# System Dynamics and Dynamic Systems Integration in Regulatory Environments

**Leeza Osipenko**
**John Farr, PhD, PE**

Stevens Institute of Technology
SEEM Dept. Burchard Bld.
Hoboken, NJ 07030
tel. (1) 973 851 7114
fax (1) 201 216 5541
eosipenk@stevens.edu
jfarr@stevens.edu

**Abstract**

System Dynamics evolved from Dynamic Systems often associated with classical mechanical engineering. However, today System Dynamics (SD) and Dynamic Systems (DS) are differentiated in theory and application. We believe that the link between SD and DS shall be reemphasized if not re-established in certain fields in order to advance system development and understanding.

In some regulatory environments (e.g. energy, medicine, ecology, aviation), the integration of SD and DS techniques can be especially beneficial. Many systems and simulations developed in these fields omit important parameters, modeling a specific problem or task. We believe that the combination of system dynamics and dynamic systems can provide for a higher level of precision in the system building process.

In this paper, using an example of clinical trials, we attempt to demonstrate how SD and DS can be used together to yield more sophisticated models.

***Key words:*** *system dynamics, dynamic systems, modeling techniques, regulatory environments, pharmaceutics.*

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## Introduction

Over the past fifty years, modeling and simulation (M&S) has become widespread almost in the entire spectrum of sciences and engineering. In most disciplines, it has replaced traditional "build and break" methods of design. In the myriad of modern computer-based modeling techniques, System Dynamics (SD) finds most of its applications in social sciences, while exact sciences continue to rely heavily upon the Dynamic Systems (DS) modeling. There are logical explanations to this: SD, using a holistic approach, involves complex feedback systems and affects soft variables producing models often used for policy recommendations, whereas, DS model a specific problem generally restricted by the exact mathematical equations.

Despite the fact that SD and DS are being used for different purposes and in general by different research communities, DS are imbedded into the development of SD and the SD theory is often used to explain the principles upon which dynamic systems are being built. The developers of system dynamics models are not always highly trained mathematicians and in certain cases they do not see the need for DS applications within their models. In turn, engineers, physicists and mathematicians working on their DS models often do not look beyond the exact mathematical solution to a given problem.

The integration of SD and DS is a complex process and it is very important to emphasize that this linking is probably beneficial only for fields involving policy, decision and complex DS models. For instance, medicine, ecology, energy, and aviation are associated with high risk and are controlled by strict engineering and governmental regulations. Most M&S in these fields are being built according to many specific parameters dictated by the industry, the government, the economic policy, and scientific calculations. The application of SD and DS separately presents only half of the picture necessary to reflect the relationships in the regulatory environments. We believe that the incorporation of both methods should allow for addressing quantifiable and non-quantifiable parameters and building models, which better portray the real world. The incorporation of SD and DS modeling techniques has been applied to a certain degree in some disciplines. For example, the Everglades Landscape Model (ELM) is a complex simulation in ecology built using several fundamental sub-models each operating at different spatial scales. These sub-models are built using the dynamic equations and then ecological process feedbacks are modeled with the help of system dynamics [5]. Also some transportation networks, spatial economics and logistics models attempted combining system dynamics and dynamic systems.

In this paper we are proposing a modeling methodology based on the integration of SD and DS. Using an example of pharmaceutical clinical trials we suggest that the SD-DS modeling technique can be feasible, efficient and necessary to produce better models in the regulatory environments.

## Background

### SD and DS in System Theory

Systems theory naturally brings together SD and DS. The Systems Theory is a trans-disciplinary study of the abstract organization of phenomena, independent of their substance, type, or spatial

or temporal scale of existence. It investigates both the principles common to all complex entities, and the (usually mathematical models), which can be used to describe them [22].

As we'll see from the information presented further in this paper, the above definition incorporates features related to SD, DS and Chaos - three parts of the systems theory. Chaos is not addressed in this work, thus we'll omit it from the discussion simply admitting the fact that, if necessary, it can be incorporated into the proposed methodology if described as a set of complex non-linear equations, which represent a Dynamic System.

