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Exploitation of patient avatars towards stratified medicine through the development of *in silico* clinical trials approaches

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Abstract— **The generation of "virtual twins" of patients (Avatars) through integration of multiscale data gained from both the clinical profile of the patient and –omics tools, could create an appropriate environment for stratification of patients in fitting cohorts of "virtual populations". Physiologically based pharmacokinetic & pharmacodynamic (PB/PK/PD) models as *in silico* clinical trial tools can estimate the PK/PD profiles in specific populations. In this work we discuss examples of how patient Avatars could be exploited in the context of *in silico* clinical trials and help in identifying novel biomarkers for personalized diagnosis. The PB/PK/PD models, neuroimaging and –omics data, may be fused together to further advance current decision making processes in clinical practice.**

Keywords: Avatars, Digital Patient, PBPK, *in silico*, genomic, personalized medicine

I. Introduction

Systems biology, focuses on complex interactions within biological systems in order to clarify the molecular mechanism of biological phenomena and disease development by using a more holistic perspective approach, through laboratory experiments and computer modeling [1],[2]. Personalized medicine, in order to prevent, diagnose and treat a disease, considers information of a person's genes, proteins and/or environmental factors [3]-[5]. Avatar technologies and the generation of "virtual profiles" that will contain medical information and monitor health status, appear to be essential for implementation of Digital Patient vision. Avatars could also act as an interface for clinico-genomic integration fusing in data derived from the advancements met in genomic research, as well as for creating "virtual populations" for conducting *in silico* clinical trials as those applied in Physiologically Based Pharmacokinetic & Pharmacodynamic models (PB/PK/PD) [6].

Advantages in genomic research and PB/PK/PD models promote the need for creating approaches for handling and exploiting all the acquired data [7], [8]. In this paper we provide some use cases of how patients "virtual twins" or Avatars could be used to assist decision making processes on diagnosis and treatment and to apply PB/PK/PD models in clinical practice. In addition, we provide some examples of how Avatars could be further used to support collaboration between several disciplines and enhance new research approaches regarding molecular, clinical and imaging profiles.

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II. Physiologically Based Pharmacokinetic Pharmacodynamic Models (PB/PK/PD)

PB/PK/PD is a mathematical modeling technique for predicting the main PK processes of absorption, distribution, metabolism and excretion (ADME) and the potential response in time (PD) of chemical compounds in humans and other animal species. PB/PK/PD models comprise three essential components for a successful generation of *is silico* clinical trials (ISCTs): i) physiology data (organ volume, constitution etc), ii) drug properties (plasma, tissue and receptor affinity, enzymatic metabolism, transport activity etc.), and iii) anatomical arrangement of organs and their perfusion by blood flow (Q) (Figure 1). The PB/PK/PD models differ from classical compartmental PK approaches in the fact that compartments represent actual organ physiology (e.g. organ weight, volume, blood flow, lipid constitution etc.) [9]. The models are developed and generated based on patients demographical, biochemical, pathophysiological, genetic and therapeutic features, such as body weight, excretory and metabolic functions, genetic polymorphisms, disease characteristics and the effects of previous treatments, which can alter dose-concentration relationships as well as concentration-effect relationships (Table 1, Figure 2) [6],[10],[11].

Till today, the development of PB/PK/PD models has found many applications towards drug research as they are reviewed in several previous papers [11], [12]. Moreover, they have gained the attention of WHO as a decision making tool for toxicity studies [13]. Briefly, some of the applications of PB/PK/PD include:

- Estimation and prediction of PK properties of compounds regarding ADME and PD response

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considering:

- Demographic data (age, Body Mass Index etc.)
- Genetic data
- Pathophysiology data and disease status

- Estimation of drug interactions with other drug, food or toxic compounds
- Administration of drugs in specific populations such as children and during pregnancy
- Combination of more than one cases as described above

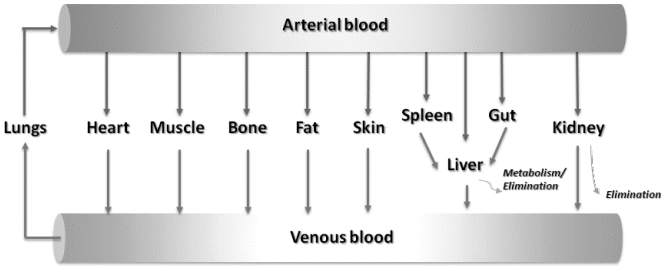

Fig 1. Schematic representation of a whole-body physiologically-based pharmacokinetic model. It should be noted that each organ is supplied by a different blood flow (Q).

