Innovative Computational Methods for Pharmaceutical Problem Solving a Review Part I: The Drug Development Process

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Abstract

Computational methods have provided pharmaceutical scientists and engineers a means to go beyond what's possible with experimental testing alone. Providing a means to study active pharmaceutical ingredients (API), excipients, and drug interactions at or near-atomic levels. This paper provides a review of this and other innovative computational methods used for solving pharmaceutical problems throughout the drug development process. Part one of two this paper will emphasize the role of computational methods and game theory in solving pharmaceutical challenges.

Keyword: computational pharmaceuticals, game theory, artificial intelligence, drug development

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I. Introduction

The drug development process (DDP) is both lengthy and expensive, consisting of five key stages: drug discovery and development, preclinical, clinical, Federal Food and Drug Administration (FDA) review, and, lastly, post-marketing surveillance (see Figure 1). Stage 1-drug discovery and development consists of efforts in identifying a key disease target such that the design of, or repurposing of, a compound can be developed to stop or reverse the effects of a disease. Once a lead compound is identified, development occurs such that preclinical trials may be conducted. During the development stage, information on the lead compound is gathered, such as absorption, distribution, metabolizing, excreting, and toxicity data, among other information. The preclinical stage moves the compound into in-vivo and in-vitro testing. The studies conducted within this stage, though not very large, provide critical information that details the compounds dosing and toxicity levels before moving to the next stage. Preclinical studies aim to answer basic drug safety questions but neglect gathering information on how the drug interacts with the human body. This information is gathered in clinical trials.

Clinical trials are the third and arguably most critical stage of the DDP. The clinical stage consists of 3 key phases starting with phase 1. Phase 1 consists of approximately 20-100 human subjects with the disease or conditions the active pharmaceutical ingredient (API) is designed to address. The purpose of this stage is to screen for safety and dosage. Phase 1 requires several months and functions as a gateway to phase 2 with a passage rate of approximately 70% of drugs in phase 1 entering phase 2. (FDA, 2018a). Once a drug candidate reaches phase 2, the number

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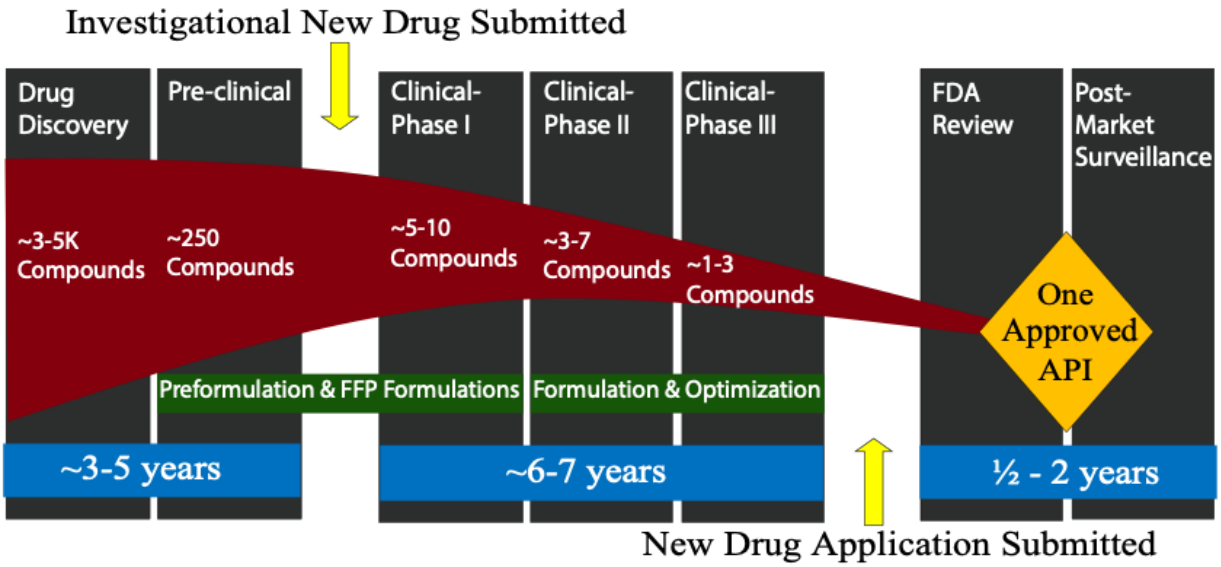

Figure 1. Graphical summary of the drug development process. Diagram has been modified and expanded from (Marsac, 2019). Where API stands for active pharmaceutical ingredient and FFP is fit-for-purpose. More on the FFP approach to early drug formulations can be found in (Qiu et al., 2017).

of human subjects participating in the study goes up to several hundred, all of whom are diagnosed with the disease or condition the API is designed to treat. Within this phase, efficacy and side effects are screened. This process can last for several months up to two years. About 33% of drug candidates that enter this stage move into to phase 3. Phase 3 extends the study to at least 300 human subjects but can reach 3,000 (FDA, 2018a). All subjects studied in this phase also have the disease or condition the API is designed to address. This phase is one of the longest-lasting, between 1-4 years. The purpose of this phase is to further screen efficacy and adverse events. Approximately 25% of drug candidates move on to phase 4, in which several thousand human subjects are screened (FDA, 2018b). This phase provides a final gateway to approval through screening safety and efficacy. Lastly, the drug candidate must be approved through regulatory agencies.

Once a drug candidate has sufficient evidence of safety and effectiveness for its intended use (provided by the preclinical and clinical phase results), the drug developers may file a new drug application (NDA). Filing the NDA signals the intent to market a drug and should be submitted to the FDA for approval in the United States.

The application should include all preclinical data, clinical data, and information concerning product labeling, directions for use, patent information, drug abuse data, and more. After review, if the drug candidate is considered safe, this stage of the DDP will refine drug labeling before the product launch (FDA, 2018b). Once a drug product is launched, stage 5 provides product safety surveillance for the drug's life cycle. This stage includes inspections of manufacturing sites, oversight of drug advertisements, adverse event recording, and more

(Campbell et al., 2020b; FDA, 2018c). Indeed, the DDP is a streamlined approach to drug development. However, the process has faced criticism.

