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Structural identifiability and observability of tumour growth models with and without chemotherapy

González Vázquez, Adriana[a], Villaverde, Alejandro F.[a,b,*]

[a] *Universidade de Vigo, Departmento de Ingeniería de Sistemas y Automática, 36310 Vigo, Galicia, España*
[b] *CITMAga, 15782 Santiago de Compostela, Galicia, España*

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Resumen

En este trabajo se presenta una guía de modelos mecanísticos para el estudio del crecimiento tumoral, basados en ecuaciones diferenciales ordinarias (EDOs). El análisis se centra en las propiedades de identificabilidad estructural y observabilidad, fundamentales para la estimación de parámetros y la obtención de predicciones fiables. Se analizan modelos representativos que incluyen procesos sin terapia y con quimioterapia. Se ofrecen resultados agrupados por tipo de modelo, proporcionando una visión general sobre su aplicabilidad y limitaciones. Esta guía está pensada como apoyo para la selección de modelos en aplicaciones biomédicas.

Palabras clave: modelos matemáticos, modelos dinámicos, biología matemática, oncología matemática, crecimiento tumoral, quimioterapia

Abstract

In this work we present a guide to mechanistic models for studying tumour growth, based on ordinary differential equations (ODEs). The analysis focuses on structural identifiability and observability, essential for estimating parameters and obtaining reliable predictions. We analyse representative models that include untreated dynamics as well as chemotherapy. Results are grouped by model type, providing an overview of their applicability and limitations. This guide is intended to support model selection in biomedical applications.

Keywords: mathematical modelling, dynamic modelling, mathematical biology, mathematical oncology, tumour growth, chemotherapy

1. Introduction

In the last decades, the growing understanding of cancer biology has led to an increasingly complex portrait of the relevant processes (Hanahan and Weinberg, 2000, 2011; Hanahan, 2022). In parallel, the utility of mathematical models in biomedicine–and more specifically, dynamic models–has become clearer. As a consequence, mathematical oncology is now a distinct area of mathematical biology (Anderson and Maini, 2018; Bull and Byrne, 2022). There is currently a wealth of computational tools that support the biomedical modelling process and allow to fully exploit the capabilities of mathematical models (Villaverde et al., 2022). The integration of mathematical and computational tools – sometimes called the dynamic systems biology approach (Klipp et al., 2005; DiStefano III, 2015; Villaverde and Banga, 2014) – has enabled the modelling of tumour dynamics and, as a result, facilitated the quantitative evaluation of the therapeutic efficiency of treatments.

Here, we adopt this approach and focus on mathematical models that are *mechanistic*, i.e., they provide explanations of the mechanism by which a phenomenon takes place; and *dynamic*, i.e., they are based on differential equations that des-

*Autor para correspondencia: afvillaverde@uvigo.gal

cribe the key aspects of their dynamics. These models can be used for many purposes (Enderling and Wolkenhauer, 2021). First of all, they encapsulate the available knowledge (or beliefs) about a process, allowing to reproduce results and test if an hypothesis is consistent with the current knowledge. They can make quantitative predictions, ideally with an estimate of the associated uncertainties. This predictive capability opens many possibilities; crucially, it allows not only to anticipate the result of a treatment, but also to optimize its design.

Thus, in the context of mathematical or computational oncology these models serve not only to encode and formalize our current understanding of tumour biology but also to provide a base for prediction and intervention. There is currently a great variety of tumour growth models of varying mathematical formalisms, purposes, and levels of detail (see e.g. Yin et al. (2019); Bull and Byrne (2022)). One aim of this paper is to provide a compact account of the most relevant ones, facilitating the choice of the most appropriate model for a given purpose. To this end, we describe a set of mathematical models that describe tumour growth, with and without chemotherapy. We consider models in ordinary differential equations (ODEs), which can describe processes that are deterministic and homogeneous. We assign an acronym to each model, and we provide their equations in a systematic notation.

The application of these models is not limited to biological insight; their ultimate goal would be arguably to guide the design and optimization of treatments, maximizing their efficacy while minimizing the adverse effects for the patient. In order to perform successfully in those applications, a model must be properly calibrated (Villaverde et al., 2022). Key tasks of the calibration process include identifiability and observability analysis (Wieland et al., 2021), parameter estimation (Fröhlich et al., 2018), sensitivity analysis (Lorenzo et al., 2024), uncertainty quantification (Simpson and Maclaren, 2023), experimental design (Banga and Balsa-Canto, 2008), and model selection (Liepe et al., 2014).

