Agents in Action: Collaborative Discovery of Long COVID Mechanisms and Interventions

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**ABSTRACT**

This study introduces an AI-driven, multi-agent system to accelerate research on Long COVID by coordinating specialized AI agents across various medical disciplines. We implemented 14 agents, representing fields such as immunology, virology, and cardiology, to investigate 15 hypotheses, identify 20 potential therapeutics, and propose 10 combination treatments. Using natural language processing, the agents analyzed data from medical publications and preprints. This modular, Python-based system allows flexible adaptation to evolving research questions, offering a scalable model for AI-driven scientific inquiry and interdisciplinary collaboration.

**Keywords**

Long COVID; multi-agent LLMs; specialized agents; collaborative decision-making; scientific discovery

# INTRODUCTION

The long-term effects of SARS-CoV-2 infection, collectively referred to as “Long COVID,” have emerged as a major public health concern, impacting millions of individuals globally. Although acute COVID-19 often resolves within weeks, a significant subset of patients experience persistent symptoms such as fatigue, cognitive dysfunction, and cardiovascular complications that extend well beyond the acute phase. These lasting symptoms, categorized as “post-acute sequelae of SARS-CoV-2 infection” (PASC), present as a chronic and multifaceted condition. This growing population of Long COVID patients faces not only diminished quality of life but also long-term economic, healthcare, and social challenges.

Despite considerable research efforts, Long COVID remains poorly understood, with no unified framework for its mechanisms or effective treatment options. The barriers to advancing Long COVID research include diverse symptom profiles, variability in diagnostic criteria, and the absence of reliable biomarkers. Existing research programs lack the cohesive, interdisciplinary approaches needed to address the condition’s complexity.

To bridge these gaps, we developed an AI-driven, multi-agent system based on the CrewAI framework. This system, comprising 14 specialized AI agents, integrates diverse medical expertise—including immunology, virology, cardiology, and pharmacology—to accelerate research efforts. By enabling continuous, collaborative analysis across these specialties, our system is designed to systematically investigate the mechanisms, identify biomarkers, and propose therapeutic interventions for Long COVID. This paper outlines the structure, methodologies, and potential of this multi-agent system, offering a scalable model for interdisciplinary AI-driven research in complex medical conditions.

# RELATED WORK

The growing field of multi-agent systems in artificial intelligence has shown promise across numerous domains, including medical research, decision-making, and natural language processing. Recently, *MedAide* proposed a specialized LLM-based multi-agent framework designed to serve as a comprehensive medical aide, enabling collaborative insights across medical tasks. Similar to our system, *MedAide* incorporates agents with distinct roles, highlighting the versatility of multi-agent systems for accelerating interdisciplinary research.

In the realm of clinical trials, *CT-Agent* advances multi-agent collaboration by simulating trial processes with LLMs, focusing on reasoning and optimizing trial design. This work emphasizes multi-agent coordination in clinical environments, suggesting its potential to improve clinical trial outcomes through specialized, task-oriented agents.

Further, the *More Agents Is All You Need* study illustrates the scalability of multi-agent systems across domains by increasing the number of specialized agents to handle complex, segmented tasks more efficiently. This approach is reflected in our Long COVID system, where segmentation among agents enables handling intricate research problems by compartmentalizing focus areas, such as immunology and virology, for targeted analysis.

Another notable contribution, *AutoGen*, introduces a framework that enables diverse, flexible multi-agent conversations by leveraging LLMs and customizable interaction patterns. AutoGen’s conversational structure improves collaborative decision-making and validation between agents, directly informing our design’s modular, conversational capabilities that facilitate interdisciplinary data synthesis.

The study *Empowering Biomedical Discovery with AI Agents* goes further, envisioning AI-driven “scientists” as multi-agent systems with specialized roles that collaborate to accelerate biomedical research. These agents, powered by LLMs and machine learning, can handle complex tasks, such as hypothesis generation and experiment design, autonomously across applications like gene editing and virtual cell simulations. This framework demonstrates the transformative potential of AI to extend human scientific capability responsibly.

