1 Identification and Significance of the Problem or Opportunity.

Nonlinear ordinary differential equations (ODEs) are widely used for modeling the dynamics of complex systems in the physical, biological, and social sciences, as well as across the engineering disciplines. Given (noisy) measurements of system inputs and outputs, researchers are faced with the "inverse problem" of estimating parameters from data relative to a statistical model of the phenomenon at hand and the measurement process. Examples of application areas include drug-disease response in pharmacology/toxicology [Peterson and Riggs, 2010, Gelman et al., 1996], thermal conductivity and heat transfer for rocketry, airflow analysis over control surfaces in in aeronautical engineering [Alifanov, 2012], facial recognition in computer vision [Aubert and Kornprobst, 2006, Bovik, 2010], dynamics of gaseous bodies with respect to background magnetic fields in astrophysics [Tobias et al., 2011], population diffusion and spatial dynamics in ecology [Gopalsamy, 2013], continuous-time asset pricing in econometrics [Johannes and Polson, 2010], soil-carbon respiration in biogeochemistry [Manzoni and Porporato, 2009], cellular regulation in systems biology [Baron and Gastonguay, 2015, Baron et al., 2013, Leclerc et al., 2016], fatigue in land and sea combat [Rubio-Campillo, 2016], and pressure changes and oceanic flow in fluid dynamics for meteorology [Charney and Phillips, 1953], to name but a few.

Inference for ODEs can be challenging, both from a statistical perspective (the solution space of a nonlinear inverse problem can have a complex geometric structure, far from the Gaussian distributions used in standard asymptotic inference) and also computationally: solving the inverse problem in a probabilistic sense requires tracing out the space of parameter values that are consistent with data and prior information. Even the simplest ODEs generally do not admit closed-form solutions, hence computational approaches are necessarily iterative, requiring a search through parameter space. Such a search is most effectively performed using gradients, which in turn raises the challenging problem of computing gradients of differential equation solutions. In this setting, problems of parameter estimation, prediction, uncertainty quantification, and hence decision-making under uncertainty, are intractable analytically and notoriously difficult to solve numerically.

Stan [Carpenter et al., 2016, Stan Development Team, 2016, McElreath, 2016] is a widely used, open-source, probabilistic programming language and Bayesian inference engine. Stan currently provides state-of-the-art Bayesian inference algorithms for inverse problems based on gradients. Full Bayesian inference is performed exactly (up to some specified precision) using Hamiltonian Monte Carlo (HMC, [Neal, 2011]), a Markov chain Monte Carlo (MCMC) method for sampling from the posterior and computing expectations; approximate algorithms, which can provide exploratory analysis and even useful estimates at orders of magitude greater throughput, include mean-field and full-rank variational inference (VI, [Wainwright and Jordan, 2008]) and simple optimization-based Laplace approximation [Gelman et al., 2013]. Stan includes a simple Runge-Kutta initial-value solver for ordinary differential equations.

We propose to extend Stan to incorporate state-of-the-art solvers for ordinary differential equations and differential algebraic equations into its inference procedures. Based on the performance of our non-stiff solvers, we believe we can achieve an order of magnitude or more speedup over the existing state-of-the-art, due to Stan's built-in efficient automatic differentiation library and efficient samplers for full Bayesian inference and optimizers for approximation Bayes through variational inference and maximum marginal likelihood. Stan provides the means to create coupled systems of differential equations through nested automatic differentiation, which provide full sensitivities (derivatives of solutions with respect to parameters) [Lee and Hovland, 2002, Serban and Hindmarsh, 2003, Carpenter et al., 2015] and thus allow Stan's derivative-based inference engines to be used with statistical models involving non-linear differential equations. The key for our proposed work will be calculating the sparse, structured Jacobians of these coupled systems to permit solutions of stiff systems of equations (typically characterized by varying time scales among the components, such as the varying absorption, distribution, metabolism, and excretion of toxins in bone, fat, blood, and organs such as kidneys).

We will also extend Stan to deal with events arising from external inputs such as discrete (bolus) dosing in pharmacology or leaf-litter decomposition by enzymes in soil-carbon modeling. These represent general improvements in the Stan language which should serve specific customers in the present commercial development.

In that way, we propose at Columbia University to serve the general science and engineering community with improvements in open-source software while at the same time at Metrum producing a product and services for which there is a strong market.

For concreteness, we will evaluate the tools produced using pharmacometric data with a range of sophisticated statistical and mathematical models in common use [e.g., Ette and Williams, 2007, Schmidt and Derendorf, 2014]. Our goal is to extend the size of data sets, sophistication of models (e.g., varying effects by patient, missing data, meta-analysis of multiple drug studies and placebo controls, increased granularity of spatio-temporal modeling, hierarchical modeling of (sub)populations), and speed of solvers by an order of magnitude or more over the state of the art, a target we believe is realistic given Stan's performance with simple non-stiff ODE solvers [Weber et al., 2014]. The result will be an even more flexible Bayesian statistics platform that supports analysis of heterogeneous collections of data conditioned on models of great stochastic and deterministic complexity and quantitative prior knowledge, leading to better calibrated and sharper (more precise) predictions [see, e.g., Gneiting et al., 2007].

