A Case Study of Chemical Organization Theory Applied to Virus Dynamics

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Abstract. 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. In order to evaluate the usefulness of this approach we apply the theory to a model by Wodarz and Nowak (*Proc. Natl. Acad. Sci. USA*, **96**(25):14464–9, 1999) describing the interaction of a virus (HIV) with immune system cells. We found three organizations, one above the other, which imply two treatment strategies: One that tries to move the system into the smallest organization containing no virus, and a second one, which is actually used in practice, moving the system into the largest organization, which contains the virus in addition to an immune response controlling the virus.

1 Introduction

Dynamical reaction network models of biological systems are rapidly increasing in size [1, 2]. In order to harness their complexity, automatic analysis methods that allow to uncover inherrent structures in these models are required [3]. Several methods have been developed to analyze the network's dynamical behavior just by considering its structural properties. When modelling biochemical reaction networks with petri nets [4, 5], the concepts of liveness, reachability, t-invariants, and p-invariants allow to investigate its potential dynamics, including steady state situations [6]. Clarke introduced stoichiometric network analysis to study stability in chemical networks [7, 8]. Metabolic pathway analysis [9] has been used to obtain feasible flux distributions of networks under steady state assumptions. Conclusions about equilibrium states and their uniqueness can be drawn using methods developed by Feinberg and Horn [10]. Here, we introduce chemical organization theory [11, 12] as another method to analyse reaction networks solely based on stoichiometry, allowing profound conclusions about the networks potential dynamics. The network is decomposed into sub-networks called organizations. These sub-networks are not separated but may overlap,

forming a hierarchy that represents the structure of the reaction network. This hierarchy of organizations is closely related to the potential dynamical behavior of the system. In contrast to other methods, no steady state assumptions are made, so that sub-networks that accumulate mass are also considered. Furthermore, our approach provides concepts for describing the dynamics of the system as a movement between organizations. In order to evaluate the properties of the theoretical concepts, we apply the theory to a model by Wodarz and Nowak [13] describing the interaction of a virus (HIV) with the immune system. The model, a four-dimensional ODE system, is relatively small so that we can use the results of a mathematical analysis to validate the outcome of our method.

2 Chemical Organization Theory

The aim of the theory of chemical organization [11, 12] is to elucidate the structure and potential dynamics of complex reaction systems. Inspired by Fontana and Buss [14], the theory allows to decompose a given reaction network into algebraically closed and self-maintaining sub-networks called *organizations*. The first property — closure — ensures that given an organization as a set of molecular species, there exists no reaction that is able to produce species not yet present in the organization using only species of that organization. In other words: An organization cannot produce any new species not yet present in the organization. We should note 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 [15].

Self-maintenance, the second requirement, guarantees that, at least in principle, all species within an organization can be produced at non-negative rates from within the organization. Independent of type of reaction dynamics assumed, all species in the organization are persistent in time. Only stoichiometric information is required to identify the set of all possible organizations, making the method well suited for biological networks, where kinetic data is often scarce.

In the following we go into more detail and present the concepts of the theory formally.

2.1 Starting Point

The starting point when applying the theory is a reaction network given by a set of molecular species $\mathcal{M}$ and a set of reaction rules $\mathcal{R}$. The theory assumes that the topology of the reaction network is known. The aim of the theory is to (1) reveal the hierarchical structure of the network, (2) predict potential dynamical behavior, (3) describe the dynamics with respect to the network's structure.

The structure of the network will be described by the set of organizations, which form a hierarchical and overlapping structure. An organization is a closed and self-maintaining set of molecular species. This approach abstracts the state of a reaction systems by a set of species that are present in that state. In other words, instead of taking, e.g., a concentration vector to represent the state of a

reaction system, we take the set of molecular species that have concentrations above zero (or above a small positive threshold Θ).

In the following, we denote sets and multisets of molecules[1] by upper cases characters, such as $A, B \subseteq \mathcal{M}$. Note that by the very nature of a set, a molecule from $\mathcal{M}$ can only appear once in a set A. The set of all sets of molecules is denoted by $\mathcal{P}(\mathcal{M})$ (power set). We use multisets in order to represent the left hand side and the right hand side of reaction rules. A multiset is like a set, but the same molecule can appear several times. $\mathcal{P}_M(C)$ denotes the set of all multisets with elements from C, e.g., $\mathcal{P}_M(\{a, b\}) = \{\{\}, \{a\}, \{b\}, \{a, b\}, \{a, a\}, \{a, b\}, \{b, b\}, \{a, a, a\}, \dots\}$. The frequency of occurrence of an element a in a multiset A is denoted by $\#(a \in A)$.

