BONE

In silico tools predict effects of drugs on bone remodelling

Liesbet Geris

Researchers have developed an in silico (computer) platform that couples tissue adaptation with cellular and molecular interactions to simulate bone adaptation to mechanical loading and progress and treatment of metabolic bone diseases. What is the benefit of such in silico tools, and how can credibility of the simulation outcomes be established?

Refers to Kameo, Y., Miya, Y., Hayashi, M., Nakashima, T. & Adachi, T. In silico experiments of bone remodeling explore metabolic diseases and their drug treatment. *Sci. Adv.* **6**, eaax0938 (2020).

The metabolic process of bone remodelling is crucial for the maintenance of healthy skeletal homeostasis and for skeletal adaptations to imposed mechanical or biological changes[1,2]. Bone remodelling is carried out by the so-called bone multicellular units (BMUs), composed of osteoclasts resorbing the old or damaged bone and osteoblasts depositing new bone. The well-balanced activities of these cells are influenced by a myriad of mechanical and biochemical factors. A disruption of this process can lead to metabolic bone diseases such as osteoporosis. The complexity of the bone remodelling process stretches across multiple spatiotemporal scales, ranging from systemic hormonal changes and mechanical loading on the level of the entire skeleton, to intracellular signalling in individual skeletal cells. This multiscale character of bone remodelling makes it challenging to fully grasp the intricacies of the disease and design appropriate treatment strategies. In silico (computer) modelling is a technology that enables the integration of phenomena across a wide range of spatiotemporal scales to obtain a holistic view on (patho)physiological processes (FIG. 1). In a new study, Kameo et al.[2] have developed an in silico experimental platform for capturing the complexities of bone remodelling and adaptation, which could accelerate research in this area and lead to novel therapies.

Historically, most in silico models of bone remodelling have focused either on the mechanical or the biochemical components of this process. Theoretical models of the mechanical mechanisms of bone remodelling date back to the nineteenth century when Julius Wolff introduced his law ('Wolff's law'), stating that bone will adapt to the loads under which it is placed[3]. Bone was described as a homogeneous material that could change under the influence of mechanical stimuli. In the past few decades of the twentieth century, both the description of bone itself (that is, the structural and material properties) and the effect of the mechanical signals on the remodelling process were refined by inclusion of basic notions of BMU biology. Osteocytes were identified as sensors of mechanical loading, activating BMUs through a cascade of biochemical processes. For the mechanical processes, various models have described different mechanical loading stimulus, including strain, strain energy density, microdamage and interstitial fluid flow. For the biochemical processes, other models have focused on the effect of endogenous and exogenous growth factors and hormones on cellular activity and cross-talk[4]. Classical pharmacokinetic/pharmacodynamic models focused mostly on the effect of administration of drugs, whereas quantitative systems pharmacology models and multiscale mechanistic models tended to also provide a detailed description of the disease itself, into which the actions of drugs could be investigated.

In their study, Kameo et al.[2] introduce a new modelling platform, called V-Bone, which is a software environment that enables the user to define in silico experiments, testing specific conditions and treatments. The platform runs the in silico model describing the bone remodelling process with the user defined inputs, coupling microscopic molecular and cellular interactions to macroscopic tissue and organ adaptations. This multiscale coupling of mechanical and biochemical factors enables the model to simulate the effects of mechanical loading on bone adaptation and reproduce important metabolic bone diseases. The simulation results are then processed by the platform into images and graphs that can easily be interpreted by the users.

The model described in Kameo et al.[2] is an extension of the authors' previous mechanics-driven modelling work and now explicitly incorporates the process of osteocytes producing biochemical signals in response to a mechanical stimulus. These biochemical signals activate osteoclasts and osteoblasts through complex signalling cascades, including pathways that are dysregulated in many biochemical bone metabolic diseases. Both mechanical and biochemical factors influence the probability of cell genesis, differentiation and apoptosis for the modelled osteoblast and osteoclast populations. To validate the model, the researchers tested the ability of the model to capture adaptation to mechanical loading, at the level of single trabeculae and a cube of cancellous bone ($0.4\,mm^3$). Subsequently, Kameo et al.[2] successfully simulated, both quantitatively and qualitatively, the experimentally observed development and progression of osteoporosis and osteopetrosis on a whole femur as induced by unloading or by abnormal expression of RANK ligand (RANKL).

After the initial qualitative checks, the model platform was quantitatively validated by simulating in vivo experiments of mice deficient in semaphorin 3A (Sema3A; a signalling molecule that inhibits osteoclastic bone resorption and promotes osteoblastic bone formation) and mice treated with Sema3A. Kameo et al.[2] compared the simulated results with results from the corresponding in vivo experiments, including structural parameters such as the bone volume over total volume and the total number of trabeculae and biological read-outs such as the spatial distribution of signalling molecules, osteoclasts and osteoblasts. Kameo et al.[2] sought to demonstrate the added value of their modelling platform in exploring and explaining the progress of osteoporosis and the effect of four

