

Computer Simulation of the Metastatic Progression and Treatment Intervention

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Abstract. In many cancer entities, the primary tumour is able to spread metastases to distant sites in our body. In the majority of cases the fatality is not caused by the primary tumour but the metastases. Despite intensive research in the last decades, many details of this process are still not understood. Our collaboration developed a computer model that enables quantitative investigations of the metastatic progression. Different models of metastatic progression were compared with clinical and experimental data to gain new insights into this process.

The computer model is based on a discrete event simulation. Analytical functions describe the growth of the primary tumour and the metastases whereas intravasation event models the invasion of cancer cells from the primary tumour into the bloodstream. Further events simulate the behaviour of this cell until it either dies or finds a new metastasis. Clinical and experimental data were analysed to investigate, whether metastases spread early or late during the course of the disease, if metastases themselves are also able to metastasize and the impact of the immune system on the process of metastasis formation.

Furthermore, different therapies such as resection of the primary tumour, chemotherapy or radiotherapy and its impact on the number of metastases and the tumour burden were simulated.

Introduction

In 2013, 223842 citizens of Germany died because of cancer. Consequently, cancer is the second most common cause of death in Germany [1]. The same holds for many other developed countries. In general, not the primary tumour is the cause of death, but in more than 90% of the cases it is the distant metastases. For the development of new treatments, it is very important to understand the process of metastatic progression in detail to identify steps, which should be the target of pharmacological intervention.

The complex process of metastatic progression consists of many consecutive steps, which are influenced by the surrounding tissue and the immune system. When the primary tumour reaches a certain tumour mass, the oxygen and nutrient supply reduces over the time. Hence, the primary tumour sends angiogenic signals for neoformation of blood vessels. Following this process, cells of the primary tumour are able to invade blood or lymphatic vessels through the basal membrane, a process that is termed intravasation. Due to intravasation, malignant cells can now move to distant organs e.g. lung or liver and are called circulating tumour cells (CTCs). During the transport through the blood vessels, 99.9% of the malignant cells undergo apoptosis or are eliminated by the immune system [2]. Some of the few remaining cells are able to leave the blood vessels and migrate into the connective tissue spaces of the colonised organ. The isolated tumour cells are called disseminated tumour cells (DTCs) and are their origin of new (micro)metastases after they have been stimulated to grow.

A micrometastasis can send angiogenic signals like the primary tumour and grow up to become a macrometastasis, if it survives [2, 3]. This whole process is called metastatic cascade, because every stage has to be complete before the next stage starts.

The metastatic process is subject of many current experimental and clinical research projects. Different mathematical models have been developed and data generated by these models were compared with clinical and experimental data to obtain new insights about this process. Common mathematical models usually focus on parts of the metastatic process e.g. molecular characteristics of a single tumour cell or the process of tumour growth. The application of these models enables for example the determination of the optimal dose for radiation therapy [4] or the development of better therapeutic strategies [5–7].

The scope of pure mathematical models is very limited in comparison with computer models which can model complex settings more easily. In contrast to pure mathematical models, computer models are also able to deliver conclusions about the range of variation of the results of the computations.

This article summarizes a computer model, which was used by our groups to analyse clinical and experimental data and to investigate alternatively treatments [8–11].

1 Methods

1.1 Compartments and events

A simulated system consists of a collection of components. These components have different properties and may be related with each other [12]. A component can be e.g. the primary tumour, which is related with the component bloodstream, because the tumour cells that form the primary tumour are able to intravasate into the bloodstream. Both components have the property ‘number of cells’. Changes of the state of a component can be described as events, e.g. changes of properties or relation between two or more components. Our computer model comprises compartments and events (see Figure 1).

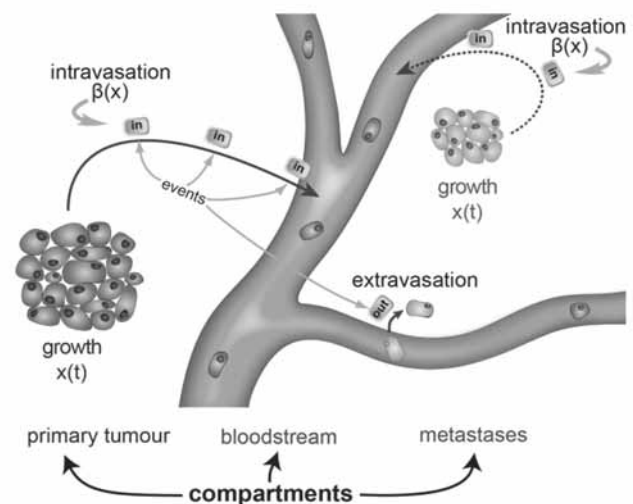


Figure 1. Schematic illustration of compartments and events. Source: [9].