System Dynamics and Dynamic Systems share common roots and basic principles. ***Figure 1*** shows the "evolution" of SD and DS in its simplest form. People have been studying dynamics since ancient times, as well as building systems, which incorporate dynamic principles. With the development of mathematics, physics, and mechanical engineering, the development of many dynamic systems and control theory became possible. System Dynamics originated in the 1960s and J. Forrester is regarded to be the father of basic principles of the modern SD theory [26]. Around the same time DS evolved dramatically with the growth of computing power. Personal computers facilitated the modeling process as well as made possible the application of SD and DS to various fields. The separation between SD and DS happened very fast and very naturally since SD found its applications in social sciences, while dynamic systems predominantly remained within the scope of exact sciences and engineering.

Before we address the differences of each modeling technique in greater detail, let's sum up the commonalities between SD and DS. Besides sharing common roots, SD and DS are the tools for designing a system, which is a whole (set, group, network), which consists of entities or elements, which are connected with each other according to certain rules or principles (interrelated, interdependent, organized, interacted, etc).

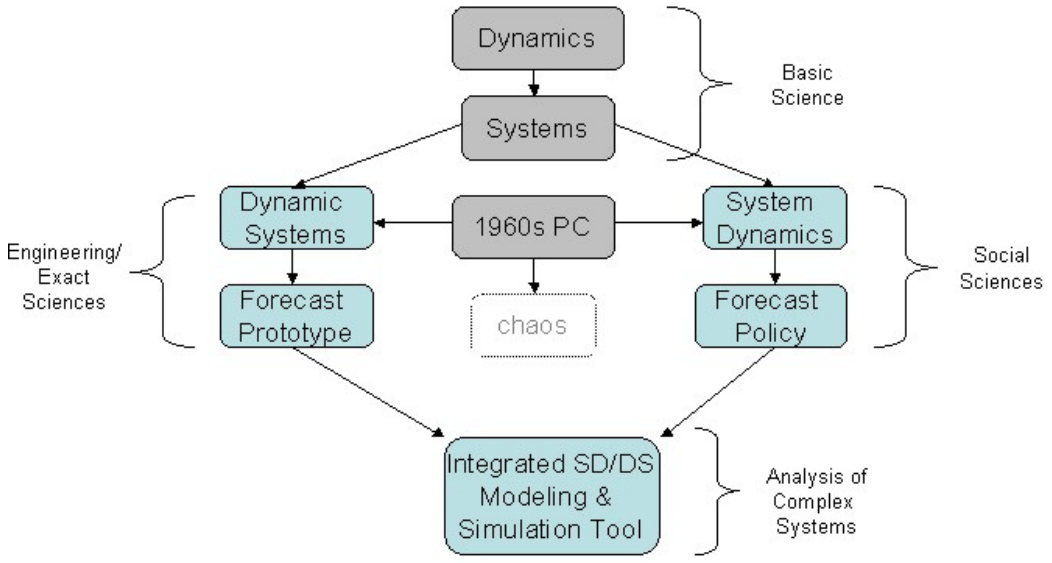


*Figure 1 Systems Theory*

SD is primarily focused on the dynamics of the system behavior while DS studies the dynamics of its parts. Since the behavior of the system is distinct from the behavior of its elements [13],

SD and DS carry on different missions modeling these behaviors. System Dynamics and Dynamic Systems are used to build models for forecasting, which produces policy recommendations or physical prototypes. Both techniques are involved with modeling, which is an intermediary (not a final answer!) for deriving hopefully helpful information if the model is well designed and implemented.

SD and DS use similar model design methodologies (but different techniques) and a very similar nomenclature. The process of model building presents a risk of unmanageable complexity in both cases.

**Dynamic System** is a system described by differential and/or difference equations [18]. In dynamic systems the present output depends on past input and the output changes with time if it's not in a state of equilibrium [18].

In order to build a dynamic system, a modeler should define specifications to be met, apply synthesis techniques if available, build a mathematical model of the system, simulate the model on a computer to test the effect of various inputs and disturbances on the behavior of the resulting system. Then, if the initial system configuration is not satisfactory, the system must be redesigned and the corresponding analysis completed. The process of design and analysis is repeated until a satisfactory system is found, then the prototype of a physical system is constructed [21].

