Image-based, personalised and multiscale modelling to predict the risk of fracture in osteoporotic patients: the VPHOP integrated project

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Authors: M. Viceconti1, K. A. Stroetmann2, R. Rizzoli3, S. J. Ferguson4, R. Müller5, K. Ito6, F. Taddei1, W. R. Taylor7, D. Testi8, G. Clapworthy9; 1Bologna/IT, 2Bonn/DE, 3Geneva 14/CH, 4Zurich/CH, 5Zürich/CH, 6Eindhoven/NL, 7Berlin/DE, 8Casalecchio Di Reno, Bologna/IT, 9Luton/UK

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Purpose

Osteoporosis is an age-related disease that progressively weakens the skeleton, increasing the probability of bone fractures, even when associated with relatively low-energy impacts. Osteoporosis is estimated to affect 200 million women worldwide - approximately one-tenth of women aged 60, one-fifth of women aged 70, two-fifths of women aged 80 and two-thirds of women aged 90 [1]. A 50-year-old woman has a 2.8% risk of death related to hip fracture during her remaining lifetime, equivalent to her risk of death from breast cancer and 4 times higher than that from endometrial cancer [2]. Nearly four million osteoporotic bone fractures cost the European health system more than €30 billion per year [3]; this figure could double by 2050. After the first fracture, the chances of suffering a further fracture increase by 86% [4].

The above clearly indicates the need to prevent osteoporotic fractures. Unfortunately, such fractures cannot simply be explained by skeletal weakening, so understanding the disease progression and the future risk of fracture is highly complex. Most patients who report a low-energy impact fracture are found to have a bone density that is lower than normal (osteopenia), but half of patients with typical low-energy fracture do not reach the level of the operational definition of osteoporosis [5]; indeed the risk of facing a low-energy fracture is inherently multi-factorial. On one hand, ageing, reduced physical activity, hormonal alterations due to the menopause, and environmental factors such as nutrition, may progressively reduce the bone mass and hence progressively weaken the skeletal structures. On the other hand, ageing is always associated with a more or less marked, but progressive, degradation of neuromotor control, which translates into an increased probability of overloading the skeleton during daily life, either through falling or by inappropriate muscle activation [6].

More specifically, the risk of bone fracture can be explained only by taking into account the systemic interaction of processes that occur at radically different space-time scales: skeletal loading and overloading (occur at the whole body scale); whole bone strength (observable at the organ scale); the biomechanical properties of the bone tissue (observable at the tissue scale); and the transformation over time of the bone tissue as a result of the interaction of various cellular populations (observable at the cellular scale) [7]. In addition, in order to be clinical useful, any predictor should be able to account also for the effect of pharmacological or interventional treatments in which a biomaterial is injected to strengthen the regions of the skeleton at higher risk.

We present here work in progress of the VPHOP European Consortium, an innovative technology for image-based, personalised and multiscale modelling of the risk of bone fracture. The aim of VPHOP is to develop multiscale modelling technology based on conventional diagnostic imaging methods that will make it possible, in a clinical setting, to predict for each patient the strength of his/her bones, how this strength is likely to change over time, and the probability that the he/she will overload his/her bones during daily life.
With these three predictions, the evaluation of the absolute risk of bone fracture will be much more accurate than any prediction based on external and indirect determinants, as occurs in current clinical practice. They will be used to: i) improve the predictive accuracy of the current clinical standards; ii) to provide the basis for an evidence-based prognosis with respect to the natural evolution of the disease, to pharmacological treatments, and/or to preventive interventional treatments aimed at selectively strengthening particularly weak regions of the skeleton. For patients at a high risk of fracture, and for whom the pharmacological treatment appears insufficient, the VPHOP system will also assist the interventional radiologist in planning the augmentation procedure. The various modelling technologies developed during the project are being validated not only in vitro, on animal models, or against retrospective clinical outcomes, but will also be assessed in terms of clinical impact and safety on small cohorts of patients enrolled at four different clinical institutions, providing a factual basis to support effective clinical and industrial exploitation.
Fig. 1: Femoral neck fracture in osteoporotic patient. From [8], reprinted with permission.

