Lie Group Analysis of a p53-mdm2 ODE Model

Gábor Horváth and Paolo Dini

Department of Media and Communications
London School of Economics and Political Science
London, United Kingdom
{g.horvath,p.dini}@lse.ac.uk

Abstract. This paper presents a symmetry analysis based on Lie groups of a system of ordinary differential equations (ODEs) modelling the p53-mdm2 regulatory pathway. This pathway is being investigated across several research groups as a biological system from which to extract dynamical and algebraic characteristics relevant to the emerging concept of Interaction Computing. After providing a conceptual motivation for the approach and some biological background for the choice of pathway, the paper gives an intuitive introduction to the method of Lie groups for a non-mathematical audience. This is followed by a general statement of the problem of finding the symmetries of a general system of four 1st-order ODEs, and then by the analysis of one such system modelling the p53-mdm2 pathway. The system chosen does not appear to harbour any symmetries, and therefore the effectiveness of the Lie group method cannot be demonstrated on this particular example. The symmetry analysis, however, helped reduce the system to a single Riccati equation for a specific choice of parameters, whose oscillatory behaviour appears to be relevant to the bio-computing perspective being discussed in a companion paper.

Keywords: Lie group, p53, symmetry, oscillation.

1 Introduction

Over the past few years, and across the DBE, OPAALS and BIONETS projects, we have mobilised a growing number of researchers and institutions in order to deepen and extend our study of the formal structure of cellular processes as the principal source of inspiration in our approach to biologically-inspired computing [5]. The rationale for this approach derives from the observation that the cell performs extremely complex functions by executing an intricate tangle of intersecting and interdependent metabolic and regulatory biochemical pathways, each of which can be considered analogous to an algorithm. Such behaviour is not planned and emerges spontaneously from the more elementary physical and chemical interactions at lower scales of description. What makes it possible is an immensely complex causal chain that links a stable periodic table of the elements to biological system behaviour through a stable set of physical laws. Thus, physical laws have bootstrapped an ecosystem that interacts with the

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biological systems living in it in such a way as to support their existence and reproduction.

Whereas the global and pervasive order construction mechanism that has enabled the bootstrapping of the ecosystem to happen is ultimately explainable through the memory-dependent dynamics of Darwinian evolution acting across many generations, a process called phylogeny, the same evolutionary mechanism has 'discovered' ways in which biological systems and their sub-systems can interact, internally and with their environments, in order to construct order during the life of the individual. These interactions are able to construct recursively nested complex structures at multiple scales, a process called ontogeny or morphogenesis, and then keep the metabolism of the adult organism running throughout its lifetime. Rather than attempting to reproduce or emulate this overwhelmingly complex and physical order construction process, our approach has been to focus on the *output* of this process, in the form, for example, of a stable metabolic or regulatory pathway. The key concept is stability: in spite of the unpredictability of the biochemical inputs to the cell, appropriate cellular functions will be performed reliably, as long as the cell or the individual is healthy.

As discussed more extensively in [5], the concept of regularity (over space, time, or different scales of description) is best formalised through algebraic symmetries. Thus, our research programme has been to analyse the hierarchical algebraic structure of the mathematical models derived from metabolic pathways, to interpret what their dynamic and computational function might be, and to then apply these algebraic structures as constraints on automata in order to obtain a model of computation that we are calling Interaction Computing. The evidence so far suggests that a stable pathway is not stable of its own accord, but is kept within the analogue of a stable 'potential well' by the pathways it is biochemically coupled to, which therefore act as constraints. As a consequence, it appears that in order to achieve the Interaction Computing vision (so far developed only conceptually) we will have to understand how multiple threads, that are performing different algorithms, need to be coupled so that they can aid or constrain each other, as the case may be.

In [5] we refer to this concept as the kernel of Symbiotic Computing, a model of computing that is meant to apply to the interaction of higher-level software constructs, such as whole services. The predominant mathematical model used to analyse the interdependence of biochemical pathways is a set of coupled, and generally non-linear, ordinary differential equations (ODEs) derived from the chemical reaction equations. The set of dependent variables in such a set of ODEs is made up of the concentrations of compounds participating in the chemical reactions. Starting from these same chemical reaction equations, the system dynamics can be discretised as a Petri net, from which a finite-state automaton can be derived. The justification for this discretisation process is discussed in [5]. Our work has then focussed on looking for algebraic structures in both mathematical models of the same pathway: Lie group dynamical symmetries

in the system of ODEs, discussed in this paper, and discrete computational symmetries in the automata [6].

This paper is part of a research framework that is documented in the following four companion papers at this same conference:

- A Research Framework for Interaction Computing [5]
  - Numerical and Experimental Analysis of the p53-mdm2 Regulatory Pathway [10]
  - Lie Group Analysis of a p53-mdm2 ODE Model (this paper)
  - Transformation Semigroups as Constructive Dynamical Spaces [6]
  - Towards Autopoietic Computing [1].

2 Oscillations in Biochemical Systems

We have focussed on the p53-mdm2 regulatory pathway because, in addition to its central role in the regulation of the cell cycle, it seemed that the oscillatory behaviour its constituents exhibit under particular conditions was too important a signature of the dynamics of the pathway to be overlooked, and felt that it could lead to useful insights for biologically-inspired algorithms and architectures. In the work discussed in [6] we are taking a close look at how oscillations can be modelled from a discrete mathematics perspective. It appears that cyclic phenomena in biochemical processes give rise to permutation groups in the hierarchical decomposition of the semigroups associated with the automata derived from such pathways. An example of a cyclic biochemical phenomenon is the Krebs or citric acid cycle, shown in Figure 1.

