Multiscale modelling of the Interaction between Tumour and Immune System

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Tutored Dissertation with Prof. Michael Stumpf

April 29, 2018

Abstract

Multiscale models are increasingly used in systems biology due to the improving computational power and scientific data available. This paper examines the use of multiscale models to describe Immune system and Tumour interaction. Various models attempting to simulate this interaction through delayed and ordinary differential equations (DDEs and ODEs) will be explained. Finally, the use of these models to optimise immunotherapies, such as dendritic cell vaccines, will be discussed.

Contents

1 Introduction

The multiscale phenomena is something which is present in our daily lives. Everything that surrounds us is organised in a hierarchical manner, where different scales are integrated to create a single system. Common examples of multiscale phenomena are our calendars organised by different time scales (days, months, years...) or the universe organised in different spatial scales (planet, system, galaxy...). One of the most interesting and complex multiscale systems we are familiar with are multicellular organisms, which are hierarchically organised in different spatial and time scales. In the spatial scale, atoms make molecules, then cells, tissues and finally all this together makes up the organism. In the time level, different processes occur at different time ranges; protein interactions occur in microseconds while cell division takes minutes or hours (Dada & Mendes, 2011) (Figure 1). All the networks in biological systems, such as gene, signalling and cellular networks, are found at these different time and scale levels, but they are not independent. They communicate and provide feedback to each other, creating in this way a network of networks which is an organism. For example, the expression of a certain molecule might affect the behaviour of a specific cell, which determines the development of a tissue (Wolkenhauer et al., 2014).

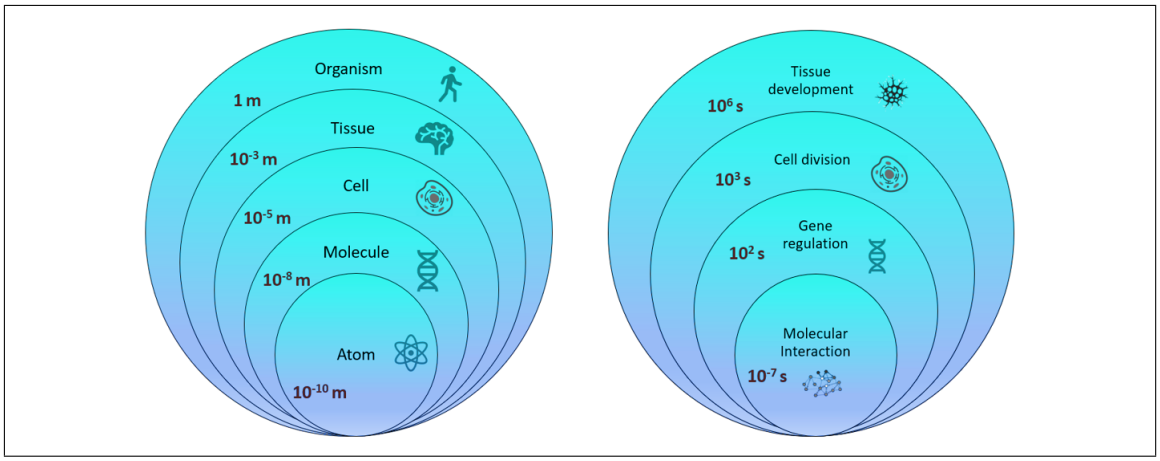

Figure 1: Spatial and Temporal Hierarchies in Systems Biology. *Left diagram shows the Spatial Hierarchies going from measure units smaller than nanometers (atom) to meters (organism). The right diagram refers to the Temporal hierarchies of processes which range from nanoseconds for molecular interactions to days for tissue development. In multiscale models, these different hierarchies are integrated into a single system. Temporal and spatial units obtained from Alon (2006).*

Multiscale modelling is a style of modelling that aims to understand the organism as a whole complex system, and not only at one level. For this, scientists develop models which integrate the different spatial and time levels into one system. The equations in these multiscale models provide insights of how the different networks interact and give feedback to each other.
Many variables and parameters define the components of the system, creating in this way a complex network which is defined with mathematical equations, and solved with computational methods. With the exponential increase of experimental data available due to developing biotechnology and bioinformatic fields, scientists are more inclined to create these multiscale models that require these big amounts of data. The Multiscale model created is constantly tested and improved to fit the new experimental results, and therefore becomes more accurate and specific to this biological system over time. Once the model is created, we can predict how the system will behave in different biochemical conditions (Alon, 2006).

