Modeling dynamics of pluripotency in ES cells

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Embryonic Stem (ES) cells are cells derived from the epiblast tissue in inner cell mass of the mammalian blastocyst[1]. ES cells are characterized by two distinctive aspects: their potential to differentiate to any adult cell type in response to proper external signals, and their ability to self-renew indefinitely in culture. Both properties are what make ES cells very appealing from both the biomedicine and developmental biology points of view. Although pluripotency is, in fact, a short transient state of cells *in vivo*, clonal populations of these cells are kept in the pluripotent state *in vitro* thanks to a network of transcription factors involving Sox2/Oct4, Nanog[2] and Tcf3. Thus, understanding the mechanisms underlying the network of proteins is a must in controlling pluripotency.

Based on comprehensive quantitative data of the key regulatory components at the single-cell level, we have developed a detailed mathematical model of the network interactions. The model, expressed in terms of stochastic molecular reactions, includes both interactions at the transcriptional and post-translational levels (see Fig. 1A). Despite the fact that previous mathematical models exist that account for the regulated fluctuations of the key factor Nanog[3], the model presented here is, to our knowledge, the first based on precise quantitative data for more than one factor. The model, mainly fed with parameters estimated from the quantitative measurements (as opposed to fitted to data) is able to reproduce the experimental distributions of mRNA and protein concentrations of the involved factors (Nanog, Oct4, Tcf3, and β-catenin. See panel B from Fig. 1).

Another novel feature of this model is the inclusion of post-translational interactions and protein complex formation, an aspect that has shown crucial in understanding the high correlations observed among the protein concentrations (see Fig. 1C).

All in all, the pluripotency model presented here, founded on solid experimental data, brings new insight to the dynamics of the underlying network of molecular regulation.

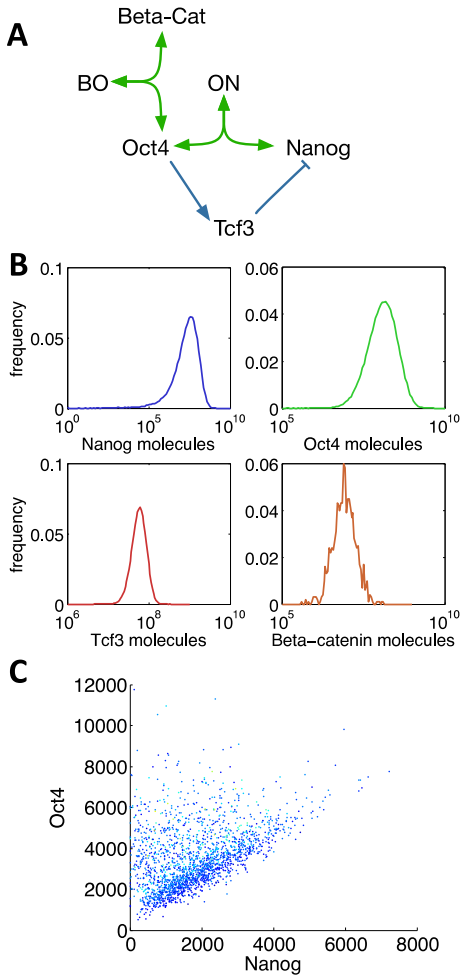

FIG. 1. Mathematical model of pluripotency dynamics. (A) Schematic representation of the network of molecular interactions. The key components of the model are the pluripotency factors Nanog and Oct4, together with Tcf3 and β-catenin. These factors interact both at the transcriptional and the post-translational levels. (B) Observed distributions of protein concentrations are reproduced by the stochastic model. Furthermore, the correlations among the species observed in the experimental single-cell data are also predicted by the model.

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