Chemical Organization Theory Applied to Virus Dynamics

Theorie chemischer Organisationen angewendet auf Infektionsmodelle

Naoki Matsumaru, Florian Centler, Pietro Speroni di Fenizio, Peter Dittrich, Friedrich-Schiller-University Jena

Summary

Chemical organization theory has been proposed to provide a new perspective to study complex dynamical reaction networks. It decomposes a reaction network into overlapping sub-networks called organizations. An organization is an algebraically closed and self-maintaining set of molecular species. The set of organizations form a hierarchical “organizational structure”, which is here a lattice. In order to evaluate the usefulness of this approach we apply the theory to five models of immune response to HIV infection. We found four different lattices of organizations, which can be used as a first classification of the models. Furthermore, each organization found can be assigned to a functional state of the system. And finally, the lattice of organizations can be used to explain a treatment strategy on a more abstract level, i.e., as a movement from one organization into another.

1 Introduction

Biochemical reaction networks in living cells are highly interconnected. In order to tackle their complexity, network theory has been successfully applied in their analysis [2]. A systematic analysis of many biological organisms revealed design principles in metabolic networks that enhance robustness and fault-tolerance of these systems [16]. Structural features contributing towards robustness in biological systems are for example feedback loops, redundancy, and modularity [28]. Such properties are vital for living organisms as they continuously have to adapt to an ever-changing environment. Because a failure of metabolite production can be fatal, analysis of metabolic networks with respect to the minimum set of reactions necessary to maintain the production leads to an understanding of the fragility of the system [17]. Adaptive properties of biological processes are structurally supported by biochemical reaction networks [3]. Although interactions within biochemical networks also include physiological effects, conformational change, and spatial constitution (cf. [8]), topological features of the reaction network have been emphasized for reliable information processing [18]. Furthermore it should be noted that natural organisms have been used as a source of inspiration for implementing artificial information processing systems [9; 10].

Precise description of the dynamical behavior of these systems requires knowledge of the kinetics and the parameters for each reaction. However, several aspects of the dynamical behavior can already be inferred from the static...
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structural information of the reaction network [1]. Correlations between the stability of steady states and the stoichiometric matrix have been studied by Clarke [6; 7]. Under steady state assumptions, feasible flux distributions of metabolic networks are also obtained from the stoichiometry information [25; 26]; and conclusions about equilibrium states and their uniqueness can then be drawn using methods developed by Feinberg and Horn [14]. Further assuming a maximum bacterial growth rate, a metabolic network reconstructed from genome sequence data has been tested with experimental data [13]. When modelling biochemical reaction networks with petri nets [23; 24], the concepts of liveness, reachability, t-invariants, and p-invariants imply potential dynamical behaviors [19].

An advantage of these approaches is that kinetic parameters, which are scarce in biological data, are not required. The analysis method investigated in this paper and described in the next section, operates on the same level of abstraction. That is, an algebraic analysis of the reaction network explains the dynamical behavior of the system. As a demonstration of how the theory connects network structure with dynamical behavior, biochemical reaction networks underlying HIV immunology models are investigated.

2 Chemical Organization Theory

Inspired by Fontana and Buss [15], chemical organization theory has been introduced [11; 27] aiming at an understanding of dynamical complex biochemical processes just taking stoichiometry into account. An organization is defined as a set of molecular species that is (algebraically) closed and (dynamically) self-maintaining. The first property, closure, ensures that applying any reaction rule to members of an organization generates its members only; the second property, self-maintenance, is a theoretical capability of an organization to maintain all of its members. Those two properties, independent of the type of reaction dynamics assumed, stabilize qualitative states of a reaction vessel: Neither new molecular species appear, nor does any existing molecular species disappear. When the theory is applied, a reaction network is decomposed into overlapping sub-networks, forming a partial hierarchy of organizations. The hierarchy is used to describe the potential dynamical behavior of the reaction system as a movement between organizations. Only stoichiometric information is required to identify all organizations, making the method well suited for biological networks where kinetic data is often scarce. In contrast to other methods, no steady state assumptions are made so that dynamical behaviors of accumulating mass are also considered. Note also that using the closure property alone can already provide a powerful tool to get insight into the structure and function of a large network consisting of several thousands of compounds [12].

