Theory of Stable Dynamical Systems

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Abstract

During development of a dynamical model to simulate the central T-cell subsystem of the human immune system, its extraordinary stability lead to the assumption that it might be deduced solely from stability considerations. We demonstrate that linear stability conditions together with additional general requirements indeed define a low number (of the order of 10) of dynamical systems from about 10^{10} possibilities for systems with up to four components. At least two of the most simple linearly stable systems play central roles in biology, indicating that stable dynamical subsystems resulting from evolutionary processes might be understood on a mathematical basis. We expect that our dynamical subsystems are generic and will be found as basic building blocks in biological, social or technical systems.

Key words: linearly stable dynamical systems, theoretical analysis, generic structures, immune system, evolution, structural biology.

Introduction

The immune system[1] fulfills the difficult task to attack and eliminate a large variety of unknown invaders (antigens such as viruses, bacteria) without harming the own tissue. Based on extensive research over the last decades, a detailed but still growing model of the dynamics of the immune system could be developed. At the heart of this very complicated structure are B- and T-cells, maturing in the bone marrow and in the Thymus, respectively. They interact mediated by chemical substances (cytokines) such as interleukins, interferons, etc. Growth of a specific subgroup of T-cells can be triggered by antigen presenting cells displaying short strings of foreign peptides (resulting from cutting an antigenic protein into small pieces) that match receptors located on the surface of the T-cells. With this mechanism, only T-cells directed against the particular antigens, are activated and multiply to initiate a process finally eliminating the antigens specifically. The vast number of T-cell subsystems (estimates give $10^7..10^{11}$ different T-cell receptors each specific for a single antigen) is permanently present and waits to be activated by an antigen attack. If one specific subsystem gets triggered, cytokine-levels change due to the immune response. As cytokines act on all subsystems in parallel, they are all influenced by the excursion of one single subsystem. It is of vital importance that these subsystems remain in a stable state under any conditions. As soon as antigens are eliminated, the subsystems involved in the elimination process, from any state of excitation, have to relax to their quiescent and stable ground state. These considerations illustrate that stability is one of the most important issues for the immune system.

A central part of the immune system, being in the focus of ongoing research on the development of allergies[2], is the interaction of two types of helper T-cells called Th1 and Th2[3] that interact by secretion of cytokines as shown in Fig. 1.

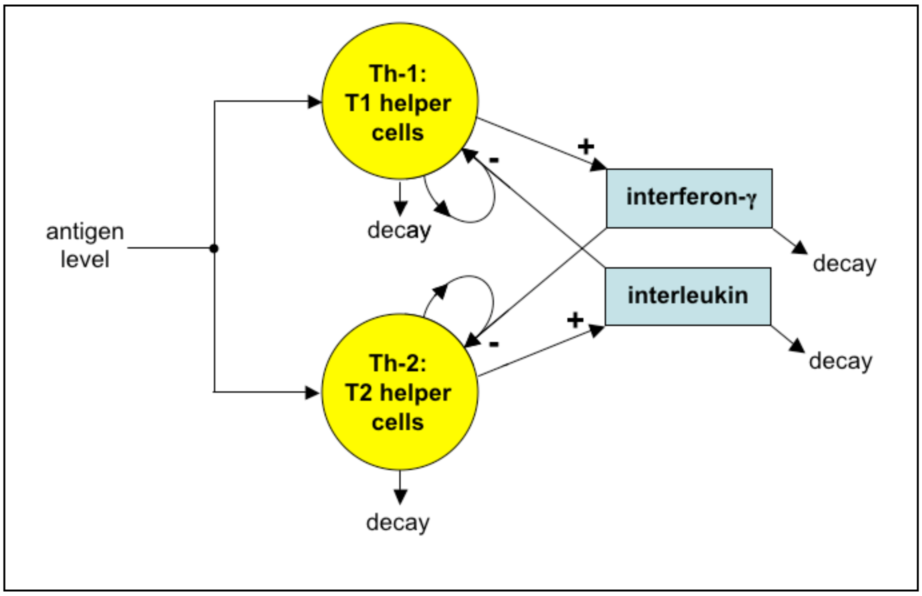

Fig. 1: Interaction of helper T-cells of type 1 and 2 mediated by interferon-γ (IFN-γ) and interleukins (IL-4, 5, 13).

Examining this symmetric interaction scheme, the fundamental questions arises, if other structures would be possible. From the modeling point of view, the main question will be how to translate the interaction scheme into differential equations, i.e., into a dynamical model. In the present paper, we answer both questions on the basis of generic stability considerations and other generic assumptions. Our result will be that there is one unique structure that can be interpreted as two cell-types interacting with two substances (the one shown in Fig. 1) and fulfilling all imposed generic conditions. Our investigation explains why evolutionary processes, starting from the most simple systems, necessarily had to find this structure.

With the same set of generic assumptions, we will analyze systems with 1, 2, 3 and 4 components. However, the method we develop in the present paper can be applied also to systems with more than four components.

Systems with 1 component

A dynamical model for a 1-component system can be written as follows:

$$\frac{dx}{dt} = a_0 + f(T) + g(T)x - \frac{x}{\tau} \tag{1}$$

f(T) and g(T) are nonlinear functions of external parameters T. In many cases, T is, e.g., temperature influencing a system, but T can be considered as a vector including more than one external influence (or force). For our investigation, we **linearize** f and g and write $f(T)=a_1\mu$ and $g(T)=a_2\nu$ with the external forces μ, ν being positive (including zero). Due to our linearization, the parameters a_i vary according to the operating point (i.e., the linearized domain around T). Further, parameter values in most biological or social systems are subject to many influences and therefore can vary in a considerable range. We assume that the parameters a_i are either positive or negative, but **we exclude their sign to change**. This assumption is important, because it defines whether we call two systems with the same structure but different parameter values to be *different* or *the same*. In many cases, stability of a system will change if the sign of certain parameters change. For similar reasons, we **restrict all variables to positive values**. For many systems, this restriction arises quite naturally, e.g., for variables describing concentrations or populations. The term $-x/\tau$ describes a decay with a **positive time constant τ** we always include into our equations. For biological, biochemical or social systems, such a decay term describes lifetimes of cells, biomolecules or individuals. In general, such systems are called **dissipative**. Finally, we impose our stability condition that **there must be a linearly stable equilibrium state for all μ, ν >0**. The equilibrium condition reads:

$$x = \frac{a_0 + a_1\mu}{\frac{1}{\tau} - a_2\nu} \tag{2.1}$$

Our condition for x to be positive, irrespective of the norms of all a_i implies $a_0 \geq 0$, $a_1 \geq 0$ and $a_2 \leq 0$. To ensure linear stability, we claim the derivative of the r.h.s. of (1) towards x to be negative:

$$\nu a_2 - \frac{1}{\tau} < 0 \tag{2.2}$$

giving once more the same condition $a_2 \leq 0$. According to (2.1), a_0 defines the value of x for $\mu=\nu=0$. By a linear transformation $x \rightarrow x - x_0$, **the equilibrium for vanishing external forces can always be shifted to any point**. In this report, we assume **zero to be the equilibrium point for vanishing external forces** and therefore, the parameter a_0 will be omitted. Further, a term $a_2\nu x$ with negative a_2 is an inhibiting external influence and drives the system into a "dead" state for large ν. To avoid such "dead" states, **we do not allow the variables to vanish with large external forces**. We therefore skip the term $a_2\nu x$ with negative a_2. The resulting absolutely stable system is therefore:

$$\boxed{\frac{dx}{dt} = a_1\mu - \frac{x}{\tau}, \quad a_1 \geq 0} \tag{3}$$

The graphical representation of the relaxation dynamics (3) is given in Fig. 2.

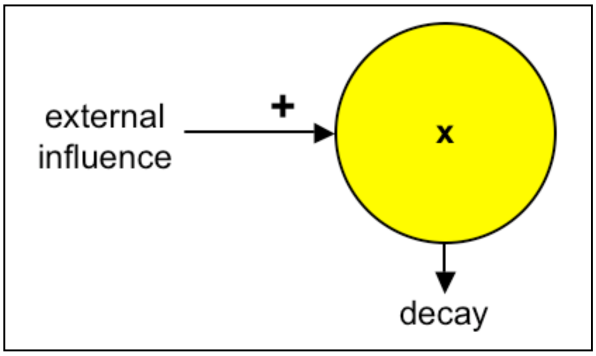

Fig. 2: Relaxation dynamics (3) for a population or substance x with an external influence (effect of μ). Decay refers to the negative term -x/τ with positive time constant τ.

Though we imposed with (2.2) only linear stability, i.e., relaxation of the system to its equilibrium after small perturbations, the analytical solution of the dynamical equation (3) for constant μ shows that the system returns to the same equilibrium point from any initial state and therefore, its equilibrium is not only linearly but also *absolutely stable*. In some nonlinear dissipative systems we will analyze below, linear stability will not exclude the existence of *limit cycles* and *chaotic dynamics*, and therefore, our linearly stable dissipative systems we will identify later might not always show stable behavior after large perturbations.