Methods and Materials

The Hypermodelling technology

The approach used by the VPHOP consortium is consistent with the vision of the Virtual Physiological Human [9], which is defined as "a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system".

Five component models were developed:

i) a body-level model, capable of predicting the probabilistic loading spectrum that the skeleton of the patient would experience during daily life;

ii) an organ-level model, capable of predicting the stresses, the strains, and the fracture of the proximal femur and thoracolumbar spine regions;

iii) a tissue-level model capable of predicting the biomechanical constitutive equation of the bone on the basis of the tissue micromorphology;

iv) a cell-level model capable of predicting how the tissue micromorphology would change over time because of the progression of the disease, or because of pharmacological treatments;

v) a constituent-level model capable of predicting how an injected biomaterial would flow into the bone tissue porosities, and how such augmentation would change the biomechanical constitutive equation.

The five component models were composed into an integrative model that predicts the patient-specific risk of fracture as the systemic interaction of all these sub-models, using what we call the hypermodelling technology, essentially a complex distributed execution environment that executes pre-defined workflows by running each component model, and ensuring that all data inputs and outputs are properly transferred and translated, as requested by a distributed and heterogeneous execution environment. The technology is built on various open source software components, including the Multimod Application Framework [10], the OpenClinica clinical research data management framework [11], and the Taverna workflow management system [12]. Since some workflow cannot be entirely automated, we introduced a special module called the Mechanical Turk, a name proposed by Amazon to indicate their crowd-sourcing Internet marketplace. By placing a mechanical turk module in a workflow, the execution process will run until it reaches that module and then stop; the job is added to the work list of the module, and it stays there until a human operator executes the requested operation (usually data processing, but also authorisation), which then automatically restarts the execution of that workflow.
The VPHOP hypermodelling environment is fully integrated with the databases of clinical information, so that the collection of the clinical information, the request of the personalised simulation, and the return of the simulation results to the clinician who requested it, are all part of a single integral workflow. While OpenClinica is used to manage all clinical textual data, the large binary objects (imaging data, instrumentation data) are managed using a new customisation of the Physiome Space biomedical data management service [13]. Physiome Space web services are also being used by the hypermodelling technology as a storage service for both the input and the output data. Figure 2 shows a logical scheme of the VPHOP hypermodelling technology.

The Hypermodelling technology currently has three end-user interfaces. The first, called Hypermonitor, is a stand-alone application targeting the biomedical engineer who runs the personalised simulations for each patient. The user interface (Fig. 3) is designed to provide the maximum efficiency to a highly specialised operator.

The second user interface, called Virtual Osteoporosis (VOP) and used by the clinical specialist, is a web application designed as an extension of the OpenClinica web interface, which is used by the various medical professionals to record all clinical data as the patient is being visited and examined. On this, some additional windows are overlapped for the request of a personalised risk assessment using the VPHOP hypermodelling technology. A separate window provides all risk factors for that patient as soon as they are computed.

The third user interface, currently being developed, will assist the interventional radiologist to plan the augmentation of the skeleton in the region of interest, and then use this information to predict how the biomaterial will fill the bone porosities, and how this will strengthen the host bone (Fig. 4).

The component models

The structure of the VPHOP hypermodel is schematically represented in Figure 5.

In the body-level model, information from wearable sensors [24] is used to estimate the frequency of common motor tasks such as level walking and stair climbing, while statistical models use a range of functional parameters to estimate the probability of a high-risk event such as falling [25]. For each of these motor tasks, personalised musculoskeletal models are used to predict the articular and muscular forces that are transmitted to the skeleton during that movement in both the proximal femur and the thoracolumbar spine [7, 14, 15]. As a result, a probabilistic loading spectrum is formed that accounts for the anatomical, functional, and activity determinants on a subject-specific basis.

The organ-level model transforms QCT imaging data into finite element models of the patient’s femoral and thoracolumbar regions, capable of predicting with excellent accuracy whether the local skeleton will fracture under a given loading condition.
Atlas-based mesh morphing techniques [18] are employed to generate a conventional partitioning of the anatomical space, which is used to combine the organ-level with the tissue-level information. While the organ-level model is entirely deterministic, it is run within a probabilistic framework [7, 6], generated by sampling the probabilistic loading spectrum.

