# Objective 1: Python Package, Supporting Manuscript, Training

## 1.1 Introduction

What is a Model?

What are the main components of a Model?

How are each of these components defined?

## 1.2 Why Python?

* + Speed – compare MATLAB to Python, see Profiling
  + Cost – Licensing cost of MATLAB
  + Community + Industry Adoption rates for each language, other languages (R)
  + Environments, Package Management
  + Language Level
  + AI Support for Python (Visual Studio Code, GitHub Copilot X)
  + Powerful existing libraries
    - Numpy, scikit, scipy, numba, p+as, matplotlib, seaborn, SALib
    - List main features, highlight functions used from each package
  + Lack of unified ODE creation + analysis workflow
    - New funding st+ards, open-source implications
    - Motivation to create a tool

## 1.3 Intended Tools

* + St+ard ODE Structure + Problem Creation
    - Parameter Dictionary
    - Initial Conditions
    - Time
    - ODE States
    - Parameter Bounds
    - Report Creation / Model Loading
    - JIT/Numba/Cython
    - Delay Differential Equation Solver
      * Pydde or in-house method
  + Parameter Sampling Modes
    - When to use Normal, Log Normal, Uniform parameter distributions
    - Log space vs normal space parameters
    - Bounded vs Unbounded (log space advantage)
  + Model Metrics
    - AUC
    - Minimum
    - Maximum
  + Global Sensitivity Analysis (SALIb)
    - eFAST Method Explainer
    - Heatmap Results
    - Individual Panels
  + Variance Based Sensitivity Sweep
    - Total System Variance
    - Per-Parameter System Variance
  + Exclusion Based Sensitivity
    - Setting each parameter to zero/current/->inf, compare trajectories
  + Sensitivity to Initial Conditions
    - +- range where nonzero
    - Try 0/nonzero states
  + Confidence Interval Generation/Parameter Exploration
    - Bootstrapping Method Explanation + Implementation
      * Capture the variability present in the data, use to construct distributions of parameters intended to replicate it
      * Bootstrapping w. tied samples
        + Multiple types of data come from one animal, thus bootstrapping must sample from ‘organisms’ rather than ‘data points’
    - MCMC Explanation + Implementation
      * Use density of parameter sampling against single data set, leveraging energy l+scape to develop intervals of parameters.
    - Comparison of Bootstrapping fit vs MCMC histograms for same problem
  + Error Function Definition
    - Comparison of loss functions, use cases
    - Use of Information Criteria (AIC, AICc, BIC)
  + Structural, Practical Identifiability
    - Python equivalent of MATLAB STRIKE-GOLDD?

## 1.4 Profiling

* + ODE Solver Optimization
    - Explainer for Runge Kutta (RK23, RK45), LSODA, BDF, Radau, DOP853
    - Timing table for example system (what are common ODE models to use?)
  + Local Minimizer
    - For use with BH or non-global parameterization, maybe local-only solve
    - Bounded vs Unbounded (see log space parameter sampling)
    - Bound Methods
      * Nelder-Mead, Powell, L-BFGS-B, TNC, SLSQP, Trust-constr
    - Unbound Methods
      * Bound methods w.o. constraints
      * CG, BFGS, Netwon-CG, COBYLA, Dogleg, Trust family
  + Global Optimizer Comparison
    - Parameter Optimization
    - Basin Hopping
    - Simulated Annealing
    - Dual Annealing
    - Other Global Search algorithms

# Objective 2: ODE Model of Influenza Infection

## 2.1 Introduction

* Influenza, viral coinfection impacts
* State of current modeling
  + Existing Model Review (COVID-19 + Dynamic Link)

