

# Games network and application to PAs system

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## Abstract

In this article, we present a game theory based framework, named *games network*, for modeling biological interactions. After introducing the theory, we more precisely describe the methodology to model biological interactions. Then we apply it to the plasminogen activator system (PAs) which is a signal transduction pathway involved in cancer cell migration. The games network theory extends game theory by including the locality of interactions. Each game in a games network represents local interactions between biological agents. The PAs system is implicated in cytoskeleton modifications via regulation of actin and microtubules, which in turn favors cell migration. The games network model has enabled us a better understanding of the regulation involved in the PAs system.

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## 1. Introduction

Systems biology consist in a global analysis to transform large data sets, coming from high throughput (post-)genomics, into knowledge in order to comprehend the complexity of living organisms. It is useless to point out that computer based analysis is central in this process. However, the advance in systems biology does not merely rely on the computing power, but also on the advance of biological computational models.

Focusing on molecular interplays, network representation is used as a privileged tool to describe and analyse the interactions. Indeed, a network represents a wide variety of regulations such as genes regulation, pathway signaling and metabolism reactions. Beyond the static representation of interactions described by networks, informations related to the dynamics must be integrated in order to model the interactions more in-depth. The challenge can be more precisely specified within the scope

of graphs and interactions analysis. It partly consists in finding a framework to model the dynamics of interactions extending their static graphs representation. In this paper, we propose an original extension of games theory, to analyse the dynamics of interactions for molecular networks.

In biology, *evolutionary game theory* has been widely used to model evolution of population resulting from Darwinian fitness (Maynard Smith, 1982; Hofbauer and Sigmund, 1998; Nowak and Sigmund, 2004). We use here the *strategic game theory* in an operating way to express complex regulatory phenomena. The goal is to explain the stability of phenomena coming from regulatory process with macroscopic rules which may identify some general features of the biological system. However, dealing with game theory implies the description of combination of interaction between any agent and, hence, the combinatorial choices ( $m^n$  for  $n$  agents with  $m$  strategies) lead to reduce the model to a few number of agents in order to be tractable by computer. Moreover, dealing with complexity relies also on ability to exhibit properties of the system. In particular, we

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investigate on the modularity of interactions. *Games network* model extends the game theory by emphasizing the locality of the interactions in the model. It enables us to describe a network as a set of dynamical local interactions which might be assimilated to biological modular interactions. The model has been applied on a realistic biological case: the PAs system implicated in cancer cell migration (Providence and Higgins, 2004).

The paper is organized as follows: in Section 3 we give the definition of games networks and the equilibria. In Section 4, we explain how games network can be used in order to model signaling pathways. Section 5 more deeply describes the application to PAs system.

## 2. Notations

In the paper, we use the following notations:

- $[a : b] = \{i \in \mathbb{Z} | a \leq i \leq b\}$  denotes a discrete interval bounded by  $a$  and  $b$ .
- Let  $A = [1 : n]$ , given  $C = \{C_i\}_{i \in A}$ , we note  $C_A = \times_{i \in A} C_i$ . Considering  $X \subseteq A$ , we note  $C_X = \times_{i \in X} C_i$  and for  $j \in A$ ,  $C_{-j} = \times_{i \in A-j} C_i$ .
- We consider the lifted version  $C_{\text{lift}} = C + \{\perp\}$  where the element *Bottom* denoted by  $\perp$  is added to  $C$ .
- Concerning the profiles or vectors, we adopt the following notations. Given  $A = [1 : n]$ , given a profile  $c \in C_A$  of a set  $C_A = \times_{i \in A} C_i$ , we note  $c_{-i} = (c_1, \dots, c_{i-1}, c_{i+1}, \dots, c_n)$ . This excludes the  $i$ th component of a profile. To distinguish the  $i$ th component of the profile from the others, we note  $(c_{-i}, \mathbf{c}_i) = (c_1, \dots, c_{i-1}, \mathbf{c}_i, c_{i+1}, \dots, c_n)$ .

## 3. Games networks

The theory of games networks is an extension of the game theory. Games networks make the representation of *modular interactions* possible, each one is supported by a subset of agents. The agents involved in local interactions are participating in the same game, i.e. the same module. The payoffs of the agents define the interaction rules. An agent is shared between several modules, but its strategies remain the same whatever the game.

In this section, we first recall some notions of game theory. Then we address the main definitions of a games network and the notion of equilibrium at the scale of network (Delaplace and Manceny, 2004).

