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A Computational Framework in Modeling Cellular Communication in Sepsis

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Abstract: - The paper proposes a model that relieves the characteristics of the patient evolution in SEPSIS as the result of correct or corrupted information transfer as the cell level, using for this aim methods which are specific for studying complex systems: nonlinear dynamics, statistical methods, data transmission and network theory. We place particular emphasis on network theory and its importance in augmenting the framework for the quantitative study of complex systems. Specifically, we discuss issues, arising from network theory, in our understanding the structure of cellular signaling networks involved in SEPSIS phenomena. Finally, we discuss the possibility to implement two simulation mechanisms, one based on autonomous (multi)agent blackboard architecture, for modeling intracellular communication, the other, based on small-world or even scale-free networks, for modeling intercellular communication.

Key-Words: - complex systems, sepsis, cellular signalling, intracellular / intercellular communication, biological networks

1 Introduction

What do metabolic pathways and ecosystems, the Internet or patient evolution in SEPSIS have in common? Until a few years ago, the answer would have been very little. The first two examples are biological and shaped by evolution, the third is a human creation, and the fourth, yet not explained, seems to be a complex mixture of biology, chemistry, genetics and immunology. However, in the last few years the answer that has emerged is that they all share similar network architectures, typical for complex systems. .

A common idea of complexity is that complex things have a long complicated history, and that complexity must be understood in the context of processes in Nature generating systems with more parts, different parts, and special relations between various kinds of parts, forming a structure which must be described on several distinct levels of organization and as involving entities with emergent properties. There are many tools that can be used in Complex Systems research (including the study of non-linear dynamical systems, chaos theory, Artificial Life, cellular automata, etc.). Based on *complex dynamic systems* a lot of research from the perspective of natural science endeavours to investigate self-organizing systems, co-operative behavior of agents, and non-linear dynamical systems creating emergent properties during their time evolution. One can consider that this category includes also processes where the transfer of information between many individuals is capital, and in particular cellular communication processes in human body.

2 Cellular signaling

Cells face a steady input of signals. All cellular decisions, like survival or apoptosis (cellular suicide), proliferation or secretion of certain compounds are governed by this complex pattern of inputs (or lack thereof). Obviously, the cell needs a way to map the set of inputs to the set of possible responses, weighting and integrating the different inputs in their context. It has to be possible for the cell to adapt to the multitude of exterior environments. Therefore the signaling network has to be robust, that means it may not fall apart because if minute changes in some parameter. To achieve this, differing levels of exterior have to be translated into one cellular state, which may change to another one on a certain threshold in the signal. This many-to-one mapping is an essential ingredient in life. This integration is the product of mechanisms on at least three levels:

1. the set of receptors, which act as a first signal filter;

2. the transduction pathways hooked up to them and their interaction, which may act as a complex switching network
3. the regulatory region on the DNA, which acts as a regulatory program for transcription factors.

The structure and dynamics of biological and technical networks have become a major topic of scientific research recently. The focus in biological network research so far has been mainly on *intracellular* networks, e.g. metabolic networks [1], gene-regulatory networks [2], or networks of protein-protein interactions [3]. What has not been taken into account yet is the *humoral* network of *intercellular* communication, which links *intracellular* signaling networks of different cells and cell types. Cells communicate in various ways. In this work, we concentrate on humoral communication through cytokine messengers in the human body in general and in a SEPSIS state especially. The related substances act as first messengers and thus are released from specific cells to regulate functions in distant target cells by binding as ligands to specific receptors. Upon binding to its receptor ligands activate intracellular second messenger systems which finally lead to changes in cellular function and/-or structure.