1.1 Background

Modern research in science and engineering is characterized by big, messy data. Scientific datasets are not just bigger in that there are more instances of the same thing—a mere increase in sample size would make our job as data analysts easier. Rather, there is more *breadth* and *complexity* to the data: more subgroups, locations, or time granularity than is currently being modeled, more partial and noisy measurements that cannot easily be incorporated into standard models, more related studies available for meta-analysis and prior formulation, more information on the physical mechanisms of measurement, more information on the population units being measured, and more fine-grained information on the predictions desired.

Consequently, in order to utilize big data we need complementary big models that can, for example, adjust the data to match sample to population, to match treatment to control groups in causal inference, or learn about interactions and variation and make individualized predictions rather than be limited to averages. Once we have big models we inevitably have multiple levels of uncertainty and variation, which can be studied using Bayesian inference, as is demonstrated in a large literature of applied statistics, including our own books and research articles. The big computational challenge is scalability: developing algorithms and implementations that work well and do not require too much storage and computation time as datasets become larger and the amount of predictive information increases.

1.2 Modeling and simulation in drug research and development

Pharmacometric data typically consists of longitudinal measurements gathered from different sources such as drug concentrations in blood plasma and pharmacological effects often resulting from a sequence of treatment events, e.g., drug doses. Mathematical modeling and simulation facilitates decision-making and risk-benefit assessment by drug developers regulators, health care providers, and patients.

Mathematical models describing measurements over time are often compartmental models formulated as systems of first order ordinary differential equations (ODEs). These models often also involve a hierarchy of random effects required to describe sources of variability, e.g., inter-individual, inter-occasion and residual variation. Highly complex systems pharmacology models describe physiologic, biochemical, and pharmacological processes at multiple scales (molecular, cellular, tissue, organ, organism and population) [e.g., Baron et al., 2013, Peterson and Riggs, 2010]. Even relatively simple compartmental models used for pharmacokinetic data analysis require solution of systems of ODEs often by computationally demanding numerical methods.

Although there are well-developed methods for solving continuous ODEs given initial values, tools for inference in models that incorporate ODEs as part of the statistical model are less-developed. Discrete events such as bolus doses into a model compartment induce discontinuities in the ODEs or their solution, which adds additional

computational complexity. We propose to evaluate and extend software tools to incorporate better methods for solving ODEs and handle discrete events.

Systems pharmacology models are very useful for applications in translational drug research–predictions of drug disposition and effects in humans based on preclinical research. The development of such models is highly challenging and resource intensive. It requires integration of large amounts of prior biochemical and physiological knowledge with a heterogeneous collection of data from in vitro, animal and human studies. Bayesian methods provide a rational approach to the model-based analysis of data conditioned on such complex models and quantitative problem-specific knowledge about the model parameters [e.g., Gelman et al., 1996, Leclerc et al., 2016].

2 Phase I Technical Objectives.

The overall objective of this proposal is to develop additional functionality within Stan to support pharmacometric applications. This includes the addition of functions for implementing compartmental PK/PD models and schedules of dosing and other discrete events. The resulting enhancements to Stan will also support other applications that would benefit from Bayesian data analysis using complex models requiring numerical solution of systems of ordinary differential or algebraic equations.

2.1 Technical Objectives

The combined scope of the proposed Phase I and Phase II work will result in a pharmacometric modeling and simulation platform that is more flexible and that provides order(s) of magnitude more scalable and more efficient Bayesian computation than available tools. This will be accomplished by extending the capabilities of Stan to include support for pharmacometric models. The goal is a software tool that combines

- numerical solution of systems of ordinary differential equations (ODEs),
- numerical solution of systems of algebraic equations,
- Bayesian methodology that permits integration of new data with prior information,
- efficient computation of posterior densities and expectations with respect to them (e.g., for event probability estimation and prediction),
- a flexible model specification language that permits
  - probabilistic models that allow multiple levels and sources of variability and uncertainty,
  - implementation of complex models that combine submodels with different stochastic hierarchies. E.g., translational models that combine linked submodels for simultaneous analysis of clinical, animal and in vitro experiments,
  - model calculations that depend on a potentially complicated sequence of events that affect the model predictions (e.g., multiple dosing, changes in non-drug treatments, time-varying model parameters).

2.2 Comparison to Existing Tools

Various existing software tools address subsets of those features, but none address them all. Shortcomings of currently available software are outlined below. Commercial tools that specialize in pharmacometric applications such as NONMEM, Monolix and Phoenix offer

- Good support for compartmental models based on ODEs and for typical schedules of dosing and other discrete events.
- Including ODE solvers specialized for stiff, non-stiff and linear ODEs
- Limited flexibility w.r.t. probabilistic model components.
- NONMEM & Monolix employ relatively inefficient MCMC algorithms for Bayesian analyses.
- Phoenix provides no support for Bayesian analysis.
- Stochastic structure of supported models is limited:
- Only Normal-Wishart priors
- Only normally distributed variability (except for residual variability)
- Cannot combine submodels with different stochastic hierarchies

Stan is in part modeled on the previous state-of-the-art tool for Bayesian inference via MCMC, WinBUGS [Lunn et al., 2000], which contains a module PKBugs for ODE solving, and for which we have the BUGSModelLibrary of sample models for testing [Gastonguay1 et al., 2010]. WinBUGS and other Gibbs-sampling based approaches provide

- inefficient MCMC algorithms compared to Stan, which is
  - two orders of magnitude more scalable, and
  - between two times faster and orders of magnitude faster, with greater speedups in more challenging problems.

