Platforms for Engineering Biomedical Experiments

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***Abstract*—Due to the highly stochastic nature of biological systems, the systematic design, validation, and verification of systems for biomedical experiments in laboratory and clinical applications are complex activities. This paper presents a platform framework for the modeling of these biological components in the context of system-level analysis. By integrating models of biological systems with those of physical engineering systems, one can obtain a set of potential architectures that satisfy the requirement specifications of the application. Such models can aid in the analysis of biomedical systems intended for applications in medical science, where the stochastic elements are the biological components themselves. A prototype application is presented that implements this platform framework for the development of a microfluidic assay device for the study of antibacterial treatments of bacterial biofilms. The results of our work indicate that looking forward, platforms will facilitate early validation and verification of biomedical devices, and enable the development of more efficient and effective experimental biomedical systems.**

***Index Terms*—Biological system modeling, biomedical engineering, system-level design, systems engineering.**

I. Introduction

MODEL-BASED systems engineering (MBSE) procedures are concerned with the development of modern-day systems through the use of models as opposed to documents. As engineering systems become increasingly complex, a key challenge is maintaining designer productivity and good economics through the use of strategic approaches to system-level design [1]. Within the worlds of large-scale electronic systems and automobile design, platform abstractions are appealing to designers because they provide a means to simplify design concerns and efficiently explore the space of potentially good design solutions [2], [3]. During the past few decades, the biomedical research community has focused their efforts on the development of devices to support a wide range of experimental purposes. The design of these devices is complicated by the stochastic nature of biological systems, and the large range of spatial and temporal scales that are of interest to researchers and clinicians. Present-day procedures for the synthesis and design of system-level architectures for experimental setups have remained largely *ad hoc*, although it is clear that reuse of "good architectural designs" from one experimental setup to the next would have performance and economic benefits. A second key weakness is the lack of an explicit pathway from biological and engineering concerns to features of an experimental setup, the data that are measured, and the algorithms that process it into information for decision making. The existence of such a pathway, which is known as traceability in the MBSE community, increases the accuracy and completeness of the design process as a whole and provides a means to model cause-and-effect relationships between experimental purposes and observed biological conditions. In turn, this capability improves the quality of decision making that is possible during experimental procedures and in the longer term, redesign of experimental facilities. A few investigators have recently applied platform ideas to the design and implementation of very specific systems involving biological and biosynthesis applications [4], [5]. In a first step toward closing these gaps, the main contribution of this paper is an exploration for how platform abstractions can also add value to the system-level design of experimental biomedical systems.

A. Experimental Biomedical Systems

Biomedical systems designed for experimental purposes are a vital aspect of today's medical field, from bench-top systems driving advances in biological science to bedside point-of-care devices in the clinical realm. Devices aiding medical researchers in advancing the science and knowledge of physiological processes allow for the continued development of new medicines and treatment methods. Similarly, devices that are capable of providing accurate diagnoses and prognoses of patients are necessary if this developing knowledge is to help clinicians improve the health and safety of future generations.

The difficulty in developing systems for biomedical assays is complicated immensely by the variant nature of biological systems [6]. The growth of living organisms is dependent upon a large number of factors unique to each system, including physiological processes, genetics, and environmental conditions. Thus, the same set of system inputs do not always result in the same set of outputs, making the design, validation, and verification of biomedical devices exceedingly difficult. Furthermore, systems designed for experimental purposes in the biomedical field are becoming progressively more technical [7]. Researchers are now interested in biological processes at the molecular level in an effort to treat ailments at their source, whereas clinicians desire tools capable of faster, more accurate, and less invasive patient analysis. Due to this added complexity, the development of biomedical systems is becoming

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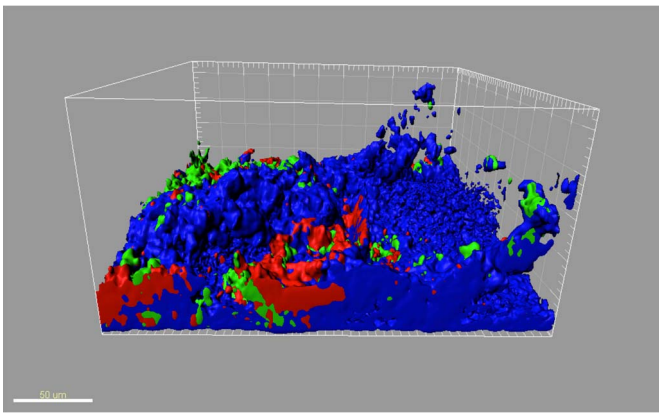

Fig. 1. Surface reconstruction of a bacterial biofilm grown in a microfluidic device, showing the highly variant nature of commonly studied biological systems.

increasingly difficult and costly, since current methods for system-level design are not capable of evaluating the highly stochastic properties of biological components [6]. Looking forward, new methods of designing experimental biomedical devices are needed if advances in medical science and treatment are to maintain or accelerate their current pace. The knowledge disconnect that exists between biological and engineering domains only aids in further compounding this design problem [6]. Due to the complex nature of biological systems, extensive knowledge of the field is typically limited to biologists and clinicians who are well versed in their areas of expertise [8].

A good case study for engineering experimental biomedical systems is the treatment of bacterial biofilms. The growth of bacterial biofilms, such as that shown in Fig. 1, for example, has been linked to as many as 65% of all microbial infections in the human body [9]. Biofilms are complex communities composed of communicating groups of bacteria, as shown in green/red in Fig. 1, and an extracellular matrix (ECM), as shown in blue [10]. The presence of the ECM limits molecular diffusion within the biofilm, whereas bacterial gene exchange in the biofilm structure promotes the development of antibiotic resistance [10], [11]. As a result, bacterial biofilms often require 500–5000 times the concentration of antibiotics for effective treatment compared with bacterial suspensions, making them of great interest in public health fields [12]. Such communities of microbes naturally display stochastic growth characteristics, making prediction of their development a limiting factor to design engineers working toward new methods of treating or investigating these biological systems. Thus, while biologists or clinicians may understand the intricacies of the biological system but not the technologies required to address their application, the design engineer may understand the state-of-the-art but lack the clinical background to apply this knowledge to applications involving biological systems.