3 Modeling cellular communication systems

The evolution in every biological phenomenon, including SEPSIS, can be considered as a result of information transfer in a complex cellular/molecular communication system. Although molecular biology is mainly focused on identification of genes and functions of their products, which are components of the system, the major challenge in analysing sepsis is to understand at the system level the biological system within a consistent framework of knowledge built up from the molecular level to the functional system level – not only gene networks, but also protein networks, signaling networks, metabolic networks and specific systems such as the immune system. At a very abstract level, a cell can be divided into two general subnetworks, a regulatory network and a metabolic network. These networks possess very different characteristics. The metabolic network is mainly occupied with substance transformation to provide metabolites and cellular structures. The regulatory network's main task is information processing for the adjustment of enzyme concentrations to the requirements of variable internal and external conditions. This network involves the use of genetic information. Table 1 present a short description of the characteristics of such networks.

Table 1. Comparison between cellular networks

Cell Network	Task	Examples
Metabolic pathway	Enzyme reactions on chemical substances	Intermediary / Secondary / Macromolecular Metabolism
Regulatory pathway	Macromolecular interactions. Direct protein-protein interactions and gene expressions	Membrane transport, signal transduction, ligand-receptor interaction, cell cycle, cell death

The complex network of biochemical reaction/transport processes and their biochemical spatial organization make the development of a predictive model of living cell a "grand challenge" problem. Cell signaling, cell motility, organelle transport, gene transcription and translation, morphogenesis and cellular differentiation cannot easily be accommodated into existing computational frameworks. Conventional approaches using the numerical integration of continuous, deterministic rate equations can provide useful when systems are large or when molecular details are of little importance. However when the resolution of experimental techniques increases, conventional models become unwieldy. Difficulties include the importance of spatial location within the cell, the instability associated with reactions between small numbers of molecular species and the combinatorial explosion of large numbers of different species. One of the first used in model molecular interactions were the stochastic methods. In the stochastic modeling approach, rate equations are replaced by individual reaction probabilities and the output has a physically realistic stochastic nature. But in the cell, various components interact in diverse manners. All cellular subsystems are highly nonlinear, and subsystem couplings are often nonlinear as well. This nonlinearity indicates that the whole system is not equivalent to the sum of its subsystems. Cell simulators must therefore allow simulation of cell subsystems in both isolated and coupled forms. To simulate coupled subsystems, it is necessary to perform computations on mutually interacting subsystems with different computational properties on a single platform. There is, however, no universal algorithm that can efficiently simulate all subsystems at once, so simulators must allow multiple computation algorithms to coexist in a single model.

4 The modeling framework for SEPSIS

Clearly in multicellular organisms, cell decisions about survival, growth, gene expression, differentiation and senescence or death, are made on the basis of external signals. These stimuli include cell-cell adhesion, growth factors, hormones, cytokines, neuropeptides, etc. The skill to integrate information from multiple sources is essential for the ability of the cell to respond appropriately to a wide range of conditions, and therefore enhances the adaptability and survival of the organism. One can consider that there are to kinds of communication mechanisms for SEPSIS modeling, both based on signal transduction in biological networks. The first mechanism can be represented by signaling intracellular networks, the other by signaling intercellular networks.

4.1 Intracell communication

Signal transduction networks allow cells to perceive changes in the extracellular environment in order to produce an appropriate response. A cellular process network mediates the transmission of extracellular signals to their intracellular targets. In general, the external signals are transmitted to the interior of the cells through receptors activating diverse signaling pathways. They can follow a single way and generate an answer or a specific cellular final process, or branch out and give rise to others. These pathways considered as a whole form an interconnected network, because pathways corresponding to different stimuli cross and generate alternative trajectories. The intracellular signaling implies several molecular processes. The signals can be as simple as the direct introduction of the signal to the nucleus and the activation of the transcription of proteins involved in the specific cellular function, which is expected. On the other hand, they can be very complicated and include multiple stages. For example, the receptor activates effector proteins like second messengers, kinases or phosphatases. They, in turn, activate transcription factor proteins, which determine the transcription of genes codifying for proteins involved in the specified cellular function.

