International Journal of Physical Medicine & Rehabilitation

OPEN ACCESS Freely available online

Review Article

Patience Pays: Game Theoretic Model for the Developmental Competition at the Motor-Muscle System

Irit Nowik*

Department of Physical Medicine, Jerusalem College of Technology, Jerusalem, Israel

ABSTRACT

We offer a new game theoretic approach to analyze the developmental competition that arises between neurons innervating a common muscle. The size principle-stating that neurons with successively higher activation-thresholds innervate successively larger portions of muscle-is thought to result from this competition, but it has not been known how, mainly because the existing experimental data on this issue seems contradictory. We define a multi-stage game in which neurons "compete" to singly innervate a maximal number of muscle-fibers. At each stage of the game, the competition at a single muscle-fiber is resolved. We show that neurons with successively higher activation-thresholds tend to win in later stages of the game and prove that because resource is limited and is needed both for competing and for maintenance of the connections won, then in order to win more competitions, it is better to win in later competitions rather than in earlier ones. We then generalize the model to a game in which players with limited resource need to decide the size of investment at each stage.

Keywords: Size principle; Synapse elimination; Nash equilibrium; Hebbian rule

INTRODUCTION

The connectivity between neurons and their targets is achieved during development (prenatal and neonatal periods) by two fundamentally different programs: Molecular guidance cues and neural activity. Molecular cues guide axons from specific regions to broadly defined target regions, and initiate the formation of connections. However, such cues are not always sufficient to establish the final connectivity (the fine tuning). In many cases the final connectivity depends also on neural activity. One form of refinement of connectivity is the elimination of connections, which occurs in many areas of the nervous system. In each of these areas, strengthening of the connections of the remaining neurons also occurs, an indication that the elimination process may be interactive and competitive. A well-studied case of this form of plasticity occurs in the motor system of vertebrates between Motoneurons (MNs) and their target muscle during the first couple of weeks after birth. A typical skeletal muscle is composed of many thousands (even several hundreds of thousands) of fibers. At birth, each muscle-fiber is innervated by several MNs and each MN innervates several muscle-fibers. But during the following couple of weeks, a competitive process, called "synapse elimination," abolishes the connections of all but one of the MNs to each of the muscle-fibers. We call this MN "the winner at the muscle-fiber." The group of muscle-fibers that are eventually singly innervated by the same MN is called a “muscle unit” [1]. Thus, in the mature system, each MN governs a single muscle unit, which is composed of all the muscle-fibers in which it has won, and there is no overlap between the muscle units. In the adult system MNs with successively higher activation thresholds have successively larger muscle units. This is called the size principle. As MNs with low activation thresholds reach their threshold before MNs with higher activation thresholds, it follows from the size principle that there exists a recruitment order among muscle units, according to their sizes; smaller muscle units are recruited earlier than larger muscle units. This permits a high precision in muscle force generation since small muscle forces, needed in fine motor tasks, are produced exclusively by small muscle units, whereas a random recruitment of a large muscle unit would have seriously disrupted the task.

Correspondence to: Irit Nowik, Department of Physical Medicine, Jerusalem College of Technology, Jerusalem, Israel, E-mail: nowik@jct.ac.il

Received: 23-May-2023, Manuscript No. JPMR-23-24327; **Editor assigned:** 25-May-2023, PreQC No. JPMR-23-24327 (PQ); **Reviewed:** 12-Jun-2023, QC No. JPMR-23-24327;**Revised:** 19-Jun-2023, Manuscript No. JPMR-23-24327 (R); **Published:** 26-Jun-2023, DOI: 10.35248/2329-9096.23.11.680

Citation: Nowik I (2023) Patience Pays: Game Theoretic Model for the Developmental Competition at the Motor-Muscle System. Int J Phys Med Rehabil. 11:680.

