­Table S1. (A) Biophysical models of TF-DNA binding. (B) Machine learning models to incorporate epigenomic information on TF binding.

**A. Biophysical models**

|  |  |  |  |
| --- | --- | --- | --- |
| Methods | Model assumptions |  | Applications |
| **Var. TFBS affinities** | **TF coop.**  | **Epi- data** |  | **HT data** | **Species** |
| Shea et al [[1](#_ENREF_1)]Bulcher et al [[2](#_ENREF_2)] | N | P1 | N |  | N | Bacteria |
| Janssens et al. [[3](#_ENREF_3)]  | Y | N | N |  | N | Drosophila |
| Segal et al. [[4](#_ENREF_4)] | Y | Y | N |  | N | Drosophila |
| Gertz et al. [[5](#_ENREF_5)] | N | P1 | N |  | N | Synthetic promoters in yeast |
| He et al. [[6](#_ENREF_6)] | Y | Y | N |  | Y | Drosophila and mice |
| Fakhouri et al. [[7](#_ENREF_7)] | Y | Y | N |  | N | Drosophila |
| Raveh-Sadka et al. [[8](#_ENREF_8)] | Y | Y | P2 |  | N | Yeast |
| Mirny [[9](#_ENREF_9)] | N | Y | P2 |  | N | Simulation data |
| This work | Y | Y | Y |  | Y | Humans and mice |
| Y: Yes. N: No. P: Partial consideration.P1: TF-TF interactions are modeled as invariant to any participating TFs. P2 : Nucleosome positions are considered but histone and DNA modifications are not modeled. Var. TFBS affinities: TFBS affinities are modeled as specific to the TFBS sequence.TF coop. : Cooperativity between TFBSs. Epi- data: Modeling epigenomic environment.HT data: Applicability to analyzing high-throughput genomic data.  |

**B. Machine learning methods**

|  |  |  |  |
| --- | --- | --- | --- |
| Methods |  | Model assumptions | HT data used |
|  | **Var. TFBS affinities** | **TF coop.** | **Epi- data** |
| Ernst et al. [[10](#_ENREF_10)] |  | Y | P2 | P1 |  | Y |
| Boyle et al. [[11](#_ENREF_11)] |  | Y | N | P1 |  | Y |
| Arvey et al. [[12](#_ENREF_12)] |  | Y | N | P3 |  | Y |
| P1 : Open chromatin regions are considered but specific histone and DNA modifications are not modeled. P2: TF-TF interactions are modeled as invariant to the specific participating TFs. P3: Both open chromatin and histone modifications are considered but only the former contributed to the predictors of the final model.  |

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