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The effect of molecular inhibition on evolutionary learning: studies in the hypernetwork architecture

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Abstract

The hypernetwork architecture is a biologically inspired learning model based on abstract molecules and molecular interactions that exhibits functional and organizational correlation with biological systems. Hypernetwork organisms were trained, by molecular evolution, to solve N-input parity tasks. We found that learning improves when molecules exhibit inhibitory sites, allowing molecular inhibition and opening the possibility of forming negative feedback regulatory pathways. Optimal learning is achieved when at least 20% of the molecules in each cell have inhibitory sites. Intra-cellular as well as inter-cellular molecular inhibitions play an important role in the information processing of hypernetwork organisms, by maintaining a balance of the molecular cascade reactions. Similar mechanisms inside neurons are considered important for memory.

Keywords: Evolutionary learning; Molecular regulation; Inhibition; Biological information processing; Homeostasis

1. Introduction

Biological systems have multiple feedback control mechanisms that operate from the molecular to the ecosystem levels (Wiener, 1948; Ashby, 1956; von Bertalanffy, 1968; Riggs, 1970; Jacob and Monod, 1961; Savageau, 1976; Thomas and D'Ari, 1990; DeAngelis, 1995).

Our work focuses on inhibitory regulatory mechanisms at the molecular level in learning systems such as biological neural networks. At this level, functionality is regulated by integration of excitatory and inhibitory molecules. An example of excitatory neurotransmitters is acetylcholine (Ach), and examples of inhibitory transmitters are the γ-aminobutyric acid (GABA), and glycine, among many others (Nicholls et al., 1992). Transmitter metabolism and physiological effects are regulated by specific regulatory molecules that respond to the environment (Black, 1986).

Inhibitory mechanisms play an important role in axon growth guidance (Dodd and Schuchardt, 1995; Goodman, 1996), synaptic plasticity (Abel et al., 1998), and in memory formation (Bhalla and Iyengar, 1999; Abel et al., 1998; Squire and Kandel, 2000).

Inhibitory molecules form the basis for negative feedback regulation (Thomas and D'Ari, 1990).

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An example of negative feedback inside neurons is in glutamate induced molecular cascades. Glutamate is a major excitatory neurotransmitter that plays an important role in memory and learning in the central nervous system (CNS) (McDonald and Johnston, 1990). Excessive amounts of glutamate can result in pathological damage in the CNS (Danysz et al., 1995). There are two types of glutamate receptors, ionotropic and metabotropic. The ionotropic receptors are for fast, and the metabotropic for slower and lasting generation of molecular cascades (Francesconi and Duvoisin, 2000). There are many types of metabotropic glutamate receptors (mGluR1-8), which have functions in regulating membrane excitability, synaptic transmission mediated by glutamate, and neurotransmitter release, among others. The mGluR1α can initiate both the $InsP_3/Ca^{2+}$ cascade where protein kinase C (PKC) is activated, and the cAMP cascade where cAMP-dependent protein kinase (PKA) is activated. Francesconi and Duvoisin (2000) found that there is negative feedback regulation of mGluR by inhibition of mGluR1α by PKC, via the $InsP_3$ pathway. Such regulatory mechanisms may play an important role in learning. Another example of negative feedback inside neurons is in the biosynthesis of catecholamine (CA) transmitters, which are involved in several neural functions (Shepherd, 1994). CA is regulated by the enzyme tyrosine hydroxylase (TH). TH is subject to feedback inhibition by its products dopamine and norepinephrine (Black, 1986).

Several approaches to the study of complex regulatory networks exist, for example Thieffry and Romero (1999) have a modulatory approach with boolean networks, and Sakamoto et al. (1998) analyze feedback inhibition with Michaelis–Menten-type reactions. However, these studies are not related to learning and memory.

Our approach to the study of the role of molecular inhibition in learning systems is to model it on the hypernetwork architecture, a hierarchical learning architecture involving molecular, cellular and organismic levels (Segovia-Juarez and Conrad, 1999). The fundamental elements of the model are abstract molecules and the interactions they form. Molecules have three sites: excitatory, inhibitory and catalytic (or active) sites. These sites and the relationship of the molecule to other molecules in its neighborhood can lead to the formation of feedback regulation networks within the cell. The hypernetwork is molded to perform classification tasks through a variation-selection algorithm acting on the structure of the molecular subunits (molecular evolution). Dynamic formation of cascades of molecular interactions initiated by input cells generate the output from the output cells.

This paper shows experimentally that learning is improved when molecules have structures that allow them to became inactive. These inhibitory features regulate the formation of cascades of molecular interactions in the cell, and open up the possibility of forming intra-cellular regulatory negative feedback loops. These mechanisms have correlations with others observed in actual neurons.