This dissertation will focus on a very complex system highly relevant for cancer therapies which is the interaction between the tumour and the immune system. An understanding of this interaction is crucial for the development of effective immunotherapy treatments. In other words, if the reaction of the immune system against tumour under specific biochemical conditions could be predicted, we would be able to create through immunotherapy, the optimal conditions for the immune system to eliminate the tumour.
The immune system is one of the best examples of how multiscale modelling is applied in systems biology. First, the links between different spatial levels can be clearly identified. The community of immune cells is completely regulated by certain molecules like cytokines, antigens and receptors. This specific case shows a cellular spatial level heavily affected by a molecular spatial level (De Visser et al., 2006). At the same time, the number of immune cells (i.e. T cells or NK cells) will have a big influence on the fate of the cancer cells, and therefore influence the growth of the tumour. Once again, a link between several spatial levels: the cellular level, the physiological level and finally if the tumour is lethal, the organism level. On the other hand, we can also observe the link between different temporal levels. Processes depending on other processes happen at different time intervals: The interaction between a naïve T cytotoxic cell and an antigen presenting cell takes microseconds. This interaction leads to maturation of T cytotoxic CD8+ cell which happens in a few hours. If the T cells cytotoxic are insufficient, the tumour will grow, and this will happen in the order of days/months depending on the growth rate of the tumour (De Visser et al., 2006). As we can notice from this brief exemplification of spatial and temporal scales, the spatial scale is more related to the organisation of components of the system and the temporal scale is more related to the organisation of processes occurring in the system.

Early models to explain the interaction between the tumour and the immune system were developed, however they were too simple. These first models only described the cellular level and lacked detail on the type of immune cells, their specific functions and their regulation by specific molecules (Bellomo & Preziosi, 2000). Those simplified models failed to explain some of the experimental data as they only modelled the interaction of two competing populations mostly in a predator prey fashion (immune cells and tumour cells). This is justified by the lack of experimental data, the lack of scientific knowledge on the field and the lack of higher computational power to solve more complex models. As these three limitations improved, more complex models appeared which started including some immune cells like CD8+ cells or NK cells (de Pillis et al., 2005). However, the predictions of these more advanced models still didn't match the experimental data as they lacked details on the regulation of the immune system. The most recent models developed use differential equations to give a complete and accurate description of the immune system and tumour interaction. They include all types of immune cells, molecules involved in regulation and tumour cells. These models allow us to obtain accurate predictions that correspond to the experimental data. This ensures the reliability of these models to calculate the biochemical conditions needed for immune system to eliminate the tumour and therefore optimise immunotherapies.

2 Interaction Models

2.1 First multiscale model

One of the first and most relevant multiscale models in this field was created by Robertson-Tessi et al. (2012). This is the first model to present a complete multiscale approach of the immune and tumour interaction, where different spatial and time scales are integrated. Like all previous models, it describes the activity of immune cells against the tumour and the growth or decrease of tumour over time. However, there are two key additional features that differentiate this model from previous ones: the immunosupressive effects and the molecular scale. This model takes into account the negative feedback provided by tumour and T regulatory cells, that suppreses the immune system. Finally, it also integrates the molecular scale by describing effects of interleukins and growth factors on immune and tumour cells. (Robertson-Tessi et al., 2012)
Every tumour in every patient has different characteristics. This model is suitable for all types of cancers as it has two control parameters that define the behaviour of the tumour: The growth rate (γ) which is how fast the tumour grows and the antigenicity (a) which describes how much antigen the tumour presents on its surface. This two parameters will be modified when modelling the fate of different tumours, according to their behaviour. (Robertson-Tessi et al., 2012)

