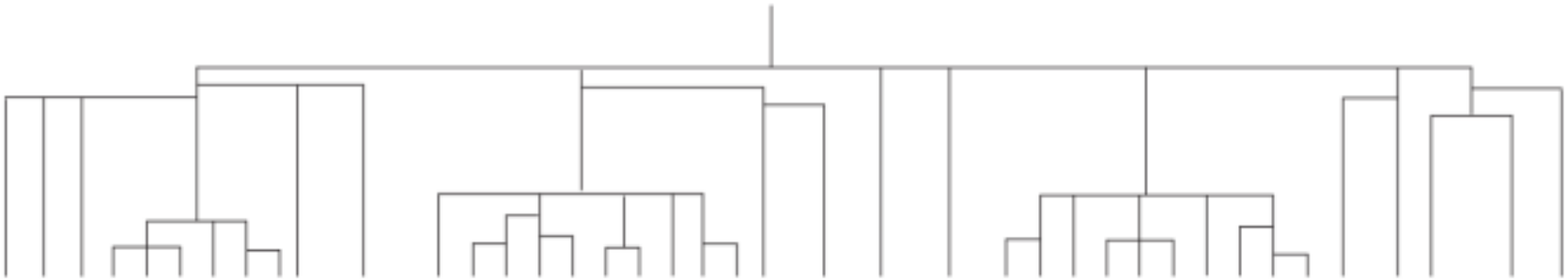
- Moving from 100s to 1000s and 10000s of samples *per PhD!*
- Efficient algorithms to analyse large-scale genomic data
  - Reference & alignment free: *less bias, de novo*
  - Platform/protocol agnostic: *future proof*
  - Computationally efficient: *not the bottleneck*
  - Cross scale: *one tool to rule them all*



after Peterson *et al.* [1]

Rapid and Basic Clustering

- Rough approximation of sample relatedness required
  - Cheap and fast
- Enables a "zooming" approach to genetic analysis



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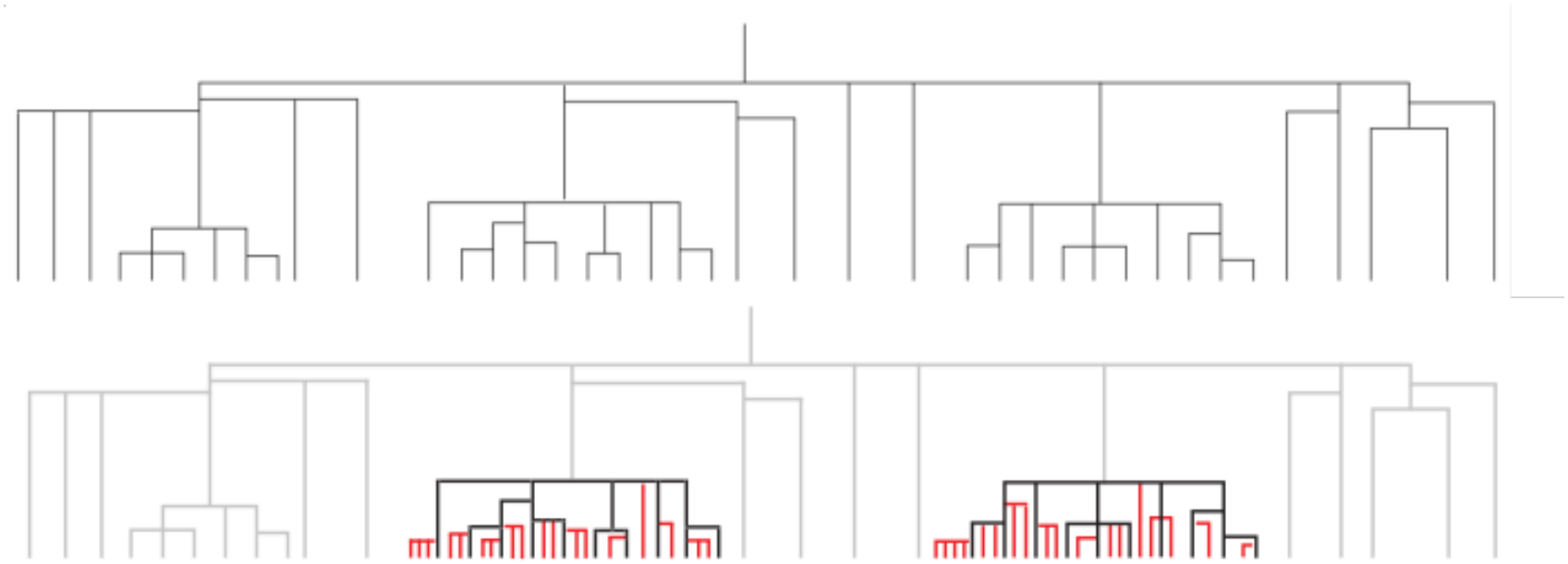