B. Integration of Biological and Engineering System Domains

To address this problem, design techniques must implement a method enabling validation and verification of system performance in the context of highly stochastic biological components, thereby assimilating the two domains [6]. Drawing upon the capabilities of systems engineering tools to model systems in the design phase, the development of platforms for engineering experimental devices is a large step toward producing more effective biomedical systems.

Fig. 2 presents the method by which these platforms allow for the integration of biological and engineering system domains. The application space defined by the clinician or biologist provides the necessary knowledge to model the operation of stochastic biological components. The developed platforms then allow for the integration of biological models with potential system architectures to create an overall design space that can effectively address the system requirements. In order to capitalize upon the added capabilities of such a technique, two key tenets of this paper are that: 1) engineers must develop methods to succinctly model a breadth of biological systems; and 2) these models must be able to integrate with system-level models capable of describing the performance of the entire engineering system. Current methods and techniques for experimental biomedical-device development simply are not capable of such full-system modeling.

II. Scope and Objectives

In order to address the limitations of current design methods for experimental biomedical systems, the work here presents platforms for the modeling, validation, and verification of device systems that contain highly stochastic biological components. By integrating models of biological systems with those of physical engineering systems, one can obtain a set of potential architectures that satisfy the requirement specifications of the application. Such models can aid in the analysis of biomedical systems intended for applications in medical science, where the stochastic elements are the biological components themselves. The models can also help with systems for patient diagnosis and prognosis, in which the stochastic elements are the physiological responses of patients to a particular assay.

By successfully implementing such platforms, device designers and engineers can ensure that results obtained from experimental tests are trustworthy representations of biological system development. These same techniques can also prevent unstable operation of the final system architecture by enabling early detection of design flaws that would be otherwise unforeseeable using traditional design methods. Fig. 3 shows ways to implement these concepts at various levels of abstraction. Semiformal models of the proposed system architecture, using modeling languages, such as the Unified Modeling Language (UML) and System Modeling Language (SysML) [13] can provide engineers with a high-level understanding of system performance and the nature of the design space, thus aiding in more efficient and cost-effective redesign, validation, and verification. These semiformal models are supported at lower levels of abstraction through detailed simulations of the system, including components to embody the stochastic biological elements. Integrating these stochastic components with well-defined physical systems enables researchers to place more confidence in the experimental testing of biomedical devices than they could previously. The benefits of this approach are far reaching: engineers, biologists, and clinicians can work together

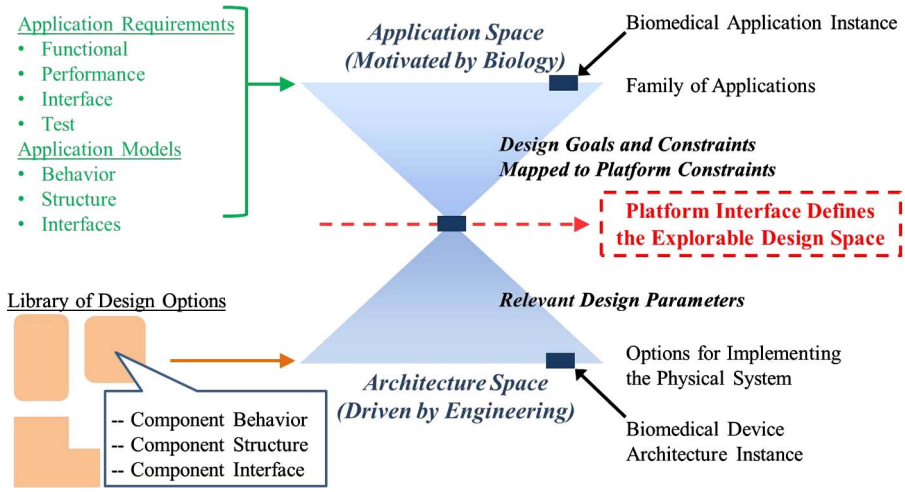

Fig. 2. Design space is defined by: 1) an application space driven by biology; and 2) an architecture space driven by engineering.

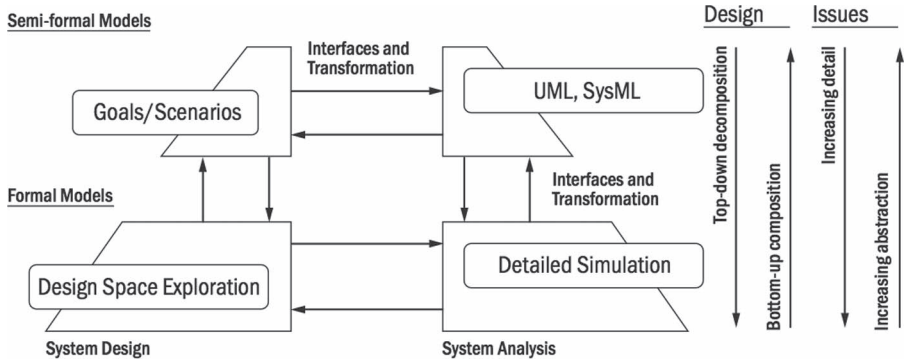

Fig. 3. Abstraction as a tool for the design of biomedical systems with integrated models of stochastic biological components.

