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Advanced Mathematical Dynamical Systems Pharmacology Modeling and Biology Applications for Drug Discovery, Development and Clinical Trials

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CEOCFO: ***Dr. Burke, according to the Applied BioMath website your company is revolutionizing drug invention. How are you doing that?***
Dr. Burke: The pharmaceutical industry is truly in the midst of a revolution: we are no longer 'discovering' new drugs, we are inventing them. Companies like Biogen, AbbVie, Vertex, Regeneron, and Genentech have realized this, and they are some of the industry leaders in innovation – that is – drug invention.

Breakthrough and disruptive technologies, developed in the 20th and 21st centuries, include smaller, faster chips enabling personal, high performance, and cloud computing, and cars and planes with increased fuel conservation, aerodynamics, and stealth technology. We see new engineering disciplines- electrical, computer, mechanical, and chemical- bridging the gap between the hard sciences and society. These approaches revolutionize thinking and technology, optimize processes, and ultimately improve people's lives. Absolutely fundamental to all engineering is the use of high powered mathematics to predict what is optimal, predict failures, understand complex systems, and design experiments.

Here, let's focus on biology, mathematics and engineering. People have understood for a long time that patterns in nature that can be represented mathematically; for example, we can identify repeating patterns in trees and plants (such as bifurcations of trunk, branches, leaves), in the human vascular system, in the arrangement of plants' seeds, or in animals' defensive swarming behaviors. Recently, our increasing mathematical understanding of patterns and complexity in biology has enabled diverse endeavors ranging from Pixar's lifelike animations to prediction of epidemics and vaccination strategies to prevent them. With advancements in understanding human disease, variability, quantitative data, mathematics, and high performance computing, comes the birth of a new discipline: Biological Engineering (a term coined by Professor Douglas Lauffenburger, the Chair of the Biological Engineering Department at the Massachusetts Institute of Technology). Also known by various other names, biological engineering approaches are bringing new understanding of how cells, tissues, and organisms work and make decisions.

Now, at Applied BioMath, we are using biological engineering approaches, applying them to drug invention (Peter Sorger at Harvard Medical School has recently coined this Systems Pharmacology). The founders of Applied BioMath, among others, have been inventing this space for roughly ten years. We are indeed revolutionizing drug invention. We are employing advanced mathematical algorithms such as dynamical systems techniques (the same math that predicts planetary orbits, the weather, mathematical ecology, and combustion theory), applying hardcore mechanistic modeling of biophysical properties of diseases and drugs, rigorously ensuring accurate representation of biology, and utilizing the vast power of supercomputing to provide tactical analysis, all on a timescale that enables decisions. Our approach has been validated in the clinic, where our predictions have been demonstrated to be 10 times more accurate than accepted industry standards. We have accelerated our customers' programs by eliminating needless assays or animal studies, experiments whose results do not change the direction of a program. We have predicted some programs' failures early. Our analysis has resulted in drugs whose properties are better suited for their tasks. The insights we have provided our customers have resulted in millions of dollars of savings.

CEOCFO: ***Is it that no one has thought of trying this in the past or that the technology wasn't developed to do so?***
Dr. Burke: This is a great question. People have certainly applied mathematics to drug invention and development in the past, and done so successfully. These efforts have included empirical pharmacokinetic and pharmacodynamics (PK/PD; PK, what the body does to a drug; and PD, what the drug does to the body) modeling for small molecules (this technique based on empirical observations), modeling the structures of compounds and proteins to predict optimal 3d structure, applying population PK in phase 3 drug development, and using bioinformatics and artificial intelligence (AI) techniques to identify patterns in large datasets.

However, what we are doing is collectively integrating high value questions not previously addressed in the middle of the drug development pipeline with mechanistic and dynamic understanding of disease complexity and drug mechanism, data, using high performance computing and dynamical systems. This approach accelerates the development of best in class drugs and reduces late stage attrition rates in the clinic.

