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From personalization to patient centered systems toxicology and pharmacology

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ABSTRACT

The ever-growing disruption of new technologies like machine learning, block chains, etc in the daily life not only concerns every consumer, but also any scientist, since such technologies explicitly or implicitly introduce novel methodologies challenging the conventional way to generate knowledge and perform science. This development also concerns toxicologists and pharmacologists. While in the past years there has been a tremendous advance in *in silico* models in some cases capable to replace *in vivo* models, we observe an ever-growing number of available bio-sensors and of computational capabilities able to track and predict the interaction between a substance and a patient in an unprecedent grade of precision. Because the fast development of these technologies precludes a comprehensive overview of the current state of the art, we think that is very important to make a critical review of the current and in our opinion most prominent application of these novel technologies in the field of toxicology and pharmacology. In this review we provide a critical analysis of the present and future of these technologies in the framework of the precision toxicology/pharmacology. Furthermore, in three theses we suggest how the current paradigm of precision and personalization will evolve to a novel cyclic paradigm where personalization is adjusted in short time cycles due to the availability of ubiquitous data.

1. Introduction

A central goal in toxicology or pharmacology is to improve the precision in the use of a substance. The study of the interactions between living organisms and chemical substances is currently based on *in vitro* and *in vivo* experiments, providing information about the best ways to disturb normal or abnormal biochemical functions, either to discover effective therapies to cure diseases or to identify adverse reactions or toxic effects of substances. This modus operandi has been in the history of the pharmacology the standard methodology.

But the fast advance in computational methods, as well as the growing availability of chemical and biological data, has challenged this traditional way to develop and classify therapies or adverse reactions. For instance, by applying in silico methods it is possible to analyze different mechanisms of action in different biological scales for different applications, from cosmetics to pharmacology, and different organisms, avoiding the use of *in vivo* models [7,5]. These methods, combined with *in vitro* methods and genotyping, have become a way to test substances before its approval, and are used as an alternative to animal models to test substance effects Valerio [34].

These methods discover how interactions can take place considering all known mechanisms of action. However, these methodologies still lack the precision required to control the interaction between the substance and the organism. Naturally by knowing the organism's genetics is possible to construct a better profile of the organism, opening the possibility to personalize doses and better predict patients' responses (positive or adverse) to targeted therapy; according to Hamburg and Collins: f*or precision medicine to realize its potential, the patient's history, environment, and lifestyle must additionally be considered* [13], since these interactions have incidence on different scales of the patient's organism. Only by properly integrating this information is possible to get precision medicine, and particularly pharmacology, going beyond genomics [29].

Precision means in this context not only the characterization of the docking, but also the control of all the possible interactions of the organism with the substance in real time. For a therapy this means to track both positive as well as adverse effects in real subjects by continuously acquiring information of relevant biomarkers as well as the general condition of the individual. Until now this has been more a vision than a reality. However, precision toxicology/pharmacology has recently become more real and practicable: In the current technological revolution, and particularly, after the ubiquity of smartphones, the miniaturization of sensors, and the fast development of efficient methods for data integration and analysis based on machine learning (ML), the door to physiological analysis in real time has been opened [13].

In this brief survey we present the recent development of the combination of ML, pervasive computing and blockchains in pharmacology/toxicology to reach the goal of a precision medicine. In this constellation the combination of these methods is no more restricted to

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the discovery of novel substances but extends to fields like the acquisition of data in real time for clinical studies, pharmacovigilance and even tracking of positive or adverse outcomes. By reviewing these novel applications and technologies we got the impression that a transformative process is currently running: more available data implies that the development of a substance does not stops after its approval, since its effect can be constantly documented, providing relevant data about the substance interaction. In the first part we provide a short overview about computational pharmacology/toxicology in the framework of precision medicine. In the second part we introduce three theses about how the combination of machine learning, pervasive computing and blockchains will transform the toxicology/pharmacology. In the third part we review the required conditions to apply these technologies. In the fourth and fifth part we review the grade of maturity of the combination of these technologies and discuss some risks but also chances in the future of this field.

2. Precision medicine/toxicology and informatics

The use of informatics and machine learning methodologies is not novel and is routinely used in biomarker development and drug discovery [20]. Drugs are developed to target specific molecular alterations, and their effects can be modulated by the activities of other genes or molecules. With the availability of large scale pharmacogenomic data is possible to systematically identify multiple biomarkers that contribute jointly to drug sensitivity, and to identify combination therapies for personalized cancer medicine [21]. The analysis of this data is however not possible if efficient techniques of analysis and efficient computing, together with large computers, were not available. According to Interlandi, "*It will require integrating pentabytes of existing health data, spread across scores of databases whose content and quality will vary widely. And it will involve storing blood and tissue samples from one million people, especially if those samples are collected at regular intervals*[1]".

From all the available methodologies, deep neural networks (DNNs) have become a cornerstone in drug development and pharmacology due to its capability to capture high level interdependences in data [6]. Neuronal Networks (NN) for deep learning are fully connected in one layer with nodes in the other layer, while nodes in the same layer are not connected. This independence, especially in the input node, allows the input of separate physiological data, while the basic neuronal network combines this data into a self-generated model. To accomplish this task, methods must be developed to define periods in the time series for a suitable combination of data for Deep Learning (DL). Missing data must also be supplemented by appropriate methods, such as matrix completeness [36,37].

The combination of data is not restricted to one level/one organism. The combination of pharmacogenomic data, animal and *in vitro* models (including organs in chips; see for instance [15], as well as in silico models [7,5], is an innovative pathway to develop novel substances and drugs and simulate pharmacological action as well as toxic reactions in organisms. In this process machine learning methods, specifically DNNs, have become a relevant methodology to predict drug properties, including pharmacological action [2] and toxicity [12], enhancing the way how responders and non-responders considering genetic signatures and individual characteristics (Fig. 1). This methodology is helpful to avoid failures in patient trials, reduce or completely abolish experiments on animals, and became the basis for personalized therapies (or assessment of adverse reactions) based on the particular profiling and genetics of the patient.