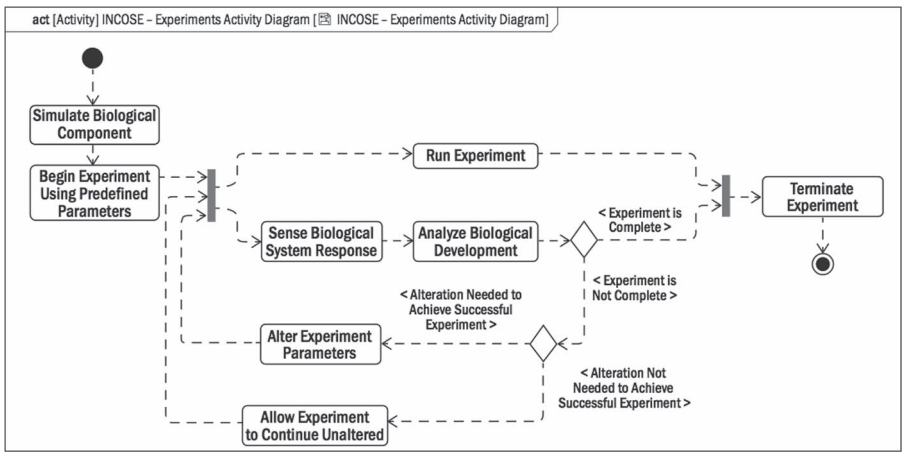

Fig. 4. SysML activity diagram showing the process flow of typical biomedical experiments.

to develop devices that are best suited for their applications, and thus most beneficial to clinicians, patients, and medical researchers.

III. Experimental Biomedical Systems

A. Experimental Processes

A typical experimental process utilizing a device architecture is shown in Fig. 4. The researcher or clinician begins with a hypothesis about their subject that is developed from prior data or patient symptoms [14], [15]. For a medical researcher or systems biologist, this hypothesis may involve a parameter or process that the experiment is intended to verify. Examples commonly include a metabolic process, the effects of a compound on a biological system (such as a candidate drug), or verification of the unique characteristics of a particular organism. For the clinician, a hypothesis may involve a patient diagnosis or prognosis, or may be geared toward determining an effective treatment for a patient's patient verified medical condition. With this hypothesis in place, an experiment begins

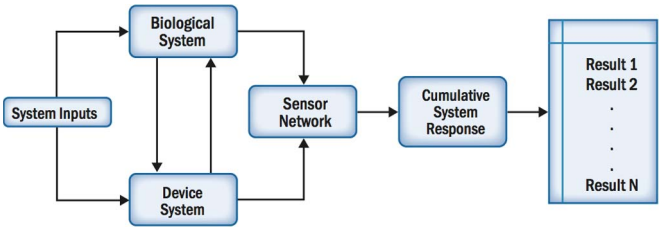

Fig. 5. High-level system architecture of biomedical device performance.

under ideally controlled conditions. At the conclusion of the established assay, the researcher or clinician inspects the outcome to determine whether the test was successful, or if alterations or repetition of the experiment is required. Due to the highly stochastic nature of biological systems, such a feedback process is common in order to verify experimental results. The goal of the design engineer is to develop device systems that can aid in reducing the number of iterations needed to achieve a required level of confidence in the result. This is particularly important in clinical applications due to the patient discomfort often associated with invasive testing (for instance, prick tests to determine skin allergies). Similarly, current medical research often utilizes high cost, low throughput methods of testing, giving strong motivation for the development of methods to limit the number of iterations needed to verify an experiment.

In order to break from the current limiting approach to biomedical device development, new techniques are needed to aid in the maturation of new device systems. The novel platforms presented here are a first step toward such methods, which can increase the overall efficiency of both device development and the operation of the devices themselves by optimizing the interactions of biological elements with the physical system.

B. Architectures for Experimental Biomedical Systems

While the physical structure of biomedical devices is diverse and typically suited to the needs of the particular application, most systems can be abstracted to the system architecture shown in Fig. 5. System inputs are typically comprised of a number of different domains, including environmental conditions and actuation or application conditions (that is, what is done to the biological system during the experiment). Depending upon the requirements of the assay, the physical device system can take any number of forms but will typically have three distinct structural elements: 1) a way to contain or integrate with the biological system or sample; 2) a way to control experimental conditions; and 3) a way to integrate with a sensor network for detection. The sensing mechanisms utilized for experimental devices also vary depending upon the application, although they typically aim to optimize a tradeoff between minimal invasiveness and achieving the required detection limit and sensitivity of the application. The cumulative effect of the physical system's interactions with the biological element results in a set of potential experimental results, each having a unique probability of occurrence. These probabilities are dependent upon the stochastic biological system, providing at the simulation level a range of statistically relevant outcomes that can be used to confirm experimental results.

Fig. 6 provides a high-level implementation of the system elements and their interactions at the component and subcomponent levels. Most biomedical devices are constructed through a similar architecture, providing strong support for the development of generalized platforms for experimental device engineering. The platforms subsequently discussed exhibit a flexible structure that can be adapted to numerous applications in the biomedical field, thus expanding the scope and influence of this paper. The development of libraries of components to represent physical system and sensory network elements would aid in the efficient development of new devices and the adaptation of existing devices to new application areas. Additionally, formal platforms capable of integrating such libraries with models of the stochastic biological components enable full-system modeling. This modeling can effectively aid efficient and proper design, validation, and verification of biomedical systems. Implementation of such a platform using existing systems languages like UML and SysML takes advantage of the maturity of these engineering tools, where implementing extensions to other modeling domains is a well-established practice. A tool for the succinct mathematical modeling of stochastic biomedical components would be such an extension of this platform.

IV. Mathematical Modeling of Biological Systems

In order to enable analysis of biomedical-device performance, engineers and designers require tools capable of accurately modeling the development of biological system components. These models must be able to simulate the development of the biological system over time, as well as predict changes of the biological system due to experimental conditions. In doing so, these models can then be integrated with higher level models of the overall experimental device to complete the platform architecture. A number of modeling methods exist for biomedical systems, and these methods differ in their modularity, implementation, and overall accuracy. We focus on one particular method, Markov chains and hidden Markov models, as particularly suitable for biomedical device applications [15]–[18].

A. Markov Chains and Hidden Markov Models

Markov chains and hidden Markov models provide a method of modeling probabilistic systems with finite states [18]. While this method has existed for over a century, only recently has it begun to see significant use in engineering applications to understand the development of systems over time. Additionally, Markov chains and hidden Markov models have been used in a number of other fields to model and predict the development of highly stochastic biological and population schema in order to emulate and predict their function [17], [19]–[21].