2. The hypernetwork architecture

The hypernetwork architecture (Segovia-Juarez and Conrad, 1999, 2001) is a biologically inspired learning model in which molecular interactions play an information processing role. It is a hierarchical model that shows the flow of influences from the macro to the micro level, and vice versa. It comprises the molecular, cellular, and organismic levels. The hypernetwork is based on Conrad's enzymatic neuron (Conrad, 1974) and percolation network models (Conrad, 1979, 1984, 1993, 1995a,b, 1997).

The molecular level consists of sets of enzyme-like structures represented by binary strings. Each molecule has a catalytic site, an excitatory site, and an optional inhibitory site.

Biomolecular self-assembly is represented by a shape complementarity interaction. An interaction is formed when the catalytic site of one active molecule matches, above a threshold value, the excitatory or inhibitory sites of a neighbor molecule. The target molecule will be active for one time step if activated; or it will become inactive for one time step if it is inhibited, regardless of any other activation.

The amount of molecules with inhibitory sites in each cell is controlled by experimental parameters. Excitatory and inhibitory receptors of the molecule allow for the possibility of inhibition and feedback regulatory networks with neighboring molecules.

The cellular space is modeled with a cellular automaton with wrap around. A molecule is placed in each cell of the grid (see Fig. 1). Each cell has three types of molecules:

- Receptors that are activated from the exterior (from the environment or molecules from other cells).
- Effectors that behave the way neurotransmitters do in neural cells. They look for receptor molecules of target cells, and if the effector catalytic site matches the excitatory or inhibitory sites of the target molecule, then the target molecule will be activated or inhibited, respectively.
- Internals that interact just with other molecules of the cell.

An organism is a set of cells along with a specification of the potential cell to cell connections. For example, cells of the first layer may interact with cells of the second layer. Actual cell to cell interactions is transiently formed by interactions of molecular effector with molecular receptors of the target cell.

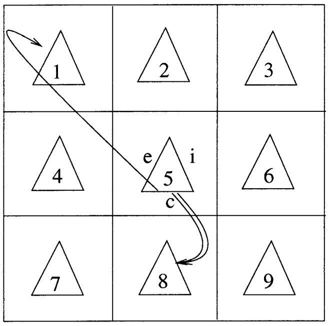

Fig. 1. Partial view of a cell. The molecule in the center interacts with its eight neighbors. Every molecule has three sites of the same size. Its excitatory (e), inhibitory (i), and catalytic (c) sites are labelled. Molecule number 5 activates molecule number 1 and inhibits molecule number 8.

Every organism has specialized cells to gather influences from the environment (input cells), to deliver the state of the organism to the environment (output cells), as well as internal cells in one or more layers. Fig. 2 shows an organism with three input cells, two layers of internal cells, and one output cell.

Output cells have readout structures that communicate the cellular state to the outside. Readout structures are placed randomly in the output cells. A readout structure is activated if the molecule where is located is activated, otherwise it stays in the inactive state.

The organism responds to external influences as follows: the input vector is split into 2-bit fractions. Each fraction activates one of the four receptor molecules of one input cell. Then, the activated molecules will trigger cascades of molecular interactions within the cell. When effector molecules became active, they look for receptor molecules of target cells for matching (activation or inhibition). Influences travel through the cells of the organism for a fixed amount of time steps, or until effector molecules of output cells are activated. At this point we stop the simulation and check the state of readout structures. The output of the cell is read as ‘1’ if any readout structure is active, or ‘0’ otherwise. In the Fig. 2 for the input ‘100 010’ the organism answers ‘0’.

The performance of the organism for a given input vector is the Hamming distance from the output to the desired output vector. In order to find the performance of the organism against a set of vectors, we apply this procedure for each input vector and we find the global error by adding the individual evaluated distances.

3. The evolutionary algorithm for hypernetwork learning

Hypernetwork organisms were trained to learn classification tasks by an evolutionary algorithm based on molecular evolution. Learning is achieved when the desired output is obtained for each input vector. If the organism does not achieve

