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Boolean network analysis of a neurotransmitter signaling pathway

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Abstract

Background: A Boolean network is a simple computational model that may provide insight into the overall behavior of genetic networks and is represented by variables with two possible states (on/off), of the individual nodes/genes of the network. In this study, a Boolean network model has been used to simulate a molecular pathway between two neurotransmitter receptor, dopamine and glutamate receptor, systems in order to understand the consequence of using logic gate rules between nodes, which have two possible states (active and inactive).
Results: The dynamical properties of this Boolean network model of the biochemical pathway shows that, the pathway is stable and that, deletion/knockout of certain biologically important nodes cause significant perturbation to this network. The analysis clearly shows that in addition to the expected components dopamine and dopamine receptor 2 (DRD2), Ca^{2+} ions play a critical role in maintaining stability of the pathway.
Conclusion: So this method may be useful for the identification of potential genetic targets, whose loss of function in biochemical pathways may be responsible for disease onset. The molecular pathway considered in this study has been implicated with a complex disorder like schizophrenia, which has a complex multifactorial etiology.

Keywords: Boolean network; Dopaminergic signaling; Glutaminergic signaling; Schizophrenia; Biochemical pathways

1. Background

A Boolean network model of the molecular pathway between two neurotransmitter systems, the dopamine and glutamate receptors, was built to identify nodes/genes crucial to this pathway, thereby suggesting a plausible method for the identification of important genes and events implicated in a complex multigenetic disorder. The rationale for this study is that the hunt for susceptible genes for a complex disorder is challenging, probably due to the interplay of minor effects of a combination of many genes (Thaker and Carpenter, 2000). The prioritization of gene(s) for investigation as candidate genes for a complex disorder is a difficult task.

Signal transduction networks like the one being studied here contains numerous interacting proteins and factors, which make them difficult to model using differential equations. Difficulty with modeling large-scale networks based on continuous differential equations includes the requirement of several biochemical details like initial concentration of reactants and kinetic values, which are rarely accessible and would require enormous computing time for stochastic simulations (Arkin et al., 1998; Huang, 1999). The advantage of Boolean network modeling is to study generic coarse-grained properties of large genetic networks and the logical interactions of genes, without knowing specific quantitative details (Arkin et al., 1998). The presented interaction molecular pathway of the neurotransmitter signaling systems is an ensemble of interacting genes and events, named as genetic network by Kauffman (1993). In this study, we have applied simple synchronous Boolean network theory (Kauffman, 1971) on

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the model biochemical pathway to investigate the overall dynamical properties, stability and most importantly the effect of perturbation of the individual nodes of the pathway.

Furthermore, we have based the choice of synchronous updation on Schonfisch's observation (Schonfisch and de Roos, 1999) wherein it was stated that the question of the difference between synchronous and asynchronous updation in a system is how we look at a real process. If we observe a process at large time intervals all cells are updated at once, that is in synchrony. However, if we refine the time-scale for the same process then at every time interval at least one event will happen, then we find asynchrony (Schonfisch and de Roos, 1999). In biological networks a change in a gene's activation state may instantly imply other state changes elsewhere in the network from this point of view; synchronous networks may be closer to reality than the asynchronous networks (Mesot and Teuscher, 2003). Furthermore, the synchronous behavior might arise from the synchronization of asynchronous elements (Glass and Mackey, 1988).

Herein, the genetic network consists of N genetic elements or nodes that represent genes, molecules and events in this interaction biochemical pathway. Each node takes a Boolean value of 0 or 1 representing the respective "inactive" and "active" status of the node. The nodes are interconnected to each other by Boolean rules (logic rules), which represents the functional interactions between the nodes defined in the biochemical pathway wiring architecture. Thereafter, the Boolean system updates itself synchronously based on the set of rules that determine the state of the system at the next step from its state at the previous step.

The results from dynamic properties of the model shows that this molecular pathway, involving the dopamine and glutamate receptors is a stable network and we were able to identify in this 16-node pathway, specific nodes, which when mutated cause maximum perturbation to the pathway. The objective of this work therefore, is to provide important genes that on their mutation cause perturbation to the network.