It is helpful to clarify the connection between cycles and oscillations by resorting to an idealised system in the form of the simple harmonic oscillator of

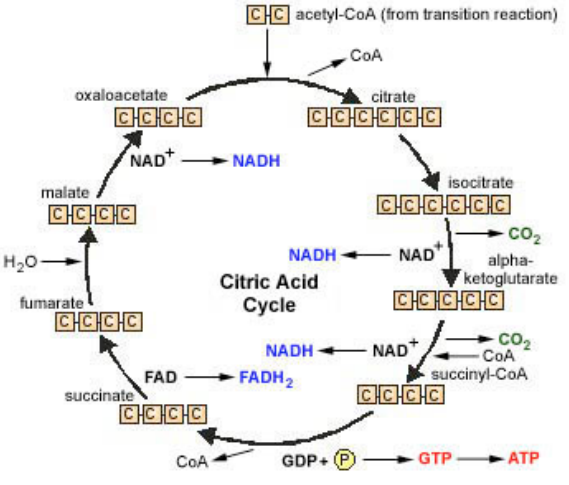

Fig. 1. Schematic of the Krebs or citric acid cycle [8]

elementary physics. As shown in Figure 2, for a simple harmonic oscillator periodic cycles (in some parameter space, which could include also Euclidean space) are mathematically indistinguishable from oscillations (in time, at a fixed point in space). For a biochemical system, the discrete algebraic analysis discussed in [6] indicates that biochemical processes such as the Krebs cycle, the concentration levels of whose metabolites can be assumed to remain constant over time, have the same 'algebraic signature' (i.e. permutation groups) as processes such as the p53-mdm2 pathway [10], in which the concentrations of the compounds oscillate as a function of time. The reason may be found in the fact that the models that give rise to these signatures describe what will happen (or what could happen, if there is a choice) to individual instances of classes of molecules or molecular complexes, but do not distinguish between instances of the same class. In simulations of the synchronized Krebs cycle and the p53-mdm2 pathway under conditions that promote sustained oscillations, indistinguishable instances of particular classes, such as citrate and active p53, appear and disappear periodically. Thus, the preliminary analytical results are confirming our initial hunch and the choice of problem.

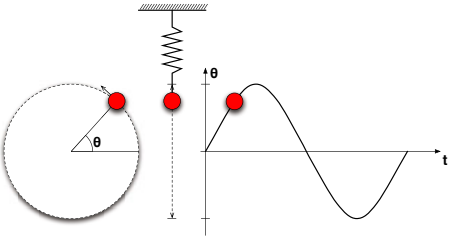

Fig. 2. Periodic behaviour of the simple harmonic oscillator

3 Background for p53-mdm2 System

A good discussion of the p53-mdm2 system is provided in [10,3], so here we summarise the highlights. Although the p53 protein participates in many pathways in the cell, we focussed on a small subset as a starting point. The p53 protein is linked to many other proteins and processes in the cell, but its coupling to the mdm2 protein appears to be particularly important for understanding cancer. Depending on the concentration level of p53, the cell can (in order of increasing concentration): (1) operate normally; (2) stop all functions to allow DNA repair to take place; (3) induce replicative senescence (disable cellular replication); and (4) induce apoptosis instantly (cell "suicide"). Therefore, p53 is a very powerful and potentially very dangerous chemical that humans (and most other animals) carry around in each cell, whose control must be tuned very finely indeed. Roughly 50% of all cancers result from the malfunction of the p53-mdm2 regulatory pathway in damaged cells that should have killed themselves.

P53 levels are controlled by a fast feedback mechanism in the form of the mdm2 protein. P53 is synthesised all the time, at a fairly fast rate; but the presence of p53 induces the synthesis of mdm2, which binds to p53 and causes it to be disintegrated. When the DNA is damaged (for instance by radiation in radiotherapy) the cell responds by binding an ATP molecule to each p53, bringing it to a higher energy level that prevents its destruction and causes its concentration to rise. Thus there are in all 4 biochemical species: p53, mdm2, p53-mdm2, and p53*, whose concentrations are modelled by 4 coupled and non-linear ordinary differential equations (ODEs).

As discussed in [10], the p53-mdm2 regulatory system is characterised by oscillatory and non-oscillatory regimes. A simplification of the p53-mdm2 system we have been working with assumes that in the absence of DNA damage with zero p53* initially the response of the system to non-equilibrium starting values of p53 and mdm2 is to create a peak of p53-mdm2 until enough p53 is destroyed and its level is brought back to equilibrium, without oscillations. On the other hand, if p53* is present because of DNA damage, then the system responds with a damped oscillation in its p53 level, until the damage is fixed. There are two ways in which Lie groups can help us with this problem: (1) by helping us solve the system of equations, as reported here in e.g. deriving a single first-order Riccati equation from the original system of 4 ODEs; or (2) providing additional information on the symmetry structure of the problem. This second aspect has not so far yielded directly usable results for this problem.

Figure 3 shows a subset of the chemical reactions associated with this pathway. Arrow heads indicate that a particular compound stimulates the production of the compound it points to, whereas a flat segment at the end of a line indicates inhibition. The small black circles with a 'u' inside indicate 'ubiquitination', which means labelling a particular compound for degradation. This system has been modelled by neglecting ATM and Arf for the moment.

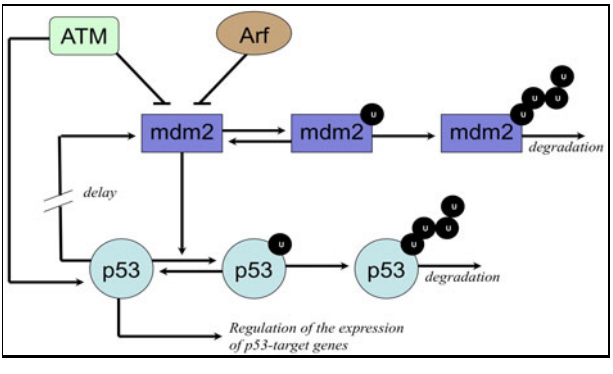

Fig. 3. Simplified interaction network for the p53-mdm2 regulatory pathway [3]

In Figure 4 the different forms of the p53 and mdm2 proteins are identified as follows: P_I = p53, M = mdm2, C = p53-mdm2 compound, P_A = phosphorylated p53, also denoted by p53*. From this type of diagram a Petri net can be easily derived, and the interdependencies between the compounds can be checked intuitively. The dotted arrows indicate promotion of gene expression.