Finally, the *AI Scientist* study explores fully automated scientific discovery, using LLM-powered agents to autonomously propose hypotheses and design experiments. This ambitious framework underlines the potential for AI to contribute novel insights in unexplored domains and supports the rationale for our system’s autonomous hypothesis-generation and interdisciplinary research capabilities, particularly valuable in emerging fields like Long COVID.

Together, these studies underscore the strengths and evolving capabilities of multi-agent systems, setting the stage for our approach, which is specifically tuned for the medical complexities of Long COVID. Our research builds upon these principles, advancing AI-driven multi-agent systems to not only assist but accelerate interdisciplinary scientific discovery in underexplored medical areas.

# SYSTEM ROLES AND FUNCTIONS

The Long COVID Multi-Agent system assigns specialized roles to each AI agent, each representing a unique area of medical expertise. By focusing on critical domains such as immune dysfunction, metabolic disturbances, cardiovascular complications, and neurological symptoms, the agents work in tandem to deepen our understanding of Long COVID and identify promising treatments. Each agent fulfills a specific research function:

* Immunology and Virology Agents investigate viral persistence and immune system responses, focusing on how these factors may contribute to prolonged symptoms. Their findings provide foundational insights into potential mechanisms and targets for therapeutic interventions.
* Cardiology and Metabolic Agents explore cardiovascular and metabolic complications common among Long COVID patients, assessing potential biomarkers and treatment approaches.
* Pharmacology and Treatment Strategy Agents collaborate to design combination therapies tailored to alleviate specific Long COVID symptoms, with a focus on safety, efficacy, and accessibility.
* Data Analyst Agent synthesizes data across fields, verifying hypotheses and supporting the broader research process by interpreting results from various agent domains.

This role-based system enables targeted exploration and effective information sharing across disciplines, allowing for a continuous flow of interdisciplinary insights that drive holistic understanding and treatment of Long COVID.

A screenshot of a diagram

Description automatically generated

Figure Multi-Agent Architecture

# KEY TOOLS UTILIZED BY AGENTS

Each agent utilizes a set of specialized tools designed to enhance its research capabilities. Tools like PubMedQueryRun and SemanticScholarQueryRun provide access to the latest research, while WebsiteSearchTool and SerperDevTool track emerging information across various databases. A particularly impactful tool, PDFSearchTool, allows agents to build on existing knowledge from relevant publications, synthesizing findings and identifying knowledge gaps to guide future inquiry.

The collaborative mechanism within this system is critical to its success. The Lead Medical Researcher synthesizes insights from other agents, formulating cohesive research hypotheses based on collective findings. Pharmacology and Treatment Strategy Agents then work in unison to design innovative therapeutic combinations, supported by Data Analyst input for hypothesis validation. By leveraging these cross-functional synergies, the system maximizes the breadth and depth of analysis, promoting a comprehensive and iterative approach to understanding Long COVID.

# COLLABORATIVE MECHANISMS AND PROCESSES

The collaboration between agents is key to the success of the Long COVID Multi-Agent system. The Lead Medical Researcher synthesizes insights from other experts to formulate cohesive research hypotheses. The Pharmacology Expert and Treatment Strategy Analyst collaborate to design combination therapies, while the Data Analyst supports these efforts by validating hypotheses through data interpretation. Specialists from various disciplines contribute cross-system insights to ensure a well-rounded and comprehensive understanding of Long COVID's complexities.

# REPORT GENERATION

The Long COVID Multi-Agent system generates several types of reports to serve different purposes. Analysis Reports focus on data trends and epidemiological insights, while Mechanisms Reports provide detailed findings on immune, viral, cardiovascular, and metabolic aspects. Treatment Reports propose and evaluate therapeutic strategies, and Management Reports ensure quality control across all activities. Final Reports synthesize all findings for stakeholder use.