Despite having general improvement and success over time, the DDP has often been criticized as a risky, slow, and expensive process (Djulbegovic et al., 2014; Kaitin, 2010; Kaitin and Dimasi, 2000; Mattina et al., 2017). Risky because the DDP involves exposing hundreds to thousands of human subjects to a drug candidate estimated to have about a 1 in 5 to 1 in 10 chance of being deemed safe to market (MIT, 2018; Seaton, 2011). In addition, the process is financially risky for the drug developer with estimates of the clinical-stage alone, costing upwards of $19 million (April, 2018), and the entire DDP estimated between $2-3 billion (DiMasi et al., 2016, 2003). Clearly, there is a need to cut costs. However, cutting costs within the DDP is challenging due to rigorous guidelines and standards that must be met. Despite the difficulty of changing the process, computational advances have streamlined decision-making (Sale, 2001).

Computational methods are now widely used throughout the DDP to yield better-informed decisions. Indeed, such methods have the potential of saving millions within the DDP (Kumar et al., 2006). For example, pharmacokinetic (PK) modeling can save resources and expedite the DDP by reliably predicting in-vivo Absorption, Distribution, Metabolism, and Excretion (ADME) properties of a drug (Gallo, 2010). PK and pharmacodynamic (PD) modeling are well established in the realm of pharmaceutical development and, for this reason, will not be mentioned further in this paper. For interested readers, the authors suggest (Andes and Craig, 2002; Barber and Bourne, 1971; De La Torre et al., 2000; Javaid et al., 1983; Meredith, 2003; Urso et al., 2002). Instead, this paper will focus on emerging computational strategies for problem-solving in the pharmaceutical industry.

This paper will first review simulations, and emulations as they are used in the DDP. Topics such as molecular modeling will be discussed including methods such as the Grand Canonical Monte Carlo and Grand Canonical Alchemical Perturbation. Artificial intelligence (AI) techniques will also be discussed.

II. Simulations, Emulations and Predictive Modeling throughout the Drug Development Process

MM and similar computational chemistry models have become deeply woven into the drug discovery process. Applications in drug discovery range from predicting the effect of ligand-mediated water displacement using the Grand Canonical Monte Carlo (Bodnarchuk et al., 2020) to modeling molecular mechanics with Poisson– Boltzmann Surface Area (MM/PBSA). Further MM is often used for identifying both potential ligands and their binding site(s) on drug targets (Borhani and Shaw, 2012). Promising examples of this type of work can be found in (Borhani and Shaw, 2012; Wang et al., 2001; Wlodawer, 2002). However, MM still needs further development. For example, despite high throughput and industrial attention, MM/PBSA, accuracies are still low. Typical correlations between predicted and experimental binding free

energy values fall between R squared values of 0.52 to 0.69. (Borhani and Shaw, 2012; Brown and Muchmore, 2009). Though it should be noted variants of MM/PBSA have been shown to improve these correlations slightly they are still low (Brown and Muchmore, 2009). Expanding on this -free energy calculations (like those used in MM/PBSA) can be categorized as alchemical free energy and conformational free energy calculations (Meng et al., 2011). Alchemical free energy methods such as free energy perturbation, and thermodynamic integration are considered some of the most promising methods for improving overall model accuracy (Brown and Muchmore, 2009; Michel and Essex, 2010; Woo and Roux, 2005). One advantage with alchemical free energy methods is their ability to account for solute-solvent interactions while allowing for changes in environmental conditions such as pH and temperature (Gapsys et al., 2016; Kilburg and Gallicchio, 2018). Indeed, the Grand Canonical Alchemical Perturbation is now used alongside the Grand Canonical Monte Carlo as it is well suited for modeling occluded binding sites where solvent exchange with bulk is important (Bodnarchuk et al., 2020; Bruce Macdonald et al., 2018). Additionally, alchemical free energy methods have even outperformed Rosetta protocols in capturing trends in the ionizing mutations of the bacterial protein, Barnase (Gapsys et al., 2016). Suggesting that despite some drawbacks, MM will be a key tool for studying, designing, and developing new drug candidates moving forward.

Over the last several decades, biologics have emerged as the next generation of therapies providing blockbuster treatments such as Humira and Insulin (Eichman, 2018; Valeur et al., 2019). Biologics, sometimes referred to as biopharmaceuticals, consist of bioengineered macromolecular products such as proteins- and nucleic acid-based drugs (Ronald, 2008). This trend is followed alongside significant efforts in computational modeling of macromolecules for drug design, such as the effort in developing anti-HIV drugs conducted by Jorgensen's group (Jorgensen, 2016; Smith et al., 2006). The progress made within the past few years has enabled the prediction and design of macromolecular structures at near-atomic accuracy (Das and Baker, 2008; Kuhlman et al., 2003). Indeed, such efforts have allowed for both computational chemistry and biology software programs to emerge. One of the most notable of these programs being the Rosetta software suite first developed by Baker's group (Das and Baker, 2008; Editors, 2020). The Rosetta software aids researchers in understanding macromolecular interactions such as protein interaction with drug compounds (Baynham et al., 2018). Further, Rosetta's de novo method has been used to inform the development of vaccines (Correia et al., 2014; He and Zhu, 2015). Rosetta also provides other ways to aid drug discovery by allowing calculations of energy functions and searching conformations. For more on Rosetta see (Alford et al., 2017; Das and Baker, 2008; Editors, 2020; Park et al., 2016). Another notable computational method applied to drug discovery and design is AI.

