# "All the genomes in the world"
## Scalable Bayesian Computation using emulation

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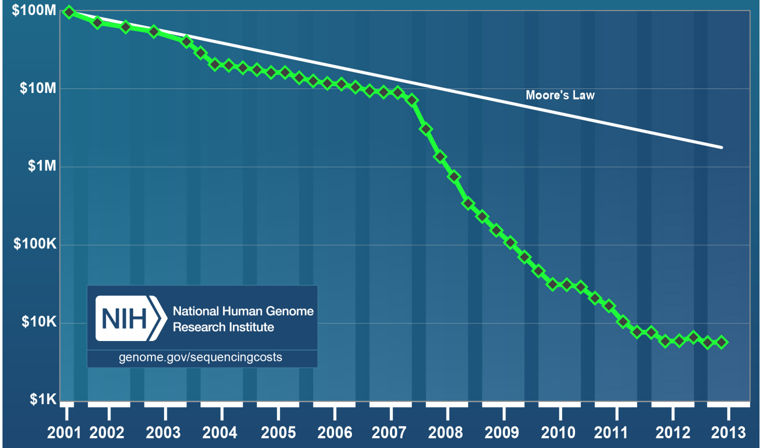
## Cost per Genome



## Background

- We will ‘soon’ be able to sequence all the genomes in the world for less than the cost of the logistics of obtaining or processing them
- Current project to sequence all 50K Faroe Islanders
- What would we do with ‘all the genomes in the world’?
- Can we run appropriate models on them?
- More modest goal: scalable framework for statistical methodology
- This includes MCMC, which I will use here
- But can be replaced by optimisation for really scary volumes of data

## Motivation

For Large datasets

- "Statistics doesn't work" – estimates get worse as we get more data! (for linear compute)
  - e.g. MCMC
- Simple analytics can extract many useful features
  - e.g. K-medians clustering, etc
- Informative in practice - and still hard to get working!
- *Exploit averaging* over lots of data
- But many interesting quantities are subtle...
- or local, so we only have a small amount of data about them
- Always a place for models closer matching reality

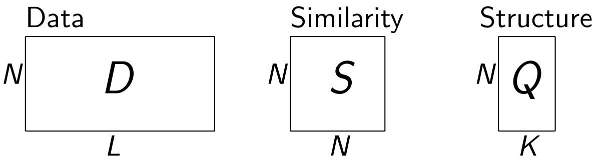
## Model of interest: FineSTRUCTURE

Clustering $Q$ with associated uncertainty from SNP data $D$

- The $N$ Individuals are highly structured (Populations)
- The $L$ SNPs are complexly correlated
- $D|S$ describes individuals with a Hidden Markov Model with each other individual as the hidden state
- $S_i$ is the vector of expected times each individual is transitioned to in the HMM
- MCMC inference for $Q$ using genetics model $S|Q$
- $S|Q$ is approximately multi-variate normal with structured covariance
- Problem: $S$ is $O(LN^2)$ to evaluate

## Similarity

$$p(D|S)p(S|Q)p(Q)$$



- Compare $N$ items about which we have a large amount of data $D$ (trivial extension: to $M = O(N)$ other items).
- Similarity $S(i,j)$ is computationally costly to evaluate
- $S$ structured by a model $Q$
- i.e. Similarity model $p(D|S)$ separates the data $D$ from the structure model $p(S|Q)$
  - If rows of $Q$ sum to 1 this is a mixture model
  - if only 1 element is non-zero it is a partitioning

## Random or convenience filtering

- See 'big data'[1] as better sampling of data
- Why not throw away elements from $D$?
  - Convenience sampling - what can we measure? $=$'data'
  - Systematic sampling - retain every n-th data point
  - Simple random sampling - retain fraction $p$
  - Stratified sampling
  - etc
- For example:
  - Use $L' \ll L$
  - Use $N' \ll N$
- Can fix $N'$ and $L'$ to fix computational cost

1: *Big data: any data that can't be processed in memory on a single high spec computer*

## Emulated Likelihood Models (ELMs)

Fundamental idea: Replace $p(D|S,\theta)$ in

$$p(D|S,\theta)p(\theta)p(S|Q,\phi)p(Q,\phi)$$

using $S^*$ computed and $S^\dagger$ emulated similarities, s.t. $S = S^* \cup S^\dagger$:

$$\hat{p}(D|S,\theta) = p(D|S^* \cup S^\dagger,\theta) = \int p(D|S^* \cup S^\dagger,\theta,\psi)p(S^\dagger|S^*,\psi)d\psi$$

- $S_{ij}$ is costly to compute, and needed for $S|Q$
- But are highly structured (e.g. clusters)
- So can emulate $S_{ij}$ rather than computing
- Choose $S^*$ to be approximately sufficient for $p(D|S,\theta)$
- Carefully downweight emulated data
- Weights are only modification to $S|Q$

## The oracle

Which $NT$ elements $S^*$ of $S$ should we evaluate?
Natural solution using oracle knowledge of the true $S$.

