Predictive Modelling of Post-Translational Regulation During Human Cell Cycle Progression

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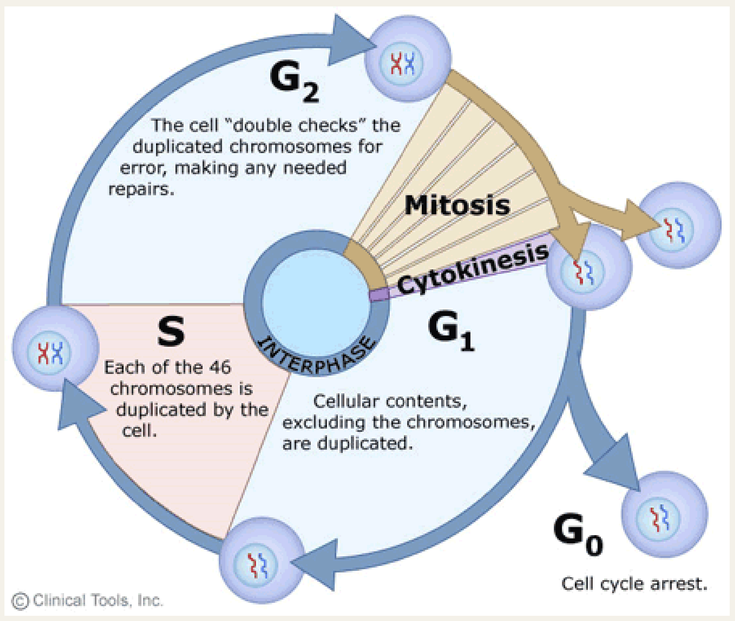
Abstract

The cell cycle is a complex phenomena of RNA and protein interactions which act as the 'kernel' of cell behaviour.

- Characterising protein interactions is crucial in understanding how cells fail (cancer, disease).
- Protein concentrations within a cell (in time) can be predicted using linear and non-linear models using corresponding mRNA and translation measurements as input.
- Outliers to the model generated are shown to contain post-translational regulatory functions by GO analysis.

Introduction

Multi-'omics (DNA, RNA, protein, epigenetic) approaches are increasingly adopted in molecular cellular analyses [1]. The central system impacting this is the cell cycle; leading in cell growth and replication.

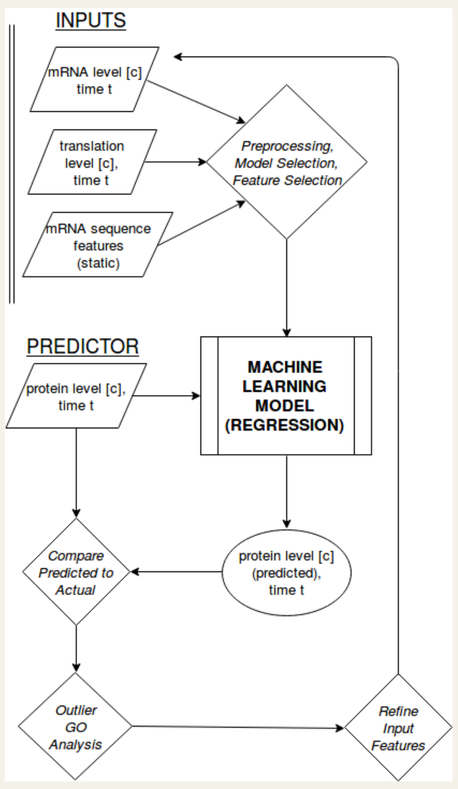


Previous models of protein concentration include both deterministic (regression)[2] and probabilistic (Bayesian, coupled-mixture)[3] approaches. These approaches have varied in success (R^2=0.5-0.86), are steady-state static samples and performed on non-human cell lines.

Methods

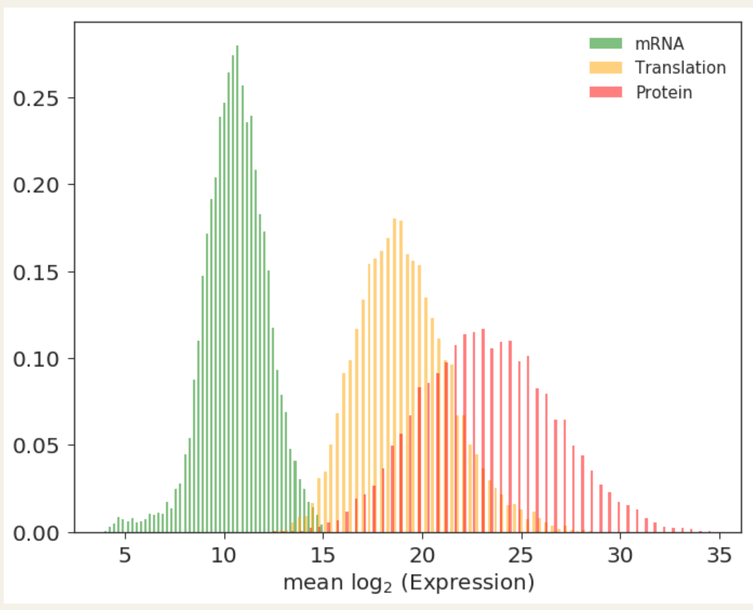
mRNA/ translation levels are drawn experimentally, sequence features are derived from online databases.

Gradient-boost tree algorithms work best across all time steps.