The late Dr. Patrick Winston defined AI as the study of the computations that make it possible to perceive, reason, and act (Winston, 1992). In essence, AI is attempting to make

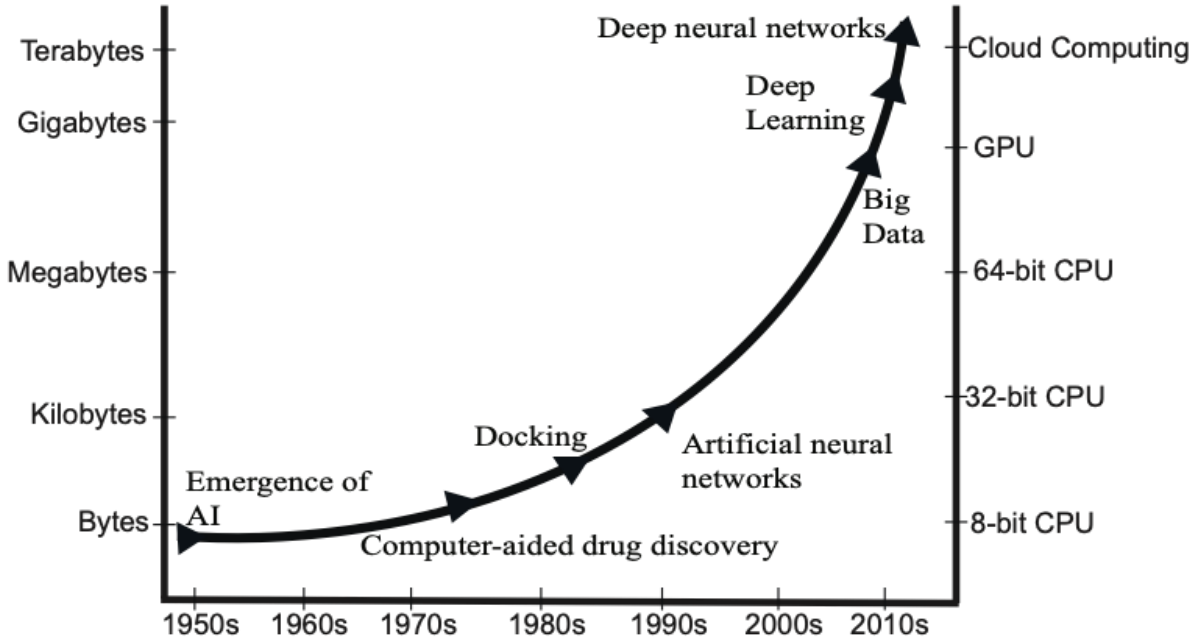

Figure 2: Graphical summary of the historical progress of artificial intelligence in drug discovery as a function of increasing data size and processor improvement. Consists of information from (Zhu, 2020).

machines mimic cognitive functions, including decision-making. The subset of AI most relevant to drug discovery, and arguably the DDP as a whole, is machine learning (ML). ML is a technique that utilizes statistical methods with the ability to learn from past data sets to detect patterns or regularities (El Naqa and Murphy, 2015). When the assumption that the near future will not be too different from the close past, holds, then this technique can make accurate predictions about the future. Making it a good fit for modeling drug compounds' physical and biological properties (Brown et al., 2020; Cherkasov et al., 2014). A further subfield of ML is deep learning (DL), which has seen a resurgence recently due to advances in big data and computing capabilities to support the method (see Figure 2 adapted from (Zhu, 2020)).

DL utilizes artificial neural networks with representation learning that adapts and learns from a large training set of data to fuel its predictive power (Lecun et al., 2015) . Since DL's resurgence, it has been used in multiple drug discovery works, with one of the most notable being Méndez-Lucio's de novo generative model that can automatically design molecules so long as the gene expression signature is provided (Méndez-lucio et al., 2020) . On the other hand, AI techniques are also helping repurpose drugs.

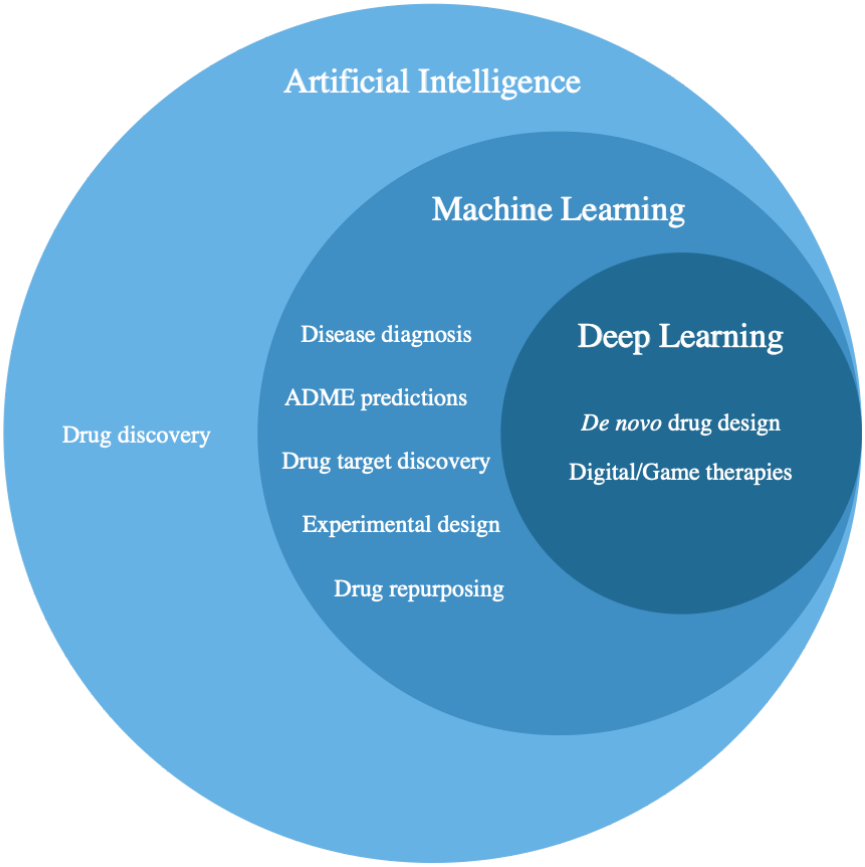

Figure 3. Graphical summary of artificial intelligence (AI) and its subfields: machine learning and deep learning, in drug development. Consists of information from (Lodder and Tiitto, 2017; Mak and Pichika, 2019).