2.3 Advantages of Stan

In contrast, Stan provides

- more efficient posterior simulation algorithms (HMC/NUTS) than other pharmacometrics and general purpose Bayesian analysis tools,
- approximate Bayesian (ADVI) and optimization methods,
- numerical solvers for non-stiff ODEs,
- only limited, primitives-based support for pharmacometrics models,
- no tools for handling typical schedules of dosing and other discrete events,
- a single simple ODE solver (no stiff solvers, no efficient solvers for linear ODEs), and
- no tools for solving nonlinear algebraic equations, which are required for steady-state solutions for ODES, a commonly encountered challenge in pharmacometric analyses.

These properties of Stan make it a highly attractive general purpose program for Bayesian data analysis and arguably the best available platform upon which to build additional features. As outlined above, Stan lacks some important capabilities required for many pharmacometric applications.

2.4 Objectives for Phase I Base

- Detailed planning and feasibility assessment for development of a suite of Stan enhancements to support pharmacometric modeling and simulation
- Development of Stan components for non-steady-state calculations for compartmental PK/PD models
- Handling of discrete events, e.g., bolus or constant rate input, piecewise constant parameters,
- Implementation of functions for analytic solutions for standard linear one and two compartment PK models with or without first order absorption.
- Functions that integrate numerical solution of ODEs with the event handler
- Non-stiff ODEs solved with Adams-Moulton or Runge-Kutta methods
- Stiff ODEs solved with Backward Differentiation Formulas (BDF)

2.5 Objectives for Phase I Option

- R package for PK/PD data handling and model implementation.
- Linear ODEs solved semi-analytically using matrix exponentials
- Function that integrates numerical solution of linear ODEs with the event handler

3 Phase I Statement of Work.

3.1 Phase I Base

Phase I Base will be limited to (1) detailed planning and feasibility assessment for development of a suite of Stan enhancements to support pharmacometric modeling and simulation, and (2) developing an initial subset of the planned components.

3.1.1 Planning and feasibility assessment

The first stage of the work will be to develop more detailed functional specifications for Stan components that fulfill the following general functional requirements: Functions that calculate the amount in each compartment of a compartmental PK/PD model at a specified time given the amount in those compartments at a previous time, Calculations based on analytic solutions for the standard linear one and two compartment PK models with or without first order absorption. Calculations based on numerical solution of a user-specified system of ordinary differential equations (ODEs). Specific functions will be required for different categories of ODEs [Byrne and Hindmarsh, 1975]:

- Stiff ODEs solved numerically via methods based on backward differentiation formulas (BDF).
- Non-stiff differential equations solved numerically via Adams-Moulton or Runge-Kutta methods.
- Linear ODEs solved semi-analytically via matrix exponential methods.

- Functions that calculate the amount in each compartment of a compartmental PK/PD model at a vector of specified times given a schedule of discrete events, e.g., bolus or constant rate doses and piecewise constant parameters. These functions will be developed by integrating the functions for calculating the compartment amounts at a single time with software for handling the event schedule.
- One or more functions for numerical calculation of the solution to a system of nonlinear algebraic equations.
- Functions that calculate the amount in each compartment of a compartmental PK/PD model at a vector of specified times under quasi-steady-state conditions resulting from a periodic input, e.g., repeated administration of equal doses at equally spaced time intervals. This requires numerical solution of both ODEs and algebraic equations in order to solve a boundary value problem.
- Integral with the development of the above functional specifications will be assessing the feasibility of implementing them within Stan. Feasibility assessment may also extend to consideration of additional functionality that may be desirable for pharmacometric and other scientific modeling applications, e.g., solutions of delay differential equations, stochastic differential equations, differential algebraic equations and partial differential equations.

3.1.2 Development of Stan components for non-steady-state calculations for compartmental PK/PD models

The software developed in this project will be written in C++. The C++ code will result in new functions in the Stan model specification language. Subject to revision based on the planning and feasibility effort described above, C++ code consistent with Stan architecture will be developed for the following tasks. A function will be constructed that calculates the solution of a system of ODEs at a specified sequence of times given a schedule of discrete events, e.g., bolus or constant rate input or piecewise constant parameters. This will be a general event handler that calls another function that returns the solution to a specific ODE system at a single time given initial values, i.e., implementing a recursive approach in which the ODEs are solved over each continuous interval given initial conditions for that interval calculated from the solution for the prior interval. Functions for calculating analytic solutions for standard linear one and two compartment PK models with or without first order absorption will be created. A function for calculating numerical solutions of non-stiff ODEs using an Adams-Moulton method will also be implemented. This will probably employ code from the Sundials collection [Hindmarsh et al., 2005]. Stan functions have already been developed for calculating numerical solutions of ODEs using Backward Differentiation Formulas (BDF) for stiff ODEs and Runge-Kutta methods for non-stiff ODEs.

Additional C++ code will be written that integrates the ODE solution functions with the event handler and exposes the results as functions in the Stan language. In addition a general purpose ODE solver function using the Adams-Moulton method will be added to Stan. The function will be consistent with the current Stan implementations of the Runge-Kutta and BDF solvers.