The organizations of the reaction networks studied in this paper form a lattice. A lattice is an algebraic structure that consists of a set of elements and two operations, union and intersection; such that given any two elements of the lattice, both their union and their intersection are elements of the lattice. A lattice can be visualized by a Hasse-diagram. Here the vertical position of an organization is determined by the number of molecules it contains. The largest organization, which always exists in a finite lattice, can be found at the top of the Hasse-diagram. At the bottom, we can see the smallest organization. Two organizations are connected by a line if the upper organization contains all species of the lower organization and there is no other organization in between them. The Hasse-diagram represents the hierarchical organizational structure of the reaction network under study.

A theorem links the dynamics of the system with the lattice of organizations by stating that each fixed point of the dynamical system is an instance of an organization. As such the organizational study can be used to find out what possible sets of molecules might be contained in a steady state. In our example the resulting steady states where already well known, and as such the results are not surprising. Yet, as predicted, they were all instances of organizations; practically confirming the possibility to use the theory as a first analysis of a system.

3 Results

Applying chemical organization theory to chemical reaction networks reveals the organizational structure of the model. Since virus (HIV) dynamics are modelled with a set of ordinary differential equations (ODEs), translation of the models into a collection of chemical reaction rules is necessary. The results of analyzing five viral dynamics models with chemical organization theory are summarized in Table 1. The level of abstraction increases from left to right. Moving from right to left requires additional information, e.g., reaction kinetics to construct an ODE model from the network model. Depending on the purpose of the model, the appropriate level must be chosen carefully. Exact quantitative analysis of the model behavior is possible with ODE models, but estimating kinetic parameters is critical as pointed out in [30]..

3.1 Basic Model

The HIV infection process involves mainly three molecular species: uninfected T cells x, infected T cell y, and free virus particles v. Provided that the concentration of each species is specified by x, y, and v, respectively, the infection dynamics can be modeled as follows [21]:

\[
\dot{x} = \lambda - dx - \beta xv \\
\dot{y} = \beta xv - a y \\
\dot{v} = ky - uv.
\]
Table 1: Three levels of model abstraction. The level of abstraction increases from left to right, and additional information is required to lower the abstraction level. At the highest abstraction level, we take organizations (sets of molecular species that are closed and self-maintaining) to understand and describe the dynamical behavior. See text for details.