2. Methods

2.1. Definition of the model: the biochemical pathway

Behavioral, biochemical and physiological studies have shown that interactions between dopamine (DA) and glutamate receptors occur, and are known to be involved in fundamental process including cellular plasticity (Calabresi et al., 1997; Hernandez et al., 2005). The interaction pathway between the mentioned neurotransmitter receptors is certainly complex and intricate (Gould and Manji, 2005), however, in this section; we describe the simplified interaction pathway between the dopamine and glutamate receptor signaling as the chosen model (Fig. 1).

The neurotransmitter, dopamine is synthesized by tyrosine hydroxylase and catabolized by COMT. Dopamine, binds to the dopamine receptor 1 (DRD1), stimulating adenylate cyclase to activate Protein kinase A, leading to the activation of DARPP32, converting it into an inhibitor of protein phosphatase-1 (Greengard, 2001; Snyder et al., 1998). After inhibition by protein phosphatase-1, activation by protein kinase A (Snyder et al., 1998) and in the presence of the ligand glutamate, the glutamate receptor is activated for calcium entry into the cell (Dingledine et al., 1999). Dopamine also binds to the dopamine receptor 2 (DRD2) to inhibit adenylate cyclase, but to activate phospholipase C in order to elevate the intracellular calcium (Yan et al., 1999). The intracellular calcium activates calcineurin, which inhibits DARPP32, thereby releasing the inhibition on protein phosphatase-1 (Greengard, 2001). So, while the DRD1 receptor signaling activates, the DRD2 signaling inactivates the glutamate receptor (Snyder et al., 1998).

In our model, we consider action of glutamate on the alpha-amino-3-hydroxy-5-methyl-4-propionate (AMPA) and NMDA (*N*-methyl-D-asparatate) receptors only. The modulatory action of the metabotrophic glutamate receptors has not been considered. The glutamate receptors are calcium channels, which interact with numerous packaging proteins like synaptic proteins and postsynaptic density proteins, involved in synaptic plasticity (Gould and Manji, 2005). Moreover, hyperfunction of the dopamine and hypofunction of the glutamate receptor-signaling pathway has been implicated in cognitive deficit observed in schizophrenia (Coyle et al., 2003; Castner et al., 2003). Candidate genes in the pathway that have been implicated with schizophrenia include COMT (Weinberger, 2005), DRD2, DRD1 (Rybakowski et al., 2005; Ambrosio et al., 2004), calcineurin (Miyakawa et al., 2003), DARPP32 (Albert et al., 2002), synaptic proteins like synaptogyrin (Verma et al., 2004) and the NMDA receptor (Coyle et al., 2003). The Boolean network model has been used to analyse this biologically important biochemical pathway.

2.2. Definition of the model: dynamics

Although, the simplifications inherent in them make Boolean networks very attractive for modeling complicated systems, a natural question arises as to how well such a model can represent a real biochemical system given that it does transform the nature of the interactions. Glass and Kauffman (1972, 1973), investigated this, and determined that discretization by Boolean networks provide an accurate general description of biochemical networks. Fig. 2 describes the logic-gate model of the pathway.

In Fig. 2, we have presented the translation of the functional relationship between the molecules/nodes of the interaction pathway to logic gates ("AND","NOT", "AND NOT"). Tyrosine hydroxylase (C1) activates itself in this model. There is an "AND NOT" gate between tyrosine hydroxylase (C1) and COMT (C3) to activate

