LaMI
Laboratoire de Méthodes Informatiques

Application of Game Theory to Gene Networks Analysis

M. Manceny, A. Lackmy, C. Chettaoui, F. Delaplace

e-mail : {mmanceny, alackmy, chetta, delapla}@lami.univ-evry.fr

Rapport de Recherche n^o 114-2005

Juin 2005

CNRS - Université d'Evry–Val d'Essonne
Cours Monseigneur Roméro
F–91000 Evry Cedex France

Application of Game Theory to Gene Networks Analysis

Matthieu Manceny[1], Alexandra Lackmy[2], Chafika Chettaoui[1,2], and Franck Delaplace[1]

[1] LaMI-Genopole®. UMR 8042 CNRS, University of Evry, France
[2] DYNAMIC, University of Paris XII, France

Abstract. In this paper, we propose a model for gene regulation based on game theory. Game theory provides a framework to model the gene interplays by considering that interacting genes play to the same game. It aims at providing a framework to express the functional behavior resulting from the adaptation imposed by the imperative of competing biological agents. The proposed model revisits the discrete model of gene regulation by considering that steady states correspond to pure Nash equilibria. We present the model on the tumor gene suppressors network.

1 Introduction

Properties of living organisms are the result of interplays between complex chemical systems. Understanding the complexity of the interaction of compounds molecular biological systems is an important but challenging problem. This puts the emphasis on models to describe, explain and predict the dynamics of such systems. In this paper, we propose a model based on game theory in order to describe regulation between genes and to compute steady states deduced from their interplays.

Game theory has been pioneering by Von Neumann and Morgenstern to define a theoretical framework to model complex interactions between players(agents) [21]. In biology, evolutionary game theory has been successfully used to model evolution of population resulting from Darwinian fitness [10–12, 15, 16]. For Wolf and Arkin ([22]), game theory is a relevant framework to express the functional behavior which governs the dynamics in the presence of biological agents in competition.

The use of game theory relies on the fact that the analysis of complex interplays is required to compute characteristic behaviors. These works are based on the following paradigm: each biological agent selects its actions (strategies), to maximize its adaptation, according to its interactions with the environment.

To explain the strategies of the biological agents, the adaptation and evolutionary stability is then preferred to the rationality of agents (which is commonly assumed in game theory). Only the agents which survive and dominate have the effective strategies.

In this paper, we use the game theory in an operating way to express complex regulating phenomena. We explain the stability of phenomena coming from regulatory process from macroscopic rules which may identify some general features of the system. The analysis is based on *strategic games*.

The paper is organized as follows: section 2 briefly recalls the main results on strategic game theory and the definition of Nash equilibrium. In section 3, we show how the game theory can be applied to analyze steady states of a gene network. The example is focused on circuits which are at the core of many regulatory process in a genetic network such as homeostasis and differentiation. We conclude in section 4.

2 Game theory

In this section, 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 [9, 13, 14, 17] for a complete overview of the game theory and its applications.

We use the following notations for sets:

- $[a:b] = \{i \in \mathbb{Z} | a \leq i \leq b\}$ denotes an interval of discrete values bounded by a and b.

Concerning the profile, or vector, we adopt the following notations. Given a profile $c^* = (c_1^*, \cdots, c_n^*) \in C$, $C = \times_j C_j$, we denote by:

- $\forall i \in [1:n], c_{-i}^* = (c_1^*, \cdots, c_{i-1}^*, c_{i+1}^*, \cdots, c_n^*)$. This excludes the i^{th} component of a profile.
- $\forall i \in [1:n], \forall c_i \in C_i, (c_{-i}^*, \mathbf{c}_i) = (c_1^*, \cdots, c_{i-1}^*, \mathbf{c}_i, c_{i+1}^*, \cdots, c_n^*)$. The notation distinguishes the i^{th} component of the profile from the others.

2.1 Strategic games

Strategic game is a model of interplays where each agent chooses its plan of action (or strategy) once and for all. These choices are made simultaneously and for each strategic choice, payoffs are associated to agents. 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 Γ is a $3-$uple $< A, C, u >$ 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, $C_i = \{c_i^1, \cdots, c_i^{m_i}\}$.*
- *$u = (u_i), i \in A$ is a vector of functions where each $u_i : C \mapsto \mathbb{R}, i \in A$ is the payoff function of the agent i.*

For a $2 \times 2-$Game which is commonly used to illustrate notions in game theory (that is a game with 2 agents and 2 strategies by agent), the game is usually represented by a Tableau.