### 3.1. Game theory

In this subsection, we summarize the main definitions of *strategic Game Theory* used in this paper. They mainly

concern the definition of the notion of *strategic game* and *Nash equilibrium*. The reader can refer to the books (Gibbons, 1992; Myerson, 1991; Nash, 1996; Osborne, 2003) for a complete overview of the game theory and its applications.

#### 3.1.1. Strategic games

*Strategic game* is a model of interplays where each agent chooses its plan of action (or strategy) once and for all, and these choices are made simultaneously. Moreover, each agent is rational and perfectly informed of the payoff function of other agents. Thus, they aim at maximizing their payoffs while knowing the expectation of other agents.

**Definition 1** (Normal or strategic representation). A strategic game  $\Gamma$  is a 3-uple  $\langle A, C, u \rangle$  where:

- $A$  is a set of players or agents;
- $C = \{C_i\}_{i \in A}$  is a set of strategy sets where each  $C_i$  is a set of strategies available for the agent  $i$ ,  $C_i = \{c_i^1, \dots, c_i^{m_i}\}$ ;
- $u : A \times C_A \mapsto \mathbb{R}$  is a payoff function,  $u_i : C_A \mapsto \mathbb{R}$ ,  $i \in A$  is the payoff function of the agent  $i$ .

#### 3.1.2. Nash equilibrium

*Nash Equilibrium* is a central concept of the Game Theory ((Nash, 1996)). This notion captures the steady states of the play for a strategic game in which each agent holds the rational expectation about the other players behavior. A *pure nash equilibrium* (pne) corresponds to a *strategic profile*  $c$  (or vector) where  $c_i$  is the strategy “chosen” by the player  $i$ .

**Definition 2** (Pure nash equilibrium of a strategic game). Let  $\langle A, C, u \rangle$  be a strategic game, a *pure nash equilibrium* is a profile of strategies  $c^* \in C_A$  with the property that:  $\forall i \in A, \forall c_i \in C_i, u_i(c_{-i}^*, c_i) \leq u_i(c_{-i}^*, c_i^*)$ .

In other words, *no agent can unilaterally deviate of a pne without decreasing its payoff*.

### 3.2. Games networks normal form

The definition of a games network mainly consists in defining a set of agents connected to a set of games. The normal form of a games network is as follows:

**Definition 3** (Games network). A games network is a 3-uple  $\langle \mathcal{A}, C, \mathcal{U} \rangle$  where

- $\mathcal{A}$  is a set of agents or players.
- $C = \{C_i\}_{i \in \mathcal{A}}$  is a set of sets of strategies.

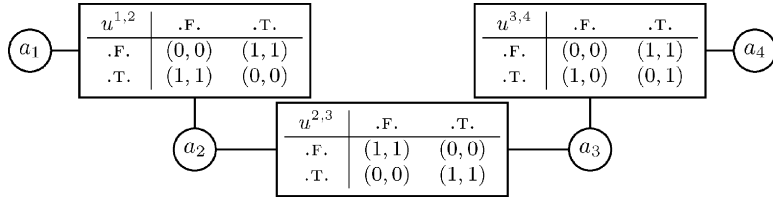


Fig. 1. Example of games network.

- $\mathcal{U} = \{\langle A, u \rangle\}$  is a set of *game nodes* where each  $A \subseteq \mathcal{A}$  is a set of agents and  $u : A \times C_A \mapsto \mathbb{R}$  is a payoff function.

A games network offers a synthetic representation to define the different interplays between several players. The structure  $\langle A, u \rangle$  totally determines a game played by a subset of agents since it is useless to include the strategies which are the same for any agent of the network.

A games network is represented by a bipartite graph  $\langle \mathcal{A}, \mathcal{U}, E \rangle$ ,  $E \subseteq \mathcal{A} \times \mathcal{U}$  where an edge  $(i, \langle A, u \rangle)$  is a member of  $E$  if and only if  $i \in A$ . Graphically, agents are represented by circles, and game nodes by rectangles (see Fig. 1 for an illustration).

### 3.3. Global equilibria

The definition of a games network allows the combination of several games into a single network. This puts the emphasis on the way that the network structure is determined, because different structures can be proposed to model the same situation. In order to compare them, it is necessary to identify the equivalence between games networks. The equivalence is based on the equilibria. Informally, two games are equivalent if their equilibria are the same. Such a condition requires to enlarge the equilibrium locally computed from game nodes to the whole games network. For that reason, we equip the theory with the *restriction operator* which allows us to focus on an arbitrary sub-game. The equilibrium at the scale of the network is named the *pure games network equilibrium* (PGne).