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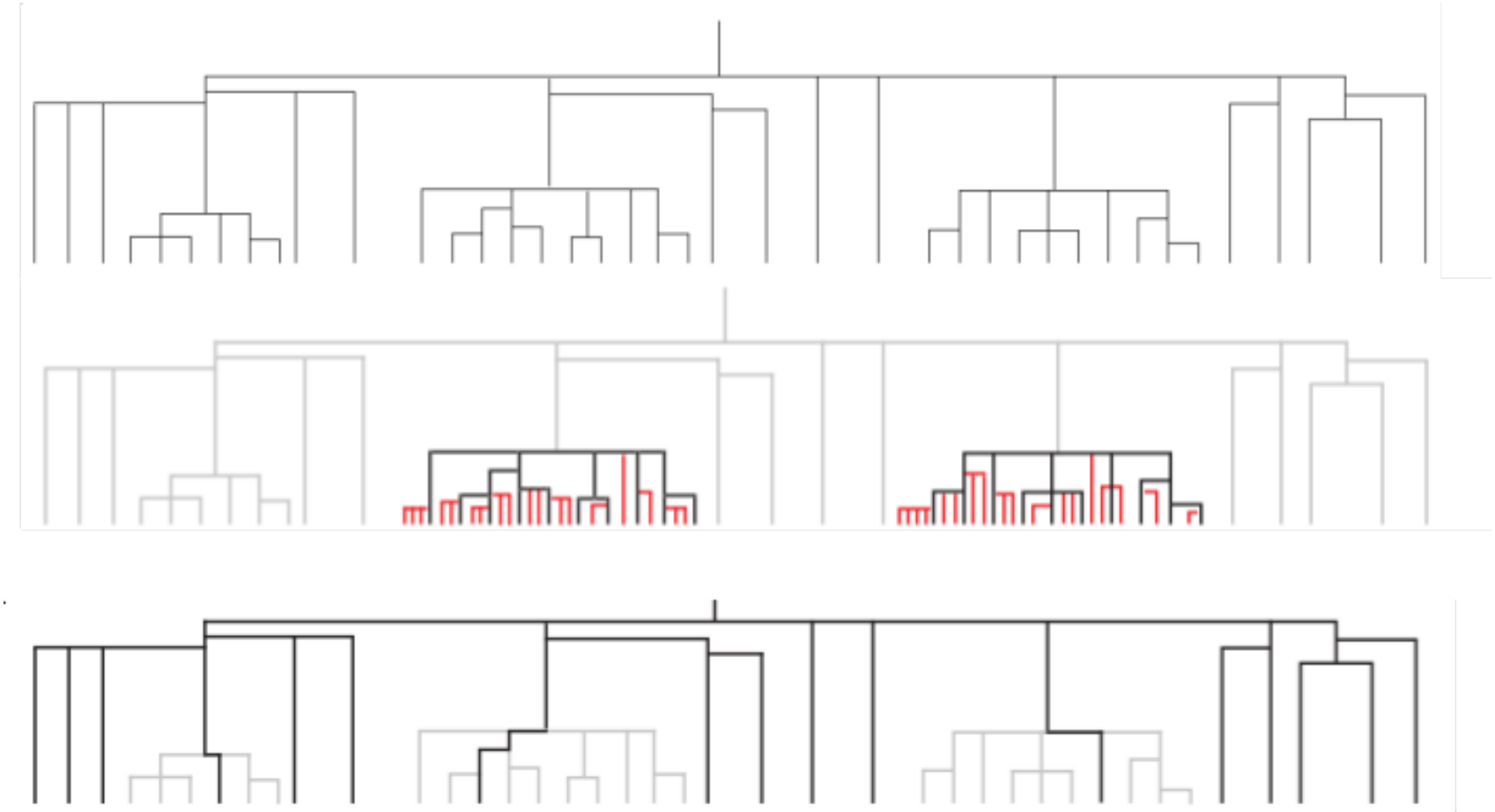