Definition 1. *Given a set $\mathcal{M}$ of molecular species and a set of reaction rules given by the relation $\mathcal{R} : \mathcal{P}_M(\mathcal{M}) \times \mathcal{P}_M(\mathcal{M})$. We call the pair $\langle \mathcal{M}, \mathcal{R} \rangle$ an* algebraic chemistry.

For simplicity, we adopt a notion from chemistry to write reaction rules. Instead of writing $(\{s_1, s_2, \dots, s_n\}, \{s'_1, s'_2, \dots, s'_{n'}\}) \in \mathcal{R}$ we write: $s_1 + s_2 + \dots + s_n \to s'_1 + s'_2 + \dots + s'_{n'}$. We also equivalently rewrite $a + a \to b$ to $2a \to b$. Note that "+" is not an operator here, but is used to separate the elements on both sides. Given the left hand side species $A = \{s_1, s_2, \dots, s_n\}$ and the right hand side species $B = \{s'_1, s'_2, \dots, s'_{n'}\}$, we write $(A \to B) \in \mathcal{R}$ instead of $(A, B) \in \mathcal{R}$. $A \to B$ represents a chemical reaction equation where A is the multiset of species on the left hand side (also called *reactants*) and B the multiset of species on the right hand side (also called *products*).

An algebraic chemistry is basically a reaction network, which represents the structure of a reaction system. Alternatively we might represent the reaction network by a directed bipartite graph, which consists of two node types: species and rules. An algebraic chemistry contains information about the stoichiometry, but no further details concerning the dynamics. Note that Def. 1 allows to define reaction rules or reaction networks that are not balanced, such as, $\{a \to a + b\}$ or $\{2a \to b,\ b \to a\}$, respectively. In chemistry, we usually demand that after a chemical reaction mass is conserved, i.e. the mass on the left hand side of a reaction rule is equal to the mass on its right hand side. Chemical organization theory was made to also handle systems that are not balanced and where mass is not necessarily conserved. An example is the HIV model investigated here.

2.2 Stoichiometric Matrix and Differential Equations

A common approach to describe chemical reaction systems is by a stoichiometric matrix, which can be used to derive an ordinary differential equation (ODE) model for the dynamics of the system, e.g., based on mass action kinetics. Given a reaction system with m molecules and n reactions the *stoichiometric matrix*

[1] We use the terms "molecular species", "species", and "molecule" synonymously.

$\mathbf{M}$ has the form:

$$\mathbf{M} = \begin{pmatrix} m_{1,1} & m_{1,2} & \dots & m_{1,n} \\ m_{2,2} & m_{2,2} & \dots & m_{2,n} \\ \dots & \dots & \dots & \dots \\ m_{m,1} & m_{m,2} & \dots & m_{m,n} \end{pmatrix} \tag{1}$$

where each row corresponds to a molecular species and each column to a reaction rule. An ODE describing the dynamics of the concentration vector $\mathbf{x} \in \mathbb{R}^m$ can be defined by

$$\dot{\mathbf{x}} = \mathbf{M}\mathbf{v}(\mathbf{x}) \tag{2}$$

where $\mathbf{v}(\mathbf{x}) = (v_1(\mathbf{x}), \dots, v_n(\mathbf{x}))^T \in \mathbb{R}^n$ is a flux vector describing the rate of each reaction depending on the current concentrations $\mathbf{x}$. When we assume mass action kinetics – as in the HIV model – an element v_j of $\mathbf{v}(\mathbf{x})$ is simply a product of concentrations of the reactants participating in reaction j (cf. Eq. (6)).

Note that $\dot{x}_i$ denotes the current production rate of molecular species i. In the following we will denote the production rate of molecule i by $f_i := \dot{x}_i$.

2.3 Static Concepts

We will now define the central concept of the theory, namely the organization as a closed and self-maintaining set of molecules. This definition does not refer to the dynamics as might be defined by an ODE. The definition refers only to the structure of the reaction system, i.e. the stoichiometry of the reaction rules.