Systems with 2 components

A system with components x and u that is controlled by an external influence (or force) μ can be written as follows, if **only bilinear or linear terms in all variables** are taken into account:

$$\begin{aligned}
\frac{dx}{dt} &= a_1\mu \begin{bmatrix} 0 \\ 1 \\ x \\ u \end{bmatrix} + a_{2,1}x \begin{bmatrix} 0 \\ 1 \\ u \end{bmatrix} + a_{2,2}u \begin{bmatrix} 0 \\ 1 \end{bmatrix} - \frac{x}{\tau_1} \\
\frac{du}{dt} &= a_3\mu \begin{bmatrix} 0 \\ 1 \\ x \\ u \end{bmatrix} + a_{4,1}x \begin{bmatrix} 0 \\ 1 \\ u \end{bmatrix} + a_{4,2}u \begin{bmatrix} 0 \\ 1 \end{bmatrix} - \frac{u}{\tau_2}
\end{aligned} \tag{4.1}$$

μ and τ_i are positive, a_i, $a_{i,j}$ can be positive or negative. The brackets [] give different possibilities for the respective terms. In general, for n components (variables), there are

$$\binom{(n+2)!+(n-1)}{n} \approx \frac{\{(n+2)!\}^n}{n!} \text{ combinations with repetitions} \tag{4.2}$$

For n=2, we can combine the different terms and the equations in 300 ways. To specify the system, a first set of generic requirements is applied:

- We require a coupling of each equation to at least one other equation for $\mu=0$ to **avoid trivial systems**, i.e., we do not choose n+1 zeros in any equation.
- We avoid combinations with $a_i x - x/\tau$, because such terms can be **combined into one term** x/τ'.
- Neither equation should read dx/dt=x{...}, because this would imply an equilibrium state x=0 independent of the other variables and of the external influences. We reject such equations due to only **weak interactions** with other components of the system. In fact, only the relaxation time constant would be influenced by other components or by external forces and the component governed by such an equation would vanish and decouple from the remaining components: A n-component system would collapse to a simpler (n-1)-component system.
- The combination $a_1\mu u+a_2 u = a_1(\mu+a_2/a_1)u = a_1\mu' u$ **does not introduce new dynamics** and so can be considered as equivalent to $a_1\mu' u$ (the linear transformation $\mu' = \mu+a_2/a_1$ eliminates the term $a_2 u$).
- We exclude equations of the form $u(a_{2,1}x+a_{2,2})$ to **simplify our analysis**. It has to be investigated later, if interesting systems are excluded by this prescription.
- **Mathematical isomorphisms** (systems becoming identical after exchanging names of variables, e.g., x and u) are excluded.

Taking into account the above stated requirements, (4.1) reduces to the following equations for the variables x and u:

$$\begin{aligned}
&1)\quad \frac{dx}{dt} = a_1\mu + a_2 u - \frac{x}{\tau_1}\\
&2)\quad \frac{dx}{dt} = a_1\mu + a_2 ux - \frac{x}{\tau_1}\\
&3)\quad \frac{dx}{dt} = a_1\mu x + a_2 u - \frac{x}{\tau_1}\\
&4)\quad \frac{dx}{dt} = a_1\mu u + a_2 ux - \frac{x}{\tau_1}
\end{aligned} \tag{5.1}$$

$$
\begin{aligned}
&1)\quad \frac{du}{dt} = a_3\mu + a_4 x - \frac{u}{\tau_2}\\
&2)\quad \frac{du}{dt} = a_3\mu + a_4 ux - \frac{u}{\tau_2}\\
&3)\quad \frac{du}{dt} = a_3\mu u + a_4 x - \frac{u}{\tau_2}\\
&4)\quad \frac{du}{dt} = a_3\mu x + a_4 ux - \frac{u}{\tau_2}
\end{aligned}
\tag{5.2}
$$

Combinations of (5.1) and (5.2) give $\begin{pmatrix} 4+2-1 \\ 2 \end{pmatrix} = \frac{5\cdot 4}{2\cdot 1} = 10$ systems to be investigated. We introduce the nomenclature i,k with k≥i (i, k=1...4) to refer to the system consisting of equation i for x and k for u. To demonstrate our stability analysis, we begin with the most simple linear **system 1,1**. The matrix of partial derivatives (we call it *stability matrix*) becomes:

$$
\begin{pmatrix} \frac{1}{\tau_1} & a_2 \\ a_4 & -\frac{1}{\tau_2} \end{pmatrix} \tag{6}
$$

It follows from basic mathematics[4] that a stationary solution is linearly stable (i.e. stable against small perturbations) if the real parts of all eigenvalues of the stability matrix are negative. Calculation of the eigenvalues λ leads to the following polynomial $P(\lambda)$:

$$
P(\lambda) = \left(\lambda + \frac{1}{\tau_1}\right)\left(\lambda + \frac{1}{\tau_2}\right) - a_2 a_4 \tag{7}
$$

The two eigenvalues are defined by $P(\lambda)=0$. τ_i are positive decay time constants, but all a_i are not restricted at the moment to positive or negative values. If the term $d=a_2a_4$ would vanish, the zero points of $P(\lambda)$ would be obvious: they would be located in the left complex half plane. However, $d>0$ shifts the graph of the polynomial downwards, and moves its right zero point towards positive real numbers as shown in Fig. 3. This means that critical combinations of the parameters a_i, and τ_i exist for which one eigenvalue gets zero, i.e., beyond these critical combinations, one real eigenvalue becomes positive. As we look for systems that are linearly stable for any combination of parameter values (however, without changing their signs), such runaway solutions for certain combinations are forbidden and we impose, e.g., $a_2<0$ and $a_4>0$ giving $d<0$.

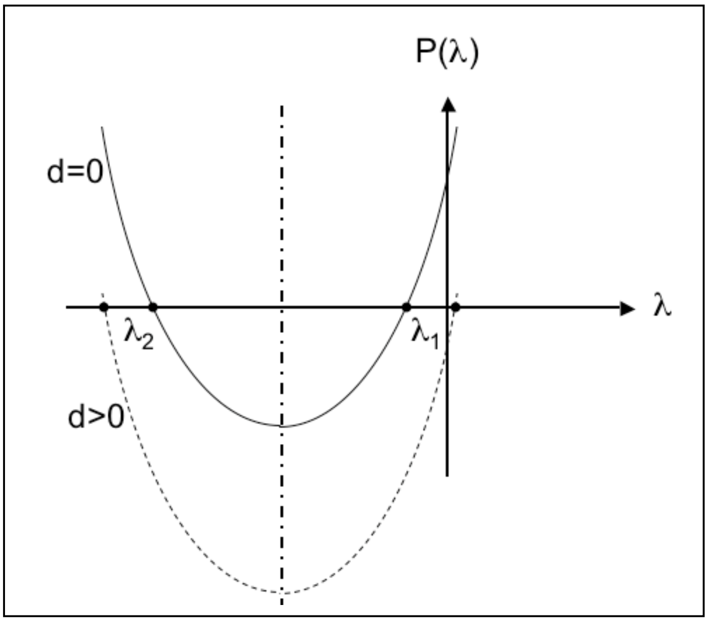

Fig. 3: Two polynomials P(λ) with $d=a_2a_4 = 0$ and d>0. At a critical value d_c, $\lambda_1=0$, and for $d>d_c$, the stationary state of the system becomes unstable. For d<0, the function is shifted upwards and the real λ approach each other until they merge. From this point on, its real parts are constant and their imaginary parts separate vertically and symmetrically to the λ-axis on the point-dashed-line (we assume the imaginary axis drawn as vertical axis on the same plot).

Because also imaginary zero points would have negative real parts, system 1,1 is acceptable from the stability point of view. However, the stationary solution for x reads

$$x = \mu\tau_1 \frac{a_1 + a_2a_3\tau_2}{1 - a_2a_4\tau_1\tau_2}, \quad a_1 > 0,\ a_2 < 0,\ a_3 > 0,\ a_4 > 0 \tag{8}$$

and would give negative values for $-a_2a_3\tau_2>a_1$. To avoid this possibility, we set $\mathbf{a_3=0}$ and find the first *system 1,1 meeting all our requirements*:

$$\boxed{\begin{array}{ll} \text{system 1,1:} & \\ \dfrac{dx}{dt} = a_1\mu + a_2u - \dfrac{x}{\tau_1} & a_1 > 0, a_2 < 0 \\ \dfrac{du}{dt} = a_4x - \dfrac{u}{\tau_2} & a_4 > 0 \end{array}} \tag{9}$$

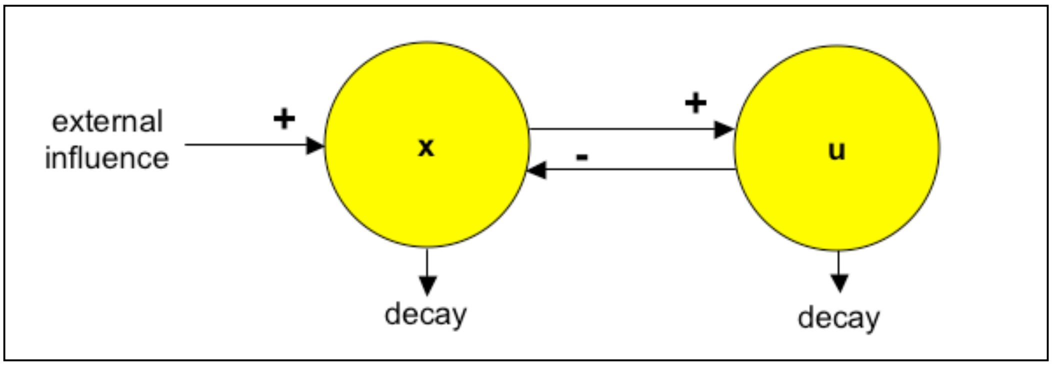

Fig. 4.1: The linearly stable 2-component system 1,1 according to equation (9).

