Needed: system dynamics for the drug discovery process

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A system dynamics structure to characterize the link between technology and critical management decisions in the drug discovery process (DDP) is needed. The DDP includes many interacting feedback loops that impact decisions executed in early stages and that influence performance in later development stages. The complexity of the DDP and the absence of systemic perspective, contributes imprecision to decision-makers' own mental models, and limits their ability to generate decisions that provoke genuine process improvements. Hence, the emergence and use of new integrated technology- and knowledge-based approaches bridge to R&D concern at least early attrition rates, critical high-content chemical lead value identification and time delay reduction for the early phase DDP.

The effective management and prioritization of resources, including the termination of underperforming projects early in the drug discovery process (DDP), are key to productivity improvement [1–17]. However, the literature is short on advise for meeting scientific and technological goals in conjunction with management goals. The DDP often is represented by a sequential or cascade model. An understanding of DDP performance issues with systematic depth, that is, with a representation of the decision steps involved within feedback loops is needed. This paper introduces a system dynamics structure (SDS) that takes into account the role of decision-makers' own mental models[3] [18–20] by linking the technology with key management decisions in the DDP. System dynamics (SD) is a set of principles that allows for both the qualitative and quantitative modeling of key feedback loops within a system with the goal of identifying its drivers and levers [21,22]. Research in SD is particularly attuned to the explicit involvement of decision-makers' own imprecise mental models [19,23] of a system. The mental models interact with the management of complex decision processes. Decision-makers, thus, often do not account for the richness of the feedback loop structure involved in processes. For example, the DDP includes a large number of feedback loops. These feedback loops, in the dynamics of the DDP, introduce time delays. The impact of early decisions in the DDP often becomes visible many years later, with dire economic consequences for an R&D portfolio, financing and additional time delays in new drug commercialization to market. Indeed, decisions executed in early stages of the DDP have a massive impact on overall performance in later development stages for firms and the industry as a whole. Moreover, the asynchronous nature of decision-making, and the lack of systemic overview of the underlying SDS of the DDP, limits decision-makers' ability to generate genuine improvements that would make an economic difference observable within a short-term horizon.

The SDS provides a synthesis for decision-makers interested in DDP improvement to meet targeted industrial milestones. The ultimate goal of the paper is to demonstrate how SD principles, employed to design an SDS applied to key steps of the DDP is helpful to characterize iterations between theory and experimentation.

The economic pressures to improve the R&D performance have led to the design and assimilation by companies of a wide array of new integrated technology- and knowledge-based approaches for

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[3] Within the context of this article: 'A mental model of a dynamic system is a relatively enduring and accessible, but limited, internal conceptual representation of an external system (historical, existing or projected) whose structure is analogous to the perceived structure of that system.' [19]. SD models, as in any model, seek to represent abstractions, yet meaningful ones, of the real object. Decision-makers continuously use mental models with the set of perceptions, attitudes and expectations built into them.

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lead identification (LI) and lead optimization (LO) of new molecular entities (NMEs) [24–34]. The emergence and use of new, integrated technology- and knowledge-based approaches impact R&D performance and concern three factors of paramount importance: (1) early attrition rates, (2) critical high-content chemical lead (HCCL) value identification and (3) time delay reduction for the early phase DDP. The influence of these factors is examined in detail, bearing in mind, that decision-makers' own mental representation about any SDS is a major driving force to improve the DDP performance by alleviating project stagnation and improving the pace of drugs to market.

First, massive R&D costs linked to NMEs, in clinical development phases, are due to high attrition rates of molecular candidates late in the process [7,35–37]. Inadequate ADMET properties account for about 50% of investigational new drug (IND) filings. This tardy high attrition rate could be significantly reduced by implementing objective and rigorous quality evaluation throughout the DDP, especially at the hit-to-lead (H2L) and LO phases [24,38]. To achieve early attrition of molecules falsely targeted as potential drug candidates, the key is to improve the process identification of molecular properties and characteristics associated with ADMET [39]. The identification of molecular properties and characteristics can be conducted by taking into account feedback interactions between computational *in silico* models and experimentation [40].

Second, regarding the critical HCCL value identification [24,38], the pharmaceutical industry is currently developing and integrating multidisciplinary optimization tools, in particular, some involve computational *in silico* methods [24–34]. The optimal design and simulation of this system requires: the simultaneous consideration of data from multidisciplinary sources, both theoretical and experimental; the identification and development of coupling functions within the SDS; and the assembly of a successful streamlining chain of tools where decisions between phases in the DDP are continuous [41].