The model includes 9 cell types and 3 cytokines. The behaviour of these components, are modelled with a mathematical system of 12 Ordinary Differential equations (ODEs), containing 41 parameters derived from experimental data. The model can be divided into growth of the tumour, population of immune cells and concentration of cytokines. The mathematical model explained below can be seen in Figure 2.
Firstly, the growth of the tumour is described with a hybrid equation of Gompartz grow and power law as the tumour grows differently when it's small or big (over 10^6 cells) (de Pillis et al., 2005). In addition, the rate of elimination of tumour cells by T CD8+ cells is also considered. However, this citotoxicity is highly suppresed by the effects of Transformation growth factor (TGF-β) on T CD8+ cells, which is taken into account. (Robertson-Tessi et al., 2012)
The second part of the model focuses on the population of immune cells. It is important to monitor the number of immune cells, as the amount of T CD8+ is affected by other cells such as dendritic cells (DCs), T CD4+ helper and T regulatory cells. For example, to obtain effector cells, immature CD8+ T cells must be activated by mature DCs. Once activated, their proliferation is induced by IL-2 and is supressed by TGF-β. Finally, as in all cell populations in this model, the rate of cell death and degradation will be taken into consideration.
Another population described are DCs, which present the tumour antigen to the naive T CD8+ cells. To be able to present it, they first have to incorporate and express the antigen and then be licensed by a T helper cell. Therefore the population depends on the antigenicity of the tumour,

on the number of T helper cells and on the immunosupressive effects of IL-10 and T regulatory cells (which inhibit maturation of DC).
As expected, T helper population is also monitored. For maturation, T CD4+ helper cells also have to be presented with the tumour antigen expressed on the surface of a DC. As the previous populations, the proliferation is inhibited by TGF-β. In this case, not only the death or degradation rates induce the decrease of CD4+ cells, but in the presence of TGF-β, T helper cells become T regulatory cells.
Finally, the T regulatory cell population is described. These cells are activated in the same way as T helper and T citotoxic cells. However their proliferation is not inhibited by TGF-β. Finally, an increment in the population is considered due to the transformation of T helper cells into T regulatory cells (Robertson-Tessi et al., 2012).
The last part of the model focuses on the molecular scale. It describes the change in concentrations of TGF-β, IL-10 and IL-2. IL-2 is dependant on the number of T helper cells. IL-10 and TGF-β are dependant on the number of T regulatory cells and tumour cells. For the three of them, we consider a rate of removal from the system (Robertson-Tessi et al., 2012).