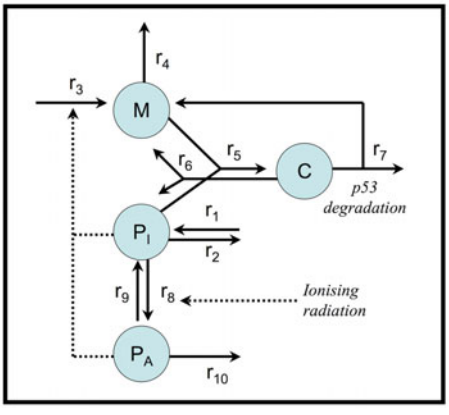

Fig. 4. Schematic of the simplified p53-mdm2 regulatory pathway [3]

The detailed description of the p53 model we use here can be found in [10]. We will use the dimensionless model described in that paper. Each of the four variables is a function of dimensionless time t. The equations are the following (subscript t indicates total derivative with respect to dimensionless time):

$$Pi_t = 1 + \beta_a Pa - (\beta_p + s\,(t))\, Pi - \alpha_c PiM + \beta_c C, \tag{1}$$

$$M_t = \alpha_{m0} + \frac{\alpha'_{m1} Pi + \alpha'_{m2} Pa}{Pi + Pa + \kappa_m} + (1 + \beta_c)\, C - (\beta_m + \alpha_c Pi)\, M, \tag{2}$$

$$C_t = \alpha_c PiM - (1 + \beta_c)\, C, \tag{3}$$

$$Pa_t = s\,(t)\, Pi - (\beta_a + \beta_p)\, Pa, \tag{4}$$

with $Pi(0) = Pi_0$, $M(0) = M_0$, $C(0) = C_0$, $Pa(0) = Pa_0$. Here, all greek letter parameters are constants, and Pa_0 is normally zero since its presence results from radiation damage. The radiation damage is modelled by the function $s(t)$. If there is no radiation, then $s(t) = 0$. If radiation is kept on a constant level, then $s(t)$ is constant. If the stimulation is a discrete pulse, then it can be modelled as $s(t) = \alpha_a e^{-\gamma t}$, with some parameters α_a and γ.

In the next section we give a conceptual introduction to why Lie groups are useful in solving differential equations. This will hopefully make the subsequent section, which is quite mathematical, more accessible to a broader audience.

4 Overview of Lie's Method

Symmetries are transformations that move a solution of the system of differential equations into another solution of the system. Understanding symmetries of a system of differential equations can be a milestone in their investigation. They can be useful for several reasons: first and most importantly if a 'trivial solution' is known (e.g. the constant function is a solution of many physical systems) then new, possibly less trivial solutions of the system can be generated. A typical example is the heat equation, where determining the symmetry group and knowing that the constant function is a solution enables us to recover its highly nontrivial fundamental solution. This example is discussed in full detail in [4], so in this section we only recapitulate the main concepts behind the method and then move to the analysis of the p53-mdm2 pathway in the next section. Second, understanding symmetries of a system of differential equations might enable us to create new methods for solving the particular system. A typical example for this application is the well-known method of solving an ODE with integrating factor. Another application of this type is explained in [2].

The fundamental idea of the method is to find a way to treat the differential equation as an algebraic equation in order to understand the underlying structure of the system better [9,7]. For this, it is helpful to first understand the basic notions of differential equations. Every differential equation consists of two different types of variables: *independent variables* and *dependent variables*. As the names suggest, the independent variables do not depend on any other variables, while the dependent variables are functions of the independent variables. One tries to find these functions when seeking a solution for a system of differential equations. What makes systems of differential equations different to systems of algebraic equations is that various differentials or derivatives of the dependent variables occur in the system. The first idea is to treat these differentials as 'new' dependent variables, which will turn the system into an algebraic system. These new dependent variables are called *prolongated variables*. Now, using the prolongated variables, the system can be treated as an algebraic system of equations, which defines a manifold in a higher-dimensional space. Every solution curve of the original system appears on the surface of this manifold.

Manifolds are topological spaces such that every point has a neighbourhood isomorphic to $\mathbb{R}^n$ for some n. In other words a manifold is a set of points which locally resemble $\mathbb{R}^n$. It can also be described as a continuously parameterisable space. Knowing these diffeomorphisms ("differentiable morphisms", also called coordinate charts) one can generalise the different notions (e.g. smooth function, vector field, tangent space, etc.) from $\mathbb{R}^n$ to manifolds and use them to perform calculations. We do not want to go deeply into the general theory of manifolds, but we want the reader to appreciate that this part of differential geometry has been heavily investigated and therefore is quite well understood. From our point of view this means that considering the manifold constructed from the system of differential equations gives us powerful tools to investigate the structural properties of the system.

As discussed in [2], if a first-order ODE is given, then there is only one independent variable (e.g. x or, perhaps more pertinent to biology and automata, time t), only one dependent variable (the function we are looking for, e.g. $u = u(x)$) and only one prolongated variable, which is the derivative of the dependent variable (e.g. $u^{(1)} = \frac{\partial u}{\partial x}$). Now, the variables $x, u, u^{(1)}$ span a three-dimensional space, which is called the *jet space*. The differential equation defines a two-dimensional surface in this three-dimensional space, and every solution curve of the original equation is a curve on this surface. Figure 5, reproduced from [2], shows an example for the differential equation

$$\frac{dy}{dx} = e^{-x}y^2 + y + e^x \tag{5}$$

Symmetries are transformations that move a solution (green curve on Figure 5) into another solution (blue curve on Figure 5). Lie's key observation was that these transformations are not discrete as in many situations (e.g. as discussed in [6]), but rather continuous, i.e. the symmetries continuously move a solution into another solution. These (the symmetries) are shown as black curves lying in the surface defining the ODE in Figure 5. Thus, for every such symmetry there exists a corresponding vector field (the *infinitesimal generator* of the symmetry), which at every point tells us the 'speed' vector of how the point is moved continuously by the symmetry. The speed at every point is shown as a red arrow tangent to the black curves in the same figure. Since solutions lie in the manifold determined by the abovementioned algebraic system, every such infinitesimal generator has to be tangent to the manifold. This is a (differential) condition, which enables us to compute the symmetries. In general the higher is the order of a system, the more conditions have to be satisfied by an infinitesimal generator, and thus the easier it is to find the complete symmetry group (in many situations knowing only a

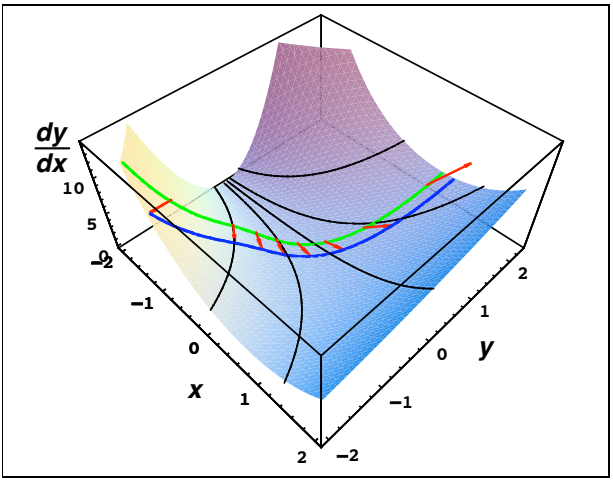

Fig. 5. Visualisation of solutions of a differential equation in the jet space

handful of symmetries can help enormously in solving a system of differential equations). After determining the infinitesimal generators, one can compute the symmetries with the so-called method of *exponentiation*, which is nothing more than the integral of a vector field to obtain a flow.