Third, a reduction in the time delay between HCCL discovery, optimization and evaluation during pre- and clinical trial phases is needed. This entails reducing the time required to execute early phases of the DDP. The identification and optimization of HCCL, in a shorter period of time, is accomplished through an iterative feedback convergent optimization process, leading to rapid and improved NMEs with greater potential for development, success and commercialization.

A system dynamics structure (SDS) for modeling the DDP

SD includes a set of principles to model complex dynamic systems, such as the one presented therein. The SDS explains how the HTS process, in conjunction with *in silico* methods can be represented with qualitative SD principles. This approach is promising because it can abstract, with meaningful scope, the complex structure of the system generating the dynamic behavior of the DDP. SD principles elucidate the HTS research process by documenting: a stable dynamic structure, including an analysis for anticipating behavior and helping identify 'hidden' influences in the structure, not readily available to the 'naked eye' [42]. The SDS showing the process is a genuine 'research tool' to diagnose, improve and research the DDP and study its underlying issues. A SDS is useful to help avoid misperception of feedback by scientists [22,43,44]. The SDS offers an opportunity to recognize the reality that the decision-maker, *qua* actor in the system, also influences systems' outcomes [45–47]. Identifying feedback loops in systems helps explain backlogs, growth, decline and cycles of material, informational and economic variables.

Interacting and interlocked feedback structures are used to represent complex systems with both reinforcing and balancing feedback loops, and associated time delays, that shape the dynamic behavior of the system. A reinforcing feedback loop shows a variable dynamic path that exhibits exponential growth or decline behavior. For example, in Fig. 1a the SDS shows that Biochemical_and_Biological_Rules lead to an increase in Target_Space, which leads to higher Targets_Selection_and_Identification, to Target_Validation, and to shaping Biochemical_and_Biological_Rules. The SDS in Fig. 1a depicts a reinforcing structure; where a preceding influence, or a cause, leads to support the next variable or effect in the same direction. The dynamic path of the reinforcing feedback loop is shown next to the SDS in Fig. 1a.[4] By contrast, a balancing feedback loop represents convergence behavior toward a goal. For example, in Fig. 1b. The number of Leads_Selected increases QSAR_Model_Precision. The increase in the QSAR_Model_Precision reduces Leads_Selection, which, in turn, leads to a lower number in Leads_Selected. The dynamic path of the balancing feedback loop is shown next to the SDS in Fig. 1b.[5]

SDSs are employed to examine decision-making issues of importance in the management of biotechnology processes [48], enterprises [49] and policy [50]. The method employed to generate the SDS described in the remainder of this paper follows a number of steps. First, an initial list of variables was generated using the literature on HTS, data and experience. Second, the variables were isolated into a subset and their dynamic path identified qualitatively. Third, the isolated variable subset was first organized into initial feedback loops, until the list of variables was exhausted. Fourth, the SDS obtained was subjected to expert opinion for comments and improvements. This led to the introduction of additional variables and feedback loops to the SDS, along with documentation from the literature and data. These research steps were followed iteratively at least five times. Sixth, once the structure of the system was elucidated and evaluated with the help of data, experience, experts, it became possible to supply a description of the DDP and shed light on the problem posited, that is, identify the main levers and drivers of the three influences related to the management of the DDP and so on.

Hypotheses, experimental strategies and decision

A high-throughput experiment (HTE) strategy inputs assays (Fig. 2), composed of biochemical or biological materials and libraries composed of small molecules or fragments. HTE outputs

[4] Following established syntax in SD research [21], a SDS shows the direction of influence between two variables, or components, using '+' and '−' signs. A reinforcing feedback loop is denoted (R) followed by an identification number, and has an even number of '−', or any number of '+' to indicate the direction of the influence between elements of the loop.

[5] A balancing feedback loop is denoted (B) followed by an identification number, and has an odd number of '−', to indicate the direction of the influence between elements of the loop.