Definition 2. *Given an algebraic chemistry $\langle \mathcal{M}, \mathcal{R} \rangle$ with $m = |\mathcal{M}|$ molecules and $n = |\mathcal{R}|$ reactions, and let $\mathbf{M} = (m_{i,j})$ be the $(m \times n)$ stoichiometric matrix implied by the reaction rules $\mathcal{R}$, where $m_{i,j}$ denotes the number of molecules of species i produced in reaction j. A set of molecules $O \subseteq \mathcal{M}$ is called an* organization*, if there exists a flux vector $\mathbf{v} \in \mathbb{R}^n$ such that the four following condition apply: (1) for all reactions $(A \to B)$ with $A \in \mathcal{P}_M(O)$ the flux $v_{(A \to B)} > 0$; (2) for all reactions $(A \to B)$ with $A \notin \mathcal{P}_M(O)$, $v_{(A \to B)} = 0$; (3) for all molecular species $i \in O$ is the production rate $f_i \geq 0$ (self-maintaining); and (4) for all molecular species $i \notin O$ is the production rate $f_i = 0$ (closure). The production rates are given by $(f_1, \dots, f_m)^T = \mathbf{M}\mathbf{v}$.*

A set C where conditions (1)-(3) apply but not necessarily condition (4) is called *self-maintaining*, since it is possible to maintain all its components from a stoichiometric point of view. If conditions (4) is true for a flux vector that obey rule (1) and rule (2), then the set C is called *closed*. The condition of closure can be defined more easily without referring to possible flux vectors:

Definition 3. *Given an algebraic chemistry $\langle \mathcal{M}, \mathcal{R} \rangle$, a* closed set *$C \in \mathcal{M}$ is a set of molecular species such that for all $A \subseteq C$ the following holds: if there is a reaction $(A \to B) \in \mathcal{R}$, then $B \subseteq C$.*

Given a set S, $S \subseteq \mathcal{M}$, it is always possible to generate its *closure* $G_{CL}(S)$ [16]. To generate the closure of a set we expand it by interacting the molecules of the set and adding to the set any newly generated molecule. When no new molecule is generated, the set is closed.

Definition 4. *Given a set of molecules $S \subseteq \mathcal{M}$, we define $G_{CL}(S)$ as the smallest closed set C containing S. We say that S* generates the closed set *$C = G_{CL}(S)$ and we call C the* closure *of S.*

2.4 Consistent Reaction Systems

We can now define a generate operator for self-maintaining sets in the same way as for closed sets by saying that the self-maintaining set generated by a set S is the biggest self-maintaining set C contained in S. This set C is not unique for arbitrary reaction systems, i.e. for arbitrary algebraic chemistries. We call chemistries where a self-maintaining set can be uniquely generated for any set by the procedure described above *consistent*. The HIV model investigated in Sec. 3 is consistent. In a consistent algebraic chemistry we can always generate uniquely for any given set $S \subseteq \mathcal{M}$ a self-maintaining set C by taking the biggest self-maintaining set C that contains S.

Definition 5. *An algebraic chemistry is called* consistent*, if the closure and self-maintaining set generated by a set can uniquely be defined, i.e. given any set $S \subseteq \mathcal{M}$, the smallest closed set that contains S and the largest self-maintaining set contained in S are unique, respectively.*

If our reaction system is consistent, a couple of interesting properties hold, which are explained in the following. First of all we define "generate self-maintaining set" formally:

Definition 6. *Given a consistent algebraic chemistry $\langle \mathcal{M}, \mathcal{R} \rangle$ and a set of species $S \subseteq \mathcal{M}$, we define $G_{SM}(S)$ as the biggest self-maintaining set C contained in S. We say that S* generates the self-maintaining set *$C = G_{SM}(S)$.*

Since in consistent reaction systems the closure and self-maintaining set can be generated uniquely, we can also uniquely define the organization generated by a set S in the following way:

Definition 7. *Given a set of molecules $S \subseteq \mathcal{M}$, the organization $O = G(S)$ generated by S is defined as $G(S) \equiv G_{SM}(G_{CL}(S))$.*

If O is an organization $G(O) = O$. The organizations are the fixed points of the "generate organization operator" G. The generate operator implies a union and an intersection operator on the set of organizations $\mathcal{O}$ of an algebraic chemistry.