There are several well documented cases supporting the fact that a better patient profiling could be helpful to avoid lethal errors. For instance, a large trial of bevacizumab in gastric cancer showed no overall benefit, yet there were strong hints of benefit in patients in North America and, to a lesser extent, in patients in Europe, but there was no observed benefit in patients in Asia who constituted most of the patients in the trial [28]. Based on a better profiling of patients, and a better integration of genetic information as well as a correct phenotyping, this kind of errors can be avoided. Furthermore, in the clinical field artificial intelligence (AI) could do a far better job in the biomarker development, helping to make a clear distinction between healthy and pathological conditions, for instance in the analysis of blood tests or in cancer classification by analyzing the immunohistochemistry of the tumor tissue [35].

However, patient variability is very complex, and environmental, socioeconomic and behavioral factors contain interactions with pheno/genotypic factors, as well as with patient co-variances, that cannot be resumed in a model. For example, it is well known that age-associated effects may be due to changes in organ function in the elderly or immaturity of metabolic pathways in infants or young children. Additionally, true reasons are less obvious, for example the impact of ethnicity, which is not only related to the individual genome, but which is also related to social and cultural aspects that affect the compliance of the individual, once a drug is approved for a treatment, as well as the kind of substances which the individual is exposed to [28].

Thus, the development, approval, prescription, monitoring, and paying of a treatment with a substance is not a simple lineal process: due that many factors have an influence in the way how an individual interacts with a substance, there is no trivial classification between responders and non-responders. Instead, this classification is dynamic. For this monitoring pervasive computing plays a decisive role.

3. Beyond a lineal model: pervasive computing in toxicology and pharmacology

3.1. Thesis 1: ubiquitous input of health data

Pervasive computing, better known as internet of things (IoT), refers to the interconnectivity and harmonization of different sensors in real time. According to Ornes, *the notion of pervasive computing entails a vision of the world in which computing isn't limited to tablets, smartphones, and laptops. The realization of this vision, called the "Internet of Things" (IoT), is the ever-expanding collection of connected devices that capture and share data. Any object, outfitted with the right sensors, can observe and interact with its environment* [26]. According to Mosa et al., the applications of IoT are not restricted to the industrial field, and extend to the medicine and toxicology, with "*devices that constantly monitor health indicators, devices that auto-administer therapies, or devices that track real-time health data when a patient self-administers a therapy. Because they have increased access to high-speed Internet and smartphones, many patients have started to use mobile applications (apps) to manage various health needs. These devices and mobile apps are now increasingly used and integrated with telemedicine and telehealth via the medical Internet of Things" (mIoT),* making them *useful tools in the practice of evidence-based medicine at the point of care* [25,8,23].

Furthermore, the combination of IoT with smartphones have an active influence on individuals, since its use (combined with social networks) influence the education, self-management and compliance of patients to a therapy and the use of substances [31]. Additionally, the combination with cellular telephony allows a fast communication between health professionals and individuals, helping to deliver fast feedback about the subjective condition during a treatment or exposition to toxic substances.

One application field of IoT is the surveying of the adherence of an individual to a therapy, for instance, improving drug compliance. "Drug compliance and adverse drug reactions (ADR) are two of the most important issues regarding patient safety throughout the worldwide healthcare sector. ADR prevalence is 6.7% throughout hospitals worldwide, with an international death rate of 0.32% of the total of the

[1] https://www.scientificamerican.com/article/the-paradox-of-precision-medicine/.

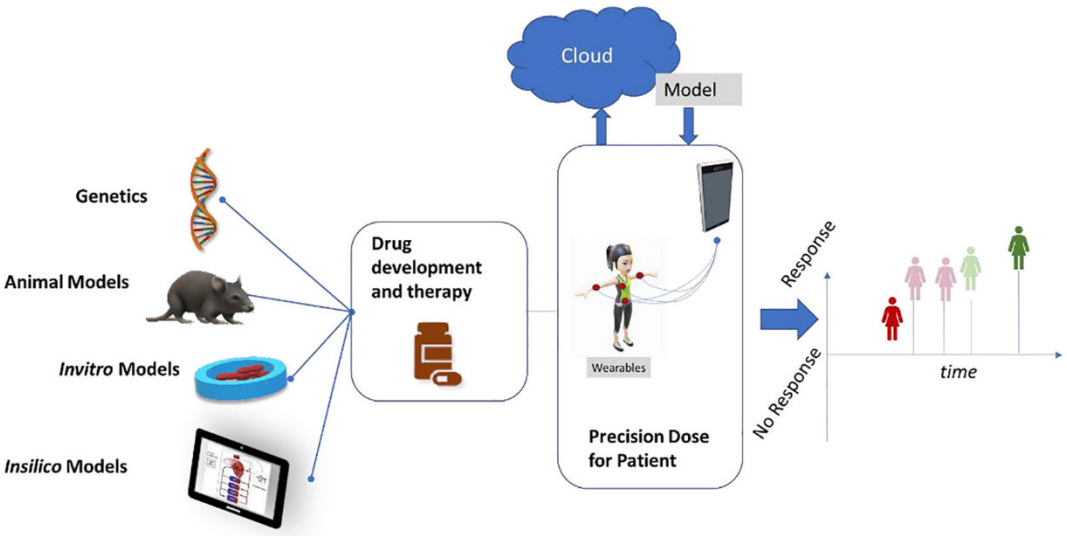

Fig. 1. The inclusion of pervasive computing has the potential to challenge the static classification between responders and non-responders. In this case, the surveillance of the patient's response to a therapy using IoT is helpful to adjust the dose of the substance, as well as co-medication, helping the patient to change from a non-responder into a responder status.

patients. This rate is even higher in Ambient Assisted Living environments, where 15% of the patients suffer clinically significant interactions due to patient non-compliance to drug dosage and schedule of intake in addition to suffering from polypharmacy. These instances increase with age and cause risks of drug interactions, adverse effects, and toxicity" [16]. To this end, ecosystems have been developed to control and monitor drug compliance, as well as in the development of smart drug dispensers helping the patients to automatically control their predetermined medication regime [27].

