# Knowledge-driven Vaccine Systems Engineering

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***Abstract*—Current vaccine development approaches are ineffective in capturing, representing and reconciling domains and disciplines knowledge and viewpoints across the vaccine development life cycle. As a result, vaccine development is a long, complex, and costly process that often results (when it succeeds) in vaccines whose potency is hard to predict and efficacy expensive to preserve. State-of-the-art vaccine development approaches fail to (1) integrate the multiplicity of stakeholders perspectives across the Vaccine Development Life Cycle (VDLC), (2) bridge the knowledge gap between multiple disciplines, and (3) formally evaluate stochastic system behaviors of biological systems in a seamless manner. This paper introduces a novel semantically-enabled framework for knowledge and behavior specification, modeling and processing in vaccine systems engineering. Data and semantic models of domains supported by sound theories and tightly coupled with Markov Chain models of biological systems are the cornerstone of our solution. Near future work includes optimal vaccine matrix design and experimental vaccine preservation systems. Looking ahead, the capabilities of the framework – demonstrated in a vaccine preservation study – will enable more effective, cheaper and faster time-to-market vaccines.**

***Keywords-Vaccine; Systems Engineering; Semantic; Ontology; Markov Chain.***

## I. INTRODUCTION

### A. Problem statement

Vaccination is a cornerstone of today's modern human being health of all ages, preventing potentially fatal and life crippling diseases. Successful vaccines – such as the one for smallpox – have rid the world of a severely contagious and potentially fatal disease. The core component of the vaccine – the vaccine antigen – is formulated and designed to be administered as an oral vaccine or injected subcutaneously. Successful vaccines provide lifelong immunity and protection of the host from contracting diseases caused by corresponding pathogens.

The effectiveness of the immunization is contingent upon multiple factors, including the nature and behavior of the pathogen, the vaccine and its development life cycle, and the host physiology. The difficulty in engineering, developing, manufacturing and delivering highly effective vaccines is complicated by its variant nature, a characteristic inherent to all biological systems [1]. In rare occasions, host physiology coupled with genetic factors and environmental conditions can adversely affect the vaccination outcome through immunosuppression or anaphylaxis (severe reactions). Stakeholders involved in the Vaccine Development Life Cycle (VDLC) – see Figure 1 – view the vaccine through significantly different lens, which makes elicitation of design requirements very difficult. For instance, researchers (e.g., Stage 1 of VDLC) are more interested in the immunological processes at the molecular level (antigen), while clinicians (e.g., Stage 7) are looking for faster, more effective, accurate and less invasive delivery tools and mechanisms. Moreover, the knowledge disconnect between the disciplines involved – biology, chemistry, engineering, manufacturing, legal, regulatory and healthcare – makes vaccine development a very convoluted process [1].

The compounding effect of these issues contributes to today's situation where vaccines (1) are available for only 10% of known pathogens harmful to human, (2) cost hundreds of millions of dollars to develop and 8 to 10 years from research to market with high failure rates, (3) have short shelf life span i.e., a year or less and, (4) require costly and stringent storage and handling conditions [2][3]. Moreover, fast genetic mutations of pathogens of deadly ailments (e.g., HIV-1) and environment factors have been enabling them to outsmart researchers for years, making vaccine development for those diseases an uphill battle. The stakes are even higher when we consider social and cultural resistances to immunization. Concerns about (and risks of) childhood autism, anaphylaxis, disabilities, contraction of vaccine associated diseases (live vaccines) and religious beliefs are among the most common arguments against vaccination [4].