Computational models in signal transduction pathways have been made using different points of view. Each research group chose the approach which seemed best for them and applied the most adequate computational tool for their purpose. This perspective involves a range from the types of information processing present at cellular level, such as sequential, parallel, distributed, concurrent and emergent; to the cognitive capabilities exhibited by certain signal transduction pathway component, such as memory, learning, pattern recognition and handling fuzzy data. In this sense, several computational approaches have been proposed to model the cellular signaling pathways, such as artificial neural networks [4], Boolean networks [5], Petri nets [6], rule-based systems [7], cellular automata [8], and multi-agent systems [9]

Table 2 summarizes the main characteristics of these computational approaches, taking into account the idea behind the approach, the cognitive capabilities that can be modeled, types of present information processing, and the part of the cellular signaling to be modeled.

Table 2. Characteristics of computational methods

Comp. approach	Characteristics
Boolean networks	The cell can be modeled as a network of two state components interacting between them. The state of each component depends of a particular boolean function.
Expert systems	The interactions (activation, phosphorylation, etc.) between signaling network components are modeled using production rules
Differential-algebraic equations	An ODE equation is built or each molecule x describing its relationship with all relevant molecules y
Cellular automata	The interaction between cells or molecules is modeled as a matrix, where the state of an element of the matrix depends on the states of the neighbouring elements.
Petri nets	The cell is seen as a connected graph with two types of nodes. One type represents elements, such as signaling molecules, the other type represents transitions.
Artificial neural networks	The proteins in signaling networks are seen as artificial neurons in ANN. Like an artificial neuron, a protein receives weighted inputs, produces an output, and has an activation value.
Distributed systems (agents)	The cell is seen as a collection of agents working in parallel. The agents communicate between them through messages.

From all this models we consider that the most adequate for sepsis dynamic of the cellular signal transduction is a collection of autonomous agents communicating between them through a shared data structure, where each agent is implemented as a neural network, a Boolean network or a molecular

automata, depending of the complexity of the task carried out by the agent and the knowledge degree or cognitive capabilities required by it.

Our proposal consists in modeling the cell as an autonomous agent (AA), which in turn is composed by a society of autonomous agents, where each agent communicates through a blackboard with others. The blackboard architecture constitutes a working environment for the bottom-up modeling of information processing systems characterized by: (1) modularity, (2) parallel, distributed and emergent processing, (3) coordination and opportunistic integration of several tasks in real time, (4) use of several abstraction or context levels for the different types of information that participate in the processing network, (5) decision making, and (6) cognitive capabilities such as adaptive action selection, memory and learning.

In Fig. 1, the structure of this AA model can be appreciated. Three main components define the structure: the blackboard, the internal autonomous agents and interface autonomous agents. The blackboard represents the cellular compartments. Different levels in the blackboard correspond to different cellular compartments through which the signal transduction takes place. In this way, the cellular membrane, the cytoplasm and the nucleus could be represented as different blackboard levels.