Other results obtained in simulation environment suggest that IoT solutions offer a feasible solution for the medication intake use case. [31]. However, there are currently more than 5881 apps which have not been properly reviewed, and only about 20 of them have been developed with the aid of health professionals [1]. Therefore, the field of IoT as smart dispensers and apps for patient adherence are a Proof of Concept that still requires a careful evaluation of its impact in a clinical field.

Beyond the patient adherence, the use of IoT offers interesting possibilities for the direct monitoring of biomarkers. In toxicology there are some research exploring the monitoring of individuals exposed to toxic substances that can be extrapolated to medical applications. For instance, Jo et al implemented *a reliable, efficient, and cost-effective internet of things (IoT) system for air quality monitoring with newly added features of assessment and pollutant prediction for the monitoring of the air quality in underground coal mines. This system is comprised of sensor modules (based on Arduino), communication protocols, and a base station, running Azure Machine Learning (AML) Studio. The results delivered by this study have shown positive results, implying an effective cost reduction in mine monitoring systems, while the security of workers get improved"* [17].

The previous example can be extended in changes in the economical *drug life cycles, as well as how a patient can response to a substance.* The effect of this technology over the initial strategy of classification between responders and non-responders devised by personal medicine (Fig. 1) is that the individual response can change/evolve in the time. According to Marcher et al. the factors listed in Table 1, that can be measured with pervasive computing in real time, are relevant to have a transition from a non-responder to a responder [22].

In all these examples the acquisition and analysis of data play a central role, either in the definition of multiparametric models or the development of methods of analysis of biomarkers. This implies that an accurate surveillance of the biomarkers, and an appropriate feedback in a treatment, can change the way that an individual respond to a substance. For instance, an individual initially classified as non-responder can become an appropriate therapy that let her to become a responder in the time (see Fig. 2).

Thus, IoT provides novel perspectives also for innovative ways of drug discovery and/or recognition of alternative targeting of substances, since the technology offers for a first time the possibility to gather critical physiological data in real time. This means, IoT is not only restricted to relative simple applications like smart pill dispensers and smartphones controlling when and how much of a medicament has been consumed. IoT offers also the possibility, together with genetic profiling, to confirm why a medicament, or a combination of medicaments, is appropriate to treat the disease of my patient, and correspondingly adapt the dose or exposition to the substance.[2]

3.2. Thesis 2: ML assisted treatment

While the previous theses only address the new availability of mass input data for medical treatment we will now have a closer look at the new possibilities of processing it. It is simply not feasible for a physician to take note of all the available data let alone evaluate it properly and base her assessment on it. Classical machine learning and big data approaches on the other hand are not only capable of handling such mass data, they already do require such large volumes of data e.g. to successfully classify patient populations and personalize treatments.

From all the available methodologies, deep neural networks (DNNs) have become a cornerstone in drug development and pharmacology due to its capability to capture high level interdependences in data [6]. Neuronal Networks (NN) for deep learning are fully connected in one layer with nodes in the other layer, while nodes in the same layer are not connected. This independence, especially in the input node, allows the input of separate physiological data, while the basic neuronal network combines this data into a self-generated model. To accomplish this task, methods must be developed to define periods in the time series for a suitable combination of data for Deep Learning (DL). Missing data must also be supplemented by appropriate methods, such as matrix completeness (Harvey et al., 2005; Recht, 2011).

[2] For instance, with 3D printers is possible to personalize the dose and combination of substances. See for example https://www.digital-health-systems.com/technologie.

Table 1
Strategies to modify a treatment response (as shown in Fig. 1) based on novel technologies.

Solutions to improve response to substance	Description	Available Mobile Technologies
Assessing whether the diagnosis is correct	Verification and if necessary estimation or inference of personal factors	**Yes** – Collection of different physiological parameters with wearables and data analysis using ML
Maximizing the response to the same drug	Measuring plasma levels may help determine if the dosage should be adjusted, in particular for individuals whose pharmacokinetic characteristics differ from that of the general population	**No** – No reliable device is available yet for precise estimation of plasma values. However, measurement of some biomarkers and metabolites in the sweat can provide indirect evidence of the effects of the current dosage – see e.g. [3]
Checking the patient's metabolic status	Checking for the concomitant administration of other drugs that induce hepatic enzymes is also useful	**Yes** – Metabolic kits[1] as well as smart patchs (see again [3]
Changing the drug	The choice of the new drug should be based on considerations such as side-effect profile and personal and family history of response to previous drug treatment	**Yes** – Use of electronic health records (EHR) (see e.g. [8]
Treatment augmentation	This strategy involves combining drugs from different classes[2]	In this case drug dispensers controlled by IoT and HER support the work required in the combination of different drugs

[1] See e.g. https://kenko.do/de/.
[2] For example, the augmentation of antidepressant treatment with lithium or thyroid (T_3) hormones.

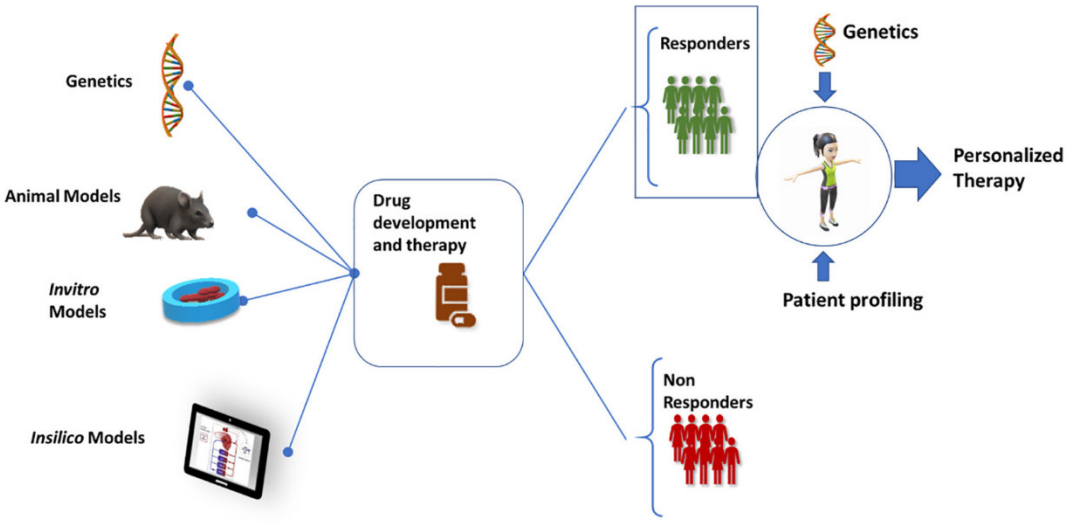

Fig. 2. Classification of patient populations of responders and non-responders based on the integration of different classes of data. When a patient is identified as a responder a personalized therapy (or assessment of adverse reaction) can be defined based on the patient profiling as well as her genetics.

