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Analytic likelihood function for data analysis in the starting phase of an influenza outbreak

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Abstract

Influenza is a disease which frequently captures media attention. Seasonal influenza epidemics still are the best data source for investigations on spreading of the disease, even when getting prepared to pandemic influenza of newly mutated strains. We investigate data from an internet based surveillance system, the *Influenzanet*. Our previous work concentrated on analysing the noise floor before the seasonal outbreak starts and the burn out of sucsceptibles at the hight and final phase of the epidemics. Both scenarions could be modelled analytically, and likelihood functions be derived rigorously. In the present study we model the start of the epidemic outbreak, and again can derive the likelihood function analytically. Our approximation captures the initial exponential growth phase of the epidemic. Especially the interplay of the noise floor and the onset of the epidemic season is of importance to understand when the outbreak happens and when still normal fluctuations in the noise floor might give erroneous alerts.

Key words: stochastic dynamics, master equation, generating function, partial differential equation, maximum likelihood, Influenzanet

1 Introduction

Recent outbreaks of influenza have allerted the public of possible pandemic spread of a new influenza virus mutation. Also seasonal influenza is driven to most extend by newly appearing slight mutations in already in humans existing strains. Hence, seasonal influenza epidemics still are the best data source for investigations on spreading of the disease, even when getting prepared to pandemic influenza of newly mutated strains.

Here we investigate data from an internet based surveillance system, the *Influenzanet*. Our previous work [1] concentrated on analysing the noise floor, before the seasonal outbreak starts, as a Poisson process and then the burn out of sucsceptibles at the hight and final phase of the epidemics. Both scenarios could be modelled analytically, and likelihood functions be derived rigorously.

In the present study we model epidemic outbreak of influenza as an susceptible, infected, recovered process (SIR). We calculate from the master equation, which is traditionally widely used in physics and chemistry [2, 3], the partial differential equation (PDE) in two variables for the generating function in order to find solutions for the master equation [2, 4, 5, 9]. However, this PDE is analytically untractable. Therefore, the start of the epidemic outbreak then is approximated by the assumption of abundantly many susceptible individuals during the onset phase. This assumption significantly simplifies the PDE to a form in only one variable, similar to the ones treated earlier [1]. It can be shown rigorously that the waning immunity transition from recovered R back to susceptibles S does not play any role during the onset of the epidemic, as defined by our assumption of abundance of susceptibles.

Though the PDE is still much more complicated than in the simple test cases treated in [1], we can solve the PDE and obtain the generating function analytically in closed form. From the generating function the likelihood for future parameter analysis can be calculated as well as the dynamics of the mean value, demonstrating clearly that we describe with our approximation of abundantly many susceptibles the exponential growth phase of the epidemic onset. Especially the interplay of the noise floor and the onset of the epidemic season is of importance to understand when the out break happens and when still normal fluctuations in the noise floor might give erroneous alerts. The analysis is applicable to influenza time series, originated from *Influenzanet*, an internet based surveillance system which has operated for a number of years successfully in the Netherland, Belgium, Portugal and Italy, and is in the process to operate in further European countries like Germany, France and the United Kingdom of the British Isles [6, 7, 8]. Such a system in parallel to the classical national medical surveillance systems could serve as an early warning system in future pandemics, since information can be spread faster than in traditional notification systems.

2 Stochastic epidemic dynamics and generating function

One of the basic epidemic process is the susceptible, infected, recovered (SIR) epidemic, in which susceptible individuals S become infected on contact with already infected I with infection rate β and recover with rate γ into the R class. Eventually, the recovered and immune R can become susceptible again with rate α. For the onset phase of an epidemic this waining susceptibility does not play any important role, as we will show below. For recurrent outbreaks in seasonal influenza this will become important though [10]. The SIR epidemic is given by the reaction scheme

$$\begin{array}{rcl} S+I & \stackrel{\beta}{\longrightarrow} & I+I \\ I & \stackrel{\gamma}{\longrightarrow} & R \\ R & \stackrel{\alpha}{\longrightarrow} & S \end{array} \qquad (1)$$

giving the following master equation (stochastic Markov process in continuous time) for fixed population size N, hence $N = S + I + R$.

The master equation for the SIR system with $R = N - S - I$, hence we only need to consider the probability of S and I, and R follows from this, is given by

$$\begin{aligned} \frac{d}{dt}p(S,I,t) &= \frac{\beta}{N}(I-1)(S+1))\ p(I-1,t) + \gamma(I+1)\ p(S,I+1,t) \\ &\quad +\alpha(R+1)\ p(S-1,I,t) \\ &\quad -\left(\frac{\beta}{N}I(N-I) + \gamma I + \alpha R\right)\ p(S,I,t) \end{aligned} \tag{2}$$

with $(R+1) = N - (S-1) - I$. In order to solve the master equation we can use generating functions or charateristic functions, obtaining an eventually easier solvable partial differential equation (PDE). In the folowing we apply the generating function to the above given master equation.