In the computer model compartments represent components such as the primary tumour, the bloodstream and metastases. These compartments will be modelled continuously or discretely. By modelling a compartment as a continuous compartment, the behaviour can be described with mathematical functions. A growth function models the growth behaviour of a compartment and a colonization rate describes the spreading behaviour of malignant cells into other compartments such as the bloodstream. In contrast, the behaviour of discrete compartments is modelled by events.

For every type of discrete compartments a set of possible event types is defined with a possibility of its occurrence. During the creation of an event action, an event will be randomly chosen from this list accordingly to its probability of occurrence.

Events describe which action is triggered at a specific time [8–10]. These events are stored in an events list sorted by the time of their occurrence. One or more compartments will be modified during the execution of an event.

Furthermore, events can be created during an execution of other events, e.g. after an intravasation event of a malignant cell from the primary tumour into the bloodstream, a new event will be created and described the new behaviour or rather the next step of this cell.

Events can be local and global events. Local events are limited to modify only one or two compartments, whereas global events are able to modify all compartments. Local events describe e.g. cell division or cell death (apoptosis). Global events are typically used to describe treatments such as chemotherapy, since this treatment affects not only the primary tumour, but also metastases.

In the discrete event simulation the current state of the system is modified at specific points in time. The number of tumour cells in the primary tumour can be decreased by cell death (apoptosis) or increased by cell division or intravasation of a single malignant cell of the primary tumour into the bloodstream. For example, the event ‘cell division’ increases the number of cells in the concerned compartment. Afterwards, two new events are generated which describe the behaviour of the mother cell and their daughter cell, e.g. apoptosis or intravasation. The event ‘Apoptosis’ decreases the number of cells in the compartment. The ‘Intravasation’ event decreases the number of cells in the compartment and increases the number of cells in the following compartment (e.g. bloodstream). A newly generated event describes the behaviour of this cell in the bloodstream, e.g. apoptosis or extravasation. The time point of this new event is generated using a Gaussian or Uniform distribution. The computation for each event will be performed separately.

In computer model described here, a continuous compartment will be used to model the growth of the primary tumour and the formation of metastases, the bloodstream is modelled by a discrete compartment (see Figure 1).

1.2 Tumour growth in continuous compartments

The number of cells x in a continuous compartment changes over time with the rate $g(x)$:

$$\frac{dx}{dt} = g(x), \quad N_0 := x(t = 0). \quad (1)$$

In a patient the tumour growth starts with a single cell $N_0 = 1$ [13]. In experiments with model organisms e.g. mice with injected tumour cells at the beginning the number of cells at the time $t = 0$ can be larger than 1.

For the growth rate $g(x)$, many functions are available, e.g. linear, exponential, logarithmic or power law functions. The most common function that describe the growth behaviour is the Gompertz function [13]. This function is a sigmoid function and is defined as

$$g(x) = a x \ln(b/x), \quad (2)$$

where a is the growth constant and b the maximum size of the tumour [9]. Integrating Eq. (2) in Eq. (1), the number of tumour cells at time t is given by

$$x(t) = b \left(\frac{b}{N_0} \right)^{-e^{-at}}. \quad (3)$$

1.3 Intravasation in continuous compartments

In our computer model, the event ‘Intravasation’ comprises all steps that are necessary to model the migration of a malignant cell from the primary tumour into the bloodstream. The intravasation event begins with the individual tumour cell breaking away from the primary tumour and degrading the basal membrane with subsequent invasion of the surrounding connective tissue. Some cells succeed to detach from this tissue and invade into the bloodstream. The intravasation event is described by the colonization rate

$$\beta(x) = m x^{\delta/3}, \quad (4)$$

where m is the colonization coefficient and δ is the fractal dimension, i.e. how well is the tumour supplied with blood [13].

The next time point to execute an intravasation event will be computed by the help of a numerical integration ensuing from the last executional time point. For this purpose a random number between 0 and 2 will be picked. The colonization rate will be numerically integrated in time until it reaches this random number. This time point will be selected for the next intravasation event [8].