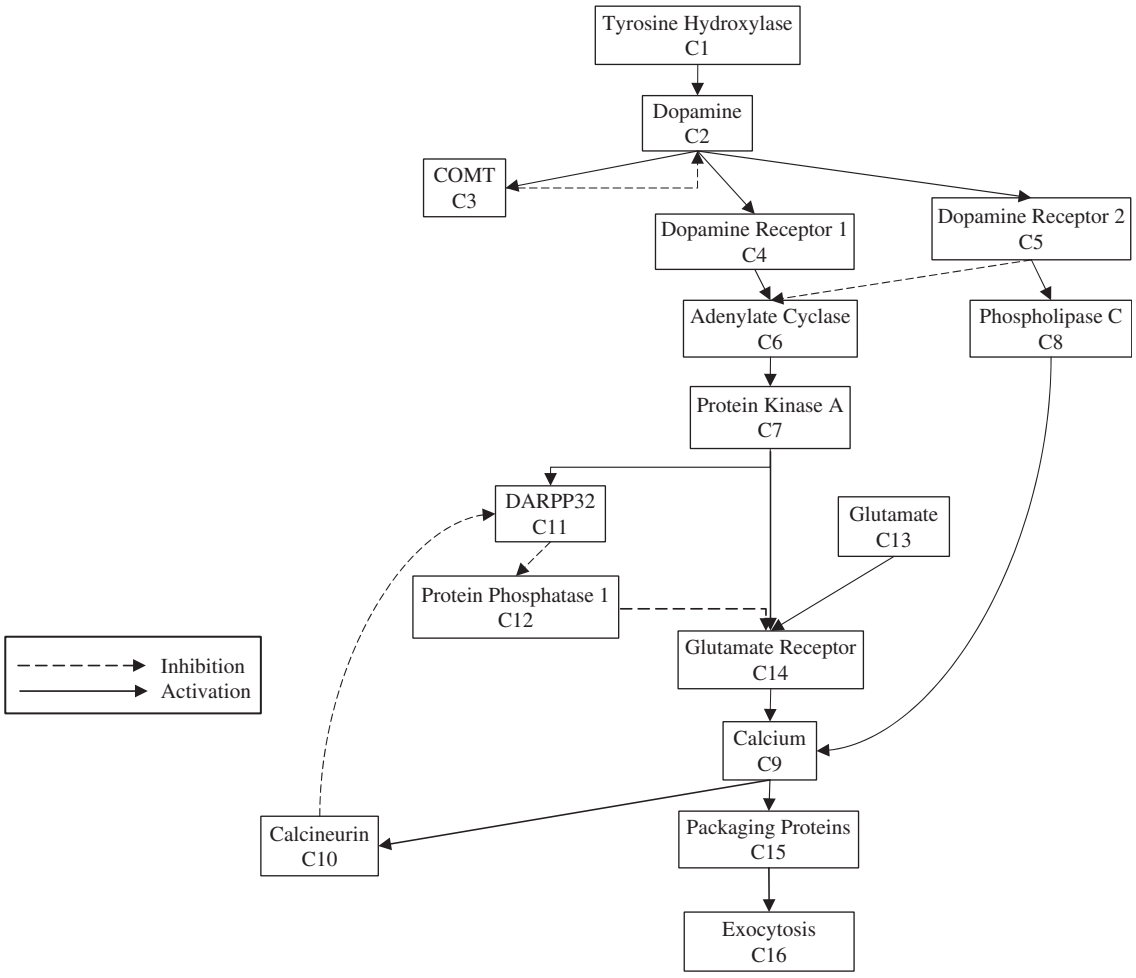

Fig. 1. The model interaction pathway between the glutamatergic and dopaminergic receptors. All the components of the model are shown in the boxes. The node number is given in each box along with the name of the node. The "continuous arrow" indicate activation, while the "discontinuous arrow" shows inhibition.

dopamine (C2) as tyrosine hydroxylase (C1) and not COMT (C3) activates dopamine (C2).

Dopamine (C2) directly activates COMT (C3), dopamine receptor 1 (C4) and dopamine receptor 2 (C5) as shown.

In this model, adenylate cyclase (C6) is activated by dopamine receptor 1 (C4) and not by dopamine receptor 2 (C5), which has been represented by the "AND NOT" gate between the input nodes, C4 and C5.

Adenylate cyclase (C6) directly activates protein kinase A (C7).

The dopamine receptor 2 directly activates phospholipase C (C8) while calcium (C9) is activated by either phospholipase C (C8) or glutamate receptor (C14). calcium (C9) then activates calcineurin (C10).

Thereafter, DARPP32 (C11), is activated by protein kinase A (C7), and not by calcineurin (C10), therefore protein kinase A (C7) "AND NOT" calcineurin (C10) activates DARPP32 (C11).