In this work we focus on the first of the tasks of the above list. These analyses assess whether is theoretically possible to infer model parameters (identifiability) and internal dynamics (observability) from measurable outputs. The relevance of identifiability in clinical applications has been recently emphasised by (Phan et al., 2023), who illustrate how the lack of identifiability can undermine predictive accuracy even in carefully constructed cancer models. Here, we perform a detailed analysis of the structural identifiability of the parameters of all the ODE models and a study of the observability of their state variables.

2. Methods

In this section, we present the mathematical framework used to describe tumour dynamics based on ordinary differential equations (ODEs). We then introduce the notions of structural identifiability and observability, which are key to determine whether model parameters and internal states can be inferred from measurable outputs. Finally, we describe the computational tools used to perform these analyses, focusing on the STRIKE-GOLDD Matlab toolbox.

2.1. Modelling framework

Ordinary differential equations are the most widely used framework for modelling tumour growth. In their general form, they can be written as:

$$M : \begin{cases} \dot{x}(t) = & f\left(u(t), x(t), \theta\right), \\ y(t) = & h\left(u(t), x(t), \theta\right), \end{cases} \tag{1}$$

where f and h are analytic functions, which are in general nonlinear; $x(t) \in R^{n_x}$ is the vector of state variables at time t; $u(t) \in \mathbb{R}^{n_u}$ is the input vector; $y(t) \in \mathbb{R}^{n_y}$, the output vector; and $\theta \in \mathbb{R}^{n_\theta}$ is the parameter vector. In the following, we will sometimes omit the time dependence for ease of notation, i.e., we may simply write x, y, u. A model's outputs are the measurable functions, which are often a subset of the state variables, or a simple function of them (e.g. a sum). For the models in which we are interested, the inputs are the treatments or therapeutic actions.

2.2. Structural identifiability and observability analysis

In this study we followed a systematic approach to evaluate the structural properties of ODE-based models of the form (1). We focused on two fundamental aspects: structural identifiability and observability, which are essential to ensure the model's reliability for parameter estimation and model prediction. Structural identifiability refers to the theoretical possibility of uniquely determining the model parameters from ideal, noise-free input-output data. When a parameter is not identifiable, different parameter sets may result in identical outputs, hindering model calibration and predictive use (Wieland et al., 2021). In real applications, non-identifiable models may lead to incorrect predictions, especially when they are used to personalize treatments or therapies. A related concept, observability, refers to the ability to infer the internal state variables of the system based on output measurements over time. This is particularly relevant in biomedical applications where some variables cannot be measured directly, but are crucial for therapy monitoring, for example. We refer to Structural Identifiability and Observability jointly as SIO (Villaverde, 2019).

We performed these analyses using the STRIKE-GOLDD toolbox (Díaz-Seoane et al., 2023), an open-source Matlab toolbox based on differential geometry methods for structural system analysis. This tool enables the examination of model properties independently of specific parameter values or experimental data, and is freely available on GitHub.

To study SIO, we considered in some cases various measurement scenarios, including individual and combined outputs. We explored different measurement configurations, such as isolated versus combined output observations, to understand their impact on the structural properties of the system.

3. ODE models of tumour growth

In this section we provide an overview of some of the main ODE models of tumour growth found in the literature. We provide their equations, and we classify the variables of each model as inputs (which can be manipulated, and usually correspond to treatments), outputs (i.e., the quantities or functions that can be measured), states (whose variation over time

is given by the model's differential equations), and parameters (constant quantities, which may be either known or unknown). This classification is required for performing SIO analyses.

3.1. Tumour growth models without therapy

In the following subsection we explore models that describe tumoural growth in the absence of treatment.

3.1.1. Exponential model (EXP)

The most basic growth model (EXP1) is the one given by the following equation (Bull and Byrne, 2022):

$$\frac{dV}{dt} = \lambda V \tag{2}$$

Its solution, which is an exponential over time, is:

$$V(t) = V_0 e^{\lambda t},$$

where $V(t)$ is the tumour volume over time, λ the net growth rate of the tumour, and V_0 the initial volume of the tumour.

