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Ethical and Legal Issues on Investment Casting of Functionally Graded Materials for Medical Automation

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***Abstract*—**Additive Manufacturing is utilized in medical automation to optimize and integrate materials in accordance to energy source type leading to treatment gaps in industrial designs for extreme biomechanical forces in relation with vibration, fluid transfer and multi-physics performance. Elastic/piezoelectric materials are strongly ordered inter-metallics for characterization of distinct features that can provide excellent compositional strength, ductility and uniformity for super elastic shape memory alloy on medical devices. Several theories can be derived to analyze and interpret complex problems on the application of functionally graded materials used in medical machineries for genome architecture. Numerical principles on fluid and thermodynamics such as Reynolds number, Darcy rule, Friction Factor and Heat Rate are integrated with fundamental equation of numerical vibrations using Helmholtz equation. Simulation by Large Eddy approach and genetic modeling can be done using Physical and Chemical Vapor Deposition following various theories on Carrera's Unified Formulations by comparing with various Classical Plate Theories, Equivalent Single Layer Theories, Layer-Wise Theories, Zig-Zag Theories and Mixed Refined Variational Theories. The subject is approached towards the distinct application of ethical and legal problems in order to resolve particular issues on biomedical works.

***Keywords*—**Additive manufacturing, genomic architecture, ethical issue, legal issue, medical device.

I. Introduction

FOR some years, research into the drug formulation field has concentrated on the quest for systems that postpone the drug release after their administration. There have been notable innovations in the field that can be discovered absolutely in the literature. The explanations that have resulted to the sustained release drug delivery system formulation originate from the desire to attain the slow release of highly water-soluble compounds, manage such compounds to the target organ or cell, attain release rates that match a given goal, diminish the number of daily administrations, and enhance compliance and minimize side effects [1].

Additive Manufacturing (AM), also termed as Three-dimensional Planning (3DP), is described as the method of combining materials to generate objects from 3D conceptual data, commonly layer upon layer, in contradiction to conventional subtractive manufacturing approaches. As the AM accuracy and the versatility methods have been enhanced, the concentration of the industries has shifted from "Rapid Prototyping" to "Rapid Manufacturing." Investment casting, also known as lost-wax casting, is a conventional manufacturing method commencing from the concept and tooling of a pattern cast [2].

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Computational drug discovery can perform challenging process acceleration to design and optimize a new drug candidate. The computational structure-based drug design (SBDD) impact on discovery of drugs has developed intensely in the past ten years due to fast improvement of more rapid architectures and better computations of high-level algorithms in a time reasonable manner. Classical molecular dynamics (MD) simulations nowadays permit SBDD implementation tactical ways that completely account for flexibility of the overall structures of drug−target model system. It is now widely acknowledged that the two major drug-binding models, namely, induced-fit and conformational selection, have supplanted Emil Fischer's rigid lock-and-key binding model. Receptor and ligand flexibility are important for correct prediction of drug binding and associated thermodynamic and kinetic properties. As an outcome, classical MD is no longer acknowledged prohibitive for effective design of drugs. It is forcing the computationally driven drug discovery frontiers in both industrial and academic institution [3].

Several computational approaches are broadly utilized in the highly intricate, longer period, and resource-intense method of drug discovery. Computational processes are vastly, but not limitedly, applied during the drug discovery early phase when fundamental research efforts determine to decipher disease-related biology, prioritize drug targets, and identify and optimize novel chemical entities for medical intervention. Primary aims of in silico processes in drug discovery include better compound generation with promising in vitro and in vivo properties. Moreover, computational analysis has a provision of crucial aid in decision making and guidance for experimental programs, thus, decreasing the number of candidate compounds to be assessed experimentally. Over the past 30 to 40 years, the computational method use in drug discovery settings has maintained its increment and computations have led to an integral aspect of discovery research [4].