Analogous analysis of **system 1,2** shows, that both conditions (no positive real eigenvalues, positive variables) can be met for all parameter values if $a_1>0$, $a_2>0$, $a_3>0$, $a_4<0$. As a last check, we have to search for complex eigenvalues crossing the imaginary axis towards the right complex half plane. For this aim, we eliminate a_2u in $P(\lambda)$ using the first equation of (5.1) to get

$$P(\lambda) = \left(\lambda + \frac{1}{\tau_1}\right)\left(\lambda + \frac{1}{\tau_2} - a_4 x\right) - a_4\left(\frac{x}{\tau_1} - a_1\mu\right) \qquad (10.1)$$

To find eigenvalues on the imaginary axis, we evaluate $P(\lambda)$ for $\lambda=i\eta$ giving the following equations for the real and the imaginary part:

$$\begin{aligned} \eta^2 &= \frac{1}{\tau_1\tau_2} + \frac{2(-a_4)x}{\tau_1} - a_1(-a_4)\mu \\ i\eta&\left(\frac{1}{\tau_1} + \frac{1}{\tau_2} + (-a_4)x\right) = 0 \end{aligned} \qquad (10.2)$$

The imaginary part of equation (10.2) implies $\eta=0$ and the real part equation becomes

$$0 = \frac{1}{\tau_1\tau_2} + (-a_4)\left\{\frac{2x}{\tau_1} - a_1\mu\right\} \qquad (10.3)$$

From the dynamical equation for x follows (for the stationary solution)

$$\frac{x}{\tau_1} - a_1\mu = a_2 u > 0 \qquad (10.4)$$

and this implies that (10.3) can never be satisfied. Therefore, no complex eigenvalues can cross the imaginary axis to the right complex half plane with any combinations of the parameter values, and *system 1,2 is linearly stable and meets all our conditions*:

$$\boxed{\begin{aligned} &\text{system 1,2}: \\ &\frac{dx}{dt} = a_1\mu + a_2 u - \frac{x}{\tau_1} \qquad a_1 > 0,\, a_2 > 0 \\ &\frac{du}{dt} = a_3\mu + a_4 ux - \frac{u}{\tau_2} \qquad a_3 > 0,\, a_4 < 0 \end{aligned}} \qquad (11.1)$$

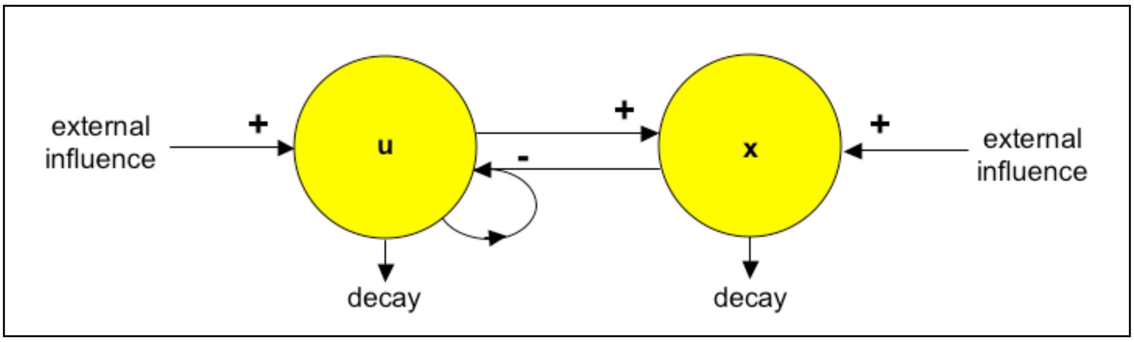

Fig. 4.2: The linearly stable 2-component system 1,2 according to equation (11.1) can be interpreted as a cell population u and a substance x produced by the cells that has a inhibitory effect on the cells.

System 1,2 shown in Fig. 4.2 is often found in a biological context: cells u stimulated by an external influence produce a cytokine x inhibiting their growth. In this context, the external influence on the cytokine x might come from other cells producing the same cytokine. The external influence on the cells u could be a stimulus for cell multiplication.

Investigation of all 10 combinations of equations (5.1) and (5.2) give the results summarized in Tab. 1. The two additional systems 2,2 and 2,4 that were found are given below as equations (11.2), (11.3) and in graphical form in Fig. 5. The two systems 1,3 and 2,3 with a_3=0 are special cases of systems 1,1 and 2,1 (2,1 is identical with 1,2 after exchanging x and u) and therefore, they give no new dynamics.

system 2,2 :

$$\frac{dx}{dt} = a_1\mu + a_2 xu - \frac{x}{\tau_1} \qquad a_1 > 0, a_2 < 0$$
$$\frac{du}{dt} = a_3\mu + a_4 ux - \frac{u}{\tau_2} \qquad a_3 > 0, a_4 < 0 \tag{11.2}$$

system 2,4 :

$$\frac{dx}{dt} = a_1\mu + a_2 xu - \frac{x}{\tau_1} \qquad a_1 > 0, a_2 < 0$$
$$\frac{du}{dt} = a_3\mu x + a_4 ux - \frac{u}{\tau_2} \qquad a_3 > 0, a_4 < 0 \tag{11.3}$$

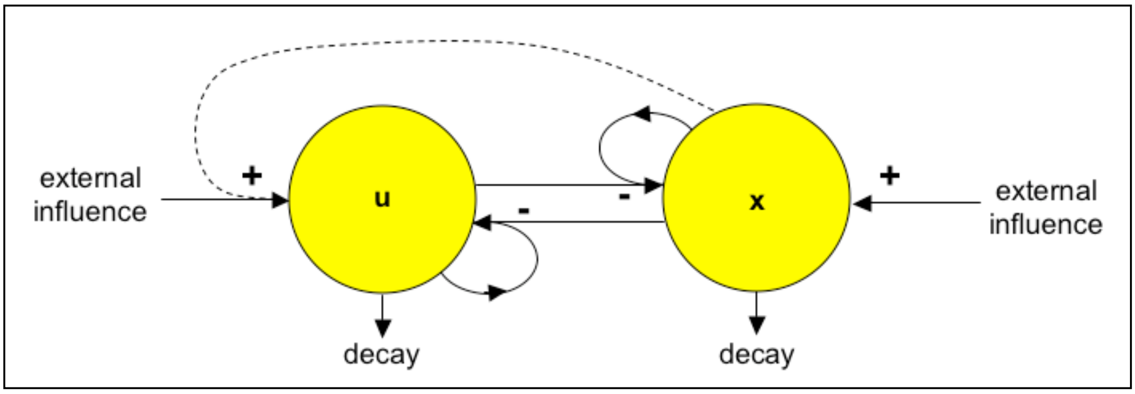

Fig. 5: The linearly stable 2-component systems 2,2 (without broken line) and 2,4 (including broken line) according to (11.2) and (11.3).

The analysis for 2-component systems shows that mainly combinations of equations 1 and 2 lead to systems meeting our conditions. **Though for systems with 3 or more components, valid systems containing equations of type 3 and 4 can surely be found, we restrict our further analysis to systems combined with equations of type 1 and 2 only.** With this restriction, we exclude systems with nonlinear external influences (such as, e.g., system 2,4) described by $a_i\mu x$, $a_i\mu y$, $a_i\mu u$ and $a_i\mu v$. Our motivation to postpone this class of systems to a later analysis is to simplify analytical calculations as well as the structure of the present report.

system	P(λ)	signs of a_i	positive u, x	stability
1,1	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}\right)\left(\lambda+\frac{1}{\tau_2}\right)-a_2a_4$	$a_1>0$ $a_2<0$ $a_3=0$ $a_4>0$	**yes**	**yes**
1,2	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}\right)\left(\lambda+\frac{1}{\tau_2}-a_4x\right)-a_2a_4u$	$a_1>0$ $a_2>0$ $a_3>0$ $a_4<0$	**yes**	**yes**
1,3	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}\right)\left(\lambda+\frac{1}{\tau_2}\right)-a_2a_4$	$a_1>0$ $a_2<0$ $a_3=0$ $a_4>0$	yes	yes
1,4	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}\right)\left(\lambda+\frac{1}{\tau_2}-a_4x\right)-a_2\left(a_3\mu+a_4u\right)$		no	-
2,2	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}-a_2u\right)\left(\lambda+\frac{1}{\tau_2}-a_4x\right)-a_2a_4ux$	$a_1>0$ $a_2<0$ $a_3>0$ $a_4<0$	**yes**	**yes**
2,3	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}-a_2u\right)\left(\lambda+\frac{1}{\tau_2}\right)-a_2a_4x$	$a_1>0$ $a_2<0$ $a_3=0$ $a_4>0$	yes	yes
2,4	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}-a_2u\right)\left(\lambda+\frac{1}{\tau_2}-a_4x\right)-a_2x\left(a_3\mu+a_4u\right)$	$a_1>0$ $a_2<0$ $a_3>0$ $a_4<0$	**yes**	**yes**
3,3	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}-a_1\mu\right)\left(\lambda+\frac{1}{\tau_2}-a_3\mu\right)-a_2a_4$		no	-
3,4	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}-a_1\mu\right)\left(\lambda+\frac{1}{\tau_2}-a_4x\right)-a_2\left(a_3\mu+a_4u\right)$		no	-
4,4	$P(\lambda)=\left(\lambda+\frac{1}{\tau_1}-a_2u\right)\left(\lambda+\frac{1}{\tau_2}-a_4x\right)-\left(a_1\mu+a_2x\right)\left(a_3\mu+a_4u\right)$		no	-

Table 1: Polynomials P(λ) for all 10 combinations of equations (5.1) and (5.2). The signs of the parameters a_i were chosen to avoid negative variables for the equilibrium state (yes in column "positive u, x"). If this first requirement could be met, the P(λ) was checked for the absence of eigenvalues with positive real parts (yes in column "stability"). Systems 1,1 / 1,2 / 1,3 / 2,2 / 2,3 / 2,4 are retained as valid systems. As we exclude "dead" equations with $a_3<0$, a_3 is set to zero in systems 1,3 and 2,3. With this restriction, these two systems are special cases of systems 1,1 and 1,2.

