Drug repurposing in breast cancer by combining bandit algorithms and Boolean networks with **NORDic**

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Boolean networks are powerful **graphical representations of dynamical gene regulation in whole pathways**. However, the development of a drug repurposing approach based on Boolean networks (see **Fig. 1.**) meets several hurdles.

Python package **NORDic** [1] allows easier development and testing of drug recommender systems using Boolean networks. As an example, we consider an application to breast cancer.

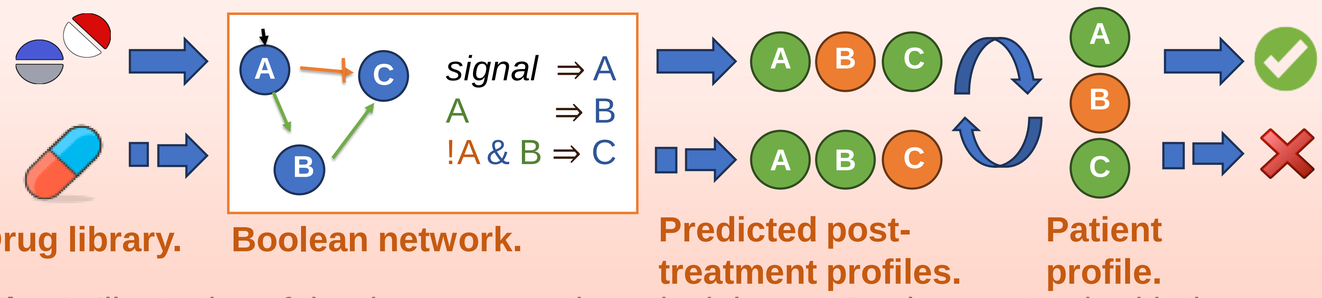


Fig. 1. Illustration of the drug repurposing principle on a Boolean network with three genes.

I. Inference of a Boolean Network associated with breast cancer

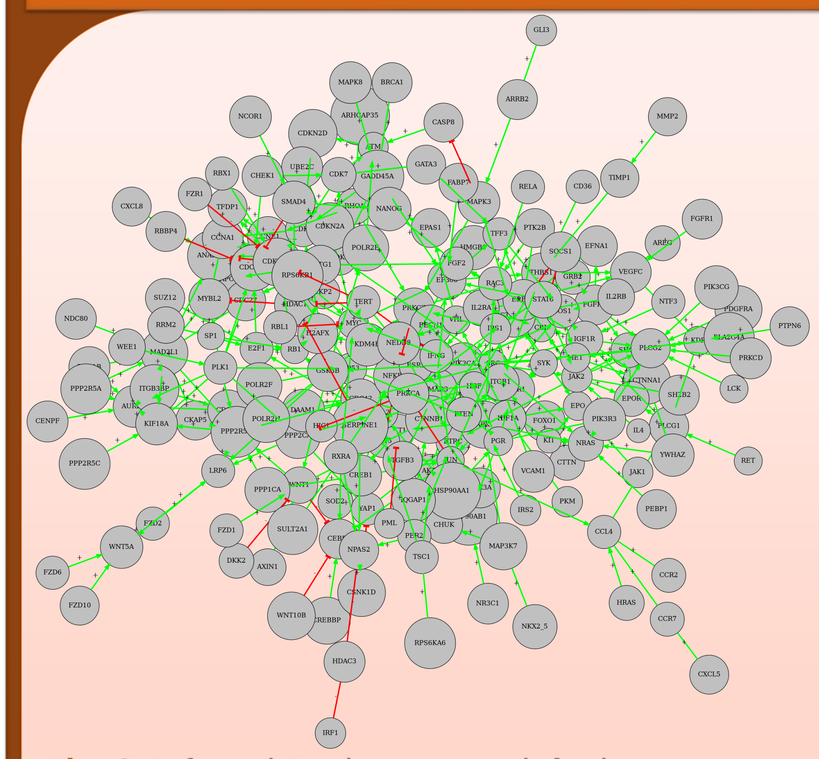
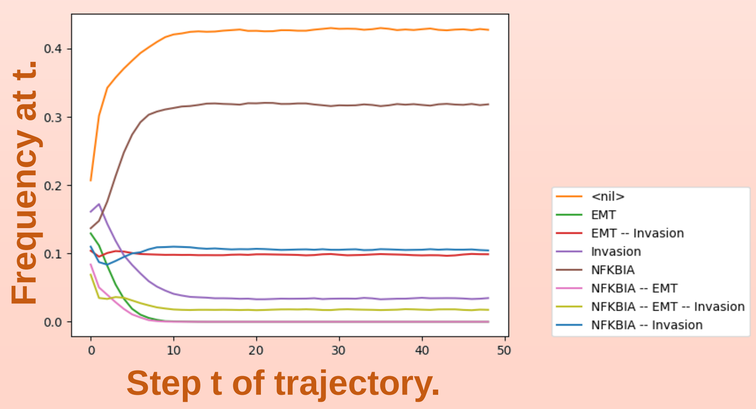


Fig. 2. Inferred Boolean network for breast cancer using **NORDic NI** (196 connected nodes, 525 edges).