LITERATURE REVIEW

Paradoxical experimental data

In contrast with the end result (i.e., the size principle) most of the experimental that have manipulated the activity of MNs during synapse elimination suggest that the more active MNs (stimulated or unblocked) are advantageous in this process the activity of some of the MNs was blocked during the competition period [2,3]. This resulted in smaller muscle units for the blocked MNs in comparison with the unblocked MNs. An experiment is an exception in the sense that blocking the activity of several MNs resulted in larger muscle units for the blocked MNs at the expense of the unblocked MNs [4,5]. Experiments that were executed on isolated muscle-fibers (*in vitro*) have all pointed to an advantage to the stimulated MN [6]. This advantage of activity is consistent with a Hebbian rule, in which success of a source in activating a target strengthens the connection between the source (here MN) and the target (here muscle-fiber). This seems to contradict the empirical fact, that in the end, the more active MNs have smaller muscle units, as how could the MNs that are advantageous at single competitions eventually win fewer competitions?

Empirical facts underlying the model

The activity level of a (target) muscle-fiber is determined by the activity levels of the MNs innervating it (which in turn are determined by the thresholds of the MNs). Hence for example, a muscle-fiber that is innervated by many relatively active MNs will be more frequently activated. It was found that the more frequently a muscle-fiber is activated, the faster its competition is resolved [7]. Thus, the competitions at the muscle-fibers end at sequential times according to decreasing activity level of the muscle fibers; from highest activity level to lowest activity level. It was also found that after winning at a muscle-fiber, the MN must allocate substantial amount of resource to strengthen and maintain the connection with the muscle-fiber. Consequently, resource limitation implies that winning at a muscle-fiber, reduces winning probabilities at other muscle-fibers [8].

The model

In line with the empirical findings described above, we define a multi-stage game (the number of stages equals the number of fibers in the muscle) in which MNs are the players, their activity levels are their strategies and the payoffs are the size of their muscle units. At each stage a single competition takes place. The order of the competitions is determined according to a descending activity level of the hosting muscle-fiber. When a MN wins at a given stage, this reduces its future winning probabilities at the remaining stages of the game.

Methods

In analyzing the model we utilize two approaches: mathematical analysis and simulations. Simulation results, biological features and implications of the model appear in Nowik, [9,10].

Preceding analysis

What do the less active MNs "do better" than the more active MNs: We prove that (in our setting) it is better to win at later competitions. Before explaining this point, we first wish to establish that indeed less active MNs tend to win in later competitions (and more active MNs tend to win at earlier competitions). Assume first (we later relax this assumption), that initially, each of the MNs innervating a common muscle-fiber has the same probability of winning it. Then a muscle-fiber in which the majority of connections are by the more active MNs will most likely be won by a more active MN. Additionally, the activity level at the muscle-fiber will be relatively high and thus, according to our model, its competition will be resolved at an early stage of the game. Similarly, a muscle-fiber in which the majority of connections are by the less active MNs will most likely be won by a less active MN and its competition will end at a late stage of the game. Hence, the less active MNs typically win at later stages than the more active MNs. But why does the fact that the less active MNs tend to win later, causes them to win in more competitions in total? Note that the limited amount of resource of a competing MN is needed both for competing and for maintaining the wins. Thus, when a MN wins at a muscle-fiber, its winning probabilities at future competitions decrease. In such circumstances we prove that it is advantageous to win in later stages of the process because this will negatively affect only the few competitions that are not yet resolved. Importantly, we show that even if the competition at the single muscle-fiber is, to some extent, biased against the less active MNs (as implied by a Hebbian mechanism), they still win in more competitions.

Reconciling the seemingly contradictory data from blocking experiments: Two blocking experiments show seemingly contradictory results. In both experiments activity of some of the MNs was blocked around half-way of the competition period. But whereas in the blocking period continued until the end of the competition period and the blocked MNs had small muscle units, activity was recovered later and the blocked MNs had larger muscle units at the expense of the unblocked MNs; obviously the blocked MNs lost in the competitions that were resolved during the blocking period, explaining the results of Ribchester and Taxt [4,5]. But at the same time, blocking specifically delayed the competitions at muscle-fibers that were innervated by some blocked MNs. This delay was not only predicted by our model, (as the overall level of activity of these muscle-fibers was reduced by the blocking), but had also been found empirically by Callaway (1989) [11]. According to our model, this delay works in favor of the blocked MNs when blocking is removed. This explains the experimental results of Callaway and Soha, in which activity was recovered, allowing the blocked MNs to benefit from the delay in their victories.