The above description of the modeling process shows that DS are primarily involved with modeling a *system*. Most of the time, but not always, it's a system, which can be physically represented in the form of a prototype. DS have holistic features but are grounded in the reductionism theory by using mathematical description of dynamic characteristics. Feedback Control is a part of the system, which maintains a prescribed relationship between the output and reference input by comparing them and using the difference as a means of control [6]. The modelers often use block diagrams, which are usually sufficient to clearly represent the entities in the model. DS rely on data from experiments or physical constants.

The simulations of DS are done using sophisticated software for solving complex mathematical equations such as MATLAB, CACSD, MATRIX, CTRL-C [20] and according to the DS theory, system dynamics deals with the mathematical modeling of dynamic systems and response analyses of such systems with a view to understanding the dynamic nature of each system and improving system performance [21].

**System Dynamics** is a methodology for studying and managing complex feedback systems, in managerial, organizational and socioeconomic context [29]. It's a method for enhancing learning within these systems [25]. SD adopts a holistic approach and helps understand the basic structure of the system and the behavior it can produce.

In order to build a SD model we need to identify a problem, develop a dynamic hypothesis explaining the cause of the problem, build a computer simulation model of the system at the root of the problem, test the model to be certain that it reproduces the behavior seen in the real world, devise and test in the model alternative policies that alleviate the problem, and implement this

solution [29]. Various software packages (Stella, PowerSim, Dynamo, VenSim, etc) are used for building system dynamics models. These programs might be conceptually similar to the DS software tools but are different in their actual applications and the type of the results produced.

System Dynamics theory came in opposition to the reductionism theory [22], and became a tool for modeling a *problem*, not a system, using the principles of systems thinking. Dynamic characteristics are defined using casual loops diagrams, which is a logic-based description (not a differential equation-based description). The system dynamics approach is used to prescribe for the decision making to timely respond to any changes, and depict how to change the physical structure, to model the physical delay time [25]. This is being done with the incorporation of the "what if" scenarios (dynamic sensitivity analysis). The ability of the SD modeling technique to use soft variables is an important difference setting SD apart from DS.

The above comparative summary highlights the differences and commonalities between SD and DS. This paper aims to help researches in both fields to get a better understanding of these differences and similarities in order to see how the incorporation of the two techniques can be beneficial for the model building.

**The Regulatory Framework**

Perhaps future research will show that the integration of SD and DS can be useful in many areas but we picked the regulatory framework to address the issue since we believe that in such environments the possibility for integration is not simply feasible but necessary. The defense sector, medicine, energy are the fields of high risk controlled by strict engineering and governmental regulations. Modeling and simulation in these fields has been stipulated by the availability of funds and remains in great demand due to the high value, which is being placed on the forecasted information. The regulatory environments will continue to demonstrate an interest in better quality models and simulations.

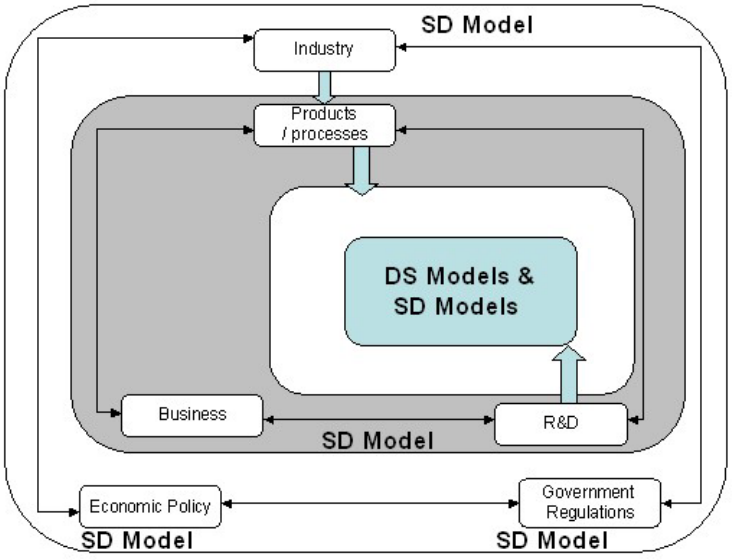


*Figure 2 – Simple Regulatory Framework*

***Figure 2*** depicts basic components of a regulatory framework. Government regulations influence the industry and economic policy, economic policy in turn, influences the industry and some of the government regulations. The industry, under certain circumstances, influences the government regulations and the economic policy. There are many examples of SD models representing relationships between these three entities. Also, SD found its applications focusing precisely on economic policy, government regulations and industry [28]. The reason, the industry entity is broken down into a few layers is that it demands both SD and DS modeling techniques and the availability of the applications. In almost any given industry a myriad of processes are being modeled using dynamic systems approach [21]. SD and DS placed in one box suggest the possibility of linking R&D processes with developed (licensed) or developing technologies (product parts, processes, etc) to build integrated models which can show a behavior of a prototype under different circumstances.