A Markov chain model can be easily visualized as a set of states, each with a probability of propagation to a future state. Fig. 7 shows a simple Markov chain. Each state of the Markov chain model represents a physical system state, with arrows showing the probability (a_{XY}) of propagation from state X to state Y in one time step. The sum of all propagation probabilities from each state must sum to 1.0, with feedback or

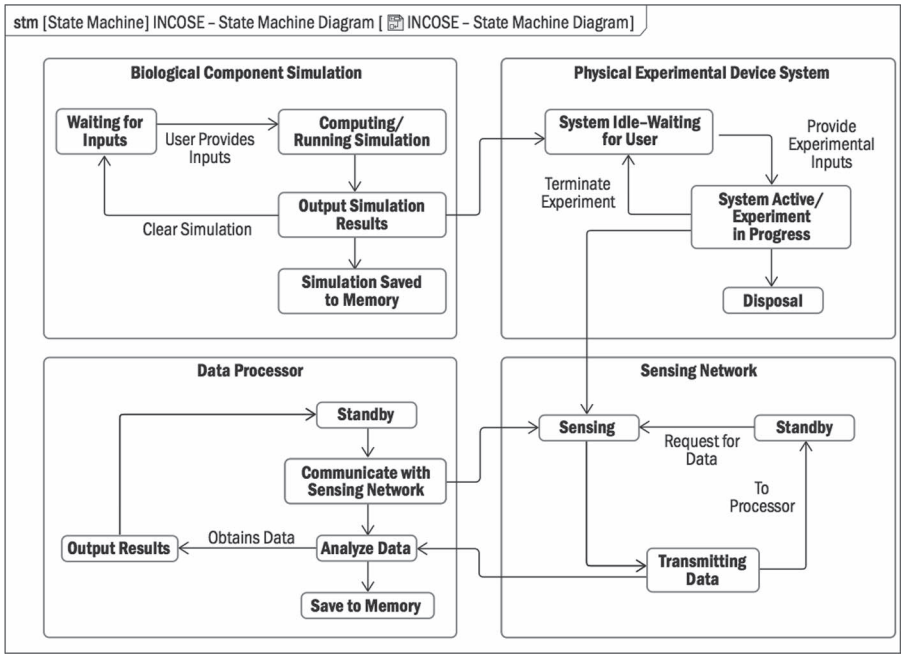

Fig. 6. SysML state machines of biomedical device components.

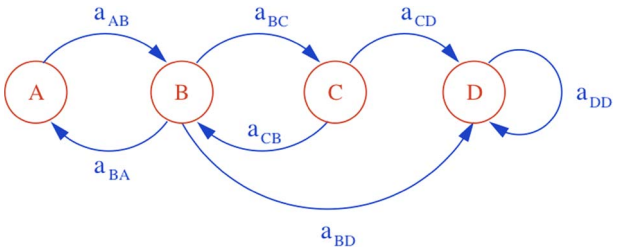

Fig. 7. Markov chain showing propagation between system states.

steady-state operation between states also being possible. Additionally, segmentation and hierarchical Markov chain models are also possible, where the probabilities of a state's propagation may be dependent upon the current state. Such a technique is easily scalable and enables the effective modeling of highly complex systems in a manner that is intuitive, adaptable, and quick to implement or alter [18].

Hidden Markov models are an extension of the Markov chain concept, where the Markov chain or network of interacting Markov chains are developed based on observed real-world performance. Behavior of a system, be it discrete in nature or a continuous spectrum, is tracked and documented. A Markov model is then developed to fit the system performance. This model then enables further analysis or prediction of future system functionality [18]. These models appear "hidden" to the model developer, who may not initially know how system states are related to the probabilities that govern fluctuation between states.

These characteristics make the use of Markov chain models and Hidden Markov models a preferred method for the representation of biological systems. Highly complex biological phenomena have already been modeled with considerable success through the use of Markov chains. Kim *et al.* [17] have successfully developed a Markov model for the progression of melanoma in patients, where data were based upon the predictive relationships between 587 independent genes. By determining the factors of greatest importance to the development of the melanoma cells, a Markov model describing ten interacting genes was produced that very nearly matched the real-world development of the system (steady-state convergence of all states was higher than 0.05 significance level). Since the development of a biological system, such as melanoma, is a continuous spectrum, physical states are lumped to collective state vectors, thus enabling a succinct analysis of the biology. This same technique can be expanded to any number of other biological systems at varying levels of abstraction. A medical researcher in the field may be interested in the physiological changes of a system at the molecular level, thus encouraging the development of a Markov model to emulate these processes in the context of a larger biological system. Similarly, a practicing clinician may be more interested in overall patient response to a particular assay, thus encouraging the development of a Markov model to predict system response at a higher level of abstraction.

In each case, such a technique is extremely valuable to a system designer attempting to develop biomedical devices for these varied applications. Established techniques are generally available to provide biological system data in all but the most complex instances. Systems biologists and medical researchers can utilize these data to formulate simplified models of the highly complex biological systems that, in turn, become valuable assets to the design engineers. The intuitive nature of Markov models enables the engineer to not only design and simulate a system with stochastic biological components but also to bridge the knowledge gap between complex biology and the engineering of complex biomedical devices [15], [22]. In doing so, the validation, verification, and potential redesign of a physical system for experimental biomedical applications can be optimized to a point that is not currently achievable using established system modeling techniques.