Systems with 3 components

We reverse now the procedure followed in the previous section and begin with the stability requirements. We will demonstrate first that a stability matrix leading to a polynomial P(λ) of the form (7) must have the generic form:

$$\begin{pmatrix} \bullet & z & 0 \\ 0 & \bullet & z \\ z & 0 & \bullet \end{pmatrix} \qquad (12)$$

In every row and every column, there is only one matrix element different from zero (z) in addition to the diagonal elements (•). All elements z or • can be constants or functions of those variables that are not restricted by zeros in the same row. With the most simple settings z= a_i and • =-1/$\tau_{\square}$, the eigenvalue problem is the following:

$$\begin{pmatrix} -\frac{1}{\tau_1} & a_1 & 0 \\ 0 & -\frac{1}{\tau_2} & a_2 \\ a_3 & 0 & -\frac{1}{\tau_3} \end{pmatrix} \bullet \begin{pmatrix} \xi \\ \eta \\ \zeta \end{pmatrix} = \lambda \begin{pmatrix} \xi \\ \eta \\ \zeta \end{pmatrix} \qquad (13)$$

To calculate the eigenvalues λ, we solve the equations

$$\begin{aligned} \eta &= \frac{1}{a_1}\xi\left(\lambda + \frac{1}{\tau_1}\right) \\ \zeta &= \frac{1}{a_2}\eta\left(\lambda + \frac{1}{\tau_2}\right) \\ \xi &= \frac{1}{a_3}\zeta\left(\lambda + \frac{1}{\tau_3}\right) \end{aligned} \qquad (14)$$

giving the polynomial P(λ)

$$P(\lambda) = \prod_i \left(\lambda + \frac{1}{\tau_i}\right) - \prod_i a_i \qquad (15)$$

with the correct form (7). Introducing a constant b instead of zero in the first row of the stability matrix (13) would give

$$\begin{aligned} P(\lambda) &= \left(\lambda + \frac{1}{\tau_2}\right)(\lambda + c_1)(\lambda + c_2) - \prod_i a_i \\ c_{1,2} &= \frac{1}{2}\left\{\frac{1}{\tau_1} + \frac{1}{\tau_3} \pm \sqrt{\left(\frac{1}{\tau_1} + \frac{1}{\tau_3}\right)^2 - 4\left(\frac{1}{\tau_1\tau_3} - a_3 b\right)}\right\} \end{aligned} \qquad (16)$$

For b=0 (16) reduces to (15). However, for b different from zero, an additional relation between the parameters has to be true for preventing real parts of eigenvalues to become positive:

$$a_3 b < \frac{1}{\tau_1 \tau_2} \tag{17}$$

As we look for systems that are stable irrespective of the values of the involved parameters, inequalities such as (17) have to be avoided.

As the choice of the matrix (12) is only one of different possibilities, we investigate variants arising from permutations of the variables: Exchanging the names of u and v in a system with variables x, u, v transforms (12) into the following matrix:

$$\begin{pmatrix} \bullet & 0 & z \\ z & \bullet & 0 \\ 0 & z & \bullet \end{pmatrix} \tag{18}$$

In the first row are the partial derivations of the x-equation in the order x, u, v. As u and v are exchanged, the second and third positions have to be exchanged. The second and third row refer to the u- and v-equations that change place according to the transformation u'=v, v'=u. The transformed system has to be arranged in the order x, u', v'. Further permutations of (18) do not result in new structures.

We explained above why we accept only matrices with a maximum of one non-zero position in addition to the diagonal element in every row. We explain now, why we require the same condition for the columns. The following equivalent stability matrices fulfill the row conditions, but not the column conditions:

$$\begin{pmatrix} \bullet & 0 & z \\ z & \bullet & 0 \\ z & 0 & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & z & 0 \\ z & \bullet & 0 \\ z & 0 & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & z & 0 \\ z & \bullet & 0 \\ 0 & z & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & z & 0 \\ 0 & \bullet & z \\ 0 & z & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & 0 & z \\ 0 & \bullet & z \\ 0 & z & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & 0 & z \\ 0 & \bullet & z \\ z & 0 & \bullet \end{pmatrix} \tag{19}$$

As all 6 matrices are equivalent, it is enough to analyze the first one. The two zeros in the second column mean that the x and v-equations are not influenced by the u-equation, i.e., the x-v-system can be solved independently, and the system can be reduced to a 2-component system influencing a 1-component system. It is therefore enough to investigate systems with a stability matrix of the form (18), i.e., we have to investigate the following differential equations (excluding nonlinear external influences and terms of the form $u(a_{2,1}x+a_{2,2})$):

$$\begin{aligned} \frac{dx}{dt} &= a_1\mu + a_2 v \begin{bmatrix} 1 \\ x \end{bmatrix} - \frac{x}{\tau_1} \\ \frac{du}{dt} &= a_3\mu + a_4 x \begin{bmatrix} 1 \\ u \end{bmatrix} - \frac{u}{\tau_2} \\ \frac{dv}{dt} &= a_5\mu + a_6 u \begin{bmatrix} 1 \\ v \end{bmatrix} - \frac{v}{\tau_2} \end{aligned} \tag{20}$$

Tab. 2 gives an overview of the results we obtained for the remaining $\begin{pmatrix} 2+3-1 \\ 3 \end{pmatrix} = \frac{4\cdot 3\cdot 2}{3\cdot 2\cdot 1} = 4$ combinations.

system	positive variables	stability	signs of a_i	valid system
1,1,1	yes	no	$a_2>0$, $a_4>0$, $a_6<0$ $a_1=a_3=0$, $a_5>0$	no
1,1,2	**yes**	**yes**	$\mathbf{a_2>0, a_4>0, a_6<0}$ $\mathbf{a_1=a_3=0, a_5>0}$	**yes**
1,2,2	**yes**	**yes**	$\mathbf{a_2>0, a_4<0, a_6<0}$ $\mathbf{a_1=0, a_3>0, a_5>0}$	**yes**
2,2,2	**yes**	**yes**	$\mathbf{a_2<0, a_4<0, a_6<0}$ $\mathbf{a_1>0, a_3>0, a_5>0}$	**yes**

Tab. 2: Overview of our results from the analysis of systems with 3 components combined from equations of type 1 and 2 according to (20).

We identified the three systems 1,1,2 / 1,2,2 / 2,2,2 as valid systems according to our requirements. The special conditions $a_1=a_3=0$ we imposed on system 1,1,2 and $a_1=0$ for system 1,2,2 helped to simplify the analysis, but they could turn out to be generalizable to $a_1>0$, $a_3>0$. These three systems are given by equations (21), (22), (23) and in graphical form in Figs. 6 and 7.

$$\begin{aligned} \frac{dx}{dt} &= a_2 v - \frac{x}{\tau_1} & &\text{system 1,1,2:} \\ \frac{du}{dt} &= a_4 x - \frac{u}{\tau_2} & &a_2 > 0, a_4 > 0, a_6 < 0 \\ \frac{dv}{dt} &= a_5 \mu + a_6 uv - \frac{v}{\tau_3} & &a_5 > 0 \end{aligned} \tag{21}$$

$$\begin{aligned} \frac{dx}{dt} &= a_2 v - \frac{x}{\tau_1} & &\text{system 1,2,2:} \\ \frac{du}{dt} &= a_3 \mu + a_4 xu - \frac{u}{\tau_2} & &a_2 > 0, a_4 < 0, a_6 < 0 \\ \frac{dv}{dt} &= a_5 \mu + a_6 uv - \frac{v}{\tau_3} & &a_3 > 0, a_5 > 0 \end{aligned} \tag{22}$$

$$\begin{aligned} \frac{dx}{dt} &= a_1 \mu + a_2 vx - \frac{x}{\tau_1} & &\text{system 2,2,2:} \\ \frac{du}{dt} &= a_3 \mu + a_4 xu - \frac{u}{\tau_2} & &a_2 < 0, a_4 < 0, a_6 < 0 \\ \frac{dv}{dt} &= a_5 \mu + a_6 uv - \frac{v}{\tau_3} & &a_1 > 0, a_3 > 0, a_5 > 0 \end{aligned} \tag{23}$$

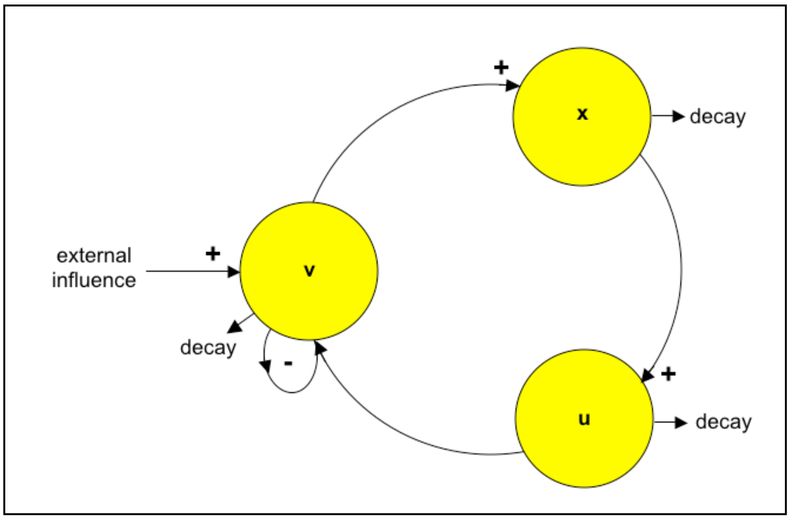

Fig. 6: System 1,1,2 according to (21).