While QCT data can be used to generate fairly accurate organ-level models of bone biomechanics, the most accurate constitutive equation, which describes the anisotropic behaviour of the bone under loading, can be derived only if the tissue morphology is known. Depending on the region of the skeleton, and on the imaging technology available, it is possible to obtain patient-specific information about the local tissue morphology only in specific cases. When this is not possible, the information that can be derived by imaging at meso-resolution is combined with population-based information contained in a large database so that, regardless of the available information, it is always possible to obtain a local constitutive equation.

Another reason for having a complete tissue morphology is that it is required to accurately predict how the progression of the disease, and eventually the treatment, will change the risk of fracture over time. The cell-level component model represents the concurrent apposition and resorption of mineralised extracellular matrix all over the surface of the existing tissue trabeculature [7, 19]. The effect of the pharmacological treatment can be calibrated using a murine model [20], but requires further calibration using human data [21].

Last, but not least, the tissue morphology is also used in combination with the treatment planning to predict how the biomaterial would strengthen the region injected [22]. This would translate into a different constitutive equation for that region and would ultimately result in a modification to the risk of bone fracture for that patient.

**Personalisation**

No matter how sophisticated the predictive model is, if the input data are not sufficiently accurate, the predictions will differ greatly from reality. In particular, given the extreme inter-subject variability of the musculoskeletal anatomy and functionality, it is essential to provide the predictive models with as much patient-specific information as possible. However, there is always a trade off between the invasiveness, the organisational impact, and the cost that quantifying a certain parameter for a specific subject involves, and the benefit that the increase of predictive accuracy produced by such personalisation will return to the patient. Thus, in practice, in most clinical applications, predictive models must be identified with an incomplete input set.

In the VPHOP project, we worked along two lines: improving imaging and instrumentation to obtain more information with lower invasiveness, impact and cost; and developing methods that combine patient-specific and population-specific information, so as to
ensure that a complete set of inputs is always available, even if this is associated with higher levels of uncertainty.

The body-level model is identified anatomically using the SterEOS imaging system. The EOS system (EOS Imaging SA, Paris, France) captures simultaneous frontal and lateral head-to-toe images of patients in the upright, weight-bearing position, using two perpendicular X-ray beams collimated in very thin, horizontal, fan-shaped beams and high efficiency detector technology [23]. A 3D skeletal atlas can be morphed on to the two radiographic images, generating a full 3D patient-specific anatomical model of the skeleton (Fig. 6). In the VPHOP project we morph a complete anatomo-functional musculoskeletal model that can be used to initialise the body-level model in multiple ways. When patient-specific motion-capture data are available, a complete anatomo-functional musculoskeletal model is used in combination with the motion data to predict the forces acting on the skeleton; this is being developed in a twin research project named NMS-Physiome. In cases in which full motion capture is not available, but rather the registrations of wearable sensors during specific ambulatory tests, the SterEOS imaging system is used to quantify a set of anatomo-functional parameters for that patient, which are used to search in a large population database for the closest-matching subject, whose predictions are then used as a surrogate.

Further information used to inform the body-level model is provided by a wearable sensor called ActiBelt [24]. This sensor is completely contained within a belt buckle and can therefore be worn by the patient for long periods without discomfort - the sensor is fitted with enough memory to record continuously for several days. Using ActiBelt in VPHOP, we developed two protocols. The first is used during the ambulatory visit and allows the quantification of a small set of neuromotor condition indicators, which are primarily used to estimate the propensity to fall [26]. The second is long-term monitoring of the patient activity levels for providing information on the relative frequency of different motor tasks.

The organ-level model is entirely identified by the 3D morphodensitometry (i.e. both the bone geometry and the bone mineral density distribution within it). In the VPHOP project, the SterEOS system has been further developed into a dual-energy imaging system (SterEOS/DE) (Fig. 6). This allows the generation of a patient-specific 3D model of the femoral or vertebral anatomy, with an estimation of the associated 3D bone densitometry. This 3D morphodensitometric information is used to initialise the organ-level model; preliminary assessment suggests a dosimetry of approximately 40 mS, which is fully compatible with clinical applications involving periodic monitoring. When a greater accuracy is required, for example for initial stratification of cohorts in large clinical trials, a regional QCT can be used. For the hip, this involves a dosage of approximately 2-4 mS [26].