The combination of data is not restricted to one level/one organism. The combination of pharmacogenomic data, animal and *in vitro* models including organs in chips; see for instance [15], as well as in silico models [7,5], is an innovative pathway to develop novel substances and drugs and simulate pharmacological action as well as toxic reactions in organisms.[3] In this process machine learning methods, specifically DNNs, have become a relevant methodology to predict drug properties, including pharmacological action [2] and toxicity [12], enhancing the way how responders and non-responders considering genetic signatures and individual characteristics (Fig. 1). This methodology is helpful to avoid failures in patient trials, reduce or completely abolish experiments on animals, and became the basis for personalized therapies (or assessment of adverse reactions) based on the particular profiling and genetics of the patient.

There are several well documented cases supporting the fact that a better patient profiling could be helpful to avoid lethal errors. For instance, a large trial of bevacizumab in gastric cancer showed no overall benefit, yet there were strong hints of benefit in patients in North America and, to a lesser extent, in patients in Europe, but there was no observed benefit in patients in Asia who constituted most of the patients in the trial [28]. Based on a better profiling of patients, and a better integration of genetic information as well as a correct phenotyping, this kind of errors can be avoided. Furthermore, in the clinical field artificial intelligence (AI) could do a far better job in the biomarker development, helping to make a clear distinction between healthy and pathological conditions, for instance in the analysis of blood tests or in cancer classification by analyzing the immunohistochemistry of the tumor tissue [35].

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Thus, the development, approval, prescription, monitoring, and paying of a treatment with a substance is not a simple linear process[4]:

[3] While test in animals get reduced.

[4] https://www.annualreviews.org/doi/full/10.1146/annurev-pharmtox-010617-052446#f1.

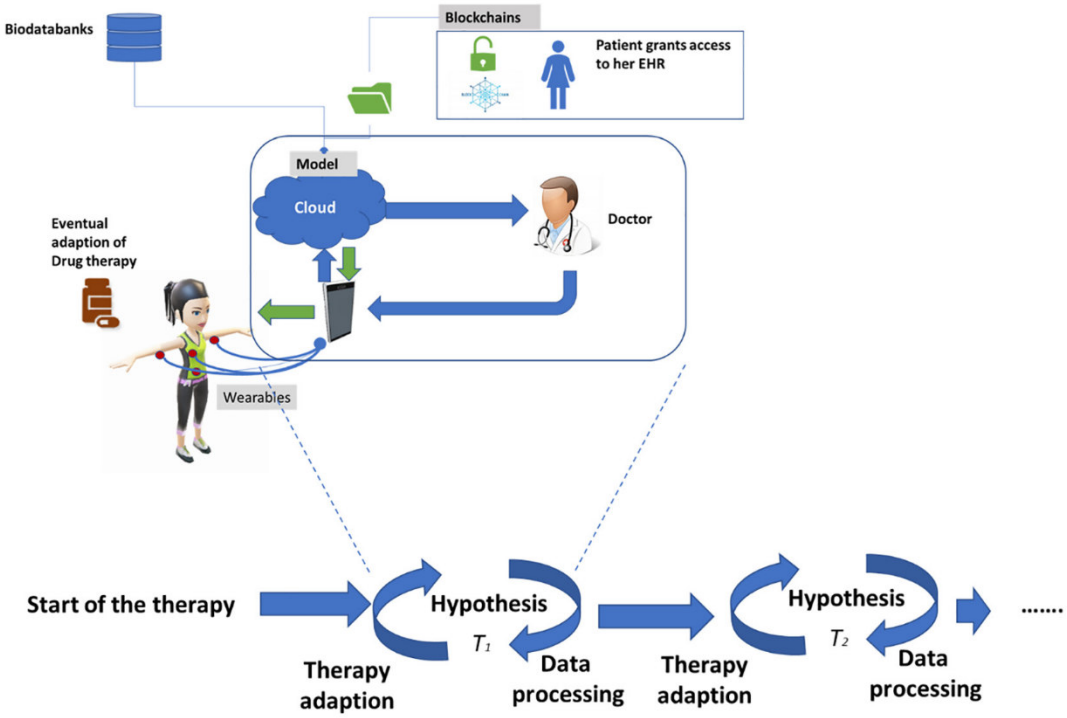

Fig. 3. Cyclic personalized therapy paradigm. The integration of blockchains for smart contracts make available patient data, helping to continuously improve models used for the assessment of the interaction between the patient and the substance. Thus, the cycle Ti – where the dosage or the exposition to the substance is readjusted – is shortened.

due to the fact that many factors have an influence in the way how an individual interacts with a substance, there is no trivial classification between responders and non-responders. Instead, this classification is dynamic. For this monitoring pervasive computing plays a decisive role.

3.3. Thesis 3: beyond the linear paradigm of anamnesis and therapy

Despite the above stated approach is based on big data processing, it only incorporates information at the beginning of the treatment, by incorporating genomics as well as relevant data about the condition of the patient and is only revalidated and adjusted after relative long exposition to a substance (see Fig. 1).

Nevertheless the direct consequence of the above stated theses is that the tracking cycles of the patient condition can be shortened ad libitum, allowing for a fast readjustment of the treatment as well as the recognition of the emergence of adverse effects (see Fig. 3).

