Automated Inference of Gene Regulatory Networks Using Explicit Regulatory Modules (*shortened version*)

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1 Introduction
- Objectives
- Boolean Networks

2 Building Cis-Regulatory Networks
- Cis-Regulatory Networks
- Building a CRN From a Boolean Network
- Analysis & Biological Insights

3 Conclusion
- Summary

Objectives

Design a modelling framework (or a general method) that:

- **Takes into account cis-regulatory action on genes.**
- **Is flexible and can be applied to current networks.**
- **Ensures some biologically-relevant constraints in networks.**

(Reminder) GRNs Seen as Boolean Networks

Boolean Network

- A set V of **vertices**/biological entities

  in state ON (1) or OFF (0)

- A set E of **edges**/vertex-pairwise interactions labelled by $+, -$

  $$E \subseteq V \times V \times \{+, -\}.$$

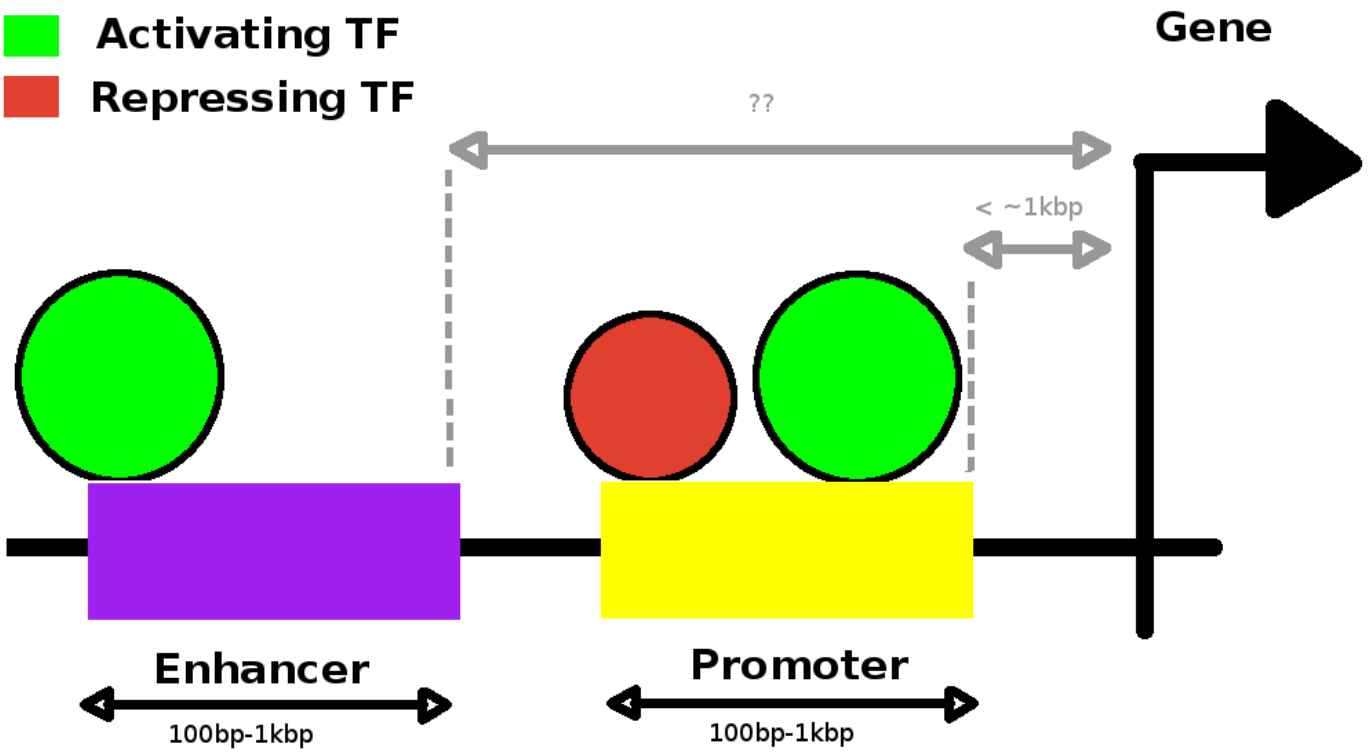
- A set F of gene **regulatory functions** $(f_g)_{g \in V}$ for each gene

  that update gene states

Transcriptional Cis-Regulatory Action

Cis-Regulatory Module (CRM)

Stretch of DNA where TFs bind & regulate expression of nearby genes **[Davidson, 2006]**.