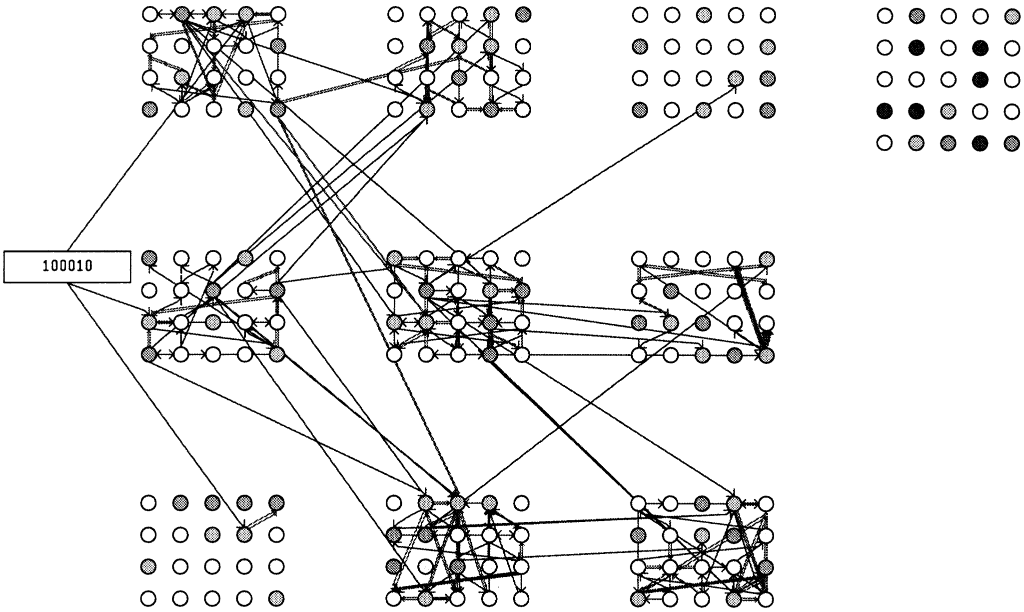

Fig. 2. A hypernetwork with three input cells, two layers of internal cells with three cells each, and an output layer with one cell. Molecules are colored circles. The lines show the interactions transiently formed by an input vector. The organism pictured receives the input vector ‘100010’ and the output cell answers ‘0’.

100% learning after the iteration, it is reproduced with molecular mutation.

At the moment of reproduction each molecule is selected for mutation with a probability of 0.8%, and, if chosen, it randomly flips a fraction of its bits. In current experiments 30% of the bits are mutated.

Once a new organism is generated we test it with the training vectors. If it has better performance than its parent, we keep it as the better individual; otherwise we use the parent to make another copy and go through the cycle for a pre-determined number of epochs, or until the organism achieves 100% learning.

Currently the hypernetwork architecture has evolution at the molecular level only. Future implementations will have evolution and regulation at the cellular level, where cells and their interactions could be evolved. Experiments on these models could yield more information about the evolution of regulatory mechanisms involving cells and tissues.

4. Formation of regulatory networks in the hypernetwork architecture

The molecular structure and the molecular relationships in a cell allow the formation of reaction cascades with inhibition. An example of activation and inhibition of molecules is shown in

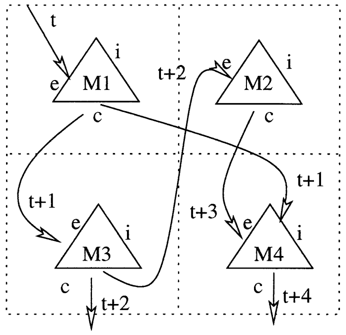

Fig. 3. Molecule M1 inhibits M4 at time ‘$t+1$’, then later after time ‘$t+3$’ M4 is ready to be activated by M2. The excitatory (e), inhibitory (i), and catalytic (c) sites of each molecule are shown.

Fig. 3, where molecule M1 activates molecule M3 and inhibits M4 at time '$t+1$'. The molecule is in an active or inactive state for one time step, then when it is back in a ready state it can be activated by another molecule.

The formation of positive feedback regulatory networks in the hypernetwork architecture is possible when a target molecule could activate one of the molecules that cause its activation in the first place. For example in Fig. 4 molecule M1 activates molecule M3 at time '$t+1$', then molecule M3 activates molecule M4 at time '$t+2$'. Later molecule M4 will activate molecule M1 at time '$t+3$', allowing the possibility of more activations of molecules M3 and M4 in future time steps.

Negative feedback regulatory networks are formed by means of the inhibitory site of the molecular structures. For example, in Fig. 5 activated molecule M1 activates molecule M3 at time '$t+1$', and molecule M3 activates M4 at time '$t+2$'. Then molecule M4 inhibits molecule M1 at time '$t+3$'. There are other possibilities for interactions depending on the structures and states of the molecules.

An instance of negative feedback regulation is shown in Fig. 6. The receptor of the cell is activated for a substring '00' and later it is inhibited by other molecules, shown in double lines.