1.4 Modelling of treatments

Our computer model provides the possibility to include different treatments such as resection of the primary tumour, chemotherapy, external beam radiation, radio embolization and radio immunotherapy into the simulation. As an example we describe the resection of the primary tumour. Other treatments are described in detail in [10].

By performing a resection of the primary tumour in a discrete compartment, the number of cells will be set to 0. Events belonging to the primary tumour will be deleted from the event list. In a continuous compartment the growth function will be replaced by $x(t) = 0$. Consequently, the colonization rate gives $\beta(x) = 0$, i.e. the primary tumour cannot longer spread malignant cells.

1.5 Modelling the dormancy state

After the extravasation of a malignant cell from the bloodstream into the surrounding tissue, some tumour cells can switch to a dormant state. In this situation, the number of cells of the affected compartment remains constant for a time span.

After a few cell division cycles from the single cell a multi-cellular cluster evolved. In some cases, the development of the cluster slows down for a limited time, so called late dormancy, and increases afterwards. The reason for this behaviour could be the beginning of angiogenesis or the different regulation of gene expression of the cells within the metastases.

Discrete compartments do not generate events concerning the growth behaviour of the primary tumour during a dormant state. After the end of the dormant state an event will be executed to reset this state to the previous state. E.g. the primary tumour will continue growing with the appropriate parameters which were valid before the dormant state had occurred.

In a continuous compartment, the current growth function will be replaced with a constant function during dormancy. Afterwards, the tumour or metastasis will resume growing with the configured parameters. During late dormancy the size of the compartment is constant and continues growing after the dormancy.

1.6 Simulation

Our computer model can be configured using an XML-File (Extensible Markup Language [14]). The simulated system can be assembled like building blocks to define the component (e.g. primary tumour, metastases or bloodstream) and their properties (e.g. growth rate or colonization rate). A XML schema defines the structure of this XML file. Many samples and the description of the schema itself are public available under [15].

At the start of the simulation, the software reads the XML file and generates all necessary compartments and already known events (e.g. treatment intervention at day X). The current state of the simulation progress will be stored in a file in Microsoft Excel format periodically. This file contains, amongst other data, current time, current size of the primary tumour and current number of cells of the metastases [10].

Since the generation of events is based on random numbers (see Section 1.3), each simulation run yields different results. Therefore, a simulation scenario will be simulated typically 100 times to obtain sufficient variance of the data. Finally, the mean value is determined from these 100 simulation runs [10].

1.7 Configuration of the simulation

A scenario with resection of the primary tumour and chemotherapy serves as an example for the configuration of a simulation (see Listing 1 in the Appendix).

A three-cycle chemotherapy starts on day 850 with an interval of 50 days (850, 900 and 950). The primary tumour will be resected on day 1100. Size of the primary tumour and number of cells of the metastases are illustrated in Figure 2.

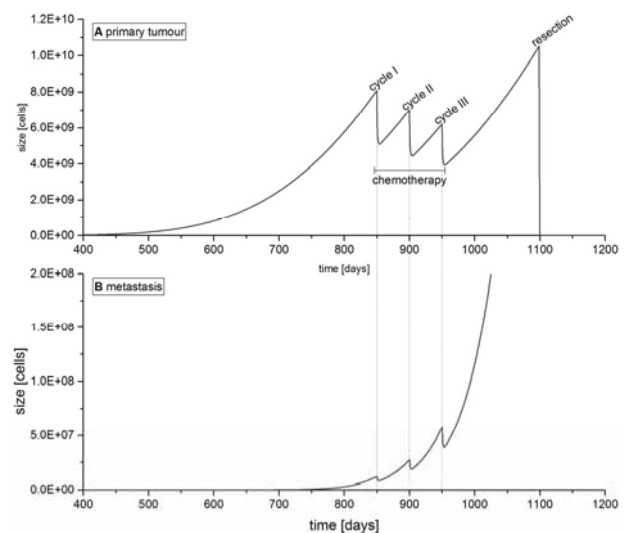


Figure 2. Impact of chemotherapy and resection of the primary tumour on the size of the primary tumour (A) and the number of cells in all metastases (B).

As shown in Figure 2A, chemotherapy influences the size of the primary tumour just for a short time. Only the resection reduces the size of the primary tumour to 0. Regarding the number of cells in all metastases, chemotherapy has also an influence for only a limited period (see Figure 2B).

2 Clinical Relevance of Late Spread Metastases

2.1 Research question

Based on clinical data of an untreated patient with hepatocellular carcinoma (HCC) and multiple metastases, among others, the following questions were examined:

1. Are metastases able to spread metastases on their own?
2. Are cells, which were spread from large tumours, still able to form metastases?