Addressing these challenges requires vaccine design and development approaches that enable stakeholders along the VDLC to answer both domain specific and cross-domain questions quickly, accurately and cheaply in the context of highly stochastic and complex biological dynamics. Leading research efforts in rational design of vaccines are piecewise and fail to address critical methodological and knowledge gaps [5]. Built upon the ability of the systems engineering discipline to bridge the gap between – and integrate – disciplines and architect systems at various levels of abstractions, the introduction of a model based knowledge-driven framework for vaccine development life cycle is a significant step forward. The three pillars of this work are that (1) formal methods must drive and support the development of models, (2) the latter must properly capture the depth and breadth of stochastic behaviors of biological systems and, (3) models must be reusable, customizable and

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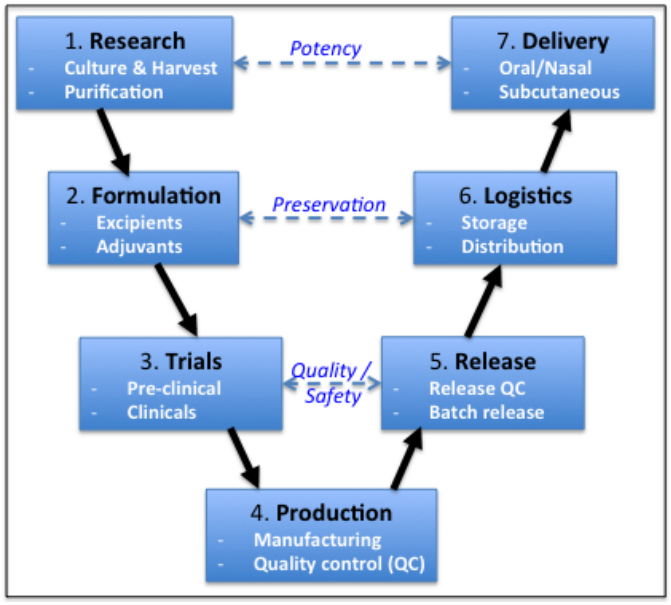


Figure 1. "Vee" model of the Vaccine Development Life Cycle (VDLC)

integrated at will for the purpose of the analysis at hand. State-of-the-art vaccine development approaches are not capable of such cross-discipline and cross-domain modeling and coverage of the life cycle [2][3][5].

### B. Project Scope and Objectives

In order to address these limitations, we aim to develop the foundational semantic infrastructure for knowledge and behavior specification, modeling and processing across the full spectrum of the VDLC. The integration of biological system dynamic models and discipline and stakeholder knowledge models will enable the emergence of novel architectures whose instantiation and execution can be checked against the requirements of a given application or analysis. For instance, a researcher – in Stage 2 of Figure 1 – can make use of the integrated knowledge models of the formulation matrix and the stochastic model of the vaccine antigen to analyze the performance of the selected matrix and validate the results against experimental outcomes and incrementally refine the models accordingly. Elements of the study and its results can be propagated to the healthcare administrator (at Stage 6) to ensure proper handling of the vaccine in order to preserve its effectiveness while in storage and transit. Here, the creation and integration of knowledge and stochastic models of both the formulated vaccine and the environment is necessary. The healthcare professional in Stage 7 concerned with patient prognostic and response to the vaccine will need stochastic models of their physiology coupled to the one of the formulated vaccine, integrated with the knowledge model of the delivery protocol.

A successful implementation of this framework in full will make these scenarios and more complex ones a reality in the day-to-day work of stakeholders across the VDLC. More importantly, it will enable progress toward the development of an integrated, evolving *"vaccine digital twin"* whose sound mathematical foundations provide confidence in analyses, speed up decision making (thus, time-to-market) and help manage complexity more effectively.

Section II provides a brief review of vaccine types, mechanisms and development processes in the context of systems engineering. Section III introduces the foundations of the vaccine development semantic framework and describes its architecture. In Section IV, we briefly highlight two research topics currently under investigation that make use of, or reinforce the capabilities of the semantic framework. A simple vaccine preservation study example is presented in Section V. We conclude this work in Section VI.

