# Protocol Flu prediction challenge – team Yale model 2 experimental

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## Preliminaries

We call this approach "experimental" as we plan to include further data sources "on the fly" when they become available. We will provide an updated version of this protcol whenever this happens. Currently, the main difference between this approach and the YaleModel1 approach is the treatment of ILI as one disease in an SIRS model (compared to two diseases – Flu and ILI without flu – in the YaleModel1. This is a difference in data source and modeling only, the calibration and prediction techniques are identical in both approaches.

## 1 Data sources

We use the ILInet data provided by the FluView website (http://gis.cdc.gov/grasp/fluview/fluportaldashboard.html). The data is transformed to cases per 100000 and are used for calibration and prediction.

As suggested by [1], we also use absolute humidity data from the National Land Data Assimilation System (NLDAS) project-2 dataset [2].

## 2 Modeling sources

We use a humidity based SIRS model developed by the Shaman group [1]. Therefore, we calculated a humidity profile for every city considered in this study. In order to obtain humidity profiles on a HHS region level, we average the humidity profiles of all cities that belong to an HHS region.

# 3 Calibration and prediction sources

## Compartmental models

We separate the population into $D$ mutually exclusive compartments. Let $X = (X_1, \ldots, X_D)$ denote the number of individuals in compartments $1, 2, \ldots, D$. Transitions between the groups are denoted with $r$ and we assume that there is a total of $Q$ transition paths. For each transition path $q_{ij}$ denotes the number of persons leaving subgroup $X_i$ for transition $j$ and $u_{ij}$ the number of persons entering subgroup $X_i$ for transition $j$:

$$q_{1j}\ X_1\ +\ q_{2j}\ X_2\ +\ \ldots\ +\ q_{Dj}\ X_D\ \longrightarrow\ u_{1j}\ X_1\ +\ u_{2j}\ X_2\ +\ \ldots\ +\ u_{Dj}\ X_D, \quad \text{for } j = 1, \ldots, r$$

The so called stoichiometric matrix $\Gamma$ is a $D \times r$ dimensional matrix. Its entries $s_{ij} = u_{ij} - q_{ij}$ describe the net effect of transition $j$ to subgroup $X_i$. In terms of ODEs the system would read as

$$\frac{d}{dt}x(t;\theta,x_0)\ =\ \Gamma\ \Lambda(x(t;\theta,x_0),\theta),\ \text{with } x(0,\theta,x_0) = x_0 \tag{1}$$

with a rate law $\Lambda = (\Lambda_1, \ldots, \Lambda_r)^T$ describing the speed of the transitions, an initial value $x_0$ and a parameter vector $\theta$.

Stochastic modeling is important in systems with small numbers of people in at least one of the subgroups, where stochastic fluctuations may have a major influence on the disease dynamics. Stochastic modeling can model each transition of a person from one subgroup to another explicitly, by choosing the transition and the time of the transition stochsatically. Both order of transitions and waiting times are stochastic quantities depending on the system's state and the rate laws. The master equation (ME, equation 2) describes the time evolution of the probability of the system to be in a state $\nu$:

$$\begin{aligned} \frac{d}{dt}P_\theta(\nu,t|\nu_0,t_0)\ &=\ \sum_{r=1}^{Q}\Big(\tilde{\Lambda}_r(\nu - s_r,\theta)P_\theta(\nu - s_r,t|x_0,t_0) - \tilde{\Lambda}_r(\nu,\theta)P_\theta(\nu,t|\nu_0,t_0)\Big) \\ P_\theta(\nu,t_0|\nu_0,t_0) &= \begin{cases} 1 & \nu = \nu_0 \\ 0 & \text{else} \end{cases} \end{aligned} \tag{2}$$

with a vector $s_j = (s_{1r}, \ldots, s_{Dr})^T$ and with a propensity $\tilde{\Lambda}$ that can be calculated from the rate law $\Lambda$ and describes the speed of the reactions in terms of particle numbers.

The Gillespie algorithm [3] is the method of choice to simulate stochastic time courses. It is an iterative algorithm simulating reaction event after reaction event using functions of random numbers to determine both time step and reaction. The resulting time course is then a discrete state continuous time Markov jump process.