"Structure-activity relationship (SAR) analysis" constitutes numerical and graphical methods as well as ligand- and target structure-based approaches which comprise, similar to others, the mathematical model derivation of SARs or compound prediction and evaluation binding modes. Comparatively, "virtual screening" and "compound design" include ligand- and structure-based processes [4]. Classical MD is a physical means for observing the atomic and molecular interaction and motion in accordance to Newton's physics. A force field is utilized for estimation of the forces between interacting atoms and calculation of the overall system energy. Subsequently, in the

event of MD simulations, the Newton's laws of motion integration produce successive configurations of the evolving system, hence, provides specified trajectories for positions and velocities of the particles over time [3]. Free energy computations of ligand–receptor binding is a naturally applied to simulate drug discovery. Numerous methods have been utilized. Grand canonical Monte Carlo simulations can determine both potential ligands and their drug target binding site(s). Mainly, the target is overwhelmed with ligands, or more usually with little fragments, which are then, slowly "evaporated," abandoning only the most tightly bound ligands. This process has been proven successful in a few cases, specifically, in the new nanomolar inhibitor design of p38 kinase [5]. "Energy calculations" constitute molecular mechanics, quantum mechanics, and combined methods, namely, for conformational analysis, molecular geometry calculations, or affinity predictions. Moreover, both "ADME (absorption, distribution, metabolism, excretion) modeling" and the systematic study of "drug-target interactions" comprise the variety of machine learning approach application and the predictive statistical model derivation [4].

Understanding the principles underlying the chemical and biological system behavior needs a thorough investigation at spatial and temporal resolutions challenging existing experimental methods. Molecular dynamics (MD) simulations are being incrementally partnered with experiments in this investigation since simulations can trace system behavior across a huge spatiotemporal region – length scales up to thousands of angstroms, with atomic precision, and timescales up to milliseconds, at femtosecond resolution. This simulation power has been further augmented by current methodological improvements. Here, the prediction for the next 25 years of MD simulations may result to especially highlighting the emphasis on the search application for novel drugs [5].

Moving apart from protocols that utilize MD for the incorporation of target flexibility into standard docking calculations, it is now feasible to execute MD simulations for long periods sufficient for the free energy landscape and kinetic profile exploration related with the overall drug-binding process, like the origination of the drug fully solvated in water to the drug−target bound state. Nowadays, a complete dynamical protein−ligand binding description event can be obtained, together with numerous accuracy degrees. This is because of the augmenting computer power, the advent of graphical processor unit (GPU) architectures, and MD software that can effectively execute on these developed hardware infrastructures [3].

It is crucial for bone fixators, orthopedic implants, external fixators, and artificial joints to have a metal component since these devices are considered to replace the intended hard tissue purposes in orthopedics. Moreover, there are devices needed for dilatation maintenance designed to exhibit plasticity or elasticity resulting to expansion and rigidity purposes. Furthermore, some metals, in the field of dentistry, are designed for dental implants, restoration, and orthodontic wire [6].

There is a long history for metal application being integrated to material science and engineering. Unfortunately, some metals are perceived to be an unfavorable component of medical devices because of health and environmental issues over metal toxicants. Regarding the strong concern on material safety for medical usage, there must be a significant effort being provided for improving the corrosion resistance and mechanical durability. Meanwhile, the technological innovation in ceramics and polymers from the past thirty years has been successful for applying these metals to several devices leading to substitution of those produced from ceramics and polymers. Despite of the material innovation, over 80% of medical devices are created from metals due to their strength, durability and toughness. The benefits of metal incorporation in medical devices are the following: (a) high strength; (b) high elasticity; (c) high fracture toughness; (d) a high elasticity and stiffness combination; and (e) high electrical conductivity. Applying these features on medical devices, metal incorporation would result to a better replacement and more opted substitution over ceramics and polymers. Research and development of technological innovation maintains its design of mechanical and surface property enhancements for application of tissue compatibility [6].

Concerning cases in several applied ethics, general principles or standards are easier to adopt for adherence than it is to develop particular or explicit rules of behavior consistent with those mechanisms adhering to those rules in practice. Subsequently, during the development of novel research domains, it is common for those engaged to legally research for rules and practices employed in similar areas to guide their tasks. In the evaluation of genomic-wide association (GWA) condition, researchers naturally support established body of ethics and law governing clinical trial for monitoring of basic issues, which in these circumstances are informed consent, respect for privacy, and distribution of results. However, distinctions between these domains of biomedical research work in contrary to very efficient or satisfactory method. Genomic studies do not comprise of administering and supervising the outcomes of any medical treatment on human subjects. As an alternative, genomic research is conceptualized around collection, analysis, and information distribution regarding individuals and society with whom the investigators may have restricted, if any, direct interaction. This influences the nature of the involved associations, so that it is a misattribution to utilize the term "subject" both as basis to people who give samples and details for GWA assessments and persons who initiate to perform clinical trials [7].