DARPP32 (C11) inhibits protein phosphatase1 (C12), which is represented by the "NOT" gate from DARPP32 (C11) for protein phosphatase1 (C12).

The node for glutamate (C13) activates itself in this model. The activation of glutamate receptor (C14), needs the presence of both protein kinase A (C7) and the ligand, glutamate (C13) therefore, a "AND" gate between protein kinase A (C7) and glutamate (C13), "AND NOT" protein phosphatase 1 (C12). Thus, (C7 "AND" C13) "AND NOT" C12 gives glutamate receptor (C14) activation.

Activation of glutamate receptor (C14), results in activation of the packaging proteins (C15) leading to the event of exocytosis (C16). The process of exocytosis of the glutamate receptor depicts an event in synaptic plasticity.

2.3. Definition of the model: calculations

This Boolean network model is a system of 16 nodes or genes wherein each gene/event has been assigned only Boolean values (ON and OFF). Each node is connected to its neighboring nodes through a structured logic rule in the network. The state of the system is defined by the pattern of states (on/off) of all its nodes. The nodes are updated synchronously, moving the system into its next state, with each state having only one resultant state. Since the

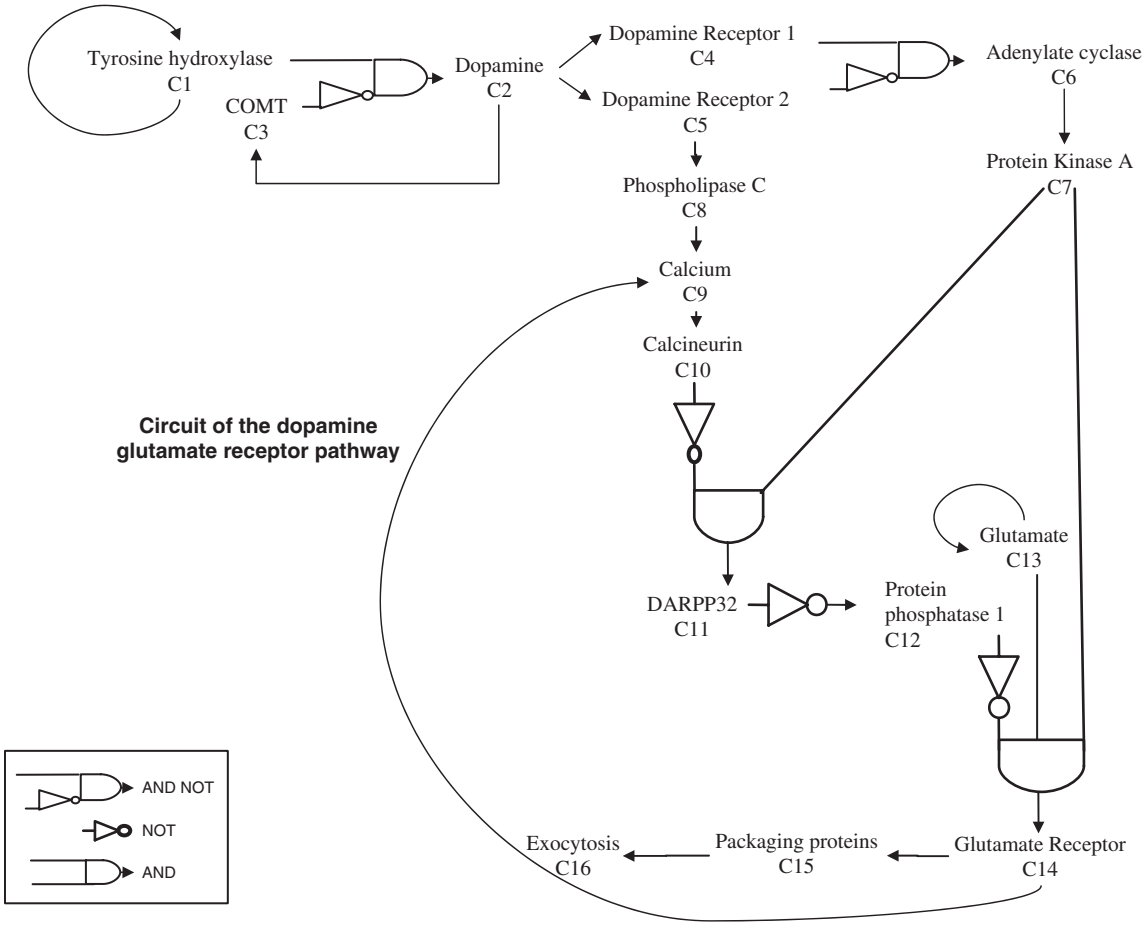

Fig. 2. The circuit of the crosstalk between the glutamate and dopamine receptor. The AND, OR (NOT AND) gates have been placed between the nodes for simulation using the Boolean network model.

number of all possible states of the system (2^n, where n is the number of nodes of the network) is limited and the transition rules are defined and the system reaches a cycle or attractor.

Furthermore, to study the time development of this discrete model with synchronous updating, we observe how the Hamming distance between two states evolves over time. All the 2^{16} states of the 16 node pathway are passed through and the simulation starts with zero states for all the 16 nodes, which implies that all the genes/nodes are switched off at the initial state.