<table>
<thead>
<tr>
<th>ODE Model</th>
<th>Reaction Network Model</th>
<th>Organizational Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: (M. A. Nowak, C. R. M. Bangham: ( \text{Science 272, 5258 (1996), 74-79.} ))</td>
<td>( \emptyset \to x )</td>
<td>( {x,y,v} )</td>
</tr>
<tr>
<td>( \dot{x} = \lambda - \delta x - \beta xv )</td>
<td>( x \to \emptyset ) ( \emptyset \to x )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>( \dot{y} = \beta xv - ay )</td>
<td>( y \to \emptyset ) ( \emptyset \to y )</td>
<td>( {x,y,v} )</td>
</tr>
<tr>
<td>( \dot{v} = ky - uv )</td>
<td>( v \to \emptyset ) ( \emptyset \to v )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>B: (M. A. Nowak, C. R. M. Bangham: ( \text{Science 272, 5258 (1996), 74-79.} ))</td>
<td>( \emptyset \to x )</td>
<td>( {x,y,v,z} )</td>
</tr>
<tr>
<td>( \dot{x} = \lambda - \delta x - \beta xv )</td>
<td>( x \to 0 ) ( \emptyset \to x )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>( \dot{y} = \beta xv - ay - pyz )</td>
<td>( y \to 0 ) ( \emptyset \to y )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>( \dot{v} = ky - uv )</td>
<td>( v \to 0 ) ( \emptyset \to v )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>( \dot{z} = cyz - bz )</td>
<td>( z \to 0 ) ( \emptyset \to z )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>C: (D. Wodarz, M.A. Nowak: ( \text{PNAS 96, 25 (1999), 14464-14469.} ))</td>
<td>( \emptyset \to x )</td>
<td>( {x,y,v,z} )</td>
</tr>
<tr>
<td>( \dot{x} = \lambda - \delta x - \beta xy )</td>
<td>( x \to 0 ) ( \emptyset \to x )</td>
<td>( {x,y} )</td>
</tr>
<tr>
<td>( \dot{y} = \beta xy - ay - pyz )</td>
<td>( y \to 0 ) ( \emptyset \to y )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>( \dot{w} = cxyw - cwyw - bw )</td>
<td>( w \to 0 ) ( \emptyset \to w )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>( \dot{z} = cwyw - kx )</td>
<td>( z \to 0 ) ( \emptyset \to z )</td>
<td>( {x} )</td>
</tr>
<tr>
<td>D: (D. S. Callaway, A. S. Perelson: ( \text{Bull. Math. Biol. 64 (2002), 29-64.} ))</td>
<td>( \emptyset \to Q )</td>
<td>( {x,y,v,y,v,B} )</td>
</tr>
<tr>
<td>( Q = \xi - fQ - \theta (u + B)Q )</td>
<td>( Q \to 0 ) ( Q \to 0 )</td>
<td>( {Q,x,y,v,y,v,B} )</td>
</tr>
<tr>
<td>( \dot{x} = s(\theta (u + B)Q - dx )</td>
<td>( x \to 0 ) ( x \to 0 )</td>
<td>( {Q,x,y,v,y,v,B} )</td>
</tr>
<tr>
<td>( -(1 - \kappa) 2xv )</td>
<td>( y \to 0 ) ( y \to 0 )</td>
<td>( {Q,x,y,v,y,v,B} )</td>
</tr>
<tr>
<td>( \dot{y} = (1 - \kappa) 2xv - ay )</td>
<td>( y \to 0 ) ( y \to 0 )</td>
<td>( {Q,x,y,v,y,v,B} )</td>
</tr>
<tr>
<td>( \dot{v} = N_T vy - uv )</td>
<td>( y \to 0 ) ( y \to 0 )</td>
<td>( {Q,x,y,v,y,v,B} )</td>
</tr>
<tr>
<td>E: (A.S. Perelson, et al.: ( \text{Science 271, 5255 (1996), 1582-1586.} ))</td>
<td>( \emptyset \to x )</td>
<td>( {x,y,v_1,v_{N1}} )</td>
</tr>
<tr>
<td>( \dot{x} = \lambda - \delta x - (1 - \kappa)kv_1x )</td>
<td>( x \to 0 ) ( x \to 0 )</td>
<td>( {x,y,v_1,v_{N1}} )</td>
</tr>
<tr>
<td>( \dot{y} = (1 - \kappa)kxv_1 - vy )</td>
<td>( v_1 \to 0 ) ( v_1 \to 0 )</td>
<td>( {x,y,v_1,v_{N1}} )</td>
</tr>
<tr>
<td>( \dot{v_1} = (1 - \eta)N_T \delta x - cv_1 )</td>
<td>( v_{N1} \to 0 ) ( v_{N1} \to 0 )</td>
<td>( {x,y,v_1,v_{N1}} )</td>
</tr>
<tr>
<td>( \dot{v_{N1}} = \eta N_T vy - cv_{N1} )</td>
<td>( x + v \to y + v ) ( y \to y + v )</td>
<td>( {x,y,v_1,v_{N1}} )</td>
</tr>
</tbody>
</table>

Since the deterministic ODE model is contrived on a basis of interactions between molecular species, the infection process can be represented as a form of chemical reaction network. Since uninfected T cells are produced at a constant rate \( \lambda \), molecular species \( x \) is considered as an input species, resulting in the reaction rule: \( \emptyset \to x \). Each species is assumed to decay in the ODE model. As a reaction rule, each species is transformed into the empty set: \( x \to \emptyset \), \( y \to \emptyset \), and \( v \to \emptyset \).