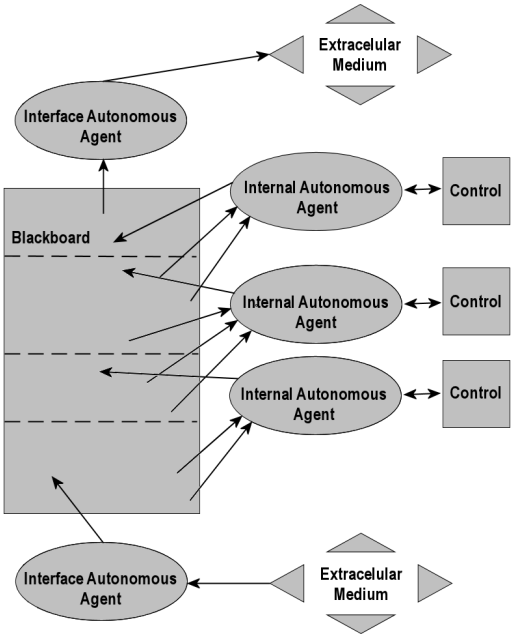

Fig. 1. Architecture of the AA model

The solution elements recorded on the blackboard represent two main types of intracellular signals: signaling molecules and activation or inactivation signals. Both types of signals are synthesized or created by internal autonomous agents (IAA). An IAA obtains a signal or combination or signals from a determinate blackboard level and transduces these into other signals on the same or other blackboard level. The way in which a signal is transduced depends of the cognitive capabilities of the IAA. On the other hand, the function of an interface autonomous agent (IfAA) is to establish the communication between the blackboard and the external medium. Not all external signals or combinations of these are recognized by an IfAA; this recognition depends both of the signal characteristics and the cognitive capabilities of the IfAA. IfAA's model the cell surface receptors and the mechanisms for the production of signaling molecules. Each agent, independently of its type, has a condition part and an action part. The way in which both parts are linked depends on the complexity of the intracellular component modeled by the agent. For this reason, agents which model complex components could use more advanced techniques, such as neural networks, or any combination of other techniques, to link both parts. Agents which model less complex components could use less sophisticated but useful techniques, such as Boolean networks or others.

4.2 Intercell communication

The most natural model for intercell communication is a topological network, i.e. a system of nodes with connecting links. The two limiting network topologies typically considered are: (i) *d*-dimensional graphs - a lattice, for example - where every node connects with a well-defined set of closest neighbors, and (ii) random graphs, where every node has the same probability of being connected to any other node. Quantities used to quantitatively describe networks include:

- The minimum number of links that must be traversed to travel from node *i* to node *j*, that is called the shortest path length or distance between *i* and *j*. A graph is connected if any node can be reached from any other node; otherwise the graph is disconnected. The average path length is the average of the minimum number of steps necessary to connect any two nodes in a connected network.;
- The local clustering is the number of actual links in a local sub-network divided by the number of possible links;
- The degree distribution, $p(k)$, is the probability of finding a node with k links. In a lattice $p(k)$ is a delta-Kronecker function while in a random graph it is a Poisson distribution.

Real networks, however, are not well described by either model because they are both clustered (high degree of local connectivity) and small-worlds (it takes only a small number of steps to connect any two nodes). A recurrent characteristic of networks in complex systems is the small-world phenomenon, which is defined by the co-existence of two apparently incompatible conditions, (i) the number of intermediaries between any pair of nodes in the network is quite small and (ii) the large local redundancy of the network - i.e., the large overlap of the circles of neighbors of two network neighbors. The latter property is typical of ordered lattices, while the former is typical of random graphs [10].

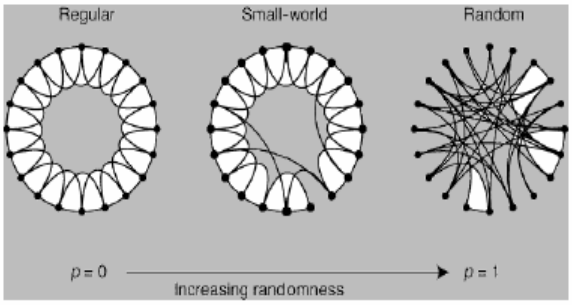

Fig. 3. A minimal model for generating small-world networks

Recently, Watts and Strogatz [11] proposed a minimal model for the emergence of the small-world phenomenon in simple networks. In their model, small-world networks emerge as the result of randomly rewiring a fraction p of the links in a d-dimensional lattice (Fig. 3, after [11]). The parameter p enables one to continuously interpolate between the two limiting cases of a regular lattice ($p = 0$) and a random graph ($p = 1$).

An important characteristic of a graph that is not taken into consideration in the small-world model of Watts and Strogatz is the degree distribution, i.e., the distribution of number of connections of the nodes in the network. The Erdos-Renyi class of random graphs has a Poisson degree distribution, while lattice-like networks have even more strongly peaked distributions—a perfectly ordered lattice has a delta-Dirac degree distribution. Similarly, the small-world networks generated by the Watts and Strogatz model also have peaked, single-scale, degree distributions, i.e., one can clearly identify a typical degree of the nodes comprising the network. Against this theoretical background, Barabasi and Albert found that that a number of real-world networks have a scale-free degree distribution with tails that decay as a power law. They suggested that consequently scale-free networks emerge in the context of growing network in which new nodes connect preferentially to the most connected nodes already in the network.