As reported above, the tissue-level model can be initialised directly or by using a combination of patient-specific and population-specific information. For the peripheral skeleton, it is possible to use HRpQCT systems, which are capable of generating bone tissue 3D imaging with a resolution sufficient to produce accurate tissue-level models.
[21]. For the hip and the spine, however, no clinical imaging system is currently capable of producing images with that resolution. In the VPHOP project, we have developed a new protocol for an existing flat-panel, C-arm CT system (XperCT, Philips Healthcare, Netherlands) that improved the spatial resolution considerably (Fig. 7); however, it exhibited a signal-to-noise ratio insufficient for accurate morphometric analyses [27]. Nevertheless, this meso-scale imaging can be used to identify some of the morphometric parameters that fully identify the bone-tissue constitutive equation. These can be used to search in a database of femoral and vertebral bones from cadavers scanned at extremely high resolution that closely match the patient’s data. The XperCT images can also be used for the pre-operative planning of the interventional treatment.

Last, but not least, the cell-level model is identified using an array of bone metabolism biomarkers that are used to define the remodelling rate in combination with other clinical information, such as age, gender, age at menopause, etc.

The combination of these modelling techniques now provides a multi-scale approach for examining the risk of fracture in the proximal femur and thoracolumbar spine in an individual patient based on consideration of his/her mechanical, anatomical and functional characteristics, as well as predicting changes to that risk over the course of time or as a result of treatment.
Images for this section:

![Femoral neck fracture in osteoporotic patient](image)

**Fig. 1:** Femoral neck fracture in osteoporotic patient. From [8], reprinted with permission.

Fig. 2: VPHOP Hypermodelling technology functional diagram.

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Fig. 3: The Hypermonitor user interface, used to design, execute, monitor, and log the personalised simulations.

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**Fig. 4:** Computer simulation of the biomaterial flow inside the bone porosities, in order to predict how the inter-trabecular space will be augmented by the injected material.

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**Fig. 5:** Conceptual representation of the VPHOP hypermodel, formed by five component models each predicting the process at different scale.

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**Fig. 6:** The SterEOS/DE imaging and modelling system. Whole-body, very-low dose, biplanar dual-energy radiography is used to initialise the body-level model with the patient-specific musculoskeletal anatomy, and the organ-level model with the bone morphodensitometry. Image courtesy of the VPHOP Consortium.

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**Fig. 7:** Registered cross-sections of XperCT (top) and microCT (bottom) images for the C3 (left) and T12 (middle) vertebrae and of the femur (right).

Results

A preliminary version of the hypermodel has been tested in a small population study. From a database of 82 clinical cases, we created a cohort of 37 female patients aged 50 or above. For each of these patients, the full clinical record was available, together with a CT scan of the hip region. The cohort had an average T-score (calculated from CT) of -2.2 (SD 0.8); thus, the population included a combination of osteopenic and osteoporotic subjects.

In this study, we used a probabilistic representation of the neuromotor control, defined by two probabilistic variables related to the ability to exert muscle force (flat probability distribution from minimum to maximum, taken from the literature) and to the possible degradation of neuromotor control (normal probability distribution with average 0, no degradation; SD 0.33, maximum 1, complete degradation leading to the highest hip reaction force).

A time-step of one year was used. For each patient, 1,500 load cycles were generated and run for each year up to 10 years of follow up, for a total of 16,500 runs per patient. The same simulations were repeated when considering pharmacological treatment. The risk was defined as the ratio between the load cycles that were predicted to produce fracture in that patient, divided by the total number of load cycles over the prediction period. This indicator is called Personal Risk at time t, PR(t); the personal risk at ten years, PR\textsubscript{10yr}, was calculated. When PR\textsubscript{10yr} > 3% (a risk threshold for hip fracture with a favourable cost-effectiveness ratio in some epidemiology studies), the risk with treatment, PR\textsubscript{10yr}^T, was also calculated.