While this model can typically describe accurately early growth stages, it fails to describe the reduced growth rates and eventual saturation due to the lack of nutrients and oxygen that vascular tumours develop *in vivo*, and also in avascular tumours cultured *in vitro*. To account for these aspects, a slightly more complex model can be used (EXP2):

$$\frac{dV}{dt} = \lambda V\left(1 - \frac{V}{K}\right) \tag{3}$$

Its solution is:

$$V(t) = \frac{KV_0}{V_0 + (K - V_0)e^{-\lambda t}}$$

with $V(t = 0) = V_0 > 0$, and $K > 0$ represents the population carrying capacity, which is the value approached by $V(t)$ as time tends to infinity.

The model can be made more flexible by introducing an additional parameter θ, resulting in (EXP3):

$$\frac{dV}{dt} = \frac{\lambda}{\theta} V\left(1 - \left(\frac{V}{K}\right)^{\theta}\right) \tag{4}$$

which leads to the following solution:

$$V(t) = K\left(\frac{V_0^{\theta}}{V_0^{\theta} + (K^{\theta} - V_0^{\theta})e^{-\lambda t}}\right)^{\frac{1}{\theta}}$$

The possible output of these models is obviously the tumour volume, which is often measured over time to assess the growth dynamics and response to treatments. A common limitation of these models is the difficulty of relating their parameters to the behaviour of single cells.

3.1.2. Power law model (POW)

The Power Law model (Gunnarsson et al., 2024) adopts a different approach for describing how cells actively divide and grow in a lower spacial dimension than the full organoid. It is given by the equation

$$\frac{dN}{dt} = aN^{\gamma}, \tag{5}$$

with $0 < \gamma < 1$, which has the following explicit solution:

$$N(t) = (N_0^{1-\gamma} + (1 - \gamma)at)^{1/(1-\gamma)}, t \geq 0.$$

where *N(t)* is the number of cells of an organoid, and a is the rate at which the cells divide. This model is useful, for example, when the growth of the tumour is restricted to its surface. Its primary measurable variable – i.e., its possible output – is the population size, which can be interpreted as the tumour volume in certain biological contexts.

3.1.3. Lotka-Volterra model (L-V)

Although originally formulated in ecological contexts, this classical model is here used in the adapted form presented by Paczkowski et al. (2021) for tumour cell interactions. It can be used to describe the dynamics of several populations, e.g. of radio-sensitive and radio-resistant tumour cells. Without modelling the effect of radiotherapy explicitly, the governing equations of this model can be written as:

$$\frac{V_S}{dt} = \lambda_S V_S\left(1 - \frac{V_S}{K_S} - \gamma_R \frac{V_R}{K_S}\right) \tag{6}$$

$$\frac{V_R}{dt} = \lambda_R V_R\left(1 - \frac{V_R}{K_R} - \gamma_S \frac{V_S}{K_R}\right) \tag{7}$$

where $V_S(t)$ and $V_R(t)$ represent the volumes of the control and resistant populations, λ_S and λ_R their growth rates, and K_S and K_R their carrying capacities. Additionally, γ_S and γ_R describe the effect that radiosensitive cells have on resistant cells and vice versa.

The possible outputs for this model are the tumour volumes of the two interacting populations, V_S and V_R. These volumes represent the measurable variables, capturing the growth dynamics of each tumour population over time. It may be possible to measure each of these volumes individually, although it is easier to obtain measurements of their sum, $V_S + V_R$.

3.1.4. Gompertz model (GOM)

This well known model assumes that an initial growth rate $a > 0$ decreases exponentially within time, according to a decay parameter $b \geq 0$. The differential equation is (GOM1):

$$\frac{dN}{dt} = ae^{-bt}N, \tag{8}$$

which, for $N(0) = N_0$, has the solution:

$$N(t) = N_0 \exp\left(\left(\frac{a}{b}\right)(1 - e^{-bt})\right), t \geq 0$$

There is an alternative formulation of this model (GOM2) that considers an initial growth rate α and a carrying capacity K, as follows:

$$\frac{dN}{dt} = \alpha \log\left(\frac{K}{N}\right)N = \alpha \log(K)N - \alpha N \log(N) \tag{9}$$

Its solution is:

$$N(t) = K \exp\left(\log\left(\frac{N_0}{K}\right)e^{-\alpha t}\right),\ t \geq 0$$

The possible output for both versions of the Gompertz model is the population size, N. This model is commonly used to describe tumour growth with saturation effects, as shown in Gunnarsson et al. (2024).