Thus, with the incorporation of pervasive computing big data is no more static but reflects the evolution of the condition of the patient. However, to reach this goal some preconditions have to be met.

4. Required preconditions

4.1. Precondition 1: distributed data storage

The classical incorporation of data bases has become unsuitable for data intensive methodologies to train machine learning methods.

One part of the problem is the constant growing of information in the health sector. For instance, in the *U.S. healthcare system alone reached, in 2011, 150 exabytes. At this rate of growth, big data for U.S. healthcare will soon reach the zettabyte (10^{21} gigabytes) scale and, not long after, the yottabyte (10^{24} gigabytes). Kaiser Permanente, the California-based health network, which has more than 9 million members, is believed to have between 26.5 and 44 petabytes of potentially rich data from EHRs, including images and annotations."* [30].

But not only the growing of the data volume, but also the diversity of information required for the training of machines, require appropriate strategies for information storage. Distributed database management systems (DDBMS) are an alternative to overcome this limitation [23]. The main concern in the use of this technology is the security in the data transfer, as well as the possibility to access data from other patients to improve the training of the models based on the Machine learning methods. In the next section we explore how new technologies like blockchains, solid and smart contracts can be used to overcome this problem.

4.2. Precondition 2: availability of computing power for data processing

The second precondition is the availability of resources to process the large amounts of data stored in conventional data banks or in DDBMS: while for current applications in medicine require the processing power of a desktop, the increase of data volume and the implementation of machine learning methods require larger machines and efficient methods able to process information in multiple nodes, which has become a novel method: "*because big data is by definition large, processing is broken down and executed across multiple nodes. The concept of distributed processing has existed for decades. What is relatively new is its use in analyzing very large data sets as healthcare providers start to tap into their large data repositories*" [30].

The use of these technologies has been enabled by the relatively simple access of cloud technologies like *Hadoop/MapReduce* and *Spark*.[5] One shortcoming in this field is that these technologies have been developed on an open source premise. This makes its application very complex, programming intensive making them not easy to be implemented. Only after recent software developments, like *Databricks*[6] for data processing and data flow programing on Spark as well as *Tensor Flow*,[7] have simplified the implementation of big-data projects: while

[5] https://en.wikipedia.org/wiki/Apache_Spark.
[6] https://databricks.com/.
[7] https://www.tensorflow.org/.

the TensorFlow library automates the creation of training algorithms for neural networks of various shapes and sizes, the spark library distributes the evaluation of different model variants in parallel nodes for hyperparameter tuning process.[8] Thus, the combination of these technologies for computationally intensive processes in model training has opened the way to real application of machine learning.

4.3. Precondition 3: security & privacy issues for DDBMS: Blockchains and solid

The last precondition that has to be met to apply the above named technologies in the realm of health care is the handling of the acquainted security and privacy issues. There are several proposals to do so. Blockchains applied to bitcoin technologies have been very popular in the past months, not only as an alternative to money exchange, but also as a method to make legal contracts. The core of bitcoins are strong encryption algorithms exploited in a new way to secure transactions. *Users' identities would be shielded by pseudonyms; records would be completely decentralized; and no one would be in charge — not governments, not banks or any central institution* [10]. For this reason, more than the bitcoins is the blockchain technology the most interesting part to apply in problems where central control is a weakness — for example, when users do not necessarily trust one another.

An additional core idea of smart contracts is the construction of a network of peers that continuously and automatically validate new transactions owning an own signature and an own time stamp; these transactions are introduced in a chain, where old and latest changes are concatenated. The network of peers verifies the integrity of the chain, such that any attempt of a fraudulent change is automatically detected and punished/blocked by the network.

A significant shortcoming of this technology is that blockchains are slow and energy intensive, since considerable computational power is required for the verification of transactions in the network of peers for any transaction, making it in principle unsustainable for instance in money transactions.

There are however other kind of transactions that require less energy and that can be extremely useful in pharmacology. For instance, the permission to access clinical data can work as a blockchain that will function as a series of switches that guide how data flow between patients, clinicians and researchers. Such kind of transactions are less frequent and thus more suitable to be implemented using blockchain technologies, also because only the switch granting access to the data is codified inside the chain, which is a central characteristic in the function of the so called smart contracts [24].

Recently, other alternatives to Blockchains to secure access to clinical information have been proposed. For instance, Huberman et al. proposed a solution in the form of a secure procedure for data mapping and/or linkage, which allows to identify the correspondence between entities in a distributed dataset. In their solution, given each party's list of attributes, the list matching protocol finds the set intersection securely. Once the set intersection is obtained, the parties may also agree on a common order to facilitate subsequent privacy preserving analytics, using as a background the definition of secret keys that are sued as exponentials in a matching protocol. The key issue in this algorithm is that if an unauthorized third part wants to get access to the protocol it should solve a discrete algorithm, which is currently a very hard computational problem [4].

When the patients gain control over their clinical data, stored in their Electronic Health Record (EHR), two goals are reached: first to avoid the formation of data siloes, like Facebook or Google, where nobody has control of the information stored, and second updates of clinical data are more frequent and performed without the intervention of third parts. Patients that grant access to their clinical data inside a blockchain model have still control over their own data [24], while novel opportunities are open. For instance, more and better data is available for research and development in pharmacology and toxicology, which is an alternative to conventional biodata banks or patient databanks. Such data is helpful to train models to better predict positive or adverse outcomes in the intake of a substance, in particular when data delivered by biomarkers is integrated and used for medical assessment (see Fig. 3). Currently there are companies and private initiatives, like the HIT Foundation (http://hit.foundation), that are implementing block chain solutions to grant access to individual clinical data, for instance by offering patients economic incentives based on bitcoins [23].

Besides the energy resources required to keep running Block Chains there are other short comes as the possibility in the near future to break Block Chains using quantum computation, which due to its computational capacity represents a serious risk to any system relying on public keys.[9] Paradoxically, quantum computation can also represent the future to code smart contracts, by relying in the phenomenon of quantum entanglement of particles: When two quantum particles are entangled, they share the same existence; this happens when they interact at the same point in space and time. After that, a measurement on one immediately influences the other, no matter how far apart they may be,[10] which is an essential characteristic to measure any attempt to change in a contract [18]. The same problem might arises in alternative methods based on the computation of discrete logarithms, in particular when processes are decodifies using quantum algorithms like the Shor's algorithm [9].