2.1 Generating function

The generating function for the master equation in two variables S and I is defined as

$$\langle x^I y^S \rangle := \sum_{I=0}^{N}\sum_{S=0}^{N} x^I y^S \cdot p(S,I,t) =: f(x,y,t) \tag{3}$$

and it generates moments of the stochastic process, once it is determined from that process. It is

$$\frac{\partial f(x,y,t)}{\partial x} = \sum_{I=0}^{N}\sum_{S=0}^{N} I x^{I-1} y^S \cdot p(S,I,t) \tag{4}$$

and

$$\frac{\partial f(x,y,t)}{\partial y} = \sum_{I=0}^{N}\sum_{S=0}^{N} x^I \cdot S y^{S-1} \cdot p(S,I,t) \tag{5}$$

and

$$\frac{\partial^2 f(x,y,t)}{\partial x \partial y} = \sum_{I=0}^{N}\sum_{S=0}^{N} I x^{I-1} \cdot S y^{S-1} \cdot p(S,I,t) \tag{6}$$

etc. and from this we obtain the moments by evaluating at point $(x,y) = (1,1)$,

$$\left.\frac{\partial f(x,y,t)}{\partial x}\right|_{x=1,y=1} = \sum_{I=0}^{N}\sum_{S=0}^{N} I \cdot p(S,I,t) = \langle I \rangle \tag{7}$$

respectively

$$\left.\frac{\partial f(x,y,t)}{\partial y}\right|_{x=1,y=1} = \sum_{I=0}^{N}\sum_{S=0}^{N} S \cdot p(S,I,t) = \langle S \rangle \tag{8}$$

and for correlations e.g.

$$\left.\frac{\partial^2 f(x,y,t)}{\partial x \partial y}\right|_{x=1,y=1} = \sum_{I=0}^{N}\sum_{S=0}^{N} SI \cdot p(S,I,t) = \langle SI \rangle \quad . \tag{9}$$

Inserting the generating function into the stochastic master equation gives a partial differential equation (PDE) to be solved. From the generating function the probability can be obtained as a back transformation via Taylor's expansion of $f(x,y,t)$ in respect to x and y. The dynamics for the generating function is given by

$$\frac{\partial}{\partial t} f(x,y,t) = \sum_{I=0}^{N}\sum_{S=0}^{N} x^I y^S \cdot \frac{d}{dt} p(S,I,t) \tag{10}$$

and by inserting the master equation Eq. (3) into Eq. (10) and taking Eqs. (4), (5) and (6) gives the following PDE

$$\frac{\partial f}{\partial t} = \frac{\beta}{N} x \cdot (x-y) \frac{\partial^2 f}{\partial x \partial y} + \gamma(1-x)\frac{\partial f}{\partial x} + \alpha(1-y)\left(Nf - x\frac{\partial f}{\partial x} - y\frac{\partial f}{\partial y}\right) \tag{11}$$

and with initial condition $p(S,I,t_0) = \delta_{S,S_0} \cdot \delta_{I,I_0}$ giving the initial condition for the generating function $f(x,y,t_0) = x^{I_0} \cdot x^{S_0}$.

2.2 Dynamics of the mean value

The dynamics of the mean values can be obtained via the generating function and its PDE as

$$\frac{d}{dt}\langle S \rangle = \frac{d}{dt}\left(\left.\frac{\partial f(x,y,t)}{\partial y}\right|_{x=1,y=1}\right) = \left.\left(\frac{\partial}{\partial y}\left(\frac{\partial f}{\partial t}\right)\right)\right|_{x=1,y=1} \tag{12}$$

and inserting the original PDE, Eq. (11), leads after some calculation to

$$\frac{d}{dt}\langle S \rangle = -\frac{\beta}{N}\langle SI \rangle + \alpha(N - \langle S \rangle - \langle I \rangle) \tag{13}$$

with $\langle R \rangle = N - \langle S \rangle - \langle I \rangle$ as one would expect from direct calculations from the master equation. The well known closed ordinary differential equation for the number of infected for the SIS system is found from here by inserting the mean field approximation, i.e. neglecting higher moments $\langle SI \rangle - \langle S \rangle\langle I \rangle \approx 0$. Hence we obtain

$$\frac{d}{dt}\ \langle S \rangle = -\frac{\beta}{N}\langle I \rangle\langle S \rangle + \alpha\langle R \rangle \tag{14}$$

respectively for $\langle I \rangle$

$$\frac{d}{dt}\langle I \rangle = \frac{d}{dt}\left(\left.\frac{\partial f(x,y,t)}{\partial x}\right|_{x=1,y=1}\right) = \frac{\beta}{N}\langle SI \rangle - \gamma\langle I \rangle \tag{15}$$

and in mean field approximation

$$\frac{d}{dt}\ \langle I \rangle = \frac{\beta}{N}\langle I \rangle\langle S \rangle - \gamma\langle I \rangle \quad . \tag{16}$$

The mean field ODEs for the SIR epidemics, Eq. (14) and (16), are the starting point of all deterministic modelling.