In a Derrida plot, pairs of initial states are sampled at defined initial distances, $H(0)$, from the entire state space, and their mean Hamming distance, $H(t)$, after a fixed time, t, is plotted against the initial distance $H(0)$. The curve above/below the line (slope), $H(t) = H(0)$, reflects instability/stability, respectively (Kauffman et al., 2003).

To investigate the significance of each node in the network we calculated the perturbation measure for the individual nodes, by modifying the Derrida plot. Perturbation calculations were performed between the normal network and each of the 16 mutated networks. A mutated network for a specific node contains forced false (0) value for that specific node in the input and output states, therefore it contains 2^{n-1} states. For perturbation calculation of each individual node, we compared the pairs of the initial states in the normal network containing true value for that specific node with the initial states in mutated network for the node, for obtaining the initial distance, $H(0)$. The mean Hamming distance, $H(t)$, after a fixed time, t (where $t = 1$), for the corresponding output states in the normal and mutated network for the node was plotted against the initial distance $H(0)$. This modified Derrida plot highlights the effect of mutation (switching genes off/0 value) due to individual genes. The perturbation calculations were normalized with respect to the slope, $H(t) = H(0)$ (Fig. 3).

The Derrida plot provides a measure of divergence/convergence of network dynamics in terms of "Hamming distance" between states. In this study we have deviated from the original Derrida plot as in the usual calculation the Hamming distance calculation over a time step is carried over a randomly selected of pair of initial states. This selection of a sample of states provides a statistical measure of the divergence/convergence of the network dynamics. In our study we have selected all (2^{15}) the states of the "knocked-out network" for each node for comparison with the corresponding states for that node in the