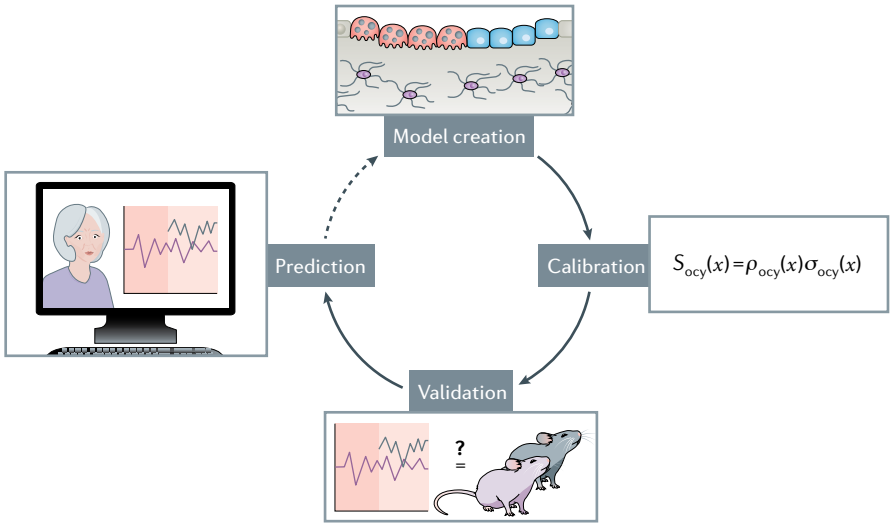

Fig. 1 | **Building an in silico model.** In the model creation phase, the precise biological question and its context are outlined. During the calibration phase, this biological question is translated into equations. In the validation phase, the model outputs are compared to experimental data. Finally, predictions can be made about treatment strategies for the patient.

common drug treatments (bisphosphonates, an anti-RANKL antibody, an anti-sclerostin antibody and Sema3A). The simulation results showed that those drugs that promote bone formation but inhibit bone resorption (such as the anti-sclerostin antibody) were more effective in improving both bone quality and quantity than the other drugs, mirroring results from clinical studies. The authors also simulated the effect of transitioning from one treatment (bisphosphonates) to another (anti-RANKL or anti-sclerostin antibodies), capturing clinical observations for tested scenarios and enabling the exploration of clinically untested scenarios.

This study is a nice illustration of the contribution that in silico models can have in biomedical studies, namely, as a virtual platform for hypothesis checking and treatment testing. Other applications for in silico models in biomedicine include the personalization of treatment strategies and the execution of in silico clinical trials. In silico model-informed drug development is not a new phenomenon; however, developments in in silico medicine this past decade have led to a vast expansion of available model technologies. Critical to the successful uptake of these new in silico tools is the rigorous establishment of model credibility and documentation thereof[5]. Building such model credibility is a multi-step process that can be captured by the abbreviation 'VVUQ' — standing for, 'verification, validation and uncertainty quantification'. Verification refers to ensuring that the simulation results correspond to the mathematical model; in other words, that no mistakes were made in translating the mathematical equations into computer code and solving them. The term validation means showing that the simulation results correspond to the physical reality in a specific context of use. Lastly, uncertainty quantification refers to ensuring that uncertainties in the model choices and parameter values are taken into account and will not lead to non-physiological results within the defined context of use. In 2018, the American Society of Mechanical Engineers, together with representatives of the medical device industry and the FDA, produced a standard for the credibility assessment of in silico models in the context of medical devices, called the ASME Verification & Validation (V&V 40) standard[6,7]. Similar initiatives in Europe focus specifically on in silico models for drug development[8]. Such initiatives provide clear regulatory frameworks to enable models such as the one developed by Kameo et al.[2] to not only be used in a research context, but be an actual part of improving and accelerating the drug development process.

In summary, bone remodelling is the result of biological and mechanical inputs acting on various spatiotemporal scales. In silico experimental platforms, such as the one presented by Kameo et al.[2], provide an integrated testing environment to investigate mechanisms of action and treatment strategies for metabolic bone diseases.

Liesbet Geris [1,2,3]

[1]*GIGA In silico medicine, University of Liège, Liège, Belgium.*

[2]*Biomechanics Section, KU Leuven, Leuven, Belgium.*

[3]*Prometheus, LRD division for skeletal tissue engineering, KU Leuven, Leuven, Belgium.*

e-mail: Liesbet.geris@uliege.be

https://doi.org/10.1038/s41584-020-0457-6

1. Seeman, E. & Martin, T. J. Antiresorptive and anabolic agents in the prevention and reversal of bone fragility. *Nat. Rev. Rheumatol.* **15**, 225–236 (2019).
2. Kameo, Y., Miya, Y., Hayashi, M., Nakashima, T. & Adachi, T. In silico experiments of bone remodeling explore metabolic diseases and their drug treatment. *Sci. Adv.* **6**, eaax0938 (2020).
3. Gerhard, F. A., Webster, D. J., van Lenthe, G. H. & Müller, R. In silico biology of bone modelling and remodelling: adaptation. *Philos. Trans. A Math. Phys. Eng. Sci.* **367**, 2011–2030 (2009).
4. Riggs, M. M. & Cremers, S. Pharmacometrics and systems pharmacology for metabolic bone diseases. *Br. J. Clin. Pharmacol.* **85**, 1136–1146 (2019).
5. US Food and Drug Administration. Reporting of Computational Modeling Studies in Medical Device Submissions https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions (2016).
6. The American Society of Mechanical Engineers. Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices https://www.asme.org/codes-standards/find-codes-standards/v-v-40-assessing-credibility-computational-modeling-verification-validation-application-medical-devices (2018).
7. Kuemmel, C. et al. Consideration of a credibility assessment framework in model-informed drug development: potential application to physiologically-based pharmacokinetic modeling and simulation. *CPT Pharmacometrics Syst. Pharmacol.* **9**, 21–28 (2020).
8. Musuamba, F. T. et al. Verifying and validating quantitative systems pharmacology and in silico models in drug development: current needs, gaps, and challenges. *CPT Pharmacometrics Syst. Pharmacol.* **9**, 195–197 (2020).

Acknowledgements
The author gratefully acknowledges funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (ERC CoG 772418) and from EOS, the programme for Excellence of Science in Belgium supported by FNRS-FWO.

Competing interests
The author declares there are no competing interests