Example of Cis-Regulatory Network

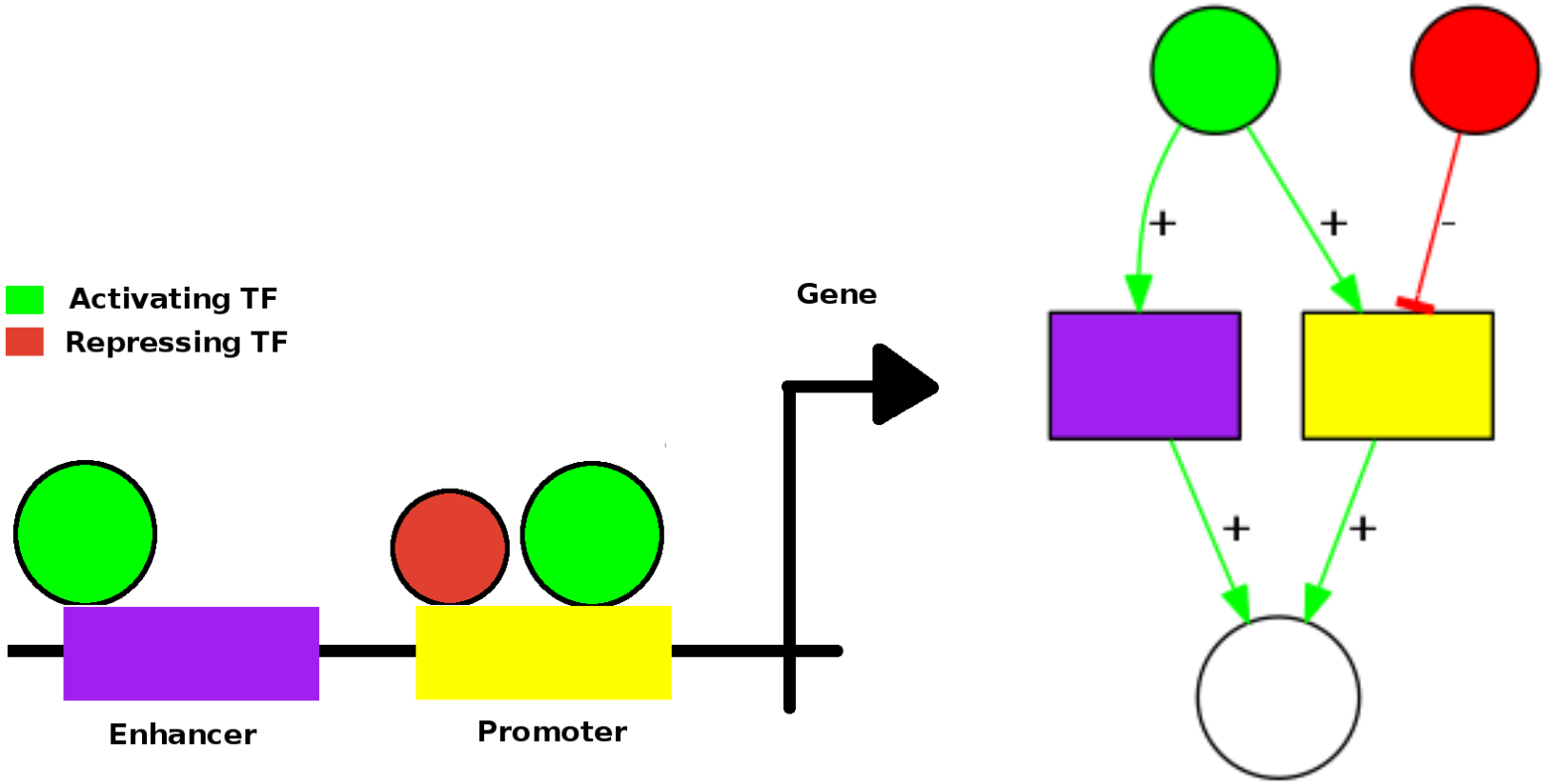
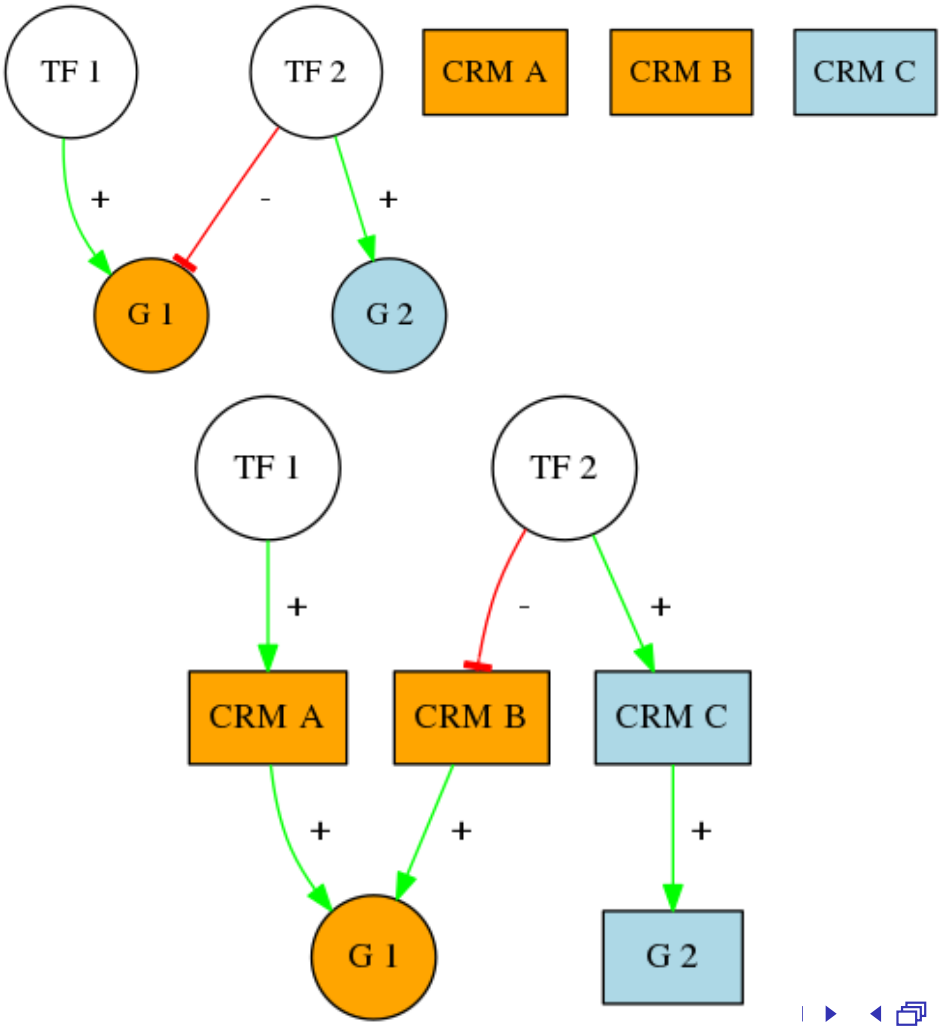


Figure: TF bindings (*left*). Associated CRN.

Illustration of Expansion Procedure

TF1 binds to CRM A, TF2 binds to CRM B and C.



→ *expansion*

Properties of Regulatory Functions in CRNs

Good news for Cis-Regulatory Networks:

Lemmas

1. All regulatory functions for CRMs and TFs are monotonous
   $\Rightarrow$ All regulatory functions for genes are **monotonous**

2. In such a modelling framework,
   All regulatory functions for genes are **decomposable**
   (by construction)

Recap

Our contributions:

→ Formal definition of CRNs:

1. Extension of **Boolean networks**.
2. Explicit implementation of **cis-regulatory modules**.
3. **Modularity** and structure of regulatory functions.
4. Modelling of **redundancy** of regulatory interactions.

→ Proofs of preservation of biologically-relevant properties (namely, **monotonicity**, **decomposability**).

→ **Code** for the expansion & network inference procedures (using a method similar to RE:IN **[Yordanov et al., 2016]**).