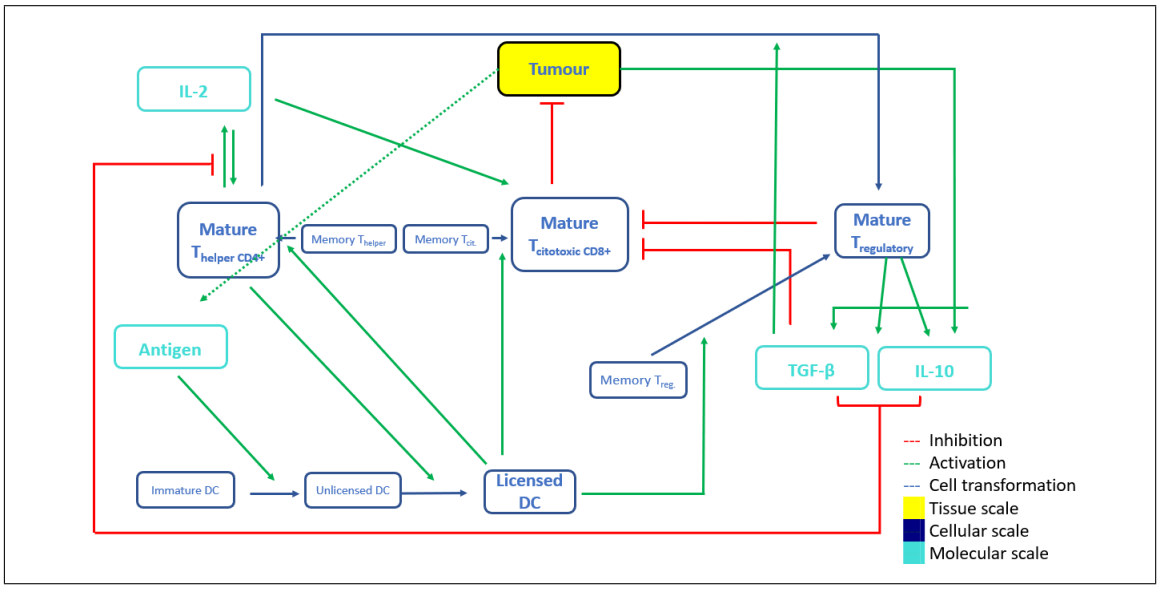

Figure 2: Diagram showing the interactions network described in this model. *This diagram shows the complex network of Tumour cells, Effector CD8+, Regulatory T, Dendritic, Helper CD4+ and memory cells; all regulated by IL-10, IL-2 and Transformation Growth Factor-β. Diagram adapted from Robertson-Tessi et al. (2012)*

The parameters are derived from different experiments in literature and adapted to the context of the model. Once the model is complete, the system of equations is numerically solved with MATLAB. Different combinations of tumour growth rate (γ) and antigenicity(a) are used and graphs are plotted showing the different fates of the tumour for each combination:
Some tumours are completely removed by the immune system. These tumours tend to have high antigenicity and low growth rate values. They can be removed because the high antigenicity generates a big immune response that can get rid of the tumour before it becomes large enough to produce TGF-β, which suppresses the immune system.
Other tumours remain in a dormant state which is actually a state of competition between immune cells and the tumour. The system finds an oscillatory equilibrium which can be easily disrupted by further mutations of the tumour or health problems of the patient. This happens when an average antigenicity and a low growth rate are combined. This stable size is always between 1 and 10^8 tumour cells (Robertson-Tessi et al., 2012).
The last situation would be the uncontrolled growth of the tumour. The model reaches this situation in case of very low antigenicities or very high growth rates. If the tumour presents almost no antigens on its surface, the immune system will not be able to respond. If the growth rate

is very high, the tumour will expand too fast and even big responses of the immune system will be suppressed by TGF-β and T regulatory cells. The three situations proposed by the model are consistent with experimental results and scientific knowledge of cancer (Robertson-Tessi et al., 2012).
For further understanding of the effect of immunosuppressive factors, the killing rates of T cells with and without T regulatory cells, TGF-β and IL-10 in the system are calculated. TFG-β and T regulatory cells have a significant suppressive effect on the model which is consistent with the experimental data. However, removal of IL-10 doesn't affect the results, which contradicts experimental data and literature. Further research on the mechanism of IL-10 suppression has to be done to improve the model.

Overall this model is good as it fits well the experimental data. It allows us to predict the fate of the tumour depending on its antigenicity and growth rate. Furthermore, it suggests optimum antigenicities at which the tumour can be eliminated, based on the growth rates. This results are highly relevant to develop efficient immunotherapies. However, there are still some improvements to be made as not all components of the immune system are included in the model. The role of the innate immune system, specifically macrophages and NK cells, is not described. Other important cytokines like TNF, IFN-α or IL-12 are also missing in the model (Dranoff, 2004).
Finally, the parameters obtained are derived from experiments in vivo and in vitro in different types of organisms with different types of cancer. The data is therefore not consistent and this might be a source of error in the model (Robertson-Tessi et al., 2012)

This is an example of a multiscale model as different spatial and temporal levels are used. Cytokines in the molecular scale directly affect the immune cell populations, which will determine the development of the tumour. Furthermore, all the processes in the model are happening at different temporal scales: maturation of CD8+ occurs at 23 unit/day while transformation of CD4+ to Treg is much slower (0.022 unit/day) (Woo et al., 2001; Mempel et al., 2004).