3.1.5. Logistic model (LOG)

A model similar to the previous one is the so-called Logistic model, where the growth rate decays linearly with the size of the population until the population reaches the carrying capacity K; it is given by the equation:

$$\frac{dN}{dt} = aN\left(1 - \frac{N}{K}\right)aN - \frac{aN^2}{K} \tag{10}$$

where $N(0) = N_0$, and with solution

$$N(t) = N_0 K\left(N_0 + (K - N_0)e^{-at}\right)^{-1}, t \geq 0$$

The main output is obviously the population size, N, which can be measured over time as the population grows and approaches its limit, K. This model is widely used to represent saturation in tumour growth (Gunnarsson et al., 2024).

3.1.6. Von Bertalanffy model (BERT)

The model proposed by von Bertalanffy (Gunnarsson et al., 2024) assumes growth as a three-dimensional ball; cell division happens only in the surface, and the deaths are uniformly distributed across the organoid at a rate $b > 0$. This model is given by the equation:

$$\frac{dN}{dt} = aN^{\frac{2}{3}} - bN,$$

with $N(0) = N_0$. It has another, more general, version that replaces the fraction $\frac{2}{3}$ with a parameter γ. In doing so, it considers that the subset of actively dividing cells occupies a lower spatial dimension. This variant has the equation:

$$\frac{dN}{dt} = aN^{\gamma} - bN \tag{11}$$

which, for $0 < \gamma < 1$, has the explicit solution

$$N(t) = \left(\left(\frac{a}{b}\right) + \left(N_0^{1-\gamma} - \frac{a}{b}\right)e^{-(1-\gamma)bt}\right)^{\frac{1}{(1-\gamma)}}, \ t \geq 0,$$

reaching the carrying capacity, $K := (\frac{a}{b})^{\frac{1}{1-\gamma}}$, as $t \longrightarrow \infty$. Reparameterizing in terms of b, γ and K, it can be rewritten as:

$$N(t) = K\left(1 + \left(\frac{N_0}{K}^{1-\gamma} - 1\right)e^{-(1-\gamma)bt}\right)^{\frac{1}{(1-\gamma)}}, t \geq 0.$$

This model is used to describe tumours with surface-level growth and saturation behaviour (Gunnarsson et al., 2024).

3.2. Tumour growth models with chemotherapy

3.2.1. Cancer-Immunity Cycle Model (CYCLE)

A recent model (Mahmoodifar and Newton, 2024) considers the synchronization of chemotherapy and immunotherapy to enhance treatment efficacy within the cancer-immunity cycle. It adopts an evolutionary game theory approach where healthy cells, cancer cells, and T-cells compete in a non-transitive dynamic, similar to a rock-paper-scissors game, modulated by the tumour micro-environment (*TME*). The aim is to explore how to synchronizing dosing intervals with the fundamental period of the cancer-immunity cycle (P_{CIC}) can improve treatment effectiveness, allowing for lower doses with reduced toxic effects. The main equations describing the model are as follows:

$$\dot{x}_1 = (f_1 - \langle f \rangle)x_1 \tag{12}$$

$$\dot{x}_2 = (f_2 - \langle f \rangle)x_2 \tag{13}$$

$$\dot{n} = \varepsilon n(1 - n)h(x_2; \theta(t)) \tag{14}$$

where :

$$h(x_2; \theta(t)) = \theta(t)x_2 + (x_2 - 1) \tag{15}$$

$$f_1 = (A(n) \cdot \mathbf{x})_1 \tag{16}$$

$$f_2 = C(t) + (1 - C(t))(A(n) \cdot \mathbf{x})_2 \tag{17}$$

$$\langle f \rangle = x_1 f_1 + x_2 f_2 \tag{18}$$

$$\dot{V}(t) = (\delta + \alpha_G)V\left(1 - \frac{V}{K}\right) \tag{19}$$

$$\alpha_G = f_2 - \langle f \rangle \tag{20}$$

$$A(n) = (1 - g(n; a))A_G + g(n; a)A_R \tag{21}$$

where :