Definition 8. *Given two organizations U and V, the organization generated by their union ($U \sqcup V$) and intersection ($U \sqcap V$) are defined as*

$$U \sqcup V \equiv G(U \cup V), \tag{3}$$

$$U \sqcap V \equiv G(U \cap V). \tag{4}$$

Lemma 1. *Given a consistent algebraic chemistry* $\langle \mathcal{M}, \mathcal{R} \rangle$ *and all its organizations* $\mathcal{O} = \{O \subseteq \mathcal{M} | O \text{ is an organization}\}$*, then* $\langle \mathcal{O}, \sqcup, \sqcap \rangle$ *is an (algebraic) lattice.*

A lattice is an algebraic structure that can be visualized by a Hasse-diagram (Fig. 1, lower right corner). Here the vertical position of an organization is determined by the number of molecules contained in it. 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, which is the organization generated by the empty set. Two organizations are connected by a line if the upper organization contains all species of the lower organization and there is no other organization between them. The Hasse diagram represents the hierarchical organizational structure of the reaction network under study.

We should note in passing that for closed sets and self-maintaining sets we can also define the "closed set intersection" and "self-maintaining set intersection", and the "closed set union" and "self-maintaining set union", respectively, in the same way as for organizations, so that we obtain also a lattice of closed sets and a lattice of self-maintaining sets, whose intersection is the lattice of organizations.

2.5 Dynamics

The static part of the theory (Sec. 2.3) deals with molecules $\mathcal{M}$ and reaction rules $\mathcal{R}$ but not with time. For that reason we have defined the concept of an *algebraic chemistry*, which is sufficient as input for the static part. In order to add dynamics to the theory, we have to formalize the dynamics of a system. In a very general approach, the *dynamics* is given by a *state space* X and a formal definition (mathematical or algorithmical) that describes all possible movements in X, so given an initial state $\mathbf{x}_0 \in X$, the formal definition describes how the state changes over time. Now, for simplicity, we assume a deterministic dynamical process, which can be formalized by a phase flow $(X, (T_t)_{t \in \mathbb{R}})$ where $(T_t)_{t \in \mathbb{R}}$ is a one-parametric group of transformations from X. $T_t(\mathbf{x}_0)$ denotes the state at time t of a system that has been in state $\mathbf{x}_0$ at $t = 0$.

For connecting the static theory with dynamics we introduce a mapping ϕ called *abstraction*, from X to $\mathcal{M}$, which maps a state of the system to the set of molecules that are present in the system being in that state. The exact mapping can be defined precisely later, depending on the state space, on the dynamics, and on the actual application.

The concept of *instance* is the opposite of the concept of abstraction. While $\phi(\mathbf{x})$ denotes the molecules represented by the state $\mathbf{x}$, an instance $\mathbf{x}$ of a set A is a state where exactly the molecules from A are present according to the function ϕ.

Definition 9. *We say that a state* $\mathbf{x} \in X$ *is an instance of* $A \subseteq \mathcal{M}$*, iff* $\phi(\mathbf{x}) = A$*.*

In particular, we can define an instance of an organization O (if $\phi(x) = O$) and an instance of a generator of O (if $G(\phi(x)) = O$). Loosely speaking we can

say that $\mathbf{x}$ *generates organization* O. Note that a state $\mathbf{x}$ of a consistent reaction system is *always* an instance of a generator of one and only one organization O. This leads to the important observation that a lattice of organizations partitions the state space X, where a partition X_O implied by organization O is defined as the set of all instance of all generators of O: $X_O = \{\mathbf{x} \in X | G(\phi(\mathbf{x})) = O\}$. Note that as the system state evolves over time, the organization $G(\phi(\mathbf{x}(t)))$ generated by $\mathbf{x}(t)$ might change. A movement in state space can thus be mapped to a movement in the set of sets of species, and finally to a movement in the set of organizations, which provides a new way of visualizing a trajectory in a high-dimensional state space (see Ref. [11, 12]).