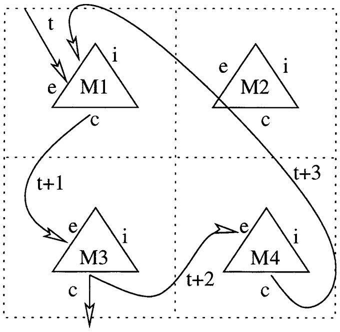

Fig. 4. Example of a positive feedback regulatory network. Molecule M1 is activated at time 't', then it activates M3 at time '$t+1$', which in turn activates M4 at '$t+2$'. Molecule M4 may activate Ml at time '$t+3$', producing more activations of molecules M1, M3 and M4. The excitatory (e), inhibitory (i), and catalytic (c) sites of each molecule are shown.

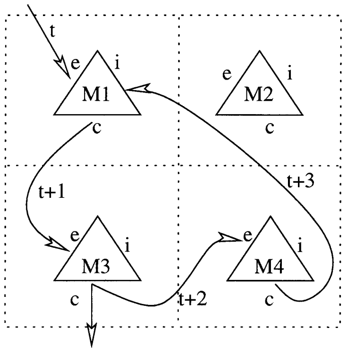

Fig. 5. Example of a negative feedback regulatory network. Molecule M1 is activated at time 't' and one of its cascade products, molecule M4, will inhibit the activation of M1 at time '$t+3$'. The excitatory (e), inhibitory (i), and catalytic (c) sites of each molecule are shown.

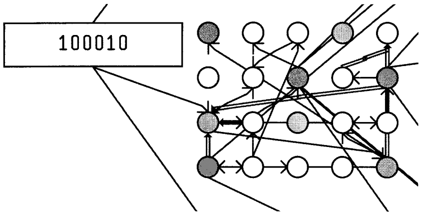

Fig. 6. The receptor of the input cell is activated by the substring '00' of the input vector, and later it is inhibited by other molecules. Inhibition is shown by double lines.

5. Experiments

To explore the effect of molecular inhibition on learning we trained organisms to solve the (four to eight)-input parity task, with and without molecular inhibition.

5.1. Task description

The N-input purity problem is to find the odd parity of 2^N binary input vectors. The organism must answer with a '1' if the input vector contains an odd number of '1' bits, or '0' otherwise. The simple case of $N=2$ (exclusive or, or XOR function) cannot be solved with single layer perceptrons (Minsky and Papert, 1969). Solving the N-input parity problem with genetic algorithms is difficult (Langdon and Poli, 1998). Multiple layer neural networks can solve the problem (Waterhouse and Robinson, 1994; Tesauro and Janssens, 1988), even in the case of $N = 10$ (Shang and Wah, 1996).

The experiments are divided in three parts. First, we observe the effect of the inhibition threshold in learning the four to six input parity tasks. Second, we study the effect of the percentage of inhibitory molecules on learning the four to six input parity tasks. Finally, we study the effect of inhibition on learning the N-input parity tasks, with $N = 4$, 6, and 8. Characteristics of the tasks and hypernetwork organisms used for training are shown in Table 1.

5.2. Effect of threshold for inhibition on learning the 4-input and 6-input parity tasks

We trained hypernetwork organisms to learn the four and six-input parity tasks, varying the threshold for molecular inhibition from 10 to 90% of the string matching. Each cell had 20% of its molecules with inhibitory sites. Fig. 7 shows the average number of epochs required for learning the task. Learning took a larger number of epochs when the threshold was low (10%), or high (90%). This corresponds to over-inhibition in the first case, and over-excitation of the molecular cascades in the second case. Fig. 7 shows that inhibition thresholds between 40 and 70% give almost the same results in the number of epochs required for learning. Unless otherwise stated, for the following experiments, we set the value of inhibition threshold to 70%.

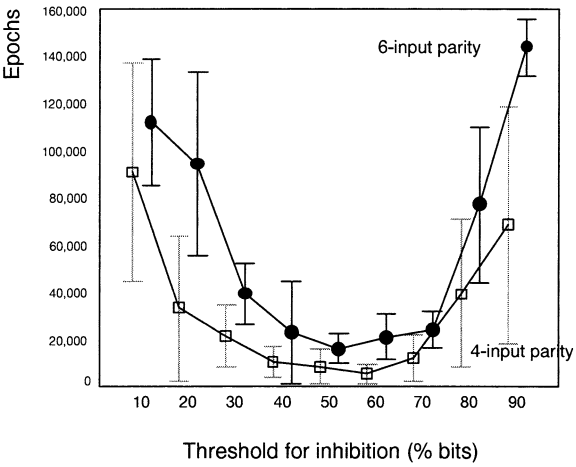

Fig. 7. Average number of epochs for learning the four and six-input parity tasks as a function of the threshold to inhibit a molecule. Each cell has 20% of molecules with inhibitory site. Average of ten runs, up to 150 000 epochs. Molecular activation threshold is 60%. Molecule string length is 14 bits per site, 95% of confidence level, $n = 10$.