Others who apply mechanistic dynamical systems approaches in pharma and biotech are limited in the types of questions they address and where they become involved in the pipeline. They tend to use mathematical or biological approximations, generalizations, and shortcuts, due to limited computing power or software, a fundamental lack of the mathematics behind approximation theory, and the difficulty of the numerical analysis required to simulate these systems. In contrast, we use proprietary techniques and tools based on Kronecker Bio, software co-developed by Joshua Apgar, PhD, our CSO and Co-founder, while he was at MIT. Our toolsets and approaches enable us to leverage high performance computing to produce hundreds of thousands of simulations based on data and mechanism. Most importantly, our team includes experienced biologists from industry who understand computational methods and actively participate in our projects. Our mathematical and biological rigor allows us to provide deep biological insights years earlier than they would surface in the clinic. This is what sets us apart from previous efforts and also from our competitors. Applied BioMath are pioneers in this field.

"Our mathematical and biological rigor allows us to provide deep biological insights years earlier than they would surface in the clinic. This is what sets us apart from previous efforts and also from our competitors... At Applied BioMath, we employ biological engineering and systems approaches to help our partners make therapeutics faster, better, and for less money, and in this way improve patients' lives!" - Dr. John M. Burke, PhD

CEOCFO: ***Were you sure you could do it in the beginning? Did you know it was just a matter of figuring out how?***
Dr. Burke: Yes, I was fairly certain dynamical systems theory, or differential equations, could be used to mechanistically understand how cells make decisions and applying these approaches to better understand human disease and to drug invention, since math is present in nature (mathematical biology has been around at least since Galileo, and there existed dynamical systems models of cell processes when I was in graduate school). It was just a question of how and where. I was very interested in the repeating patterns in tree branches and in other things that are alive. You see these bifurcations in human anatomy and development as well. Your arm extends from your shoulder as one bone, goes to two bones, then there's a 'chaotic' regime (your palm and back of the hand) and then five fingers. Stem cells divide and divide and then all of a sudden some of those cells become blood cells, some become skin cells, some nerve cells and so on. In graduate school, I was interested in how cells make decisions: initiating with ligand-receptor interactions, through signal transduction cascades, and culminating in protein synthesis, and feedback. To better understand these types of systems that depend on time and parameters and space, we use differential equations. I was interested in controlling these systems mathematically and understanding their steady states. To my surprise, the value of this pursuit was not self-evident. The first time I gave a seminar to the math department about applying mathematical biology to understanding how cells make decisions, one of my professors asked, "John, why are you modeling proteins? Why do we care about proteins? Proteins are in hamburgers!" That's when I knew I'd have a battle on my hands - convincing people of the value of integrated dynamical systems approaches in studying cells (and in understanding human diseases and how to modify them).

Upon graduation, I was very fortunate to be employed as a postdoctoral fellow at MIT, where I used these approaches I had developed in graduate school, in collaborations with experimentalists and modelers, to understand apoptosis (programmed cell death) and growth factor signaling, critical processes in homeostasis, immunology, and cancer. While at MIT, and later Harvard Medical School, I provided consulting services to large pharma and smaller biotechs. I started to investigate the intersection of Biological Engineering and drug invention and development.

My trial-and-error-based learning, and my exposure to the drug development culture, continued when I was hired to be the global head of modeling approaches at a top 15 pharma company. Unfortunately, my champion at that company left shortly after I joined. A Vice President approached me and said, “Well, better update your resume. You seem like a nice guy, but we do not need your talents here”. Instead of giving up, I dug in. It was during this tenure that I identified additional extremely high value questions that could be addressed using biological engineering approaches in the middle of the drug development pipeline. With my group, I showed that with some very timely analysis (taking about 3-4 months), systems pharmacology could not only accurately reproduce assay results but could also be used to make predictions and influence those critical Go/No-Go decisions, accelerate timelines, and reduce risk. Our results were validated experimentally. We helped save anywhere from hundreds of thousands to several millions of dollars from projects’ budgets, accelerated the development of best-in-class (BIC) drugs, and helped identify failures quickly. ABM’s other Co-founders, our Scientific Advisory Board (SAB), and I saw that the time was ripe to bring these revolutionary approaches to drug invention to the industry at large.