Also, the ethical implications of block-chain based data sharing are still open. What happens if a patient withdraws consent for a trial that is immutably recorded on a blockchain? And unscrupulous researchers could still add fake data to a blockchain, even if the process is so open that everyone can see who adds it. Once added, no-one can change that information, although it's possible they could label it as retracted [11]. Additionally, there is an open economic question: which is the price of sharing information, and how to compute the economic incentives for a patient to share her information?[11] All these aspects must be still cleared for a robust application of this technology.

The latest proposal to address the security and privacy issues appropriately while maintaining the seamless exchange of data via the internet thus making it accessible for the cloud computing power to process it is "solid" (derived from "social linked data"). Solid results from a project led by Tim Berners-Lee, inventor of the World Wide Web, taking place at MIT. The project intends to evolve the way web applications work today, resulting in preserving true data ownership by individuals as well as improved privacy. Solid is a proposed set of conventions and tools for building decentralized social applications as envisioned by us in the future healthcare based on Linked Data principles. They build on and extend the founding technologies of the world wide web (HTTP, REST, HTML) while being fully backwards compatible with the existing web. The main enhancement is that the web becomes a collaborative read-write space, passing control from owners of a server (i.e. patients in the realm of healthcare) to the users of the specific data in that system (i.e. physicians, medical experts and KI). The Solid specifications are available on GitHub at https://github.com/solid/solid-spec. …

[8] https://databricks.com/blog/2016/01/25/deep-learning-with-apache-spark-and-tensorflow.html.

[9] https://singularityhub.com/2017/11/05/is-quantum-computing-an-existential-threat-to-blockchain-technology/.

[10] https://www.technologyreview.com/s/611022/if-quantum-computers-threaten-blockchains-quantum-blockchains-could-be-the-defense/.

[11] This topic is under test by some companies trying to reverse the equation of free data owned by large companies: http://www.bbc.com/capital/story/20180921-can-you-make-money-selling-your-data.

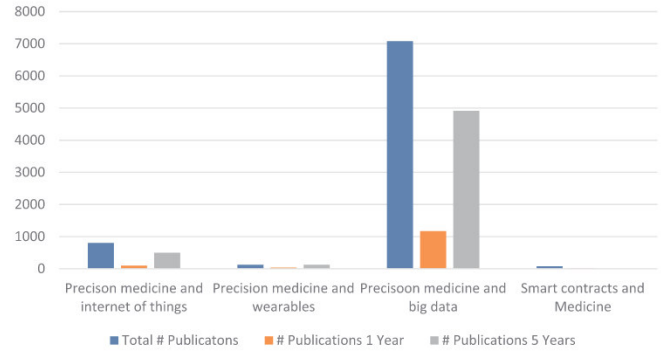

Fig. 4. Number of publications by topic in the past 1 and 5 years.

5. Hype or future?

The combination of IoT, Machine learning and blockchains had bring an explosion of commercial developments and research works exploring novel concepts in the health sector, in particular in precision medicine. Besides the high number of apps, there are a considerable number of publications exploring this topic, as is shown in the table below, with a large number of publications exploring the relation between big data and precision medicine. Few publications specifically explore the relation between internet of things (or wearables) and precision medicine.

The rapid development, implementation and commercialization of these technologies makes difficult to estimate whether these developments are more a hype than a robust technology. Given there are still too few peer-reviewed works in this field, it seems too early to make a critical evaluation of the impact of these technologies, and besides big data analysis (centered in molecular recognition and genetics), the combination of all these technologies seems to be more a hype.

According to Gather, five Hype Cycles has been identified to evaluate the associated risk in an emerging technology (see Fig. 4):

- **Innovation Trigger:** A potential technology breakthrough kicks things off. Early proof-of-concept stories and media interest trigger significant publicity. Often no usable products exist, and commercial viability is unproven;
- **Peak of Inflated Expectations:** Early publicity produces several success stories — often accompanied by scores of failures. Some companies take action; many do not;
- **Trough of Disillusionment:** Interest wanes as experiments and implementations fail to deliver. Producers of the technology shake out or fail. Investments continue only if the surviving providers improve their products to the satisfaction of early adopters;
- **Slope of Enlightenment:** More instances of how the technology can benefit the enterprise start to crystallize and become more widely understood. Second- and third-generation products appear from technology providers. More enterprises fund pilots; conservative companies remain cautious;
- **Plateau of Productivity:** Mainstream adoption starts to take off. Criteria for assessing provider viability are more clearly defined. The technology's broad market applicability and relevance are clearly paying off.[12]

To predict whether each of the reviewed technologies are a hype or a solid technical background to develop innovative applications is still very premature. According to the analysis above, Machine learning is currently an innovator trigger, IoT is just at the peak of inflated expectations, and big data as well as mobile health monitoring are in the thought of disillusionment. Block chains are not contemplated in this analysis, and perhaps will soon reach a though of disillusionment. Furthermore, the heterogeneity in the outcome of this analysis does not contemplate the integrated use of all these technologies.

Also, the classification of mobile health monitoring as a though of disillusionment must be critically considered. This can be true for fitness and sport. But in medicine this field is still an innovation trigger considering both the development of novel biosensors as well as the integration of data and modeling using machine learning. This will allow the jump from a personalized to a precision medicine/toxicology-pharmacology (beyond the genes), which is essentially based on patient centered systems – based for instance on block chain like technologies – that grant access of relevant clinical information. Only with a robust availability of information, far from siloes, can be possible to reach a plateau of productivity (Fig. 5).