## II. Vaccine Systems Engineering

### A. Vaccines: Types and Development Challenges

Vaccines play a critical role in combating infectious disease and improving overall quality of living. There are several different types of vaccines: *live attenuated* vaccines (e.g., oral polio vaccine), *inactivated* vaccines (e.g., injectable polio vaccine), *subunit* vaccines, *toxoid* vaccines, *conjugate* vaccines, *DNA* vaccines (e.g., Hepatitis B) and *recombinant viral vectors* vaccines. The differences between the types of vaccines stem from the structure and properties of their core-component, i.e., the antigen. A vaccine achieves immunity through a complex process in the body and protects the host by inducing immune mechanisms capable of rapidly controlling replicating pathogens or inactivating their toxic components. One such mechanism is raising antibodies against the vaccine antigen.

The development of vaccines of any type is a complex, expensive and high-risk undertaking, as many candidates fail in pre-clinical studies (Stage 3 of VDLC). The key to success here lies in the vaccine's ability to induce an effective and sustained immune response, have minimal side effects, and be produced cost-effectively at large scale. Because of the complex nature of vaccine manufacturing, it is important to be able to understand, control and/or predict the factors that impact the efficacy, stability and safety of the vaccine along its process-engineering pathway.

### B. Systems Engineering of Vaccines

The vaccine development life cycle can be represented similarly to the well known systems engineering "Vee" model, as shown in Figure 1. The first stage of vaccine development involves the selection of a candidate vaccine (exploratory stage) from a fundamental research laboratory and its testing using animal models (pre-clinical stage), followed by the development of small case scale material and formulation to make material for phases I, II and III studies (clinical development). Phase I includes safety tests among 10-100 human subjects to evaluate clinical responses. Then, phase II looks at the evaluation of immune responses in 100-3,000 subjects. Finally, in phase III, large scale studies are conducted to test vaccine efficacy and tolerance. Only vaccines that successfully pass trials are eventually mass produced. On the right side of the model, the vaccine is thoroughly tested before its release, then distributed in lots, and finally administered to the host. Three cross-cutting concerns between stages are identified: quality/safety, preservation and potency. However, unlike traditional systems engineering "Vee" models, the concerns are non-binding and there are no rigorous feedback mechanisms between successive stages, nor formal requirements flow down and traceability process.

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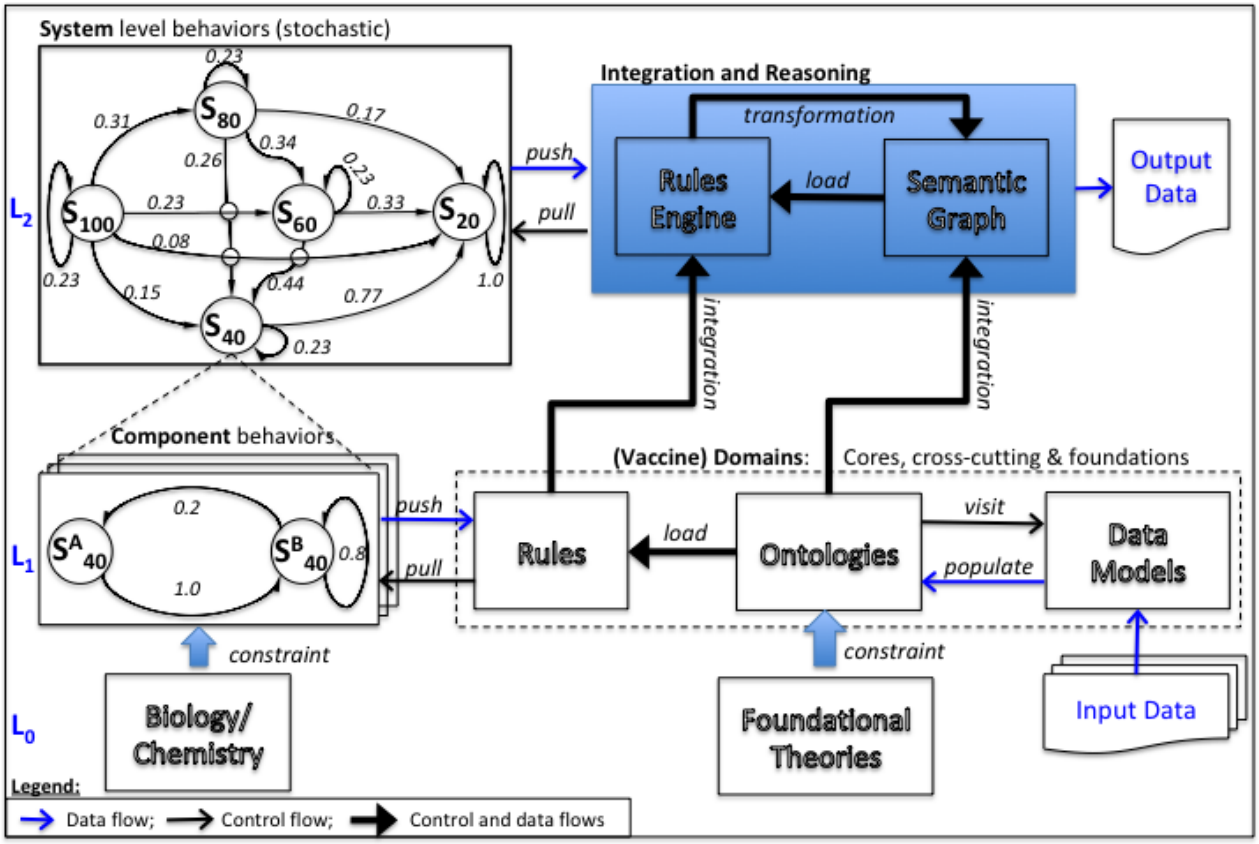