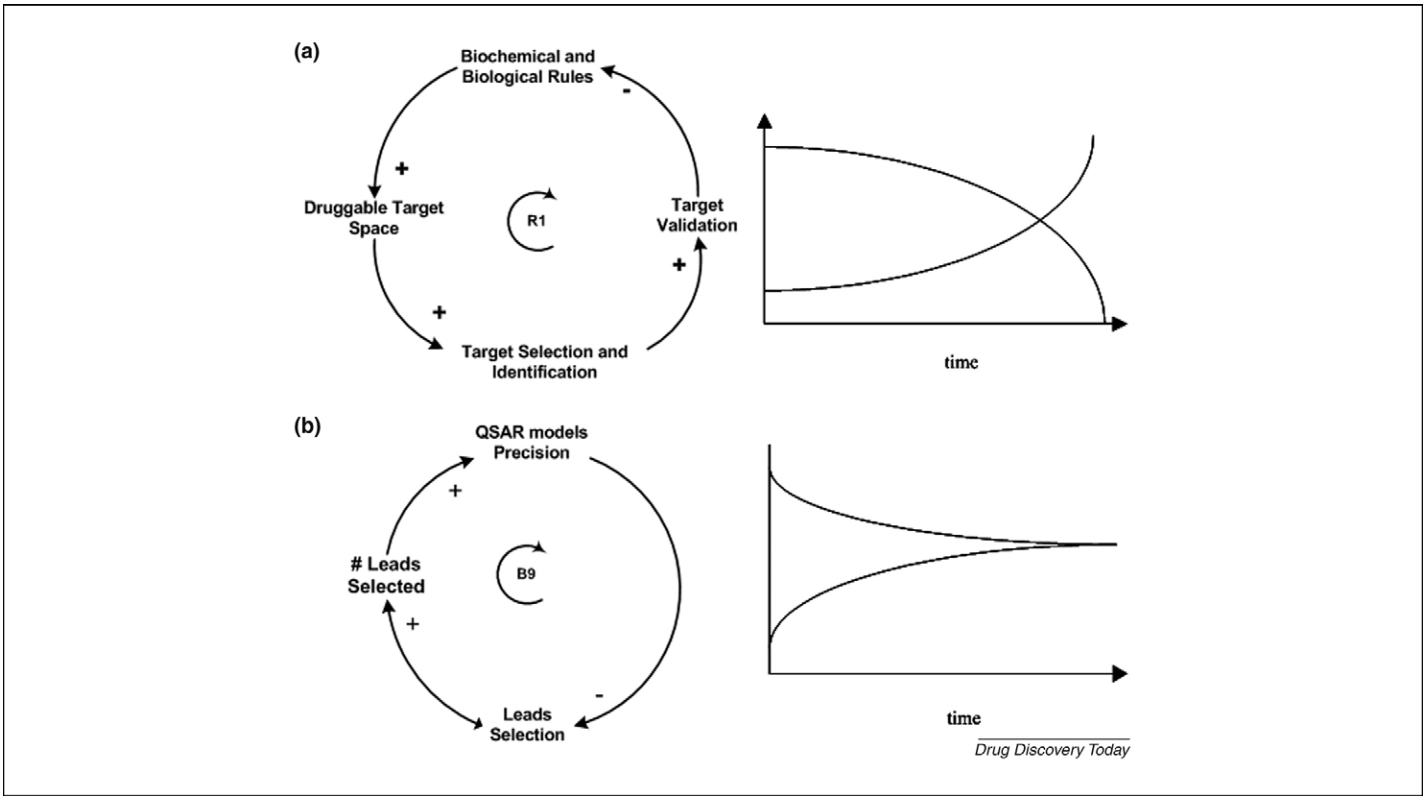

FIGURE 1

(a) Top: structure of reinforcing feedback loop and associated behavior. **(b)** Bottom: structure of balancing feedback loop and associated behavior.