6. Discussion: paradigm change from linear personalization to a systematically accompanied patient centric approach

In this brief review we have covered recent literature in the field of pervasive computing and machine learning applied to precision pharmacology and toxicology. These technologies allow a combination of relevant clinical data containing information of the behavior and environment of the patient. This data analysis goes beyond the analysis of the individual's genome. The interpretation of this data is relevant to understand the interaction between a substance and the organism and is decisive for adverse or therapeutic responses. This brings for a fist time the promise to increase the precision how the positive and adverse action of substances takes place in an individual, without accounting all the complexity required in a whole integration of genomic information to deduce the patient's response to the substance, which is a common shortcoming of conventional precision medicine [14].[13] This also opens the possibility to better account a more dynamical classification of patients beyond the rather static division between responders and non-responders, as well as the implementation of a linear patient personalization (Fig. 1). In particular, a new cyclic paradigm arises, where a treatment or individual's exposition to a substance can be readjusted according to the measurement and prognose of the patient condition in real time.

Perhaps this development will stimulate a revolution in pharmaceutical industry. One interesting field is the treatment of rare diseases: currently its treatment is extremely expensive and brings low revenues, in part because there are few patients suffering rare diseases and because such treatments must be adjusted for each patient. With the combination of information technologies, the option to adjust the dose to get a response to the substance (Fig. 2 and Table 1) opens the possibility to make more profitable this treatment. This also challenge the blockbuster paradigm, since the profit is not generated with the massive commercialization of one dose for one substance, but with the combined commercialization of a substance with the associated digital services for personalized adjustment of the dose (and combination with other substances, as is shown in Fig. 2). Also, relevant, a cyclic paradigm also represents a paradigm change in the production methodologies in the pharmaceutical industry: in the future the problem will be not the upscaling of production processes of generic drugs, but the design of innovative production processes of medicines in low scales, some of them based on 3D printing, allowing a constant adaption of the dose and substance combination in a single charge [19].

This can be helpful for instance for the retargeting of substances, even known substances as ibuprofen. One example is the treatment of cystic fibrosis: ivacaftor, which is an expensive substance developed on basis of genetic profiling, was roughly equal to that of three far-lower-

[12] https://www.gartner.com/technology/research/methodologies/hype-cycle.jsp.

[13] https://www.scientificamerican.com/article/the-paradox-of-precision-medicine/.

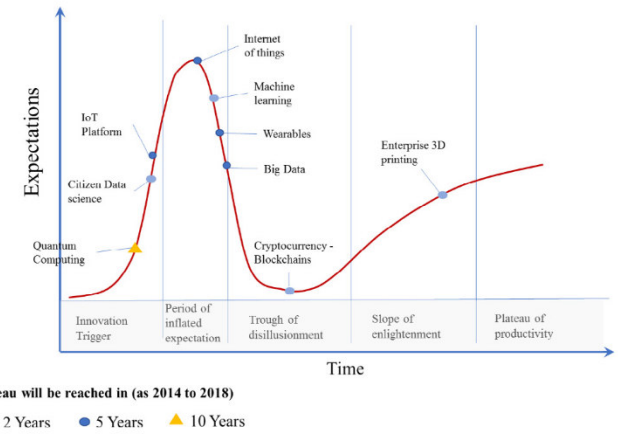

Fig. 5. Hype cycle according to Garthner with evaluations of the technologies from 2016 to the present (see link in footnote 15).

tech, universally applicable treatments: high-dose ibuprofen, aerosolized saline and the antibiotic azithromycin [32].

One critical aspect is the rapid but less controlled development of technologies in IoT, as well as the fast development of apps, since many of these applications have been developed without the assistance of health professionals. The second big problem is that this precision can be gained when data is combined, and accurate predictions are made on trained models. For this training real and accurate clinical data is required, which is difficult to be accessed from available data banks. Regarding this problem, block chains are a promise to get access to this information, considering that each patient grants access to parts of her clinical data stored in EHR by means of smart contracts. With the combination these technologies the paradigm of precision medicine (and in this way precision medicine/toxicology), based on integration of relevant physiological data, and patient centered medicine (far from data silos and with patients controlling their clinical information) becomes more real and concrete.

But the increase in the amount of available data represents a formidable problem for its integration in suitable models, considering that all this data is heterogeneous and has different quality. Additionally, we should not forget the environment foot imprint that these new technologies are generating: while large computational power and cloud solutions are already consuming a lot of energy (about 75 TWh[14]), block chain applications will require much more energy, making them prohibitive due to the amount of produced heat and greenhouse gases.[15]

How to clean, integrate and manage such amounts of data still represents a big problem, which perhaps requires specific solutions based on few data or clever defined bias in data evaluation [33] depending on how the substance will be administrated. Here will perhaps be also valid the same criteria as in medicine: good doctors only require few parameters to recognize and predict the condition of a patient; bad doctors instead ask for more and more parameters, that paradoxically increases the uncertainty in the assessment of the condition of the patient.

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[14] https://digiconomist.net/bitcoin-energy-consumption.

[15] The expected consumption of energy only for block chains in fintech applications in 2019 will surpass the amount of energy consumed in the USA in 2018.