Figure 2. Simplified architecture of the framework

## III. Semantic Framework for Vaccine Development Life Cycle

The development of semantic architectures for VDLC is complicated by the multiplicity of stakeholders' perspectives across the VDLC, the need to bridge the knowledge gap between multiple disciplines, and formally evaluate stochastic system behaviors of biological systems. We report in this section on a novel semantic-driven framework that addresses these challenges through a careful investigation, selection and integration of technologies, theories and models from relevant disciplines, domains and types.

### A. Logic-based Semantics and Semantic Web Technologies

In order for core vaccine knowledge to be integrated, shared and reused across the various stages of the life cycle depicted in Figure 1, it must (1) be captured, represented in a clear, unambiguous way with respect to the associated domain and the context of use and, (2) lend itself to automated processing and reasoning by machines. Thus, data must be enriched by sound semantics to ensure accuracy of facts and inferencing.

Thanks to their sound mathematical foundations and decidability as fragment of first order logics, Description Logics (DL) formalisms have been shown effective in tackling the first part of this challenge [6]. A summary of description logic concepts constructors can be found in [7]. DLs provide the mathematical foundations on top of which machine and human readable ontological languages, such as the web ontology language (OWL) can be built in a systematic way. They enable the creation of ontologies, which are engineering artifacts that provide explicit specifications of the intended meaning of a vocabulary used to describe a given domain. Ontological models provide semantic meanings that enrich the way models can be branched and integrated across domains of knowledge automatically. These capabilities are critical to this work given the strong need to understand intricate relationships spanning multiple domains and components and their ultimate affects on the vaccine performance. In [8], we have identified and described the necessary extensions to the basic DL, leading to $\mathcal{SHOIN}$ and $\mathcal{SROIQ}$ DLs as appropriate logic-based formalisms for semantic framework like the one we are introducing in this work. OWL2 DL is computationally decidable and will support ontologies representations in our framework.