Thus, continuing the example of a first-order ODE, every symmetry moves a solution curve continuously into another solution curve. The speed of this movement is a vector field, which has to be tangent to the surface, since the solution curves lie on (in) the surface. The requirement to be tangent places a condition on the vector field. If a vector field satisfying this particular condition is found, the corresponding symmetry can be obtained by exponentiating the vector field.

Every symmetry corresponds to a vector field (the infinitesimal generator of the symmetry), such that if we move a solution curve along the flow corresponding to this vector field, then we again obtain solution curves. These symmetries form a (continuous) group called a *Lie group*. It is at first a bit difficult to see that Lie groups also have a manifold structure, and therefore that they have a tangent space at every point. However, looking again at Figure 5, we can see that the green solution curve is 'carried along' by the black curves, which act as a 'flow', into the blue solution curve. Thus, in this case the Lie group (technically this is a Lie subgroup, see below) is a transformation from the plane to the plane that can also be 'lifted' onto the same surface that defines the 'shape' of the differential equation. Moreover, for each point on the solution curve the Lie subgroup can be visualised as a 1-dimensional manifold, i.e. as one of the black curves.[1]

For the example shown in Figure 5, the Lie subgroup is [2]:

$$\begin{aligned} x'(x, y, \varepsilon) &= x + \varepsilon \\ y'(x, y, \varepsilon) &= y e^{\varepsilon}. \end{aligned} \tag{6}$$

Here ε is the continuous parameter of the Lie subgroup (i.e. $\varepsilon \in \mathbb{R}$). Although the above transformation maps the whole xy-plane to itself, it is convenient for the sake of this discussion to identify (x, y) with the green curve and (x', y') as the blue curve. Hence, we can easily see that the red arrows correspond to a finite value of ε (and this is indeed how they were generated in this figure). As $\varepsilon \to 0$, we approach the identity element of the subgroup, the green solution will therefore map to itself, and each of the red arrows becomes infinitesimal and tangent to its black curve at its intersection with the green solution. The tangent space at the identity is called the corresponding *Lie algebra* of the Lie group. The elements of a Lie algebra are vector fields, i.e. every element is a collection of vectors.

In Figure 5 the red arrows form a vector field, which is an element of the Lie algebra. This vector field corresponds to a symmetry, which is an element of the Lie group. We can consider the 1-dimensional manifold generated by this symmetry as one of the Lie subgroups of this equation's Lie group. It can be

[1] More precisely, the Lie subgroup is composed of the whole family of black curves, which corresponds to a particular transformation or symmetry.

visualised by the 'flow' shown in Figure 5, with the red arrows being the speed of the flow at every point. Of course, there could be more than one symmetry in any given system, and that is in fact generally the case. Almost all information of the Lie group is contained in the Lie algebra. Via this correspondence, one can replace non-linear conditions describing a symmetry by relatively simple infinitesimal conditions describing the corresponding Lie algebra element. Formally, the Lie algebra is formed by the vector fields of the infinitesimal generators of the symmetries lying in the Lie group. Every symmetry uniquely determines its infinitesimal generator and, by the exponentiating method, for every vector field there exists a corresponding symmetry. Thus knowing the Lie algebra of the symmetries is equivalent to knowing the symmetries themselves.

Since by definition a symmetry is a transformation that leaves something invariant, what is it that these symmetries leave invariant? It turns out that an equivalent definition to what has already been given is to say that a transformation of the dependent and independent variables of a system, as defined above, is a symmetry if it leaves *the functional form* of the system invariant; in other words, if the system of (ordinary or partial) differential equations looks *identical* when expressed in the new variables as when it is expressed in the old variables. We might be happy to believe that at face value, but it turns out that we can again use Figure 5 to improve our understanding. The transformation given by Eq. (6) is such that, when substituted into the original ODE, Eq. (5), the resulting ODE in the new variables will look identical. Therefore, the graph of the new ODE will look identical to Figure 5. Therefore, the geometrical visualisation of what a symmetry preserves is *the shape of the surface corresponding to the system when plotted in the jet space.* Of course, for anything but a single, first-order ODE it is not possible to 'see' this actual 'surface', but hopefully Figure 5 is clear enough to provide an intuitive understanding of the more general case. So now we can probably also see why symmetries map solutions to solutions. Since they map the ODE surface to itself, any set of points such as the green curve will be mapped to another set of points on the same surface. But all the points on the surface satisfy the ODE, by construction. Hence solutions are necessarily mapped to solutions, and this statement generalises to higher-dimensional systems.

It is instructive to think briefly about the converse case, i.e. what happens when we transform the system with a map that is *not* a symmetry. Quite simply, what will happen is that the functional form of the ODE will look different to Eq. (5), and hence the original surface will be mapped to a *new and different* surface. Hence, not all of the red arrows will necessarily be tangent to the original surface as instead they are in Figure 5.

The invertible transformations of a mathematical object that leave some feature of its structure invariant always form a group. This is the case here as well, as *all* Lie symmetries together, and not only each single one as discussed two paragraphs above, can be shown to satisfy the axioms of *the same* group. Thus, as we have already stated, each set of symmetries written as Eq. (6) (i.e. $\exp(\varepsilon \mathbf{v})$ for all $\varepsilon \in \mathbb{R}$) is more properly called a Lie *subgroup* of the system.

