A mathematical model to predict cancer nanomedicine delivery

Dr Zhihui Wang is a researcher at the Houston Methodist Research Institute. He is a leading expert in the fields of computational biology, modelling-aided drug target discovery, biophysical modelling of drug transport, and multiscale cancer modelling. Together with Dr Prashant Dogra, the team have developed a computational model that improves our understanding of the relationship between key nanoparticle properties, the way they distribute across the whole body, and tumour delivery efficiency. This has exciting potential for use in the field of cancer nanomedicine.

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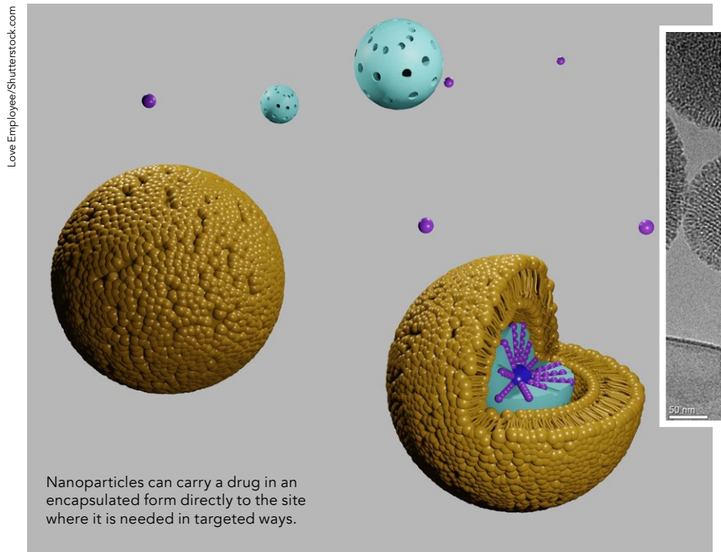
Nanotechnology is science and engineering conducted at an incredibly small size: the nanoscale. One nanometer is a billionth of a meter, which is a scale that can sometimes be challenging to truly understand in a meaningful way. For example, small particles in the nanoscale size range (these are called nanoparticles) take on different properties than if they were in a larger (otherwise known as macro) form. Their reactivity, strength, conductivity, and even colour can differ substantially between the nano and macro scales. An especially striking example of these differences is found in 'nanotubes' made of carbon, which are 100 times stronger than steel – but six times lighter.

Nanoparticles are already being used in a number of industries. There are hopes that they will boost energy efficiency, help to clean the environment, and increase manufacturing production at reduced costs. Perhaps nowhere though has there been as exciting potential as in medicine, where nanoparticles may be used to carry drug in an encapsulated form directly to the site where the drug is needed in targeted ways, thus increasing the amount of drug delivered to where it is needed while reducing side effects due to off-target delivery. The application of nanotechnology to medicine is revolutionising the way we diagnose and treat human diseases.

Being able to accurately predict how nanoparticles will react in certain situations is a powerful and useful tool for researchers – especially when it comes to medical scenarios, such as the delivery of cancer drugs to tumour sites. This would allow for clinicians to design treatment strategies optimised to individual patients, in order to maximise the likelihood of treatment success and improve patient outcome. Now, Dr Wang, Dr Dogra and their fellow researchers at the Houston Methodist Research Institute have created a computational model that demonstrates notable success toward this goal.

NANOTECHNOLOGY IN MEDICINE

Synthetic nanoparticles used for biomedical applications typically range from a size of between 1-100 nanometers. To put this size into perspective, we can compare it to a human hair, which is ~100 micrometers thick. That means roughly 10,000 nanoparticles could be stacked end to end across the diameter of one human hair. Nanoparticles are similar in size to many biological structures and molecules. For example, a single influenza virus is roughly 130 nm in diameter, while a molecule of haemoglobin is around 6nm. The similarity in size between nanoparticles and systems at the single-cell scale make it possible for nanoparticles to directly interact with and influence these systems, which makes nanoparticles extremely useful for biomedical research and applications. Nanomedicines offer many advantages over traditional 'free' drug delivery (that is, drug that is not encapsulated), including improved solubility compared to the same drugs at the macro level, increased stability of sensitive drugs to physiological degradation, improved absorption into tissues, and better targeting to specific sites of disease.



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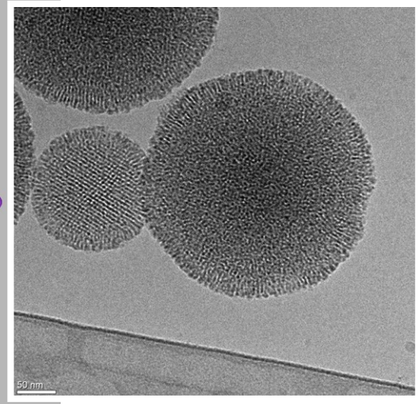

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Nanoparticles can carry a drug in an encapsulated form directly to the site where it is needed in targeted ways.