2.2 Simulated scenarios

To examine these questions, four different scenarios were simulated (Table 1). In scenario A both the primary tumour and the metastases can spread new metastases. In scenario B just the primary tumour is able to do so. Scenario C and D model the case where late spread tumour cells of large tumours or metastases are not able to form new metastases.

For the simulation three values were chosen in relation to the maximum size b for the size of the tumour, where the disseminated cells cannot form metastases any longer: 10^8 , 10^9 and 10^{10} cells. In Scenario D, such as in scenario B, metastases are not able to spread metastases on their own.

| late disseminated tumour cells... | metastases are able to metastasize | metastases are not able to metastasize |
|-----------------------------------|------------------------------------|--|
| are able to metastasize | A | B |
| are not able to metastasize | C | D |

Table 1. Simulated scenarios. Source: [9].

2.3 Results

The results are shown in Figure 3. The diagrams show the cumulated quantity of metastases in relation to the size. Scenarios A and B did not differentiate in the range of the clinical data (squares, circles and triangles), which were determined on days 1110, 1237 and 1310 after the estimated origin of the primary tumour through CT-Scans. Only in the range of small metastases ($< 10^6$ cells) differences on day 1310 were recognizable.

This is because metastases must reach a certain size to be able to form metastases on their own. Therefore, the CT-Scans can apparently detect metastases spread by the primary tumour only. Only in the later process (day 1310) metastases from metastases could develop.

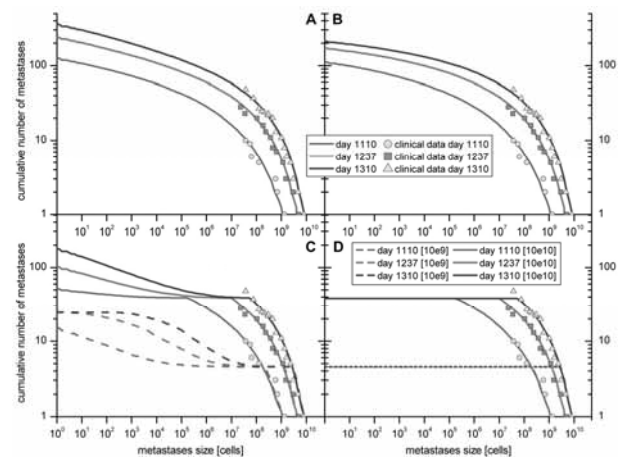


Figure 3. Results of the simulated scenarios A-D. The circles, squares and triangles represent the clinical data on different days.

From the available data it is not possible to make a reliable statement, if metastases can form metastases on their own. Data from more detailed investigations would be needed to answer this question. However, it turned out that in the range of these scenarios the question is not of clinical relevance, since metastases derived from the primary tumour alone contribute enough cells to the fatal tumour burden.

To answer the question whether large tumours or metastases are still spreading malignant cells, which are able to form metastases, scenario C and D were examined. Therefore, different sizes were chosen as limit values, whereby the primary tumour or the metastases spread cells are not able to build metastases anymore.

At a limit value of 10^9 cells it is recognizable that the data from the simulations (dotted line in C and D) did not match the clinical data (circles, squares and triangle). Thus cells, which are spread from a primary tumour or metastases that are bigger as 10^9 cells, are able to form metastases. The clinical data and the simulation results are close together at the size of 10^{10} cells. The clinical data does not cover the whole range of size of the metastases. Therefore the question can also not be answered unequivocally [8, 10]. However, it turns out even here, that the question is not of clinical relevance for the analysed scenarios.

3 Metastatic Progression under the Influence of Treatments

3.1 Research question

The influence of different treatments on the progression of metastasis formation was investigated with the aid of the computer model. The relevance of an early diagnosis on the therapy result was evaluated.

3.2 Simulated scenarios

The study was performed on the basis of the clinical data of a patient with HCC as in Section 2. The following treatments were simulated [15]: resection of the primary tumour, cycle specific and cycle non-specific chemotherapy, external beam radiation, radio immunotherapy, radio embolization and a combination of resection and a cycle specific chemo therapy. The complete parameterization of the examined scenarios is shown in Table 1 in [15]. In all scenarios the therapy start is simulated for day 700 (early diagnosis) and for day 1500 (late diagnosis). Scenarios were considered where the metastases had the ability to form metastases themselves or not.