Semantic web technologies integrated with reasoner through Application Programming Interfaces (e.g., Jena) provide a way forward in addressing the second part of the above-mentioned challenge [8]. Together, the eXtensible Markup Language (XML), the Resource Description Framework (RDF) and OWL as hierarchical layers of the semantic web technology stack, allow for the implementation of reasoning that can prove whether or not assertions in the knowledge base are true or false in almost real-time (decidability). Thus, semantic web technologies are great enablers of automated processing and reasoning over sparse, across-domain information. In the context of VDLC, they will organize and merge the sources for answering biological and engineering questions using corresponding semantic models (ontologies, rules and computation extensions).

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### B. Mathematical Modeling of Systems Biology

The effective capture and representation of the behavior of the biological systems (e.g., vaccine antigen, host physiology) across the VDLC necessitates models that accurately capture the essence of unfolding biological (and underlining) chemical processes at various level of abstractions. Such models must allow the simulation of the system behavior over time and predict changes caused by interactions with other systems and the environment. Modeling schemes of biological phenomenons and systems emphasize various aspects such as body metabolism, genetic networks, neuronal systems or processes (e.g., intracellular processes). These models have been shown appropriate for cellular level analyses and studies but they are ineffective in capturing biological phenomenons that occur at higher levels of abstractions (e.g., tissue, organs)[9]. Thus, we will choose Markov models which have been demonstrated effective in modeling and predicting the behavior of highly stochastic biological [10] and biomedical systems [11]. Plus, they are not domain specific and they lend themselves well to integration through segmentation mechanism to domain specific models. *Markov chain (MC)* – see top left corner of Figure 2 – states ($S_i$), in our framework, represent a valid biological or chemical state with arrows between states annotated with their probability of propagation. Feedback between states and steady-states are allowed with the constraint that all propagation probabilities at each state must sum to one (1). *Hidden Markov models* extend Markov chain models and are developed from observed system performance (e.g., lab experiments). The resulting model is then used to further the analysis of the system and predict future behavior.

### C. Simplified System Architecture

The proposed knowledge-driven framework shown in Figure 2 makes use of logic-based semantics emulated by semantic web technologies and MC to provide rigorous formalisms to models across the VDLC. It is modular and its building blocks are chosen and integrated depending on the needs and requirements of a given application. The architecture is organized into three layers as follows.

*Foundation Layer ($L_0$).* The mathematical foundations needed by architectural models reside here. Foundation theories (for known cross-cutting domains such as time, physical quantities, communication, etc.) are distinguished from biological and chemistry laws or well-accepted domain standards (e.g., CDC Standard for Adult Immunization Practice). One such theory is Allen Temporal Interval Calculus (ATIC), which has been shown effective in supporting formal description and reasoning in the temporal domain [8].

*Domain Knowledge Layer ($L_1$).* The VDLC knowledge is organized into three groups: core domains (e.g., vaccine antigen, host), cross-cutting domains (e.g., storage condition, vaccine schedule) and foundation domains (e.g., time, physical quantity). Each domain knowledge is encoded in the form of a "semantic block" made of (1) an ontology, (2) set of rules, and (3) interfaces that enable communication between semantic blocks and linking with computation platforms and Markov models of system biology via customized builtin functions. Data models provide the templates for input data to be processed by the semantic block. DLs provide the formalisms needed by core domains knowledge while theories such as the ATIC will constrain models of some cross-cutting domains (e.g., vaccine schedule). Requirements are captured as a cross-cutting domain that makes use of foundation knowledge to formally encode and process input textual requirements.

*Integration Layer ($L_2$).* Bridging the knowledge gap between disciplines in the framework requires (1) the integration of domain specific knowledge at level $L_1$ on both the semantic and stochastic behavior sides, and (2) linking them to emulate system level behavior for the application under consideration. The resulting (system) semantic graph is transformed as rules – integrated to stochastic models of the system behavior – are fired. It can also act as semantic controller as it could encode defined system metrics whose instances could be checked against system requirements (as constraints). We will trust the Whistle scripting environment [12] with the controlled and systematic assembly of the models, as well as simulation and output generation.