References

[1] I. Ahmed, N.S. Ahmad, S. Ali, S. Ali, A. George, H. Saleem Danish, E. Uppal, J. Soo, M.H. Mobasheri, D. King, et al., Medication adherence apps: review and content analysis, JMIR MHealth UHealth (2018) 6.
[2] A. Aliper, S. Plis, A. Artemov, A. Ulloa, P. Mamoshina, A. Zhavoronkov, Deep learning applications for predicting pharmacological properties of drugs and drug repurposing using transcriptomic data, Mol. Pharm. 13 (2016) 2524–2530.
[3] S. Anastasova, B. Crewther, P. Bembnowicz, V. Curto, H.M. Ip, B. Rosa, G.-Z. Yang, A wearable multisensing patch for continuous sweat monitoring, Biosens. Bioelectron. 93 (2017) 139–145.
[4] G. Bellala, B.A. Huberman, Securing Private Data Sharing in Multi-Party Analytics, Social Science Research Network, Rochester, NY, 2016.
[5] F.Y. Bois, J.G.D. Ochoa, M. Gajewska, S. Kovarich, K. Mauch, A. Paini, A. Péry, J.V.S. Benito, S. Teng, A. Worth, Multiscale modelling approaches for assessing cosmetic ingredients safety, Toxicology 392 (2017) 130–139.
[6] H. Chen, O. Engkvist, Y. Wang, M. Olivecrona, T. Blaschke, The Rise of Deep Learning in Drug Discovery, Drug Discov Today (2018).
[7] J.G. Diaz Ochoa, J. Bucher, J. Niklas, K. Mauch, Multi-scale modeling for individualized spatiotemporal prediction of drug effects, Toxicol. Lett. 221 (Supplement) (2013) S83–S84.
[8] D.V. Dimitrov, Medical internet of things and big data in healthcare, Healthc. Inform. Res. 22 (2016) 156–163.
[9] M. Ekerå, J. Håstad, Quantum algorithms for computing short discrete logarithms and factoring RSA integers, Post-Quantum Cryptography, Springer, Cham, 2017, pp. 347–363.
[10] A. Extance, The future of cryptocurrencies: bitcoin and beyond, Nat. News 526 (2015) 21.
[11] A. Extance, Could bitcoin technology help science? Nature 552 (2017) 301–302.
[12] M. Gao, H. Igata, A. Takeuchi, K. Sato, Y. Ikegaya, Machine learning-based prediction of adverse drug effects: an example of seizure-inducing compounds, J. Pharmacol. Sci. 133 (2017) 70–78.
[13] M.A. Hamburg, F.S. Collins, The path to personalized medicine, N. Engl. J. Med. 363 (2010) 301–304.
[14] J. Interlandi, J. Interlandi, The Paradox of Precision Medicine.
[15] S. Ishida, Organs-on-a-chip: current applications and consideration points for in vitro ADME-Tox studies, Drug Metab. Pharmacokinet. 33 (2018) 49–54.
[16] A.J. Jara, M.A. Zamora, A.F. Skarmeta, Drug identification and interaction checker based on IoT to minimize adverse drug reactions and improve drug compliance, Pers. Ubiquitous Comput. 18 (2014) 5–17.
[17] B. Jo, R.M.A. Khan, An internet of things system for underground mine air quality pollutant prediction based on azure machine learning, Sensors 18 (2018).
[18] E.O. Kiktenko, N.O. Pozhar, M.N. Anufriev, A.S. Trushechkin, R.R. Yunusov, Y.V. Kurochkin, A.I. Lvovsky, A.K. Fedorov, Quantum-secured blockchain, Quantum Sci. Technol. 3 (2018) 035004.
[19] A.A. Konta, M. García-Piña, D.R. Serrano, Personalised 3D printed medicines: which techniques and polymers are more successful? Bioengineering 4 (2017).
[20] M.W. Libbrecht, W.S. Noble, Machine learning applications in genetics and genomics, Nat. Rev. Genet. 16 (2015) 321–332.
[21] Y. Liu, T. Fei, X. Zheng, M. Brown, P. Zhang, X.S. Liu, H. Wang, An integrative pharmacogenomic approach identifies two-drug combination therapies for personalized cancer medicine, Sci. Rep. 6 (2016) 22120.
[22] J.-P. Macher, M.-A. Crocq, Treatment goals: response and nonresponse, Dialogues Clin. Neurosci. 6 (2004) 83–91.
[23] P. Mamoshina, L. Ojomoko, Y. Yanovich, A. Ostrovski, A. Botezatu, P. Prikhodko, E. Izumchenko, A. Aliper, K. Romantsov, A. Zhebrak, et al., Converging blockchain and next-generation artificial intelligence technologies to decentralize and accelerate biomedical research and healthcare, Oncotarget 9 (2017) 5665–5690.
[24] A. Maxmen, AI researchers embrace Bitcoin technology to share medical data, 2018.
[25] A.S.M. Mosa, I. Yoo, L. Sheets, A systematic review of healthcare applications for smartphones, BMC Med. Inf. Decis. Making 12 (2012) 67.
[26] S. Ornes, Core concept: the internet of things and the explosion of interconnectivity, Proc. Natl. Acad. Sci. 113 (2016) 11059–11060.
[27] J. Pak, K. Park, Construction of a smart medication dispenser with high degree of scalability and remote manageability, J. Biomed. Biotechnol. 2012 (2012).
[28] R.W. Peck, The right dose for every patient: a key step for precision medicine, Nat. Rev. Drug Discov. 15 (2016) 145–146.
[29] R.W. Peck, Precision medicine is not just genomics: the right dose for every patient, Annu. Rev. Pharmacol. Toxicol. 58 (2018) 105–122.
[30] W. Raghupathi, V. Raghupathi, Big data analytics in healthcare: promise and potential, Health Inf. Sci. Syst. 2 (2014).
[31] K. Serdaroglu, G. Uslu, S. Baydere, Medication intake adherence with real time activity recognition on IoT, In 2015 IEEE 11th International Conference on Wireless and Mobile Computing, Networking and Communications (WiMob), 2015, pp. 230–237.
[32] H. Svanström, B. Pasternak, A. Hviid, Use of Azithromycin and Death from Cardiovascular Causes, 2013.
[33] H. Taniguchi, H. Sato, T. Shirakawa, A machine learning model with human cognitive biases capable of learning from small and biased datasets, Sci. Rep. 8 (2018) 7397.
[34] L.G. Valerio Jr., In silico methods, Academic Press, Oxford, 2014, pp. 1026–1029 third ed..

[35] M.E. Vandenberghe, M.L.J. Scott, P.W. Scorer, M. Söderberg, D. Balcerzak, C. Barker, Relevance of deep learning to facilitate the diagnosis of HER2 status in breast cancer, Sci. Rep. 7 (2017) 45938.
[36] N.J.A. Harvey, D.R. Karger, K. Murota, Deterministic network coding by matrix completion, Proceedings of the Sixteenth Annual ACM-SIAM Symposium on Discrete Algorithms, Society for Industrial and Applied Mathematics, Philadelphia, PA, USA, 2005, pp. 489–498.
[37] B. Recht, A simpler approach to matrix completion, J. Mach. Learn. Res. 12 (2011) 3413–3430.