The reason we do not see the DS models of government regulations and economic policy (there are a few quantitative econometric models) is simply because these fields deal with a lot of noisy data and soft variables which are not used in the development of the DS models, which, as you recall from the above definition, are described by the differential or difference equations.

Now using an example from the pharmaceutical industry we attempt to analyze how this scheme can be challenged and improved with the integration of the SD and DS methods.

**Clinical Trials Example**

We picked to illustrate the integration of SD and DS techniques using an example of clinical trials from the pharmaceutical industry. Both, pharmacokinetics (PK) (influence of body on the drug) and pharmacodynamics (PD) (influence of the drug on the body) [23] rely on dynamic systems to build models, which are widely used by many pharmaceutical companies. The dynamic systems are built using the compartmental (predict) and non-compartmental models (don't predict), or Bayesian models [23]. This is a complicated process: the drug in the body is constantly undergoing change and it is not easy to track every single state at every single moment. Thus, in order to design non-compartmental or compartmental models, the space is being ignored, the finite number of computations is being reduced and processes where possible are being lumped together [23]. This is an example of reductionism approach often used in the creation of dynamic systems. These three strategies are expressed in the form of mathematical (usually partial differential) equations, which can be solved using various methods (integration, sum of exponentials, extrapolation to infinity, trapezoidal, log-trapezoidal rule) [23]. PK and PD parameters are descriptive, observational and quantitative, however, in building the dynamic systems, only the quantitatively expressed ones are used.

**Pre-clinical stage**

***Figure 3*** represents a simple block diagram for building a compartmental model. Basic PK parameters (Volume, MRT, AUC, AUMC[1]) need to be estimated to create an algorithm to quantify this procedure [23]. However, as we mentioned above, this procedure omits a lot of environmental (space) causes. These are generic approximations, which do not take into

[1] M Mean Residence Time (MRT), Area Under the Curve(AUC), Area Under the First Moment Curve(AUMC)

consideration a myriad of various conditions that a patient (not a generic model of a human body) might have.

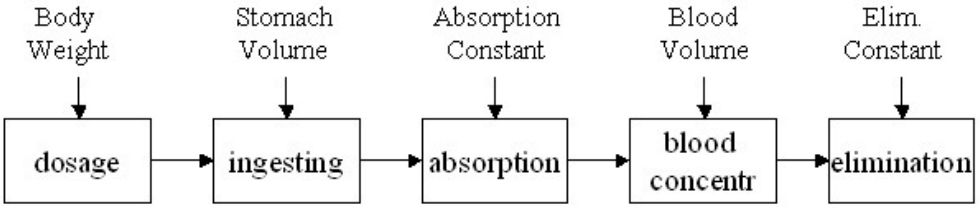


*Figure 3 – Basic Components of the PK Model*

This it the first example of how system dynamics can be incorporated into the complex dynamic systems modeling process. The PK/PD theory is well established to model chemical processes (examples available in [1,2,3,9,15,16,17,19,23]); now, let's place this system into an environment which can better describe the actual patients intending to take a drug. ***Figure 4*** shows a simple casual loop diagram depicting a few entities that can influence the model's results. The components can be modeled separately for simplicity, e.g. PK/PD model and allergies, but then, these parts can be aggregated to see the actual performance of the drug under multiple conditions. This is an example of incorporation of many "what if" scenarios, which can give more elaborate answers than a basic PK/PD dynamic system. Having the information of the drug performance under a wide range of various conditions can save time and money when it comes to the actual clinical trials in vivo.