Significantly, scale-free networks provide extremely efficient communication and navigability as one can easily reach any other node in the network by sending information through the "hubs", the highly-connected nodes. The efficiency of the scale-free topology and the existence of a simple mechanism leading to the emergence of this topology led many researchers to believe in the *complete* ubiquity of scale-free network. Note that scale-free networks are a subset of all smallworld networks (but the inverse may not be true) because (i) the mean distance between the nodes in the network increases extremely slowly with the size of the network and (ii) the clustering coefficient is larger than for random networks. In fig.4 a graph model present a scale free network and is property of assortativity.

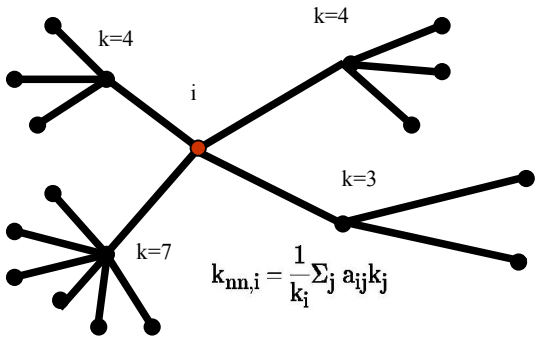

Fig. 4. A scale free network graph

For the example in fig. 4 we have:

$$k_i=4;\ k_{nn,i}=(3+4+4+7)/4=4.5$$

In our approach to model intercellular communication in SEPSIS, the basic network model consists of cell types as nodes and of *intercellular* signaling species (first messengers) connecting the nodes. Because communication between cell types occurs in an explicit direction and various kinds of communication might exist, the resulting graph is directed. Between each node pair multiple edges (in both directions) are possible. Also edge weights (at least for the name/type of the connection) are necessary to reflect biological communication in a realistic manner. Thus, we do not model each individual cell, but the principal connections between cell types. In contrast to most other network models investigated recently this *intercellular* network possesses connectivity complexity rather

than node complexity. The number of cell types in the human body is small (approximately 200) and fixed. The number of edges in contrast is principally orders of magnitude higher and varies over time. So, one of the challenges for future work will be to deal analytically and explanatory with this kind of complexity. Because it is not clear from the data, whether ligands from a ligand-receptor interaction will always establish communication these connections are called *potential communication.* The resulting bipartite graphs might need more sophisticated analyzing methods, but could serve as a base for dynamical modeling the *intercellular* communication for its similarity to scale-free nets.

6 Conclusions

The common characteristic of all complex systems is that they display organization without any external organizing principle being applied; a central characteristic is adaptability. Complex systems are about adaptation, self-organization and continuous change; the best metaphor may be a biological system. In this work we focus on SEPSIS, one of the more complicated processes due to the diversity of involved cellular pathways.

The paper tries to answer to some essential questions? As far as modeling is concerned, what has already been tried? Which research groups exist, and what is their approach? What kinds of models for networks exist? What kind of data is needed to support the various models? These answers allow to construct two dedicated mechanism for both intracellular and intercellular communication. The first is an agent-based system where cognitive capabilities are coded using behavior based paradigms and the blackboard architecture, combined with other artificial intelligence techniques. Recruiting these techniques, the complexity of the topology and cognitive capacities of intracellular signaling system can be studied. The second is a highly inhomogeneous scale-free network in which a few highly connected cells play a central role in mediating interactions among numerous, less connected cells. There will be a lot of future work to make this model efficient, especially by using its self-similarity property in order to decide only of a few numbers of connections. One possible function of this model is to activate output only if the input signal is persistent and to allow a rapid deactivation when the input goes off [12].

The edge complexity could be reduced in different respects. However, meaningful measures and intuitive visualization still need to be developed. For instance a clustering of the network derived from the connectivity distribution of the nodes might show sub-networks of intense communication or the impact of distinct nodes for the whole system. Network modeling, quantitative analysis and laboratory experiments have to be combined in various ways to gain new insights.

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