## Calibration

Observations $y_1, \ldots, y_n$ are obtained at time points $t_1, \ldots, t_n$. These might be for example weekly diagnoses of new cases. However, there is no need for equidistant observations. We use an iterative

procedure to update our knowledge with each new observation. Let us assume that we can summarize our prior knowledge on the parameters before the first observation in a prior distribution $\pi_0(\theta)$. We use each new observation $y_i$ to update our knowledge on the parameter $\theta$ by multiplying our prior with the probability to observe $y_i$:

$$\pi_i(\theta|y_1,\ldots,y_{i-1},y_i) \;=\; \pi_{i-1}(\theta|y_{i-1},\ldots,y_1)\mathcal{P}(y_i|y_1,\ldots,y_{i-1};\theta) \tag{3}$$

Note that the posterior at time $t_{i-1}$, $\pi_{i-1}$, is as well the prior at time $t_i$. For $i = 1$ we set $\pi_0(\theta|y_0) = \pi_0(\theta)$ as we do not have an observation at time $t_0$. The two following subsection will explain a) how to set up a suitable approximation for $\mathcal{P}$ and b) how to propagate a sample of the distribution $\pi_i$ through time.

**MSS method**

We will use the multiple shooting for stochastic system's method to approximate $\mathcal{P}$ in a way that is fast enough to be computational feasible but still accurate enough to allow for reliable calibration and prediction. The MSS method has been developed in a systems biology context [4–6] and already successfully applied to calibration and prediction in epidemics [7]. This subsection will briefly summarize it, for details we refer the reader to the original publications.

Let $\Pi(\cdot|Y_i)$ denote the belief state at time $t_i$ given the accumulated observations $Y_i$. Now by conditioning on the epidemic state at time $t_{i-1}$, i.e. $\nu_{i-1}$, the probability function $\mathcal{P}(\cdot|y_1,y_2,\ldots,y_{i-1};\theta)$ in Eq. (3) can be calculated as:

$$\mathcal{P}(y_i|y_1,y_2,\ldots,y_{i-1};\theta) = \sum_{\nu_{i-1}\in\Omega_{i-1}} P(y_i|\nu_{i-1};\theta)\;\Pi(\nu_{i-1}|y_1,y_2,\ldots,y_{i-1};\theta), \tag{4}$$

where $\Omega_{i-1}$ is the support of the belief state at time $t_{i-1}$. By conditioning on the state of the epidemic at time $t_i$, the probability function $\mathcal{P}(\cdot|y_1,y_2,\ldots,y_{i-1};\theta)$ in Eq. (4) can be calculated as:

$$\begin{aligned}&\mathcal{P}(y_i|y_1,y_2,\ldots,y_{i-1};\theta)\\ &\quad= \sum_{\nu_i\in\Omega_i}\sum_{\nu_{i-1}\in\Omega_{i-1}} P(y_i|\nu_i,\nu_{i-1};\theta)p(\nu_i|\nu_{i-1};\theta)\;\Pi(\nu_{i-1}|y_1,y_2,\ldots,y_{i-1};\theta).\end{aligned} \tag{5}$$

Calculating the probability function (5) can be computationally difficult. First, it requires calculating or approximating the transition probability $p(\nu_i|\nu_{i-1};\theta)$ for each pair $(\nu_i,\nu_{i-1}) \in \Omega_i \times \Omega_{i-1}$, and second, it involves enumeration over the set $\Omega_i \times \Omega_{i-1}$, which can be prohibitively large even for simple epidemic models.

We will first describe a way to approximate $p$ such that it is still accurate enough for calibration and prediction but also computationally fast enough to be applied to realistic size models. After that we will address the belief state $\Pi$.

**Approximating state transition probabilities**

Finding the exact state transition probability function $p(\cdot)$ can be difficult, and in many cases impossible, as state spaces in epidemic models can be quite large or unbounded. To overcome this problem, we employ a linear noise approximation (LNA) method to approximate the probability distribution of the new epidemic state $\nu_i$ given the previous state $\nu_{i-1}$, i.e. $p(\nu_i|\nu_{i-1};\theta)$. The LNA has been previously used to estimate parameters of stochastic biochemical reaction models [5, 6]. Here we extend Zimmer and Sahleâs method [6] to calibrate stochastic epidemic models where the

true epidemic state is only partially observable.

To approximate the probability distribution of $\nu_i$ given the state $\nu_{i-1}$ , the LNA method uses an ordinary differential equations (ODE) model to approximate the *expected* behavior of the epidemic over the period $[t_{i-1}, t_i]$ and to identify a co-variance matrix to characterize the uncertainty around the epidemic behavior over this interval. We use the following notation to denote the ODE epidemic model used by the LNA method:

$$\begin{aligned} \frac{d}{dt}x(t, x_0; \theta) =& \Gamma\Lambda(x(t, x_0; \theta), \theta), \\ x(0, x_0; \theta) =& x_0. \end{aligned} \tag{6}$$

In the ODE system (6), the vector $x(t, x_0; \theta)$ is the epidemic state of the ODE model at time $t$ given the initial state $x_0$, the vector $\Lambda(x(t, x_0; \theta), \theta)$ denotes the instantaneous changes in the epidemic when at state $x(t, x_0; \theta)$, and the matrix $\Gamma$ describes how the instantaneous changes at time $t$ impact the epidemic state at time $t + \Delta t$ (see subsequent sections for an example).

