James McMurray

Project Title: Predicting Phenotype through Interaction of Genotype, Epigenotype and Environment with Probabilistic Models

Location: Max Planck Institute for Intelligent Systems, Tübingen, Germany

Supervisor: Bernhard Schölkopf

Background:

- Completed MPhys degree in **Physics** at the University of Exeter in July 2013.
- Completed two programming internships in Germany during university (at Uni Konstanz and Uni Tübingen).
- Also completed research project on Social Network Analysis - awaiting publication.
- Became interested in Machine Learning after completing "MOOCs" on **Coursera** by Andrew Ng and Daphne Koller, and on Udacity by Peter Norvig.

Research Interests:

- Models which combine different sources and forms of information, i.e. combining genetic, epigenetic and environmental data.
- Causal inference from observational data.
- Consumer personalized medicine.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 316861

Overview:

- Work has largely focussed on **causal inference** and **unsupervised learning**.
- Throughout the work I have used the **GPy** software package developed by Neil Lawrence's group in Sheffield.
- Including some of Max Zwiessele's work on the Bayesian GPLVM.
- Focussed on work with possible clinical applications (cancer diagnosis) - with the **DREAM9 challenge** and **TCGA** data.
- Have also worked on some more theoretical areas such as causal inference, however I do not think it is currently mature enough to be applicable scientifically.
- Interested in working on more **practical applications** - hope to co-operate with other nodes to this end.

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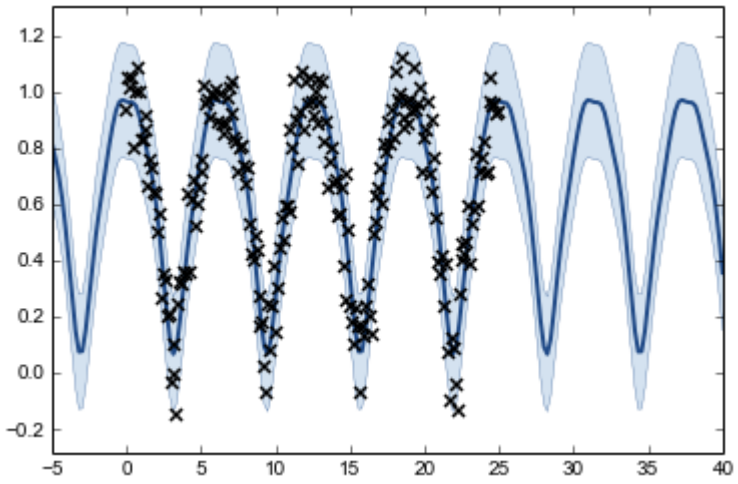
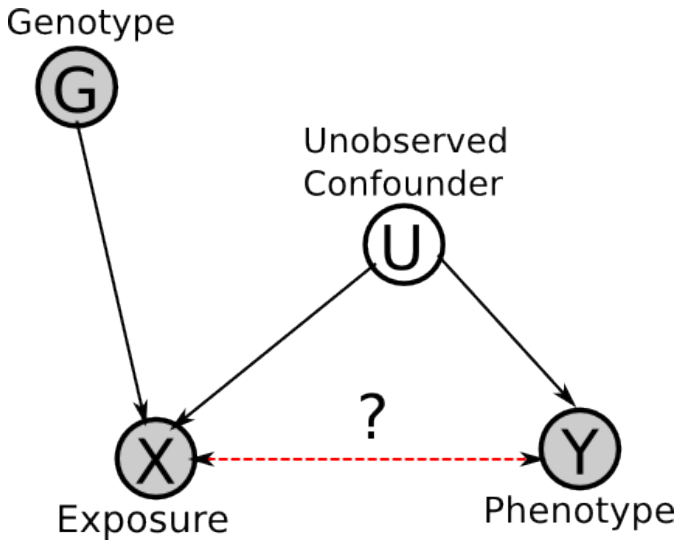
Start of project:

- Started by learning background to **causal inference** methods and **Gaussian Processes**.
- Interested in methods to deduce **causal direction** of interactions from **observational data**.
- Gaussian Processes are a non-parametric, Bayesian non-linear **regression** method.
- Provide a convenient way of incorporating **prior information**.