5 Lie Symmetry Analysis of p53-mdm2 System

5.1 The General Symmetry Conditions

The general discussion in this subsection builds on the work reported in [4]. The methods described in this report can help understand the analysis of the system of differential equations modelling the p53 network described in [3]. As discussed above, the version of this model that we are currently analysing uses four variables, each depending on the time t. Therefore, we examine first a general system of four ODEs in four variables:

$$\begin{aligned} u_t &= f(t,u,v,y,z), \\ v_t &= g(t,u,v,y,z), \\ y_t &= p(t,u,v,y,z), \\ z_t &= q(t,u,v,y,z). \end{aligned} \tag{7}$$

As in Section 3, the subscript t denotes derivation with respect to dimensionless time. In Section 4 we explained that a symmetry of a system of differential equations is a mapping which moves solution curves to solution curves. Every symmetry has an infinitesimal generator, which is a vector field $\mathbf{v}$ of the form

$$\begin{aligned} \mathbf{v} = {} & \tau(t,u,v,y,z)\,\partial_t + \phi(t,u,v,y,z)\,\partial_u \\ & + \psi(t,u,v,y,z)\,\partial_v + \mu(t,u,v,y,z)\,\partial_y \\ & + \nu(t,u,v,y,z)\,\partial_z. \end{aligned} \tag{8}$$

Here, $\partial_t = \frac{\partial}{\partial t}$, $\partial_u = \frac{\partial}{\partial u}$, $\partial_v = \frac{\partial}{\partial v}$, $\partial_y = \frac{\partial}{\partial y}$, $\partial_z = \frac{\partial}{\partial z}$ denote the corresponding basis vectors, or equivalently the corresponding partial differential operators. If $\mathbf{v}$ is an infinitesimal generator of a symmetry, then the flow of the symmetry (i.e. the mapping $(t,u,v,y,z) \to \Psi(\varepsilon,t,u,v,y,z)$) can be computed by exponentiating:

$$\exp(\varepsilon\mathbf{v})(t,u,v,y,z) = \Psi(\varepsilon,t,u,v,y,z),$$

where

$$\begin{aligned} \Psi(0,t,u,v,y,z) &= (t,u,v,y,z), \\ \frac{d}{d\varepsilon}\Psi(\varepsilon,t,u,v,y,z) &= \mathbf{v}\big|_{\Psi(\varepsilon,t,u,v,y,z)}. \end{aligned}$$

Let $\mathbf{v}$ be an infinitesimal generator of a symmetry of (7) in the form of (8). Moreover, for an arbitrary function $\zeta(t,u,v,y,z)$ let us define the following operator:

$$S(\zeta) = \zeta_t + f\zeta_u + g\zeta_v + p\zeta_y + q\zeta_z. \tag{9}$$

Then the symmetry conditions for the system (7) are the following:

$$\begin{aligned} &- f_t\tau - f_u\phi - f_v\psi - f_y\mu - f_z\nu \\ &\qquad - fS(\tau) + S(\phi) = 0, \qquad (10)\\ &- g_t\tau - g_u\phi - g_v\psi - g_y\mu - g_z\nu \\ &\qquad - gS(\tau) + S(\psi) = 0, \qquad (11)\\ &- p_t\tau - p_u\phi - p_v\psi - p_y\mu - p_z\nu \\ &\qquad - pS(\tau) + S(\mu) = 0, \qquad (12)\\ &- q_t\tau - q_u\phi - q_v\psi - q_y\mu - q_z\nu \\ &\qquad - qS(\tau) + S(\nu) = 0. \qquad (13) \end{aligned}$$

Let us observe that for arbitrary $\tau(t,u,v,y,z)$ the following coefficients always satisfy the symmetry conditions (10–13):

$$\begin{aligned} \phi(t,u,v,y,z) &= f(t,u,v,y,z)\cdot\tau(t,u,v,y,z),\\ \psi(t,u,v,y,z) &= g(t,u,v,y,z)\cdot\tau(t,u,v,y,z),\\ \mu(t,u,v,y,z) &= p(t,u,v,y,z)\cdot\tau(t,u,v,y,z),\\ \nu(t,u,v,y,z) &= q(t,u,v,y,z)\cdot\tau(t,u,v,y,z). \end{aligned}$$

This is equivalent to the vector $\mathbf{v}_\tau$ always being an infinitesimal generator of a symmetry:

$$\mathbf{v}_\tau = \tau\partial_t + f\tau\partial_u + g\tau\partial_v + p\tau\partial_y + q\tau\partial_z.$$

In fact, taking a closer look at this infinitesimal generator we can observe that it corresponds to the symmetry where the flows are exactly the solution curves of the system (7). Thus $\mathbf{v}_\tau$ does not move a solution curve into another solution curve, but rather moves *along* the solution curves. (For a more detailed explanation, see Section 3.3.2 of [4].) This symmetry does not give us any 'new' or useful information on the system (7). Therefore let us call the infinitesimal generator $\mathbf{v}_\tau$ (for arbitrary $\tau(t,u,v,y,z)$) a *trivial* infinitesimal generator.

The infinitesimal generators form a Lie algebra: i.e. if $\mathbf{v_1}$ and $\mathbf{v_2}$ are infinitesimal generators of some symmetries, then $\mathbf{v_1}+\mathbf{v_2}$ and $[\mathbf{v_1},\mathbf{v_2}]$ are infinitesimal generators, as well. We define an equivalence relation on the Lie algebra of infinitesimal generators. We call two infinitesimal generators equivalent, if their difference is a trivial infinitesimal generator, i.e. $\mathbf{v_1}$ and $\mathbf{v_2}$ are equivalent (denoted by $\mathbf{v_1}\sim\mathbf{v_2}$) if and only if $\mathbf{v_1}-\mathbf{v_2}=\mathbf{v}_\tau$ for some $\tau(t,u,v,y,z)$. It is easy to see that this relation is indeed an equivalence relation, which captures the nontrivial symmetries.

If $\mathbf{v} = \tau\partial_t + \phi\partial_u + \psi\partial_v + \mu\partial_y + \nu\partial_z$ is an infinitesimal generator, then $\mathbf{v}\sim\mathbf{v}-\mathbf{v}_\tau = (\phi - f\tau)\partial_u + (\psi - g\tau)\partial_v + (\mu - p\tau)\partial_y + (\nu - q\tau)\partial_z$. Thus every infinitesimal generator is equivalent to one with coefficient $\tau = 0$. Thus without loss of generality we can assume that $\tau = 0$. Then the symmetry conditions of the system (7) are

$$
\begin{aligned}
-f_u\phi - f_v\psi - f_y\mu - f_z\nu + S(\phi) &= 0,\\
-g_u\phi - g_v\psi - g_y\mu - g_z\nu + S(\psi) &= 0,\\
-p_u\phi - p_v\psi - p_y\mu - p_z\nu + S(\mu) &= 0,\\
-q_u\phi - q_v\psi - q_y\mu - q_z\nu + S(\nu) &= 0,
\end{aligned}
$$

where S is defined by (9).