2.3 Application to the onset of the epidemic in a linearized model

We now approximate for the initial phase of the SIR epidemics the master equation by the assumption of an abundant number of susceptible individual, hence the reaction scheme has to be altered in the first component as

$$S^* + I \quad \xrightarrow{\beta} \quad I + I \tag{17}$$

with S^* a constant for the number of susceptibles, hence $S - 1 \approx S^*$ etc. The master equation for this process is given by

$$\begin{aligned} \frac{d}{dt}p(I,t) \quad &= \quad \frac{\beta}{N}S^*(I-1)p(I-1,t) + \gamma(I+1)p(I+1,t) \\ &\quad - \left(\frac{\beta}{N}S^*I + \gamma I\right)p(I,t) \end{aligned} \tag{18}$$

and with the definition for the constant $\tilde{\beta} := \frac{\beta}{N}S^*$ we obtain

$$\frac{d}{dt}p(I,t) = \tilde{\beta}(I-1)\,p(I-1,t) + \gamma(I+1)\,p(I+1,t) - \left(\tilde{\beta}I + \gamma I\right)\,p(I,t) \quad . \tag{19}$$

Due to the autocatalytic first reaction which creates from one infected two infected, the force of infection increases, such that we expect an exponential increase of the number of infected, which is characteristic for the intial phase of an epidemic. We also observe here that the waining immunity transition proportional to α vanishes from the master equation due to our approximation.

Since the S-dependence in the master equation drops out, the generating function is now simply defined as

$$\langle x^I \rangle := \sum_{I=0}^{N} x^I \cdot p(I,t) =: f(x,t) \tag{20}$$

and it generates moments of the stochastic process, once it is determined from that process. It is

$$\frac{\partial f(x,t)}{\partial x} = \sum_{I=0}^{N} I x^{I-1} \cdot p(I,t) \tag{21}$$

and $(\partial f/\partial x)|_{x=1} = \langle I \rangle$.

Inserting the generating function into the stochastic master equation gives a partial differential equation PDE to be solved. From the generating function the probability can be obtained as a back transformation via Taylor's expansion of $f(x,t)$ in respect to x, see Eq. (3),

$$p(I,t) = \frac{1}{I!}\left.\frac{\partial^I f(x,t)}{\partial x^I}\right|_{x=0} \quad . \tag{22}$$

The dynamics for the generating function is given by

$$\frac{\partial}{\partial t}f(x,t) = \sum_{I=0}^{N} x^I \cdot \frac{d}{dt}p(I,t) \tag{23}$$

and by inserting the master equation Eq. (19) into Eq. (23) gives after some calculation the following PDE

$$\frac{\partial f}{\partial t} \; = \; \left((1-x)(\gamma - \tilde{\beta} x)\right) \frac{\partial f}{\partial x} \tag{24}$$

and with initial condition $p(I,t_0) = \delta_{I,I_0}$ giving the initial condition for the generating function $f(x,t_0) = x^{I_0}$. With these intial conditions, given we found a solution of Eq. (24), we obtain via the back transformation Eq. (22) the solution $p(I,t|I_0,t_0)$ to be used for the likelihood function.

This PDE can be solved by the separation ansatz $z(x,t) = u(x) \cdot v(t)$ and to include initial condition using another function $\Phi(z)$ as

$$f(x,t) := \Phi(z) = \Phi(u(x) \cdot v(t)) \quad . \tag{25}$$

Inserting this ansatz into the PDE gives

$$\begin{aligned} \frac{\partial}{\partial t} f(x,t) &= \frac{d\Phi}{dz} \cdot \frac{\partial z}{\partial t} = \frac{d\Phi}{dz} \cdot u(x) \frac{\partial v}{\partial t} = (1-x)(\gamma - \tilde{\beta} x) \frac{\partial f}{\partial x} \\ &= (1-x)(\gamma - \tilde{\beta} x) \frac{d\Phi}{dz} \frac{\partial z}{\partial x} \\ &= (1-x)(\gamma - \tilde{\beta} x) \frac{d\Phi}{dz} \cdot \frac{\partial u}{\partial x} v(t) \end{aligned} \tag{26}$$