The LNA assumes that the probability distribution of $\nu_i|\nu_{i-1}$ can be properly approximated by a normal distribution $\mathcal{N}(\mu_i, \mathrm{cov}_i)$. The mean vector $\mu_i$ is the solution of ODE system (6) with $\nu_{i-1}$ as the initial condition (i.e. $\mu_i = x(t_i - t_{i-1}, \nu_{i-1}; \theta)$) and the variance matrix $\mathrm{cov}_i = \Sigma(t_i - t_{i-1}, \nu_{i-1}; \theta)$ is the solution of the following ODE systems [8, 9]:

$$\begin{aligned} \frac{d}{dt}\Sigma(t, \nu_{i-1}; \theta) &= J(x, \theta)\Sigma(t, \nu_{i-1}; \theta) + \Sigma(t, \nu_{i-1}; \theta)J(x, \theta)^T + D(x; \theta) \\ \Sigma(0, \nu_{i-1}; \theta) &= 0_{K\times K}. \end{aligned} \tag{7}$$

In the ODE system (7), $J(x, \theta) = \Gamma\frac{d}{dx}\Lambda(x, \theta)$ and $D$ is a $K \times K$ matrix with the $(i, j)$ entity equal to $\sum_{k=1}^{K} \Gamma_{jk}\Gamma_{jk}\Lambda(x, \theta)$, where $K$ is the number of compartments in the epidemic model.

An important question remains about how well this proposed LNA method approximates the probability distribution of epidemic states. Relying on an extensive numerical analysis, we will demonstrate in the Results section that for the epidemic scenarios considered, our method yields accurate parameter estimations and reliable predictions. We also note that our method does not rely on a single LNA model to approximate the entire epidemic trajectory. For each observation period $[t_{i-1}, t_i]$, it generates a new LNA model to approximate the epidemic behavior only over this particular period.

### Updating belief states

It remains to address the belief state $\Pi$. We will first describe one possibility according to previous work on the MSS method. This idea is more general is it can be used with general observation probabilities $P$. The second is specificically designed for gaussian observation noise.

One way to simplify the computational complexity of Eq. (5) is to represent the belief state $\Pi(\cdot|Y_i)$ as a step function that takes 1 for the most probable state (denoted by $\hat{\nu}$ ) and 0 elsewhere. This allows us to approximate the function $\mathcal{P}(\cdot)$ in Eq. (5) with:

$$\tilde{\mathcal{P}}(y_i|y_1, y_2, \ldots, y_{i-1}; \theta) = \sum_{\nu_i \in \Omega_i} P(y_i|\nu_i, \hat{\nu}_{i-1}; \theta)p(\nu_i|\hat{\nu}_{i-1}; \theta), \tag{8}$$

where $\hat{\nu}_{i-1}$ represents the most likely epidemic state given observations $Y_{i-1} = (y_1, y_2, \ldots, y_{i-1})$. By the definition of epidemic states, the transition from state $\nu_{i-1}$ to $\nu_i$ generates a unique set of observations, and it it trivial to find whether the state transition $\hat{\nu}_{i-1}$ to $\nu_i$ can generate the observation $y_i$ (see design of performance analysis for an illustrative example). Therefore, for a given observation $y_i$, the probability $P(y_i|\nu_i, \hat{\nu}_{i-1}; \theta)$ in Eq. (8) is equal to 1 if the transition from state $\hat{\nu}_{i-1}$ to $\nu_i$ results in observing $y_i$, and is zero otherwise. To calculate $\tilde{\mathcal{P}}(y_i|\hat{\nu}_{i-1}; \theta)$ in Eq. (8), it only remains to identify the state transition probability function $p(\nu_i|\hat{\nu}_{i-1}; \theta)$ and a state estimation scheme.

We now describe how to update our belief about the true state of the epidemic, denoted by $\Pi(\cdot)$, once new observations $y_i$ are obtained. We first note that $\Pi(\cdot)$ is defined to return 1 for the most likely state $\hat{\nu}$ , and zero elsewhere. Therefore, given the state $\hat{\nu}_{i-1}$ at time $t_{i-1}$, the probability of observing $y_i$ during the interval $[t_{i-1}, t_i]$ is equal to $P(y_i|\nu_i, \hat{\nu}_{i-1}; \theta)p(\nu_i|\hat{\nu}_{i-1}; \theta)$ (see the discussion prior to Eq. (5)).

