Society for Industrial and Applied Mathematics

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Response to the National Institutes of Health Request for Information

on the NIH Artificial Intelligence (AI) Strategy

The Society for Industrial and Applied Mathematics (SIAM) is an international community of 13,000 individual members. Almost 500 academic, manufacturing, research and development, service and consulting organizations, government, and military organizations worldwide are institutional members. Our members come from many different disciplines but have a common interest in applying mathematics in partnership with computational science to advance the benefits of artificial intelligence (AI) by improving federal research efforts and applications across sectors, including in the areas of health and biomedical research, protecting data and privacy, and ensuring reliability and security in computational models and algorithms. Through publications, research, and community, the mission of SIAM is to build cooperation between mathematics and the worlds of science and technology. Thank you for the opportunity to respond to the Request for Information (RFI) on the NIH Artificial Intelligence (AI) Strategy.

AI holds tremendous promise to revolutionize biomedical research in the understanding of chronic diseases, diagnostics, and development of treatments. Historically, NIH has lagged physical science agencies in their AI investments, and we are pleased to see NIH develop a focused and dedicated initiative to take advantage of this promising technology while addressing privacy, data-readiness, and other issues. An AI initiative could invest in research moonshots to develop AI that will truly work and be trustworthy for health applications. Further research is also needed to address AI use in healthcare to accelerate the development and deployment of reliable AI that provides accurate diagnosis and treatments for all patients. AI is accelerating at such a speed that NIH needs to keep up with the advancements of this emerging field and related technology like digital twins. In the absence of dedicated funding, NIH may fail to develop and adopt AI that could shape the future of the U.S. healthcare system.

As applied mathematicians and computational scientists, the SIAM community appreciates efforts both to advance foundational artificial intelligence, as well as to build partnerships that enable specific application areas. In this response, we focus on several foundational themes and pillars, including support for interdisciplinary research collaborations, trust and privacy, data-readiness, and workforce development as well as infrastructure needs to seed innovation and partnerships to drive forward NIH’s capacity and impact.

1. Strategic Architecture

While AI has made tremendous strides over the last few years, further investment is needed to continue the cycle of innovation, build AI systems for the particular needs of the health and biomedical research communities, and ensure that AI can be relied upon and trusted. NIH should focus on supporting a broad range of projects and leveraging convergent teams at different sizes to encourage maximum innovation.

Interdisciplinary Research Collaborations

NIH should ensure that its initiatives encourage researchers with biomedical expertise to work with those with mathematical, computing, and computational knowledge to advance AI foundations and application uses. This could include support for new Common Fund programs, expansion of R35 and other innovative mechanisms to encourage team-based science, and major center opportunities. It is important to maintain a balance of award types to enable researchers to access the initiative at different career stages and levels of NIH familiarity. This will allow more researchers with AI expertise in a variety of science disciplines to adapt to NIH needs and contribute their expertise to health challenges. Study Sections that specifically recruit expertise from applied mathematics, engineering, computing, or physical science research communities are also critical to ensure that AI approaches get fair consideration in review.

Trust and Privacy

New mathematical foundations are needed for the development of AI methods that are explainable and reliable thus engendering trust. It is also critical to address privacy challenges so that AI can be appropriately used in health contexts involving sensitive data. Many AI models focus on prediction accuracy without a focus on explainability. For biomedical applications, prediction without insight is seldom enough. In medical settings, where the cost of error can be detrimental, we need to seek means to verify the validity of models and the assumptions they are built on. A key area of exploration is the development of interpretable models and algorithms that provide insight into why and how a model produces a particular output. This requires investment in techniques for explainable, derivable, and verifiable AI models. Generative models that are based on first principles can also be used to augment measured data or where data is challenging to obtain. Formal methods should be explored to better certify new AI models and their consistency with known biological and physical theories.

The National Academy reports on data privacy[1] lay out excellent recommendations for how to advance AI research that respects privacy. A few additional points worth noting include:

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[1] National Academies of Sciences, Engineering, and Medicine. 2024. *Toward a 21st Century National Data Infrastructure: Managing Privacy and Confidentiality Risks with Blended Data*. Washington, DC: The National Academies Press. https://doi.org/10.17226/27335

- As current generation models reach a limit in terms of using available data to train models, one needs to consider the use of synthetic data where data generated by AI models or digital twins can then be used to train AI systems.
- One needs to ensure that blended data sets that integrate individual data sets that have the required personal medical data privacy guarantees, continue to have the needed privacy guarantees.
- Open access is an important driving goal but also poses challenges for national security and competitiveness in the era of AI-enabled science and engineering. The US has invested heavily for the last 70 years to create large and important datasets resulting from large surveys for social, behavioral and health data. It is important to consider the use of these data sets to provide a competitive advantage to US companies and academic institutions.