2.2 Improved multiscale model

The latest multiscale model created in the field of Immune and Tumour interactions was done by Qomlaqi et al. (2017). It is quite similar to the multiscale model by Robertson-Tessi et al. (2012), but this model integrates the native immune system by describing the effects of Natural Killer (NK) cells on the tumour. Additionally, it describes not only the cell division of cancerous cells, but also the cell division of immune cells, which other models did not go into depth in. Finally, due to the improvement of experimental techniques, the parameters are derived from the experimental data in Ajami (2012)'s studies, which is a consistent source. In this experiment, they inoculate C57/BL6 mice with B16-F10 melanoma and make measurements for 28 days after inoculation. Gene expression, immune cell populations and tumour size are all measured every 3 days. All parameters used for this model are from one type of mice with one type of cancer, which ensures the model's accuracy.

The mathematical model is composed of 10 delayed differential equations (DDE's) that describe tumour growth and immune system response (Qomlaqi et al., 2017). This complex model can be seen in Figure 3:
The first equation describes the growth of the tumour with a Compartz function like in the previous model. The decay of cancerous cells due to the T CD8+ cells and NK cells is included in the equation. However, the killing rates are suppressed by T regulatory cells.
The population of NK cells is modelled with a Michaelis-Menten equation, dependent on Il-2 and on the cell division duration (Ullberg & Jondal, 1981). Michaelis equation is used to describe the saturation of the effect of IL-2 on recruiting NK cells, as IL-2 has a maximum effect on recruitment and recruitment is not infinite with infinite IL-2 concentrations. Furthermore, their numbers are proportional to the number of circulating lymphocites, and suppressed by T regulatory cells.
T CD8+ cells population is dependant on number of naive T CD8+ cells and DCs. Furthermore, the proliferation is promoted by IL-2 and suppressed by T regulatory cells. This population is also modelled with a Michaelis-Menten function, as the IL-2 cytokines have a limited effect on T CD8+

production, which corresponds to the maximum rate achieved by the system.
Production rate of mature DCs which then influence mature T CD4+ helper and T CD8+ cells, is dependent on rate of tumour antigens.
Concentration of IL-2 is proportional to the number of T CD8+ cells and T CD4+ cells. However, there is a positive feedback reflected in the equation, in which IL-2 induces proliferation of T cells, which itself then induces production of IL-2.
T regulatory cells, which suppress T CD8+ and T CD4+ proliferation and function are also described in the model. Their proliferation is induced by IL-2 and TGF-β.
Finally, T CD4+ helper cells population is modelled with an equation that considers number of naive T helper, IL-12 (produced by DCs), DCs and suppression by T regulatory cells.
In all of the cell populations modelled above, the duration of cell division for proliferation and the death rate and degradation rates are taken into account (Qomlaqi et al., 2017).

