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EPSILON: an eQTL prioritization framework using similarity measures derived from local networks

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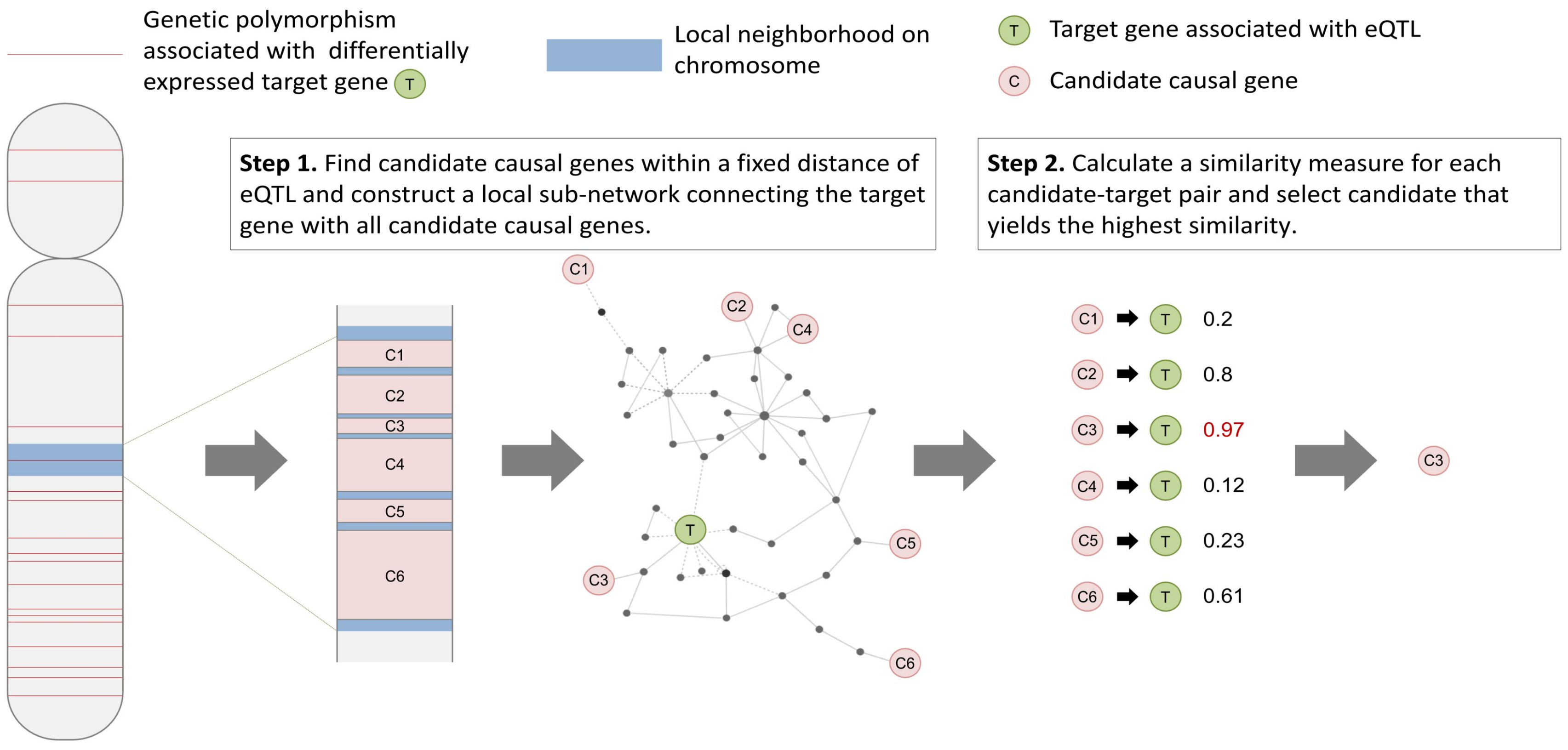
Introduction

- We used **SNP** data and **gene expression** data of ***S. cerevisiae*** to detect **eQTLs** using three different mapping methods
  - Non parametric regression
  - Mixed models
  - Elastic net
- Using a **physical interaction network**, we **prioritized** eQTLs spanning multiple genes to individual *causal* genes using a graph node **kernel** based approach
- Evaluating using **knockout pairs**, and when compared to random assignment or a shortest path approach, we obtained **superior results**
- Published in Bioinformatics:
  - *Verbeke,L.P.C. et al. (2013) EPSILON: an eQTL prioritization framework using similarity measures derived from local networks. Bioinformatics (Oxford, England), 29, 1308–16*
  - Software available at **bioinformatics.intec.ugent.be/epsilon**

Method



Genetic polymorphism associated with differentially expressed target gene T

Local neighborhood on chromosome

T Target gene associated with eQTL

C Candidate causal gene

Step 1. Find candidate causal genes within a fixed distance of eQTL and construct a local sub-network connecting the target gene with all candidate causal genes.