Based on **[2]**, the module **Network Identification (NI)** in **NORDic** allows the **automated inference of a disease-related Boolean network**, simply from a Protein-Protein Interaction network on genes of interest, by combining several public databases. For the breast cancer network, we have considered a subset of 251 genes which were prioritized for breast cancer through either literature or an community-enrichment approach **[3]**, and experiments on the MCF-7 cell line (see **Fig. 2.**).

In order to validate the network, we have checked **whether it could reproduce unseen phenotypes from gene perturbation experiments**. Across 56 experiments extracted from the literature, the inferred network could accurately predict the reported phenotype 67,8% of the time (see example in **Fig. 3.**).



Phenotype at t = 50 (bold type: in [4])	**No EMT No Invasion NFKBIA is inactive**	EMT Invasion NFKBIA is inactive	No EMT Invasion NFKBIA is inactive	**No EMT No Invasion NFKBIA is active**	EMT Invasion NFKBIA is active	No EMT Invasion NFKBIA is active
Frequency across 10,000 trajectories	**0.43**	0.10	0.03	**0.32**	0.02	0.10

Fig. 3. Prediction of profiles from the inferred Boolean network when gene MYC is knocked-out and frequency of each phenotype across 10,000 trajectories of length 50.

II. Development of a standard benchmark for drug repurposing approaches

The **Drug Simulation (DS)** module in **NORDic** (since v2.0) implements a modular and ready-to-use scoring approach (function *simulate*) (see **Fig. 4.**)

In our breast cancer application,

do Boolean networks actually improve the prediction of drug effect on MCF-7 cells? (see **Fig. 5.**)

Fig. 5. ROC Curves obtained on network-oriented drug repurposing approaches ("BN-based" named methods) and the baseline L1000 CDS^2 **[5]**.

The positive (resp., negative) class comprise of drugs with negative (resp., nonnegative) IC_{50} *z*-scores from the GDSC database **[6]**.

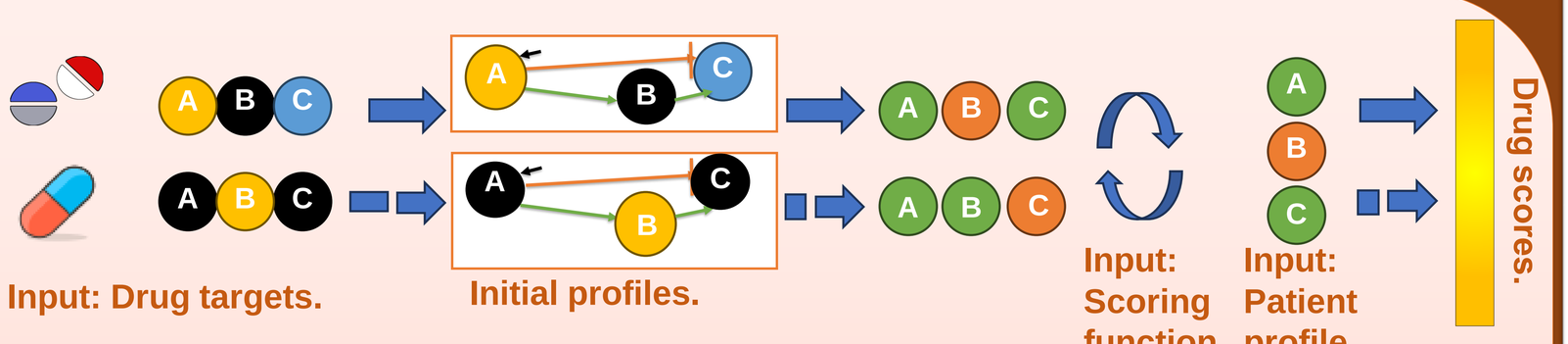
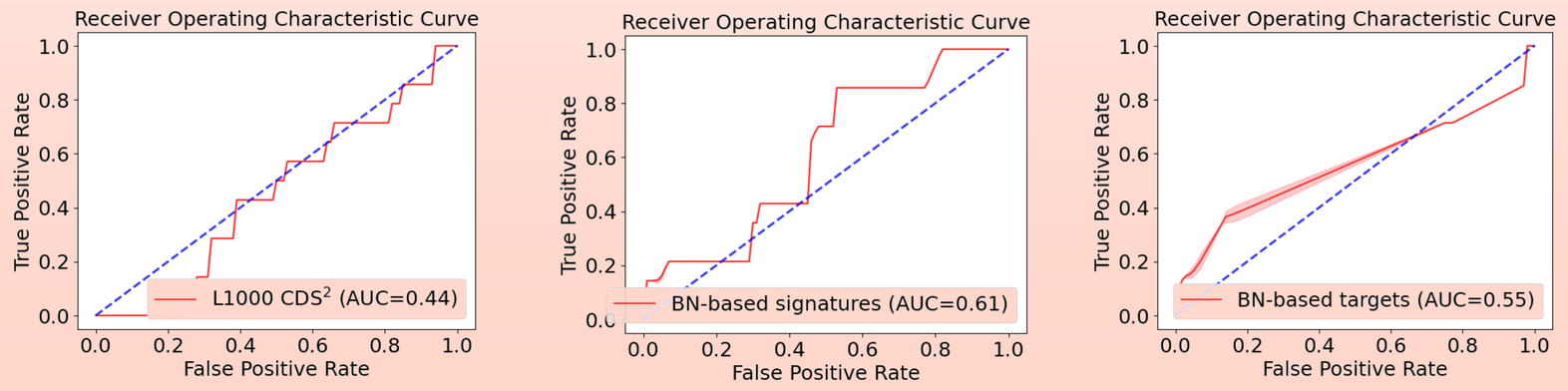