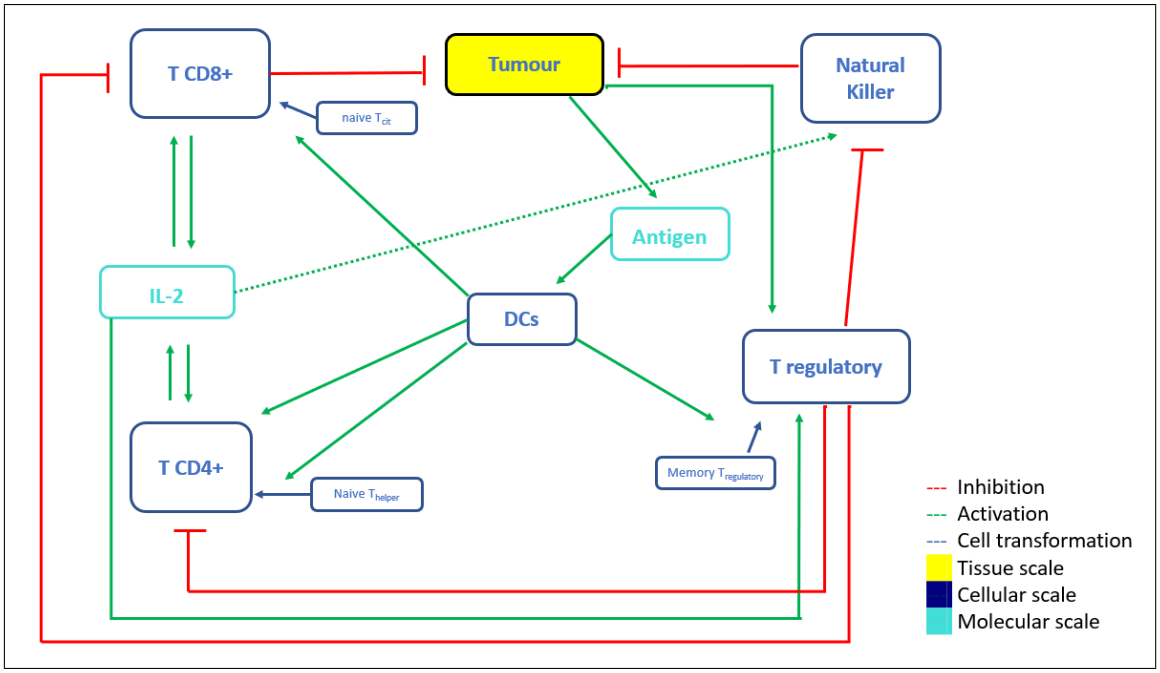

Figure 3: Diagram showing interaction network described in this model. *This diagram shows interaction of NK cells, T cells, Dendritic cells, naive cells and IL-2 with Tumour cells. Compared to the first model, this one lacks detail on TGF-β, maturation of DCs and IL-10. Adapted from Qomlaqi et al. (2017).*

To see how reliable their model is, Qomlaqi et al. tested it with experimental data from Ajami. First, they put the tumour values to 0 and simulated the response of the immune system in a tumour free environment. As expected, no change in immune system populations was observed. They subsequently established the tumour values to 5×10^5 which is the amount of B16-F10 melanoma cells inoculated in Ajami's experiment. The results of the simulation were very similar to the experimental results with an amount of error of only 8.7%, calculated with normalized root mean square error (NRMSE) (Qomlaqi et al., 2017). Those matching results were the populations of tumour cells, T regulatory cells and T helper cells. The rest of the populations and concentrations of cytokines where predicted from the simulation (CD8+, DCs, Naive CD8+ and CD4+, and NK cells).

This model gives more accurate predictions than the previous model by Robertson-Tessi et al., as the parameters come from a single experiment. However, the model remains highly specific to mice and to B16-F10 type melanoma. The model could probably be used for other organisms or types of cancer, however the accuracy would not be ensured. Due to the increase in accuracy from the previous model, some factors like TGF-β, immature DCs, IL-10 or antigenicity are lost. Furthermore, it still misses some key details of parts of the immune system such as macrophages, Tumour Necrosis Factor (TNF), Interferon alpha (FN-α) or antibodies (Karin & Greten, 2005).

3 Optimisation of Immunotherapy with Multiscale models

The goal of multiscale models is to understand the immune system better and to use the predictions of the model to provide optimum dosages in immunotherapy (Robertson-Tessi et al., 2012; Qomlaqi et al., 2017). In this case, they were specifically used to simulate dendritic cell vaccines. The following diagram explains the functioning of DC vaccines.