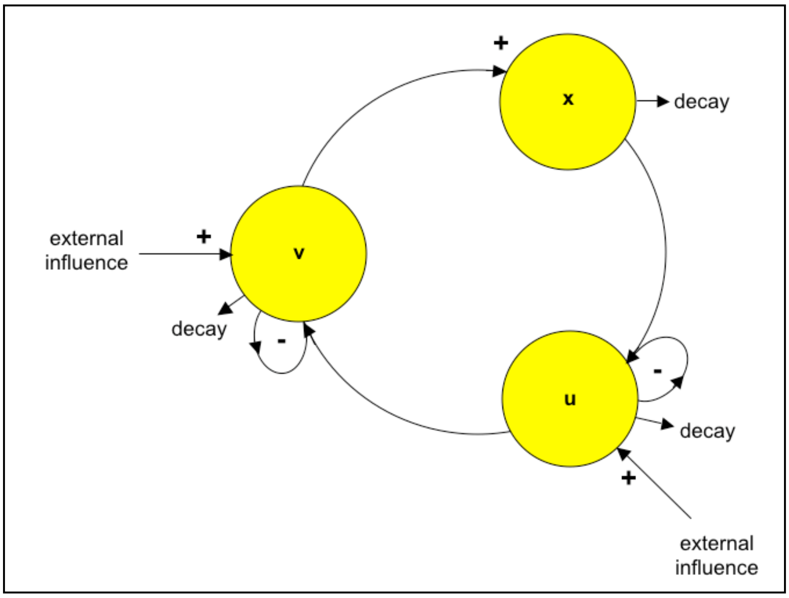

Fig. 7.1: System 1,2,2 according to (22).

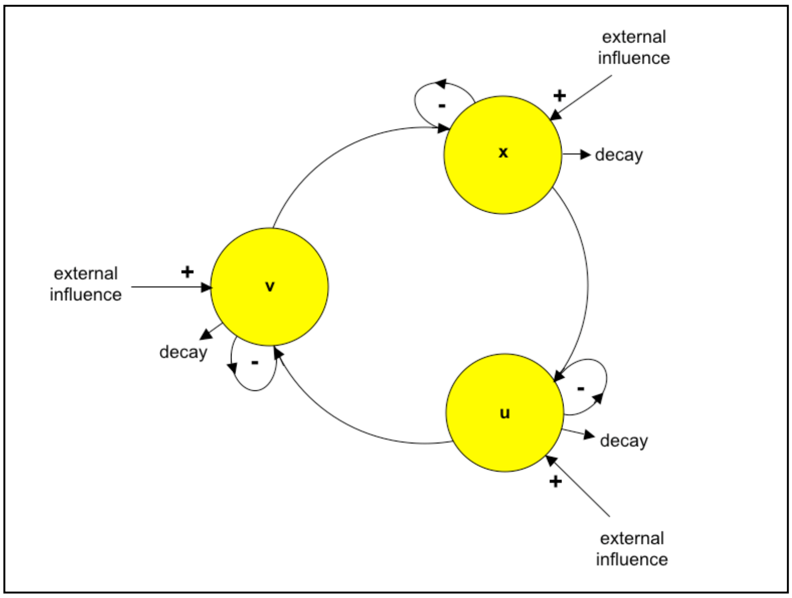

Fig. 7.2: System 2,2,2 according to (23).

We would like to add some comments concerning two other systems:

System 1,1,1 referenced in Tab. 2 is excluded due to stability reasons. Its polynomial $P(\lambda)$

$$P(\lambda) = \left(\lambda + \frac{1}{\tau_1}\right)\left(\lambda + \frac{1}{\tau_2}\right)\left(\lambda + \frac{1}{\tau_3}\right) - a_2 a_4 a_6 \tag{24.1}$$

gives for $\lambda = i\eta$ the following conditions resulting from $P(i\eta) = 0$:

$$\begin{aligned} &\eta^2 \sum_i \frac{1}{\tau_i} = -a_2 a_4 a_6 + \prod_i \frac{1}{\tau_i} \qquad a_2 < 0, a_4 > 0, a_6 > 0 \\ &\qquad \eta^2 = \sum_{i \neq j} \frac{1}{\tau_i \tau_j} > 0 \end{aligned} \tag{24.2}$$

We can therefore separate the τ-terms from the a-terms giving

$$\left\{\sum_{i \neq j} \frac{1}{\tau_i \tau_j}\right\}\left\{\sum_i \frac{1}{\tau_i}\right\} - \prod_i \frac{1}{\tau_i} = -a_2 a_4 a_6 > 0 \tag{25}$$

The negative product term is cancelled by the same positive term from the product {}{} and so, the l.h.s. of (25) is a sum of positive terms. For any choice of the τ_i it is possible to choose a set of a_i that meet the condition (25), i.e., complex eigenvalues are found on the imaginary axis and therefore, system 1,1,1 gets oscillatory unstable for many parameter combinations.

System 1,2,3 with $a_2 > 0$, $a_4 < 0$, $a_6 < 0$, $a_1 = 0$, $a_3 > 0$, $a_5 > 0$ *is an example of a valid system with nonlinear external influence* we excluded from further investigations to simplify the present analysis.

Systems with 4 components

We follow our procedure developed for 3 component systems and begin with the stability matrix and its 9 possible permutations. There are two symmetry groups shown in (26): an asymmetric group with six elements and a symmetric group with three elements.

asymmetric group

$$\begin{pmatrix} \bullet & 0 & z & 0 \\ 0 & \bullet & 0 & z \\ 0 & z & \bullet & 0 \\ z & 0 & 0 & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & z & 0 & 0 \\ 0 & \bullet & z & 0 \\ 0 & 0 & \bullet & z \\ z & 0 & 0 & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & 0 & z & 0 \\ z & \bullet & 0 & 0 \\ 0 & 0 & \bullet & z \\ 0 & z & 0 & \bullet \end{pmatrix}$$

$$\begin{pmatrix} \bullet & 0 & 0 & z \\ 0 & \bullet & z & 0 \\ z & 0 & \bullet & 0 \\ 0 & z & 0 & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & 0 & 0 & z \\ z & \bullet & 0 & 0 \\ 0 & z & \bullet & 0 \\ 0 & 0 & z & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & z & 0 & 0 \\ 0 & \bullet & 0 & z \\ z & 0 & \bullet & 0 \\ 0 & 0 & z & \bullet \end{pmatrix} \qquad (26)$$

symmetric group

$$\begin{pmatrix} \bullet & 0 & z & 0 \\ 0 & \bullet & 0 & z \\ z & 0 & \bullet & 0 \\ 0 & z & 0 & \bullet \end{pmatrix} \Rightarrow \begin{pmatrix} \bullet & 0 & 0 & z \\ 0 & \bullet & z & 0 \\ 0 & z & \bullet & 0 \\ z & 0 & 0 & \bullet \end{pmatrix} \Rightarrow \left(\begin{array}{cc:cc} \bullet & z & 0 & 0 \\ z & \bullet & 0 & 0 \\ \hdashline 0 & 0 & \bullet & z \\ 0 & 0 & z & \bullet \end{array}\right)$$

Within the two symmetry groups, all elements are connected by **permutations** of the equations as explained above (see (12), (18) and (19)).

The symmetric group consists of systems composed of two non-interacting 2-component systems. This property can be understood with the third element, where the two non-connected subsystems are indicated with broken lines. The symmetric group can therefore be *reduced to 2-component systems* we discussed above.