Zidovudine, Atomoxetine, Rituximab, and Rituximab are just a few of many drug compounds that have been successfully repurposed (Pushpakom et al., 2018). In essence, drug repurposing is an industry movement to develop marketed drugs for other diseases; they were not originally marketed to treat. It is an approach that aims to lower risks (e.g., unexpected adverse events) and development costs associated with the DDP (Brinkman et al., 2020; Pushpakom et al., 2018). AI has proved helpful in drug repurposing, allowing for the screening of thousands of drugs to treat a target disease in a short amount of time. For this reason, it was employed to identify existing drugs for the treatment of COVID-19 (Gordon et al., 2020; Ke et al., 2020; Olena, 2020). For more on AI's role in drug discovery, repurposing, and design, the authors suggest the following articles (Aliper et al., 2016; Brown et al., 2020; Hessler and Baringhaus, 2018; Mak and Pichika, 2019; Michie, 1968; Pushpakom et al., 2018; Yang et al., 2019; Zhavoronkov et al., 2020; Zhu,

2020). Further, AI's utility in the DDP extends beyond the drug discovery stage (J. Chen et al., 2018) and this will be discussed in the next section.

Pre-clinical

A lead compound is moved into in-vivo and in-vitro testing during the preclinical stage to begin investigating the compound's safety. Further characterizing of the compound's physicochemical properties, which is often referred to as pre-formulation, takes place. The pre-formulation stage is used to inform the formulation process throughout development. Formulation is critical as functional excipients have been shown to stabilize otherwise non-stable compounds and provide adequate bioavailability to otherwise non-orally bioavailable compounds (Arce et al., 2020; Liechty, 2010; Williams et al., 2013). Making pre-formulation vital to the drug candidate's potential success. Like other stages, AI techniques have begun informing the pre-formulation process. For example, Ebube's artificial neural network (ANN) for the characterization of physicochemical properties of amorphous polymers. In this study the ANN was trained on experimental data of polymer properties, including water-uptake profiles, glass transition temperatures, and viscosity values. The software was then tested and found to have a low percent error when making property value predictions on different amorphous polymers and their physical blends (Ebube et al., 2000). Other techniques, such as population data-driven models, have been developed to inform early-stage excipient choice. Campbell and Lodder's population data-driven model mines databases for intake and shipping amounts on cyclodextrin (BCD) as a food additive. By utilizing this data, predictions of daily exposure to the population are made such that formulation amounts may be kept below that level. Allowing formulators to avoid adding significantly to BCD exposure of human subjects. Thereby, obviating the need for extensive preclinical formulation and toxicology studies- speeding a lead compound to the clinic and cutting development costs (Campbell et al., 2020b; Lodder, 2017).

Clinical

The Clinic

The clinical stage of the DDP consists of multiple phases and subphases. Starting with phase 1, a small subsample of the population is exposed to the candidate compound. Involving potential health risks and misconceptions for the patients while providing high financial risk for the sponsoring company (April, 2018; Kaitin, 2010; Pentz et al., 2012). For these reasons, care must be taken in the planning and development of phase 1 studies. The studies must provide accurate and rapid information, such as maximum tolerated dose (MTD). Phase 1 designs can be categorized into two main groups based on the algorithms used: rule-based designs (such as the commonly used 3 + 3 design) and model-based designs (e.g., the continual reassessment method (CRM)). These algorithms, at their core, use statistics to design trails that minimize the number of patients receiving sub-therapeutic or toxic doses and maximize the number of patients treated at therapeutic dosing range (Lin and Shih, 2001; Wong et al., 2016). Although model-based designs such as CRM have proven to be more accurate and efficient when optimizing for MTD,

they cannot compare to the practicality and simplicity of rule-based algorithms. For this reason, the rule-based 3+3 design has been used in at least 80% of phase 1 trials (Z. Chen et al., 2018). With extensive use of the 3+3 design, researchers have developed tools to facilitate its use, such as Chen's interactive calculator for operating characteristics of phase 1. Here Chen and colleagues developed a stand-alone interactive software for convenient calculations of these critical operating characteristics. Using this software allows users to avoid the complex formulas and need for extensive statistical knowledge- making the 3+3 design even easier to use (Z. Chen et al., 2018). Variants of the 3+3 design have been developed for more complex investigations, such as the 3+3+3 design proposed by Braun and Alonzo to extend the concepts of 3+3 to two-drug combination therapies (Braun and Alonzo, 2011). Similar design models have been developed for phases 2 and 3. Typically these models aim to reduce sample size while still gathering the necessary information (Khan et al., 2012). AI is also beginning to emerge as a technique to make clinical trial designs more efficient (Harrer et al., 2019). MIT researchers have described novel and non-trivial reward functions for self-learning reinforcement learning (RL) algorithms for dose de-escalation studies during clinical trials to alleviate chemotherapy toxicity (Shah, 2020; Yauney and Shah, 2018). For more on this, the authors recommend the following articles (Ho, 2020; Peck et al., 2020; Shah, 2020).

Drug Processing, Manufacturing, and Storage

During the DDP's clinical stage, the drug will undergo stringent development "behind the scenes" to ensure the drug will be practical and safe to market. This consists of developments regarding drug processability, scale-up, formulation, and storage stability. Information relating to the drug's stability over time, how the drug will be stored, and how it will be formulated are critical. Without optimizing each of these elements, the compound can be rendered useless and fail to gain FDA approval. Computational techniques based on fundamental engineering principles such as thermodynamics and fluid mechanics are often used throughout these developments. The knowledge gained through these techniques directly feeds information that influences decision-making on scale-up and machine parameters. One commonly employed technique is computational fluid dynamic (CFD) modeling, which is often used for the optimization and scale-up of unit operations such as fluidized beds, pan coaters, hot melt extruders, and spray-dryers (Hyvärinen et al., 2020; Ketterhagen et al., 2019; Poozesh and Bilgili, 2019; Sarkar et al., 2019). Combining CFD with other numerical modeling has allowed for a more holistic investigation of processing and manufacturing than could be done with experimental methods alone (Pandey et al., 2017). For instance, spray-drying is complex in terms of machine parameter interactions, making it difficult to experimentally isolate any one variable. However, utilizing CFD and numerical methods has given insight into droplet atomization, droplet drying kinetics, and the droplet formation process(Mezhericher et al., 2009; Poozesh et al., 2020, 2018). Such information aids in developing a successful manufacturing process and the scale-up of said process. These aspects are critical to the DDP as it would be devastating to a candidate compound that is deemed safe and efficacious, but unable to be produced on a mass scale such that patients may benefit. Furthermore, advances in CFD occur at a rapid pace, and a notable method that is beginning to emerge is the use of CFD emulators.