## IV. Work in Progress

The architecture introduced and briefly described in Section III is generic and high level enough to be customized for various applications and challenges throughout the VDLC. We are working toward its use and adaptation to tackle two important challenges in the VDLC: determining and characterizing the best formulation mix for a vaccine and designing experimental vaccine preservation systems.

### A. Topic 1: Vaccine Formulation Design

The challenge of retaining potency (or efficacy) of the vaccine until it is administered remains an open challenge for researchers [13][14]. The potency of the vaccine has to be preserved throughout the VDLC from its formulation (Stage 2 of VDLC) to the administration (Stage 7) through manufacturing (Stage 4) and subsequent steps. The design of the best vaccine matrix (i.e., the formulate) able to stabilize, preserve and improve host immune response is a multi-domain, multi-disciplinary and complex integration problem for which the architecture developed in this work can help address. For each vaccine, design of experiments will help narrow down the most effective excipients (stabilizers and preservatives) and adjuvants from a list of over 370 substances that are Generally Recognized As Safe (GRAS) [15]. Then, both knowledge and stochastic models of selected substances will be integrated in the framework along with the ones of the vaccine and the pathogen. The response will be traded across multiple objectives (e.g., potency, infectivity), conditions (e.g., temperature, moisture) and configurations of the mixture.

### B. Topic 2: Experimental Vaccine Preservation Systems

Under the current state-of-the-art of vaccine technologies, the most effective matrix cannot preserve it from becoming subpotent due to inappropriate and suboptimal storage, handling and transportation, especially under challenging infrastructural, economical and environmental conditions [16][17]. This project will build from the results from Topic 1 and previous related work in biomedical devices [11] to analyze, develop and verify prototype adaptive platform-based containers for vaccines handling and storage. The focus will be on enabling and demonstrating system resilience to frequent changes in environmental conditions such as the ones currently observed along the vaccine supply chain [17]. Another interest

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of the project will be to understand mechanisms through which decisions (e.g., vaccine type, matrix elements) early in the VDLC ultimately constraint and affect preservation platforms (to be) used in vaccine supply chain downstream. Thus, we plan to extend the capability of the framework introduced in this work by integrating it with graph-based database platforms [18].