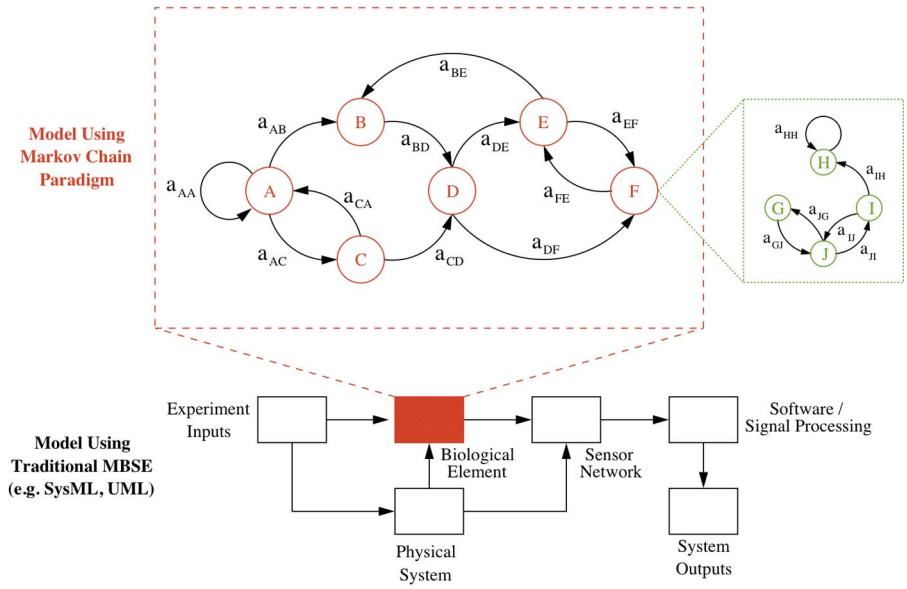

Fig. 8. Platform implementation for engineering experimental biomedical device systems.

V. Platform Implementation

By combining the modeling mechanisms available for physical engineering systems with the Markov modeling techniques presented for biological systems, a comprehensive platform is realized for the full-system design of experimental biomedical devices. Borrowing from the high-level system architecture in Figs. 5 and 6, this framework platform creates a union of the biological and engineering domains that enables the simulation of a full biomedical system. Fig. 8 showcases how such a union is achieved, where the biological element is modeled as a component in the system architecture.

It is possible to model the full-system architecture by using established modeling platforms, such as UML and SysML, since many of them have reached a level of maturity to support extensions to other languages and tools. In order to utilize the platform for overall engineering of the biomedical system, the implementation process follows a straightforward path. The following high-level view of this process outlines the steps useful for the holistic design of experimental biomedical systems, where the implementation of these steps is application dependent:

1) Gather relevant data of the biological system at a level of abstraction coincident with the application requirements. These data will be used to formulate a Markov model of the biological system component.
2) Formulate a Markov model describing the biological component. An iterative process is often used to achieve convergence of such a model, as well as to define the appropriate segmentation of finite states for continuous systems [17], [18].
3) Represent the validated Markov model using a tool capable of integrating with the physical system model. This biological element will exist as an extension from the modeling platform (e.g., SysML or UML) used to define the larger device system.
4) Design the proposed physical device components and how these components relate using the modeling platform. An additional component should be also represented in the system model that will extend to the biological component.
5) Perform simulation, validation, and verification of the complete system model. The results of these analyses will provide a means of redesign and device optimization for the particular experimental application.

The outputs generated from this system analysis provide a range of potential experiment outputs based on the operation of the physical system and the development of the stochastic biological system. The value of obtaining such a resultant set is paramount to the design engineer, as it allows them to directly address real-world concerns that are not otherwise visible in the design phase. In the prototyping phase of device development and beyond, this same analysis can be used to verify proper device operation to confirm the results of experiments and to detect and avoid undesirable system performance. Such analyses are currently difficult and exceedingly time consuming using established methods, giving a platform for experimental biomedical-device development considerable value to the medical field as a whole.

VI. Medical Drug Screening for Antibiotic Development

This section presents a prototype application of the presented platform for engineering experimental biomedical systems. Drug screening for the development of new pharmaceuticals is a major area of concentration in the biomedical field. In order to enable high-throughput screening of prospective antibiotics for bacterial infections, a microsystem was developed that is capable of arrayed experiments and non-invasive sensing.

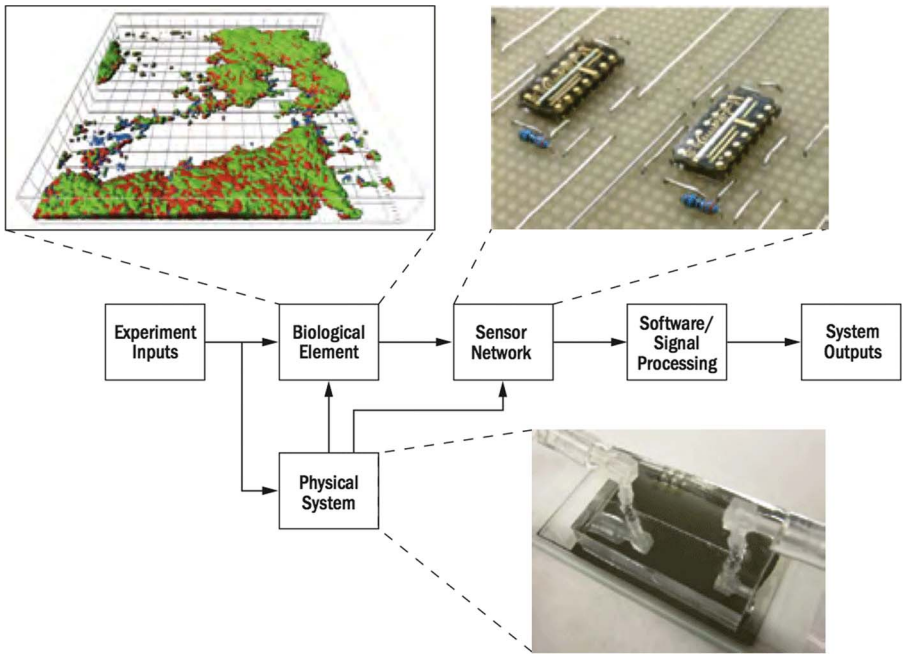

Fig. 9. Bacterial imaging is performed using confocal microscopy and the microfluidic device is fabricated using soft lithography in system outputs polydimethylsiloxane. The sensors are charge-coupled devices with 128 × 1 pixel arrays.