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De novo technical control

- Sample DNA not very physically distictive
  - Mix-ups and contamination occur
- Catching mix-ups early important
  - Not just for your own data: SRA not so perfect

Ath 80 FIGURE HERE

Technological Overview

- k-mer analysis
- Hashing and Probablistic Data Structures
- Population and RunFrequency Hashes
- (Weighted) Inner Products

k-mer analysis

- Analyse k-length words of sequences

$k = 3$

```
ACGTGT
ACG
 CGT
  GTG
   TGT
```

k-mer analysis

- Analyse k-length words of sequences
- Computationally and biologically appropriate
  - Fast
  - Constant-memory (using `khmer`)
  - Scalable and parallelisable
  - Cross-scale

$k = 3$

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Hashes and Hash Functions

- Hash function e.g.

```
hash('ACG') => 5234315134
```

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  ```

- "Hash": a probablistic data structure
  - Constant memory
  - Easy set operations and inner product
  - Implicit de Bruijn graph
  - Implemented in C Titus Brown's `khmer`
  - AKA Countgraph, Counting Bloom Filter

Hash

- Vector of large prime length (e.g. 1e9 + 7)
- Indexed modulo length ($bin = h(w_i) \mod prime$)

0	0	0	0	0	0	0	0	0

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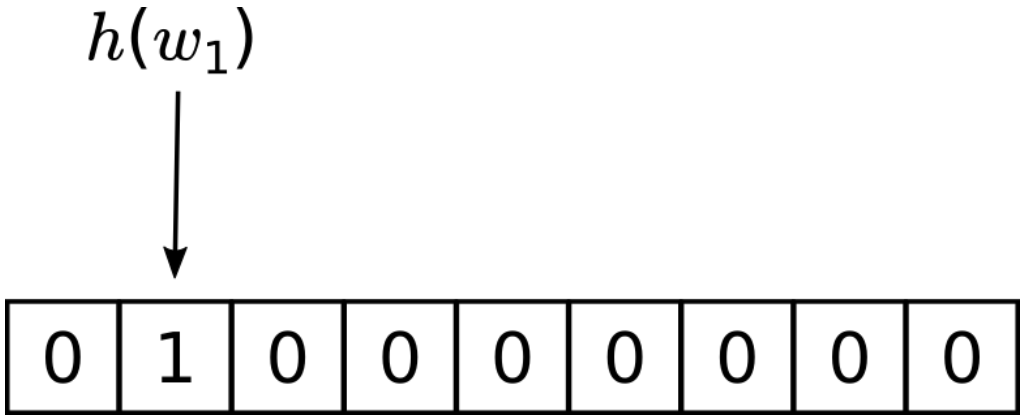