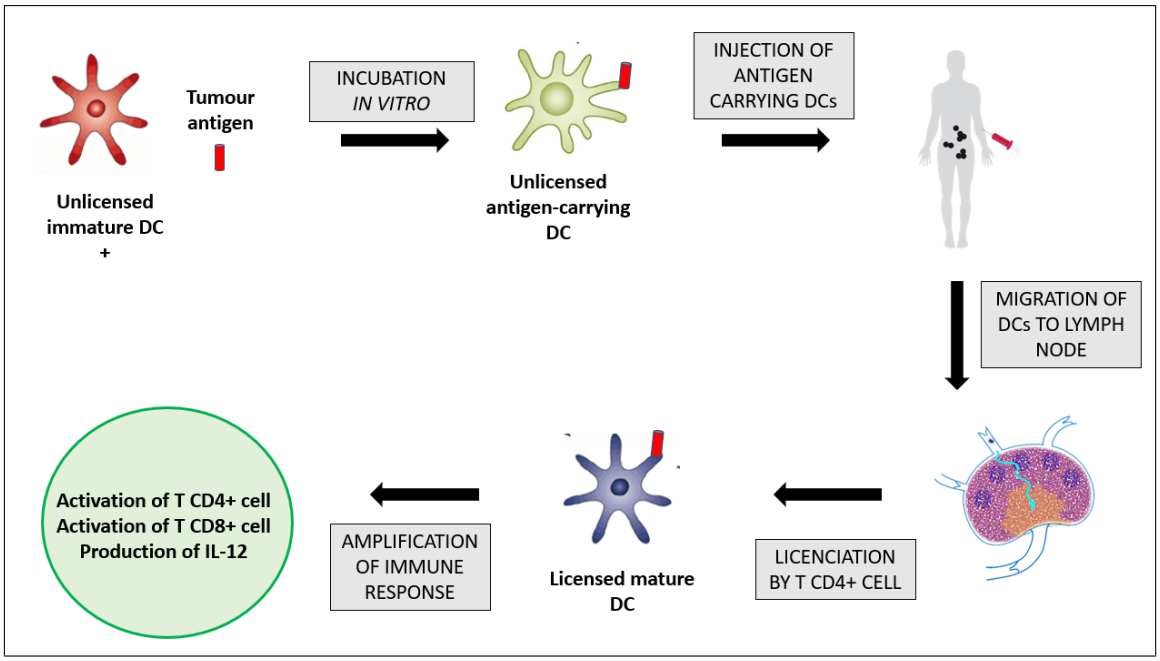

Figure 4: Amplification of immune response by DC vaccines. *DC vaccines are injections containing DCs incubated with tumour antigen. Once in our system, they migrate to lymph nodes and are licensed by T CD4+ cells. These mature DCs can now activate T CD4+ and T CD8+ cells, and produce IL-12. Because the tumour itself does not normally produce an effective inflamatory response, due to the lack of antigenicity, DC's are not activated and the immune response is ineffective. If we provide the organism with activated DC's, the immune response will be amplified and will effectively compete against the tumour (Figdor et al., 2004; Gilboa, 2007)*

In Robertson-Tessi et al.'s model, the number of unlicensed DC cells in the body is increased with every injection. Since they consider injections are not toxic, unlimited therapy can be applied. They run simulations with different tumour growth rates, different intervals between injections and different number of DC cells injected each time. Every tumour reacts differently to different DC vaccines. Smaller tumours are easier to eliminate as there is still no immunosuppression by TGF-β. DC vaccines fail to remove tumours with a growth coefficient over 350. Intervals of 14 days are shown to be optimal for this model. The optimum number of DC cells is around 2×10^6 per injection (Robertson-Tessi et al., 2012).

Qomlaqi et al.'s model also increases the number of DC cells for every injection. However, their model has a fixed antigenicity and growth coefficient as the tumour is always B16-F10 melanoma. Additionally, they consider that DC therapy has side effects and the number of injections was reduced to 3. They find the optimal interval is to apply injection at 4.7th, 5.75th and 6.79th day after inoculation of the mice with tumour cells. Optimal dose in each injection is 9.78×10^5 cells (Qomlaqi et al., 2017), which is not too different from the prediction by Robertson-Tessi et al. .

Both models give different predictions as they are built differently and correspond to different type of tumours. However both reach the conclusion that the tumour can be eliminated by DC vaccine and that there is an optimal dose of DC cells which cannot be passed since it would lead to increased immunosuppression and growth of the tumour.

4 Conclusion

Multiscale modelling is a technique that integrates different spatial and temporal scales to give a more complete understanding of a biological system. These spatial and temporal levels interact and regulate each other. The increasing amount of data and improvement of computational power is making multiscale modelling an increasingly popular field (Dada & Mendes, 2011).
Interaction of the immune system and tumour is one of those complex biological systems which can only be fully understood by building a multiscale model. The molecular cytokine level regulates the cellular level which determines the fate of the tumour. At the same time, different processes like tumour growth and cell interaction are happening at different time scales. All of this is connected into a single system, described by the multiscale model. Some multiscale models have been developed in this field, however some work still needs to be done to increase the complexity of the model.
Overall, understanding the interaction between the immune system and the tumour is crucial for development of efficient immunotherapy treatments and could be a noticeable advantage in the battle against cancer.

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