A. Prototype Application

The developed system contains all of the architectural components previously mentioned in this article. A microfluidic platform provides a physical module capable of containing an environment suitable to the development of a biological system, in this case an infectious bacterial biofilm. Additionally, a sensor network external to the microfluidic device enables continuous monitoring of bacterial growth or colony formation, where the cumulative outputs of the system can have a range of possibilities depending upon the stochastic biological system. Such architecture makes this application an ideal candidate for the use of the proposed design platform, since reliance on the biological component makes system performance difficult to predict.

The device itself utilizes a microfluidic channel to grow bacterial biofilms under controlled conditions. The mature biofilms are then treated with candidate drugs in order to determine their levels of efficacy in depleting the bacterial films. Bacterial cultures, growth media, and the candidate antibiotics are supplied to the device via interface tubing, which allows an external syringe pump to control flow rates in the system. Sensing of bacterial growth is achieved through optical density (OD) detection. As the biofilm grows, it becomes increasingly absorbent to incident light (optically dense), thereby enabling biofilm monitoring via the amount of light transmitted through a biofilm sample [23]. Sensing of this transmission is achieved by a 1-D array of photopixels placed underneath of the microfluidic growth chamber, where the analog voltage output of a particular pixel in the array is inversely proportional to the biofilm OD in the corresponding region of the microfluidic chamber. In practice, each pixel of the array is periodically polled, e.g., every 5 min, to obtain data indicating the OD of the biofilm within the microfluidic channel proximate to each pixel at that point in time. The change in OD for a region of biofilm corresponding to a particular pixel of the array can be traced over time by computing a change in OD. Similarly, the optical densities measured by each pixel of the array may be averaged to determine an estimate of the overall OD of the biofilm in the microfluidic channel at a particular time. An estimation of the overall biofilm OD can be computed each time the pixels of the array are polled to determine the overall change in biofilm OD with time. The change in OD ($\triangle$OD) for a particular pixel is computed as the negative logarithm of the ratio of the analog voltage output by the pixel at a particular point in time to an initial analog voltage output by the pixel (at time $t = 0$), i.e., $\triangle \mathrm{OD} = -\log 10(\mathrm{VCCD}/\mathrm{VCCDo})$.

The advantage of this sensing mechanism is that it provides a means of non-invasive and continuous detection of biofilm growth that is otherwise difficult to obtain [24]. Additional study of the biofilm is achievable through end-point measurements of density and morphology using confocal microscopy. Fig. 9 provides an overview of this architecture with the system components highlighted via images of the prototyped devices.

A Markov model of the bacterial biofilm component enables the formal validation and verification of this biomedical system. The current high-level model of the biofilm development process is implemented through the use of the tool presented by Yang. To investigate target characteristics of the network, an engineer uses the software package to specify a network of interacting Markov chains (referred to as Markov chain cells in this paper) that simulates interactions in these cells. Through reduction techniques utilizing symmetry in the Markov chain network, highly complex models can be analyzed that would otherwise go beyond the computational capacity of most systems [25].

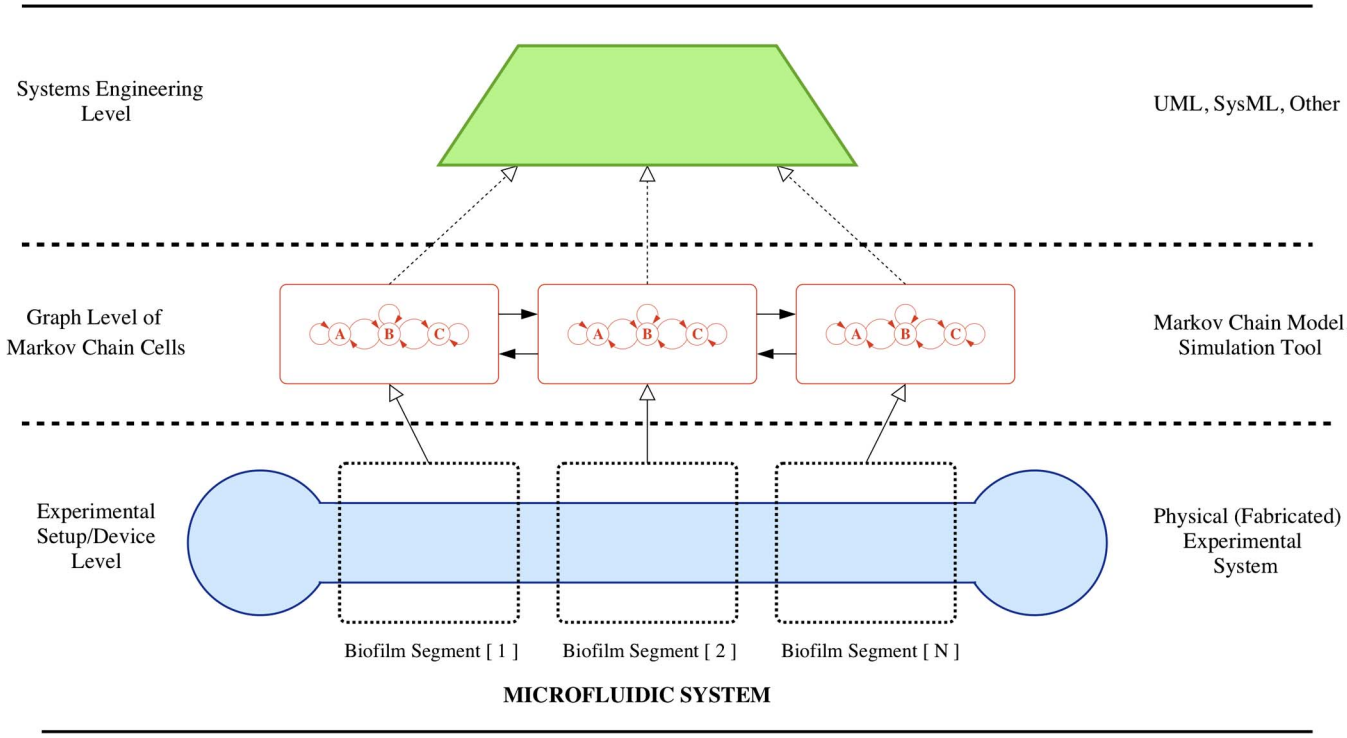

Fig. 10. Visual representation of the biofilm Markov-model implementation.