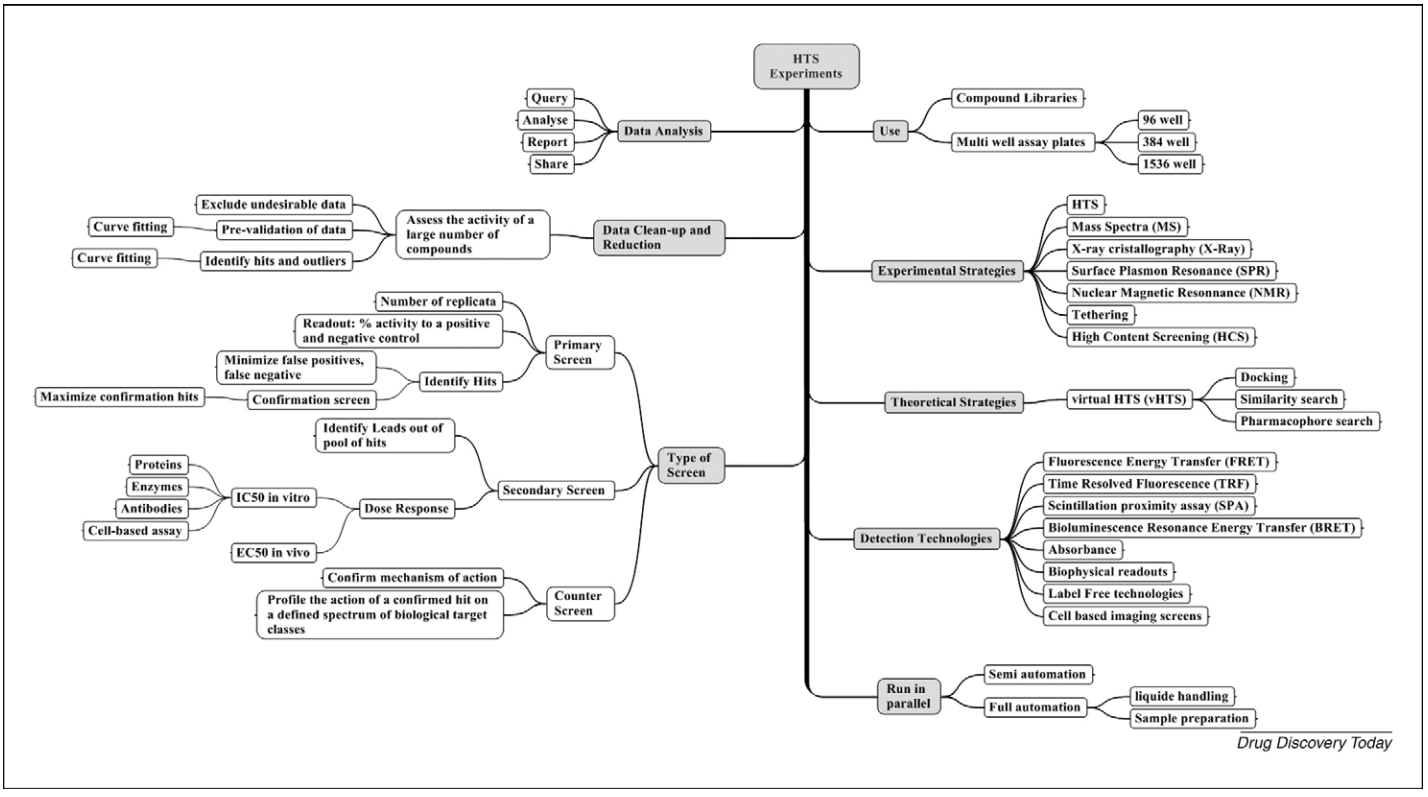

FIGURE 2

Detailed map of the high-throughput experiment (HTE) variable. The input of HTE uses assays composed of biochemical or biological materials, and libraries composed of small chemical molecules. HTE strategies are of two types: experimental or theoretical. The output of HTE experiments are experimental and/or *in silico* data.