II. Methods

A. Drug Engineering Principles (Computational Structure-Based Drug Design)

Kinetic modeling of general extraction, isolation of bioactive compounds and human catalytic reactions involves reactor data involving integral and differential methods of deriving rate expressions from varying change in concentrations and molar fractions per unit of time, and thus, for Gibbs free energy, where varying change in pressure is calculated using various principles of fluid dynamics, is needed to determine rate

constants based from the second law of thermodynamics involving principles of ideal gas law and entropy change. Rate constants are necessary in order to observe the constant ratios between reaction rates and reactant concentrations. The expression constants describe the time functions starting from the initial concentration at t=0 until the desired time with corresponding change in concentration. Derivation of Gibbs free energy is similar to determination of activation energy based from Arrhenius equation. Eyring-Polanyi equation is used to determine the Gibbs free energy or basically, the free energy available to do the kinetic analysis as a thermo-fluid dynamic function for expressing the spontaneity of a reaction.

a. Gibbs Free Energy

Arrhenius equation is a mathematical derivation of rate constants from the relationship between the colliding molecules in the chemical reaction following the collision theory and exponential form of energy profiles using the activation energy concept. From the natural logarithm of Gibbs free energy equation, Eyring-Polanyi equation can be derived by replacing collision concept with transition state theory, wherein, varying energy profiles may result from the differential form of enthalpy involving change in temperature as a function of entropy and change in pressure as a variable of system volume.

b. Change in Pressure

A packed bed is usually evaluated as a porous medium, in which the Newtonian fluid flow follows Darcy's law at low Reynolds numbers. The total pressure drop across a bed of particles is a result of the frictional interaction between the fluid and the particles as well as the gravitational potential energy change brought about by the rising fluid. The frictional pressure drop across a packed bed during one-dimensional flow is described by two terms namely a viscous energy loss term, proportional to fluid velocity, and an inertial energy loss term, proportional to fluid velocity squared. The well-known and frequently utilized Ergun (1952) equation was originally formulated semi-empirically to predict the pressure drop for Newtonian flow through a packed bed of predominantly spherical particles. It has served well and is still utilized extensively, especially in chemical engineering. The original Ergun equation was obtained by straightforward addition of the Blake–Kozeny and the Burke–Plummer equations [8].

c. General Extraction Kinetic Reaction

Solvent extraction follows a kinetic reaction series of varying concentration change per unit of time as the molar fraction of bioactive molecules increase in the solvent per length of time as a result of its affinity transfer from the plant concentration material. Rate constant is the function of the plant concentration and shows the relationship of concentration change as a result of extraction of bioactive molecules per change in time.

d. Isolation of Bioactive Compounds Kinetic Reaction

Isolation of active medicinal component from a plant material following a general extraction protocol is a kinetic reaction showing the transfer of a bioactive medicinal compound, from one component to another, or the extraction solvent comprising of several functional groups from various therapeutic components. Rate constant is the function of varying molar fraction of bioactive component equivalent to concentration change per change in time to determine the rate expression of two components.

e. Mass Transfer Equations

e.1 Unsteady-State Molecular Diffusion

Unsteady-state molecular flux is the partial change in concentration of one component per unit of time showing the diffusivity of another component to be transferred from the previous component as a function of partial concentration change of two components in respect to varying change in time and direction.

e.2 Flux using Rate Equations

Molecular flux for drug delivery system is the negative slope of the rate constant in liquid phase as a function of partial change in concentration of component A in respect to variations per unit of time and direction. Rate constant expresses the diffusion of one component to another component as a result of concentration gradient, hence, transfer of molecules from higher concentration to lower concentration.

f. Human Catalytic Kinetic Reaction

Enzymatic kinetic reactions show the change in concentration of bioactive natural compounds per unit of time indicating the relationship of rate constant as a function of the product of active component concentration and number of enzymes involved in the reaction leading to change in bioactive component concentration due to metabolism and change in number of enzymes due to conjugation.