$$g(n; a) = \tanh\left(\frac{n}{a}\right) \tag{22}$$

The variables in these equations are as follows: x_1 and x_2 are the fractions of healthy and cancer cells in the total population, respectively. The variable n represents the T-cell response level, which indicates immune activity. The chemotherapy control variable, $C(t)$, ranges from 0 (no chemotherapy) to 1 (maximum chemotherapy), while the immunotherapy control variable $\theta(t)$ takes values between 2 (no immunotherapy) and higher values to indicate active immunotherapy. The timescale parameter ε determines the relative speed of the immune response compared to cancer cell dynamics, and δ represents the natural immunity's limitation in counteracting tumour growth entirely. The parameter α_G is the instantaneous growth rate of the cancer cell fraction, and K represents the carrying capacity or upper limit of tumour volume. The matrices A_G and A_R are the payoff matrices for tumour growth and regression, respectively, while $g(n; a)$ is an interpolation function that modulates the transition between tumour growth and regression based on immune response level.

3.2.2. Tumour evolution with cytostatic and cytotoxic effects model (CYTO)

This recent model presented by (Nieto et al., 2024) includes the dynamics of tumour volume $V(t)$, that are governed by two key parameters: a and b. Parameter $a > 0$ represents the cytostatic effect; it inhibits tumour growth without necessarily causing its reduction, so it acts like a mechanism of slowing down the proliferation of the tumour cells. Parameter $b \geq 0$ accounts for the cytotoxic effect, modelling the active destruction of tumour cells. When $b > 0$, the model accounts for tumour regression, typically due to the action of chemotherapy or the effect of the immune system. The model equation is:

$$\frac{d^2V}{dt^2} - \frac{2}{V}\left(\frac{dV}{dt}\right)^2 + \left[\dot{\phi}(a-b) - \frac{\ddot{\phi}}{\dot{\phi}}\right]\frac{dV}{dt} + (\dot{\phi})^2 abV = 0 \quad (23)$$

Both parameters (a and b) interact with a time-scaling function $\phi(t)$, whose derivatives $\dot{\phi}$ and $\ddot{\phi}$ control how fast the tumour grows or shrinks over time. The interplay between a, b, and the shape of $\phi(t)$ determines whether the tumour volume $V(t)$ grows, stabilizes, or decreases over time. To analyse this model it is necessary to rewrite it as a system of first order derivatives, resulting in the following equations (CYTO2):

$$\frac{dV}{dt} = x_2 \quad (24)$$

$$\frac{dx_2}{dt} = \frac{2}{V}x_2^2 + \left(\dot{\phi}(a-b) - -\frac{\ddot{\phi}}{\dot{\phi}}\right)x_2 - (\dot{\phi})^2 abV \quad (25)$$

3.2.3. Cancer growth model with chemotherapy and boosting of the immune system (CIVC)

The CICV model presented by (Jawad et al., 2023) describes the interaction between tumour cells $C(t)$ and immune cells $I(t)$, incorporating the effects of chemotherapy and vitamin intake. It is defined as the following system of ODEs:

$$\frac{dC}{dt} = r_1 C(1 - r_2 C) - \frac{\alpha_1 CI}{k_1 + C} - \beta_1 C \quad (26)$$

$$\frac{dI}{dt} = \delta - \alpha_2 CI + \frac{\alpha_3 C^2 I}{C^2 + k_2} - \beta_2 I + \gamma \quad (27)$$

The parameter r_1 is the tumour's growth rate, r_2 defines the inverse of its carrying capacity, α_1 is the immune killing rate, and k_1 is a Michaelis–Menten-type saturation constant. Chemotherapy is represented by β_1, the rate at which it kills tumour cells directly. The parameter δ represents the baseline production rate of immune cells, α_2 quantifies the suppression that tumour cells do on the immune system, and α_3 models the stimulation of immune cells due to tumour presence, following a Holling type III response, that is modulated by the constant k_2. The parameter β_2 is the death of immune cells due to natural and treatment causes. Finally, γ is the rate at which regular vitamin intake enhances immune cell production.