Definition 2 (Representation of a $2 \times 2-$Game by a Tableau). *Given a $2 \times 2-$game $\left\langle \{1,2\}, \left((c_1^1, c_1^2), (c_2^1, c_2^2)\right), (u_1, u_2) \right\rangle$, such that the payoff values are:*

$$\begin{array}{llll} u_1(c_1^1, c_2^1) = w_1 & , & u_2(c_1^1, c_2^1) = w_2 \\ u_1(c_1^1, c_2^2) = x_1 & , & u_2(c_1^1, c_2^2) = x_2 \\ u_1(c_1^2, c_2^1) = y_1 & , & u_2(c_1^2, c_2^1) = y_2 \\ u_1(c_1^2, c_2^2) = z_1 & , & u_2(c_1^2, c_2^2) = z_2 \end{array}$$

Then the tableau is defined as follows :

	c_2^1	c_2^2
c_1^1	(w_1, w_2)	(x_1, x_2)
c_1^2	(y_1, y_2)	(z_1, z_2)

2.2 Nash equilibrium

Nash equilibrium is a central concept of the game theory ([14]). 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* corresponds to a *strategic profile* c (or vector) where c_i is the strategy "chosen" by the player i.

Definition 3 (Pure Nash equilibrium of a strategic game). *Let* $< A, C, u >$ *be a strategic game, a* pure Nash equilibrium *is a profile of strategies* $c^* \in C$ *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 pure Nash equilibrium without decreasing its payoff.*

A pure Nash equilibrium can be considered as *a best reply* for all the agent, that is the response which maximizes the outcome while considering the strategies of the other agents.

3 Application to Gene Regulatory Networks

Game theory can be applied for each interaction occurring in a gene network. However, its interest relies on interaction when the expression of a gene has an impact on the other genes. Hence, the gene game becomes really strategic when genes reciprocally regulate themselves. Circuits of genes in gene network embody such interplays. In this section, we examine each component of a game by considering its respective use for the definition of a model. We study the case of elementary regulation and elementary circuits. We finally present our results on the biological example of the tumor gene suppressors ([8, 23]).

3.1 Model

Genetic regulation consists in the control of the expression of the rate of transcripts of genes. In models of genetic regulation, two possible actions are considered: activation and inhibition. A gene activates a target gene if the increase of its expression rate leads to the increase of the expression of the target. In contrary, in an inhibiting activity, the increase of the expression of the regulatory gene leads to a decrease of the expression of the target. This is often modeled as a labeled graph where an edge represents a regulatory activity. The inhibition is modeled by an edge having a minus sign whereas a plus sign label of an edge represents an activation (see Fig. 2).

States are defined by expression levels which discretize the production rate of proteins. In discrete model of regulation, such as René Thomas'model ([19, 20]) and its generalizations ([3, 18]), a specific level corresponds to a capability to interact with other genes. The ability to regulate gene at a given level cannot necessary be maintained in another level. For the corresponding model some important concepts have to be defined.

Strategies are used to characterize the different observable states of a system. Thus, strategies depend on the states of the agent. For genetic regulation, levels are strategies, because a level characterizes a specific capability to interact with other genes in a discrete model ([3, 4, 19, 20]).

The payoff function plays an essential rule in the modeling of the dynamics because it governs the computation of Nash equilibria which define the steady states of the system. From each value attributed to strategy profiles, we are able to determine an order on configurations. Thus, order on outcomes classifies the response of a given agent according to a fixed configuration for other agents. The order may change from a configuration to another. It qualifies the adaptation of the response.

In order to describe how the modeling proceed, we detail it on elementary regulations: a gene activating, or inhibiting, another gene.

3.2 Application to elementary regulation

The regulatory interplays are mainly described by the outcome given for each configuration of states. We aim at determining some general rules which govern the payoffs. Since equilibria remain identical up to a positive linear transformation, many payoff functions can fit to model the regulation. However, they must maintain the same relative local order between configuration of strategies. Hence, we investigate on the determination of general rules which govern order of the payoffs for each agent. One of this rule is to *privilege the expression*.

More precisely, let us consider the case where x activates y. Let us suppose that x has the strategy 0, that is x has no positive influence on y, so y should be in state 0 rather than in state 1. If the strategy of x is 1, x has a positive influence on y, and the best state for y is 1. The relations between the different states of y are well defined, according to the state of x: the payoff for $((x = 0), (y = 0))$ is greater than the payoff for $(0, 1)$, and the payoff for $(1, 0)$ is inferior to the payoff for $(1, 1)$. That can be considered as a qualitative view.