PR\textsubscript{10yr} exceeded 3% in 9 patients out of 37 (24%). The average PR\textsubscript{10yr} for those 9 patients was 15.1% (SD 11.1%). After simulating treatment, the PR\textsubscript{10yr}^T in the 9 patients selected was reduced to 5.1% (SD 6.4%, min 0.1%, max 16.2%), roughly one third of the pre-treatment risk in the same patients. The PR\textsubscript{10yr}^T still exceeded 3% in 4 patients (11% of the overall sample). Thus, the multi-scale model predicted that 24% of the patients would fracture without treatment, and 11% with treatment. This is in good agreement with clinical trials for bone drugs, suggesting that around 50% of the fractures are avoidable by treating with antiresorptive drugs.
Conclusion

In this study, a preliminary version of the VPHOP hypermodelling technology was used to conduct a confirmation study on the efficacy of antiresorptive pharmacological treatments in avoiding osteoporotic fractures. In spite of some limitations of this prototype compared with what will be the final version of the hypermodelling technology, to be ready by June 2012, we found that the multiscale, mechanistic model of the low-energy bone fracture event, when sufficiently personalised, is capable of predicting clinically relevant information, with conclusions very close to those observed epidemiologically.

Deployment of the VPHOP technology cannot, of course, complicate the clinical pathway for patients suspected of being at risk of osteoporotic fractures. However, the technology can be used in a progressive way, with patients at very low risk identified with minimal effort, and the most sophisticated imaging reserved only for those patients at truly high risk.

As soon as the technology development is completed, it will be tested on a cohort of close to 250 patients, with and without prevalent fracture, who have been recruited and examined at four European clinical centres, in order to confirm the clinical usability of this technology on large cohorts. However, a preliminary cost-benefit analysis conducted recently [29] may already suggest some exploitation scenarios.

In spite of the social importance of musculoskeletal ageing conditions, the rate of innovation in this sub-domain of medicine has been frustratingly low in the last five years, in terms of both pharmacological and technological breakthroughs. A strange "spiral of death" makes clinicians tepid about innovation in this field and results in the biomedical industry moving R&D investment elsewhere. Of course, one trend nurtures the next in a process that is heading towards complete stagnation. There are two separate problems here: the cost of clinical trials, and the cost-benefit analysis of new technological investments in osteoporosis.

A recent study [28] found a statistically significant difference between the three most commonly used bisphosphonates only after the cohort was properly corrected for member characteristics. Another issue is that the end-point for most clinical trials is frequently remote in time. This implies that, to validate a new bone medication, recruitment of a very large cohort is required which, combined with the long-term follow-up, makes these studies exceedingly expensive. However, the VPHOP technology could be used to properly stratify the initial cohort in terms of personalised risk of fracture with the scope to: a) reduce the variability, and b) follow up only a smaller number of patients with the highest risk of fracture. Thus, the VPHOP technology could be used to drastically reduce the cost for clinical trials on osteoporosis drugs.

With respect to the longer-term scenario of large-scale deployment of the VPHOP technologies, it is clear that if we limit our analysis to the costs we face for each patient
who enters the clinical pathway, any advanced technology such as VPHOP will always be more expensive than the usual DXA/FRAX pathway [29]. However, if we conduct our cost analysis to consider the total cost of care, i.e. including the costs involved with the treatment of patients who do experience bone fractures, preliminary data suggest that the VPHOP hypermodelling technology could actually produce a significantly lower total cost of care, when compared to the current standards. While these preliminary results will have to be confirmed by large clinical trials, it is comforting to discover that advanced technologies can pay back not only in terms of increased benefits, but also in terms of reduced costs.
References


Personal Information

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- Istituto Ortopedico Rizzoli (IT) - Project Coordinator
- University of Sheffield (UK) - Scientific Coordinator
- Technische Universiteit Eindhoven (NL)
- Empirica Gesellschaft für Kommunikations und Techn. mbH (DE)
- SCS srl (IT)
- Charité - Universitätsmedizin Berlin (DE)
- Eidgenössische Technische Hochschule Zuerich (CH)
- Universite de Geneve (CH)
- Universitaet Bern (CH)
- Sylvia Lawry Centre for Multiple Sclerosis Research e.V. (DE)
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More information is available at the project web site: http://www.vhop.eu/