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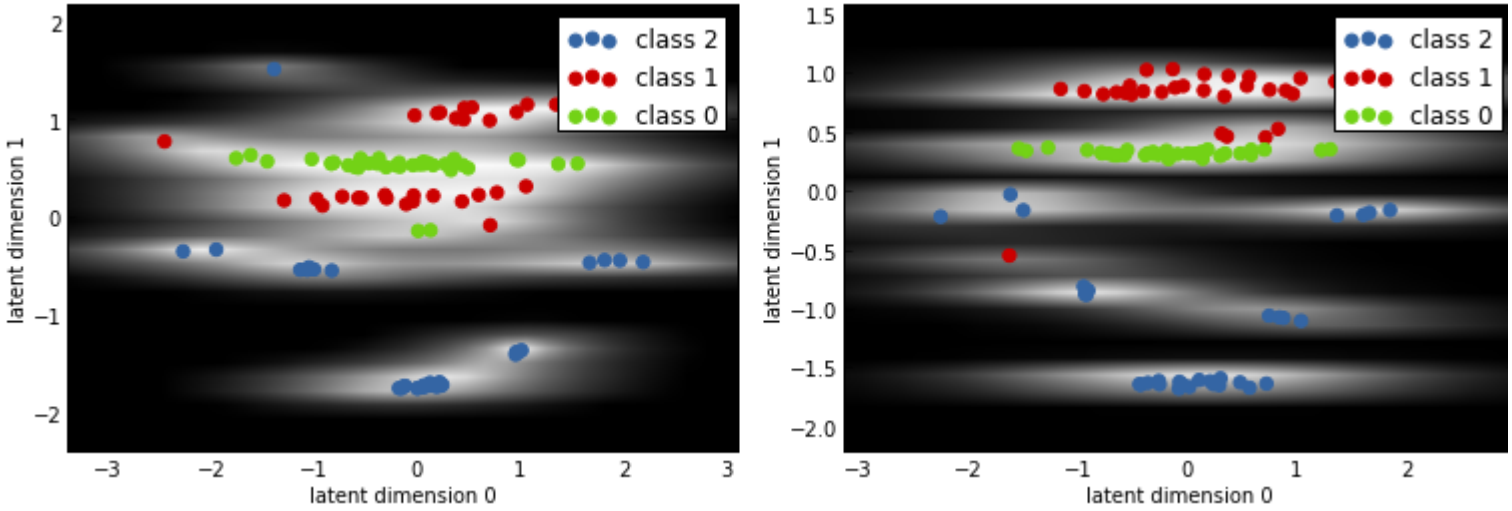
Invariant GPLVM:

- Started implementation of the IGPLVM, an extension of the Gaussian Process Latent Variable Model, using the **GPy** Python module from Neil Lawrence's group in **Sheffield** (other ITN node).
- IGPLVM was originally developed by Kun Zhang, a post-doc at Tübingen.
- Allows one to infer instantaneous causal relations amongst observed variables.
- However, in biological applications it is often difficult to interpret instantaneous relations.
- Also introduces storage dependency on the number of dimensions of the original data.



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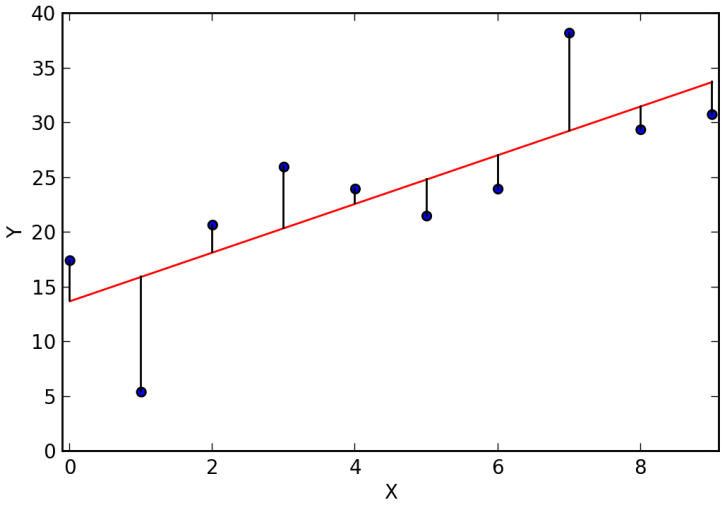
eQTL discovery and independence-based regression:

- Did some work on **eQTL** (expression Quantitative Trait Loci) discovery with the assistance of Oliver Stegle (previously at Tübingen, now a group leader at the European Bioinformatics Institute).
- Aim is to find which SNPs are significantly correlated with changes in gene expression.
- Wanted to see if **HSIC**-based regression methods (HSIC is the Hilbert-Schmidt Independence Criterion), work better than the Maximum Likelihood approach when the model assumptions do not hold (i.e. there are causal SNPs which we do not consider, etc.)
- However, could not outperform the Maximum Likelihood approach in simulations.



- HSIC-based regression tries to maximise the independence between the residuals and the regression variable (x).
- Has applications in causal inference.

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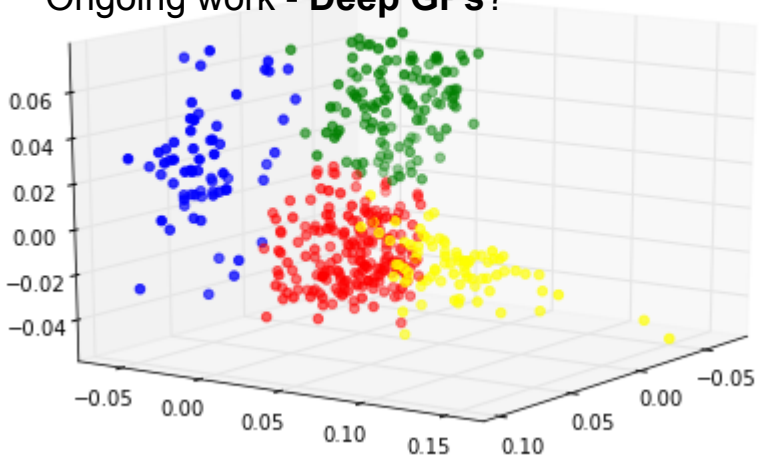
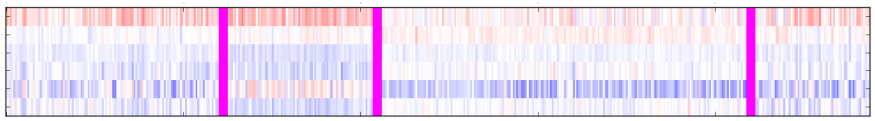
Investigating cancer subtypes in TCGA data:

- The Cancer Genome Atlas (TCGA) provides a lot of public data of various types (RNASeq, DNA Methylation, MicroRNA, SNPs (restricted access), expression arrays, etc.) for many different types of cancer.
- Main aim is to discover links between the different types of cancer.
- Verhaak, R.G., et al. (2010) **Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1**. Cancer Cell. **17** (1):98-110 - used Factor Analysis and Consensus Clustering.
- Attempt to repeat using **GPLVM** and **K-means**.
- Find different significant genes.
- Ongoing work - **Deep GPs**?