5.3. Effect of the number of molecules with inhibitory site on learning the four and six-input parity tasks

The relation between the number of molecules with inhibitory ability in each cell and learning is observed in Fig. 8A. The number of epochs decreases when the percentage of molecules with inhibitory sites increases. Moreover, the average number of molecules with inhibition sites increases with the number of inhibitory molecules (Fig. 8C),

Table 1
The N-input parity task and characteristics of the corresponding hypernetwork organisms used for training

N-input parity		Organism			
N	Number of vectors	Number of input cells	Number of internal cells	Number of output cells	Total number of molecules
4	16	2	6	1	245
6	64	3	6	1	265
8	256	4	6	1	285

All organisms have input and internal cells with 20 molecules each, and one output cell with 25 molecules each. Each input and internal cell has four receptor and four effector molecules. Output cells have five receptor and five effector molecules. The rest of molecules are internals. Fig. 2 is an example of an organism used to train the six-input parity task.

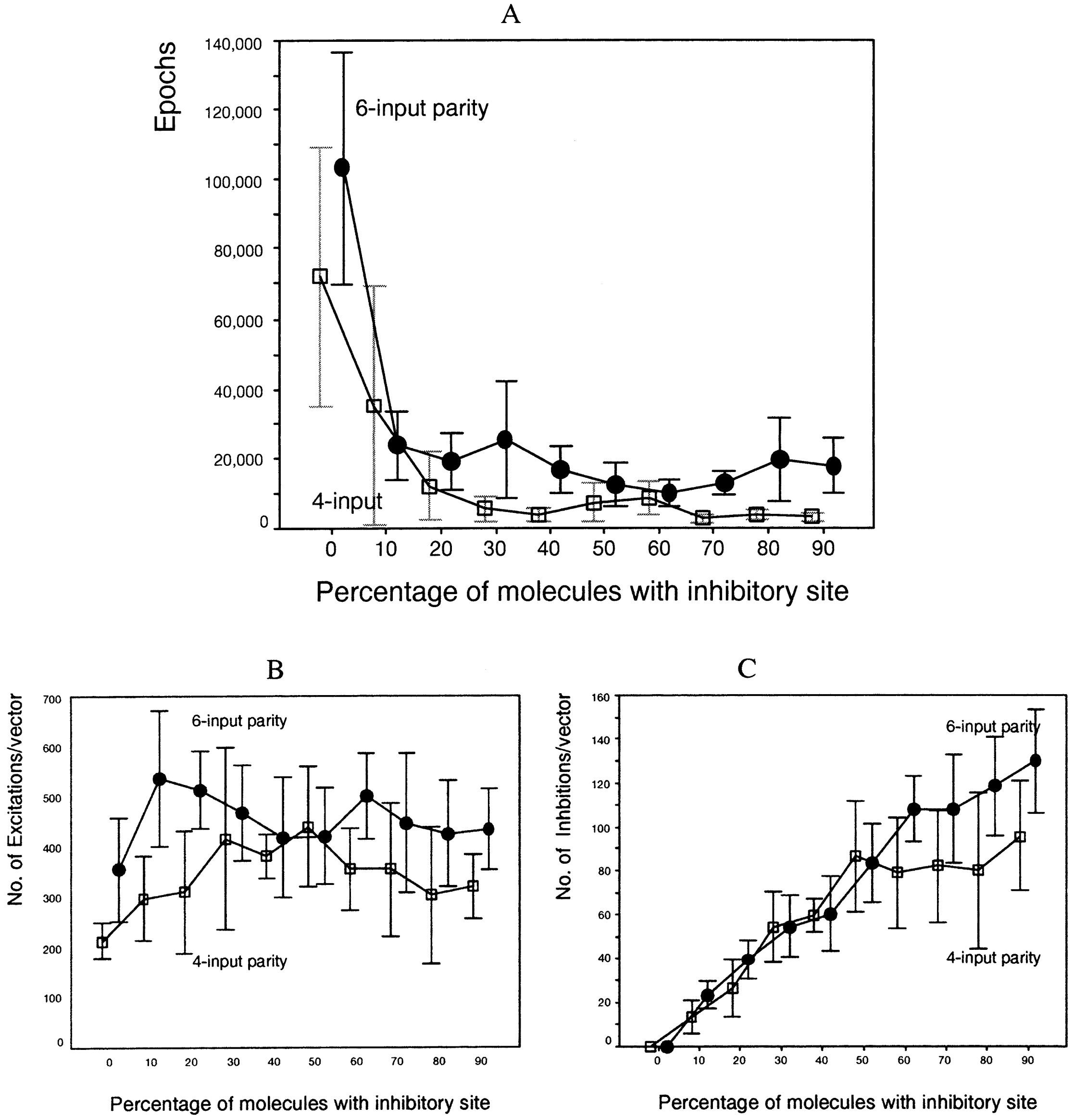

Fig. 8. The effect of the percentage of molecules with inhibitory sites per cell while learning the four and six-input parity tasks. (A) Effect on the number of epochs for training. (B) Average number of excitations the organism exhibits with an input vector. (C) Average number of inhibitions the organism exhibits with an input vector. Molecular excitation threshold is 60%s molecule string length is 14 bits per site, the confidence interval is 95%, $n = 10$, up to 150 000 epochs.