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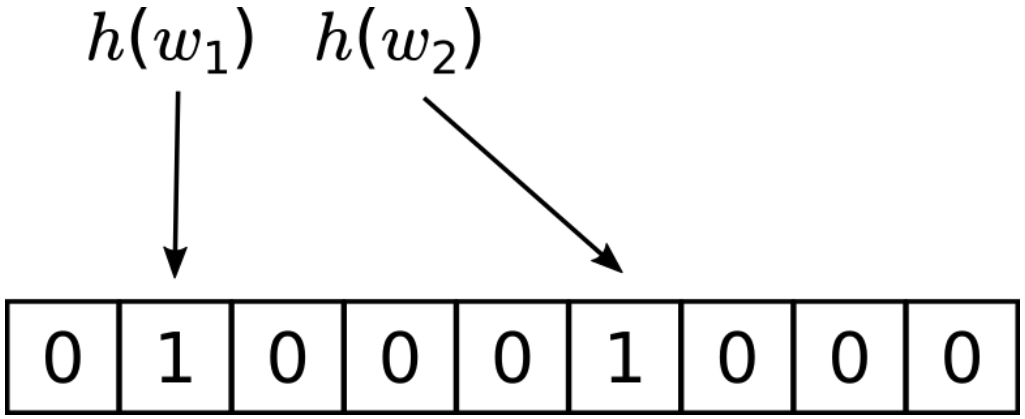

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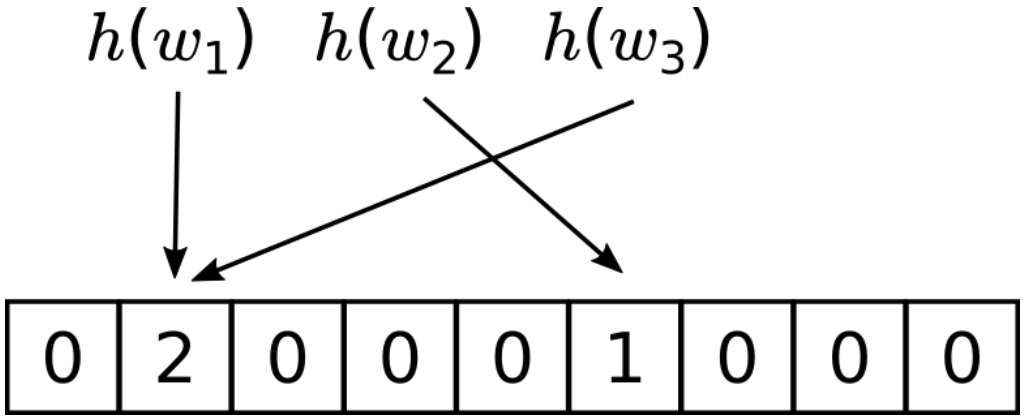

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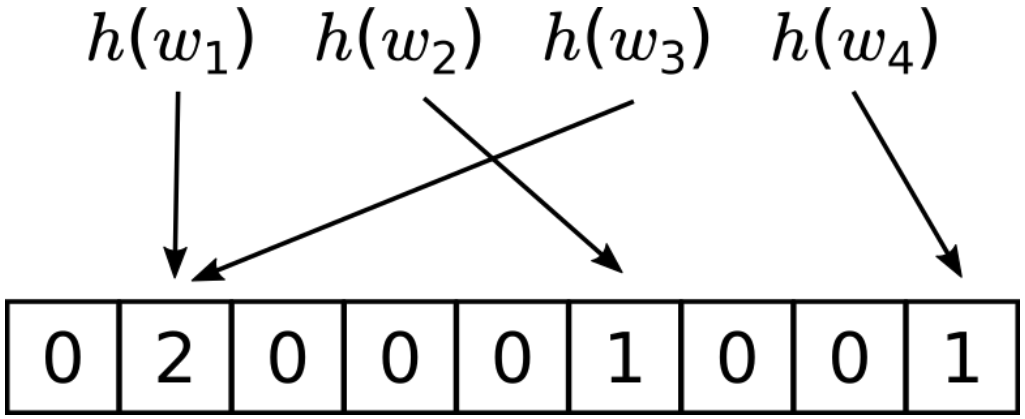