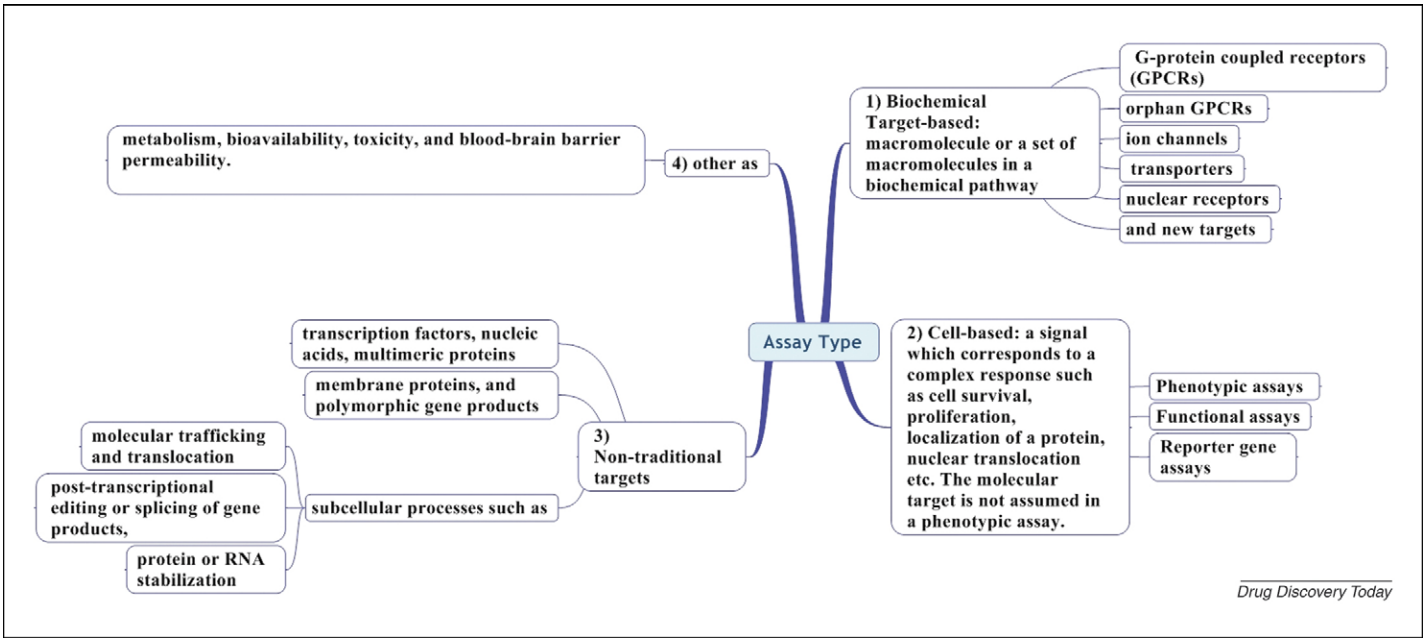

FIGURE 3

Detailed map of assay type.

can be either experimental or *in silico* data. There is an hypothesis matched with each HTE strategy type. For instance, HTS technology [24,25,51] (Fig. 3) embodies, as an underlying principle, that the molecular recognition of small molecules by biochemical macromolecular targets is the first and foremost important factor in new drug development. By contrast, a high-content screening (HCS) strategy rests on changes in sub-cellular functions owing to the presence of an exogenous molecule. Thus, two types of hypotheses, fundamental to HTE, are molecular recognition and systems biology. Molecular recognition implies a target-based strategy and uses biochemical materials, whereas systems biology implies a cell-based strategy and uses cellular materials [12]. Both cell-based and target-based strategies serve as the basis for assay development and as input materials for HTE and both need, for interaction, libraries of small molecules or fragments. The validation of the molecular recognition hypothesis is measured by experimental-binding affinity as an output information feedback. Binding affinity implies that the fundamental requirement for a drug is to bind to its target. A specific molecule can become a drug if, and only if, a specific target recognizes it. The decisions taken along the DDP are based on the types of sets of rules derived from the initial hypothesis. The decision rules enable decisions on the type of molecules to synthesize, screen, test and optimize and to determine whether milestones for hits and/or leads finding have been met. Moreover, *in silico* technologies produce data that inform researchers on how to develop, test and validate hypotheses for HTE implementation. Hence, the various types of data from both *in silico* and experimental domains provide information for testing and validating hypotheses, which translate into new decisions, actions and results. Once experimental and *in silico* output data are obtained, they become inputs for hypotheses inference and are followed by validation and optimization of the kind of decisions and strategy rules. This iterative process converges until a suitable series of hits and leads has been obtained. A comparison of the various approaches to hit identification, that is molecular recognition, changes in sub-cellular function and fragment-based approaches, highlights the importance of scientists' mental models underlying the choice of research hypotheses entering into the DDP. At the same time, it shows different points of view for the hit identification paradigm.

Resource prioritization, including the identification and termination of underperforming projects early in the process, and effective decision-making between phases, are the main decision tradeoffs in the DDP. Information feedback about *in silico* and experimental data alters these decisions within the context of existing frames and decision rules. In addition, information feedback informs theoretical models originating from scientists' own mental models and determines which research hypotheses to choose. As scientists' mental models change, the structure of the DDP is altered, leading to a portfolio of alternative decision rules and strategies. Hence, the same information processed and interpreted by different decision rules can lead to an alternative decision set [52].