Fig. 4. Illustration of the generic scoring approach used in **NORDic DS** (reusing example in **Fig. 1.**).



III. Combination of scoring with adaptive drug testing

An adaptive procedure to test drugs using Boolean net**works might be less computationally expensive and yields guarantees on the recommendation error**. The **Drug Repurposing (DR)** module in **NORDic** (since v2.0) implements a bandit algorithm **[7]** which leverages drug feature vectors in order to identify the *m* top drug candidates (score-wise) with high probability *1-π* within a small number of tests (see **Fig. 6.**).

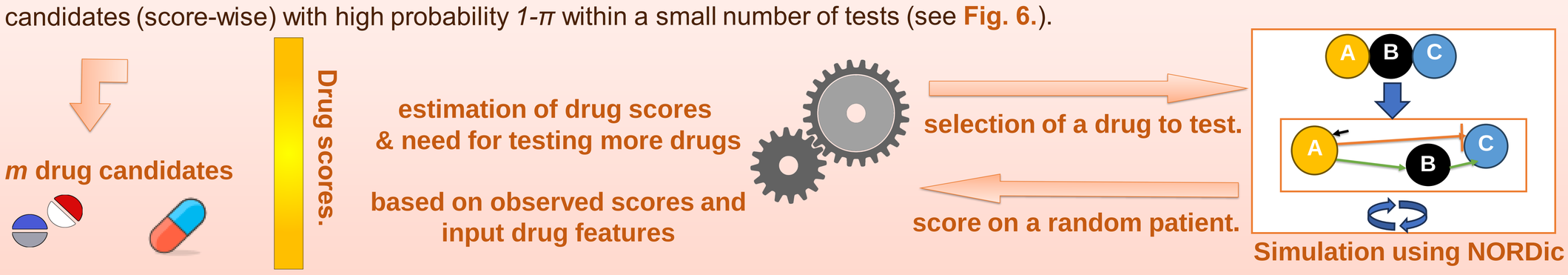


Fig. 6. Illustration of the adaptive procedure used in **NORDic DR** (reusing example in **Fig. 1.**).

In our application to breast cancer, in a grid-search approach → 6,032 simulation steps (N patients=104 x N drugs=58)
in the bandit approach → average of 5,340 simulations across 500 iterations (π=10% and m=1)

Discussion

NORDic is an open-source Python package which aims at providing **reproducible, modular pipelines for the inference and analysis of Boolean networks. It implements a generic pipeline for drug repurposing.**
This package is hopefully a step towards faster and more robust development of network-based drug repurposing.

[1] NORDic v2.4.2. DOI: 10.5281/zenodo.7693088
[2] Réda & Delahaye-Duriez. DOI: 10.1007/978-3-031-15034-0_5
[3] López-Cortés et al. DOI: 10.1038/s41598-018-35149-1
[4] Wang et al. DOI: 10.1186/bcr975
[5] Duan et al. DOI: 10.1038/npjsba.2016.15
[6] Yang et al. DOI: 10.1093/nar/gks1111
[7] Réda, Tirinzoni & Degenne. arXiv:2111.01479

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GitHub code repository