The asymmetric group consists of six elements that show up as symmetric pairs with respect to the main diagonal. The symmetric pairs (located vertically one on top of the other in (26)) are connected by the two permutations 1-3 and 2-4. A 2-3 permutation and a 1-2 permutation connects the pairs in (26) horizontally. As all six elements are connected by permutations, they represent the same system, and we can restrict our investigation to the first element:

$$\begin{pmatrix} \bullet & 0 & z & 0 \\ 0 & \bullet & 0 & z \\ 0 & z & \bullet & 0 \\ z & 0 & 0 & \bullet \end{pmatrix} \qquad (27)$$

Due to our above explained restrictions, there remain only $\begin{pmatrix}2+4-1\\4\end{pmatrix}=\frac{5\cdot4\cdot3\cdot2}{4\cdot3\cdot2\cdot1}=5$ combinations of the following equations to be investigated:

$$\begin{array}{llll}
1) & \frac{dx}{dt}=a_1\mu+a_2u-\frac{x}{\tau_1} & 2) & \frac{dx}{dt}=a_1\mu+a_2ux-\frac{x}{\tau_1}\\
1) & \frac{dy}{dt}=a_3\mu+a_4v-\frac{y}{\tau_2} & 2) & \frac{dy}{dt}=a_3\mu+a_4vy-\frac{y}{\tau_2}\\
1) & \frac{du}{dt}=a_5\mu+a_6y-\frac{u}{\tau_3} & 2) & \frac{du}{dt}=a_5\mu+a_6yu-\frac{u}{\tau_3}\\
1) & \frac{dv}{dt}=a_7\mu+a_8x-\frac{v}{\tau_4} & 2) & \frac{dv}{dt}=a_7\mu+a_8xv-\frac{v}{\tau_4}
\end{array} \tag{28}$$

Systems combined of equations of type 1 and 2 have the following stability matrix:

$$\begin{pmatrix}
-\frac{1}{\tau_1}+a_2u\cdot\begin{bmatrix}0\\1\end{bmatrix} & 0 & a_2\cdot\begin{bmatrix}1\\x\end{bmatrix} & 0\\
0 & -\frac{1}{\tau_2}+a_4v\cdot\begin{bmatrix}0\\1\end{bmatrix} & 0 & a_4\cdot\begin{bmatrix}1\\y\end{bmatrix}\\
0 & a_6\cdot\begin{bmatrix}1\\u\end{bmatrix} & -\frac{1}{\tau_3}+a_6y\cdot\begin{bmatrix}0\\1\end{bmatrix} & 0\\
a_8\cdot\begin{bmatrix}1\\v\end{bmatrix} & 0 & 0 & -\frac{1}{\tau_4}+a_8x\cdot\begin{bmatrix}0\\1\end{bmatrix}
\end{pmatrix} \tag{29}$$

leading to the eigenvalue-polynomial:

$$\begin{aligned}P(\lambda)=&\left(\lambda+\frac{1}{\tau_1}-a_2u\cdot\begin{bmatrix}0\\1\end{bmatrix}\right)\left(\lambda+\frac{1}{\tau_2}-a_4v\cdot\begin{bmatrix}0\\1\end{bmatrix}\right)\left(\lambda+\frac{1}{\tau_3}-a_6y\cdot\begin{bmatrix}0\\1\end{bmatrix}\right)\left(\lambda+\frac{1}{\tau_4}-a_8x\cdot\begin{bmatrix}0\\1\end{bmatrix}\right)\\
&-a_2a_4a_6a_8\begin{bmatrix}1\\x\end{bmatrix}\cdot\begin{bmatrix}1\\y\end{bmatrix}\cdot\begin{bmatrix}1\\u\end{bmatrix}\cdot\begin{bmatrix}1\\v\end{bmatrix}\end{aligned} \tag{30}$$

The **system 1,1,1,1** (all upper values in brackets [] in (30)) gives the same structure for $P(\lambda)$ as the above investigated system 1,1,1 and *has to be excluded* due to the possibility of complex eigenvalues with positive real parts.

System 2,1,1,1 (equivalent to system 1,1,1,2) leads to

$$P(i\eta)=\left(i\eta+\frac{1}{\tau_1}-a_2u\right)\left(i\eta+\frac{1}{\tau_2}\right)\left(i\eta+\frac{1}{\tau_3}\right)\left(i\eta+\frac{1}{\tau_4}\right)-a_2a_4a_6a_8x=0 \tag{31}$$

The real and imaginary parts give the conditions

$$\eta^4 - \eta^2\left\{\sum_{i\neq j}\frac{1}{\tau_i\tau_j} - a_2u\sum_{i=2}^{4}\frac{1}{\tau_i}\right\} - a_2a_4a_6a_8x = 0$$

$$\eta^2 = \frac{\sum_{i\neq j\neq k}\frac{1}{\tau_i\tau_j\tau_k} - a_2u\sum_{i\neq j\neq 1}\frac{1}{\tau_i\tau_j}}{\sum_{i=1}^{4}\frac{1}{\tau_i} - a_2u} \qquad (32)$$

For the **special case $a_3=a_5=a_7=0$**, we can find the following relation from the four equations defining system 2,1,1,1

$$a_4a_6a_8x = \frac{u}{\tau_2\tau_3\tau_4}, \quad a_3 = a_5 = a_7 = 0 \qquad (33)$$

to eliminate x in (32). With $a_2<0$ and all other parameters as well as u,x positive, the second equation of (32) always gives two real η (symmetric to zero) that can be inserted into the first equation giving:

$$\left\{\sum_{i\neq j\neq k}\frac{1}{\tau_i\tau_j\tau_k} - a_2u\sum_{i\neq j\neq 1}\frac{1}{\tau_i\tau_j}\right\}^2 + \frac{-a_2u}{\tau_2\tau_3\tau_4}\left\{\sum_{i=1}^{4}\frac{1}{\tau_i} - a_2u\right\}^2$$
$$= \left\{\sum_{i=1}^{4}\frac{1}{\tau_i} - a_2u\right\}\left\{\sum_{i\neq j\neq k}\frac{1}{\tau_i\tau_j\tau_k} - a_2u\sum_{i\neq j\neq 1}\frac{1}{\tau_i\tau_j}\right\}\left\{\sum_{i\neq j}\frac{1}{\tau_i\tau_j} - a_2u\sum_{i=2}^{4}\frac{1}{\tau_i}\right\} \qquad (34)$$

A combination of parameters such that (34) holds would mean that two symmetric imaginary eigenvalues would be about to enter the right complex half plane and the system would show oscillatory instability. To exclude such instability, we have to show that (34) never holds. On the l.h.s. of (34), we have 49+25=74 positive terms, on the r.h.s. we have 5·7·9=315 positive terms. Using basic mathematics, it can be shown that all 74 terms show up among the 315 terms also on the r.h.s. (a practical way to prove this is to arrange all terms as powers of ($-a_2u$) and to prove the cancellation separately for power 0, 1, 2, and 3). The result is that (34) becomes the form

$$0 = \text{sum of positive terms} \qquad (35)$$

what obviously never can be true. System 2,1,1,1 has therefore no oscillatory instability and the last point we have to show is that its variables in the stationary states are always positive. We set the time derivatives of the dynamical equations to zero and solve the equations analytically giving:

$$x = \frac{1}{2\alpha}\left\{-1 + \sqrt{1 + 4\alpha a_1\tau_1 u}\right\}$$
$$\alpha \equiv -a_2a_4a_6a_8\tau_1\tau_2\tau_3\tau_4 > 0 \qquad (36)$$

From (36) follows x>0 for all possible parameter values and from the remaining linear equations we get also y, u and v positive. *All our requirements for a system to be accepted are met by system 2,1,1,1 according to equations (37).* Fig. 8 shows the system in graphical form.

$$\begin{array}{|ll|}\hline \text{system } 2,1,1,1: & a_2 < 0\,,\, a_4 > 0\,,\, a_6 > 0\,,\, a_8 > 0 \\ \dfrac{dx}{dt} = a_1\mu + a_2 ux - \dfrac{x}{\tau_1} & a_1 > 0\,,\, a_3 = a_5 = a_7 = 0 \\ \dfrac{dy}{dt} = a_4 v - \dfrac{y}{\tau_2} \quad \dfrac{du}{dt} = a_6 y - \dfrac{u}{\tau_3} \quad \dfrac{dv}{dt} = a_8 x - \dfrac{v}{\tau_4} & \\ \hline \end{array} \tag{37}$$

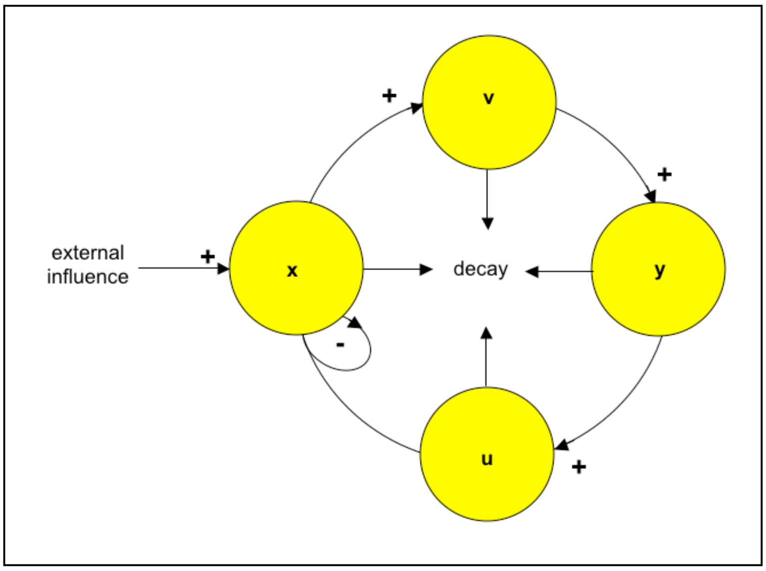

Fig. 8: Linearly stable 4-component system 2,1,1,1.

The difference to our stable 2-component system 1,2 (Fig. 4.2) is the series of three substances acting on one another without being influenced directly by external forces instead of only one substance that can be externally influenced. Further investigations have to show if the condition a_3=a_5=a_7=0 (i.e. no external influence on y, u, v) is necessary or could be omitted.