Hash Operations

- Population sum, or hash frequency

		2		2		1		1	
		2	1	7		1			
	1	1				1	6		
	1					2	3		
Population Sum	2	5	1	9	0	5	9	1	0

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	1	1				1	6		
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Population Sum	2	5	1	9	0	5	9	1	0
Frequency	2	3	1	2	0	4	2	1	0 / 4

k-mer based clustering

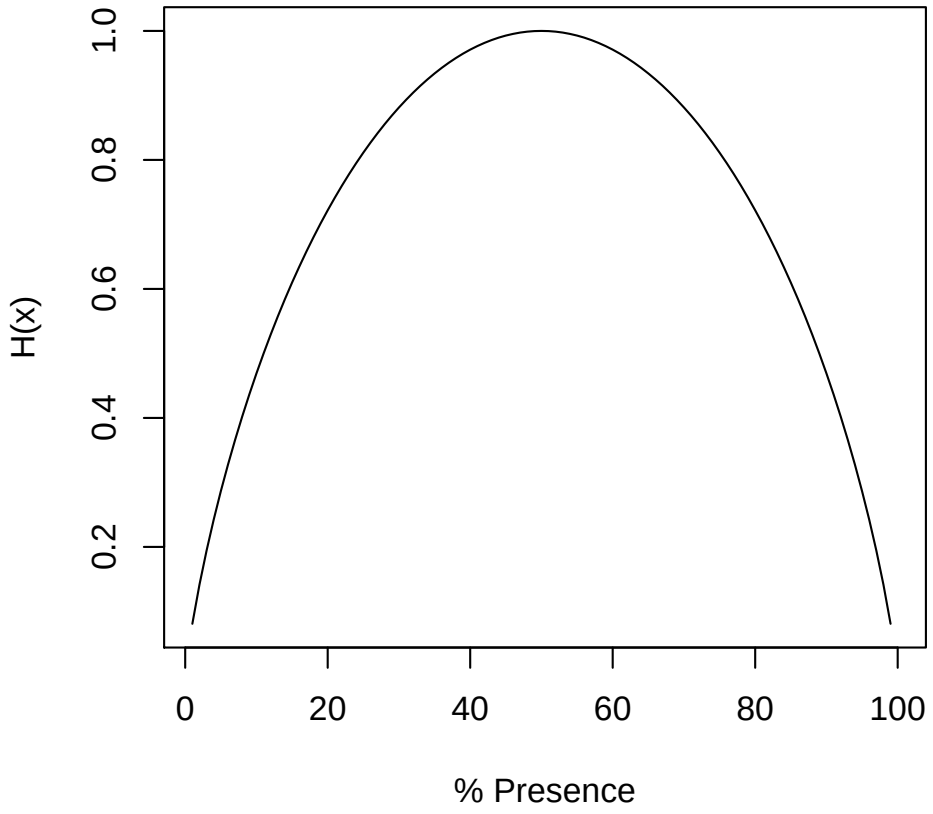
- Alignment-free sequence clustering is a whole field
- $D2$ and friends
- Most require sequence gene/genome
- Many use inner product as similarity measure

Characterizing the D2 Statistic: Word Matches in Biological Sequences

Sylvain Forêt, Susan R. Wilson, and Conrad J. Burden

Shannon Entropy

- Measure of Information
- $-\sum_i p_i log(p_i)$



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- The k-mer Weighted Inner Product
  - Extends alignment-free seq comparison to raw NGS data
- Algorithm:
  - For each sample: count all k-mers into a Hash
  - For each analysis set, i.e "population":
    - Calculate the informational entropy of hash frequency (H)
    - For each pair of samples A and B, calculate $\sum_{i=0}^{n} A_i \cdot B_i \cdot H_i$