#### 3.3.1. Restriction

**Definition 4** (Strategy profile restriction). Let  $\mathcal{A} = [1 : n]$  be a discrete interval representing a set of agents, let  $C = \{C_i\}_{i \in \mathcal{A}}$  be a set of strategy sets. Given a strategy profile  $c \in C$ , we define its restriction to a subset  $A \subseteq \mathcal{A}$ , denoted by  $c \downarrow_A : C \times 2^{\mathcal{A}} \mapsto C_{\text{lift}}$ , as follows:

$$(c \downarrow_A)_i = \begin{cases} c_i & \text{if } i \in A \\ \perp & \text{otherwise} \end{cases}$$

We extend the restriction operator by removing bottom elements ( $\perp$ ) of the profile, but the order of the other values is conserved in the resulting profile. We note the composition of the removals and restriction operation as follows:  $c \downarrow_X$ .

**Example 1.** Let  $\mathcal{A} = [1 : 4]$  and  $c = (c_1, c_2, c_3, c_4)$ . Let  $A = \{1, 3\}$ , we have  $c \downarrow_A = (c_1, \perp, c_3, \perp)$  and  $c \downarrow_{\mathcal{A}} = (c_1, c_3)$ .

#### 3.3.2. Global equilibria

A games network equilibrium corresponds to a compatible association of local equilibria. We assume that agents follow the *single played strategy* rule, that is an agent plays the same strategy for every connected games.

**Definition 5** (Pure games network equilibrium). Let  $\Gamma = \langle \mathcal{A}, C, \mathcal{U} \rangle$  be a games network, let  $c^* = (c_1, \dots, c_n)$  be a strategy profile of every agent.  $c^*$  is a pure games network equilibrium of a subset  $U \subseteq \mathcal{U}$  (noted  $c^* \in \text{PGne}_\Gamma(U)$ ) iff:  $\forall \langle A, u \rangle \in U$ ,  $c^* \downarrow_A$  is a pure Nash equilibrium of the game  $\langle A, (C_i)_{i \in A}, u \rangle$ .

#### 3.4. An example of games network

Let us consider  $\Gamma = \langle \mathcal{A}, C, \mathcal{U} \rangle$  the games network of Fig. 1. We have:

- $\mathcal{A} = \{a_1, a_2, a_3, a_4\}$ , the agents.
- $C_i = \{.F., .T.\}$ ,  $\forall i \in \mathcal{A}$ , the strategies of the agents.
- $\mathcal{U} = \{\langle A_{1,2}, u^{1,2} \rangle, \langle A_{2,3}, u^{2,3} \rangle, \langle A_{3,4}, u^{3,4} \rangle\}$ , the game nodes where  $A_{1,2} = \{a_1, a_2\}$ ,  $A_{2,3} = \{a_2, a_3\}$ ,  $A_{3,4} = \{a_3, a_4\}$  and the payoffs functions are shown in Fig. 1.

To compute the PGne of  $\Gamma$ , let us compute the pne of each sub-game:

$$\begin{aligned} \text{pne}_{1,2} &= \text{pne}(\langle A_{1,2}, u^{1,2} \rangle) = \{(.F., .T.); (.T., .F.)\}. \\ \text{pne}_{2,3} &= \text{pne}(\langle A_{2,3}, u^{2,3} \rangle) = \{(.F., .F.); (.T., .T.)\}. \\ \text{pne}_{3,4} &= \text{pne}(\langle A_{3,4}, u^{3,4} \rangle) = \{(.F., .T.)\}. \end{aligned}$$

Thus, we can compute the PGne of  $\Gamma$ :  $\text{PGne}_\Gamma = \{(.T., .F., .F., .T.)\}$ .

#### 4. Methodology for biological applications

In this section we describe each component of the game network theory and we place them in biological context. More specifically, we describe the methodology in the context of signaling pathways.

Schematically, agents represent biological objects which can either be proteins, metabolites or molecules. The network describes the structure of the interactions between these biological agents. The strategies represent the characteristic states of an agent which correspond to the relevant configurations for the studied system. The last parameter of games network is the payoff. It models the dynamics of the considered interactions.

After introducing these terms we will give more details in the case of signal transduction network.

##### 4.1. Agents and network

We take a particular interest in an example of signal transduction network concerning the cancerous cells migration. In this model, agents are more specifically molecules and complexes. The network describes the formation of complexes and the regulation phenomenon which occur in the studied signaling process.