The Markov chain network used to describe this system is comprised of two distinct domains: the physical conditions of the experiment that affect the bacterial biofilm and an array of identical Markov cells to describe the biofilm structure. Biofilm Markov cells represent discrete sections of the film within the microfluidic chamber, where the state of each cell is dependent upon the states of adjacent cells, as well as the states of the experimental conditions. Fig. 10 shows the abstraction of the bacterial biofilm system as it is currently implemented and follows directly from the architecture presented in Fig. 3. As this Markov model continues to mature, a clear path is to expand the model to a generalized 2-D biofilm with a suite of influencing experimental factors. Such advancements will permit the model's use in any number of biomedical design processes for applications dealing with bacterial biofilms.

B. Modeling of a N-Cell Biofilm

An N-cell biofilm was modeled with two key experimental condition variables: nutrient concentration in the system growth media and damaging shear stress due to fluid flow around the film. Each of these variables was provided binary values (low or high), and the biofilm elements were simplified to a system of three distinct states (reduced, moderate, and mature). The next-iteration state of each biofilm element is dependent upon its own cell's current state, the current states of its adjacent cells, and the current states of the experimental conditions. Using Bayesian statistics, Yang *et al.* [25] found that the number of states for the biofilm model was

$$X = 2 * 2 * 3N. \tag{1}$$

Through the tool's symmetry reduction methods, the system simulation was condensed from this set of possible states to a model with $0.75 * X$ number of states, a 25% decrease in the overall model size. By establishing an observer in the tool to track the number of biofilm cells in each of the three developmental stages, a full spectrum of theoretical biofilm growth characteristics is obtained that agrees with intuitive expectations (i.e., a near Gaussian profile). Future improvements to this model and its implementation in the simulation tool are expected to reduce this model even further, as previous implementations of its symmetric reduction principles have achieved orders-of-magnitude reductions in system size.

C. Experimental Device and Procedures

Analysis of the prototype device of Fig. 9 enables further improvements and development of the microsystem. To reduce the footprint of the microsystem and the number of complex connections to external fluid sources and flow rate controllers, six microfluidic growth chambers and accompanying photopixel arrays are integrated in parallel and on a single chip. The photopixel arrays and supporting electronics are integrated on a printed circuit board (PCB) fixed beneath and aligned to the microfluidic channels, with external electrical connections to the PCB occurring via a single pair of electrical connectors.

The resulting microsystem shown in Fig. 11 further optimizes several critical factors of the drug screening device. First, the microsystem features increased capabilities for parallel assays compared with traditional systems used in biofilm studies, such as cell colony counting or fluorescent or confocal microscopy, which require large-scale machinery to operate and are limited to performing end-point measurements on a single

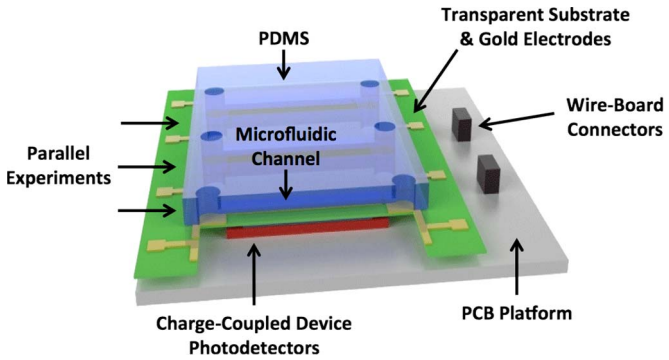

Fig. 11. Full-system schematic of the integrated microsystem. The device is based on a PCB platform supporting system electronics, external connectors, and the charge-coupled devices used to detect changes in biofilm OD. Microfluidic channels formed in PDMS enable six parallel experiments on a single chip. Patterned gold electrical contacts allow for electrical signals to be applied to biofilms [26], [27].

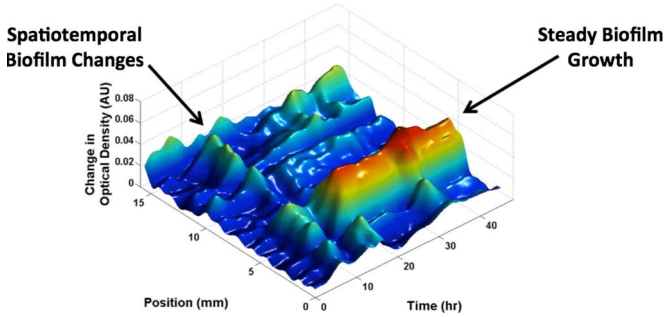

Fig. 12. Spatiotemporal changes in biofilm OD over time. An E. coli biofilm is matured in a microfluidic growth chamber over 48 h. Spatiotemporal measurements obtained by a charge-coupled device integrated with the microfluidic growth chamber are captured periodically to determine changes in biofilm OD over time. The resulting data display spatiotemporal changes in biofilm morphology, including the presence of dense biofilm segments flowing through the microfluidic chamber, as well as static areas of high-density biofilm growth.

biofilm sample at a time. Second, the developed microsystem uses reduced fluid sample volumes for drug screening experiments on the scale of several microliters, as compared with the milliliter volumes required in larger systems. Third, the developed microsystem provides capabilities for enhanced experimental control, including temperature, sample flow rate, etc., as the developed system can be operated within environmental control chambers, such as incubators and can utilize precise instruments for providing fluid samples to the biofilms, such as syringe pumps. The developed system provides increased sensing reliability and precision through the use of robust electrical connections in the integrated PCB and off-chip integration with data acquisition and instrument automation software.