5.2 The General p53 Model

In Eqs. (1)-(4), $s(t)$ represents the radiation stimulus, which induces the creation of Pa-type p53 molecules from Pi-type p53 molecules. The function $s(t)$ can have three different interesting forms depending on three situations:

1. When there is no stimulus at all, i.e. $s(t) = 0$. This can be considered as initial situation, when $Pa = 0$, and Pa will stay 0, as $Pa_t = 0$. This extremely simplifies the system by basically eliminating the variable Pa and the function $s(t)$.
2. When there is no stimulus (i.e. $s(t) = 0$), but there is some initial Pa value.
3. When it is kept at a constant level, i.e. $s(t) = \alpha_a$ is constant.
4. When the stimulation is a discrete pulse 'insult' at time zero, which can be modelled as $s(t) = \alpha_a e^{-\gamma t}$, with some parameters α_a and γ.

There is another simplification that can be done, which corresponds to the saturation of the system, i.e. to the expression

$$\frac{\alpha'_{m1}Pi + \alpha'_{m2}Pa}{Pi + Pa + \kappa_m}. \tag{14}$$

When κ_m is much bigger than Pi and Pa, we simply neglect the latter two in the denominator and replace (14) by

$$\alpha_{m1}Pi + \alpha_{m2}Pa,$$

where $\alpha_{m1} = \alpha'_{m1}/\kappa_m$ and $\alpha_{m2} = \alpha'_{m2}/\kappa_m$. Thus we consider the following system:

$$
\begin{aligned}
Pi_t &= 1 + \beta_a Pa - (\beta_p + s(t))\, Pi \\
&\qquad - \alpha_c PiM + \beta_c C, && (15)\\
M_t &= \alpha_{m0} + \alpha_{m1}Pi + \alpha_{m2}Pa + (1+\beta_c)\, C \\
&\qquad - (\beta_m + \alpha_c Pi)\, M, && (16)\\
C_t &= \alpha_c PiM - (1+\beta_c)\, C, && (17)\\
Pa_t &= s(t)\, Pi - (\beta_a + \beta_p)\, Pa. && (18)
\end{aligned}
$$

5.3 No Stimulus

In this situation there is no radiation stimulus at all, i.e. $s(t) = 0$. Moreover, as it is an initial situation, $Pa = 0$, as well. Incorporating it to the equations (15–18) and renaming the variables to u, v and w yields

$$
\begin{aligned}
u_t &= 1 - \beta_p u - \alpha_c uv + \beta_c w,\\
v_t &= \alpha_{m0} + \alpha_{m1} u - \beta_m v - \alpha_c uv + (1+\beta_c)\, w,\\
w_t &= \alpha_c uv - (1+\beta_c)\, w.
\end{aligned}
$$

Now, $\mathbf{v} = \phi(t,u,v,w)\,\partial_u + \psi(t,u,v,w)\,\partial_u + \rho(t,u,v,w)\,\partial_w$ is a symmetry if the functions ϕ, ψ and ρ satisfy the symmetry conditions:

$$(\beta_p + \alpha_c v)\,\phi + \alpha_c u\psi - \beta_c \rho + S(\phi) = 0, \tag{19}$$

$$(-\alpha_{m1} + \alpha_c v)\,\phi + (\beta_m + \alpha_c u)\,\psi - (1+\beta_c)\,\rho + S(\psi) = 0, \tag{20}$$

$$-\alpha_c v\phi - \alpha_c u\psi + (1+\beta_c)\,\rho + S(\rho) = 0, \tag{21}$$

where the operator S is defined by

$$
\begin{aligned}
S(\zeta) = \zeta_t &+ (1 - \beta_p u - \alpha_c uv + \beta_c w)\,\zeta_u\\
&+ (\alpha_{m0} + \alpha_{m1} u - \beta_m v - \alpha_c uv\\
&\qquad + (1+\beta_c)\, w)\zeta_v\\
&+ (\alpha_c uv - (1+\beta_c)\, w)\,\zeta_w.
\end{aligned}
$$

Adding (21) to equations (19) and (20) and using the additivity of S yields

$$
\begin{aligned}
\beta_p\phi + \rho + S(\phi+\rho) &= 0,\\
-\alpha_{m1}\phi + \beta_m\psi + S(\psi+\rho) &= 0.
\end{aligned}
$$

Now, if the parameters are $\beta_p = 1 = \alpha_{m1} = \beta_m$, then these equations are further simplified to

$$\phi + \rho + S(\phi+\rho) = 0, \tag{22}$$

$$-\phi + \psi + S(\psi+\rho) = 0. \tag{23}$$

From (22) we immediately obtain that

$$\phi = -\rho + \xi_1,$$

where ξ_1 is a solution to $\xi_1 + S(\xi_1) = 0$. Substituting it into (23) we obtain that

$$\psi = -\rho + \xi_2,$$

where ξ_1 and ξ_2 satisfy

$$\xi_1 + S(\xi_1) = 0, \tag{24}$$

$$-\xi_1 + \xi_2 + S(\xi_2) = 0. \tag{25}$$

To find the general solutions to equations (24) and (25) can be really hard, but we were able to find solutions by chance:

$$
\begin{aligned}
\xi_1 &= c_1 \cdot e^{-t},\\
\xi_2 &= c_1 \cdot t \cdot e^{-t} + c_2 \cdot e^{-t}.
\end{aligned}
$$

Inspired by the fact that we can find nice nontrivial examples for the functions $\xi_1 = \phi + \rho$ and $\xi_2 = \psi + \rho$, we introduce the following coordinate change:

$$y(t) = u(t) + w(t), \tag{26}$$
$$z(t) = v(t) + w(t). \tag{27}$$

With these new coordinates, $u = y - w$, $v = z - w$ and equations (19–21) become

$$\begin{aligned} y_t - w_t &= 1 - y + w - \alpha_c (y - w) \cdot (z - w) \\ &\quad + \beta_c w, \\ z_t - w_t &= \alpha_{m0} + y - w - (z - w) \\ &\quad - \alpha_c (y - w) \cdot (z - w) + (1 + \beta_c) w, \\ w_t &= \alpha_c (y - w) \cdot (z - w) - (1 + \beta_c) w, \end{aligned}$$

which is equivalent to the system

$$y_t = 1 - y, \tag{28}$$
$$z_t = \alpha_{m0} + y - z, \tag{29}$$
$$w_t = \alpha_c w^2 - (1 + \beta_c + \alpha_c y + \alpha_c z) w + \alpha_c y z. \tag{30}$$