3.1.3 Software development practices

Stan is developed using current best-practices for production software development. These rely on a combination of test-driven interface design, established coding standards, thorough code reviews, exhaustive unit tests, and ongoing continous integration testing on all supported platforms.

Stan's software distributions, including the source version control repositories and the official releases, along with the Wiki used for design documents, and the issue tracker for feature requests and bug reports, are hosted by GitHub.[1] The entire distribution and the in-development code are open access, and available through the public-facing GitHub web site. All work is carried out in branches and submitted to be merged with the development

[1] `http://github.com/`

branch through pull requests which are openly code reviewed. All behavior must be thoroughly tested, both with unit tests for the local functionality and integration tests to guard against breaking things end-to-end with local changes.

3.1.4 User-facing changes

Stan has over 1500 registered users on its users list and has seen over 200 academic publications across science, engineering, business, and sports. The results of this project will involve extensive additions to the user-facing documentation. This includes interface-by-interface walk-through tutorials and example models. Stan is increasingly being included in third-party textbooks, and we strive for backward compatibility so that these references are not made obsolete. Stan also has a dedicated web site, which is also managed through GitHub.

3.1.5 Collaboration plan

The project will be a close collaboration between personnel at Metrum Research Group and the Stan development team based at Columbia University. Metrum scientists provide expertise in pharmacometrics. In most cases they will be responsible for initial functional specifications and will often develop prototype code for the desired functionality in Stan. The Stan team will collaborate with Metrum scientists to refine the functional specifications. They will adapt or replace the prototype code to develop Stan code suitable for inclusion in publicly released versions of Stan. Part of that process will include rigorous testing to assure the code functions as intended.

The main coordination mechanisms we use are GitHub for version control and code review, Jenkins for continuous integration testing, weekly Google+ hangouts for online meetings as well as additional meetings as needed. In this particular case, we are within public transportation distance of each other, which will facilitate regular face-to-face meetings with whiteboards.

3.2 Phase I Option

3.2.1 R package development

R (`https://www.r-project.org/`) is a statistics software package widely used by pharmacometricians and other scientific fields. Users can develop additional R components and make them available as easily installed packages. An R package will be developed to provide a more familiar and user-friendly tool for the following tasks:

- Translation of data sets formatted for NONMEM (`http://www.iconplc.com/innovation/solutions/nonmem/`) into Stan-compatible formats
- Model specification
- Model execution using either the rstan or cmdstan interfaces to Stan
- Tabular and graphical analyses of Stan output specialized for pharmacometric applications
- The component functions will be programmed in the R language. They will be made available to the community via open distribution sites, e.g., CRAN (`https://cran.r-project.org/`) or R-Forge (`https://r-forge.r-project.org/`).

3.2.2 Development of additional Stan components for linear compartmental PK/PD models

A large fraction of pharmacometric models are based on systems of linear ODEs with constant coefficients. Such models can be solved semi-analytically via a matrix exponential approach. A matrix exponential method can solve applicable ODEs much more rapidly than the multi-step numerical methods implemented as part of Phase I Base. A Stan function for calculating non-steady-state and steady-state solutions of linear ODEs using matrix exponentials will be developed. The specific computational approach will be identified during the Phase I planning. A variety of algorithms have been proposed [Moler and Van Loan, 2003] and implemented in various languages, e.g., FORTRAN [Sidje, 1998] and C++ (`https://people.sc.fsu.edu/~jburkardt/cpp_src/matrix_exponential/matrix_exponential.html`).

As with the ODE solvers described in section 3.1.2, a Stan function integrating the matrix exponential solver with the event handler will be developed.

4 Related Work.

4.1 Metrum Research Group

Metrum Research Group, established in 2004, is an innovative provider of pharmacometric modeling and simulation services and solutions to support biomedical decision-making. Metrum scientists employ complex pharmacostatistical models to analyze data arising from pre-clinical, clinical, and post-marketing studies. The models used typically include a hierarchy of random effects to describe various sources of variability, e.g., inter-individual and residual variability. Often they describe longitudinal outcomes using the solutions of systems of nonlinear differential equations. In other words, Metrum scientists regularly work with the kinds of models this proposal seeks to implement in Stan.

In addition to the modeling and simulation services, Metrum has developed and distributed open source software tools to facilitate pharmacometric modeling tasks. This includes the R packages metrumrg [Bergsma et al., 2013] and mrgsolve [Baron and Gastonguay, 2015]. Dr. Gillespie, the principal investigator, developed BUGSModelLibrary [Gillespie and Gastonguay, 2009], programs that augment the Bayesian modeling platform WinBUGS [Lunn et al., 2000] with functions for pharmacometric modeling. This includes functions for handling schedules of discrete events, e.g., dosing, and numerical solution of differential and algebraic equations.

Metrum also has experience with commercial software development and marketing. Metrum offers a high performance cloud computing platform-as-a-service called Metworx `http://metrumrg.com/metworx.html` that provides users with managed, on-demand grid computing for as many environments and cores as needed.