DISCUSSION

Applying game theory to the micro-level processes in Biology

Traditionally, Game theory has been applied to biology through evolutionary games where strategy selection is driven by natural selection and as such, may be considered as a "macro-level" analysis [12]. However, there are many interactive competitive processes that occur at a short time span and would thus benefit from a micro-level analysis. Properties such as the size principle, which emerge as a consequence of competition endows the system with adaptation capabilities, such that the outcome may be fine-tuned to fit the environment. In accordance with this idea, provides an equation that yields predictions regarding the magnitude of the size principle under different conditions.

Generalization of the game MNs play

By having a high activation threshold, a MN is so to say, “choosing” to invest more in later (rather than in earlier) stages of the game and this means handling one's resources more efficiently. This insight motivated the generalization of our model to a multi-stage game where each player has limited resource that he needs to spend on increasing the probability of winning each stage, but also on maintaining the assets that he has won in previous stages. Thus, the players’ strategies must take into account that winning at any given stage negatively affects the chances of winning in later stages. We find the Nash equilibrium when the initial resources of the players are not too small [12]. There are similarities between our game and the well-known Blotto game [14-16].

CONCLUSION

In Blotto games, two players distribute forces across several battlefields that take place simultaneously. At each battlefield, the player who allocates the larger force wins (or in some variations, have higher winning probability). Our generalized model adds a new feature which changes the nature of the game, in making the winnings costly. The players thus do not know beforehand how much of their resources will be available for investing in winning rather than on maintenance, and so the game cannot be formulated with simultaneous investments, as in the usual Blotto games, but rather must be formulated with sequential stages.

REFERENCES

1. Lichtman JW, Colman H. Synapse elimination and indelible memory. Neuron. 2000;25(2):269-278.
2. Smith MJ. Evolution and the Theory of Games. Press. 1982.
3. Ribchester RR, Taxt TO. Motor unit size and synaptic competition in rat lumbrical muscles reinnervated by active and inactive motor axons. J Physiol. 1983;344(1):89-111.
4. Ribchester RR, Taxt T. Repression of inactive motor nerve terminals in partially denervated rat muscle after regeneration of active motor axons. J Physiol. 1984;347(1):497-511.
5. Callaway EM, Soha JM, Essen DC. Competition favouring inactive over active motor neurons during synapse elimination. Nature. 1987;328(6129):422-426.
6. Balice-Gordon RJ, Lichtman JW. Long-term synapse loss induced by focal blockade of postsynaptlc receptors. Nature. 1994;372(6506): 519-524.
7. Ridge RM, Betz WJ. The effect of selective, chronic stimulation on motor unit size in developing rat muscle. J Neurosci. 1984;4(10): 2614-2620.
8. Kasthuri N, Lichtman JW. The role of neuronal identity in synaptic competition. Nature. 2003;424(6947):426-30.
9. Nowik I. The game motoneurons play. GEB. 2009;66(1):426-461.
10. Nowik I, Zamir S, Segev I. Losing the battle but winning the war: game theoretic analysis of the competition between motoneurons innervating a skeletal muscle. Front Comput Neurosci. 2012;6:16-20.
11. Callaway EM, Soha JM, Van Essen DC. Differential loss of neuromuscular connections according to activity level and spinal position of neonatal rabbit soleus motor neurons. J Neurosci. 1989;9(5):1806-1824.
12. Nowik I, Nowik T. Games with costly winnings. Int Game Theory Rev. 2017;19(04):175-180.
13. Borel E. La theorie du jeu et les equations integrals a noyan symmetrique. CR Acad Sci. 1921;173:1304-1308.
14. Borel E. The theory of play and integral equations with skew symmetric kernels. Econometrica: J Econometric Society. 1953:97-100.
15. Lichtman JW, Colman H. Synapse elimination and indelible memory. Neuron. 2000;25(2):269-278.
16. O'brien RA, Ostberg AJ, Vrbova G. Observations on the elimination of polyneuronal innervation in developing mammalian skeletal muscle. J Physiol. 1978;282(1):571-582.