Nanomedicines (nanoparticle-loaded drugs) are used to improve the treatments of patients suffering from a range of disorders, including cancer, multiple sclerosis and emphysema. Most of these deliver the drug in particles called vesicles, which are self-contained structures of fluid or gas enclosed by an outer lipid bilayer. These very small carriers can be used to load drugs or genetic materials and transport them. Termed nanocarriers, they have the potential to package and protect cargos that are too toxic, fragile, insoluble, or unstable to be delivered as free drugs. A recent example is the development of lipid nanoparticle-based vaccines to immunise the human population against SARS-CoV-2, the virus behind the global COVID-19 pandemic. Nanocarriers can also be equipped with a variety of triggering mechanisms designed to make them release their cargo on demand, according to the right intracellular or extracellular environmental stimuli. This is particularly valuable when it comes to cancer treatment.

ACCURATE DRUG DELIVERY IN CANCER NANOMEDICINE

The targeted delivery of drugs is extremely important for improving cancer treatment. We want to be able to target cancerous tumours, as opposed to the healthy tissue within organs. However, achieving delivery to only the desired areas within the body is a challenging problem. By adjusting the physicochemical properties of nanoparticles, including their size, shape, and surface characteristics, engineers are discovering ways to fine-tune particles so that they are delivered, along with their therapeutic cargo, to the intended therapeutic target. Changes in these parameters may impact the nanoparticles efficiency of delivering therapeutic agents to tumour sites.

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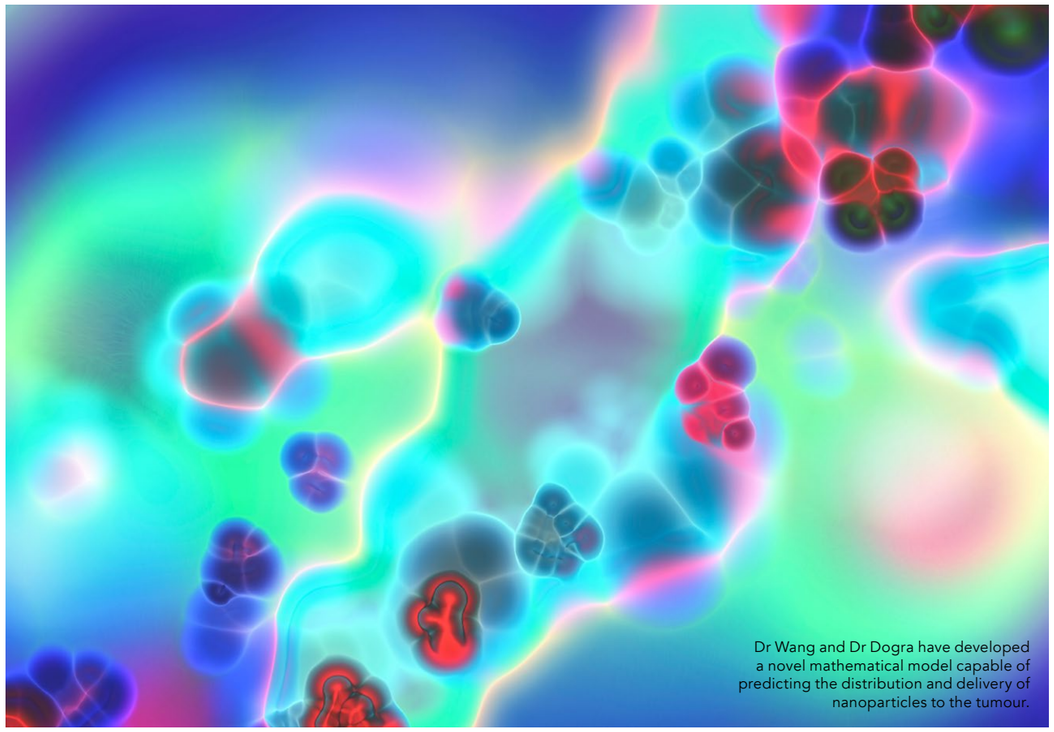
For clinical applications, it is critical that the synthesis of nanoparticles is precisely controlled to make sure they have the exact desired physical and chemical properties. This ensures the nanoparticles are safely and efficiently delivered, without causing any adverse or unwanted side effects. To this end, Dr Wang and his team have come up with a way to solve this problem through a predictive mathematical model that can accurately predict how nanoparticles will distribute within a body.