4. Results and discussion

In this section we report the results of the analyses of structural identifiability and observability of the models described in the previous section. The results are summarized in Tables 1–2. Each model is analysed at least once, and possibly more (for multiple output configurations, indicated in the columns 'Outputs') if there are several feasible options.

Table 1 shows the results for models without treatment. All of them are fully identifiable and observable, although it is important to note that in the case of the Lotka-Volterra model it is necessary to measure the sum of both volumes (or, naturally, both of them separately, if possible) to achieve identifiability.

Table 2 summarizes the results for the chemotherapy models. In the CYCLE model, key system parameters such as the payoff matrices (A_G, A_R), the interpolation factor a, the timescale parameter ϵ, and the carrying capacity K are identifiable, while δ and α_G remain unidentifiable; all state variables are observable if V is the measured output. The CYTO model (or, more precisely, for its first-order version, CYTO2) is fully identifiable and observable under the assumed measurements. The identifiability of the CICV depends on the measured variable: with the output C all parameters are identifiable; however, when I is the measured output, parameters like r_2, α_1, k_1, α_2, and k_2 become unidentifiable. Overall, the chemotherapy models show structurally better identifiability properties compared to the immunotherapy models.

5. Conclusion and future directions

In this paper we have assembled a set of 12 dynamic models of tumour growth found in the literature. We have focused on mechanistic models that describe the physical and biochemical details of the processes involved in tumour growth using ODEs. It would be unrealistic to attempt to include every model ever presented; instead, we have selected a number of representative models of each of the main classes. Our selection includes some ODE models without therapeutic interventions and others that describe the effect of chemotherapy.

The abundance and variety of models naturally leads to the question of how to choose the most appropriate one for a particular purpose. The decision should take into account, among other factors, the level of detail required and the availability of the data that is necessary to constrain the model. To facilitate this choice, for each model we have discussed the measurements that are typically available, or feasible, and how they relate to the model variables. Sometimes, there may be more than one possible model that is compatible with the requirements; in this case, one may use a model selection technique to determine the one that provides the best balance between complexity and ability to fit the data Liepe et al. (2014).

Another important aspect to consider is whether the model allows us to estimate its unknown components reliably. This depends on two properties: identifiability, which refers to the ability to determine the model parameters from the available data, and observability, which refers to the ability to infer the internal variables from the measurements. If a model is not identifiable or observable, its predictions may be uncertain or misleading. Therefore, these properties should be analysed before applying a model, especially when it is used for designing treatments or making patient-specific predictions.

In this paper we have contributed to this endeavour by analysing the structural identifiability and observability of the

Tabla 1: Identifiability and observability summary for the tumour growth models without treatment.

Acronym	Identifiable Parameters	Unidentifiable Parameters	Observable States	Unobservable States	Outputs
EXP	All	–	All	–	V
POW	All	–	All	–	N
L-V	$\lambda_S, \lambda_R, K_S$	K_R, γ_R, γ_S	–	V_R	V_S
L-V	$\lambda_S, \lambda_R, K_R$	K_S, γ_R, γ_S	–	V_S	V_R
L-V	All	–	All	–	$V_S + V_R$
GOM	All	–	All	–	N
LOG	All	–	All	–	N
BERT	All	–	All	–	N

Tabla 2: Identifiability and observability summary for the tumour growth models with chemotherapy.

Acronym	Inputs	Identifiable Parameters	Unidentifiable Parameters	Observ. States	Unobserv. States	Outputs
CYCLE	C_t, θ_t	AG, AR, a, ϵ, K	δ, α_G	All	–	V
CYTO2	$\dot{\phi}, \ddot{\phi}, b$	All	–	All	–	V
CICV	β_1, γ	All	–	All	–	C
CICV	β_1, γ	$r_1, \delta, \alpha_3\beta_2$	$r_2, \alpha_1, k_1, \alpha_2, k_2$	–	C	I

models. Since these properties depend on the outputs, i.e., on the variables that are available for measurement, we have considered those possible combinations of measurements that are experimentally feasible. For some models more than one output configuration is possible; in those cases we have performed several analyses for each model. Our results, summarized in Tables 1 and 2, shed light on our theoretical ability to obtain mechanistic insights from such models, and can be used as a guide for choosing an appropriate model for a particular application. Future work could extend this analysis to spatial or stochastic models (based on Partial Differential Equations), where SIO properties may vary and require adapted tools.

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