2.6 Fixed Points are Instances of Organizations

In this section we present a theorem [12] stating that every fixed point must be an instance of an organization. In other words, in a continuous dynamical reactions system given by an ODE, we cannot obtain a stationary state with a combination of molecular species that are not an organization. For the theorem, we have to specify formally the abstraction function:

Definition 10. *Given a dynamical system* $\dot{\mathbf{x}} = f(\mathbf{x})$ *and let* $\mathbf{x}$ *be a state in* X*, then the abstraction* $\phi(\mathbf{x})$ *is defined by*

$$\phi(\mathbf{x}) = \{i | x_i > \Theta, i \in \mathcal{M}\}, \quad \phi : X \to \mathcal{P}(\mathcal{M}), \quad \Theta \geq 0 \tag{5}$$

where x_i *is the concentration of molecular species* i *in state* $\mathbf{x}$*, and* Θ *is a threshold chosen such that it is smaller than any positive coordinate of any fixed point of* $\dot{\mathbf{x}} = f(\mathbf{x}), x_i \geq 0$.

Theorem 1. Hypothesis: *Let us consider a general reaction system whose reaction network is given by the algebraic chemistry* $\langle \mathcal{M}, \mathcal{R} \rangle$ *and whose dynamics is given by a differential equation* $\dot{\mathbf{x}} = \mathbf{M}\mathbf{v}(\mathbf{x}) = f(\mathbf{x})$ *as defined before. Let* $\mathbf{x}' \in X$ *be a fixed point, that is,* $f(\mathbf{x}') = \mathbf{0}$*, and let us consider a mapping* ϕ *as given by Def. 10, which assigns a set of molecules to each state* $\mathbf{x}$*.* **Thesis:** $\phi(\mathbf{x}')$ *is an organization. (Proof see Ref. [12].)*

This theorem implies that the organizations of a reaction network represent all species combinations that possibly can occur in fixed points. Hence, the hierarchy of organizations is closely related to the system's potential dynamical behavior. In the presence of kinetic information, concrete fixed points can be computed applying classical tools from dynamical systems theory to each organization seperately. Some organizations will be found to have fixed points while others not. Yet there will be no fixed point that is not related to an organization.

3 Case Study: HIV Immunology Model

In this section, we apply chemical organization theory to a model of immunological control of HIV developed by Wodarz and Nowak [13]. The model has been

developed in order to explain the effect of various drug treatment strategies. Especially it shows, why a drug treatment strategy does not try to remove the virus, but aims at stimulating the immune defense, such that the immune system controls the virus at low but positive quantities. The aim of this section is to show that chemical organization theory can reveal even in such relatively small models a structure (lattice of organizations), which can be used to describe the dynamics of the model and to explain the strategy of a drug treatment from a different perspective.

3.1 The Model

In the model, there are four molecular species: uninfected $CD4^+$ T cells x, infected $CD4^+$ T cells y, cytotoxic T Lymphocyte (CTL) precursors w, and CTL effectors z. The concentration of each species is specified by x, y, w, and z, respectively. The dynamics is given by an ordinary differential equation (ODE) with kinetic parameters $a, b, c, d, h, p, q, \beta$, and λ:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xy \\ \dot{y} &= \beta xy - ay - pyz \\ \dot{w} &= cxyw - cqyw - bw \\ \dot{z} &= cqyw - hz \end{aligned} \tag{6}$$

From the given deterministic ODE model, chemical reaction rules are derived, which form a reaction network, so that the theory can be applied: The ODE model includes a decay term for each species. Therefore, for each species we have a reaction rule transforming each molecular species into the empty set: $\mathsf{x} \to \emptyset$, $\mathsf{y} \to \emptyset$, $\mathsf{w} \to \emptyset$, and $\mathsf{z} \to \emptyset$. We observe in passing that, since all species decay, the set of organizations must be a lattice with one well defined largest and one well defined smallest organization (see Ref. [12] for a proof).

Since the concentration of uninfected $CD4^+$ T cells x increases with a constant rate λ, molecular species x is considered as an input (or inflow) species, resulting in a reaction rule $\emptyset \to \mathsf{x}$.