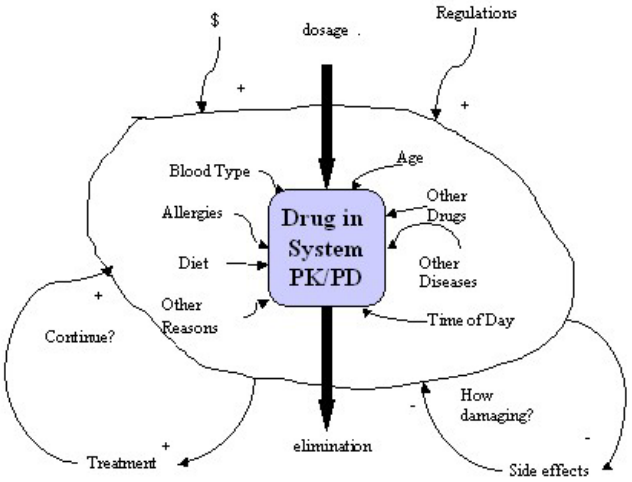


*Figure 4 - DS Model in SD Environment*

Modeling and simulation is considered valuable in the integration of PK/PD knowledge for decision-making, but such simulations are still severely impeded in its successful integration into the clinical drug process [2]. A variety of barriers from the absence of cost-benefit analysis to the shortage of trained personnel causes this situation, but one main point is the lack of the actual tool which allows, using PK/PD outcomes test efficiently a myriad of the "what if" scenarios in the given environment and help with the decision-making process. Today, successfully

implemented PK/PD models yield useful information about the generic drug properties, make some clinical trials more efficient, but do not challenge the actual procedure, which remains costly and time-consuming. However, there are already successes in this field, which should give more confidence to researches and model builders. Pharsight corporation built a WinNonLin[2] dynamic system for Provigil and using the obtained results and their knowledge management tools helped Cephalon, Inc (Provigil producer) to save 25% of the trial costs by eliminating a 300mg arm when the model predicted that 200mg was enough. The savings were in millions of dollars [17]. There are many possibilities of such and higher dimensions given by the application of system dynamics principles to the dynamic systems used in pre-clinical trials.

Most models are being built using data from clinical trials and currently the developers are investigating how to estimate parameters using this data [15]. SD-DS combination might be the tool to help with this process. By studying the system behavior through the use of feedback loops, instead of only expecting a particular system behavior through the entered algorithms, a system developer might be able to learn certain properties of the system, which have not been exhibited before. As it was mentioned above, the currently applied methods for parameter estimation (non-compartmental, compartmental models) use a reduced number of inputs to fit the algorithm, however, clinical trials provide a big array of data which can be used in SD modeling and produce a new technique for parameter estimation.

**Clinical Trial Stage**

Pharsight concludes that 30% of trials provide no useful information and many trials fail which results in staggering costs for a drug-developing company [17]. Many other drug candidates fail because of unforeseen effect of human metabolism, such as toxicity and unfavorable pharmacokinetic profiles [3].

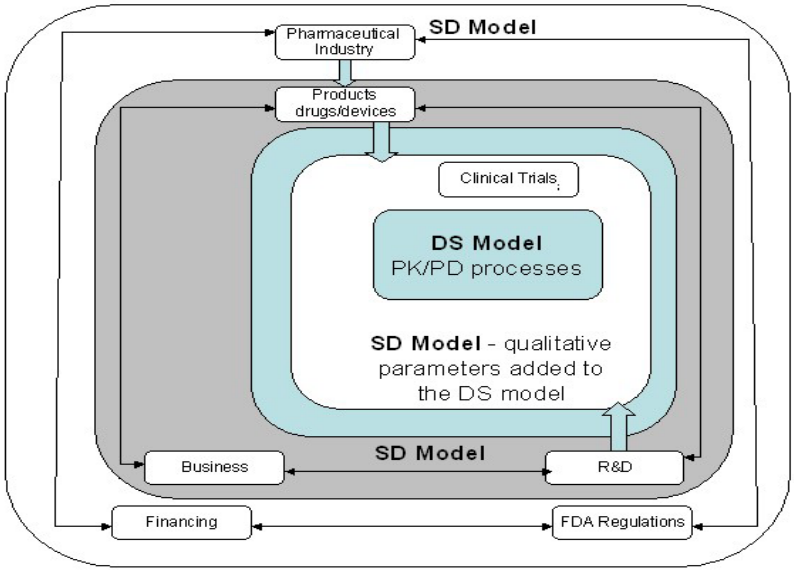


*Figure 5 – Clinical Trails within the Basic Regulatory Framework*

[2] WinNonLin – Software package for building PK/PD models

Currently a number of systems are being proposed to take care of the drugs, which are 'destined' to fail the clinical trials before they get to this stage. The search for an ideal system continues. In fact, as we'll see from the below example, once again, an incorporation of SD techniques to already existing PK/PD models can actually leave those drugs at the computer simulation level without taking an unexcused risk of testing them on animals and humans.