The infection with HIV transforms an uninfected T cell \( x \) into an infected cell \( y \), which is denoted by
The term $\beta$ represents the rate of virus production by infected cells. This interaction can be described by the ODE model as $\dot{x} = \beta x y$. The term $\dot{y}$ is also included in the right-hand side of the equation. The term $\dot{z}$ is derived from the ODE model by considering the self-maintaining sets of molecular organizations. The smaller organization contains only uninfected cells, while the larger organization contains all three molecular species. The equilibrium of the ODE model corresponds to the two organizations.

3.4 Quiescent Cell

Since the target cell must be activated by the infection, the term $\dot{Q}$ is associated with the activation of the infected cell. The ODE model is constructed as follows:

$$\dot{Q} = \lambda - dQ - BQ - dQ$$

The term $\lambda$ represents the conversion of quiescent cells into activated cells. The term $dQ$ represents the decay of quiescent cells. The term $BQ$ represents the infection of quiescent cells by the virus. The term $dQ$ is the decay rate of the quiescent cell species.

Mathematical analysis of the model reveals the existence of two distinct equilibrium states: an infected state and a non-infected state. The smaller organization corresponds to the non-infected state, while the larger organization corresponds to the infected state. The ODE model is solved to determine the conditions under which the system can reach the infected state.

Conclusion

The Chemical Organization Theory applied to virus dynamics provides a new perspective on the interaction between the virus and the host cell. The ODE model and the Chemical Organization Theory are complementary tools for understanding the dynamics of viral infections.

References

[1] Chemical Organization Theory Applied to Virus Dynamics

[2] Mathematical Analysis of the ODE Model

[3] Equilibrium States of the ODE Model


[5] Mathematical Analysis of the ODE Model
and self-maintaining. The other organization indicates the activation of the quiescent cell by the other antigen B. Both organizations contain the activated form of the T cell x. They only differ in the antigen responsible for the infection. The analysis using organization theory allows to distinguish between the two infection scenarios.

### 3.5 Drug Effect

Perelson et al. [22] developed a viral dynamics model to analyze the effects of two antiretroviral drug treatments. The reverse transcriptase inhibitor, blocking the infection with HIV, is represented in the model as coefficient \(1 - \kappa \) \((0 \leq \kappa \leq 1)\). High efficacy of the drug corresponds to \(\kappa \approx 1\). We should note that the perfect inhibitor is represented by \(\kappa = 1\), and set \([x]\) is the only organization although it is impractical to assume perfect inhibitions. The second antiviral drug, the protease inhibitor, impairs the protein synthesis process in the cell with efficacy \(\eta\) so that infected T cell y produces non-infectious virus \(v_{\text{NI}}\): \(y \rightarrow y + v_{\text{NI}}\). When the inhibition failed with probability \(1 - \eta\), the HIV reproduction reaction becomes \(y \rightarrow y + v\) where \(v\) represents normal infectious free virus.

Considering also the extreme values of drug efficacy \(\eta\), there are three different networks with respect to the proliferation of HIV giving rise to three different organizational structures. In case the drug is not applied to the patient or does not have any effect \((\eta = 0)\), only the infectious virus is generated. This is identical case with the HIV infection model discussed before. The smallest organization is the set containing only uninfected T cell x, and above it, free virus particle v and infected T cell y are joined to form the organization. By setting \(\eta = 1\), perfect inhibition of the infectious virus proliferation is modelled and only the non-infectious virus is produced from the infected T cell. The organization corresponding to the virus infected state is, in this case, composed of non-infectious virus \(v_{\text{NI}}\) instead of the infectious type. Statistically speaking, however, reproduction processes of both infectious and non-infectious virus are present in the dynamical reaction system, and the efficacy parameter is set to a value within \(0 < \eta < 1\) to model the practical situation. If both of the reactions are included in the network simultaneously, the set containing both infectious and non-infectious virus is found to be an organization.

### 4 Discussion

In this study we have shown that different models of immune response to HIV infection possess different lattices of organizations. As we can see in Table 1, a lattice provides a quick overview of the model’s structure and its potential dynamics. We can see which kind of species together can constitute a steady state, namely exactly those forming an organization.