CEOCFO: ***Would you please walk us through a couple of examples of when someone turned to you, what they were looking to find and how math enabled them to find it?***
Dr. Burke: Here’s one case study that seems to resonate with people, at least in the pharma industry: our partner was trying to make a fast follower drug for an exciting target. However, there were some problems. They were behind their competitor. Their candidate was a weaker binder (binding is a molecule’s propensity to “stick” to a particular protein or target), which most people believe is indicative of a less optimal drug. They really didn’t understand what their internal assays were telling them about the molecule and the disease biology. They were on the verge of killing the project when they reached out to us. We came in very rapidly, performed our analysis and told them, “Don’t stop the project; accelerate this into the clinic, because you are actually in a best-in-class “Goldilocks” situation - in this case, a binder that’s neither too weak nor too tight allows you to dose less frequently and still maintain high coverage.” That was good news for everyone! Less frequent dosing makes the patient’s life easier and his or her compliance with the dosing regimen more likely; he or she may only need to take the drug every week instead of every two days. We helped our partner go into clinical development faster, with a better drug. It turns out that this drug is doing very well in the clinic right now. And our client’s competitor that was two years ahead, has halted in the clinic. We think that’s because they decided their drug won’t be competitive due to having to dose too frequently. They wasted all of this time and greater than $100M in R&D expense, while our customer got to leap frog ahead. Presently, our customer’s drug is in phase 2, and is poised to be first in class and BIC.

CEOCFO: ***What were you measuring? Were you measuring a dosage and how many times it worked and then just going into massive numbers so you could see what would happen after a million times?***
Dr. Burke: We, as modelers, do not technically measure anything. What we do is mechanistically (fit for purpose) model the bi-molecular interactions of the biophysics of a disease and the drug for *in vitro* and *in vivo* systems, and in humans. We are tracking over time, and sometimes location, the chemical species of the model (including concentration of the drug, amount of target covered by the drug, rates of target synthesis and elimination, etc.). By varying the model parameters (which are based on biophysics and can be experimentally determined) and running hundreds to millions of perturbations of the model, we can simulate patient variability and how drug parameters impact the disease *in silico*. Consultation among our biologists, our modelers, and our customer’s project team enables us to generate hypotheses and design experiments. Using the data these experiments generate, our model is iteratively evolved and our prediction certainty increases. Understanding the sensitivity of the inputs allows us to tune the system according to a multitude of simulated patient types and drug properties. Therefore, we can hypothesize, “If I change this parameter, and this other, by an optimal amount determined using systematic approaches, I could achieve the required increase in positive outcomes while still meeting target inhibition, dosing frequency, dosing route goals, desired endpoints and the like, for as many patients as possible.”

CEOCFO: ***What are the challenges in simulating reactions in the body as opposed to statistics extrapolated from survey responses? How are you able to account for all of the differences in human reaction?***
Dr. Burke: That is an excellent question. One obvious weakness is that nobody knows all of the reactions that are going on in the body. We work with our customers and incorporate information from existing scientific literature and their scientific expertise to produce a descriptive diagram of the biology, which we then codify into a mathematical model (dynamical system). This diagram is typically displayed during our first meeting with the customer where we kick-off the partnership. Extrapolated survey responses, which I am assuming you mean as ‘Big Data’, is not what we do.

Working with our partners, we use prior knowledge networks (of known or hypothesized molecular interactions) to generate dynamic and kinetic models. To use mathematics to represent such a deep relationship between biological

activity and drug mechanism of action, the disease needs to be fairly well researched. With knowledge of mechanism comes the full power of predictive quantitative systems modeling. The great thing about this approach is that the model will fail – and it is in these failures, and understanding when and why they occur, that modeling can accelerate the understanding of human disease and drugs years before entering the clinic.