- Use a loss function $\mathcal{L}(S^*)$
- Seek $\operatorname{argmin}_{S^*(T)} \mathcal{L}(S^*(T))$
- Choices for $\mathcal{L}$ might be:
  - KL divergence between the true and the emulated posterior
  - A loss based on model usage (e.g. is the clustering correct? Control the false positive rate, etc)
- Choose $T$ based on acceptable loss

## Building blocks of a real Emulated Likelihood Model

The oracle is too costly. We instead must:

- Iteratively choose the next $S_{ij}$ to add to $S^*$
- From a limited set produced by a restriction operator $\mathcal{R}(S^*)$
- Construct an estimator $\hat{\mathcal{L}}$ for $\mathcal{L}$
- Decide on the next point to evaluate using $\operatorname{argmin}_{S_{ij}} \mathbb{E}\left(\hat{\mathcal{L}}(S^* \cup S_{ij}) | S^*\right)$
    - We can consider different histories to evaluate performance
- Stopping rule: convergence of $\hat{\mathcal{L}}$

$\hat{\mathcal{L}}$ can be implicit from $\mathcal{R}$, if it returns points ordered by $\mathbb{E}(\hat{\mathcal{L}})$

## The emulator

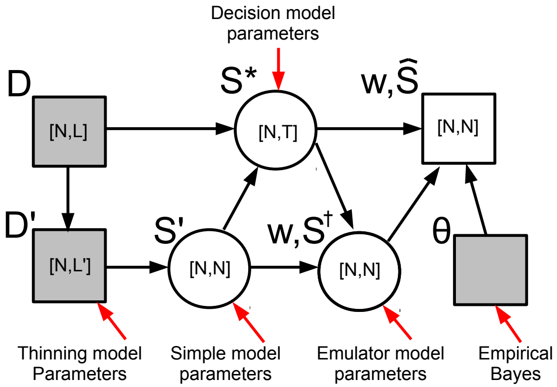
'Machine learning' emulator with the usual caveats:

- Rarely optimal, rarely unbiased
- Prediction error estimated using online cross validation
- Respects computational constraints:
  - $L \gg N$: Consider $O(N^2 + LN)$ algorithms
  - $N \gg L$: Consider $O(LN)$ algorithms
  - Massive data: Consider $O(LN^\alpha + N)$ algorithms with $\alpha < 1$.
- Yet ... Low rank similarity matrices can be nearly losslessly reconstructed*

*Candes & Plan 'Matrix completion with noise', Proc. IEEE, 2010

## Fast finestructure - outline

Emulator:

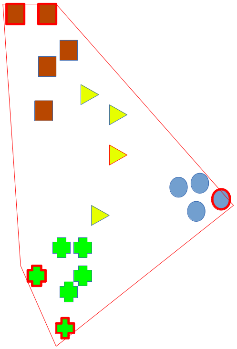


*S* becomes the data for inferring *Q*:

$$\left[p(D|\hat{S},\hat{\theta})\right] p(S|Q,\phi)p(Q,\phi)$$

## Fast finestructure - decision and emulation

- Decision $\mathcal{R}$: Choose item to evaluate $i_t^*$ using the *point most distant to all evaluated points*
- We are evaluating $S^*$ in entire rows
- Emulation: Predict $S^\dagger_{\cdot i}$: mixture model $S_i^* = \mathrm{MM}(S_{i*}^*)$, and regression on $\hat{S}_{ij} = \mathrm{LM}(S_{ij}^*, S_{ij}')$
- Implicit loss function $\mathcal{L}$:
  - Minimise the *maximum* prediction error
  - Finds outliers and clusters
  - $S^*$ form convex hull of $S$



## Fast finestructure - in practice

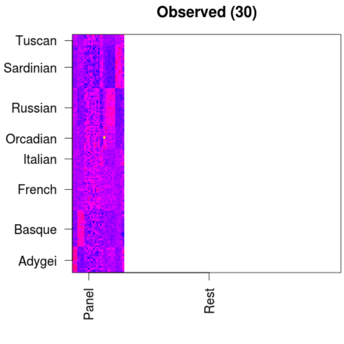
- Computation of $S$ costs $O(N^2L' + NT^2L) \ll O(N^2L)$
- Current datasets: $L = 10,000,000$, $N = 5000$, $L' = 10,000$ $T = 100$, predicted saving ratio is 100