while the number of excitations is kept almost constant (Fig. 8B).

Hypernetwork organisms take advantage of the formation of inhibitory interactions and eventually negative feedback loops. A way to see the importance of inhibitory interactions is to analyze when hypernetwork organisms answer ‘0’. Hypernetwork organisms answer ‘0’ by showing no

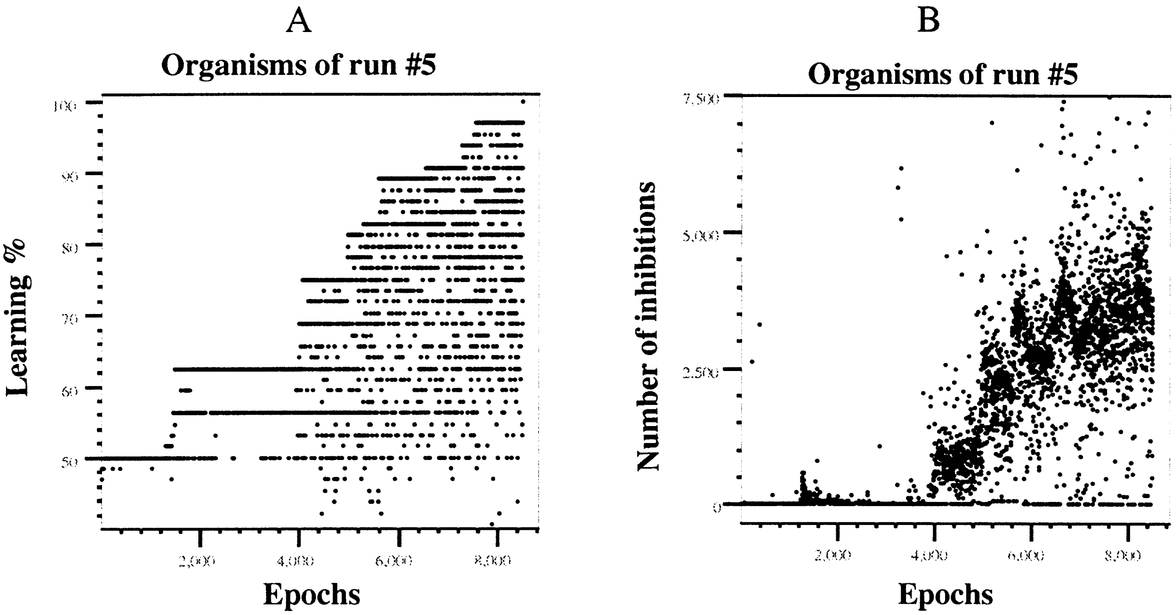

Fig. 9. (A) Scatterplot of learning behavior of hypernetwork organisms is learning the six-input parity task. (B) Scatterplot of the number of inhibitory interactions that occur when the organisms answer ‘0’ while learning the six-input parity task. The figures are from one run, and each dot represents one organism. Molecular excitation threshold is 50%, molecular inhibition threshold is 50%, molecule string length is 14 bits per site, up to 150 000 epochs.

activity on the readout molecules of output cells after activation of the molecular interaction cascades. This can be achieved in two ways: (a) by forming specific structures that will not be activated by some input vectors, but will be activated by others, and (b) by explicit inhibition of some cascades of interactions.

For example, Fig. 9A shows a scatterplot of the performance of organisms and Fig. 9B shows a scatterplot of the number of inhibitory interactions it takes an organism to answer ‘0’ while it is learning the six-input parity task. The organism increases the number of inhibitory interactions while learning. The organisms are using successively more inhibitory mechanisms to get the output cell in order to answer ‘0’ correctly.