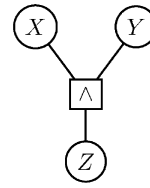
##### 4.2. Strategies and payoff

We must consider these two parameters together because the payoff corresponds to a numerical result associated to each configuration of strategies. Thus, we must be able to compute the payoff for situations which correspond to a combination of strategies. In the model, a configuration of strategies embodies a characteristic situation. In this context, the computation of the payoffs consists in assembling a set of experimental results, where each one corresponds to a biological situation. Basically, according to the biological experiments, we found two ways to compute the payoffs: *the Game Coding Function approach* (GCF) and *the Monotonous Payoff Function approach* (MPF).

**The GCF approach** is used to encode a function in a game. In this approach, some agents correspond to arguments and one agent corresponds to the solution of this function.

Given a strategic game  $\langle A, C, u \rangle$  and a function  $f : C_1 \times \dots \times C_{n-1} \mapsto C_n$ , let us consider that the  $n$ th agent's strategies correspond to the result of  $f$ . The payoff of the game is defined according to the GCF if and only if:

$$\forall c \in C_A, \forall i \in A - \{n\},$$



$(c_x, c_y, c_z)$	$u_x$	$u_y$	$u_z$
<b>000</b>	<b>0</b>	<b>0</b>	<b><math>\alpha</math></b>
001	0	0	0
<b>010</b>	<b>0</b>	<b>0</b>	<b><math>\alpha</math></b>
011	0	0	0
<b>100</b>	<b>0</b>	<b>0</b>	<b><math>\alpha</math></b>
101	0	0	0
110	0	0	0
<b>111</b>	<b>0</b>	<b>0</b>	<b><math>\alpha</math></b>

Fig. 2. Complexation payoff table.

$$u_i(c) = 0 \wedge u_n(c) = \begin{cases} \alpha, & \text{si } c_n = f(c_{-n}) \\ 0, & \text{sinon} \end{cases}, \alpha > 0$$

By using the rule, we can notice that the set of Nash equilibria corresponds to  $(c_{-n}, f(c_{-n}))$ ,  $\forall c \in C_A$ , that is the set of image by  $f$ . The GCF approach is used to describe complex formation. Given two complexes  $X$  and  $Y$  which interact together to form another complex  $Z$ . If we consider that only two strategies  $\{0, 1\}$  exist which respectively represent the absence and the presence of the complexes then the function is a logical AND.

We have eight configurations to consider. The payoff of the agent  $Z$  is  $\alpha$ , ( $\alpha > 0$ ) when  $c_x \wedge c_y = c_z$ . In this case, the Nash equilibria correspond to biological situations where the complex is formed in presence of both reactants or absent if one of the reactants is missing. Other situations are not Nash equilibria. The corresponding payoffs are listed in Fig. 2 and Nash equilibria written in bold.

**In the MPF approach** the payoff function is monotonous to the measurements given by experiments and defined in the space phase.

Given a game  $\langle A, C, u \rangle$ , we assume that the observed measure can be described by a set of functions  $f_i : C_A \rightarrow \mathbb{R}$ , which defines the evolution of the observed measure associated to the agent  $a_i$ , a concentration for instance. The payoff function fulfills the following property:

$$\forall a_i \in A, \forall c, c' \in C^2, f_i(c) \leq f_i(c') \Rightarrow u_i(c) \leq u_i(c')$$

The monotony is used to model the regulatory interaction in a network. This aspect will be more detail in Section 5 devoted to the application to PAs (plasminogen activator system).

#### 5. Application to PAs

In this section, we model a process of signal transduction implied in the migration of cancerous cells. We want to evaluate the qualitative dynamics of the process. Cancerous cells can migrate from a tissue to another to

propagate the pathology. The process can be viewed as the response to a promigratory signal. The transduction of this signal is the model we are interested in. If we model this process and if we can determine its dynamics, we will be able to plan the cellular migration. In the first part of this section we describe the cell migration process and we introduce the mechanism of the plasminogen activator system (PAs). Then, we apply the games network modeling to the process.

5.1. Cellular migration and the PA system (PAs)

The cellular migration is a complex process which can be described as a succession of stages: adhesion, contraction, de-adhesion (Lauffenburger and Horwitz, 1996). We are interested in the PAs system which participates in the establishment of a molecular bridge between the cell and the extra-cellular matrix. This bridge leads to the migration of the cell (Chazaud et al., 2002). PAs system is composed of a protease uPA (urokinase plasminogen activator), a receptor uPAR (Receptor of urokinase) and a specific inhibitor PAI-1 (plasminogen activator inhibitor-1)(Providence and Higgins, 2004). The sequence of interactions implied in the promigratory process is as follows: PAI-1 can bind to VN (the vitronectine, a protein of the extra cellular matrix) which makes the activated form of PAI-1 stable. Once PAI-1 activated, it clings to a complex formed by uPA and uPAR. The complex is internalized by a receptor  $\alpha 2$  M-LRP (Low-density lipoprotein receptor-related protein) inside the cell. Then uPAR is recycled on the front of the cell. The transduction of PAI-1 induces the modifications of cellular morphology and the cytoskeleton of actine necessary to the migra-

tion. These modifications imply the regulation of the activation of GTPases Cdc42 and RhoA (Ridley, 2001).