4.2 Andrew Gelman and the Stan Development Team

4.2.1 Core Stan Platform

Carpenter, Gelman, and Lee have been core contributors to the design, implementation, documentation, and maintenance of Stan since its inception in January 2011. Gelman provides the statistical direction, and Carpenter and Lee are the two full-time software developers. This work was initially funded in part through two grants:

- Department of Energy (DE-SC0002099 Petascale Computing)
- National Science Foundation (CNS-1205516: Stan: Scalable Software for Bayesian Modeling)

It is currently funded in part through the following grants:

- Alfred P. Sloan Foundation (G-2015-13987: Stan Community and Continuity)

- Office of Naval Research (Informative Priors for Bayesian Inference and Regularization)
- Institute of Education Sciences (Statistical and Research Methodology: Solving Difficult Bayesian Computation Problems in Education Research Using Stan)

4.2.2 ODEs in Stan

Carpenter, Gelman, and Lee have worked for Novartis AG as consultants to develop the capability to solve initial value problems for ordinary differential equations in Stan and to work on methodology for drug-disease PK/PD models including multilevel models for patient populations and meta-analysis. This work was funded by two groups within Novartis; contacts are

- Novartis, Switzerland: Dr. Sebastian Weber (+41 61 324 6217)
- Novartis, United States: Dr. Wenping Wang (+1 862 778 9009).

The first short contract was completed in December 2013 and there are two contracts currently ongoing.

5 Relationship with Future Research or Research and Development.

The Stan functions developed in Phase I are both valuable deliverables in their own right and foundations upon which additional functionality will be developed in Phase II. For example the ODE solver and event handler functions developed in Phase I will be used again in the development of functions for performing steady-state calculations. Probable Phase II objectives include development of Stan functions for:

- Numerical solution of nonlinear algebraic equations
- Calculation of the amount in each compartment of a compartmental PK/PD model at a vector of specified times under quasi-steady-state conditions resulting from a periodic input, e.g., repeated administration of equal doses at equally spaced time intervals. This requires numerical solution of both ODEs and algebraic equations in order to solve a boundary value problem.
- Automatic selection between the BDF and Adams-Moulton solvers based on assessment of ODE system stiffness
- Within chain parallel computation for hierarchical model structures commonly used in pharmacometrics

Other potential Phase II objectives include development of functions for numerical solution of delay differential equations, stochastic differential equations, differential algebraic equations and partial differential equations. All of the aforementioned Phase II objectives would build on the code developed in Phase I.

6 Commercialization Strategy.

OVERVIEW

The successful development of the Stan ODE technology, will result in the delivery of novel services and solutions to customers engaged in data science and quantitative analytics. Given the strong track record of Metrum Research Group in the pharmaceutical and biotechnology industries, the commercialization strategy is primarily focused on private sector opportunities in these markets. Extension of the commercialization plan to defense, and other government or private markets is also plausible, and will be discussed briefly.

Opportunity

The challenges of identifying new therapeutic strategies for unmet medical needs, along with intense competition, rising research and development costs, increased regulatory scrutiny, and post-marketing third party payor expectations, require innovators in this space to efficiently apply available information to decision-making in the product development cycle. Data science, modeling and simulation, allow for a quantitive understanding of the problem. Bayesian data analysis methods, in particular, are well suited to this sort of quantitative decision support, in that they allow for the formal inclusion of prior information and projections of posterior probabilities of potential decision outcomes. As the complexity of these models grows with increasing information content and better mechanistic insights, the capabilities of existing analysis tools are stretched and even exceeded.

Tools which allow for efficient hierarchical Bayesian data analysis of models specified as a system of differential equations are needed to advance the quantitative decision-making process. Few solutions exist (see section 2.2 Comparison to Existing Tools), and all are significantly limited in scope, capability, or computational efficiency when compared to the proposed Stan ODE technology.

Intellectual Property

The Stan ODE technology will be distributed as part of the existing open-source Stan software project `http://mc-stan.org/` under a public license. This has been a common distribution strategy for other Bayesian modeling tools such as OpenBUGS (`http://www.openbugs.net`), and JAGS (`http://mcmc-jags.sourceforge.net`) , the R statistical software (`https://www.r-project.org`), and operating systems, such as Linux (`https://www.debian.org`). Our strategy is to develop or extend value-added intellectual property (IP) around the open-source product, as successfully demonstrated by other commercial entities, such as Red Hat (`http://www.redhat.com`), Revolution Analytics (`http://www.revolutionanalytics.com`), and R Studio (`https://www.rstudio.com`).

Commercialization Context

Metrum Research Group has provided services and solutions (nearly 300 different contracts) to more than 120 different companies and research centers in the pharmaceutical and biotech space. This customer base includes 13 of the 15 largest global pharmaceutical companies and 7 of the top 10 biotech companies. The services include: 1). contract modeling and simulation to support biomedical decision making and regulatory filings, 2). training on the application of advanced modeling and simulation methods and strategies, and 3). consulting on the qualification and management of software and computational infrastructures in regulated industries, such as pharmaceuticals. Solutions include: 1). open-source tools for pharmacometrics applications `http://metrumrg.com/opensourcetools.html`, 2). the METAMODL library of disease models and curated data sets `http://metrumrg.com/metamodl.html`, and 3). a high performance computing Platform-as-a-Service (PaaS) solution called METWORX `http://metrumrg.com/metworx.html`. In addition to the scientific team, the company also employs marketing, business development, accounting, quality/compliance, information systems, project management, and related support staff.