The **symmetric system 2,2,1,1** (equivalent to system 1,1,2,2) has the following P(λ):

$$P(\lambda) = \left(\lambda + \frac{1}{\tau_1} - a_2 u\right)\left(\lambda + \frac{1}{\tau_2} - a_4 v\right)\left(\lambda + \frac{1}{\tau_3}\right)\left(\lambda + \frac{1}{\tau_4}\right) - a_2 a_4 \frac{uv}{\tau_3 \tau_4} \tag{38}$$

In (38) the product $a_6 a_8 xy$ has been replaced by $uv/(\tau_3\tau_4)$ according to the dynamical equations for the **special case** $\mathbf{a_5=a_7=0}$. From (38) follows that a_2, a_4 be negative, and the stationary states obey the relations

$$\begin{array}{lll} x = \dfrac{a_1\mu}{\frac{1}{\tau_1} - a_2 v} & y = \dfrac{a_3\mu}{\frac{1}{\tau_2} - a_4 u} & a_1, a_3, a_6, a_8 > 0 \\ u = \dfrac{a_1 a_6 \tau_3}{\dfrac{1}{\tau_1} + \dfrac{-a_2 a_3 a_8 \tau_4 \mu}{\frac{1}{\tau_2} - a_4 u}} & v = \dfrac{a_3 a_8 \tau_4 \mu}{\frac{1}{\tau_2} - a_4 u} & a_2, a_4 < 0 \end{array} \tag{39}$$

The u-equation can be solved giving

$$u = \frac{\tau_1}{2(-a_4)}\left\{-b + \sqrt{b^2 + 4c\frac{-a_4}{\tau_1}}\right\}$$
$$b = \frac{1}{\tau_1\tau_2} - a_2a_3a_8\tau_4\mu + a_1a_4a_6\tau_3\mu\,, \quad c = a_1a_6\mu\frac{\tau_3}{\tau_2} \qquad (40)$$

Only the solution with the positive sign in front of the square root leading to u>0 has been retained, i.e., there is always exactly one solution for any arbitrary choice of the parameters (meeting the conditions a_2, a_4<0). The polynomial (38) leads to the following conditions for P(iη)=0:

$$\eta^4 - \eta^2\left\{\left(\frac{1}{\tau_1} - a_2v\right)\left(\frac{1}{\tau_2} - a_4u + \frac{1}{\tau_3} + \frac{1}{\tau_4}\right) + \left(\frac{1}{\tau_2} - a_4u\right)\left(\frac{1}{\tau_3} + \frac{1}{\tau_4}\right) + \frac{1}{\tau_3\tau_4}\right\} + \frac{1}{\tau_3\tau_4}\left\{\frac{-a_4u}{\tau_1} + \frac{-a_2v}{\tau_2} + \frac{1}{\tau_1\tau_2}\right\} = 0$$
$$\eta^2\left\{-a_2v - a_4u + \sum_i \frac{1}{\tau_i}\right\} = \sum_{i\neq j\neq k} \frac{1}{\tau_i\tau_j\tau_k} + \frac{-a_2v - a_4u}{\tau_3\tau_4} + \left(\frac{1}{\tau_3} + \frac{1}{\tau_4}\right)\left(\frac{-a_4u}{\tau_1} + \frac{-a_2v}{\tau_2}\right) \qquad (41)$$

u and v have to be inserted into (41) from (39) and (40), leading to an extremely complicated expression. However, analogous to the procedure explained before, we can prove that no solution exists by reducing (41) to an equation of type (35). Therefore, *system 2,2,1,1 is a second system with 4 components that meets all our conditions*. The system is given in graphical form in Fig. 9.

system 2,2,1,1:

$$\frac{dx}{dt} = a_1\mu + a_2vx - \frac{x}{\tau_1} \qquad \frac{dy}{dt} = a_3\mu + a_4uy - \frac{y}{\tau_2} \qquad a_1 > 0, a_3 > 0, a_5 = a_7 = 0$$
$$\frac{du}{dt} = a_6x - \frac{u}{\tau_3} \qquad \frac{dv}{dt} = a_8y - \frac{v}{\tau_4} \qquad a_2 < 0, a_4 < 0, a_6 > 0, a_8 > 0 \qquad (42)$$

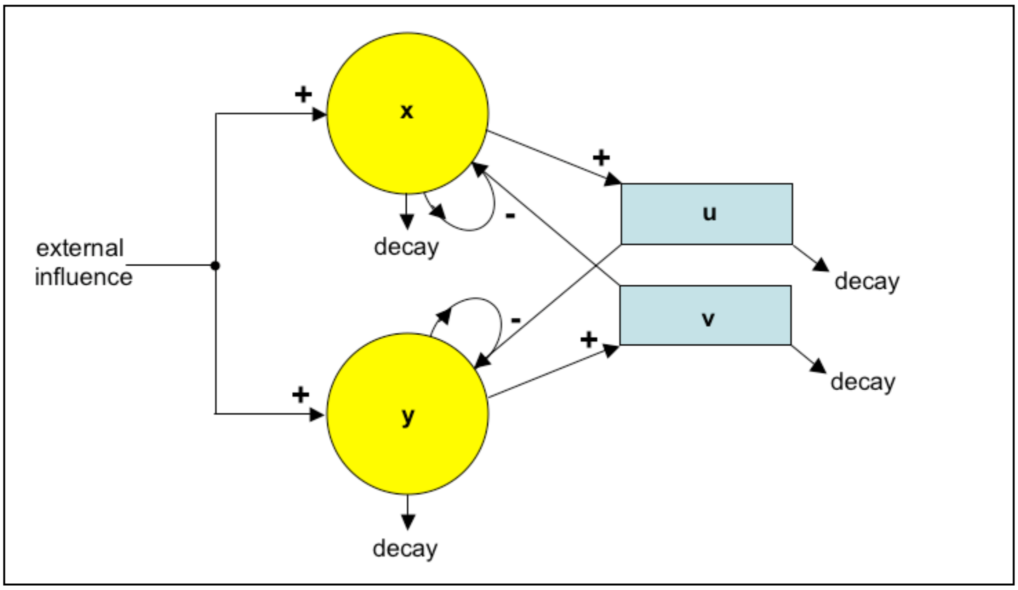

Fig. 9: Linearly stable 4-component system 2,2,1,1 according to equations (42).

The structure of this system is equivalent to the T1-T2-cell system, the basic building block of the immune system, shown in Fig. 1. Here, x, y are T1 and T2 helper cells, u, v are interferon-γ and an indicator for Interleukins 4, 5, 13, respectively. Fig. 10 shows the same system in a form more familiar for scientists working in the field of system dynamics.

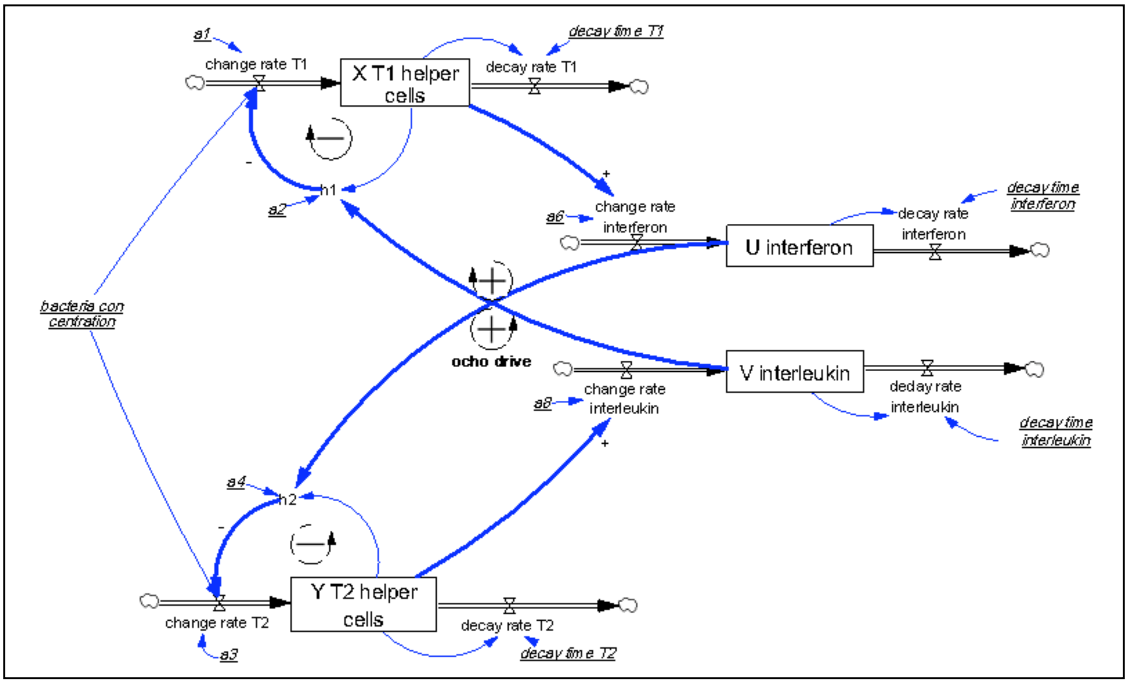

Fig. 10: Linearly stable 4-component system 2,2,1,1 in system dynamics view.

Summary of imposed conditions and results

For didactic reasons, we introduced our conditions step by step at the place where we needed them. To avoid the impression of arbitrariness, we sum up here the entire list of conditions to show once again their generic character.