To evaluate the capabilities of the developed microsystem for antibiotic drug screening, a series of biofilm growth experiments are conducted, in which E. coli biofilms are matured within the microfluidic growth chambers and biofilm OD measurements provide insight to average and spatiotemporal changes in biofilm OD. Results of the studies obtained by OD monitoring are verified through conventional microscopy methods (not shown). Fig. 12 shows results of these studies, in which spatiotemporal changes in biofilm OD are tracked over a period of 48 h as the biofilm matures. Specifically, biofilm OD measurements are periodically obtained by each pixel of the 1-D array, such that spatiotemporal changes in OD can be traced with time. As shown in Fig. 12, such spatiotemporal changes can include the propagation of biofilm mass along the microfluidic channel with time, as indicated by the left-hand arrow in Fig. 12, as well as the growth of biofilm in a fixed location in the microfluidic channel, as indicated by the right-hand arrow of Fig. 12. By plotting spatiotemporal changes in biofilm OD, one can gain increased insight into biofilm development and treatment that is not obtainable by traditional microscopy or cell colony counting methods.

VII. Discussion

A. Experimental Biomedical System Capabilities and Limitations

Our prototype application utilizes high-level system models of bacterial biofilm structure and of an experimental device for performing drug screening studies relating to the development of antibiotic treatments. The current state of these models is such that the modeling of biological system development and experimental device operation are generally distinct from one another. Simulation results pertaining to the biological biofilm component are considered with respect to the development of the device system, for example, to determine requirements of the device system for detecting the presence of reduced, moderate, and mature biofilms. Thus, the biofilm model represented by the Markov chain of interacting biofilm segments, forms a basis for requirements development with respect to the device system. The current biofilm model provides results that track our expectations of biofilm growth, and can be described in terms of environmental conditions, including flow-induced shear stress and available nutrient concentrations within microfluidic growth chambers.

The biofilm model demonstrated in this paper represents a proof of concept architecture for the modeling of bacterial biofilms as biological systems. Consideration of additional environmental conditions, variables accounting for biofilm treatments methods, and variables describing the biological biofilm system can aid in increasing the accuracy and granularity of the current bacterial biofilm model without losing the advantages of abstracting the complex biological system [3], [4], [22]. Additionally, data from prior bacterial biofilm studies may be integrated with learning techniques, such as the Viterbi method and others, to further tune the established biofilm model.

While the current biofilm model functions as a separate entity from the physical system model that defines the prototype drug screening microsystem, results obtained from bacterial biofilm simulations drive the design of the current drug screening microsystem. This technique enables optimization of many factors relating to the design of the device system, and further interfacing of the device and biological system models will further reduce the efforts of system developers, as modifications in the device or biological system regimes will have traceable effects on the operation of the device or on the development of the modeled bacterial biofilm [1], [2]. As the biological system model matures, we anticipate new applications to antibiotic

treatments and/or industrial bacterial colonization will be possible, for example, to water purity [5].

B. Prototype Device for Drug Screening Applications

The prototype device system developed here has value beyond the presented work as a research tool for scientific studies in microbiology and drug research by leveraging the unique advantages of the platform. Integration of linear photopixel arrays provides insight into both average and localized changes biofilm OD, such as localized growth, detachment, or aggregation of biofilm mass. In comparison to traditional methods of imaging biofilm structure and morphology, including confocal and fluorescence microscopy, this platform demonstrates sufficient resolution and detection limits for biofilm investigations without the bulk or expense associated with these systems. As discussed, modeling of the bacterial biofilm system aided the tuning of design parameters relating to the prototype device, for example, to ensure device sensitivity for the spectrum of biofilm development stages. Furthermore, the high throughput experimental capabilities of the platform, using controlled sample flows and small volumes with high environmental control [28]–[32], aids other microbiology studies that typically utilize static growth environments and require time-consuming experiment repetition due to the natural variance of microbial growth [24], [33]. The developed platform enables the correlation of OD measurements to other common measurements, such as optical absorbance, with limited calibration. Additionally, in contrast to traditional detection methods, such as confocal microscopy, fluorescence microscopy, or bacterial colony counting, that are limited to end-point evaluations of biofilm structure and density, the developed system enables monitoring of overall and spatiotemporal biofilm changes in real time. The capabilities of the developed prototype to perform high throughput drug screening tests with real-time, *in situ* measurement gives promise for the continued development and use of the prototype system in future microbiology and drug screening research efforts.

VIII. Conclusion and Future Work

A. Conclusion

State-of-the-art procedures for the design of biomedical systems for experimental purposes are less than ideal. From the standpoint of clinicians, patients, and medical researchers, the causes of less-than-optimal system performance can often be traced back to knowledge disconnects between biologists and engineers. The platform solution proposed in this paper enables the development of biomedical systems that consider both biological phenomena and engineering requirements in a unified view, without the compromise of information that currently characterizes device development in biological and biomedical fields. Biomedical systems and biological experiments developed under this paradigm can achieve greater efficacy and efficiency than is currently possible given the current methods of device development.

The proposed method has been validated in an application involving development of bacterial biofilms in microfluidic devices. Markov chain models of biological systems were developed and then integrated with device system models, the latter being represented by visual modeling languages such as UML and SysML. We have shown that system-level models can describe the interactions between the stochastic biological system and the physical device system. This combination of system-level modeling abstraction and lower level modeling abstraction enables formal validation and verification of the biomedical-device system for experimental applications.

B. Future Work

To bring benefits of the proposed platform to fruition, our future work will explore methods of integrating tools for modeling biological systems with well-established device modeling systems. This architectural framework will lay the foundation for a collaborative effort between biologists, clinicians, and systems engineers, leading to new libraries of biological and device components to support the work of these disciplines. These models will be extended into the experimental domain, where the transient response of biological systems to changes in experiment parameters and human interaction is of interest. Looking ahead, there is a strong need for the integration of biological system models, device system models, and biological response or human interaction models, with the cumulative model providing functional predictions of biomedical-device performance in near real-world scenarios. Enhanced insight will reduce the costs associated with device and experiment redesign, and increase the confidence with which medical researchers pursue drug development and discovery, biomedical device development, and new testing methodologies.

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