However, that being said, we do not need to know all of the reactions in a body. We just need to know the right ones, and how important or sensitive these reactions are. If, for example, we develop a fit-for-purpose model that can recapitulate all (>90%) of your lab data, animal data, and human data, then that can be good enough to reduce risk. This imperfect, but useful, model can then enable decision makers to invent and develop drugs faster, better, and for less money. Additionally, this modeling approach, along with high performance computing (HPC), can enable the rapid comparison of multiple hypothesized disease mechanisms. If perturbing a majority of model parameters for multiple hypotheses essentially yield similar results, and one can identify the most sensitive parameters or knowledge gaps where changes are drastic, this then leads to systematic experiments that can bring intellectual property for our partners of the mechanisms of disease. In this way, a model can act as a central repository of data and hypotheses to bring clarity.

CEOCFO: ***How are you encouraging people to understand and make use of what you can do?***
Dr. Burke: I believe the biggest obstacle to wide spread adoption of mechanistic dynamical systems modeling and biological engineering approaches in drug invention is a lack of understanding of what it can, and cannot, provide. This is still an emerging field. It's math based. It's new to many in the pharma world. It takes a while for something new to become adopted, especially something so disruptive. It's not disruptive in the sense that it displaces existing industry; it is disruptive to people's thinking and understanding. How can something so "math-y" explain life- something that has long been thought of as anything but "math-y"? We work to counter this prejudice. We host educational webinars throughout the year. We founded an industry-academic seminar series, in which we collaborate with Cambridge, MA, area universities, biotechs, and pharma to create a support network, share ideas, and help train future modelers in our field. We are active on social media, trying to raise awareness of the benefits of systems approaches in general. We sponsor conferences and by presenting at them, we work to educate the pharma industry as to the very significant benefits of mechanistic modeling. When we meet with prospective clients, we present case studies (also summarized on our website) of prior work, challenges faced, questions answered, and insights gained. We focus not only on biological insights and on helping our partners make better drugs, faster, and for less money; we also focus on ROI. We strongly encourage prospective clients not to take our word for it, but to listen to our customers. Quotes on our website from satisfied customers include the authors' individual and company names, and we could not put those up there without permission. We put new customers in touch with existing customers so they can ask their own questions. I'm very proud of the team at Applied BioMath and the care and diligence they have shown our customers.

CEOCFO: ***Does the drug development community understand the need for systems approaches or is it that two different disciplines don't come together easily?***
Dr. Burke: I believe that the drug development community does understand that society, through the cost of prescription drugs, is paying for the failures, and recognizes the need for this to change. At the same time, I believe that these two very different disciplines, biology and mathematics, don't mesh easily.

The rate at which new drugs fail is about 95%. That's staggering. For every new drug that gets approved to be marketed, the revenue it generates needs to cover not only the costs of creating that drug, but also all of the costs associated with 19 failures. And that's a major factor contributing to why prescription drugs are so expensive. According to a recent Tufts University study, the average cost to bring a novel medicine to market is approximately $1.5B. So on average, each medicine on the market today needs to generate at least $1.5B in revenue over the lifetime of the patent. Not every marketed drug generates $1.5B in revenue. This "arms race" is unsustainable, and people are looking for a better way. In 2004, the FDA issued a statement that just a 10% reduction in failure rates, we will save, on average, $100M per drug. With over 8,000 pharma companies worldwide, each working on between about five and one hundred fifty projects, the potential for savings is enormous. We believe our mechanistic modeling approaches can help achieve the FDA's goal. Widespread adoption could lead to annual savings, across the pharmaceutical industry, in excess of $15B each year. The downside is that uptake is slow. Inertia is a very powerful force. There's prevailing wisdom that says, "This is how I learned how to do drug R&D, so this must be the right way." Others have been burned in the past by early practitioners of the biology-math interface, who promised the moon, but fell well short of meeting expectations.