Emulators are a statistical model of a simulated model estimated from the simulation's observed input-output (Grow and Hilton, 2018). In essence, once established, emulators can replace the simulation, which can dramatically cut down the computational cost with the potential of simplifying the modeling. Aspects that would be useful in CFD simulations of pharmaceutical unit operations as these models can become extremely complex, computationally costly, and time-consuming to run (Moonen and Allegrini, 2015). Although not prevalent in pharmaceutical literature when writing this paper, the authors suspect a growing interest to occur over the next several decades as other industries such as environmental engineering further utilize and advance the technique (Albert, 2020).

Computational methods useful for informing decisions in formulation and stability will generally be models of solid-state materials or solid-liquid interactions. The modeling of polymer-solvent diffusion with Monte-Carlo simulations is one example (Gartner and Jayaraman, 2019). Such a simulation is critical to formulation and stability as even a 1% water content has shown to induce phase separation in amorphous solid dispersions, thereby decreasing the stability of the drug formulation as a whole (Mugheirbi et al., 2017). Nevertheless, Gartner and Jayarman's simulation, alongside similar simulations, could decrease the time and costs currently being used on studying environmental effects on drug formulations. Another example is Schwartz's optimization of formulation via computer analysis (Schwartz et al., 1973). Other methods of solid-state modeling include ML techniques and for a review of these topics see (Schmidt et al., 2019).

FDA Review and Post-marketing Surveillance

FDA's new drug application (NDA) review process consists of 6 steps. I) First, the drug sponsor and FDA will host a review meeting before the NDA is filed. Assuming all goes well within this meeting II), the drug sponsor will then be responsible for formally asking the FDA to approve their drug by electronically submitting a completed NDA. The NDA will include all animal and human data, the analyses of the data, data regarding the drug's behavior in the body, and how it is manufactured, which includes formulation. III) Upon submitting the NDA, the FDA has a 60-day window to decide whether the application should be filed for review. IV) Assuming the NDA is filed, the review process will then take place. Evaluation of the drug's safety and effectiveness will be of top concern. If declared safe and effective, the FDA will then move into V) developing the drug labeling with the drug sponsor before VI) inspecting the manufacturing site where the drug product will be produced. Although humans stay at the heart of decision-making within this stage, computers are still utilized throughout the process for data transfer and communication. Computers play a more central role in post-market surveillance. For example, FDA's computerized MedWatch system allows for easy reporting and storing of adverse event data. Internal utilization of computer power has emerged within the FDA, such as the FDA's site selection model used to prioritize on-site inspections. An outcome of the Pharmaceutical Quality for the 21st Century — A Risk-Based Approach initiative, the model ranks manufacturing sites by a numerical score (Campbell and Lodder, 2021; CDER, 2018). The score reflects the manufacturing site's probability of failing cGMP. The model works through analyzing top-level components while considering the possible risk factors to produce the

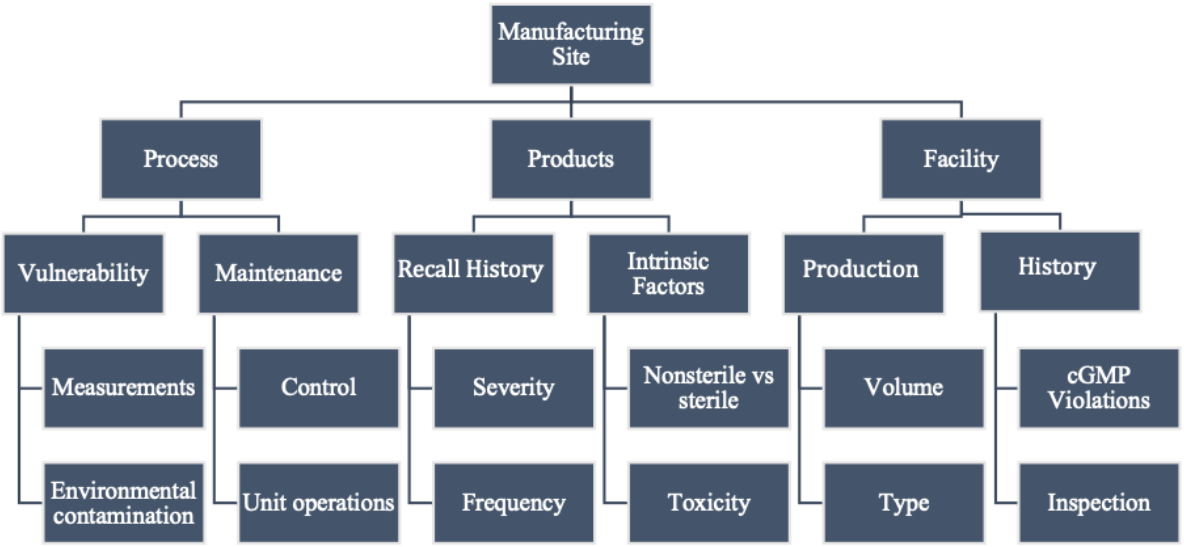

Figure 4: Representative of FDA's site-selection model hierarchy. Conceptually the tool works by deconstructing the manufacturing site into three components: process, products and facility. These components can be thought to summarize the various risk factors of the site. These risk factors are then weighted and mathematically combined to output a site risk-score in which the manufacturing site is ranked for inspection.

manufacturer's score (see Figure 4). For more details on the FDA's site selection tool, see (Campbell and Lodder, 2021; FDA, 2004).

Next, we will begin our discussion of gaming as a novel tool to solve pharmaceutical problems. The following several sections are intended to provide the reader with fundamental knowledge of game theory and gaming in a scientific context. For those already familiar with these concepts, these sections may be skipped over. The sections following these introductions will discuss gaming as a tool in which it relates to the field of pharmaceuticals and the DDP, such as its role in molecular problem-solving.