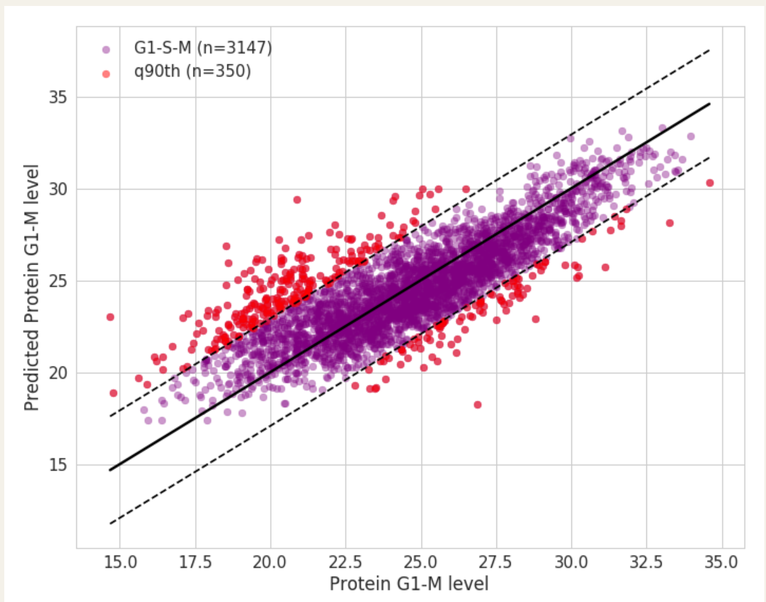
Results

We build from previous experimental work [1] which measures mRNA (microarray), translation (PUNCH-P) and protein (MS) in time-series:

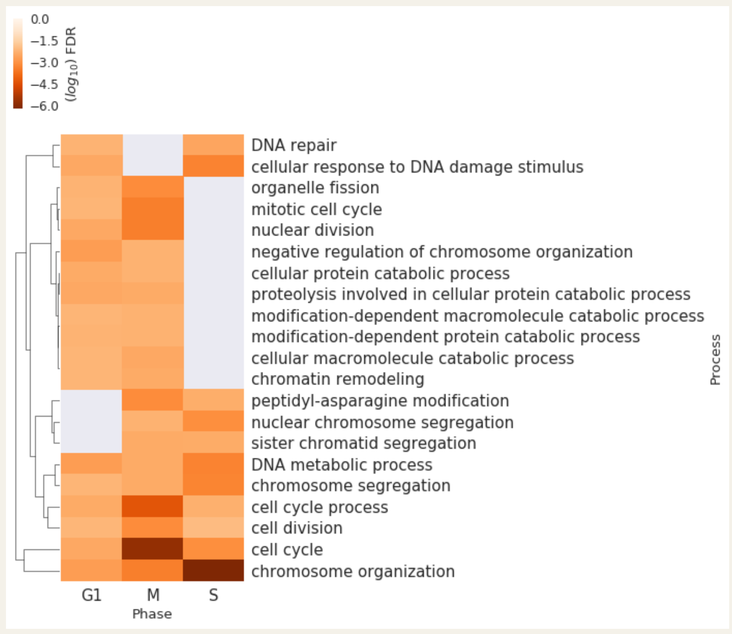


Dataset consists of 6700 RNA, 4000 translation and 5500 protein. Protein variance and subsequent complexity from a single mRNA strand leads to many-many relationships (difficult mapping). Modest correlation (r_s=0.4) between mRNA and protein less than originally anticipated.

Incorporating sequence feautres in addition as inputs to the regression model, correlation/accuracy improves substantially (r_s=0.82) between predicted and actual protein across all timesteps:



Outliers to model from *a priori* are predicted to be post-translationally regulated. We see which gene functions are *most frequent* using clustered GO analysis on outlier samples.



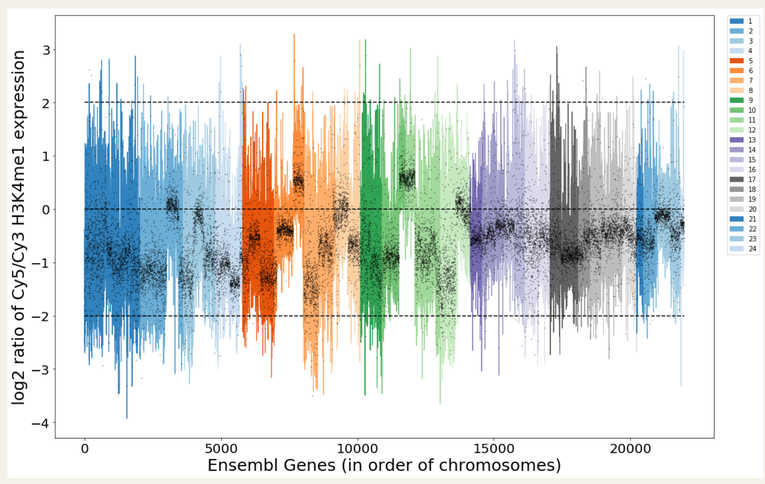
Clustering of cell cycle, protein breakdown (catabolism) and DNA-interacting processes dominate outlier function, which supports *a priori* hypothesis.

Conclusions

- Translation is vastly more important in predicting protein than mRNA (alone).
- Sequence-derived features regarding the mRNA/protein partly and cumulatively contribute somewhat to protein prediction.
- Post-translational regulation is established as dominant in outliers to a pre-protein input model – particularly overestimated proteins.
- Newly formed dataset provides a benchmark for human time-series predictive proteomics and translatomics.

Future Work

Sequence-derived features alone will not build a substantial model; thus our future work is primarily to extract additional *multi-'omic* features such as DNA methylation, halflives and histone modifications to use as input.



Extending the resolution of the time-series model will be challenging (only 3 timesteps), by integrating protein-protein interaction (PPI) networks and higher-resolution mNRA experimental data to develop confidence intervals.

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