Boundary of the HTS's system dynamics structure (SDS)

This section overviews the SDS of the H2L process with a focus on HTS technology. Figure 4 proposes the first SDS, or influence diagram (ID), corresponding to the full H2L process, that is, from hit identification to lead selection, and from optimization to IND entry into clinical phases. The HTS process comprises five main steps, often represented in the literature in a cascade model, which occults a paramount perspective on this feedback loops-laden structure and decision steps involved in the DDP. The DDP steps are: (1) the building of libraries of small molecules, (2) the optimization and validation of biochemical assays, (3) the automation to perform HTS screening, (4) the primary screening to generate data for use in hits identification and confirmation screening and (5) the secondary screening and counter screening for the selection

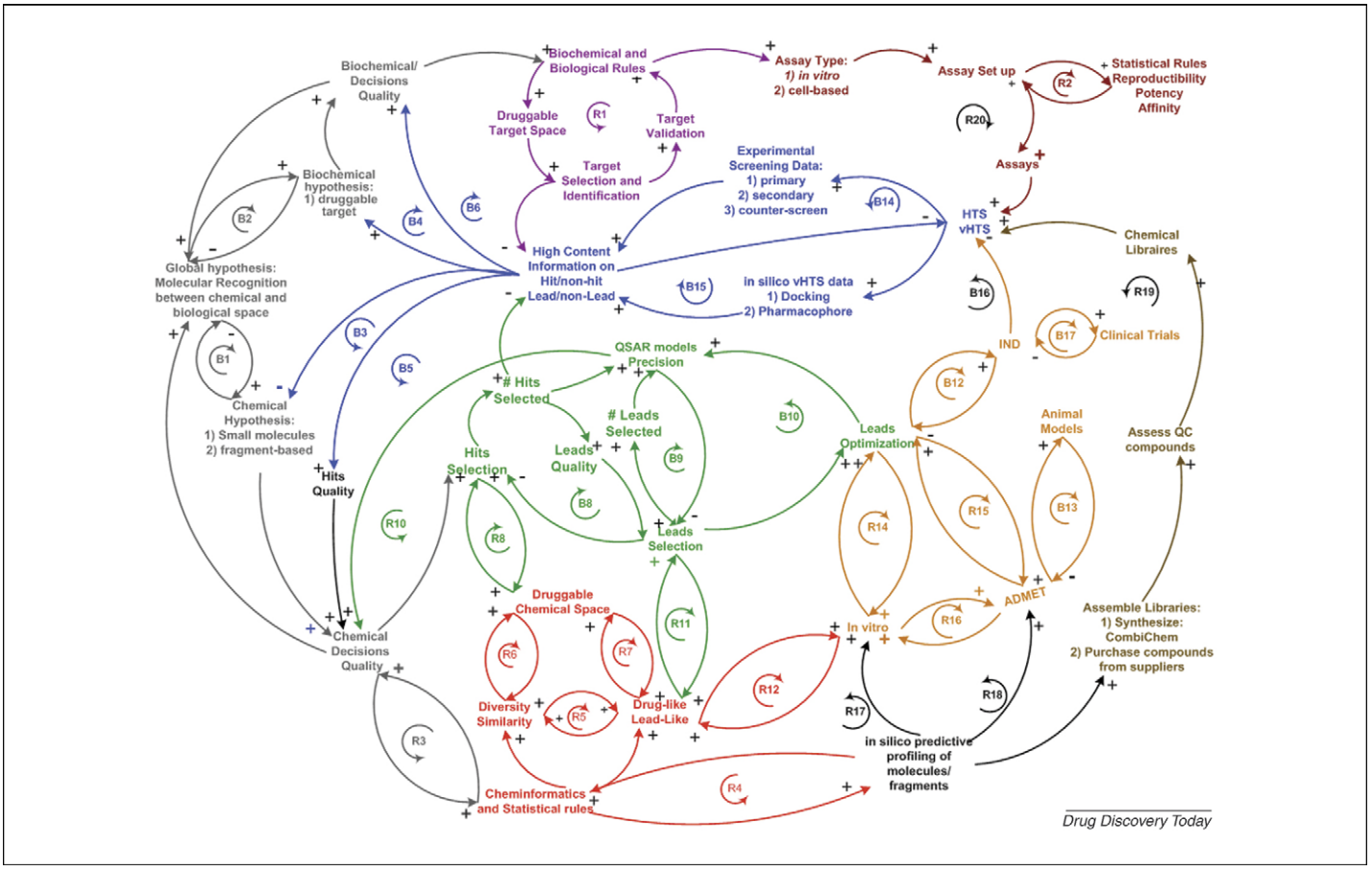

FIGURE 4

System dynamic structure (SDS) from hit-to-lead to optimization to investigational new drug in the HTS process.

of lead series from the initial pool of hits. Thus, the entire H2L is an elimination and converging process, based on the information gained from *in vitro* biochemical and biophysical tests and from *in vivo* ADMET tests, where quantitative structural activity relationship (QSAR) models have been developed for lead identification and optimization.