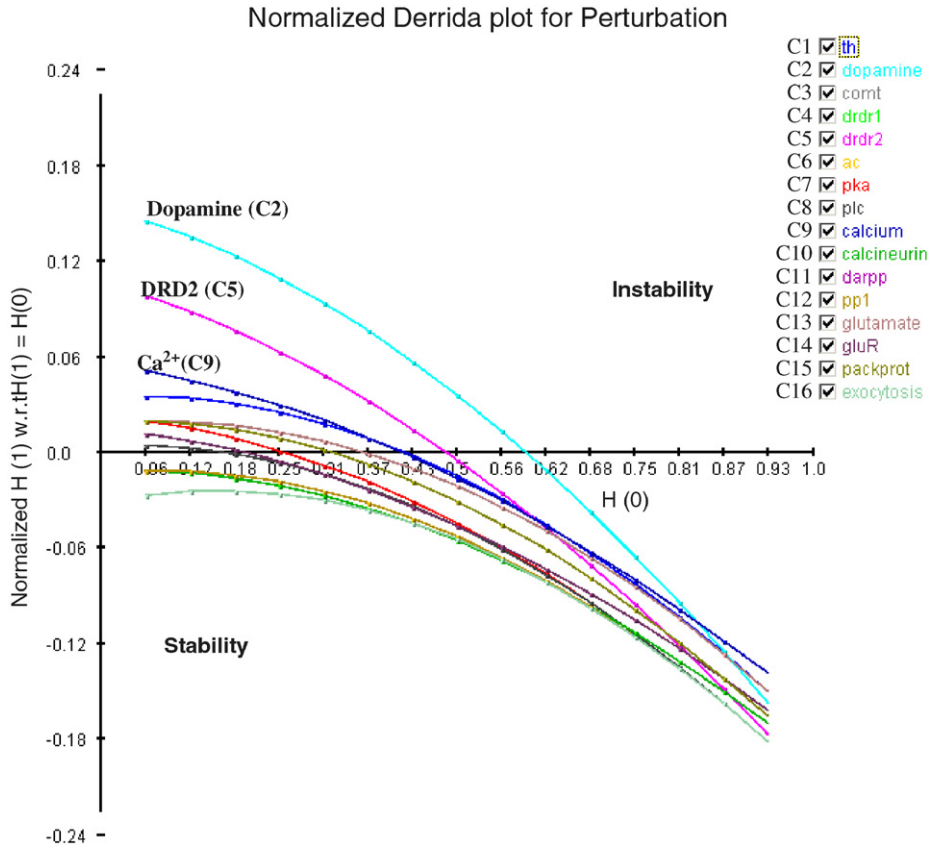

Fig. 3. Pertubation caused by each of the 16 nodes in this network. Maximum perturbation is cause by dopamine, followed by DRD2 and calcium.

"normal network". Therefore, an absolute score of the order-chaos measure of the perturbation caused by each node of the network has been calculated after a single time step (Fig. 3).

3. Results and discussion

Using the dynamic model, it is possible to study the time evolution of the nodes in the interaction pathway network. This network, which involves the interaction between the dopamine and the glutamate receptor pathway, is important from the aspect of the drug treatment and symptoms in schizophrenia. To find what effect mutation of nodes would have on the network, we perturbed the network by switching "off" each of the nodes one at a time for each simulation. Thereafter, the effect of the node perturbation on the network is calculated for each node.

The results of the node perturbation ("knock-out") on the network highlights three important nodes namely dopamine, Dopamine receptor 2 and calcium in the order of significance. In our study, we also calculated other perturbations to the network such as incorporating a NOT gate to the rules one at a time for each node of the network. The perturbation results remain exactly the same, with dopamine, dopamine receptor 2 and calcium still remaining the crucial nodes for all the networks with the rule perturbations.

The results reinforce the existing knowledge about the system. In this network (Fig. 3), dopamine and DRD2 are crucial nodes, signifying that in the dopamine and glutamate receptor crosstalk, dopamine levels are critical. In fact, dopamine dysregulation has been proposed to worsen synaptic connectivity and NMDA function (Laruelle et al., 2005). There are several dopamine receptors, D1-like (D1 and D5 receptors) and D2-like (D2–D4 families) that have been implicated with the disease (Rybakowski et al., 2005; Ambrosio et al., 2004; Xing et al., 2003; Muir et al., 2001). In our network we had both DRD1 and DRD2 receptors but DRD2 receptor, which is inhibited via treatment with antipsychotic drugs (Laruelle et al., 2005), turns out to be more critical than DRD1. However, it is interesting to note that among the several nodes Ca^{2+} ion becomes an important node in the pathway.

Furthermore, the altered calcium responses point to a specific set of pathways that may allow us to narrow the target for identifying the defect of calcium regulation directly through the action of the calcium channels (Breen et al., 1999) or indirectly via binding to various proteins like calcineurin (Miyakawa et al., 2003), neuronal calcium sensor-1 protein (Negyessy and Goldman-Rakic, 2005) or

even via molecules like LIM that link protein kinase C with calcium channel (Kato et al., 2005). The study indicates that the Boolean rule formalism of biochemical pathway suggest biologically relevant information regarding which node(s) or gene(s) are important for the network. So it may be used for large genetic networks for an insight into plausible genetic targets for the genetic studies.

4. Conclusion

The purpose of modeling this network between two neurotransmitter-signaling systems is to show that a Boolean network may be used as a tool to understand the dynamics of a network which may help identify dominant components of the network. We are aware that beyond these 16 nodes other genes in different pathways are likely to contribute to the disease (schizophrenia) etiology; however, our analysis in this paper is restricted to an important pathway which has defined involvement in schizophrenia etiology.