The difference in organizational structure (naturally) reflects the way the model has been extended. For example, changing the basic model by adding the immune response (Table 1, Row 1 and 2) results in a new organization to appear, which represents the infection antagonized by the immune response \(z\). Extending the model does not necessarily change the lattice structure, as shown by the CTL memory model (Table 1, Row 3). The intention of the modelers is to emphasize effects of CTL memory precursor \(w\) for long-term viral load control mediated by CTL. The ODE model is designed for a steady state to contain both the CTL precursor and CTL effector \(z\). This design principle is realized in the organizational structure as the largest organization to contain both the precursor and the effector.

The fourth model is an example for extending Model A such that the organizations are not arranged in a chain in the Hasse diagram. The main concern of the model developers is to include quiescent cells Q, but the reason of the lattice structure not being in a chain is the general antigen B in addition to HIV virus particle v. From the organizational structure, both antigens B and v appear with activated T cell x. Only v of the two antigens is associated with infected T cell y, as intended by the model design.

Through the last model (Table 1, Row 5), we demonstrate how parameters could be handled in the static reaction network analysis. The quantity of some parameters determines the reaction network structure leading to different results of the static analysis. The efficacy of protease inhibitors represented by \(\eta\) is our example. Infected T cell y probabilistically produces infectious virus \(v\) or non-infectious virus \(v_{\text{NI}}\) as shown in the reaction network model of ODE Model E. Seeing the reaction as a stochastic process, the network structure alternates between them. When analyzing such a network with chemical organization theory, three cases are considered depending on the value of \(\eta\). Two of them are described as the success and the failure of the protease inhibitions represented by \(\eta = 0\) and \(\eta = 1\), respectively. The other case \(0 < \eta < 1\) takes a probabilistic view such that both reactions (infectious and non-infectious virus proliferation) occur in the whole system. We obtained lattices that differ only in their species composition. The other important parameter in this model \(\kappa\), the efficacy of reverse transcriptase inhibitors, affects the results of our analysis in a trivial way.

Here, we would like to show that the strategy of a drug treatment can be explained on a relatively high (i.e., less detailed) level of abstraction using the lattice of organizations, namely as a movement from an organization representing an ill state to an organization representing a healthy state (see [20] for details). In Fig. 1 two strategies are illustrated for the model of Wodarz and Nowak [29].
first one tries to move the system into the smallest organization \(\{x\}\), where no virus is present at all. An alternative strategy may move the system into the largest organization, where the virus is present, but also an immune system response controlling the virus. There are drugs available that can bring down the virus load by several orders of magnitude. If by this procedure the virus could be completely removed, the system would move into the smallest organization, because set \(\{x, w, z\}\) is not self-maintaining and thus the system moves down into organization \(\{x\}\). However, it has been observed that although the virus load can be decreased below detection limit, the virus cannot be fully removed. Hence, after stopping the treatment the virus will reappear. Therefore, the actual strategy described by Wodarz and Nowak is not to move the system into the lowest organization, but into the highest organization. In practice, this is achieved by applying the drug periodically allowing the immune defense to increase [29].

It is important to note that choosing the right level of abstraction depends on what should be explained. The lattice of organizations is a suitable level of abstraction for describing the overall strategy. However, how an actual drug treatment should look like in order to move the system into the largest organization cannot be answered by chemical organization theory. For this we have to choose a more detailed level of abstraction, e.g., the ODE model, which provides information on how the system can move from one organization to another.

In summary we can conclude from our study that the theory of chemical organizations appears as a useful tool, which creates a first, rough map of the structure and potential dynamical behavior of a reaction system. The obtained scaffold, i.e., the lattice of organizations, can guide further more detailed analysis, which may study the dynamics within or in-between organizations using classical tools from dynamical systems theory. The results of more detailed studies can in turn be explained and summarized with respect to the lattice of organizations resulting in a global picture.

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References


[17] S. Klant and E.D. Gilles. Minimal cut sets in biochemical reaction...


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