B. Ethical and Legal Principles

1. Products Liability

Products liability is the protective term for the manufacturer, seller, or other supplier's liability of chattels, to a person who experiences physical injury inflicted by the chattel. Products liability may depend upon the manufacturer or supplier's negligence, upon a warranty theory, or upon strict liability in tort. Theories on strict liability were exposed onto the picture for the past fifty years, but have become the supreme ground of liability for products' manufacturers. However, this "revolution" in the common tort law via the broad application of strict products liability is not as radical as it was previously perceived. Developments in negligence and warranty law anticipated the application of strict liability in several jurisdictions. Furthermore, elements of negligence law, particularly the "reasonableness" norm, have gradually moved back into the strict liability basis in cases charging product design and warning defects [9].

2. Development of Theories of Recovery

a. Warranty

The performance by the buyer of goods against the seller for warranty breach is a hybrid, "produced by the illicit intercourse of tort and contract," and characterizing the features of both.

Originally, a warranty breach performance emerged from the tort trespass action on the case for presumed duty breach. This error had created to be a misrepresentation form, in the deceit nature, and not at all explicitly ascertained from it. On the last half of the 17th century, precedents such as Cross v. Gardiner, 1 Show.K.B. 68, 89 Eng.Rep. 453 (1689), and Medina v. Stoughton, 1 Ld.Raym. 593, 91 Eng.Rep. 1297 (1700), established the evidence that the tort performance would depend for fact affirmation ("express warranty"), even one created in the absence of its falsity knowledge and lack of negligence. As an outcome, warranty became a strict liability form in tort. Subsequent to the decision of Stuart v. Wilkins, 1 Doug. 18, 99 Eng.Rep. 15 (1778), over a period of more than a century, warranties had gradually been considered as express or implied contract terms of sale, and the performance on the agreement became the common treatment for any breach [9].

Although the performance is in the form of contract breach, its fundamental tort behavior has sometimes been acknowledged by the employment of statutes applicable to torts, such as survival of tort performances. Gosling v. Nichols, 59 Cal.App.2d 442, 139 P.2d 86 (1943). Or the limitation statute for torts. Rubino v. Utah Canning Co., 123 Cal.App.2d 18, 266 P.2d 163 (1954). Or the comparative negligence application statute. JCW Electronics, Inc. v. Garza, 257 S.W.3d 701 (Tex. 2008) (finding that implied warranty breach of merchantability is an action cause grounded on tort and thus, added within the comparative liability principle enacted by the legislature using that language). Several jurisdictions permit recovery for wrongful death emerging out of warranty breach, when the performance would not lie for a common contract breach. See for example Greco v. S.S. Kresge Co., 277 N.Y. 26, 12 N.E.2d 557 (1938); Kelley v. Volkswagenwerk Aktiengesellschaft, 110 N.H. 369, 268 A.2d 837 (1970) [9].

b. Implied Warranty

The principle in such cases does not rely upon contractual duties, but rather on the mechanism that the original performance of delivering an article a mistake, in the event that due to the lack of those attributes which the manufacturer was entitled for having it, the lack of which could not be readily traced by the consumer, the article is dangerous for the designs for which the consumer would commonly use it [9].

It would be unfair to acknowledge a principle that would allow manufacturers of goods to make a need for their products by depicting that they have characteristics which they, in fact, do not have, and then, since there is no contract privity occurring between the consumer and the manufacturer, reject the consumer right to recover if damages yield from the lack of those attributes, when such lack is not readily apparent [9].

"An exclusion to the principle can be announced by courts when the case is not an isolated event, but common in its feature, and the occurring principle does not equal with justice. Under such situations a court must, if free from some statute restraint, announce a principle that must meet the full law interpretation." Mazetti v. Armour & Co., supra [9].

3. Strict Liability in Tort

Civil Code Section 1769 states that: "In the lack of express or implied contract of the parties, acceptance of the goods by the by the buyer must not dismiss the seller from responsibility in damages or other legal mitigation for breach of any promise or warranty in the agreement to sell or the sale. However, if after acceptance of the goods, the buyer is unsuccessful to provide notice to the seller of any promise or warranty breach within reasonable period after the buyer knows, or used to know of such breach, the seller must not be responsible therefor [9].

III. Discussion

A. Computational Structure-Based Drug Design Results

A porous medium or material is a solid structure or matrix permeated by an interconnected mesh of pores occupied by a fluid. Numerous organic entities such as rocks, soils, biological tissues like bones and man-made products such foams and ceramics can be considered a porous media. To functionalize these porous entities, certain determinants or factors have been established, involving porosity, permeability and solid phase dimensions, such as fiber diameter and spacing between fibers for fibrous porous entities investigated herein. The porosity of a porous entity is the fraction of void space that is consumed by air or some other fluid to the total volume. With the porosity of the porous entity becomes a single, linear function or variable of the density of the porous material [10].