Here, the solution to (28) is almost the same function as ξ_1:

$$y(t) = 1 + c_1 \cdot e^{-t}.$$

Substituting this solution into (29) we obtain a solution for $z(t)$ similar to ξ_2:

$$z(t) = 1 + \alpha_{m0} + c_1 \cdot t \cdot e^{-t} + c_2 \cdot e^{-t}.$$

Thus the original system (19–21) reduces to the Riccati equation

$$\boxed{\begin{aligned} w_t = \alpha_c w^2 &- (1 + \beta_c + \alpha_c (2 + \alpha_{m0} \\ &+ (c_1 + c_2) \cdot e^{-t} + c_1 \cdot t \cdot e^{-t})) w \\ &+ \alpha_c \cdot \left(1 + c_1 \cdot e^{-t}\right) \\ &\cdot \left(1 + \alpha_{m0} + c_1 \cdot t \cdot e^{-t} + c_2 \cdot e^{-t}\right). \end{aligned}} \tag{31}$$

Had we found a solution to equation (31), $u(t)$ and $v(t)$ could be expressed in the following way:

$$u(t) = 1 + c_1 \cdot e^{-t} - w(t),$$
$$v(t) = 1 + \alpha_{m0} + c_1 \cdot t \cdot e^{-t} + c_2 \cdot e^{-t} - w(t).$$

The constants c_1 and c_2 are determined by the initial conditions:

$$c_1 = u(0) + w(0) - 1,$$
$$c_2 = v(0) + w(0) - 1 - \alpha_{m0}.$$

Unfortunately equation (31) cannot be solved in general, unless at least one solution can be found. Nevertheless, it can be solved numerically. Figure 6 shows the solution curve for the following choice of parameters [3]:

$$\begin{aligned} u(0) &= 3.5 & v(0) &= 0.008 & w(0) &= 0.993 \\ \alpha_{m0} &= 0.00005 & \alpha_c &= 35 & \beta_c &= 0.005. \end{aligned}$$

One can read from the figure that w increases in time until it reaches a maximum, then it decreases, which is consistent with its decaying factor.

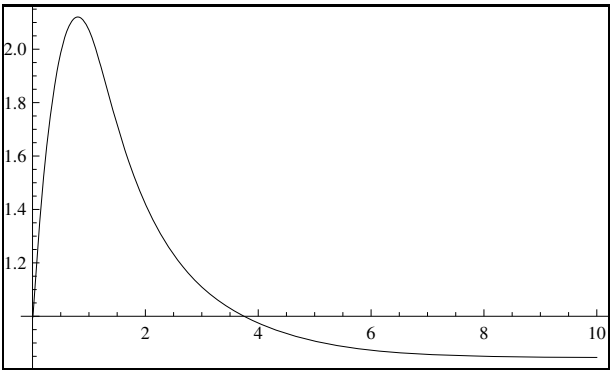

Fig. 6. Numerical solution to (31). The horizontal axis is the dimensionless time t, the vertical axis is w.

5.4 No Stimulus with Initial *Pa* Value

Let us assume now that there is no radiation, i.e. $s(t) = 0$, but unlike before there exists some active p53 initially, i.e. $Pa(0) = a_0 > 0$. Incorporating it into Equations (15–18) and renaming the variables to u, v, w and x yields

$$\begin{aligned} u_t &= 1 - \beta_p u + \beta_a x - \alpha_c uv + \beta_c w, \\ v_t &= \alpha_{m0} + \alpha_{m1} u + \alpha_{m2} x - \beta_m v - \alpha_c uv \\ &\qquad + (1 + \beta_c) w, \\ w_t &= \alpha_c uv - (1 + \beta_c) w, \\ x_t &= -(\beta_a + \beta_p) x. \end{aligned}$$

Again, we can introduce the same coordinate change (26) and (27) inspired by the examination of the symmetry conditions of the system:

$$\begin{aligned} y(t) &= u(t) + w(t), \\ z(t) &= v(t) + w(t). \end{aligned}$$

Using this coordinate change we obtain

$$x_t = -(\beta_a + \beta_p)\, x, \tag{32}$$

$$y_t = 1 + \beta_a x - \beta_p y + (\beta_p - 1)\, w, \tag{33}$$

$$z_t = \alpha_{m0} + \alpha_{m2} x + \alpha_{m1} y - \beta_m z + (\beta_m - \alpha_{m1})\, w, \tag{34}$$

$$\boxed{w_t = \alpha_c w^2 - (1 + \beta_c + \alpha_c y + \alpha_c z)\, w + \alpha_c y z.} \tag{35}$$

Again, we observe that if $\beta_p = 1$ and $\alpha_{m1} = \beta_m$, then the equations (32–34) can be solved after each other. In particular the solution for (32) is

$$x(t) = c_1 \cdot e^{-(1+\beta_a)t},$$

for an arbitrary constant c_1. Substituting this result into (33) we obtain a solution:

$$\begin{aligned} y(t) &= 1 - x(t) + c_2 \cdot e^{-t} \\ &= 1 - c_1 \cdot e^{-(1+\beta_a)t} + c_2 \cdot e^{-t}, \end{aligned}$$

for an arbitrary constant c_2. Substituting this result into (34) we obtain a solution for $z(t)$. If $\beta_m \neq 1$ and $\beta_m \neq 1 + \beta_a$, then

$$\begin{aligned} z(t) &= \frac{\alpha_{m0}}{\beta_m} + \frac{1}{(1-\beta_m)} \\ &\quad + \frac{\alpha_{m2}\beta_m - \alpha_{m2} - \beta_a\beta_m}{(\beta_m - 1 - \beta_a)(\beta_m - 1)} \cdot x(t) \\ &\quad + \frac{\beta_m}{\beta_m - 1} \cdot y(t) + c_3 \cdot e^{-\beta_m t} \\ &= 1 + \frac{\alpha_{m0}}{\beta_m} + \frac{\beta_m - \alpha_{m2}}{1 + \beta_a - \beta_m} \cdot c_1 \cdot e^{-(1+\beta_a)t} \\ &\quad + \frac{\beta_m}{\beta_m - 1} \cdot c_2 \cdot e^{-t} + c_3 \cdot e^{-\beta_m t}, \end{aligned}$$