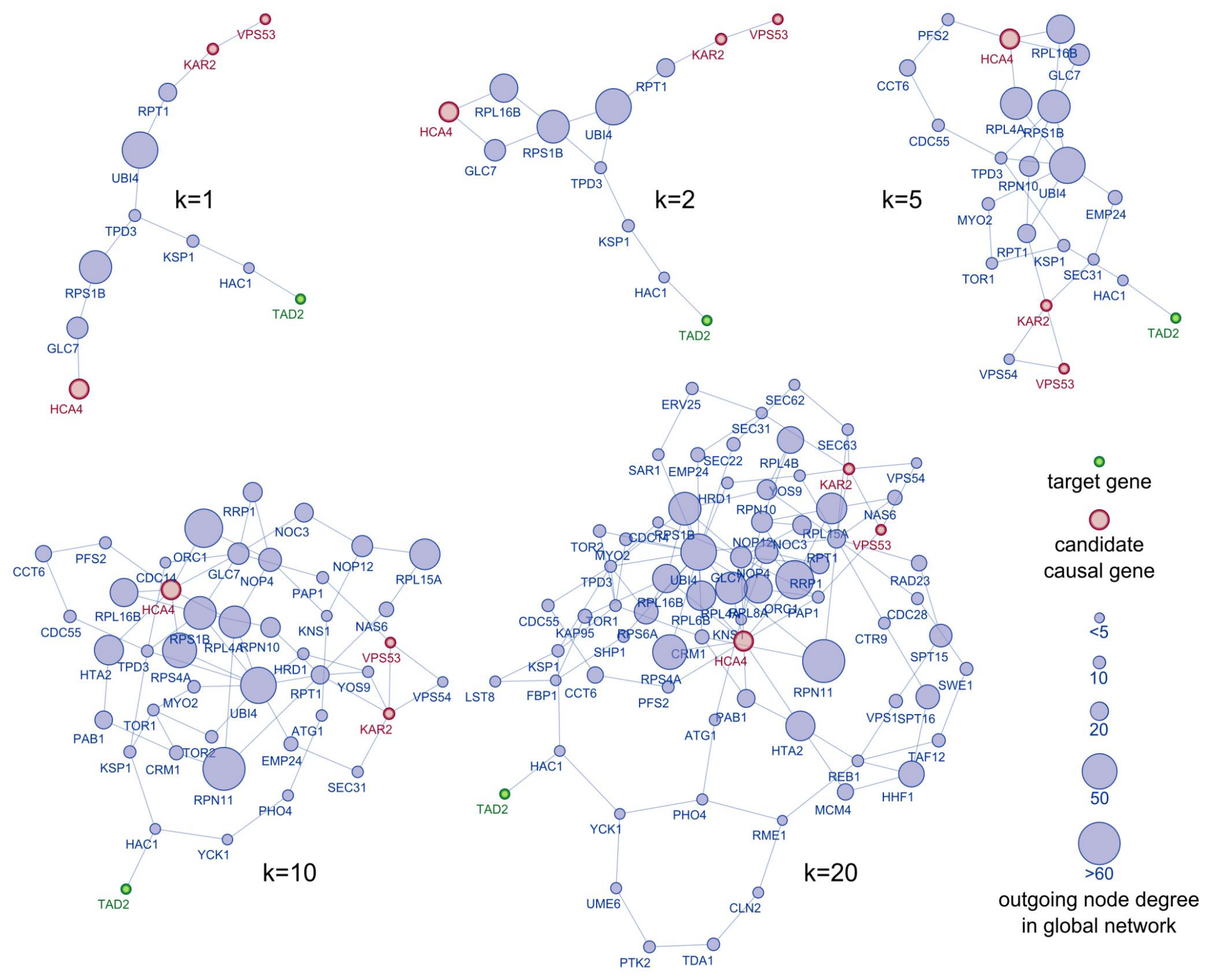
Step 2. Calculate a similarity measure for each candidate-target pair and select candidate that yields the highest similarity.

Kernel based similarity

- Kernels are functions calculated on graph nodes (each gene is a node in the interaction graph), producing node similarity matrices
- The kernels we use are typically used for recommendation tasks like
  - Customers who bought this also bought …
  - People you may know …
  - Web page importance ranking
- We are not the first to use kernels for prioritization (see e.g. Nitsch et *al.*,2010, *BMC bioinformatics*, *11*, 460) but to our knowledge, this is a new application

Local networks

- Calculating kernels on the global interaction network yields bad performance
- Better to first find a local subnetwork, and then calculate similarity measures
- We use a variant of the Dijkstra shortest path algorithm to connect multiple candidate causal genes in an eQTL to a target gene: **k-trials shortest paths**
- The algorithm tries at trial *k* to find an alternative path, after making the path found at trial *k-1* slightly more expensive



Results

- Three different eQTL mapping methods
- Evaluation using Hughes (2000) knockout dataset
- Local kernel based prioritization consistently outperforms both reference methods
- Maximum number of retrievable knockout pairs depends on the eQTL mapping method and the network at hand
- Results are comparable or superior to results mentioned in literature, see e.g.
  - Suthram, S., Beyer, A., Karp, R. M., Eldar, Y., & Ideker, T. (2008). eQED: an efficient method for interpreting eQTL associations using protein networks. *Molecular systems biology*, *4*(162)
  - Stojmirović,A. and Yu,Y.-K. (2009) ITM Probe: analyzing information flow in protein networks. *Bioinformatics (Oxford, England)*, **25**, 2447–9.