The perturbation measure of each of the nodes of this Boolean network allows us to suggest nodes of importance based on the extent of perturbation caused in the network by their mutation. These nodes that show maximum perturbation to this model network appear to be in conformance to the biological data, which supports their role in schizophrenia.

As a network, the abnormalities in the dopamine system has been implicated in psychiatric and neurological syndromes, including Parkinson's disease, schizophrenia, bipolar disorder, attention deficit hyperactivity disorder (ADHD) and Gilles de la Tourette syndrome (Salgado-Pineda et al., 2005). It is necessary to understand the importance of this receptor system in this context, wherein the dopamine receptors enables dopamine to modulate glutamate transmission via mechanisms that involve elevated intracellular calcium (Bergson et al., 2003; Gupta et al., 2006). This interaction is in keeping with the current models regarding dopamine hyperactivity with respect to schizophrenia with the added emphasis to calcium signaling as a potential candidate.

Calcium may serve as an important link between the two receptor systems, in the model pathway involving glutamate-induced excitotoxicity and dopaminergic overactivity in schizophrenia. Regulation of calcium influx intracellularly may slow the development of symptoms and eventually reduce neuronal damage seen in schizophrenia. Furthermore, Yarlagadda suggests that calcium may be a common denominator in our understanding of the pathophysiology of schizophrenia and could serve as a marker for the disease (Yarlagadda, 2002).

In addition, this paper could guide further analysis of calcium-related pathways. As an extension of this study, Verma et al. (2005) studied MLC1 gene, encoding a putative non-selective cation channel expressed exclusively in brain, and found association with schizophrenia and bipolar disorder patients.

Furthermore, evidences reported by Koh et al. reinforce that in schizophrenia brains, abnormalities have been detected in Ca^{2+}-stimulated cascades like phosphoinositide pathway, Ca^{2+} channels, and the Ca^{2+}-dependent molecules like calcineurin. Koh has hypothesized that the multifactorial causes, may eventually disturb Ca^{2+} signaling, which, in this case, would constitute the central mechanism underlying abnormal brain function in this disease (Koh et al., 2002).

The fact that most relationships in complex pathway are nonlinear, and there exist numerous feedback loops so most intuitive observations often may not follow expected response. The Boolean network model is far easier to use when compared to models based on kinetic constants simply because kinetic models depend on many factors like initial concentration of substrates, rate constants and other parameters, which are difficult to obtain for signal transduction pathways. The central aim of this simplistic Boolean network model is to help to provide a tool, which could help identify important nodes; nodes may be genes or cellular components in a network given a complex biochemical pathway. In multigenetic disorder like schizophrenia, combination of minor effects of gene(s) may contribute to the disease; this model shows the perturbation effect of the genes/events of a pathway and may help prioritize the genes for further study. Of course, the inherent simplicity of Boolean models is based on the assumption that only the active and inactive states of the genes are considered and states of all genes are synchronously updated.

This body of work may yet not be ready for wholesale translation into clinical practice. However, with advances in this work there may be insights into the etiology, pathophysiology and treatment in future. Pathway analysis of systems is intriguing especially because many more pathways are still unknown. Furthermore, pathway study of complex disorders is indeed far more complicated, due to heterogeneity in symptoms and response to treatment.

The Boolean network model simplifies the network but helps capture the dependency of the nodes with respect to each other. Despite the inherent simplicity, the analysis has yielded three important nodes as crucial to the network with the lead for calcium influx as a candidate parameter. This allows the search for gene networks involved in calcium homeostasis.

Therefore, this Boolean network model may serve as a useful tool to identify important nodes in otherwise complex biochemical pathway of interacting nodes. The interesting thing is that the model reiterates current knowledge confirming its essential fidelity to biological processes. Whether the process could be used successfully to target genes or metabolites of cells is subject to further experimental validation.

Therefore, a simple model of this kind could be an important tool to gain insights by way of choosing candidate genes from otherwise very complex interactions and crosstalk pathways.

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