## 2.2 Model Development

* Data Sources
  + Voluntary Infection (Viral Challenge Studies)
    - Memoli (2015) 1
      * 46 participants
      * wild-type A(H1N1)pdm09
      * Nasal Virus
      * Symptoms and Severity
      * Serum Cytokines
        + TNF-A
        + IFN-Y
        + IL-6
        + G-CSF
    - McClain (2013) 2
      * 17 influenza participants, 20 RSV/HRV
      * A/Wisconsin/67/2005 (H3N2)
      * Serum leukocytes, monocytes
    - Woods (2013) 3
      * 41 participants
      * A/Brisbane/59/2007 (H1N1) and A/Wisconsin/67/2005 (H3N2)
      * Symptoms and Severity
      * Serum transcriptomics per 8 hours for 7 days
    - Wilkinson (2012) 4
      * 41 participants
      * H3N2 WS/67/05 and H1N1 BR/59/07
      * Nasal Virus
      * Symptoms and Severity
      * Serum CD4+ and CD8+ T Cells
    - Fritz (1999) 5
      * 15 participants
      * A/Texas/36/91 (H1N1)
      * Nasal Virus
      * Nasal Cytokines
        + IL-6
        + TNF-A
        + IFN-Y
        + IL-10
        + MCP-1
        + MIP-1a/b
    - Hayden (1994) 6
      * 34 participants, 16 with infection and placebo
      * A/Kawasaki/86
      * Nasal Virus
      * Symptoms and Severity
    - Hayden (1998) 7
      * 20 participants
      * A/Texas/36/91
      * Nasal Virus
      * Symptoms and Severity
      * Nasal Cytokines
        + IL-6/8
        + IFN-A
        + TNF-A
    - Hayden (1999) 8
      * 117 participants, 8 with infection and placebo
      * A/Texas/36/91(H1N1)
      * Nasal Virus
      * Symptoms and Severity
      * Nasal Cytokines
        + IL-5,6
        + IFN-A,Y
        + TNF-A
    - McBride (2017) 9
      * 101 participants, 32 with infection and placebo
      * A/Wisconsin/67/2005 (H3N2)
      * Serum and Nasal Cytokines
        + IL-6/8/10
        + IFN-Y
        + TNF-A
        + IP-10
        + MCP-1
    - Zaas (2009) 10
      * 57 participants, 17 influenza, 9 symptomatic. 20 HRV/RSV.
      * A/Wisconsin/67/2005
      * Data from clinical infection (Ramilo 2007)
      * Serum transcriptomics
    - Memoli (2016) 11
      * 65 participants
      * 2009 A(H1N1)pdm
      * Symptoms and Severity
      * Nasal Virus
    - Skoner (1999)
      * Nasal IL-6
  + Clinical Infection
    - Fiore-Gartland (2017) 12
    - Hall (2013) 13
    - Oshansky (2014) 14
    - Wong (2018) 15
    - Wong (2021) 16
    - Allen (2017) 17
    - Cohen (2019) 18
    - Cole (2017) 19
    - Dunning (2018) 20
    - Jha (2019) 21
    - Lee (2009) 22
    - Lau (2010) 23
    - Tang (2019) 24
    - Herberg (2013)
    - Parnell (2012) 25
    - Parnell (2011) 26
    - Ramilo (2007) 27
    - Zhai (2015) 28
    - Choreño-Parra (2021) 29
    - Sellers (2021) 30
    - Mudd (2020) 31
    - Hagau (2010) 32
    - Martinez-Ocaña (2013) 33
* Data Compartment
  + Nasal Wash
  + Blood/serum
  + Organ

Each ODE Mechanism + State

* + Host Cells
    - Susceptible
    - Eclipse
    - Infected
    - Dead
  + Virus
  + Cytokines
    - Interferons
      * Alpha
      * Beta
      * Gamma
    - GM-CSF
    - IL-6
    - TNF-A
  + Immune Cells
    - Neutrophils

From [10.1016/j.jtbi.2011.01.052,](https://doi.org/10.1016%2Fj.jtbi.2011.01.052) -d\_N,V V N – d\_N N . Do neutrophils exhaust when clearing virus?