The infection by HIV viruses transforms a T cell x into an infected T cell y, which is denoted by the term βxy and the reaction rule $\mathsf{x} + \mathsf{y} \to 2\mathsf{y}$. The destruction of the infected $CD4^+$ T cells y by the CTL effectors z as specified by the term pyz is transformed into $\mathsf{y} + \mathsf{z} \to \mathsf{z}$. Note that this is a catalytic reaction with respect to the effector z because the concentration of z is not effected by this reaction. CTL precursor w multiplies with the catalytic help of both the infected and uninfected $CD4^+$ T cell in accordance with the term $cxyw$, which results in the reaction rule $\mathsf{x} + \mathsf{y} + \mathsf{w} \to \mathsf{x} + \mathsf{y} + 2\mathsf{w}$. When the infected $CD4^+$ T cell y is detected by the CTL precursor w, the precursors differentiate into effectors z as captured by the rule $\mathsf{y} + \mathsf{w} \to \mathsf{y} + \mathsf{z}$. The corresponding term in the ODE model is $cqyw$.

The whole set of reaction rules reads: $\mathcal{R} = \{\ \emptyset \to \mathsf{x},\ \mathsf{x} \to \emptyset,\ \mathsf{y} \to \emptyset,\ \mathsf{w} \to \emptyset,\ \mathsf{z} \to \emptyset,\ \mathsf{x} + \mathsf{y} \to 2\mathsf{y},\ \mathsf{y} + \mathsf{z} \to \mathsf{z},\ \mathsf{x} + \mathsf{y} + \mathsf{w} \to \mathsf{x} + \mathsf{y} + 2\mathsf{w},\ \mathsf{y} + \mathsf{w} \to \mathsf{y} + \mathsf{z}\ \}$.

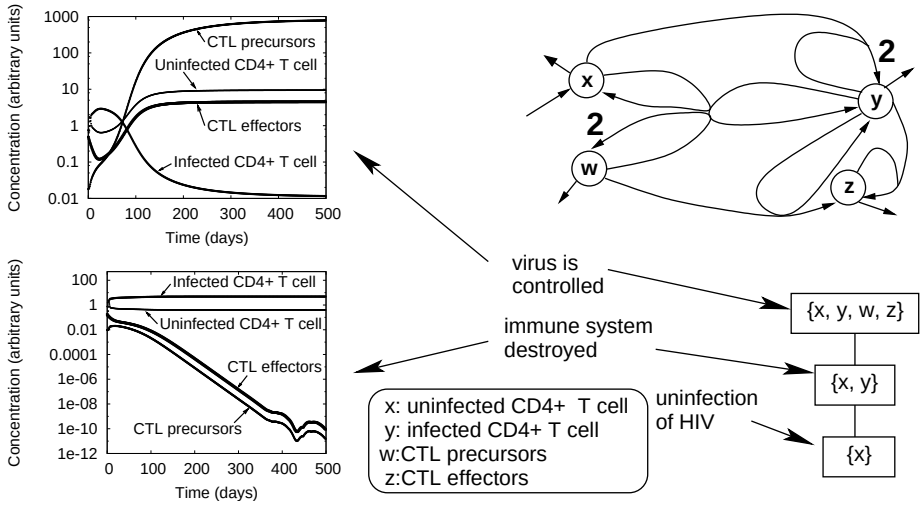

Fig. 1. Illustration of the analysis of the HIV immunological response model by Wodarz and Nowak [13]. The ODE model given in Eq. 6 is transformed to a chemical reaction network (right top). The resulting hierarchy of organizations is shown as a Hasse diagram (right bottom). Two of the organizations represent the attractors: virus under control (top) and immune system destruction (middle). Dynamic simulations leading to both attractors are shown on the left. Parameters were taken from [13] as follows: $\lambda = 1$; $d = 0.1$; $\beta = 0.5$; $a = 0.2$; $p = 1$; $c = 0.1$; $b = 0.01$; $q = 0.5$; $h = 0.1$. Initial concentrations for left, top plot: $x = 0.74$; $y = 0.75$; $w = 0.018$; $z = 0.49$. Initial concentrations for left, bottom plot: $x = 0.75$; $y = 0.14$; $w = 0.0095$; $z = 0.17$.