3.3 Results

As an example, the influence of the resection of the primary tumour will be discussed here.

In the case of an early diagnosis and the subsequent early therapy (resection), there is a temporarily stagnation on the formation of new metastases if metastases are able to metastasize (see Figure 4A) or rather a complete stagnation else (see Figure 4B).

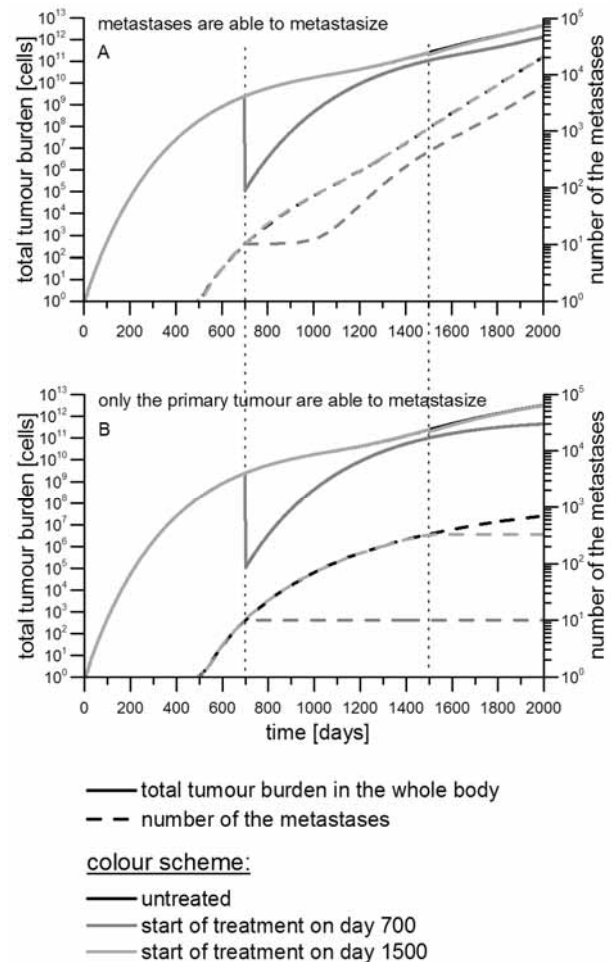


Figure 4. Results of the resection of the primary tumour on tumour burden and number of metastases on day 700. In scenario A, the primary tumour and the metastases are able to spread malignant cells. In scenario B, only the primary tumour is able to do so. Adapted from: [16].

In the case that metastases can form metastases on their own a late therapy has hardly any influence on the number of the metastases. In the case that only the primary tumour is able to spread metastases the quantity of metastases stagnates after the resection. The late therapy has yet no relevant influence in terms of the overall tumour burden (see Figure 4B) [8–10].

The results illustrate the importance of an early diagnosis and the associated early start of the treatment. The continuation of the treatment is of great importance as otherwise the advantage of the early therapy will be lost [10].

4 Influence of Natural Killer Cells on the Process of Metastatic Progression

4.1 Research question

The immune system has different defence mechanisms to recognize and eliminate malignant cells. Natural Killer (NK) cells play an important role in the fight against tumour cells as their main function is to eliminate malignant cells [17–19]. If a NK cell is slated for killing, it releases granules, which contain different toxic proteins and consequently destroy malignant cells. Several studies show that a decreased activity of NK cells facilitates metastatic progression, while with a higher activity slows this process down [20–22].

With the help of our computer model it was determined on which part of the metastatic spread NK cells have the biggest impact. In particular the influence on the growth of the primary tumour, the survival of the tumour cells in the blood and the formation of metastases was examined [8–11].

4.2 Simulated scenarios

For this purpose, data from experiments with mouse models were analysed. Rag2 mice do not have the „recombination-activating gene 2” (rag2) which leads to the dysfunction of B- and T-lymphocytes, hence a specific immune response is absent in these mice. Therefore human tumour cells can be engrafted in this mouse strain. Pfp/rag2 mice are additionally devoid of the perforin gene (pfp), which disables important NK-cells activity. In mice from both strains 10^6 human HT29 colon cancer cells were injected subcutaneously. After termination of the experiment the primary tumour was measured and the number of spontaneously formed lung metastases was determined.