for an arbitrary constant c_3. If $\beta_m = 1 + \beta_a$, then

$$\begin{aligned} z(t) &= 1 + \frac{\alpha_{m0}}{1 + \beta_a} \\ &\quad + (\alpha_{m2} - 1 - \beta_a) \cdot c_1 \cdot t \cdot e^{-(1+\beta_a)t} \\ &\quad + \frac{1 + \beta_a}{\beta_a} \cdot c_2 \cdot e^{-t} + c_3 \cdot e^{-(1+\beta_a)t}, \end{aligned}$$

for an arbitrary constant c_3. If $\beta_m = 1$, then

$$\begin{aligned} z(t) &= 1 + \alpha_{m0} + \frac{1 - \alpha_{m2}}{\beta_a} \cdot c_1 \cdot e^{-(1+\beta_a)t} \\ &\quad + c_2 \cdot t \cdot e^{-t} + c_3 \cdot e^{-t}, \end{aligned}$$

for an arbitrary constant c_3. If $\beta_m = 1$ and $\beta_a = 0$, then

$$z(t) = 1 + \alpha_{m0} + (1 - \alpha_{m2}) \cdot c_1 \cdot e^{-2t} + c_2 \cdot t \cdot e^{-t} + c_3 \cdot e^{-t}.$$

for an arbitrary constant c_3.

Substituting these solutions into (35) the original system (19–21) reduces to a rather complicated Riccati equation. Had we found a solution to this equation, we could express $u(t)$ and $v(t)$ in the following way:

$$u(t) = y(t) - w(t),$$
$$v(t) = z(t) - w(t).$$

The constants c_1, c_2, c_3 are determined by the initial conditions $x(0)$, $u(0)$, $v(0)$, $w(0)$:

$$c_1 = x(0),$$
$$c_2 = x(0) + u(0) + w(0) - 1,$$

and if $\beta_m \neq 1$ and $\beta_m \neq 1 + \beta_a$, then

$$c_3 = \left(\frac{\beta_m}{\beta_m - 1} + \frac{\beta_m - \alpha_{m2}}{\beta_m - 1 - \beta_a}\right) \cdot x(0) + \frac{\beta_m}{1 - \beta_m} \cdot u(0) + v(0) + \frac{1}{1 - \beta_m} w(0) + \frac{\beta_m}{\beta_m - 1} + \frac{\beta_a + 1 - \beta_m}{\beta_m - 1 - \beta_a} \cdot \left(1 + \frac{\alpha_{m0}}{\beta_m}\right).$$

If $\beta_m = 1 + \beta_a$, then

$$c_3 = -\left(1 + \frac{1}{\beta_a}\right) \cdot x(0) - \left(1 + \frac{1}{\beta_a}\right) \cdot u(0) + v(0) - \frac{1}{\beta_a} \cdot w(0) + \frac{1}{\beta_a} - \frac{\alpha_{m0}}{1 + \beta_a}.$$

If $\beta_m = 1$, then

$$c_3 = \frac{\alpha_{m2} - 1}{\beta_a} \cdot x(0) + v(0) + w(0) - 1 - \alpha_{m0}.$$

If $\beta_m = 1$ and $\beta_a = 0$, then

$$c_3 = (\alpha_{m2} - 1) \cdot x(0) + v(0) + w(0) - 1 - \alpha_{m0}.$$

Figure 7 shows the solution curve for the following choice of parameters [3]:

$$x(0) = 0 \qquad u(0) = 3.5 \qquad v(0) = 0.008$$
$$w(0) = 0.993 \qquad \alpha_{m0} = 0.00005 \qquad \alpha_c = 35$$
$$\beta_c = 0.005 \qquad \beta_m = 1 \qquad \beta_a = 0.5.$$

It looks quite similar to the one shown in Figure 6, i.e. an overdamped system.

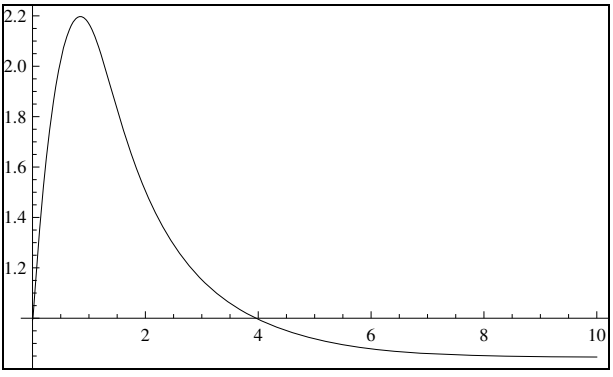

Fig. 7. Numerical solution to (35). The horizontal axis is the dimensionless time t, the vertical axis is w.

For other choices of parameters this system can indeed oscillate, as shown in [10]. In this paper our objective was to seek Lie symmetries and/or analytical solutions in order to gain insight into the analytical structure of the system, so we prioritised these activities over a study of the oscillations per se.

6 Conclusion

It is interesting that by making use of the transformation

$$w(t) = r'(t)/r(t)$$

the Riccati equations (31) and (35) can be transformed into linear ODEs in the new variable $r(t)$. However, because the coefficients of these ODEs are complicated functions of time, neither is integrable. Thus for this example we conclude that the Lie symmetry analysis has not been particularly useful, so far, beyond helping us see the possibility to reduce the original problem to a Riccati equation for a particular choice of parameters. The objective to gain insight into the analytical structure of the system has nonetheless been partially achieved, since the Riccati equation gives us a good starting point for further investigation.

Rather than an indication that there are no dynamical symmetries hiding in this regulatory pathway, this result is more likely a consequence of the simplicity of the p53-mdm2 ODE system chosen to represent it. More precisely, from the point of view of a mathematical model that is meant to capture the most important aspects of the physical phenomenon this model might be too simple. On the other hand, as a mathematical problem it is already rather complicated and practically impossible to solve analytically. So we need to look for a better model that is more expressive physically but simpler mathematically, which is not easy to do. More variables are in general used as part of this pathway, so that the next logical step is to enlarge the system to 5 or 6 equations. The present analysis has already helped us see quite a few features of the problem, and therefore provides a starting point upon which to build a more in-depth investigation.

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