Concerning the initial experimental set on "undisturbed" porous entity, it was taken off from the permeameter and greatly fluffed manually to disturb its microstructure. The fluffed entity was then placed back into the permeameter and tested under the same set of conditions. Differences in the permeability between the "disturbed" or "fluffed" entity and the "undisturbed" entity are noticed, especially in the high porous domain indicating the permeability sensitivity to the microstructure of the porous media. Consistent outcomes were acquired which exhibited that the permeability difference because of fluffing or repacking of the porous media only happened in the extremely high porosity regime and disappeared if the porosity was below 96.5%. Permitting for the fact that these testing samples had recently been revealed to either static or dynamic compactions or compressions via the use of the porous-walled cylinder-piston apparatus, conclusion has been made that the repeated mechanical compression effect on the entity structure, and hence, permeability was restricted to the extremely high porosity regime. It explains why in the dynamic compression or compaction experiments, one acquired consistent pressure production for the similar initial porosity of the porous media, even though the entity was "fluffed" between trials greatly similar in this permeability experiment. In the event of the dynamic compression method, the porosity declines sharply and passes the 96.5% threshold rapidly subsequent to the release of piston. Hence, for the main part of the compression or compaction method, the porous entity possesses almost similar permeability for various trials [10].

For the application of lift generation, when the porous material undergoes rapid compaction or compression, it is

chosen to obtain the lift from the transient trapped air supply as much as possible. This is attained by selecting a porous medium with extremely low permeability and extremely weak solid phase structures. These applications comprise soft squeeze dampers, and a soft porous bearing which produces substantially improved lift and hence, major reduction frictions as a surface plane glides over it [10].

Improved sampling processes, which depend on physical pathways, can redesign the free energy of the studied event as a variable of a few reaction coordinates, often termed as collective variables (CVs), having the ability to account for appropriate degrees of freedom of protein−ligand binding and unbinding. The free energy projection along the appropriate degrees of freedom is termed as the potential of mean force (PMF). By mechanism, it can be utilized for extraction of both thermodynamic and kinetic information [10].

B. Ethical and Legal Issues

Several ethical and legal problems can be raised pertaining to medical automation. The drug and catalytic development process through the application of computational structure-based design can result for faster assessment relating to various mass transfer, fluid, and thermodynamic principles. Additive manufacturing in investment casting of medicinal intervention yields vast genomic architecture as an analytical tool to evaluate drug delivery system and catalytic function, in a faster and more economical means.

Product design is a significant ethical concern in strict products liability in tort as all resulting harms caused by a defect in the design of the drug products or medical devices is subjected for recovery claim. Moreover, drug products and medical devices are regarded to deliver its intended performance, yet, adverse drug reactions and other allergic reactions had been resulted as a legal offense due to breach in implied warranty, and still, can be subjected for a claim of damages due to suffered injury. Hence, drug engineering must be strictly monitored by appropriate experts in a particular field prior to clinical trials, in order to exercise the reasonable care standard not to commit negligence, either by procedures or by drug experts, subjected to warranty issues.

IV. Conclusion

Genomic studies naturally corroborate established system of ethics and law beyond administering and supervising the results of any medical treatment on human subjects. Through the use of additive manufacturing (AM) in investment molding of therapeutic intervention can rapidly produce vast data beneficial to drug delivery system. Computational structure-based drug design (SBDD) is an algorithmic tool for fast evaluation of drug discovery vital for genetic design and development of drug products. This computational concept tool can also be applied for catalytic development of medical devices. This innovative process is a combination of free energy assessment involving variations in pressure and temperature in order to optimize drug products and medical devices leading to numerous investigations of several drug delivery systems and catalytic functions. Hence, computer-assisted structure-based design for fast assessment of molecular dynamics is a very promising innovation on analysis of drug products and medical devices using the principles of mass transfer, fluid dynamics and thermodynamics. The design of drug products and medical devices must be strictly evaluated in order to prevent negligent conduct of drug experts concerning strict manufacturing liability. This impediment in drug engineering assessment raises the quality of drug products and medical devices to lessen adverse drug reactions and other allergic reactions resulting to a defect in product design which may be subjected for ethical and legal concerns in strict products liability.

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