These numbers served as the basis for the following simulation. In both mouse strains a dormancy of the metastasis was included in the simulations and in the group pfp/rag2 additional a late dormancy. Dormancy occurs directly after extravasation of malignant cells and stops cell proliferation for a given time span. Just after the end of the dormancy the tumour cells resume to proliferate as parametrized. Late dormancy occurs when a metastasis reaches a random size between 10 and 100 cells, remains for a certain time in this dormant state and continues growing after that.

4.3 Results

Results of the computer simulation show, that NK cells decelerate the growth of the primary tumour. Additionally 80% of the cells in the blood were eliminated, which were otherwise able to form metastases without the activity of the NK cells. NK cells also make it difficult for the disseminated tumour to settle in the lung for nearly 30 days. These cells remain for that time in a dormant state [8–11].

Experimental data of the group pfp/rag2 could not be fitted with the observed results when the dormant state was set directly after the extravasation in the model. Only with late dormancy the calculated data correlated with the experimentally obtained data. One possible explanation may be that metastases suffer after some cycles of cell division from nutrient deficiency and thus must first induce angiogenic signals to ensure nutrient supply. Further research is necessary at this point to explain the observed late dormancy [8–11].

5 Discussion

Computer simulations were shown to be a valuable tool to examine the process of metastasis formation in addition to experimental research and clinical studies. The developed computer model with its building block structure offers the possibility to investigate different scenarios with events and compartments. These include different descriptions of the tumour growth, spreading rates of metastatic tumour cells and the influence of therapies on tumour growth and metastasis formation. The model provides the possibility to analyse clinical or experimental data in more detail and to verify different model assumptions quantitatively. Predictions about the development of the metastatic progression can be made based on this model. This is particularly valuable to formulate new hypotheses based on data generated by this simulation.

The current version of our computer model includes an idealized process of therapy and does not consider resistance against the treatment methods. Furthermore, the impact of the radiotherapy on the healthy tissue is not considered. Our models of treatment interventions such as chemotherapy and radiation therapy are currently not validated by clinical data [10]. In the current research modelling of treatment interventions will be further developed with a range of new clinical and experimental data.

Compared to other existing models (e.g. [13] or [23]), our computer model is not only able to include different growth and spread behaviour of primary tumours and metastases easily but also to include a broad range of treatment interventions such as resection of the primary tumour, chemotherapy, external beam radiation, radio embolization and radio immunotherapy as a single treatment or in combination.

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Appendix

```

1 <functions>
2   <gompertzFunction functionID="growthrate">
3     <growthRate>0.00286</growthRate>
4     <tumorSize>7.3e10</tumorSize>
5     <startSize>1</startSize>
6   </gompertzFunction>
7   [...]
8   <colonizationRate functionID="colrate">
9     <colonizationCoefficient>5.3e-8
10    </colonizationCoefficient>
11    <fractalDim>0.663</fractalDim>
12  </colonizationRate>
13 </functions>
14 [...]
15 <hostOrgans>
16   <hostOrgan organID="liver">
17     <name>liver</name>
18   </hostOrgan>
19   <hostOrgan organID="blood_vessels">
20     <name>blood</name>
21   </hostOrgan>
22 </hostOrgans>
23 [...]
24 <compartments>
25   <continuousCompartment compart
26     mentID="p_tumor">
27     <hostOrgan organRef="liver"/>
28     <successor compartmentRef="blood"/>
29     <isPrimaryTumor>true</isPrimaryTumor>
30     <resectionTime>1100</resectionTime>
31     <name>primary tumor</name>
32     <growthFunction function
33       Ref="growthrate"/>
34     <colonizationRate function
35       Ref="colrate"/>
36   </continuousCompartment>
37   <discreteCompartment compartment
38     ID="blood">
39     <hostOrgan organRef="blood_vessels"/>
40     <discreteCompartmentType
41       typeRef="blood_Type"/>
42   </discreteCompartment>
43 </compartments>
44 <globalTreatments>
45   <chemotherapy>
46     <time>850</time>
47     <quantity>3</quantity>
48     <interval>50</interval>
49     <cyclingCellsFraction>
50       0.5</cyclingCellsFraction>
51     <drugSensitivity>1</drugSensitivity>
52     <drugDecay>1</drugDecay>
53   </chemotherapy>
54 </globalTreatments>

```

Listing 1. Code snippet of a simulated scenario with a resection of the primary tumour and chemotherapy. In line 2 the growth function and in line 8 the colonization rate is defined. A 3-cycle chemotherapy is carried out starting on day 850 with an interval of 50 days. The resection of the primary tumour is on day 1100.



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