Data-Readiness

AI needs data and data requires investment before it can be efficiently used for AI. Investment is needed in research and development to create an integrated suite of data lifecycle methods and tools, informed by the specific needs of the NIH research community. Techniques that lead to data harmonization and normalization, such as data cleaning, validation, and error correction must be developed to overcome the natural heterogeneity of data sources which is in inherent conflict with the need for data fusion. Open research questions remain around analyzing highly distributed data sources, enabling data discovery and integration, tracking data provenance, coping with sampling biases and heterogeneity, ensuring data integrity, privacy, security, and sharing, and visualizing massive datasets.

Workforce

While the NIH has done commendable work to support a diverse and strong future biomedical workforce, NIH must enhance workforce development in biomedical AI particularly as well as in related fields. Training is necessary both to foster researchers with specific expertise in biomedically-relevant AI and to ensure that NIH-supported researchers generally are trained with highly developed quantitative skills and the ability to work in interdisciplinary teams. Programs should also look to explicitly foster joint training between the mathematics, computing, and statistics communities and those engaged in biomedical research. The current R25 training programs in data science are an important component, but NIH should also consider funding shorter-term programs to foster training partnerships between different communities. NIGMS has supported short courses in the past through the R25 mechanism, with many course participants going on to illustrious careers in the quantitative biosciences community. SIAM recommends that NIH re-establish these kinds of opportunities focused on AI topics, which could include workshops, travel, or summer programs to enhance awareness and cross-collaboration.

NIH's T32 program helps to fill workforce needs by incentivizing universities to create whole new graduate programs focused on areas relevant to biomedical research. The T32 program currently emphasizes the importance of strong foundations in data science to advances in biomedical research and could be expanded to include priorities around AI-relevant training. This program is complementary to the F series, which supports individual undergraduate, graduate, and postdoctoral researchers through fellowships. Both programs should be viewed as models for workforce development in a field where computation is increasingly important to scientific and engineering progress.

Finally, NIH should prioritize programs that foster the development of a more interdisciplinary workforce. Most relevant to such efforts is the K series, which focuses on career development for senior postdoctoral fellows or faculty. Specifically, the K25 program exists to help researchers with quantitative backgrounds gain exposure and apply their skill sets to NIH-relevant problems. Such mechanisms will be critical to solving health-related challenges using AI.

2. Research & Innovation Actions

AI and Modeling Intersections

Research focused on the intersection of modeling and AI can unlock tremendous progress in biomedical discovery and action. While recent AI advances have been driven by progress in image recognition and language processing, biomedical research domains pose a fundamentally different set of challenges that current AI systems are not well-equipped to address. Biomedical data is often sparse, heterogeneous in type and scale, and reflects complex biophysical, behavioral, and neurological processes. Objectives such as interpretability, physical consistency, and causal understanding go far beyond conventional accuracy metrics. *These new challenges require a novel class of mathematically sound and scalable AI methods that are capable of learning from limited data, reasoning under uncertainty, providing reliable solutions, and incorporating biophysical, behavioral, and neurological knowledge.* Meeting these challenges offers a unique opportunity to push AI in transformative new directions—making biomedical research not only a key beneficiary of AI but also a driver of its next frontier.

There are many potential applications in biomedical research leveraging modeling and AI together. A few ideas:

- Mathematical and computational methods are also needed to develop models of population health, environmental and social determinants of health. Advances in such methods can lead to new insights into mental health, addiction and even for treatment chronic diseases such as diabetes and hypertension.

- Knowledge driven AI models are essential to develop explainable and trustworthy models. Such models can lead to more efficient training or neurosymbolic models that can be used to develop algorithmic understanding of biological systems. Such a development can likely lead to new advances in synthetic biology, development of artificial organ systems and novel intervention strategies that are precise and personalized.
- Multi-scale multi-theory and multi-type models that can lead to holistic models of human systems need to be developed. Current focus on individual diseases, individual networks and organs leads to a fragmented understanding of the systems. AI-based systems can help develop such models that are computationally efficient as well as explainable.

There are many other promising areas of AI for health with high-impact use cases around understanding root causes and addressing interlocking chronic diseases and pain disorders, personalized diagnostics and treatments, computational mental health, and others. Advances in multi-level modeling that could bring together disparate sources of data from sensors, clinical settings, DNA and molecular analysis, and others would revolutionize our understanding and ability to address numerous diseases and health issues.

Applied mathematics and computational science are critical components of a future AI research agenda to build a more resilient healthcare system. Mathematical, computational, and data science research and modeling will be critical to strengthening supply chain resilience and optimization, improving decision-making amid uncertainty, and understanding group dynamics amid crises. As AI systems become pervasive, NIH has a unique opportunity to fund and advance Human-AI systems – such systems will help with more efficient use of health system resources that are stretched. They can also help address emerging challenges in caring of elderly populations, as well as individuals with disabilities.