The Stan ODE technology will be commercialized as both services and solutions. This new technology will enable extension of modeling and simulation services related to multi-scale systems pharmacology, target-mediated drug disposition, physiologically based pharmacokinetics, and Bayesian adaptive dosing regimens and trial designs. New training services are also anticipated around Bayesian modeling and in these same topic areas. Commercialization via value-added products and solutions is also planned. These include: software qualification packages, graphical user-interfaces, and extended technical support. The new technology will also be integrated into existing Metrum Research Group commercial products and solutions. The METAMODL library will be extended to include Bayesian hierarchical implementations of existing and new disease models. The METWORX PaaS product, which allows for on-demand, auto-scaling, distributed cloud computing will integrate the Stan ODE

technology in a regulatory compliant workflow, facilitating enterprise adoption of the tool. In addition METWORX will provide the computational backbone for between-chain and later, within-chain parallel processing of Bayesian ODE models in Stan.

MARKET ASSESSMENT

In the translational through post-marketing phases of the pharma/biotech product cycle, the current market for pharmacometrics-related modeling and simulation services is estimated at $100 million annually. This includes the related market of quantitative systems pharmacology (QSP), as well as the more traditional applications of pharmacokinetic-pharmacodynamic (PK-PD) modeling, disease progression modeling, trial simulation, and training in all of these areas. Metrum Research Group's current market share is approximately 7%. In addition to the services market, a market for pharmacometrics products and solutions has developed over the past two decades. These products and solutions include traditional desktop or server data analysis software, therapeutic area data/model libraries, and a nascent market for managed and qualified high performance computing solutions. The current market for pharmacometrics products and solutions is approximately $60 million annually. Metrum Research Group's current market share is approximately 1%. Similar markets exist in other quantitative fields, and the most logical targets for expansion would be statistics/biometrics, toxicology, and systems biology groups within the pharmaceutical/biotech sector. In addition, the Stan ODE technology, and value-added IP will be applicable to markets in defense, economics, and ecology. The size of these markets has not been quantified.

REVENUE FORECAST

We estimate Metrum Research Group services, products, and solutions revenues directly related to the Stan ODE technology of $2 million in the first two years of commercialization, with growth to $30 million annually within 10 years in the pharmaceutical/biotechnology sector alone. We also anticipate that Stan ODE technology will facilitate introduction and growth of the METWORX solution to new markets outside of pharma/biotech. Revenue growth for those markets is unknown.

7 Key Personnel.

7.1 Metrum Research Group

WILLIAM R. GILLESPIE

The University of Iowa, Ph.D., Pharmacy, 1987
The University of Michigan, M.S., Pharmacy, 1980
Wayne State University, B.S., Pharmacy, 1976

RELEVANT EXPERIENCE

For nearly 30 years Bill has been involved in the development and application of pharmacometric methodology for enhancing drug treatment, development and regulation. From 1980 to 1984, Bill was a Medical Research Associate with the Biopharmaceutics Unit of The Upjohn Company. From 1987 to 1993, he was Assistant Professor of Pharmaceutics at The University of Texas at Austin, College of Pharmacy. In 1993 he joined the Center for Drug Evaluation and Research, U.S. Food and Drug Administration where he served as the Associate Director for Scientific Affairs, Office of Clinical Pharmacology and Biopharmaceutics. From 1997 to 1999 he was the Vice President for Pharmacokinetic Research and Development at GloboMax LLC. He then joined the Pharsight Corporation as a Senior Scientific Consultant from 1999 to 2007. His research interests include theoretical and computer analysis of pharmacokinetic and pharmacodynamic systems. Recent efforts have concentrated on the use of Bayesian modeling and simulation to optimize decision-making in clinical drug development and treatment. He is currently seeking to make Bayesian modeling and simulation methods more accessible via training

programs and development of software tools.

RELEVANT AWARDS

2014 ISoP Innovation Award

RELEVANT PUBLICATIONS

1. Jorge Luiz Gross, James Rogers, Daniel Polhamus, William Gillespie, Christian Friedrich, Yan Gong, Brigitta Ursula Monz, Sanjay Patel, Alexander Staab, and Silke Retlich. A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes mellitus. *BMJ Open*, 3:e001844 (http://bmjopen.bmj.com/content/3/3/ 2013.

2. James A. Rogers, Daniel Polhamus, William R. Gillespie, Kaori Ito, Klaus Romero, Ruolun Qiu, Diane Stephenson, Marc R. Gastonguay, and Brian Corrigan. Combining patient-level and summary-level data for alzheimers disease modeling and simulation: a beta regression meta-analysis. *J Pharmacokinet Pharmacodyn*, 39(5):479–98, 2012

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4. G. Stagni, A. M. Shepherd, Y. Liu, and W. R. Gillespie. Bioavailability assessment from pharmacologic data: method and clinical evaluation. *J Pharmacokinet Biopharm*, 25(3):349–362, Jun 1997.