***Figure 5*** shows how clinical trials fit within the basic regulatory framework. The drug approval process in the USA has four stages: pre-clinical research, clinical research, FDA approval and Marketing. In the field of system dynamics there have been a number of models developed describing various parts of the above processes [3,12,14]. Clinical trials usually have four phases. There is a set of specific FDA regulations for each phase of the trail and there is a budget determined for each phase. Most of the time clinical trials are paid by the pharmaceutical company itself or, on some occasions, by the government. While there is some flexibility on the financial side, there is no flexibility on the side of meeting specific FDA regulations.

Each of the four phases can be modeled using compartmental and non-compartmental models. But as we've seen above, these are logically simplified (but very mathematically complex) systems with a limited number of parameters, clearly defined by specific mathematical relationships. Some attempts have been made to use computer modeling of clinical trials, but only as a comparative tool to the actual clinical results, not as a method capable to substitute certain parts of the actual clinical trials since the methods used are not yet sufficiently refined to provide reliable answers. A few studies indicated that the clinical trial results of all the drug dosages besides the placebo group fell within the predicted scores from the computer simulations [16]. However, up to date, very little research and studies have been done in this direction. The developers of dynamic system models for clinical trials are deeply involved in parameter estimation and calculations. The relationships between the basic parameters have been long established by the fixed equations, which are *not* being placed in the context of a specific environment. What this means is: whenever a dynamic system yields specific results, their

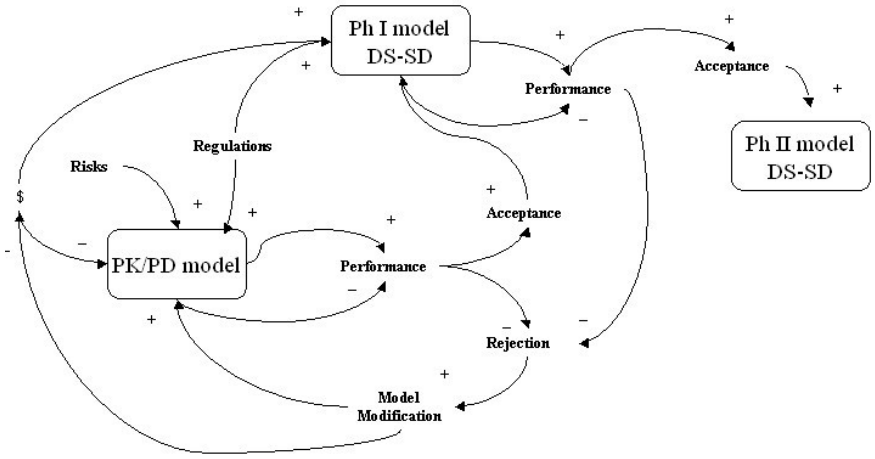


*Figure 6 - A Part of a Casual Loop Diagram of the Clinical Trials Process*

mathematical values are recorded, summarized in the form of a written report and presented to the FDA for approval to get a permission for clinical trials. Many "what if" scenarios are not modeled and no computerized forecasts are done to see the feasibility of the FDA approval.

***Figure 6*** presents a small part of a casual loop diagram, which can help analyze the behavior of the system for clinical trials. Above we've described the SD-DS relationships that occur within the boxes (PK/PD model, Ph I trial, etc.) The feedback loops depict the existence of non-linearity and the complexity of the system, but it can be simulated by parts to make the task manageable and the results easily interpretable. This approach will not eliminate clinical trials, but it can help decrease the number of stages, the duration of the trials and their cost, since many properties of a drug and its behavior in the given environment (what we are trying to introduce with the SD-DS simulation) will become available from the SD-DS simulations. In particular, we believe that phase IV of clinical trials can be eliminated since all its features can be addressed in shorter time at the earlier stages (see [4] for the description of phases).