Chemical and biochemical hypotheses feedback loops

The SDS in Fig. 4 depicts the main feedback loops of the HTS process with 20 reinforcing and 15 balancing feedback loops. The balancing loops B1 and B2 specify the global hypothesis with the chemical and biological domains defining the boundary of the SDS. The more complete and detailed is the Global_Hypothesis, that is, the molecular recognition between chemical and biological spaces [53–56], the better focused are the Chemical_ and the Biochemical_Hypotheses. Thus, less refinement is required for either one of these hypotheses. The SDS encompasses the Chemical_ and Biochemical_Hypotheses contoured by balancing loops B3 and B4. These two loops are linked with other sets of interlocked loops, that is, they are bridging a set of influences within the Global_Hypothesis. They bridge both chemical and biological domains within the HTS/virtual HTS (vHTS) paradigm. First, the feedback loop B4 includes the following set of influences: Biochemical_Decisions_Quality, Biochemical_ and Biological_Rules, Assay_Type, Assay_Set-up that influences Assays, HTS, vHTS, and HCCL, that influences back the Biochemichal_Hypothesis. Second, the feedback loop B3, includes the following set of influences: Chemical_Decision_Quality, Cheminformatics_ and Statistical_-Rules, Predictive_Profiling, Assemble Libraries, Assess_QC compounds, Chemical Collections Libraries, with HTS, vHTS, and HCCL, closing the feedback loop on the Chemical_Hypothesis. The overall dynamics of this structure appears regulated by two balancing feedback loops, owing to the set of two opposing influences between HCCL and Chemical_Hypothesis (loop B4) and HCCL and Biochemical_Hypothesis (loop B3). The driver in that process is Higher_Content_Quality_Information, the output of the screening process. Indeed, the higher quality information from HTS and/or vHTS data enables the validation of the original Chemical_ and Biochemical_Hypothesis. Experimental and/or *in silico* data are gathered and processed to provide high-content information on the nature of the hit/non-hit and lead/non-lead from screens. The high-content information is reused for target selection and validation and for H2L, LO and IND. Thus, balancing loops B3 and B4 represent the following: as the high-content information from each screening experiment increases, the pressure for developing better chemical and biochemical hypotheses is eased. In turn, better chemical and biochemical decisions are executed in the selection of druggable molecules, fragments and targets, leading to higher quality screens. This process results in higher content value information on both biochemical and chemical materials, and translates, at the end of the process, into higher quality IND and lower attrition rates.

From H2L to IND and molecule attrition feedback loops

The balancing loop B5 depicts hits selection showing how a higher level of HCCL improves the quality of screened hits. This is followed by improved decision-making for hits selection that provides a minimum quantity of selected hits for QSAR models, which in turn, puts less pressure on new information from HCCL. The loop B5 depends on the two balancing loops B14 and B15, where a higher HCCL leads to a reduction in screening experiments. The feedback loop B5 is interlocked with many more loops represented in Fig. 4.

The Cheminformatics_ and Statistical_Rules are necessary for the selection of true active hits [52,57]. Simultaneously, cheminformatics and statistical rules increase the resolution of the druggable chemical space for the selection of more druggable hits through the reinforcing drug-like/lead-like properties. Thus, an increased exploration of the druggable chemical space [53,54,56,58,59] improves the quality of the drug-like/lead-like properties leading to the development of better cheminformatics and statistical rules [52]. These rules can define the similarity and diversity amongst molecules in the searchable chemical space. Thus, hit selection is entangled with a proper set of rules defining a druggable space with a higher level of resolution though drug-like/lead-like properties, searchable with diversity and similarity *in silico* algorithms.