Now, the most probable state at time $t_i$, $\hat{\nu}_i$, is the one that leads to the highest probability of observing $y_i$:

$$\hat{\nu}_i = \arg\max_{\nu_i \in \Omega_i} P(y_i|\nu_i, \hat{\nu}_{i-1}; \theta)p(\nu_i|\hat{\nu}_{i-1}; \theta). \tag{9}$$

**Re-sampling to avoid filter degeneracy**

The above described methodology to evaluate the probability to observe a sequence $y_1, \ldots, y_n$ can be very flexibly combined with various optimization techniques such as global optimization, gradient based or Bayesian approaches. Here, we choose a Bayesian approach. A posterior distribution $\pi_i$ is calculated based on a prior $\pi_{i-1}$ and its update by the probability $P(y_i|y_1, \ldots, y_{i-1}; \theta)$ as in equation (3). Filtering techniques [1, 10] update a sample from the prior distribution with the probability of the current observation to calculate a posterior distribution.

Therefore, we initially sample $M$ parameters $\theta_1, \ldots, \theta_M$ from a prior parameter distribution $\pi_0$ and $M$ initial states $\nu_{0,1}, \ldots, \nu_{0,M}$ from a prior state distribution $\Pi(\nu_0)$. We consider the initial states as an additional dimension of the parameter and denote $\vartheta = (\theta, \nu_0)$. For each of the vectors $\vartheta_m, m = 1, \ldots, M$ we calculate the probabilities $\pi_i(\vartheta_m)$ recursively. This results in a weighted sample of parameters $\vartheta_1, \ldots, \vartheta_M$ with weights $w_1, \ldots, w_M$.

One potential drawback of this procedure is so called filter degeneracy. We use a finite set of parameters $\vartheta_1, \ldots, \vartheta_M$ as a sample of our prior distribution and weight it with the probability of each new upcoming observation. After some observations and weighting it might happen that only very few parameters $\vartheta_m$ have some weight and all the others have weights that are several orders of magnitude lower. In the extreme scenario, only one parameter vector $\vartheta$ is left and all others have negligible weights. This is a serious issue for calculating confidence intervals or performing reliable predictions as it means that our posterior is basically a point distribution.

To deal with it, one needs two things: 1) a mechanism to detect it and 2) a mechanism to resolve it.

**Detection of filter degeneracy** is relatively simple. One needs to calculate which fraction of parameter vectors substantially contribute weights to the overall sample. One way to do this is

described in [11]: As a first step, the weights are normalized:

$$\tilde{w}_m = \frac{w_m}{\sum_{j=1}^{M} w_j}$$

Then, the so called effective sample size $N_{\text{eff}}$ is estimated as a measure of (non-)degeneracy (comp geo paper):

$$\hat{N}_{\text{eff}} = \frac{1}{\sum_{m=1}^{M} w_m^2} \tag{10}$$

In the beginning all particles have equal weight and, hence, $N_{\text{eff}}$ is $M$. In the other extreme, if all weight is on one particle, $N_{\text{eff}}$ is 1. Therefore, one way of detection of degeneracy is to determine a threshold value $N_C$ below which one takes measures to re-sample the particles. The calculation of $N_{\text{eff}}$ it not time-consuming and, hence, one can easily perform this check in every iteration.

It is unfortunately a bit more difficult, how to **resolve the filter degeneracy**. We will present one approach which was successful for us but note that IMIS [12] presents an alternative. As soon as filter degeneracy is detected, re-sample $L$ parameters $\tilde{\vartheta}_1, \ldots, \tilde{\vartheta}_L$ from $\vartheta_1, \ldots, \vartheta_M$ according to current weights $w_1, \ldots, w_M$. Use these sample and a kernel density estimation to calculate

$$\hat{f}(\vartheta) = \frac{1}{Mb} \sum_{l=1}^{L} K\left(\frac{\vartheta - \tilde{\vartheta}_l}{b}\right) \tag{11}$$

with a bandwidth $b$ and a kernel $K$.

Next, $M$ new points are sampled from this density $\hat{f}$ and the new weights are calculated with

$$w_m = \prod_{k=1}^{i} \mathcal{P}(y_i | y_1, \ldots, y_{i-1}, \theta_m) \tag{12}$$

with $i$ being the current iteration and the $m$-th initial state estimate $\nu_{0,m}$ determined by the state component of $\vartheta_m$.