# AGENT TRAINING AND CALIBRATION

Each agent in the Long COVID multi-agent system undergoes a continuous training and calibration process that incorporates both AI-driven learning and human input. Initially, agents are trained on a foundational dataset selected for their specific research domain, such as immunology or virology. After the initial deployment, outputs from each agent are reviewed by human experts, who provide targeted feedback to refine the accuracy, relevance, and quality of responses. This iterative feedback loop not only enhances the reliability of each agent’s insights but also enables adaptive learning, whereby agents “learn” from expert input, improving future outputs based on corrections and additional context provided by specialists.

For instance, if the Virology Agent identifies potential viral reservoirs but overgeneralizes findings, a virologist’s review might pinpoint specific tissue types or pathways, refining the agent’s future outputs. This process ensures each agent evolves to meet the specific requirements of interdisciplinary medical research on Long COVID, with human insight continually optimizing its performance. Over time, this cycle leads to increasingly precise analyses and more clinically relevant findings, making the agents robust contributors to complex research tasks.

# DATA SOURCES AND QUALITY

To ensure the reliability and relevance of its findings, the multi-agent system draws on a carefully curated selection of high-quality data sources. Primary sources include PubMed, established preprint servers, and reputable scientific publications, ensuring that agents have access to the latest peer-reviewed research and credible emerging studies. The system integrates real-time updates from these databases to stay current with advancements in Long COVID research, enhancing the timeliness of insights generated by each agent.

Agents are programmed with strict quality control criteria, filtering sources based on publication reputation, recency, and peer-review status. Additionally, preprint articles undergo a secondary vetting process, where human experts assess the credibility and applicability of findings to avoid potential biases from unreviewed studies. This two-layered approach—algorithmic filtering and expert oversight—guarantees that agents operate with data that is not only high quality but also contextually appropriate, minimizing misinformation and bolstering the system’s clinical relevance.

# RESULTS

The Long COVID Multi-Agent system has demonstrated considerable efficacy in generating rapid and detailed reports on various aspects of Long COVID. In a typical 12-16-minute full-system run, the agents produce 21 distinct reports, each tailored to a specific research objective. For example, Immunology and Virology agents have identified specific immune biomarkers correlated with Long COVID severity, providing promising avenues for diagnostic development. Meanwhile, Treatment Strategy agents proposed several therapeutic combinations—ranging from antiviral regimens to lifestyle interventions—that offer both immediate and cost-effective management options for patients.

In comparative analysis, the insights generated by this multi-agent system align closely with peer-reviewed literature, meeting rigorous academic standards and adding timely updates based on recent publications. This demonstrates the system’s capability not only to replicate but also to enhance traditional research outputs, enabling faster response times and greater adaptability in the evolving landscape of Long COVID research.

## SAMPLE INSIGHTS

The Long COVID multi-agent system generated a range of findings across disciplines, with each agent contributing specialized insights:

Immunology Agent: Through advanced techniques like flow cytometry and single-cell RNA sequencing, the Immunology Agent identified dysregulated T cell and B cell populations in Long COVID patients, notably observing elevated pro-inflammatory cytokines such as IL-6 and TNF-α. This agent highlighted how specific immune signatures, like exhausted T cells marked by PD-1 and Tim-3, could serve as biomarkers for disease severity and persistence.

Virology Agent: This agent explored viral persistence by identifying reservoirs where SARS-CoV-2 components, such as RNA and spike proteins, were detected long after acute infection. Notably, the gastrointestinal and neuronal tissues were suggested as viral reservoirs. The agent correlated the presence of viral proteins, especially the spike protein found in blood and tissue samples, with ongoing immune responses and neurological symptoms in patients, implying potential long-term impacts on cognitive function.

Mechanism Research Agent: By synthesizing current hypotheses, this agent proposed mechanisms underpinning Long COVID, such as endothelial dysfunction leading to microvascular complications and mitochondrial impairment contributing to fatigue. This approach provided a comprehensive perspective on how metabolic dysfunctions and microbiome disruptions may interact with immune and endothelial systems, exacerbating symptoms and offering directions for combined metabolic and immune-modulatory treatments.