III. Basic Game Theory

This section begins by describing game theory and its methodologies in a traditional, behavioral, and algorithmic light before moving into essential elements of games and standard games.

Game Theory: Traditional, Behavioral and Algorithmic

The collective action problem, or sometimes referred to as the social dilemma, is described as a situation in which individuals would gain more by cooperating; however, they often fail to cooperate due to conflicting interests (Liebrand, 1983). The social dilemma concept is fundamental to game theory as it can be used as a model for many game interactions; such is the case for the famous Prisoner's dilemma game (Liebrand, 1983). Game theory is especially equipped to find optimal strategies for such dilemmas (Anderson et al., 2016). As known today, game theory was established by John Von Neumann and Oskar Morgenstern in their publication Theory of Games and Economic Behavior. In this text, Neumann and Morgenstern showed that economic and social questions could be described in games of strategy (Anderson et al., 2016). Since then, games of strategy have been used to bring quantitative insights into war and economic decision-making. Neumann and Morgenstern's methods also became the standard in applying game theory.

Game theory methodology begins by establishing a game description. Then the goal is to identify stability in the game, with the standard approach being to assume the agents playing will adapt their decision-making to conform to a Nash equilibrium. Nash equilibria is a proposed solution to non-cooperative games in which, given one player's strategies, the other player has nothing to gain by changing their own. Nash equilibria and other refined solutions to games have been extensively studied and, therefore, will not be further defined in this paper; however, the interested readers are pointed to the following sources for further information (Daskalakis et al., 2009; Munro, 1992; Nash, 1950; Sethi, 2008). The last step involved in game theory methodology is to translate the game's solution into practical terms.

Today, game theory is used in a wide range of industries outside of warfare and economics, including law and philosophy (Anderson et al., 2016). Mass amounts of work have shown that game theory can accurately predict behavior in many situations. Despite this, there are still situations in which traditional game theory fails to accurately capture human behavior (Goeree and Holt, 2001). For example, the Traveler's Dilemma is a game that experimentally converges or diverges Nash equilibrium depending on the bonus/malus parameters used (Capra et al., 1999). For this reason, subfields of game theory have emerged, such as behavioral game theory (BGT), which has used in neuroscience problem-solving (Camerer, 2009; Wright and Leyton-Brown, 2012). BGT is distinct compared to traditional game theory as it does not seek to pinpoint a correct strategy or action by mathematical models beforehand. Instead, BGT is driven by empirical data (e.g., experiments and observations) to develop a model. That is, BGT is fundamentally based on the concepts of traditional game theory (TGT), but methodology differs. In BGT, the methodology starts with a game or naturally occurring situation. Once a game is identified, it should be classified into a standard game such that TGT can provide predictions

based on one or two fundamental game theory principles. Experimentation is then conducted, and if behavior differs from the predictions, formal game theory is extended to incorporate the proposed explanation for the inconsistency (Camerer, 1997). There are four prominent models used in BGT; Quantal Response Equilibrium, Level- k, Poisson–Cognitive Hierarchy, and Quantal Level-k (Wright and Leyton-Brown, 2010). Although out of the scope of this paper, formal definitions of each model can be found elsewhere (McKelvey and Palfrey, 1995; Wright and Leyton-Brown, 2012). Another important subfield of game theory is algorithmic game theory or AGT.

AGT utilizes mechanism designs that ask how one can design systems such that agents' selfish behavior results in desired community goals (Mavronicolas et al., 2007). Mechanism designs are extended to algorithms in AGT and termed algorithmic mechanism designs (AMD). AMD considers computational tractability to concepts of mechanism design and focuses on optimization problems of complex networks such as the Internet (Mavronicolas et al., 2007). The Internet and similar complex networks are often made up of intelligent agents or software entities that carry out some set of operations on behalf of a user or another program with some autonomy level. These agents must collaborate in actions in which they are involved; however, complex networks breed selfish natures, so the need for game-theoretical strategies emerges. Typically, non-cooperative games (see section Basic Elements and Types of Games) are used to provide solutions and insights into problems such as congestion, security, and routing. AGT has also been extended into scientific fields such as computational biology. For instance, Lamiable compared a novel game theory-based algorithm to a more traditional global optimization approach to predict conformations of large RNA molecules (Lamiable et al., 2013). By taking advantage of RNA's hierarchical structuring, with a secondary structure-forming first and a tertiary structure following the researchers were able to decompose molecules into helices and junctions- located between said helices. From here, an initial secondary structure is formed that lacks any tertiary structuring. This initial confirmation represents a shaping in which nodes are locally stabilized but neglects the possibility of more long-distance interactions. To implement tertiary structuring and hence the possibility for long-range interactions the researchers used a game theory-based algorithm that took a local egoistical approach. The algorithm allowed each

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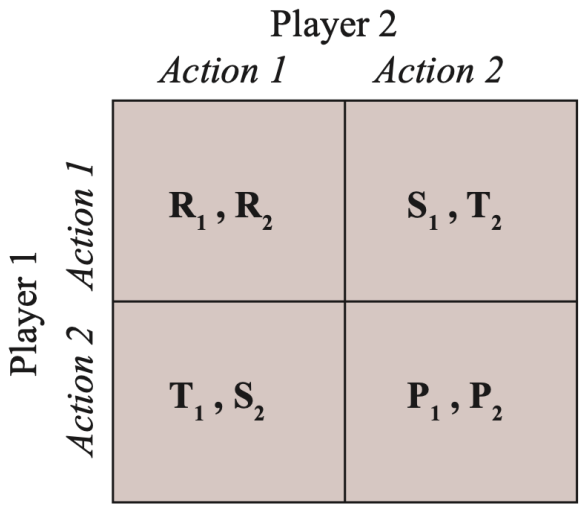

Figure 5: Generic two-player simultaneous, game matrix with payoffs R, T, P, and S. Where the subscripts indicate players 1 or 2, respectively. The payoff is an ordinal utility number assigned to a player at the outcome.

node to maximize its own payoff function while considering the forces applied to each node. The results of this study showed that the game-based algorithm provided a more authentic prediction of tertiary links between architectural elements of the RNA molecules. For more on AGT, see (Elkind and Leyton-Brown, 2010; Roughgarden, 2008).

