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A mathematical modelling framework to dissect the integration of multiple signals controlling random X chromosome inactivation

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Gene expression is tightly regulated, integrating genetic and epigenetic information to produce a spatio-temporal quantitative output. How developmental genes integrate multiple signals to produce the correct expression pattern remains poorly understood. As a model for developmental gene regulation, we investigate the lncRNA Xist, which is essential for X chromosome inactivation (XCI). A number of trans-acting factors and cis-regulatory elements act synergistically and cross-talk with the pluripotency network to ensure random female-specific and mono-allelic Xist upregulation at the onset of differentiation. Mono-allelic expression is thought to be ensured through initial stochastic Xist upregulation with a low probability and subsequent stabilization of the mono-allelic state through negative feedback regulation. We quantified Xist expression at the single cell level during differentiation of female mouse embryonic stem cells with both Flow-FISH and single cell RNA-sequencing. We found that Xist expression was highly heterogeneous across cells with a subset of cell failing to upregulate Xist and expression levels varying over two orders of magnitude, which is in agreement with the proposed slow stochastic up-regulation. In the next step we will assess how quantitative perturbations of candidate regulators modulate the Xist distribution. To allow a mechanistic interpretation of these experiments, we are establishing a mathematical modelling framework. We perform stochastic simulations of Xist expression with a series of alternative hypotheses of promoter regulation. We identify those model topologies which can reproduce the experimentally measured Xist distribution using Approximate Bayesian Computation. Subsequently the selected model will be used to infer properties of the system and dissect the contributions of different factors in XCI. This work will provide a mathematical framework to understand how multiple inputs are integrated to achieve XCI.