- we impose the stability condition that for all external influences μ>0 and for all parameter values (not changing signs), a stationary state exists and is stable.
- the stationary state with all variables being zero must result from μ=0.
- equilibrium values for all variables must be positive for all parameter combinations and all μ>0.
- each component decays, described by a positive time constant.
- quadratic terms like x^2 are excluded, only bilinear terms are allowed, such as ux, vx, etc. (linearization around equilibrium).
- neither equation should read dx/dt=x{...}, because this would imply an equilibrium state with x=0 only or equilibrium states for all x (with {}=0). For

both cases, the terms within the brackets {} would have to fulfill conditions that cannot be true for arbitrary choices of the parameters.

- We require a coupling of each equation to at least one other equation for $\mu=0$ to avoid trivial systems.
- the combination $a_1\mu u+a_2u = (a_1\mu+a_2)u = a_1\mu' u$ does not introduce new dynamics and so can be considered as equivalent to $a_1\mu' u$.
- mathematical isomorphisms (systems getting identical after exchanging its variables) are considered as one and the same system.

All of the above stated conditions arise quite naturally in a biological or sociological context. However, we omitted systems with nonlinear external influences of type $a_i\mu x$ and equations of the form $u(a_{2,1}x+a_{2,2})$ to simplify our analysis. It is an open question, how many interesting systems are lost by these restrictions.

The main result of our mathematical analysis is a reduction of the number of valid systems from about 10^{10} to 10. From these 10 most simple systems, at least 2 are of central importance in a biological context. The 10 linearly stable systems are summarized in "stenographic" form in Fig. 11.

The number 10^{10} for possible system configurations is derived from the 4-component systems according to relation (4.2):

$$\begin{Bmatrix} (4+2)!+(4-1) \\ 4 \end{Bmatrix} = \begin{pmatrix} 723 \\ 4 \end{pmatrix} \approx \frac{720^4}{4!} \approx 1.12\cdot 10^{10} \qquad (43)$$

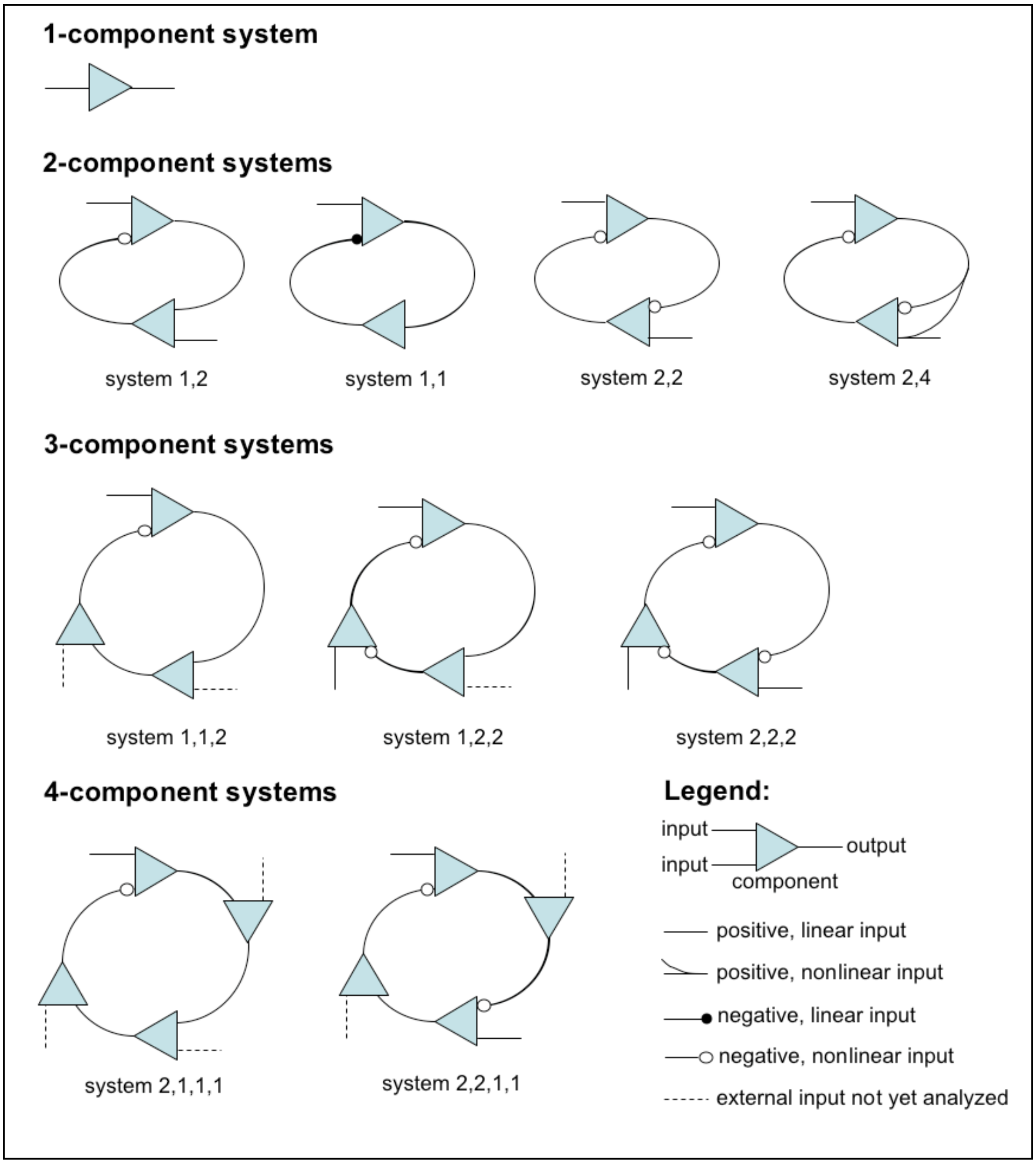

Fig. 11: Overview of the ten most simple linearly stable systems found among about 10^{10} different possibilities. Components with inhibitory nonlinear inputs (open circles) may be interpreted as cells, the other components as chemical substances. Broken lines refer to external inputs that were neglected in this report to simplify calculations. All components are assumed to have a decay-term driving the respective variables to zero when all external influences (forces) are absent. Systems with nonlinear external influences of type $a_i\mu x$ and equations of the form $u(a_{2,1}x+a_{2,2})$ were omitted in 3- and 4-component systems. Also systems 2,2,2,1 and 2,2,2,2 were not yet analyzed.

Discussion

We have analyzed interactions in systems with up to four components based on a set of conditions we imposed on them. Most of our conditions are based on general requirements we think are mandatory for a lot of systems where stability in a very large parameter space is an important issue. However, our set of restrictions might be too strong for certain classes of systems (only systems with linear external influences, no equations of the form $u(a_{2,1}x+a_{2,2})$). Therefore, our resulting ten systems have to be considered as a subset of all conceivable linearly stable systems with up to four components. A first extension of this minimal subset might follow from the inclusion of additional external influences (indicated by broken lines in Fig. 11). Then, more systems would be found if we considered also nonlinear external influences. In addition, weaker conditions might enlarge the class of linearly stable systems. We would like to point out that our stability analysis only ensures linear stability against small amplitude oscillations around stationary states. Nonlinear systems can display large amplitude nonlinear oscillations (called limit cycles) not detected with our linear analysis, i.e., some of our systems might show this type of instability and will have to be cancelled from the list of absolutely stable systems.

Though the number of possibilities grows quicker than exponentially with increasing number of components n (see (4.2) and (43)), the number of most simple stable system configurations found for n=1,2,3,4 was not increasing: we found one to four systems for every n. The next step to analyze the about 10^{16} 5-component systems seems feasible and might indicate how a search for systems with more components might go on. It is an interesting open question, if solutions can be found for every n or if there exists an upper limit for the number of components. A different but also important question concerns the stability of systems resulting from the combination of many systems with four and less components. In the immune system, the helper cell subsystems are built upon specific T1 and T2 cells resulting in a large number (in the order of 10^7 to 10^{11}) of parallel 2,2,1,1-subsystems that are interconnected by a few substances (such as interferons and interleukins). What are the conditions that an interconnection of stable systems remains stable?

Considerable activity in the field of system dynamics was devoted to define *generic structures* over the last decade[5] resulting in the definition of a series of useful tools (e.g. generic system archetypes, generic infrastructures) supporting model conceptualization, systemic thinking, and communication to share dynamic insights. In contrast, our classification is based on mathematical concepts and has to be considered as a theory aimed towards *understanding* of system structure rather than a set of practical rules helping *model building and communication*. We think that the combination of both, theory and practical rules, are the ingredients having the potential to boost the development of the field of *system dynamics*. Our approach towards a theory of stable systems seems to have a considerable potential for further development.

Conclusions

We have developed a theory of stable dynamical systems based on imposed generic conditions and some simplifications. We found the surprising result that our requirements were strong enough to reduce the variety of possible systems from the order of 10^{10} to 10. Several additional candidates are open to be analyzed further. It is interesting that two of the ten most simple systems play basic roles in biology, where stability in extremely varying conditions is mandatory. We think that the here presented theory of stable systems reveals important generic dynamical structures that can be used as building blocks for larger systems. It is open for further investigations, if the theory can be extended to systems with five or more components and to interactions of different systems. A general theory of stable dynamical systems would boost development of the interdisciplinary field of *system dynamics*. Further applications for such a theory could be found in the upcoming new research field called *structural biology* dealing with models to simulate the very complex biochemical reactions within a living cell.

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