This casual loop diagram will produce a complex model, which will be operating at two different levels simultaneously. the 'micro' – DS level and the 'macro' - DS in the context of SD models. The tracking of the levels separately might be important in order to control for errors, however, the results should be interpreted from the system as a whole.

**SD-DS Modeling Technique**

When we are dealing with so-called hybrid models, which use both SD and DS, we need to consider a few things. First, there is a need for collaboration between the model developers, which is likely to lead to the group model development. As illustrated in previous works, this technique can be very efficient due to the knowledge sharing and parallel development of various parts of the model. If a particular group or a person is interested in incorporating the SD or DS into their model, there is certainly an assumption that the developers are equipped with necessary knowledge about the part of the modeling process they are adding to their model. The collaboration between SD and DS developers can be very effective since two groups already share a lot of common knowledge and nomenclature and will be able to easily communicate their ideas to each other and find optimal solutions.

This combination of modeling techniques is likely to advance the modeling process. Perhaps, to address all aspects of the SD-DS model development, we would need a customized software package, but even with current tools the integration of SD-DS can be done efficiently. By putting the two dynamic modeling techniques together, the developers can observe the behavior of the DS prototype under various conditions within one model, which will provide not only the information expected from the modeling process (the result), but also reveal various new techniques in the model building process itself. The detailed development of the methodology for the SDDS model building can be a separate research topic.

**Limitations**

Since both system dynamics and dynamic systems have plenty of limitations of similar and distinct nature, SD-DS model certainly incorporates some of these limitations and produces

others. Complexity is a risk factor in both model-building techniques and it will remain in the SD-DS modeling approach. Though, complexity is not necessarily a threat. The models promise to become larger but the capability of testing models by parts will remain. Depending on the industry and the application of the technique, the costs might increase for the modeling and simulation part, but attempting this modeling approach can save money in the long run. Certain DS systems and certain SD models are not compatible and the developers should be aware of that and apply SD-DS hybrid to the processes that can benefit from the use of such modeling tool.

Depending on the field of application, an access to a good quality data usually presents a problem. SD-DS models might be difficult to validate but possible using sensitivity analysis, physical prototypes, real-world examples, expert opinions and other modeling techniques.

**Conclusions**

An axiom, which no modeler can forget, is that computer simulations help to build intuition or to refine calculations, but they do not give birth to genuine discovery [8]. In this paper we are proposing the modeling methodology based on the integration of system dynamics and dynamic systems modeling techniques. Using an example of pharmaceutical clinical trials we suggest that the combination of SD and DS can be feasible, efficient and necessary to produce better models in the regulatory environments such as medicine, energy, various sectors of the defense industry, ecology, etc. However, other possible applications can be found.

If the SD-DS modeling technique is applied in the proper field, it helps produce a more sophisticated system without necessarily increasing complexity to an unmanageable level. Even though, the system has more components, it remains rather transparent since the DS and SD parts are incorporated in the way that it augments the understanding of the model rather than makes it more difficult.

Models and simulations can never replace observations and experiments but they constitute an important and useful complement [18]. SD-DS technique presents a synergy of processes, which yields a synergy of the results. By placing a sophisticated dynamic systems model into an environment, described by true casual interrelationships, we can gain more knowledge about its behavior under different assumptions. It will allow us make better quality decisions with a higher level of precision which should help industries to save money and decrease the number of physical experiments.

**Future Work**

Dynamic Systems deal with the dynamics of the process, while system dynamics deals with the dynamics produced by the system behavior. Do not confuse this with the definitions given in the background section stating that DS model systems and SD models processes. Here we talk about the issue of dynamics. Does the incorporation of the two modeling techniques affect the dynamic behaviors in any way (synchronizes them or serves as an impediment)? DS and SD have a capability of modeling the time lags of different nature: DS - between the physical processes, SD - between the decision processes. Can these time lags be synchronized

efficiently? Also, it would be interesting to create a few models in the interdisciplinary groups and analyze the effectiveness of the process, as well as the quality and performance of the designed models.

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