Basic Game Elements and Types of Games

As the field of game theory has developed, distinct terminology and classification systems have emerged. This section will provide a brief overview of common terminology used and how games are classified.

Classifying games:

Zero-sum and non-zero-sum games: In zero-sum games, the payoff of all players add to equal zero. That is, points earned by one player come at the loss of points from another player. Non-zero-sum games, the payoff of players does not equal zero. Therefore, in non-zero-sum games, one player's benefit does not necessarily come at the loss of another.

Cooperative and Non-Cooperative games: In Cooperative games, players are allowed to communicate between themselves. This opens the door for players to corporate, and for actions to emerge that are beneficial for the whole. In non-cooperative games, players are not given the privilege of communication.

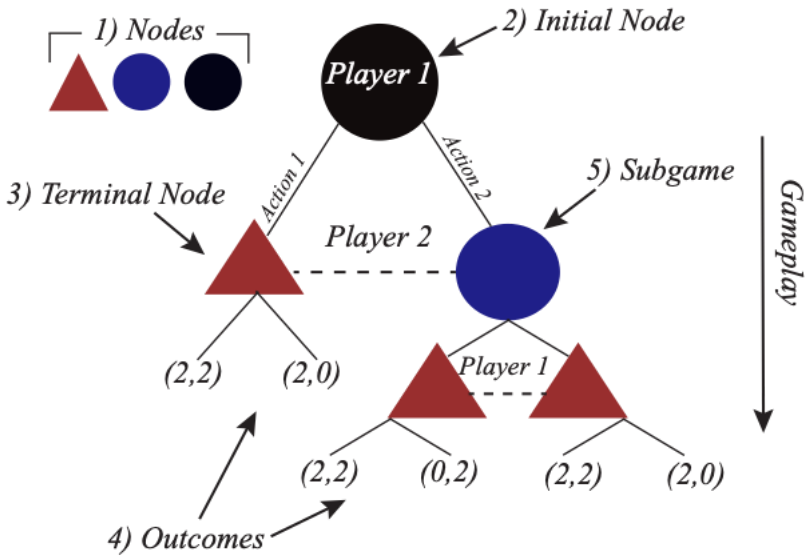

Figure 6: Generic game tree where 1) Node is a point at which a player chooses an action. 2) Initial node is the point at which the first action in the game occurs. 3) Terminal node: any node which, if reached, ends the game. Each terminal node corresponds to an 4) outcome. 5) Subgame: any connected set of nodes and branches descending uniquely from one node. Arbitrary payoff values are presented in parenthesis with the first coordinate corresponding to player 1's reward and the second coordinate corresponding to player 2's reward for any given outcome. Note that extensive-form games reach equilibrium differently than normal-form games (Munro, 1992).

Perfect and imperfectly informed games: In perfectly informed games, players are aware of the other players' past actions. This is the opposite of imperfectly informed games where at least one player is unaware of other players' previous actions.

Static and Dynamic games: Dynamic games require players to take turns to act. Static or simultaneous games, each player must act without knowing the action taken by the other players. That is dynamic games; players act one after another while static game players, in essence, act simultaneously.

One-shot and Repeated games: One-shot games are games in which the players play the game once and for all. Repeated games are played in iteration. Repeated games allow for modeling the psychological side of a continuous relationship, including the concepts of reputation, threats, and promises.

Normal-form and Extensive-form games: Normal- or strategic-form games can be described by matrices (see Figure 5), whereas extensive form games are described by game trees (See Figure 6) (Ilhan and Anderson, 2016). For a further description of the difference between normal- and extensive-form games, see Figure 7 in the Standard Games section.

Beyond terminology, understanding the general structure and basic elements of a game, allows players to decide how to play the game. Game strategies are defined as a program instructing a player which action to take at every node (where player decision-making must occur- see Figure 6). Strategies can be pure, mixed, or hybrid approaches. Pure strategies players take the same action repeatedly. On the other hand, players can play a mixed strategy in which the action chosen is done according to a probability distribution over all possible actions. Next, standard games will be presented.

Standard Games

As mentioned, the concept of social dilemma is fundamental to many game models such as stag hunt, the prisoner's dilemma, the bargaining problem, the snowdrift game, the unscrupulous diner's dilemma, and the centipede game (Mckelvey et al., 1992; Nash Jr., 1950; Sui et al., 2015; Teng et al., 2013). Additionally, the volunteer's dilemma and tragedy of the commons are used to study varying conditions of social dilemmas (Diekmann, 1985; Hardin, 1968). One of the most fundamental of these games is the stag hunt (SH). This game differs from its more famous counterpart, the Prisoner's dilemma, as it holds two pure-strategy Nash equilibria compared to one. This added degree of complexity allows SH to have a substantial relationship to the Prisoner's dilemma allowing circumstances that have been described as Prisoner's dilemmas to also be interpreted as a SH (Fang et al., 2002) . For example, climate change contracts are often debated as to whether they are a prisoner's dilemma or SH, given varying assumptions (II, 2016; Szathmáry and Smith, 1995). SH began as a story by philosopher Jean Jacques Rousseau in his Discourse on Inequality (Skyrms and Irvine, 2001). Rousseau describes a situation in which hunters can remain faithful to their post such that the hunters may receive a stag. With the hunters having the inability to take down a stag alone, it is vital to remain faithful. However, given the opportunity to take down a hare on one's own, Rousseau sees that one cannot doubt a hunter would go off in pursuit of the hare in spite of it being less desirable (Rousseau, 1761). The discourse left many questions concerning the social contract and was eventually turned into the SH game (see Figure 7a). The traditional SH game (see Figure 7a) is described similarly to Rousseau's story by imagining two hunters that must choose independently (simultaneously played) to hunt a stag or hare. If both players cooperate and choose to hunt a stag, both do well and get the cooperating reward R. If one player cooperates, that is deciding to hunt a stag- but the other defects-that is deciding to hunt a hare-, the non-cooperative player gets the temptation reward T (the hare). In contrast, the cooperating player goes home hungry with nothing receiving the sucker's payoff S.