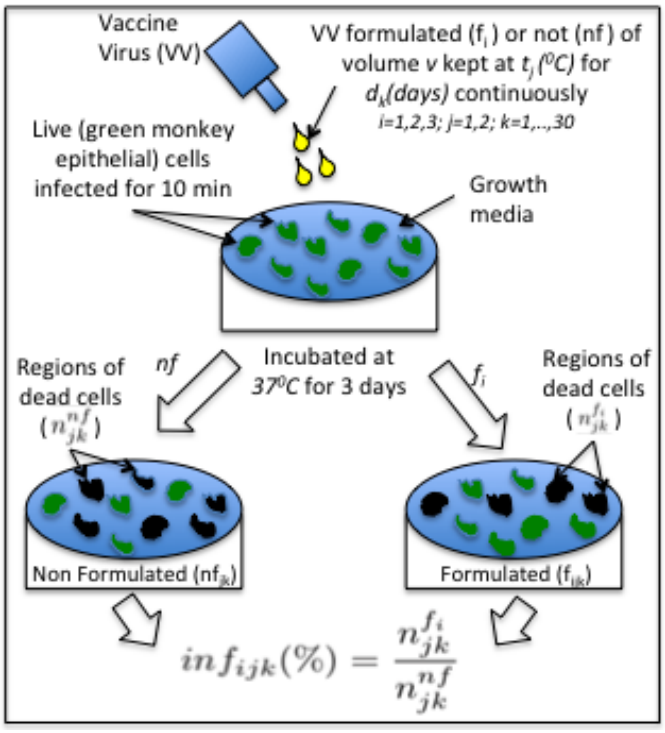


Figure 3. Schematics of the OPV preservation experiment

## V. Prototype: Vaccine Preservation Study

### A. Experiment Set Up and Methodology

We illustrate the basic implementation and use of our framework in a simplified Oral Polio Vaccine (OPV) formulation study for which the corresponding experiment is pictured in Figure 3. The study seeks to evaluate how well given formulations ($f_i$) preserve the effectiveness of the OPV (live attenuated) under stringent preservation conditions (temperature) such as the ones observed in Sub Saharan Africa. In a simplified experimental design, a volume *v* of a formulated OPV (vaccine antigen virus, VV) kept at temperature $t_j$ during $d_k$ days, is administered to $n$ numbers of host cells (live, green monkey epithelial cells). The host cells are infected with the virus for 10 mins, and the excess vaccine removed. A layer of agarose gel is placed on top of the host cells and the cells are incubated at $37^0C$ for 3 days. Then, the gel is removed and the host cells is stained. Finally, dead regions of the cells or plaques $n_{jk}^{f_i}$ are counted. The same experiment is repeated for all the formulations and for the non-formulated VV and $n_{jk}^{nf}$ is recorded. The infectivity – i.e., how well the vaccine was preserved by a given formulation $f_i$– is computed as follows.

$$inf_{ijk}(\%) = \frac{n_{jk}^{f_i}}{n_{jk}^{nf}} \quad (1)$$

The framework represents the actual experiment through the capture and modeling of core elements relevant to the study. Simplified ontologies and rules for the biology domain (cell, vaccine and pathogen) and the experiment domain (parameters, set up) are created and integrated as described in Section III. The behavior of the VV is modeled using instances of the simple MC pictured on the top left corner of Figure 2. The states $S_p$ ($p \in P = \{20, 40, 60, 80, 100\}$) represent the virulence of the vaccine, which can only degrade from $p = 100\%$ to $p = 20\%$ in this simplified prototype. The transition probabilities depend on the experimental setup and they are driven by a "degradation factor" $k_{ijk}^{tf}$ which characterizes the ability of the system to maintain itself in a state $S_p$ under the given experimental setup. It's defined as follows.

$$k_{ijk}^{tf} = \left[\frac{T_{Max} - t_j}{T_{Max} t_j (100 - C_{f_i})}\right]^{\frac{d_k}{d_{Max}}} \quad (2)$$

where $T_{max}$ is the maximum allowable exposure temperature for the experiment and $C_{f_i} \in (0, 100)$ is a coefficient characterizing the "degradation resistance" of a given formulation. One such formulation for the OPV can comprise antibiotics Neomycin and Kanamycin as preservatives and $MgCl_2$ as stabilizer. As indicated in research Topic 2, design of experiments is a way forward to narrow down the list of candidate formulations. The transitions between states ( $S_p$) are computed as follows.

$$a_{ijk}^{tf}|_{p,q} = (1 - \Delta_{ijk}^{tf}|_{p,q}) k_a k_{ijk}^{tf} \quad (3)$$

where $\Delta_{ijk}^{tf}|_{p,q}$ is the gap of virulence between a state of virulence $p$ and one of virulence $q < p$ in $P$ and $k_a > 0$ is a balancing coefficient allowing the probabilities to sum to 1 as per Markov Chains modeling rules. We note that $a_{ijk}^{tf}|_{20,20} = 1$ to capture the fact that any decrease of the virulence of the VV below 20% is beyond the sensitivity level of our analysis thus, not relevant. This results into a full MC model driving the generation of the values of $n_{jk}^{f_i}$ and $n_{jk}^{nf}$ that we use to calculate the infectivity of the VV when mixed with the cell. The MC is implemented as a built-in function linked to the rule that determines the value of the infectivity based on the experiment setup. Given the small size of our prototype input/output data, there is no need to implement full data models for this instance of the framework.