Engineering and systems approaches, integrated with biology, mathematics, HPC, and asking the right questions at the right time, are the keys to success. At Applied BioMath, we take the biology seriously. Our biology group is led by an Executive Director who has a PhD in biology. She has over 20 years of experience in large pharma, from early discovery

to toxicity, through managing clinical trials in Europe and Asia, and in biomarker strategy. Our biology-modeler team member pods are critical to model development, analysis, and simulation results. We aim to allay the fears of our customers by working as part of their project teams, being transparent about what is in the model, reporting on all outcomes (not just the favorable ones), and letting the data and predictions lead us to the correct conclusions, even if they run counter to what the program team hopes will be the outcome. To date, this has been a very successful approach. All of our customers have come back for follow-on engagements, as well as working on additional partnerships. Due to Applied BioMath's iterative approach, we've even had a few customers who have expanded our engagement while we've still been completing our first project. We've been profitable and cash flow positive since our second year in business; we're growing exponentially, and we're hiring as fast as we can.

CEOCFO: ***You mentioned scaling up. However, are you able to handle volume if it should double tomorrow?***
Dr. Burke: That's another great question. Yes, we can handle a doubling of volume when it happens. One big advantage we have is our toolsets. As I mentioned before, one of our Co-founders, our Chief Science Officer Dr. Joshua Apgar, co-developed Kronecker Bio (a software platform specifically designed for systems modeling that enables HPC simulations in the life-sciences) while pursuing his PhD in Bruce Tidor's lab at MIT. Since then, we have developed proprietary toolsets that sit on top of Kronecker Bio which enable our scientists to be extremely efficient at creating and running mechanistic models. We continue to innovate around this core to constantly develop better algorithms and approaches, which more rapidly perform model simulation to enable model development, benchmarking analysis and visualization. In fact, the National Institutes of Health recently awarded us a $1.5M Direct to Phase II grant to continue developing our tools. We have the Key Opinion Leaders in systems approaches and biological engineering on our Scientific Advisory Board - in addition to accomplished industry executives, we include professors and clinicians from MIT and Harvard Medical School. They introduce us to their doctoral students and postdocs so we can maintain a pipeline of highly qualified job candidates. We're also connected with most of the universities across America and Europe performing relevant research, including MIT, Harvard Medical School, Harvard, Tufts, Georgia Tech, UNC, UC San Diego, UC Berkeley, Arizona State University, University of Buffalo, and University of Pittsburgh, to name a few. We have developed a robust network of contractors and consultants with PhDs and experience in our field, which we can bring in as demand increases. The great thing is, as more and more companies incorporate these approaches into their drug programs, more and more universities are offering advanced degrees in biological engineering, mathematical biology, and systems approaches, and more and more people are enrolling in and graduating from these types of programs. So the talent pool is dramatically increasing as well.

CEOCFO: ***Why is Applied BioMath so important today?***
Dr. Burke: Applied BioMath is so important today because drug invention and development is expensive, it's difficult, and the low-hanging fruit has likely already been picked. We are now focusing on co-drugging targets and personalized medicine. This deep dive into human disease biology and therapeutics requires a much deeper understanding of the factors at work. Developing and running assays and animal models to test these concepts is very expensive and time consuming, not to mention inefficient. We are looking at hitting multiple pathways, in more complex diseases, where there do not exist good animal model systems. Pharmaceutical companies and biotechs are pushing the envelope in the invention of newer and better drugs and drug concepts; for example, bispecific and trispecific antibodies, antibody drug conjugates, small molecule-large molecule combinations, cell therapies, and nanoparticle delivery mechanisms. Society wants drugs brought to market faster and for less money. Clinicians do not like to prescribe new drugs to patients unless quality (and length) of life are significantly improved. At Applied BioMath, we employ biological engineering and systems approaches to help our partners make therapeutics faster, better, and for less money, and in this way improve patients' lives!

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