1. Initialization
   (a) Choose an initial prior probability function $\pi_0(\theta)$.
   (b) Choose an initial set of parameters $\{\theta_1, \ldots, \theta_l\}$.
2. Calibration: For each observation $y_i$, $i \in \{1, 2, \ldots\}$,
   (a) Calculate the probability $\tilde{\mathcal{P}}(y_i|Y_{i-1}; \theta_m)$ for every $m = 1, \ldots, M$ (using Eq. (8) and the method we described).
   (b) Update the parameter posterior distribution: $\pi_i(\theta|Y_i) \leftarrow \tilde{\mathcal{P}}(y_i|Y_{i-1}; \theta_m)\pi_{i-1}(\theta|Y_{i-1})$ for every $m = 1, \ldots, M$.
   (c) Update the belief state $\Pi(\nu_i|Y_i; \theta_m)$ for every $m = 1, \ldots, M$ (through solving optimization problem (9)).
   (d) Check whether degeneracy occurs by comparing the effective sample size $N_{\text{eff}}$ (10) with a threshold $N_C$.
   (e) If step (d) detects filter degeneracy: use a density estimate $\hat{f}$ (11) to re-sample new parameters.

Figure 1: An algorithm for real-time calibration of stochastic compartmental epidemic models including mechanisms against filter degeneracy

**Prediction**

Predictions are done based on the posterior distribution of the parameters and states and with the help of the simulation model. Let us denote our prediction target with $Z$ where $Z$ can be a very general target (e.g. next weeks cases or peak timing). We are interested in calculating the probability density $P(Z = z)$. This can be done by:

$$P(Z|Y_i) = \int_{\theta \in \Theta} \int_{\nu_i \in \Omega_i} P(Z|\nu_i; \theta)\ \Pi(\nu_i|Y_i; \theta)\ \pi_i(\theta|Y_i)\ d\nu_i\ d\theta. \tag{13}$$

where $P(Z|\nu_i; \theta)$ is the probability to observe $Z$ given $\nu_i$ and $\theta$. This probability can be calculated with the help of the simulation model.

Re-sample $\tilde{\vartheta}_1, \ldots, \tilde{\vartheta}_{\bar{L}}$ from the current weighted sample $\vartheta_1, \ldots, \vartheta_L$ according to its weights $w_1, \ldots, w_L$. Carry out $\bar{L}$ simulations initialized with the state estimate $\hat{\nu}_i$ that corresponds to the parameter $\theta_l$ until the time of the target $Z$.

# 4 Specifications

- The humidity based SIRS model has four parameters, $L$, $D$, $R0max$, $R0min$ and two initial states: $S_0$ and $I_0$. We use 1000 parameter to cover this 6 dimensional space, initially uniformly distributed on $[365, 3650] \times [1.5, 7] \times [1.3, 4] \times [0.8, 1.2])$ and $[50000, 70000] \times [5, 100]$.
- We use an additional Gaussian observation noise of standard deviation 10.
- We use 100 draws from the posterior to run the simulation model to obtain predictions.

- Density estimation for re-sampling: we use Mathematica's Gaussian mixture kernel function with max 5 mixture kernel (for run time reasons) and a bandwidth of 100 for $L$, 0.5 for $D$, 0.5 for $R0max$, 0.025 for $R0min$, 1000 for $S_0$ and the median of the re-samples for $I_0$.
- Density estimation for target posteriors: We use Mathematica's Smooth Kernel Distribution density estimation function.

Historical priors are calculated for the target Season Onset", "Season Peak Week" and "Season Peak Percentage" by taking the data from years 1997/1998 to 2015/2016 without the atypical 2009/ 2010 season, the Mathematica function Smooth Kernel Distribution is used here as well for density estimation. Additional tuning is performed for these targets as follows:

- Season Onset: if 99% quantile of posterior smaller than minimum of historical prior OR 1% quantile of posterior greater than maximum of historical prior, use historical prior, else, truncate posterior with minimum and maximum of historical priors from EW2 onwards not for season onset anymore.
- Season Peak Week: if epidemic week no later than week 6, then, historical prior otherwise target posterior.
- Season Peak Percentage: if 99% quantile of posterior smaller than minimum of historical prior OR 1% quantile of posterior greater than maximum of historical prior, use historical prior, else, truncate posterior with minimum and maximum of historical priors.
- From EW 1 onwards - 1-4 week predictions: posterior is truncated on [0,13100] based on historical experience.

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