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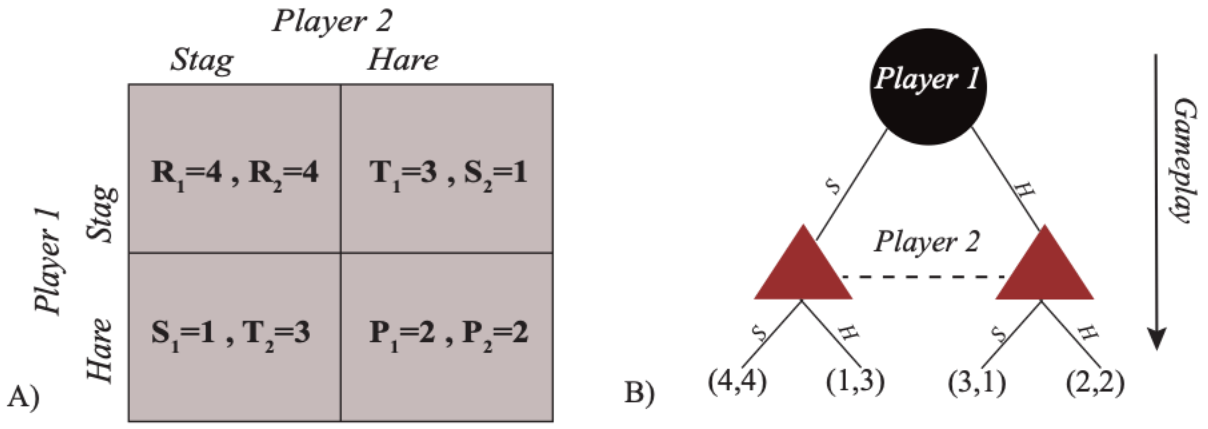

Figure 7: Stag hunt game descriptions A) normal-form simultaneously played B) extensive-form sequentially played with payoffs of $R > T \geq P > S$. Where $R = 4, T = 3, P = 2$,and $S = 1$.

Traditionally, the game is played simultaneously with payoffs $R > T \geq P > S$. Alternatives of SH may be played sequentially, as depicted in Figure 7b. SH can also be generalized into N-player form as described by (Pacheco et al., 2009). Where it is generally agreed that cooperation becomes more difficult as N (number of players) becomes larger due to the problem of trust multiplying.

IV. Game Theory in Pharmaceutical Development

Nash equilibrium assumes that beliefs are consistent with actual decisions. However, beliefs are not likely to be confirmed out of equilibrium, and in such cases, learning will occur. Since this discovery, a large body of work has incorporated learning into models of adjustment in games. For example, RL is often deployed for these tasks (Erev and Roth, 1998). On the other hand, game theory is often utilized in AI when multiple agents are solving logical problems. Indeed, game theory is often used in multi-agent AI systems, Imitation and Reinforcement Learning, and Adversary training in Generative Adversarial Networks (GANs). In addition, one of the oldest AI algorithms -MiniMax algorithm originates from game theory. Beyond supplementing network AI systems game theory has found utility in other areas of science and technology.

Game theory has influenced areas of science, including pharmaceuticals. Indeed, many AI-based examples described in the section Simulations, Emulations, and Predictive Modeling throughout the DDP were possible due to game theory. Yet, there are more examples such as, game theory-driven dosing regimens (Chmielecki et al., 2011; Enriquez-Navas et al., 2016). Yauney and Shah game theory-driven dosing regimens explored reward incentives for their

chemotherapy selecting algorithm as a function of reducing mean tumor diameter (MTD) (Yauney and Shah, 2018). Here the game was between the RL agent and the tumor. The agent was given a choice to dose Temozolomide (TMZ) or procarbazine, lomustine, and vincristine (PCV) chemotherapies with different dosing options depending on the therapy chosen. These choices functioned as the agents' action set within the game. Various penalties and rewards for the agent's actions were explored, with the base incentive being MTD reduction. This study found that the learned dosing and expert dosing regimen agreed well (Yauney and Shah, 2018). Others have used game theory to optimize pharmaceutical product flows by modeling interactions within the PSC (Nagurney et al., 2013). Using a basis in non-cooperating gaming, the model investigated interactions between pharmaceutical firms and contractors in outsourcing activities such as selecting a contractor. Assumptions for these games included that the pharmaceutical firms are cost-minimizing, and the contractors are profit-maximizing. Nash-Bertrand equilibrium characterized the game, which fulfills variational inequality for both the firm and the contractors. Game theory has also been used to provide insights into the business of the pharmaceutical industry.

Game theory provides insights into pharmaceutical companies as commercial businesses. For example, the bargaining game has been used to model the interactions between regulators and pharmaceutical firms (Wright, 2004). In Wright's, work game theory was implemented to understand the interactions for price negotiations and regulations in Australia. A country alongside the Netherlands, New Zealand, and the United Kingdom which regulates pharmaceutical prices consumers pay. The theoretical game model investigated the implications of the Australian Pharmaceutical Benefits Scheme design. The results of this study suggested that although firms agreed on lower prices with regulators the firms receive higher payoffs than in unregulated systems.

VII. Conclusions

Technological breakthroughs of the 20th and 21st centuries have provided significant advancements in computer sciences. Much of the computational advancement, especially in the realm of ML, has a basis in game theory. Allowing innovative computational methods to solve complex problems. This paper showed that despite challenges set forth by heavy regulation and strict guidelines innovative computational methods have improved problem-solving capabilities in the pharmaceutical industry. Complex processes that have otherwise been too time consuming and costly to study can now readily be modeled. Thereby, catapulting the industry into the 21st century of problem solving. Game theory especially has allowed for innovative computational methods to emerge for solving pharmaceutical problems that traditional methods alone could not. This paper has described the science of game theory and revealed its role in solving pharmaceutical problems.

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