The relationship between the performance and the variability in the number of inhibitions that developed during learning for nine organisms is shown in Fig. 10. The learning curve of run #5 is shown in Fig. 9. The standard deviation (S.D.) of the number of inhibitions tends to decrease when the performance increases, while the mean tends to increase. These figures suggest that at the beginning of the learning process, organisms explore several molecular structures which results in large variation in the number of inhibitions when they answer ‘0’ as output. Finally when they reach 100% learning, they find an optimal number of inhibitory interactions.

5.4. Effect of inhibition on learning the four to eight input parity tasks

Learning is improved when molecules with inhibitory sites are introduced in the organism. This improvement is expressed in the number of epochs needed to achieve learning, and in the final performance after a number of epochs.

Table 2 shows the average number of epochs required for learning the four to eight input parity tasks. The number of epochs needed to solve the problem is significantly larger, and the number of organisms that achieve 100% learning is smaller when molecules do not have inhibitory sites. The average number of epochs in case of $N = 8$ is closed to 150 000 because simulations were

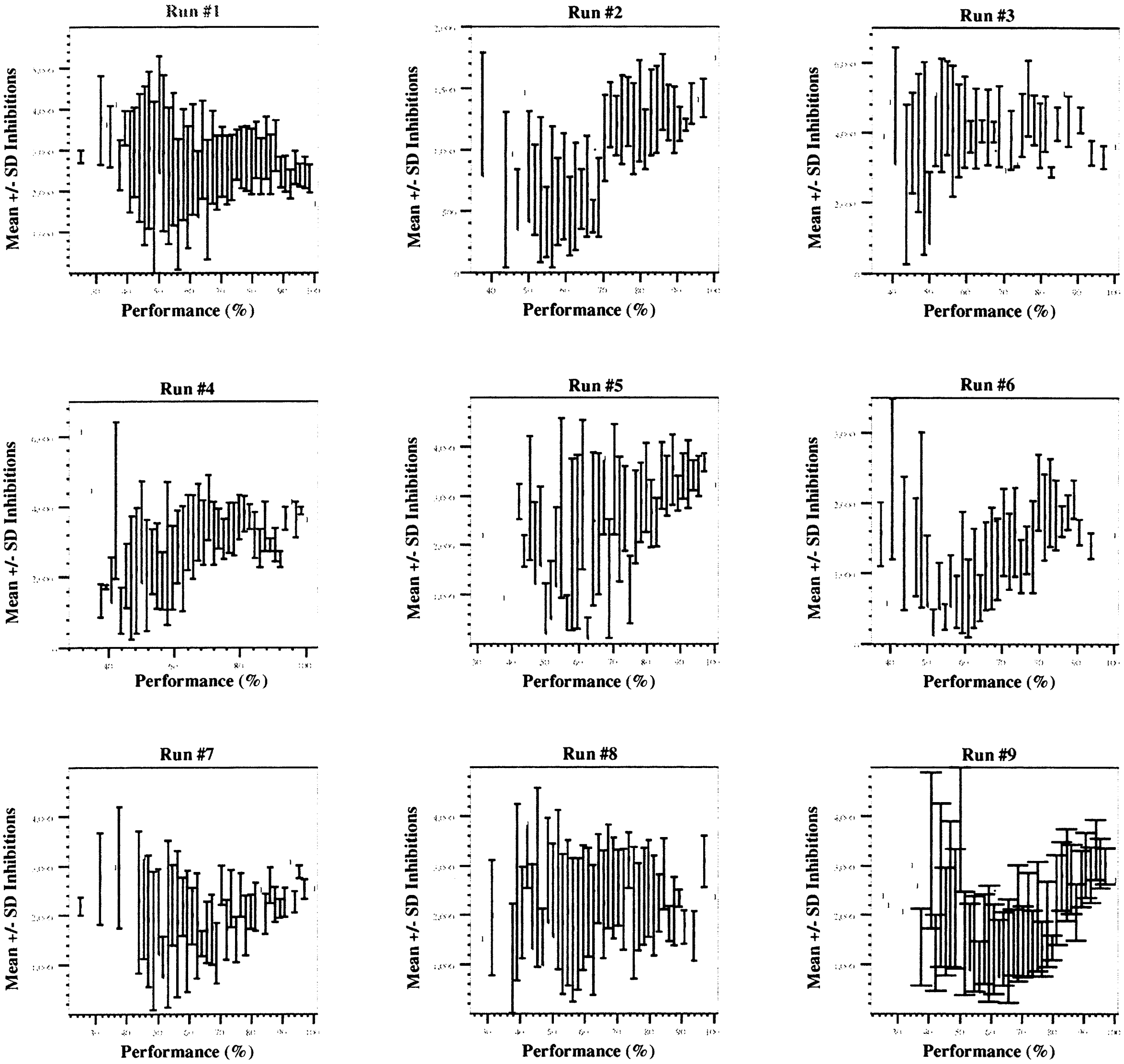

Fig. 10. Nine plots of the performance against the number of inhibitory interactions when the output is ‘0’, while learning the six-input parity task. Molecular excitation threshold is 50%, molecular inhibition threshold is 50%, molecule string length is 14 bits per site, up to 150 000 epochs.

stopped at this point. This bias is observed in Table 2.