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MARC R. GASTONGUAY

Georgetown University, Ph.D. Pharmacology, 1994
University of Connecticut, B.S. Pharmacy, 1989

RELEVANT EXPERIENCE

Gastonguay has more than 20 years experience in applying mathematical modeling and simulation to problems in clinical pharmacology and drug development across industry, government, and academic settings. He is als an entrepreneur, founding two private companies, and a non-profit organization. He is currently President and CEO of Metrum Research Group, Scientific Director of Metrum Institute, and a member of the adjunct faculty at the University of Connecticut, Department of Biomedical Engineering and the University of Pennsylvania, Perelman School of Medicine.

RELEVANT AWARDS

2011 Innovation Award, American Society of Pharmacometrics
2010–2015 Marcum Tech Top 40 Award, Connecticut Technology Council
2014 Fellow, International Society of Pharmacometrics

RELEVANT PUBLICATIONS

1. Flockhart, D., Bies, R.R., Gastonguay, M.R., Schwartz, S.L. Big Data: Challenges and Opportunities for Clinical Pharmacology. *Br J Clin Pharmacol*, Feb 2016 [Epub ahead of print].

2. Eudy, R.J., Gastonguay, M.R., Baron, K.T., Riggs, M.M. Connecting the Dots: Linking Osteocyte Activity and Therapeutic Modulation of Sclerostin by Extending a Multiscale Systems Model. *CPT Pharmacometrics Syst Pharmacol*, 4(9):527-36, Sep 2015 [Epub].

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4. Knebel, W., Rogers, J., Polhamus, D., Ermer, J., Gastonguay, M.R. Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD. *J Pharmacokinet Pharmacodyn*, 42(1):45–65, Feb 2015.

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6. Jin, Y., Bies, R., Gastonguay, M.R., Wang, Y., Stockbridge, N., Gobburu, J., Madabushi, R. Predicted impact of various clinical practice strategies on cardiovascular risk for the treatment of hypertension: a clinical trial simulation study. *J Pharmacokinet Pharmacodyn*,41(6):693-704. Dec 2014.

7.2 Columbia University

ANDREW GELMAN

Massachusetts Institute of Technology, B.S. Mathematics, 1985
Massachusetts Institute of Technology, B.S. Physics, 1986
Harvard University, Ph.D. Statistics, 1990

RELEVANT EXPERIENCE

Gelman has decades of experience in applying Bayesian data analysis to scientific applications, and has developed many widely-used methods for Bayesian inference, computation, and model checking. Examples include the standard method for monitoring the convergence of iterative simulations (Gelman and Rubin, 1992), a seminal paper on posterior predictive checking (Gelman, Meng, and Stern, 1996), path sampling (Gelman and Meng, 1998), prior distributions for hierarchical models and logistic regression (Gelman, 2006, Gelman, Jakulin, et al., 2008). Gelman is also one of the creators of Stan, the Bayesian software that is central to this proposal.

RELEVANT AWARDS

2012 Open Source Software World Challenge award for Stan: An R and C++ package for Bayesian sampling
1998 Outstanding Statistical Application award from the American Statistical Association for "Physiological pharmacokinetic analysis using population modeling and informative prior distributions."

RELEVANT PUBLICATIONS

1. Kucukelbir, A., Ranganath, R., Gelman, A., and Blei, D. (2015). Automatic variational inference in stan. In *Advances in Neural Information Processing Systems* (pp. 568–576).

2. Gelman, A., Lee, D., and Guo, J. (2015). Stan A Probabilistic Programming Language for Bayesian Inference and Optimization. *Journal of Educational and Behavioral Statistics*, 1076998615606113.

3. Bob Carpenter, Andrew Gelman, Matt Hoffman, Daniel Lee, Ben Goodrich, Michael Betancourt, Marcus Brubaker, Jiqiang Guo, Peter Li, and Allen Riddell. (2016) Stan: A probabilistic programming language. *Journal of Statistical Software* in press.

4. Hoffman, M. D., and Gelman, A. (2014). The no-U-turn sampler: Adaptively setting path lengths in Hamiltonian Monte Carlo. *The Journal of Machine Learning Research*, 15(1), 1593–1623.

5. Gelman, A., Jakulin, A., Pittau, M. G., and Su, Y. S. (2008). A weakly informative default prior distribution for logistic and other regression models. *The Annals of Applied Statistics*, 1360-1383.

6. Gelman, A. (2006). Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). *Bayesian Analysis*, 1(3), 515–534.

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9. Bois, F. Y., Gelman, A., Jiang, J., Maszle, D. R., Zeise, L., and Alexeef, G. (1996). Population toxicokinetics of tetrachloroethylene. *Archives of Toxicology*, 70(6), 347–355.

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11. Gelman, A., and Rubin, D. B. (1992). Inference from iterative simulation using multiple sequences. *Statistical Science*, 457–472.

BOB CARPENTER

Michigan State University, B.S. Mathematics, 1984
University of Edinburgh, Ph.D. Cognitive and Computer Science, 1989

RELEVANT EXPERIENCE

Carpenter has decades of experience in programming language design and open-source software development. He was an associate professor of computational linguistics at Carnegie-Mellon University, a research scientist at Bell Laboratories (Lucent), then worked as a production programmer at SpeechWorks and Alias-i. Carpenter designed the programming language component of Stan and is its principal developer. His first open-source package (ALE, for natural language grammar development) implements the theory from his first book (Carpenter 1992) and is still in use in natural language processing and linguistics. His second open-source package (LingPipe; for statistical natural language processing) is widely deployed in production and is cited in over 1000 publications. He is now a research scientist in the department of statistics at Columbia University, working full time on Stan.