Combining AI methods with mathematical and computational modeling can provide new insights in the development of integrated systems models. A particularly rich direction is the topic of Digital Twins — digital twins can be developed by one more human systems at varying scales (from molecules, to cells, organs and networks), providing unprecedented opportunities to combine wet lab biology with AI technologies leading to a holistic study of these systems while at the same time reducing animal experiments. NIH should consider how to advance the recommendations laid out in the NASEM study on the state of the art and challenges in developing advanced digital twins.[2] Additional information on social digital twins can be found at Socio-Technical Digital Twins.

[2] National Academies of Sciences, Engineering, and Medicine. 2024. Foundational Research Gaps and Future Directions for Digital Twins. Washington, DC: The National Academies Press. https://doi.org/10.17226/26894.

AI for Advancing Research and Reproducibility

Many scientists are exploring ideas and developing new insights, but the field of scientific machine learning is still evolving. Alphafold13, Google's breakthrough technology for predicting protein conformations, showcased the potential for ML to outperform traditional scientific approaches. Other potential roles for ML in biomedical research include automatically monitoring and running experiments or series of experiments, improved methods for combining simulation results and experimental data, and the generation of new hypotheses from data. Quite likely, the most important ideas have not yet been thought of. Artificial intelligence and machine learning have enormous potential to impact the processes of biomedical research, but broad investments in mathematics and computing will be required to realize these opportunities.

Current biomedical research faces a reproducibility crisis, with 70% of researchers unable to reproduce others' experiments, a problem exacerbated by AI systems prone to hallucinations and lacking verifiable reasoning chains. NIH should seek to leverage formal methods (automated theorem provers and reasoning engines) to enable verifiable, deductive derivation of predictive models from first principles. Unlike pattern-matching approaches that capture local correlations, formally-derived models demonstrate enhanced generalizability by encoding fundamental biological principles rather than dataset-specific patterns. This approach addresses the "black box" problem hindering clinical adoption by providing transparent, auditable reasoning chains essential for FDA approval and physician trust. Following successful integration of formal methods with AI in physics (e.g., PhysLean library), this paradigm shift would establish a rigorous foundation for biomedical discovery that prioritizes both empirical fit and theoretical soundness, enabling more reliable discoveries and successful clinical translations.

3. Intramural-Extramural Synergy

AI research requires large-scale infrastructure, which keeps advancements out of reach for many other than the most highly resourced companies. NIH can help advance a more robust ecosystem for AI-fueled biomedical innovation and enable university research efforts through investments in federal AI infrastructure that are made available to users through a competitive process to make sure the most promising research gains access. NIH should invest in national-scale data infrastructure, benchmark datasets, simulation libraries, and interoperable tools that allow scientists to train, test, and deploy AI models in ways that are reproducible and collaborative.

NIH supports a large array of data repositories both intramurally and extramurally and should support combined access so that these resources can be analyzed for intersecting insights. Partnerships with the National Science Foundation and Department of Energy could also expand access to high performance computing researchers for the extramural NIH community. This could include participation in the *National AI Research Resource* (NAIRR) and building on National Cancer Institute partnerships with DOE for use of their facilities.

As the non-traditional computing hardware industry evolves and the roles of different enterprises change, NIH should remain open to establishing new types of collaborations and relationships with both existing and emerging industrial partners.

4. Partnerships and Ecosystem Building

Computational science has always been an interdisciplinary endeavor, drawing on mathematics, computer science, and application domains. With the growth in the importance of data science and AI, the field is becoming even broader. NIH can benefit through partnership with agencies such as NSF, DOD and DOE with their major AI expertise and access to a vast community of AI-focused researchers.

Establishment of additional coordination and engagement between the applied mathematics and computational science community and the wide-ranging federal healthcare and biomedical research will improve the nation's preparedness, health systems, drug development and approval pathways. For example, NIH and FDA recently collaborated with NSF on a program to catalyze the development of digital twins for biomedical and healthcare technologies to improve clinical trials. NIH should continue to seek these kinds of collaborations to bring together researchers from computer science, applied math, and engineering along with those in health operations, behavioral science, regulatory science, and biomedical research to foster new ways to evaluate medical devices, better modeling for disease preparedness, and the development of new tools. The NSF *National AI Research Institutes* provide another good model for interagency collaboration and involve the partnership of several agencies, including the United States Department of Agriculture (USDA), Department of Homeland Security (DHS), Department of Education (ED), and DOD. NIH should join this program to harness breakthrough research for population health or other priority challenges.

Sincerely,

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