A possible model to *privilege the expression* is to add that the payoff for $(0, 0)$ is less than the payoff for $(1, 0)$. Quantitatively, we decide to give a null payoff for $((x = 0), (y = 0))$, which represents the state where there is no activity. Table 1 represents the simplest tables we can define with natural numbers for activation and inhibition.

$x \xrightarrow{+} y$	0	1
0	0	−1
1	1	2

$x \xrightarrow{-} y$	0	1
0	1	2
1	0	−1

In tables, x is the regulator and y is the regulated agent. The tables give the payoff for the regulated gene y. Strategies of the first column are those of x, and strategies of the first raw correspond to those of y.

Table 1. The Elementary payoff function for genetic regulation

Once the elementary payoff functions are defined, we can combine and adapt them in order to form a more complex regulatory game.

3.3 Application to elementary circuits

Two kinds of circuits are usually distinguished: *positive* and *negative*. The first ones have an even number of minus signs while the last ones have an odd number. René Thomas claims [19] that positive circuits are involved in differentiation process whereas negative circuits play an essential rule in homeostasis. Positive circuits produce multi-stationarity, that is several potential steady states which are reachable according to the initial state.

Elementary circuits are composed of two nodes and two edges. They are considered as paradigms of regulation involved in differentiation and homeostasis. Figure 1 shows the four possible elementary circuits, the tableau of the payoff function corresponding to each circuit and the pure Nash equilibria which can be computed from the payoffs. Circuits 1 and 2 are positive circuits whereas circuits 3 and 4 are negative ones.

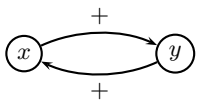
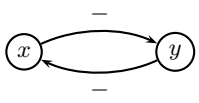
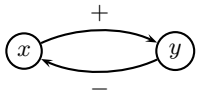
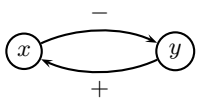
Elementary circuits	Tableau Forms	Pure Nash equilibria
1) 	$x \overset{+/+}{\longleftrightarrow} y$ | 0 | 1 0 | $(0,0)$ | $(1,-1)$ 1 | $(-1,1)$ | $(2,2)$	$\{(0,0),(1,1)\}$
2) 	$x \overset{-/-}{\longleftrightarrow} y$ | 0 | 1 0 | $(1,1)$ | $(0,2)$ 1 | $(2,0)$ | $(-1,-1)$	$\{(1,0),(0,1)\}$
3) 	$x \overset{-/+}{\longleftrightarrow} y$ | 0 | 1 0 | $(1,0)$ | $(0,-1)$ 1 | $(2,1)$ | $(-1,2)$	$\{\}$
4) 	$x \overset{+/-}{\longleftrightarrow} y$ | 0 | 1 0 | $(0,1)$ | $(1,2)$ 1 | $(-1,0)$ | $(2,-1)$	$\{\}$

Fig. 1. Elementary circuits, tableau forms and pure Nash equilibria

Bringing the results to the effect of the circuit regulation, we observe that the *pure Nash equilibria are steady-states which correspond to the multi-stationary states whereas the lack of pure Nash equilibria is representative of the presence of feedback loops which leads to homeostasis.*

More precisely, for case 1) we have two possible states which are $(0,0)$ and $(1,1)$. The former corresponds to the absence of protein productions for x and y. This leads to a steady state where no gene are expressed. The latter corresponds to the presence of the both proteins which is the other steady state of the circuits.

It is worth noting that each of the 4 circuits has mixed Nash equilibrium[1]. For instance, in case 3), the circuit admits the state $((1/2,1/2),(1/2,1/2))$ as a mixed Nash equilibrium.

[1] Mixed Nash equilibria are an extension of pure Nash equilibria, which correspond to a probabilistic distribution over the strategies of each agent.

This state corresponds to a situation where agent x plays its $0-$strategy once on two and its $1-$strategy one time out of two (in the same way for agent y). Such an equilibrium might be assimilated to a singular state.

3.4 Tumor gene suppressors game

Gene modeling has been applied on various realistic cases including transduction signaling ([6]). In this subsection, we focus on gene regulation occurring for tumor gene suppressors.