* + - Natural Killer Cells (Implied early IFN-G producing cell)
    - T Cells
      * IFN-G+ CD4+/CD8+T cells from Ivan’s paper
    - Macrophages
      * Alveolar (Ivan)
      * Inflammatory
* Homeostasis Restoration
  + Target Cell Regeneration
  + Immune signaling shutoff
    - IFN-A, IFN-B, IFN-Y, IL-6, GM-CSF
  + Immune cell timeline after infection
    - T-cells, NK, DC, macrophages (alveolar + inflammatory), neutrophils
* Sensitivity
  + Local (Sweep)
  + Global (eFAST)
  + Interactive Plotting
  + Parameter Exclusion
  + Initial Conditions

# Objective 3: Virtual Patient Cohort

* Clinical + Experimental Data
  + Limitations of data, need to first build+parameterize to mouse data
  + Use of Experimental Voluntary Infection to convert between Mouse + Human data
    - Nasal cytokine and viral loads from Fritz, Hayden, Hayden, and McBride
  + Use of Clinical Infections to develop Virtual Patient Cohort
    - Clinical Variability (Find causes of individual variability in clinical respiratory disease progression)

1. Memoli, M. J. *et al.* Validation of the Wild-type Influenza A Human Challenge Model H1N1pdMIST: An A(H1N1)pdm09 Dose-Finding Investigational New Drug Study. *Clin. Infect. Dis.* **60**, 693–702 (2015).

2. McClain, M. T. *et al.* Longitudinal analysis of leukocyte differentials in peripheral blood of patients with acute respiratory viral infections. *J. Clin. Virol. Off. Publ. Pan Am. Soc. Clin. Virol.* **58**, 689–695 (2013).

3. Woods, C. W. *et al.* A Host Transcriptional Signature for Presymptomatic Detection of Infection in Humans Exposed to Influenza H1N1 or H3N2. *PLOS ONE* **8**, e52198 (2013).

4. Wilkinson, T. M. *et al.* Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. *Nat. Med.* **18**, 274–280 (2012).

5. Fritz, R. S. *et al.* Nasal Cytokine and Chemokine Responses in Experimental Influenza A Virus Infection: Results of a Placebo-Controlled Trial of Intravenous Zanamivir Treatment. *J. Infect. Dis.* **180**, 586–593 (1999).

6. Oral LY217896 for prevention of experimental influenza A virus infection and illness in humans. https://journals.asm.org/doi/epdf/10.1128/AAC.38.5.1178 doi:10.1128/AAC.38.5.1178.

7. Hayden, F. G. *et al.* Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *J. Clin. Invest.* **101**, 643–649 (1998).

8. Hayden, F. G. *et al.* Use of the Oral Neuraminidase Inhibitor Oseltamivir in Experimental Human InfluenzaRandomized Controlled Trials for Prevention and Treatment. *JAMA* **282**, 1240–1246 (1999).

9. McBride, J. M. *et al.* Phase 2 Randomized Trial of the Safety and Efficacy of MHAA4549A, a Broadly Neutralizing Monoclonal Antibody, in a Human Influenza A Virus Challenge Model. *Antimicrob. Agents Chemother.* **61**, e01154-17 (2017).

10. Zaas, A. K. *et al.* Gene Expression Signatures Diagnose Influenza and Other Symptomatic Respiratory Viral Infections in Humans. *Cell Host Microbe* **6**, 207–217 (2009).

11. Memoli, M. J. *et al.* Evaluation of Antihemagglutinin and Antineuraminidase Antibodies as Correlates of Protection in an Influenza A/H1N1 Virus Healthy Human Challenge Model. *mBio* **7**, e00417-16 (2016).

12. Fiore-Gartland, A. *et al.* Cytokine Profiles of Severe Influenza Virus-Related Complications in Children. *Front. Immunol.* **8**, (2017).

13. Hall, M. W. *et al.* Innate Immune Function and Mortality in Critically Ill Children With Influenza: A Multicenter Study. *Crit. Care Med.* **41**, 224–236 (2013).

14. Oshansky, C. M. *et al.* Mucosal immune responses predict clinical outcomes during influenza infection independently of age and viral load. *Am. J. Respir. Crit. Care Med.* **189**, 449–462 (2014).