### B. Results

For the prototype simulation, we select three formulations $f_i$ with low ($C_{f_1} = 5$), medium ($C_{f_2} = 50$) and high ($C_{f_3} = 95$) degradation resistance. Also, we assume the VV samples are conserved at ambient ($t_1 = 25^0C$) and body ($t_2 = 37^0C$) temperatures respectively, over selected periods of duration $d_k \in (1, .., 30)$ days. In order to assess the performance of our formulations, we refer to the acceptable infectivity threshold for administration of oral polio vaccine, which is $inf_{ijk} = 40\%$ [19]. The latter is known as the "infectivity threshold" below which the formulation is considered ineffective to ensure full potency of the vaccine. Figure 4 shows the result of the simulation for $t_1$ with $T_{Max} = 40^0C$. The formulations outperform each other as their $C_f$ is higher up to the 2/3 of the maximum exposure time around $d = 20$ days, right before the potency baseline is crossed (around $d_b = 21$ days for all). After that, there seems to be no

additional benefit in higher $C_f$. Similar results (not shown) are observed for $t_2 = 37^0C$. This suggests that this vaccine should be considered ineffective after 20 days of continuous exposure to higher temperatures ($t \geq 25^0C$), no matter the formulation used. However, this result needs to be verified through laboratory experiments. The results will be used to refine the model defined and introduced in this work (for the given vaccine), and will then be validated through actual observations on selected vaccine formulations.

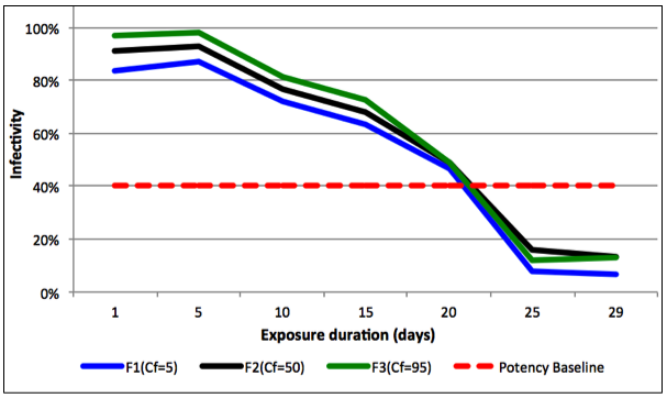


Figure 4. OPV infectivity simulation results at $t = 25^0C$ for 3 formulations

## VI. Conclusion and Future Work

An innovative, semantically-enabled framework for knowledge and behavior specification, modeling and processing for vaccine systems engineering has been presented in this paper. This work is motivated by the limitations of current vaccine development approaches in capturing, representing and reconciling domains and disciplines knowledge and viewpoints across the vaccine development life cycle in an effective manner. As a result, vaccine development is a long, complex, and costly process that often results (when it succeeds) in vaccines whose potency is hard to predict and expensive to preserve. Current limitations are compounded by the highly stochastic nature of biological components involved (e.g., vaccines, pathogens) and knowledge disconnect between chemists, biologists, clinicians and the public stemming mostly from the lack of intuitive understanding of biological components and processes. In this work, we have shown that the implementation of a knowledge-driven framework is a promising and feasible solution that can result into successful vaccine systems engineering. Data and semantic models of domains supported by sound theories and tightly coupled with Markov Chain models of biological systems are the cornerstone of our approach. A key benefit is the ability to represent the system at various levels of abstractions in conformance to stakeholder viewpoints and the problem at hand. The core capabilities of the framework have been successfully demonstrated in a prototype vaccine preservation study.

Bringing the benefits of the framework introduced in this work to day-to-day work of stakeholders across the VDLC necessitates further work. This should include the refinement and validation of the framework for various vaccine types, analyses and cross-cutting concerns (e.g., potency, preservation, safety) and various environmental conditions. Design of experiments (as indicated in Topic 1) and actual laboratory, production and field assessment will be needed. Collaboration between stakeholders (including Systems Engineers) along the VDLC needs to be fostered in the development of domain and discipline knowledge used by the framework. An expansion of ongoing efforts in ontology development (e.g., vaccine ontology) is highly suitable [20].

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