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Networks and games for precision medicine

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ABSTRACT

Recent advances in omics technologies provide the leverage for the emergence of precision medicine that aims at personalizing therapy to patient. In this undertaking, computational methods play a central role for assisting physicians in their clinical decision-making by combining data analysis and systems biology modelling. Complex diseases such as cancer or diabetes arise from the intricate interplay of various biological molecules. Therefore, assessing drug efficiency requires to study the effects of elementary perturbations caused by diseases on relevant biological networks. In this paper, we propose a computational framework called *Network-Action Game* applied to best drug selection problem combining Game Theory and discrete models of dynamics (Boolean networks). Decision-making is modelled using Game Theory that defines the process of drug selection among alternative possibilities, while Boolean networks are used to model the effects of the interplay between disease and drugs actions on the patient's molecular system. The actions/strategies of disease and drugs are focused on arc alterations of the interactome. The efficiency of this framework has been evaluated for drug prediction on a model of breast cancer signalling.

1. Introduction

The analysis of the patients' omics profiles (genome, metabolome, proteome, etc.) will soon become a standard for customized molecular-based diagnosis and treatment by contrast to a "one-size-fits-all" strategy based on a one-to-one correspondence between diseases and drugs (Ginsburg, 2009; Mirnezami et al., 2012). *Precision medicine* is an emerging branch of medicine that uses omics data to improve clinical decision-making by designing new tools for the personalization of therapies and their risk/benefit assessment. Addressing this challenge puts the focus on the causality study of the pathogenesis at molecular level.

However, the causal relationship between omics information and disease phenotypes remains elusive. Indeed, a disease phenotype is rarely a consequence of an abnormality in a single gene product but involves complex interplays of various biological molecules (Barabási te al., 2011). For instance, patients with sickle cell anaemia, which is caused by a unique well-defined genetic event in a single gene (classic Mendelian disease) can exhibit highly variable phenotypes in the clinic (Ballas, 2011; Schadt, 2009). This variability is due to the interaction of the mutated gene with other individual-dependant genetic variants (Sebastiani et al., 2010; Schadt, 2009). Therefore, understanding the pathogenesis at molecular level requires to conceive frameworks facilitating the discovery of causes altering the molecular system of a living organism. This challenge logically focuses on biological networks modelling the causal interplays of molecules (Delaplace et al., 2010).

The main approaches in this field study the location of dysfunctional molecules in networks and the nature of network alterations leading to diseases. The works (Barabási, 2007; Barabási te al., 2011; Gustafsson et al., 2014) study the formation of specific molecular subnetworks, called modules, supporting diseases. This approach is motivated by the hypothesis that network modules support key molecular functions disrupted in disease (Davidson, 2010; Milo et al., 2002). In Oti et al. (2006), authors confirm the fact that proteins involved in the same disease have a higher propensity to interact with each other, forming a tightly interconnected entity in the interactome. Thereby, disease should likely alter a functional module or being themselves modules supporting a dysfunctionality (disease modules).

In Zhong et al. (2009), a network-perturbation approach is used to explain molecular dysfunctions underlying human diseases. The genetic events causing diseases are expressed as perturbation of both edges and nodes of the interactome. Schematically, a genetic event leading to the expression of an inoperative protein is modelled by a node deletion while genetic events inducing loss or gain of interaction are respectively modelled by an edge deletion or

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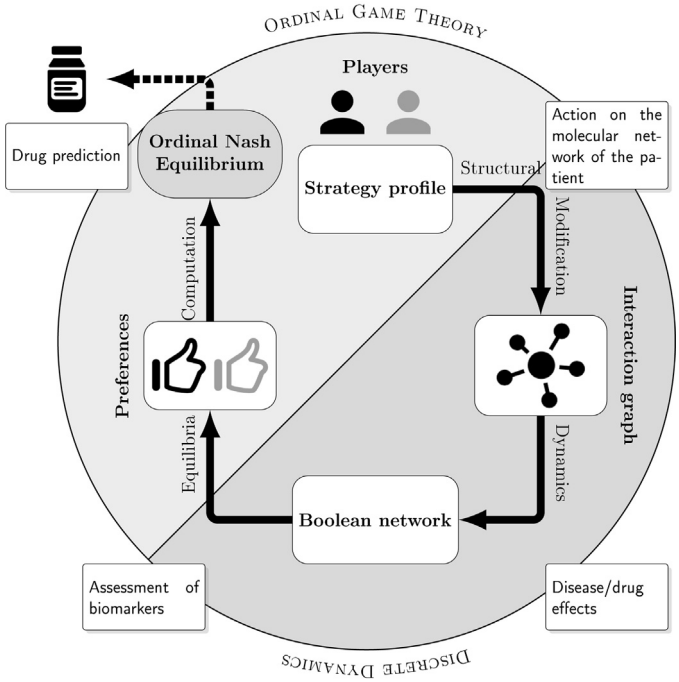

Fig. 1. Overview of the Network-Action Game method.

addition (*edgetic* perturbation). They uncovered experimental and computational evidences that these network alterations occur in human Mendelian diseases. It is worth noting that the perturbation on networks induced by diseases are formalized by elementary topological modifications of molecular interaction networks: nodes or edges are added or deleted. Hence, the complexity of disease should rely on the impact of these topological perturbations on the physiological processes controlled by these networks. For instance, cancer cells acquire the ability to maintain proliferative signalling notably by defecting feedback loops regulating cell division (Hanahan and Weinberg, 2011). Therefore, a deeper understanding of disease/therapy mechanisms relies on the prediction of the consequences of these elementary actions on the dynamics of molecular networks.