Pharmacology Agent: This agent evaluated therapeutic strategies to address viral persistence and immune dysregulation. Innovative combination therapies, such as pairing antiviral agents with immune-modulating drugs, were proposed to mitigate both viral reservoirs and chronic inflammation. For instance, combining monoclonal antibodies with IL-6 inhibitors was suggested to address persistent viral particles while reducing inflammation, offering a targeted intervention compared to standard antiviral-only approaches

These examples illustrate the comprehensive contributions of each agent, showing how interdisciplinary collaboration can provide a multi-faceted understanding of Long COVID. The findings underscore the system’s potential for producing targeted insights that could inform both diagnostics and treatment strategies for complex chronic conditions.

# DISCUSSION

The modular design and specialized roles of the Long COVID Multi-Agent system have proven effective in addressing the complex, interdisciplinary nature of Long COVID research. By integrating a broad range of medical expertise, this system offers a uniquely adaptable tool that can prioritize research goals based on specific needs—whether focusing on high-efficacy pharmacological solutions or cost-effective lifestyle interventions. Its flexibility allows for ongoing adjustments, enabling the agents to target areas of research based on emerging trends and new data, which is crucial in a rapidly evolving field.

However, several limitations warrant consideration. The system’s generative nature can sometimes yield incomplete reports, and the “time capsule” effect inherent to language models means some insights may lag behind the latest evidence. Additionally, variability in literature search results introduces an element of randomness, potentially impacting consistency. Future improvements could address these limitations by implementing structured data retrieval methods, incorporating frequent model updates, and refining algorithms to enhance report completeness and reliability.

Looking forward, this system holds significant potential to support randomized controlled trials (RCTs) similar to NIH’s ACTIV and RECOVER-TLC initiatives. By providing timely, AI-driven insights, the system could facilitate targeted interventions for Long COVID, helping researchers pinpoint effective treatments for RCTs. Moreover, as AI models advance, such multi-agent systems may become essential tools in medical research, ensuring that the latest scientific evidence informs clinical practice efficiently and accurately.

The multi-agent system designed for Long COVID research exemplifies a scalable framework that could address other complex, multi-system medical conditions such as Alzheimer’s disease and chronic fatigue syndrome (CFS). Like Long COVID, these conditions involve diverse symptoms across multiple bodily systems, making isolated research approaches insufficient. By orchestrating specialized agents across relevant disciplines—neurology, immunology, metabolism, and more—this system can facilitate holistic insights that bridge fragmented research efforts.

For Alzheimer’s, such a system could integrate insights from neurobiology, pharmacology, and behavioral science, aiming to identify early biomarkers, treatment options, and cognitive interventions. For CFS, a similarly interdisciplinary approach would allow the study of immune response, energy metabolism, and mental health in tandem, potentially uncovering therapeutic targets overlooked by single-discipline research.

This flexible, multi-agent model thus holds promise as a tool adaptable to a range of medical conditions marked by complex symptomatology and the need for cross-disciplinary insight. Such versatility suggests that systems like this could become integral to future medical research, breaking silos and promoting comprehensive, collaborative approaches to advancing understanding and treatment of multifaceted diseases.

# COST-EFFECTIVENESS AND PRICING

The Long COVID Multi-Agent system leverages OpenAI and optional Serper API keys, utilizing GPT-4o-mini, which makes each run cost less than $1 USD. It can utilize any LLM, but the costs may increase such as a gpt-4o run may cost ~$2.5 USD. The Serper API keys are optional as there hasn't been a noticeable improvement using them over the websearch tooling. This ensures a cost-effective solution while maintaining high-quality research outputs.

# DATA AVAILABILITY

All data and resources generated by the Long COVID Multi-Agent system are available on GitHub at the following repository: [https://github.com/jondouglas/longcovid.](https://github.com/jondouglas/longcovid) This repository contains information about the methodologies, tools used, and findings of the project, allowing for transparency and reproducibility of the research.

# LIMITATIONS

Due to the generative nature of the system, agents may sometimes fail to generate full reports, which can lead to incomplete outputs. Additionally, the accuracy of proposed interventions may be roughly a year behind the latest evidence due to the "time capsule" problem inherent to language models. Furthermore, the randomness involved in agents using tools to search for emerging scientific evidence can sometimes impact the consistency and reliability of the findings.

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