A	0	2	0	2	0	1	0	1	0

$\bullet$

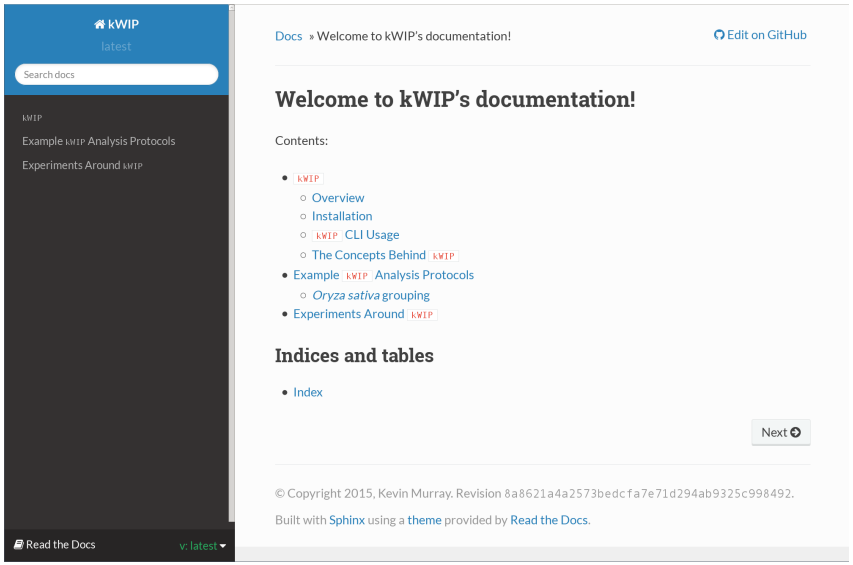
B	0	2	1	7	0	1	0	0	0

$\bullet$

H	h_1								h_n

kWIP

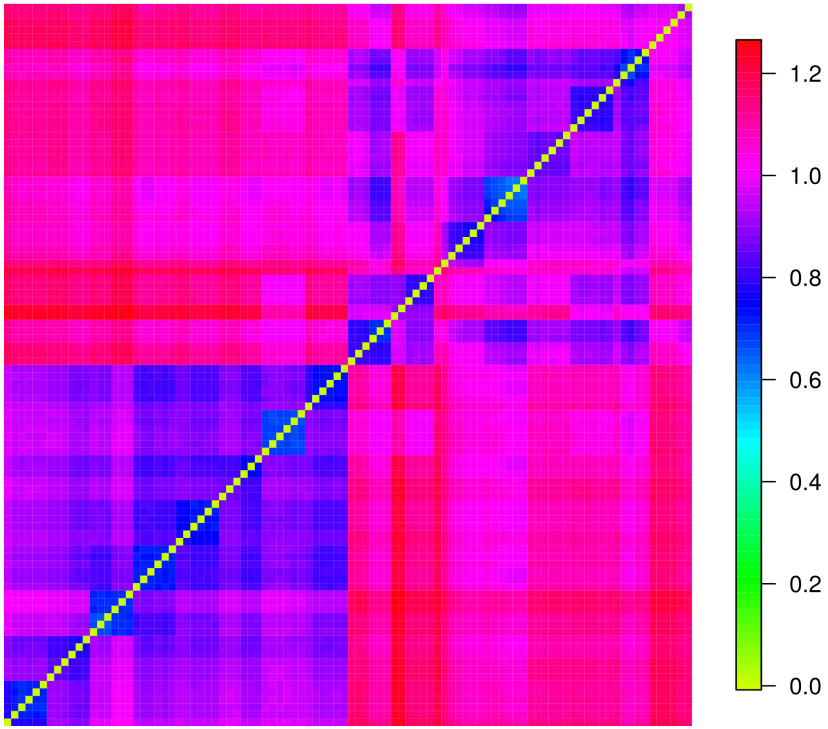
- The software:
  - C++, >2000 lines of code
  - Uses `khmer` for *k*-mer counting & hashing
  - Parallelised, ≈ 10 hrs for 96 rice samples.
  - GNU GPL licensed, source code released on GitHub