In this paper, we combine two theoretical frameworks: *Game Theory* and discrete models of dynamics (*Boolean networks*) to determine the best drug to administrate to a patient. The clinical decision-making is modelled using Game Theory, that defines the process of selection by the *players* of an action among alternative possibilities (Chettaoui et al., 2007; Osborne and Rubinstein, 1994), while Boolean networks are used for modelling the effects of the interplay between disease and drugs on the patient molecular system. Boolean networks are used in biology to study the dynamics of molecular networks (modelled as *interaction graphs*), which represent functional interactions between molecules (Abou-Jaoudé et al., 2009; Ciliberto et al., 2005; Thomas and Thieffry, 1995). Such a dynamics evolves towards equilibria interpreted at the molecular level as the patient health condition or illness. The physician and the disease are considered as *players* of a game, each of them having *strategies* of action that correspond to a drug administration and to a genetic event, respectively. In a game, combinations of strategies, called *strategy profiles*, modify the patient interaction graph, therefore modifying the associated Boolean dynamics and its equilibria. From the assessment of biomarkers at these equilibria, players' preferences are determined, and then, the interpretation of the Ordinal Nash equilibrium leads to the discovery of the best physician action (drug). Fig. 1 recalls the main steps of the framework described above.

The paper is structured as follow: after recalling the main features of Boolean networks and Ordinal Game Theory, we detail the theoretical framework called *Network-Action Game* in Section 2 and show its application to drug prediction in breast cancer in Section 3.

2. Network-Action Game

We first introduce the two theories composing the Network-Action Game framework: Boolean networks and Ordinal Game Theory and we then show their coupling.

2.1. Boolean networks

A *Boolean network* is a discrete dynamical system of a population of agents defined by a family of propositional formulas determining the evolution of the agents. The dynamics is defined by a transition system on a set S representing all the possible states of the agents and transitions represent their evolution.

Let A be a set of agents, a (Boolean) state is defined as a mapping $s : A \mapsto \mathbb{B}$ associating to an agent in A a value from $\mathbb{B}$ and S denotes the set of mappings representing the states.

Let $F = (f_a)_{a \in A}$ be a family of propositional formulas, each f_a is a function defining the state of a from the states of all the agents (seen as propositional variables). An asynchronous[1] *Boolean network* is defined as a pair $\langle A, F\rangle$ and its model of dynamics is a labelled transition system $(S, \longrightarrow, A)$ where the transition relation labelled by agent a and denoted $\xrightarrow{a} \subseteq S \times S$, updates the state of agent a only. Formally, it is defined as:

$$s \xrightarrow{a} s' \stackrel{\text{def}}{=} (s'[a] = f_a(s) \wedge s[a] \neq f_a(s) \wedge (\forall x \in A \backslash \{a\} : s[x] = s'[x])).$$

Hence the global dynamics is the union of the transitions labelled by agents (*i.e.*, $\longrightarrow = \bigcup_{a \in A} \xrightarrow{a}$).

The *signed interaction graph* associated to F, $G = \langle A, \rightarrow, \delta\rangle$ represents all the signed interactions defined by F between agents in A. The sign of the arc is given by a labelling function δ and may be + for increasing relation, − for decreasing one and ± otherwise. Such a graph can be inferred from the syntax of the propositional formulas in minimal[2] disjunctive normal form, where $a_i \xrightarrow{-} a_j$ stands for the occurrence of negative literal $\neg a_i$ in f_{a_j}, $a_i \xrightarrow{+} a_j$ for the occurrence of positive literal a_i in f_{a_j}, and $a_i \xrightarrow{\pm} a_j$ for both. Fig. 2 shows a Boolean network, its model of dynamics and signed interaction graph.

A state s is an *equilibrium* for $\longrightarrow$, if it may be reached infinitely often, *i.e.*, $\forall s' \in \mathbb{B}^n : s \longrightarrow^* s' \Rightarrow s' \longrightarrow^* s$, where $\longrightarrow^*$ denotes the reflexive and transitive closure of $\longrightarrow$. We denote by $E_{\longrightarrow}$ the set of all equilibria of $\longrightarrow$. An *attractor* is a set of equilibria that are mutually reachable and a *steady state* is an attractor of cardinality 1. In Fig. 2, the states (1, 0, 0) and (0, 1, 1) are steady states.

2.2. Ordinal game

An Ordinal Game models strategic decision-making based on the definition of a *preference relation* amongst combination of players' strategies. Each *player* has a set of possible *strategies* and a *strategy profile* represents a particular combination of strategies. A *preference relation* defines the preference, for a player, between each pair of strategy profiles and a *preference graph* represents the union of the preference relations of all players.

Formally, an *Ordinal Game* is a triple $\langle P, (C_p)_{p \in P}, (\preceq_p)_{p \in P}\rangle$ where:

[1] Asynchronous means that the state of at most one agent is updated at each transition.

[2] In a minimal disjunctive normal form the conjunctions are the prime implicants.