5.2. Modeling with games network

In this section, we use the games network to model PAI-1 process of transduction. According to the previous section, agents participating in the games are the 7 previously mentioned biological agents that are PAI-1, VN, uPA, uPAR, LRP, RhoA, Cdc42. Moreover we add 4 other agents:  $c_1$  represents the activation of PAI-1,  $c_2$  represents the formation of a dimer uPA/uPAR,  $c_3$  represents the formation of a complex PAI-1/uPA/uPAR and  $c_4$  represents the internalisation of the complex PAI-1/uPA/uPAR. Strategies of the agents are partly represented in Table 1. The other agents follow this definition: their strategies are (1) if they are present in the environment and (0) if not.

The corresponding games network is described in Fig. 3. Games  $K_i$ ,  $1 \leq i \leq 4$  correspond to a complexation. Hence they follow the GCF rules. Their payoffs are described in Fig. 2. Recall that each equilibrium fulfills the following property:  $(a, b, a \wedge b)$ . The game  $R$  is a game of regulation of the GTPases which does not have any influence on the network. It means that the network is regulated by the game  $U$  where the payoff is described in the table above.

At least, we find the biological steady states. This corresponds to an important part of the modeling because it determines the different possible states that the biological system is able to reach.

According to experiments, both Nash equilibria, written in bold in Fig. 3, correspond to characteristic biological states. The first one (0, 0) corresponds to a

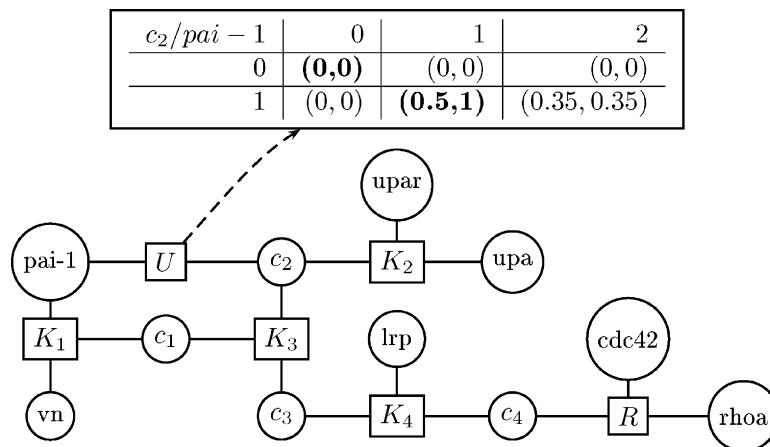


Fig. 3. Network of transduction of PAI-1.

Table 1  
Table of strategies

Agent	Its strategies	Description
PAI-1	0	No affinity for VN
In $K_3$	1	Strong affinity for VN
PAI-1	0	Low concentration C
in	1	Medium concentration C
$U$	2	High concentration C
$c_1$	0	PAI-1 is not activated
	1	PAI-1 is activated by VN
$c_2$	0	A dimer uPA/uPAR is not formed
	1	The dimer is formed
$c_3$	0	A complex PAI-1/uPA/uPAR is not formed
	1	The complex is formed
$c_4$	0	The complex PAI-1/uPA/uPAR is not internalized by LRP
	1	The complex PAI-1/uPA/uPAR is internalized
RhoA	0	Low expression level
	1	High expression level
Cdc42	0	Low expression level
	1	High expression level

non-migratory state and the last one (0.5, 1) corresponds to a promigratory state. By definition, the GCF does not restrict strategies of the “input” agents because whatever the combination of their strategies, there always exists a Nash equilibrium including them. So, the global equilibrium mainly relies on the Nash equilibria of game  $U$  because it selects configurations of strategies (Section 3).

## 6. Conclusion

In this paper we have presented a theoretical framework based on game theory. It emphasizes the notion of local interaction between agents. It has been applied

to the PAs system in order to model the interactions involved in the model. It appears to confirm the presence of two characteristic states which correspond to different physiological configurations. It is based on the assumption that Nash equilibria correspond to biological steady states. The extension of this work is to confirm the relationships between Nash equilibria and steady states. We attempt to bridge the gap between games Network model and molecular model such as Generalized Mass Action (Eberhard and Antonio, 2000).

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