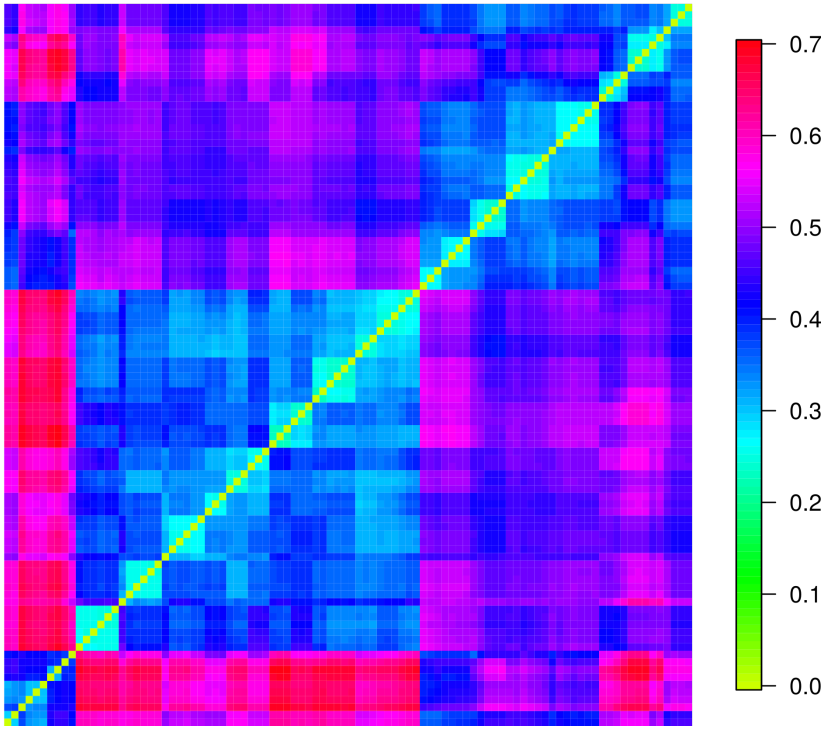
kWIP Experiments

- 3000 rice genomes:
  - 3000 rice lines from known families
  - Analysing in sets of ≈ 100, from all major groups
  - Recover known grouping w/ kWIP, not w/ unweighted IP
  - Sensitive to read depth
- Simulation
  - Fake population genome sequencing studies
  - Experiments in progress, early results positive
  - Test limitations of kwip

WIP



IP



Asymmetric Tree simulation

- Now for an Jupyter notebook

Thanks

- My collaborators: Cheng Soon Ong, Christfried Webers, Norman Warthmann
- Advisors: Justin, Norman, Sylvain, Gavin and Barry
- C. Titus Brown, Michael Crusoe, Camille Scott (DIB-lab) @ UC Davis
- Kenneth McNally/IRRI
- Yourselves

References

- Peterson, B. K. *et al.* Double Digest RADseq: An Inexpensive Method for De Novo SNP Discovery and Genotyping in Model and Non-Model Species. *PLoS ONE* **7,** e37135 (2012).
- Brachi, B., Morris, G. P. & Borevitz, J. O. Genome-wide association studies in plants: the missing heritability is in the field. *Genome biology* **12,** 232 (2011).

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Missing heritability in the field?

- Find more diversity in the field!
- Sample natural populations
  - Ecological hypotheses of trait selection, adaptation
  - Sample widely as possible across non-uniform genetic diversity

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- Find more diversity in the field!
- Sample natural populations
  - Ecological hypotheses of trait selection, adaptation
  - Sample widely as possible across non-uniform genetic diversity
- Now **complexity limited**: complex kinship & population structure
- Mandates development of economic, accurate large scale population genomics