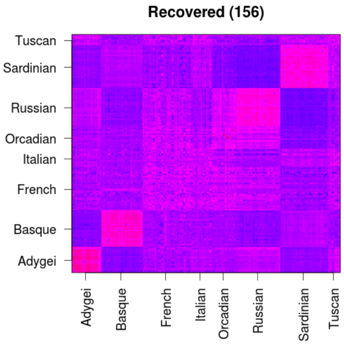
We can save up to factor 10000 by reducing $T$, the cost of the linearised model on the reduced dataset. $L$ will not grow beyond this, but $N$ will - can introduce an emulation step for $S'$

## Fast finestructure - Parallel MCMC algorithm

A parallel tempering algorithm for when MCMC parallelises poorly

- Evaluate the unlinked model $S'$
- Master node: perform MCMC clustering to find $\hat{Q}_t$ using $\hat{S}_t$, when there are $t$ rows $S^*_t$ computed
- Worker nodes compute $S^*_{\cdot i}$ in the order chosen by the master
- Stopping rule: posterior distribution of $\hat{Q}$ converges
  - No new information added when increasing $t$
  - (Or if the MCMC is slower than the evaluation of $S$, sometime afterwards)


Observed (30)
Tuscan
Sardinian
Russian
Orcadian
Italian
French
Basque
Adygei
Panel
Rest


Recovered (156)
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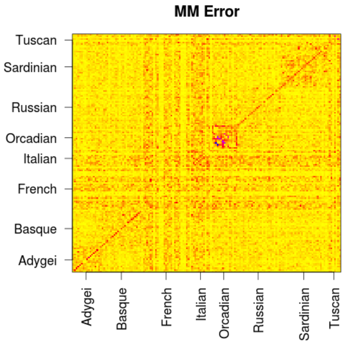
Russian
Sardinian
Tuscan


MM Error
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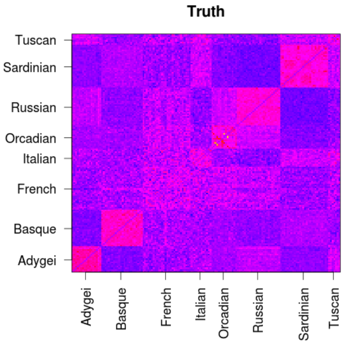
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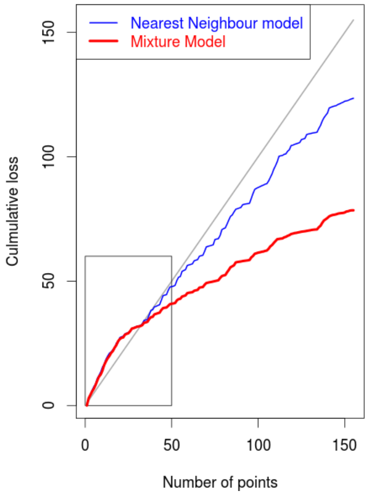
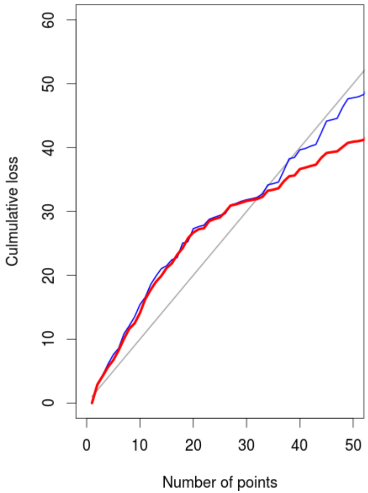
Sardinian
Tuscan



Nearest Neighbour model
Mixture Model
Culmulative loss
Number of points
0
50
100
150



Culmulative loss
Number of points
0
10
20
30
40
50
60

## Emulated Likelihood Models for general Bayesian problems

General emulation for big (but not so big) problems

$$\hat{p}(D|S,\theta) = \int p(D|S^* \cup S^\dagger, \theta) p(S^\dagger|S^*, \theta, \psi) d\psi$$

- i.e. Can use $\theta$ to emulate $S^\dagger(\theta)$ - e.g. regression in $(S, \theta)$ space
  - Gaussian Process for $S_{ij}(\theta)$ is a natural choice
- If $S^\dagger$ is an unbiased estimator of $S^*$ this is a pseudo-marginal approach (and hence targeting the correct posterior)

## Discussion

- Goal: Approximate answers to the right questions using exact answers to the wrong questions
- Machine learning is increasingly important for large datasets
- Statistical modelling still has a place
- Proposed the Emulated Likelihood Model:
    - Full statistical modelling
    - Machine learning algorithms used for the calculation
    - Statistical estimation of parameters is retained but approximated