Cell division is a highly conserved and strictly regulated process in eukaryotic cells. This process, preceded by a long phase of preparation called interphase, ends with the formation of two identical daughter cells that contain the same genetic information as the mother cell. The cell cycle can be divided into two principal steps: interphase, composed of three successive phases ($G1$, S and $G2$), and cell division denoted as *mitosis*. A cell spends most of its lifetime in interphase; for instance, in rapidly dividing cells interphase generally takes 16 to 24 hours so that mitosis lasts only 1 to 2 hours ([1]). The $G1$ phase consists of optimal growth, S phase results in DNA duplication and $G2$ phase permits DNA reparation of damages that occurred during the replication ([2]).

There are various mechanisms that monitor cell cycle progression and keep the integrity of genetic information ([1, 2]). Indeed, some genes defined as *tumor gene suppressors* are able to arrest cell cycle in critical checkpoints, to repair DNA injury or induce cell death. We are interested in cell regulation by $p53$-$p21$/cyclin-dependent-kinase 2 pathway. The $p53$ gene suppressor prevents $G1/S$ transition by stimulating $p21$ gene transcription. The $p21$ protein takes part in this regulation by inhibiting protein kinases expression like cyclin-dependent-kinase 2 ($cdk2$) ([23]).

In tumor cells, $cdk2$ protein has to be associated with the cyclin E protein, to down-regulate $p53$ transcription. These cells despite mutations are able to go through the checkpoint $G1/S$ and to continue the cell cycle ([8]). Network which corresponds to these data is shown on Fig. 2.

Thus, we can consider that the network has 2 steady states. On the first one, $p53$ and $p21$ are activated and prevent the $G1/S$ transition. On the second one, $p53$ and $p21$ are inactivated but $cdk2$ is activated and allows the cell division.

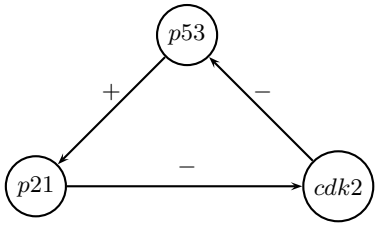


Fig. 2. The tumor gene suppressors network

To model the regulatory network from Fig. 2, we have to consider the different relations between genes. Table 2 gives the payoffs associated to each of the three edges from the network.

$p53 \xrightarrow{+} p21$	0	1
0	0	−1
1	1	2

$p21 \xrightarrow{-} cdk2$	0	1
0	1	2
1	0	−1

$cdk2 \xrightarrow{-} p53$	0	1
0	1	2
1	0	−1

Table 2. Payoffs associated to each edge of the regulatory network from Fig. 2

Thus, we have to build the final payoffs. Because we have 3 genes, there is 8 possibilities for the configurations of the network. Table 3 explains the final payoffs. For example, if we consider the first row, all the genes are in state 0. With the payoffs from Table 2, we can determine that because $p53$ and $p21$ are in state 0 the payoff associated to $p21$ is 0...

Strategies			Payoffs		
$p21$	$p53$	$cdk2$	$p21$	$p53$	$cdk2$
0	0	0	0	1	1
0	0	1	0	0	2
0	1	0	1	2	1
0	1	1	1	−1	2
1	0	0	−1	1	0
1	0	1	−1	0	−1
1	1	0	2	2	0
1	1	1	2	−1	−1

Pure Nash equilibria = { (0,0,1) , (1,1,0) }

Table 3. Payoffs and pure Nash equilibria associated to the network from Fig. 2

Once we have the payoffs, we can determine the pure Nash equilibria (Table 3). The two pure Nash equilibria found are $(p21 = 0, p53 = 0, cdk2 = 1)$ and $(p21 = 1, p52 = 1, cdk2 = 0)$. The first one corresponds to cell division and the last one to prevent the $G1/S$ transition, which is what was expected.

4 Discussion and future work

In this paper, we have proposed to model gene regulation by formulating the gene interplays as a game. In gene games, a strategy represents a characteristic level of expression which corresponds to a regulatory ability. In this context, pure Nash equilibria represent discrete characteristic configurations of gene states and their computation depends on the payoff function. The definition of the payoff function is central in the model to explain the equilibria. This appears to follow some global rules at the scale of the game. In fact, the payoff is monotonous compared to the expected concentration rate of the translated proteins.

Perspective of this work is to extend the model to scale in number of genes and in complexity. The model provides a suitable framework for games with a small number of interacted genes. However, in order to enlarge the number of processed genes at the scale of an organism, one needs to revisit the model. The goal is to have computational framework which efficiently process large set of interacted genes. Moreover, dealing with

complexity does not merely relies on number of genes scaling but also on ability of analysis. In particular, we investigate on the modularity of gene interactions.