- Clinical differences:

Cluster 0:
Dead: 91/120(75.8333333333%)
Mean Survival time of dead: 40.20
Cluster 1:
Dead: 65/82(79.2682926829%)
Mean Survival time of dead: 41.82
Cluster 2:
Dead: 139/206(67.4757281553%)
Mean Survival time of dead: 37.68
Cluster 3:
Dead: 47/65(72.3076923077%)
Mean Survival time of dead: 528.38



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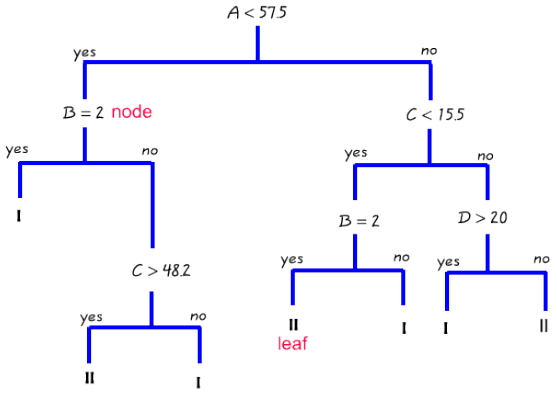
DREAM9 AML Prediction challenge:

- DREAM programme provides annual challenges in Bioinformatics.
- Chose AML (**Acute Myeloid Leukemia**) Outcome Prediction challenge.
- AML is a very lethal form of leukemia.
- Only approximately a quarter of the patients diagnosed with AML survive beyond 5 years.
- Provided with medical covariates and proteomics data.
- Consists of three sub-challenges:
  1. Predicting whether a patient will go in to remission or not (classification).
  2. Predicting the length of remission (regression).
  3. Predicting the overall survival time (regression).
- Have tried many approaches so far, most successful have been **Random Forests**, sometimes combined with the **GPLVM** for dimensionality reduction.



- The Random Forests algorithm uses an ensemble of Decision Trees to make its predictions.

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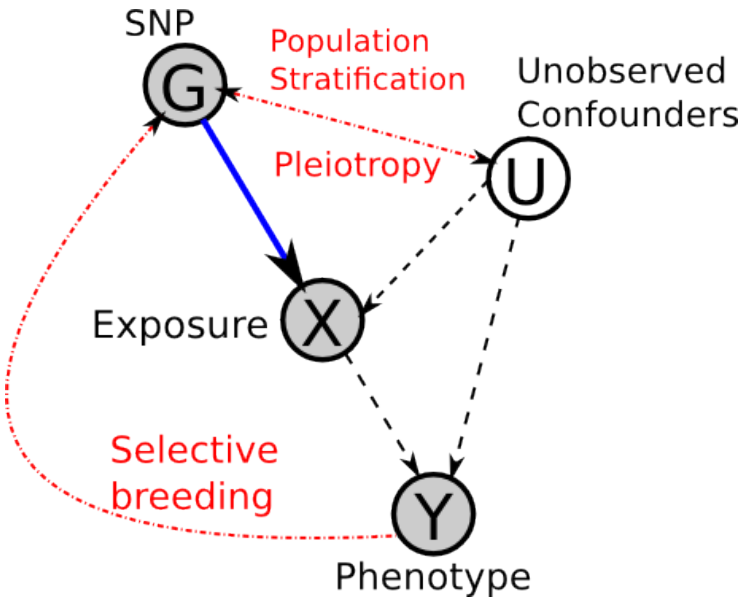
Causal inference in epidemiology?

- I believe there are many possible applications of causal inference in epidemiology.
- A classic example is **Mendelian Randomisation** - whereby the genotype is used as an instrumental variable for causal inference, to determine if the environmental exposure (X) has an effect on the disease/phenotype (Y).
- Can we improve the robustness using intermediate epigenetic measurements, etc.?
- Can we determine the necessary covariates to observe.?



- I would appreciate any data for this problem!

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Conclusion

- The importance of Machine Learning and Personalized Medicine will only increase as more data becomes available, and data access restrictions are relaxed.
- To take advantage of this, we need viable methods to extract actionable information from the data.
- The **MLPM ITN** provides us with an excellent opportunity to work on cutting-edge methods with world-class institutions and scientists.
- In addition to the opportunities to receive great training from summer schools and workshops.
- I hope to develop practically applicable methods for Personalized Medicine, such as the problems of cancer diagnosis.
- I hope I can co-operate with other nodes in the network, and make the most of the opportunities we have.

Thanks for your time!

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