TABLE I
EXAMPLES OF PATIENT'S DATA REQUIRED FOR THE GENERATION OF A VIRTUAL PATIENT PROFILE

Demographic data	Sex Weight Height Body surface area (BSA) BMI (Body mass index)
Physiology data	Hematocrit Plasma proteins Albumin Alpha-1-acid glycoprotein (AGP) Blood pressure Creatine phosphokinase (CPK) Glomerular Filtration rate (GFR) / renal function Glucose levels
Pharmacogenetic data (i.e. Metabolic enzymes)	Cytochrome P450 (CYPs) CYP2C9 CYP2C19 CYP2D6 Thiopurine methyltransferase (TPMT) Glutathione S-transferases Glucuronosyltransferase (UGTs)
Genetic data	Single Nucleotide Polymorphisms (SNPs) G6PD deficiency Coagulation factors Genetic Syndromes
Life-style	Dietary habits Alcohol Smoking Complementary –Alternative medicines

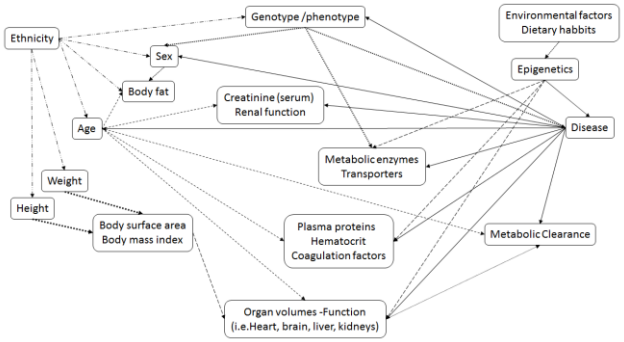

Fig. 2. Correlation and linking of population characteristics with physiology data that play role in the ADME processes of drugs. The relationships create a more complex network of multiple relations in most of the cases. (Based in works of Jamei *et al* 2009 [6] and Cheeti *et al* 2012 [10]).

III. THE –OMICS VIEW OF PERSONALIZED MEDICINE

The completion of the Human Genome Project (HGP) and the rapid development of genome-based technologies started a new era of personalized medicine with molecular analyses to be a part of modern diagnosis of disease [14]. Nowadays, genomic information can provide evidence and early diagnosis regarding susceptibility and molecular mechanism of a disease as well as, data regarding the interplay between hereditary, nutritional, environmental and lifestyle factors (food, exercise etc.) plus possible drug response [15]-[17]. Genome-wide association studies (GWAS) along with the development of bioinformatics have successfully identified genetic loci that are associated with phenotypes and diseases [18], [19]. To date, the National Human Genome Research institute catalog reports the association of more than 7000 Single Nucleotide Polymorphisms (SNPs) with more than 700 complex traits ranging from cancer and complex diseases such as diabetes (type I and II) to more common traits such as body mass index etc. [20]. Especially for disease risk assessment, analysis of genome characteristics and creation of integrated Personal Omics Profile (iPOP) can reveal risk probabilities comparing with population's genetic characteristics (Figure 3) [21].

These population and individual traits are needed in the development of "virtual populations" based on the physiology as they are created in most of cases in PB/PK/PD models.

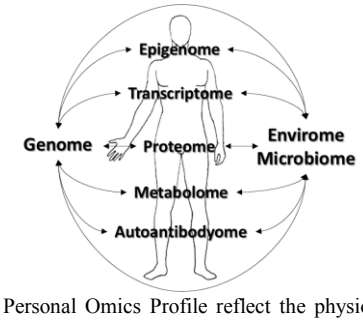

Fig.3 Interactive Personal Omics Profile reflect the physiological state of the body (adopted with slight modifications from Chen and Snyder [2]).

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IV. HEALTH AVATARS LINKING ISCT AND –OMICS TOOLS

Further development of –omic technologies and *in silico* approaches has raised issues of how all these data could be manipulated and translated into clinical level driving decision making approaches and leading medicine to a new era [22]. In this respect, Avatars could link several -omic with PB/PK/PD models (Figure 4). Constructing Avatars through integration of data gained from –omics tools will enhance the stratification of patients in meaningful subgroups and the creation of appropriate "virtual populations" which could be applied for generation of ISCTs. Such information-rich Avatars could be introduced into PB/PK/PD platforms for creating information regarding a patient's PK/PD profile and vise-versa (as is explained in the example below). In addition, results from PB/PK/PD could be organized in order to identify individuals with similar biological background or for example to provide additional clinical data in cases where they're not easily attainable and the treating physician needs fast and accurate answers in order to avoid as much as possible "guesswork" for a specific patient.