In biological networks, groups of co-expressed genes are observed. Each group can be viewed as a module representing a set of local interactions. With the game theory model, each gene is interacting with all the other genes. It would be interesting to refine this model to deal with modularity. This extends the model by integrating local interactions pioneered in Game Theory by Ellison ([7]).

By considering the size scaling and the modularity of the regulatory networks, we propose to include the locality in model. This leads to extend game theory into the Theory of Games Networks. The reader may refer to [5] for the formalism of Games Networks.

References

1. B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and Watson J. D. *Molecular Biology of the Cell*. Garland, 1983.
2. Y. Bassaglia. *Biology cellulaire*. Maloine, 2001.
3. G. Bernot, F. Cassez, J.P. Comet, F. Delaplace, C. Müller, O. Roux, and O. Roux. Semantics of biological regulatory networks. In *Bio-Concur*, September 2003.
4. G. Bernot, J.-P. Comet, A. Richard, and J. Guespin. A fruitful application of formal methods to biological regulatory networks: Extending thomas' asynchronous logical approach with temporal logic. *Journal of Theoretical Biology*, In Press, 2004.
5. F. Delaplace and M. Manceny. Games network. Technical Report 101-2004, Laboratoire de Méthodes Informatiques (LaMI), CNRS-UMR 8042, Université d'Évry-Val d'Essonne, 2004.
6. F. Delaplace, A. Petrovna, M. Malo, F. Maquerlot, R. Fodil, D. Lawrence, and Barlovatz-Meimon G. The "PAI-1 game": towards modelling the plasminogen activation system (PAs) dependent migration of cancer cells with the game theory. In *WSEA*, volume accepted, 2004.
7. Glenn Ellison. Learning, local interaction, and coordination. *Econometrica*, 61(5):1047–71, September 1993.
8. J.S. Foster, D.C. Henley, A. Bukovsky, P. Seth, and Wimalasena J. Multifaceted regulation of cell cycle progression by estrogen: Regulation of cdk inhibitors and cdc25a independent of cyclin d1-cdk4 function. *Molecular and Cellular Biology*, 21:794–810, 2001.
9. R. Gibbons. *Game Theory for Applied Economists*. Princeton University Press, 1992.
10. J. Hofbauer and K. Sigmund. *Evolutionary Games and Population Dynamics*. Cambridge University Press, 1998.
11. B. Kerr, M.A. Riley, M.W. Feldman, and B.J. Bohannan. Local dispersal promotes biodiversity in a real-life game of rock?paper?scissors. *Nature*, 418:171–174, 2002.
12. J. Maynard Smith. *Evolution and the Theory of Games*. Cambridge University Press, 1982.
13. R. B. Myerson. *Game Theory : Analysis of Conflict*. Harvard University Press, 1991.
14. J. F. Nash. *Essays on Game Theory*. Edward Elgar Publishing Limited, 1996.
15. M.A. Nowak and Sigmund K. Phage-lift for game theory. *NAture*, 398:441–443, 1999.
16. M.A. Nowak and K. Sigmund. Evolutionary dynamics of biological games. *Science*, 303:793–799, 2004.
17. M. J. Osborne. *An introduction to game theory*. Oxford University Press, 2003.
18. S. Pérès and J.-P. Comet. Contribution of computation tree logic to biological regulatory networks : example from pseudomonas aeruginosa. In C. Priami, editor, *Proceedings of the 1st Intern. Workshop CMSB'2003*, LNCS 2602, pages 47–56. Springer-Verlag, 2003.
19. R. Thomas. Regulatory networks seen as asynchronous automata : A logical description. *Journal of Theoretical Biology*, 153, 1991.
20. R. Thomas, D. Thieffry, and M. Kaufman. Dynamical behaviours of regulatory networks - I . biological role of feedback loops and pratical use of the concept of feedback loop. *Bulletin of Mathematical Biology*, 57(2):247–276, 1995.
21. J. Von Neumann and O. Morgenstern. *Theory of games and economic behavior*. Princeton University Press, Princeton, New Jersey, first edition, 1944.
22. D.M. Wolf and A. Arkin. Motifs modules and games in bacteria. *Current Opinion in Microbiology*, 6:125–134, 2003.

23. K.H. Wrighton, C.M. Prele, A. Sunters, and Yeudall W.A. Aberrant p53 alters DNA damage checkpoints in response to cisplatin: downregulation of CDK expression and activity. *International Journal of Cancer*, 112(5):760–770, 2004.