A graphical representation of the network is shown in Fig. 1, upper right corner. Since the number of molecular species $|\mathcal{M}|$ is four and the size of the reaction rule set $|\mathcal{R}|$ is nine, the stoichiometric matrix $\mathbf{M}$ is the following:

$$\mathbf{M} = \begin{array}{c} \mathsf{x} \\ \mathsf{y} \\ \mathsf{w} \\ \mathsf{z} \end{array} \begin{pmatrix} 1 & -1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 \end{pmatrix}$$

where each row corresponds to a molecular species (x, y, w, z from the top) and each column corresponds to a reactions. As we can see, the stoichiometric matrix does not contain all information of the reaction network. For example, the reaction rule $\mathsf{y} + \mathsf{z} \rightarrow \mathsf{z}$ appears only as the column vector $(0, -1, 0, 0)^T$.

3.2 Lattice of Organizations

For applying the theory we check every possible set of species (i.e. 16 sets) whether it is closed and self-maintaining. As a result we found three organizations. The Hasse diagram is depicted in Fig. 1, lower right corner. The smallest

organization consists only of the "healthy cells" x (uninfected CD4$^+$ T cells). There cannot be a smaller organization (i.e. the empty set) because x is an input species and therefore the empty set is not closed.

Since x is an input species, the set $\{\mathsf{x}\}$ is obviously self-maintaining. Looking at the reaction rules, we can see that x alone cannot produce anything else, thus the set $\{\mathsf{x}\}$ is closed. Formally, we can show that $\{\mathsf{x}\}$ is an organization by choosing a flux vector $\mathbf{v} = (1, 1, 0, 0, 0, 0, 0, 0, 0)^T$, which fulfills all conditions given in Def. 2: all flows within the organization are positive, all flows outside are zero, and $\mathbf{Mv} = (0, 0, 0, 0, 0, 0, 0, 0, 0)^T$ which is not negative in any component.

The second organization, $\{\mathsf{x}, \mathsf{y}\}$, contains "healthy cells" x together with "ill cells" (infected CD4$^+$ T cells). Looking at the reaction network, we can see that $\{\mathsf{x}, \mathsf{y}\}$ is closed, because there is no reaction rule that allows to produce w or z just using x and y alone. We can show that $\{\mathsf{x}, \mathsf{y}\}$ is self-maintaining with the flux vector $\mathbf{v} = (10, 1, 1, 0, 0, 1, 0, 0, 0)^T$ and the production rate $\mathbf{Mv} = (8, 0, 0, 0)^T$.

The largest organization contains all species and is thus obviously closed. From reaction rules, we can see that since x can be produced at an arbitrarily high rate, we can also produce y, z, and w at arbitrarily high rates when we can freely choose the flux vector $\mathbf{v}$. For $\mathbf{v} = (100, 1, 1, 1, 50, 1, 50, 10)^T$, for example, $\mathbf{Mv}$ is positive in all components and therefore $\{\mathsf{x}, \mathsf{y}, \mathsf{w}, \mathsf{z}\}$ is self-maintaining.

3.3 Connecting with Dynamics and Explaining a Drug Treatment Strategy

From a mathematical analysis [13] and simulation studies [17] it is known that the model has two modes of behavior belonging to two asymptotically stable fixed points: One of the attractors is characterized by high virus load and no CTL precursors and effectors present. This state is interpreted as the complete destruction of the immune defense. The organization $\{\mathsf{x}, \mathsf{y}\}$ represents this attractor. When the HIV virus is controlled by the immune defense, all four molecular species are present in the system, constituting the other attractor. This state is reflected in the largest organization $\{\mathsf{x}, \mathsf{y}, \mathsf{w}, \mathsf{z}\}$. The smallest organization $\{\mathsf{x}\}$ can be interpreted as the condition where no CD4$^+$ T cell is infected by the HIV virus.

After identifying the lattice of organizations, we can use it to explain the strategy of a drug therapy: Looking at the lattice of organizations, we can describe two strategies for a drug therapy: The first one tries to move the system into the smallest organizations $\{\mathsf{x}\}$, 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 the set $\{\mathsf{x}, \mathsf{w}, \mathsf{z}\}$ generates[2] organization $\{\mathsf{x}\}$. However, it has been observed that although the virus load can be decreased below detection limit, the virus cannot be fully

[2] Note that we use the word "generate" as a precisely defined technical term.

removed so that the virus appears again after stopping the treatment. Therefore, the actual strategy of a drug therapy 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.

4 Conclusion

We can see that the strategy of a drug treatmen 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. 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 treat 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 chose 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.

From this perspective, the theory of chemical organization 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 set 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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