A typical example for cases where clinical data are missing could be the pre-operative period applied for patients following anticoagulant or anti-platelet therapies due to dysfunction of the haemostatic mechanism. These therapies are also cases where pharmacogenomic data are taken into account and several algorithms have been created in order to integrate data regarding PK/PD response [23],[24]. We present an example of generation of an ISCT for the anticoagulant agent S-warfarin in three different patients with same characteristics except for the metabolizing enzyme of S-warfarin (CYP2C9). All three patient needs to go on surgery and a pre-operative period should be applied in order for the anticoagulant agent to be cleared from the body. The ISCS was generated through the PB/PK/PD simulation platform of Simcyp® (Simcyp®, Ltd, UK, www.simcyp.com). The administration of S-warfarin (10 mg/24h) was simulated in three male patients 40-41 years old with a discontinuation of the administration after the 10th day. Assuming that these profiles are linked though Avatars with real life's patients, the results reveal for patient 1 (PT1) the concentrations of S-warfarin will reduce below minimal effective concentrations almost 24 hours earlier than the other two patients (PT2 & PT3) after discontinuation of treatment on 10th day (Figure 5).

The generation of Avatars also could help for building up more "virtual populations" with data easily accessed and shared regarding the physiology/pathology/genetic status of the participant and thus provide more accurate results. Also Avatars can be further used as an alert point for research into several scientific disciplines and teams –such as academia, industry, institute and hospitals –serving also as a linking point of collaboration. A typical example is the process of data obtained from neuroimaging analysis towards the diagnosis of several CNS disorders such as Alzheimer's dementia and mild cognitive impairment. Today for CNS disorders bio-imaging analysis techniques are applied in diagnosis, while novel and promising bio-signal analysis techniques [25] based on EEG evaluation have been proposed, as discussed in previous works [26]. In this respect, interpretation of the results from diagnostic tests and bio-image/ signal analysis in Avatars could create a more easily handled approach with data sharing between several scientific groups in order to create holistic approaches including molecular diagnosis and gene expression, Magnetic Resonance Image processing, quantitative EEG analysis, biochemical testing etc. all of which could be embedded for further development of *in silico* clinical trials tools. This process will give new aspects in research field towards the building of more powerful techniques (e.g. neuroimaging with imaging databases) and provide possible evaluation ways of the developing tools. Finally, and more importantly, for clinical practice this approach would supplement the diagnostic picture of an individual, and by clustering Avatars with similar profiles initiate "stratified medicine".

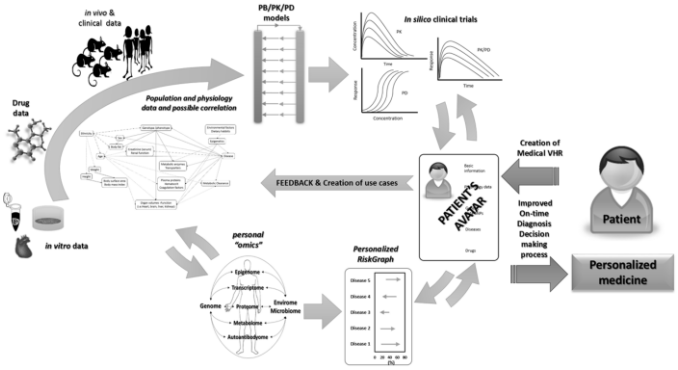

Fig.4. Graphic representation of integrating data from ISCT and -omics tools utilizing patient's Avatar towards the development of personalized treatments.

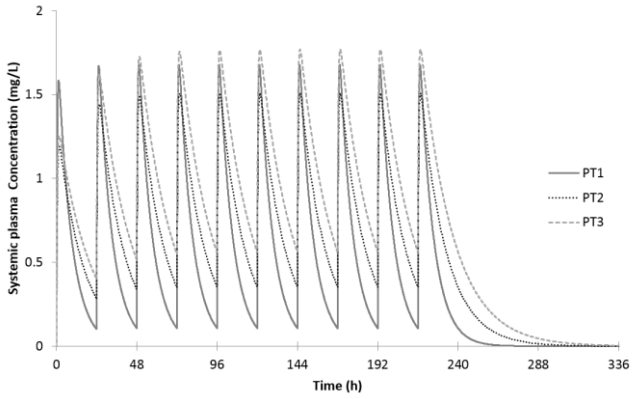

Fig.5 PK profile of S-warfarin administered in three patients with same characteristics except of the metabolizing enzyme CYP2C9. Simulation of a clinical trial through Simcyp® platform (www.simcyp.com).

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V. Conclusion

Over the upcoming years it is generally accepted that medicine will shift from being reactive into be predictive, personalized, preventive and participatory [22]. Avatars can play the role of integration interfaces between the continuous development of personalized clinic-genomic data and PB/PK/PD models, as well as, of novel bioinformatics and biotechnology tools and methods as a part of "stratified medicine" in selected groups of patients contributing to the fast advancement of personalized medicine. Despite the fact that many issues have to be resolved in several levels (biomedical informatics, computational biomedicine, bioinformatics, biology, education etc.) before the Avatar patient's twin vision is realized, a focused interdisciplinary collaboration encompassing computer science mathematics, biology and pharmacology is expected to significantly accelerate this process.

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