Table 3 shows the average performance for learning the four to eight input parity tasks. It shows that organisms that have molecular inhibition show better learning than the ones that did not. We obtain 100% learning with inhibition in $N = 4$ and $N = 6$, but without inhibition organisms have more difficulty learning the parity tasks.

6. Discussion and conclusions

The major findings from the experiments are:

a) Hypernetwork learning improves when molecules exhibit inhibitory structures. The improvement is expressed in the number of epochs and the performance of organisms at the end of the simulations.

Table 2
Average number of epochs for learning the N-input parity task $N = 4$, 6, and 8, with and without inhibition

N	With inhibition			Without inhibition		
	Mean epochs	±	100% Learning	Mean epochs	±	100% Learning
4	11 348	9978	10	72 081	37 151	8
6	18 969	7848	10	103 249	33 517	7
8	119 810	25 789	5	142 127	12 805	2

Runs where terminated when learning was achieved or 150 000 epochs were reached. Threshold for molecular inhibition is 70%, threshold for molecular excitation is 60%, percentage of molecules with inhibitory sites is 20%, the confidence level is 95%, $n = 10$.

Table 3
Average performance for learning the N-Input parity task

N	With inhibition			Without inhibition		
	Mean learning	±	100% Learning	Mean learning	±	100% Learning
4	100	0	10	95.0	7.5	8
6	100	0	10	93.4	8.7	7
8	96.8	2.7	5	82.8	11.4	2

Runs where terminated when learning was achieved or 150 000 epochs were reached. Threshold for molecular inhibition is 70%, threshold for molecular activation is 60%, percentage of molecules with inhibitory sites is 20%, the confidence level 95%, $n = 10$.

b) Learning times are shortened when the threshold of inhibition molecules is between 20 and 70%. If there are two few or too many inhibitory interactions the organism struggles to keep an internal balance, resulting in difficulties in performing the task.
c) The number of inhibitory molecules in the cell should be greater than 20% to decrease the number of epochs needed for learning.
d) The number of inhibitory interactions increases linearly with the percentage of inhibitory molecules in the organism. However, at the same time, the number of excitatory interactions is not significantly affected. This suggests that organisms use inhibitory mechanisms when possible in order to restrict over-excitation in the internal molecular cascades.
e) The relevance of inhibitory interactions is shown by an increase in the number of inhibitions when organisms answer '0' (showing no activity in their readout structures.)

Experimental results show that, in the hypernetwork architecture, learning improves when the molecules have functional inhibition sites allowing inhibition and formation of molecular negative feedback regulation inside cells. Moreover, the number of molecules with inhibitory capacity could be large in proportion to the total number of molecules. This suggests a likelihood that more molecular inhibitory mechanisms will be discovered in biological systems.

Hill and Villa (1997) found that when a balance between excitatory and inhibitory neural synapses exists they may help in forming spatio-temporal representations, and Thomas and D'Ari (1990) state that negative feedback loops generate homeostasis.

The formation of reaction cascades and inhibitory mechanisms are discovered by molecular evolution in the course of learning to solve classification problems (i.e. surviving challenging environments). Positive and negative feedback regulatory networks are randomly formed during evolution on the basis of their excitatory and inhibitory molecular interactions. A systematic study of the evolution of such regulatory loops is left for future work.

Intra-cellular as well as inter-cellular molecular inhibition plays an important role in the information processing by hypernetwork organisms, keeping a homestatic balance of the molecular cascade reactions. These regulatory mechanisms are important for learning difficult problems, because they are necessary for the regulation of the readout molecules of output cells.

The hypernetwork architecture exhibits key elements of biosystems, and the experiments show that, with the molecular evolution learning algorithm, molecular level inhibition and the possibility of forming negative feedback regulation are important mechanisms to improve learning. Future implementations will incorporate evolution and regulation at the cellular level, where cells and their interactions could be evolved. Experiments on these models could give more information about the evolution of regulatory mechanisms involving cells and tissues.

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