A PREDICTIVE MODEL FOR CANCER NANOMEDICINE

Nanoparticle-mediated cancer therapy has only been partially successful in the past. One of the main reasons behind this clinical translation is that the majority of nanoparticles, once inside a patient, are not delivered to the intended target. To improve nanoparticle design in order to overcome this shortcoming, there needs to be a better understanding of the tumour delivery efficiency of nanoparticles in the context of both their systemic pharmacokinetics and the tumour microenvironment. Mathematical models can be a valuable tool for achieving this. One way to gain this understanding is through mathematical modelling, wherein researchers design mathematical descriptions of the key biological and physical processes involved in nanoparticle delivery in order to allow for rapid study of how nanoparticle properties affect their delivery via computer simulations.

Dr Wang and his team's goal is to improve the "quantitative" (measurable) understanding of the relationship between key nanoparticle properties, the way they distribute across the whole



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Dr Wang and Dr Dogra have developed a novel mathematical model capable of predicting the distribution and delivery of nanoparticles to the tumour.

body, and how efficiently they are delivered to tumours. To achieve this, they developed a novel mathematical model capable of predicting the distribution and delivery to the tumour.

By using nanoparticle properties as inputs for the model, and then validating it with experimental data from rats, the researchers were able to confirm that their model accurately predicted nanoparticle behaviour. They then used the model to computationally investigate the vast multidimensional parameter space (the space of possible parameter values that define a particular mathematical model) in order to discover how nanoparticle design can be improved to increase delivery to tumours.

This allowed for the visualisation and quantification of how the nanoparticles behaved across the whole body. Knowledge of this was essential for a comprehensive understanding of the nanoparticles' pharmacokinetics and pharmacodynamics. The team identified several key parameters related to nanoparticle and tumour properties, which were found to govern the distribution and tumour deliverability of nanoparticles. Their analyses revealed a number of the key parameters governing nanoparticle delivery to the tumour, including the size of the nanoparticles and the rate at which they degraded.

They developed a novel mathematical model capable of predicting the distribution and delivery to the tumour.

FUTURE BENEFITS OF THE MODEL

This mathematical model can serve as a valuable tool in the future to guide the design and development of nanoparticles to optimise their delivery to solid tumours. An understanding of these parameters will also help to maximise their safety and avoid any unwanted side effects.

Dr Wang and Dr Dogra will continue to work on improving the predictive power of the model through incorporating additional key parameters and measurements, such as advanced imaging and molecular parameters. Integrating *in vivo* imaging with mathematical modelling is a valuable tool that, in addition to the pharmacological evaluation of macromolecules, can provide insights into mechanisms of transport barrier-induced drug resistance or therapy failure. They may also integrate the model with other multiscale models. This would allow them to build a predictive modelling platform for simulating disease progression and gaining a more complete pharmacokinetic understanding of various test drugs and novel nanoparticle formulations. This can also support the development of novel strategies to improve drug delivery to tumours and personalise cancer treatment for individual patients.

Behind the Research

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Research Objectives

Zhihui Wang's research focuses on integrating mathematical, physical, and statistical methods with experimental investigations and patient data analysis to quantitatively study cancer progression and invasion, to help improve prediction of treatment efficacy and optimise treatment planning.

Detail

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Bio

Zhihui Wang: Dr Wang is a leading expert in the fields of computational biology, modelling-aided drug target discovery, biophysical modelling of drug transport, and multiscale cancer modelling.

Prashant Dogra: Dr Dogra develops mathematical models to study disease progression to support development of drugs and drug delivery systems in infectious diseases, neurodegenerative disorders, and cancer.

Funding
This work has been supported in part by the National Science Foundation Grant DMS-1930583, the National Institutes of Health (NIH) Grants 1R01CA253865, 1U01CA196403, 1U01CA213759, 1R01CA226537, 1R01CA222007, and U54CA210181.

Collaborators

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- Professor Vittorio Cristini, Houston Methodist Research Institute, Houston, TX, USA

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Personal Response

Where do you see the most exciting potential for improving the predictive model in the future?

"As a next step, the model will be updated to include additional nanoparticle parameters, such as surface charge and surface chemistry, as these are considered critical in affecting the pharmacological activity of nanoparticles. For this, extensive data mining from published preclinical studies will be conducted to identify empirical relationships between nanoparticle properties and tumour delivery efficiency. These will serve as additional inputs for the model, and thus improve its predictive power and applicability in providing optimal nanoparticle design guidelines."

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