Hits selection is closely related with the development of QSAR models for further use in leads selection and optimization. An important relationship between the balancing loop, B7, of QSAR models, and of hit selection (loop B5) is established when hits are chosen for the development of QSAR models. A minimum number of hits (#Hits Selected) is necessary to build QSAR models. An improvement in theoretical QSAR models leads necessarily to better chemical decisions, which in turn, requires a smaller number of hits as inputs in the design of QSAR models. At the same time, better cheminformatics and statistical rules, increase the high-content value of hits selection as input for QSAR model design. Moreover, better QSAR models are amenable to improved *in silico* profiling of molecules and/or fragments. As the quality of hits improves, the quality of leads improves too, this translates into a reduced number of high quality leads (loop B8). Leads Selection influences a number of variables: QSAR_Models, Drug-like/lead-like, In_Vitro, ADMET, and Leads_Optimization. Hits_-Selection, Leads_Selection, *in silico*_Predictive Models and Leads_Optimization are interrelated. It is difficult to describe one in isolation of others. Both hits and leads served as inputs in the development of QSAR models. For lead series, however, it is only after selection from a pool of high quality hits. This process, known as H2L, is iterative and converges only when HCCL series are obtained. Improved QSAR models bring less leads selection. The same holds true for the Leads_Optimization. The variable Improved_Quality_Level reduces the number of leads as inputs for optimization. This is achieved by the development of better QSAR predictive models, the improvement of the *in vitro* and ADMET data obtained. These loops are entangled with feedback loops (R13) from QSAR predictive models and with *in silico* predictive profiling of molecules and/or fragments. This particular interaction can follow two directions: one towards Leads_Optimization, or the other towards Hits_ and Leads_Selection (via loop R4). This dynamic influence is one of the most pivotal in this SDS because it connects both experimental and *in silico* data through the predictive profiling of compounds. This results in higher quality INDs entering clinical trials. An increased level of lead optimization with high-content information obtained from ADMET data provides a higher level of IND necessitating less leads optimization. Also, as the number of INDs increases, the number of HTS experiments decreases. Finally, as the number of INDs entering into clinical trials with success increases, the level of IND to be treated goes down.

Lead series success on attrition rate feedback loops

In the DDP, it is of paramount importance to examine the rate of success of lead discovery, based on hit selection and compound attrition. Until recently, a major perceived limitation of HTS technology was its low rate of hit success, relative to initial expectations [52]. A proposed solution to this problem is to increase the number of molecules to screen. However, increasing the number of molecules to screen does not necessarily translate into improved productivity in finding new hits [60,61]. Besides experimental errors, the SDS really shows the set of the reinforcing and balancing feedback loops that cause, in practice, the number of hits not to increase as expected. The fundamental set of causes for the limited performance of HTS, relative to expectations, has more to do with the choice of research hypotheses within the mental model held by scientists onto which screening is based: the molecular recognition, the quality of both chemical and biochemical decisions and the cheminformatics and statistical rules, such as type I and type II errors [52]. The hypothesis that generates these errors is applied to the identify false positive and negative in high-throughput experiments [52,57,62].

Conclusion

The system dynamics structure models the DDP, based on a set of principles requiring the multidisciplinary conjunction of knowledge and expertise from experimental and theoretical domains. For example, the modeling of the early DDP with the SDS can help shed light on the desired net global effect. That is, on costs and economic value generation, of the attrition rate obtained prior the DDPs' clinical phase studies, relative to the one obtained during clinical phase studies, as a result of integrating technology-based and knowledge-based discovery technology. The SDS targets the improvement of the costly drug attrition rate with the identification of HCCL presenting specific properties for a precise therapeutic application within the shortest time span within limits of established criteria and filters known for a technology in perennial evolution. In short, key performance improvements in the knowledge-based development of new drugs are obtained by the identification and integration of theoretical solutions with the virtual optimization of complex systems using SD. This method can show the DDP locus of value-added benefits.

The main relationships in the SDS show the interplay of HTS technology- and knowledge-based information feedback loops in the context of decision-making, stemming from decision-makers' own mental models. The SDS integrates the interplay between *in silico* and experimentation that produces data that create novel mental models which lead to the emergence of new sets of rules and strategies in the design of new experiments applied to the next iteration until convergence ensues from experimental and

theoretical strands. Hence, the SDS effective integration to represent both real and theoretical data, involving constant iteration between experimentation and learning in the virtual world, and between experimentation and learning in the real world, expands the mental model of decision-makers.

The SDS shows that the global, chemical and biological hypotheses are necessary for the implementation of decision-makers' mental models based on alternative considerations. This brings the question: are improved mental models needed to reach convergence during the DDP? Or, is it an approach based on the conjunction of mental models looking at alternative views, such as what is currently developed for bridging chemical and biological spaces, which will secure full convergence during the DDP?

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