RELEVANT AWARDS

2012 Open Source Software World Challenge award for Stan: An R and C++ package for Bayesian sampling

RELEVANT PUBLICATIONS

- B. Carpenter, A. Gelman, M. Hoffman, D. Lee, B. Goodrich, M. Betancourt, M. Brubaker, J. Guo, P. Li, A. Riddell. 2016. Stan: A Probabilistic Programming Language. *Journal of Statistical Software*. In press.

- D. Lee, B. Carpenter, P. Li, M. Betancourt, A. Gelman. 2014. Stan: A Platform for Bayesian Inference. Paper presented at the *3rd NIPS Workshop on Probabilistic Programming*.

- S. Weber, B. Carpenter, D. Lee, F. Bois, A. Gelman, A. Racine. 2014. Bayesian Drug Disease Model with Stan—Using published longitudinal data summaries in population models. *Abstracts of the Annual Meeting of the Population Group in Europe*.
- D. Lee, B. Carpenter, P. Li, M. Betancourt, A. Gelman. 2014. Stan: A Platform for Bayesian Inference. *3rd NIPS Workshop on Probabilistic Programming*.
- B. Carpenter, M. Hoffman and A. Gelman. 2012. Stan: Scalable software for probabilistic modeling. *1st NIPS Workshop on Probabilistic Programming*.
- B. Carpenter. 1992. *The Logic of Typed Feature Structures: With Applications to Unification Grammars, Logic Programs, and Constraint Resolution*. Cambridge Tracts in Theoretical Computer Science. Cambridge University Press.

DANIEL LEE

University of Cambridge, MASt Statistics, 2009
Massachusetts Institute of Technology, B. S. Mathematics with Computer Science, 2004

RELEVANT EXPERIENCE

Daniel is a researcher at Columbia University and has been a core developer of Stan since its start in 2011. He has been applying Bayesian methods to problems including PK/PD models. Prior to Columbia, he worked as a software engineer for defense contractors in San Diego.

RELEVANT AWARDS

2012 Open Source Software World Challenge award for Stan: An R and C++ package for Bayesian sampling

RELEVANT PUBLICATIONS

- B. Carpenter, A. Gelman, M. Hoffman, D. Lee, B. Goodrich, M. Betancourt, M. Brubaker, J. Guo, P. Li, A. Riddell. 2016. Stan: A Probabilistic Programming Language. *Journal of Statistical Software*. In press.
- A. Gelman, D. Lee, and J. Guo. Stan: A probabilistic programming language for Bayesian inference and optimization. 2015. *Journal of Educational and Behavioral Statistics*.
- D. Lee, B. Carpenter, P. Li, M. Betancourt, A. Gelman. 2014. Stan: A Platform for Bayesian Inference. *3rd NIPS Workshop on Probabilistic Programming*.
- S. Weber, B. Carpenter, D. Lee, F. Bois, A. Gelman, A. Racine. 2014. Bayesian Drug Disease Model with Stan—Using published longitudinal data summaries in population models. *Abstracts of the Annual Meeting of the Population Group in Europe*.

8 Foreign Citizens.

None at either Metrum Research Group or Columbia University.

9 Facilities/Equipment.

9.1 Metrum Research Group

Since the primary focus of this project is computer software and development, the equipment requirements are primarily suitable computer hardware and software resources. All Metrum scientists are equipped with a recent

model Apple MacBook Pro. Most production computation is done on Amazon Web Services (AWS) cloud compute servers using the Ubuntu operating system. The software required for the proposed project is installed on the standard machine image configuration used by Metrum, e.g., Gnu C++ compiler, R, Gnu Fortran, NONMEM, LaTeX, Stan, git and subversion version control software.

9.2 Columbia University

At Columbia University, all participants are equipped with recent Apple Macbook Pro personal computers. The Stan project has three dedicated servers with 64GB and 8 cores each, one for each of Mac OS X, Linux, and Windows, along with two dedicated workstations for web hosting and remote debugging on Windows and Linux. The Stan team has access to two Linux clusters, one shared by statistics and astronomy with 384 cores, and one shared by 24 departments with 2672 CPU cores, 35 of which are high end 256-gigabyte memory nodes, and 45,000+ NVIDIA K40 and K20 GPU cores. All of the software required for individual computers for this project (see the list above) is free and open source. Source version control, issue trackers, and project web servers are provided by GitHub, mailing lists for user and developer groups is supplied by Google, and continuous integration for the interfaces by Travis; all of these services are free to open-source projects.

10 Subcontractors/Consultants.

Approximately 50% of the project work will be conducted by the Stan development team based in Columbia University. The key personnel in that group are listed in section 7.

11 Prior, Current or Pending Support of Similar Proposals or Awards.

No prior, current, or pending support for proposed work.

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Marc R. Gastonguay1, William R. Gillespie, and Robert J. Bauer. Comparison of MCMC simulation results using NONMEM 7 or WinBUGS with BUGSModelLibrary. *Abstracts of the Annual Meeting of the Population Group in Europe*, 2010.

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