15. Wong, S.-S. *et al.* Severe Influenza Is Characterized by Prolonged Immune Activation: Results From the SHIVERS Cohort Study. *J. Infect. Dis.* **217**, 245–256 (2018).

16. Wong, S.-S. *et al.* Activated CD4+ T cells and CD14hiCD16+ monocytes correlate with antibody response following influenza virus infection in humans. *Cell Rep. Med.* **2**, 100237 (2021).

17. Allen, E. K. *et al.* SNP-mediated disruption of CTCF binding at the IFITM3 promoter is associated with risk of severe influenza in humans. *Nat. Med.* **23**, 975–983 (2017).

18. Cohen, L. *et al.* A Modular Cytokine Analysis Method Reveals Novel Associations With Clinical Phenotypes and Identifies Sets of Co-signaling Cytokines Across Influenza Natural Infection Cohorts and Healthy Controls. *Front. Immunol.* **10**, 1338 (2019).

19. Cole, S. L. *et al.* M1-like monocytes are a major immunological determinant of severity in previously healthy adults with life-threatening influenza. *JCI Insight* **2**, e91868 (2017).

20. Dunning, J. *et al.* Progression of whole-blood transcriptional signatures from interferon-induced to neutrophil-associated patterns in severe influenza. *Nat. Immunol.* **19**, 625–635 (2018).

21. Jha, A. *et al.* Patterns of systemic and local inflammation in patients with asthma hospitalised with influenza. *Eur. Respir. J.* **54**, 1900949 (2019).

22. Lee, N. *et al.* Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J. Infect. Dis.* **200**, 492–500 (2009).

23. Lau, L. L. H. *et al.* Viral Shedding and Clinical Illness in Naturally Acquired Influenza Virus Infections. *J. Infect. Dis.* **201**, 1509–1516 (2010).

24. Tang, B. M. *et al.* Neutrophils-related host factors associated with severe disease and fatality in patients with influenza infection. *Nat. Commun.* **10**, 3422 (2019).

25. Parnell, G. P. *et al.* A distinct influenza infection signature in the blood transcriptome of patients with severe community-acquired pneumonia. *Crit. Care* **16**, R157 (2012).

26. Parnell, G. *et al.* Aberrant Cell Cycle and Apoptotic Changes Characterise Severe Influenza A Infection – A Meta-Analysis of Genomic Signatures in Circulating Leukocytes. *PLOS ONE* **6**, e17186 (2011).

27. Ramilo, O. *et al.* Gene expression patterns in blood leukocytes discriminate patients with acute infections. *Blood* **109**, 2066–2077 (2006).

28. Zhai, Y. *et al.* Host Transcriptional Response to Influenza and Other Acute Respiratory Viral Infections – A Prospective Cohort Study. *PLOS Pathog.* **11**, e1004869 (2015).

29. Choreño-Parra, J. A. *et al.* CXCL17 Is a Specific Diagnostic Biomarker for Severe Pandemic Influenza A(H1N1) That Predicts Poor Clinical Outcome. *Front. Immunol.* **12**, (2021).

30. Sellers, S. A., Fischer, W. A., Heise, M. T. & Schughart, K. Highly dampened blood transcriptome response in HIV patients after respiratory infection. *Sci. Rep.* **11**, 4465 (2021).

31. Mudd, P. A. *et al.* Distinct inflammatory profiles distinguish COVID-19 from influenza with limited contributions from cytokine storm. *Sci. Adv.* **6**, eabe3024 (2020).

32. Hagau, N. *et al.* Clinical aspects and cytokine response in severe H1N1 influenza A virus infection. *Crit. Care* **14**, R203 (2010).

33. Martinez-Ocaña, J. *et al.* Plasma cytokine levels and cytokine gene polymorphisms in Mexican patients during the influenza pandemic A(H1N1)pdm09. *J. Clin. Virol. Off. Publ. Pan Am. Soc. Clin. Virol.* **58**, 108–113 (2013).