separating the PDE into two ODEs for $v(t)$ with $dv/dt = v(t)$ and $u(x)$ with $du/dx = (1/(1-x)(\gamma - \tilde{\beta} x)) u(x)$ and arbitrary function $\Phi(z)$. After integration we find the special solutions

$$v(t) = e^t \qquad , \qquad u(x) = \left(\frac{x-1}{x - \frac{\gamma}{\tilde{\beta}}} \right)^{\frac{1}{\tilde{\beta}-\gamma}} \tag{27}$$

and as solution for the separation ansatz

$$z(x,t) = \left(\frac{x-1}{x - \frac{\gamma}{\tilde{\beta}}} \right)^{\frac{1}{\tilde{\beta}-\gamma}} \; e^t \quad . \tag{28}$$

To determine the function $\Phi(z)$ from the initial condition $f(x,t_0) = x^{I_0}$ we insert for time t_0

$$f(x,t_0) = x^{I_0} = \Phi(z) = \Phi \left(\left(\frac{x-1}{x - \frac{\gamma}{\tilde{\beta}}} \right)^{\frac{1}{\tilde{\beta}-\gamma}} \; e^t \right) \tag{29}$$

and from $z = \left(\frac{x-1}{x - \frac{\gamma}{\tilde{\beta}}} \right)^{\frac{1}{\tilde{\beta}-\gamma}} \; e^{t_0}$ we determin $x(z)$ as

$$x = \frac{\frac{\gamma}{\tilde{\beta}} \left(z \, e^{t_0}\right)^{\tilde{\beta}-\gamma} - 1}{\left(z \, e^{t_0}\right)^{\tilde{\beta}-\gamma} - 1} \tag{30}$$

and finally insert this into $\Phi(z)$ giving

$$\Phi(z) = \Phi\left(\left(\frac{x-1}{x-\frac{\gamma}{\tilde\beta}}\right)^{\frac{1}{\tilde\beta-\gamma}} e^{t_0}\right) = \left(\frac{\frac{\gamma}{\tilde\beta}\left(z\, e^{t_0}\right)^{\tilde\beta-\gamma}-1}{\left(z\, e^{t_0}\right)^{\tilde\beta-\gamma}-1}\right)^{I_0} \quad . \tag{31}$$

Up to now we considered for $\Phi(z)$ only the initial time t_0. Now we take z for all times t to obtain the general solution for the generating function in the special case of $\beta = 0$ $f(x,t) = \Phi(z(x,t)$ with $z(x,t)$ from Eq. (28). We finally obtain the general solution for all times

$$f(x,t) = \left(\frac{\frac{\gamma}{\tilde\beta}(x-1)\, e^{(\tilde\beta-\gamma)(t-t_0)} - \left(x-\frac{\gamma}{\tilde\beta}\right)}{(x-1)\, e^{(\tilde\beta-\gamma)(t-t_0)} - \left(x-\frac{\gamma}{\tilde\beta}\right)}\right)^{I_0} \tag{32}$$

and from this we can obtain via Eq. (22) the probability $p(I,t)$, respectively the transition probability $p(I,t|I_0,t_0)$ needed for the likelihood function [1], because we used the initial conditions as described above.

From Eq. (32) we can also calculate the solution for the mean value as

$$\langle I(t)\rangle = \left.\frac{\partial f(x,t)}{\partial x}\right|_{x=1} = I_0\, e^{(\tilde\beta-\gamma)(t-t_0)} \tag{33}$$

giving an exponential time dependence. This demonstrates that our approximation of abundantly many susceptibles describes the exponential growth phase of the SIR epidemics.

2.4 Constructing the likelihood function

For observed data points in a time series $(I_0, I_1, ...I_n)$ at times $(t_0, t_1, ...t_n)$ we have the joint probability of data points under the model assumption

$$\begin{aligned} p(I_n,t_n,I_{n-1},t_{n-1},...,I_1,t_1,I_0,t_0) &= \prod_{\nu=0}^{n-1} p(I_{\nu+1},t_{\nu+1}|I_\nu,t_\nu)\cdot p(I_0,t_0) \\ &= \prod_{\nu=0}^{n-1} \frac{1}{I_{\nu+1}!}\left.\frac{\partial^{I_{\nu+1}} f(x,t_{\nu+1})}{\partial x^{I_{\nu+1}}}\right|_{x=0}\cdot p(I_0,t_0) \end{aligned} \tag{34}$$

and inserting the solution of the stochastic process Eq. (32) we obtain the likelihood function for the model parameters $\tilde\beta$ and γ

$$L(\tilde\beta,\gamma) = \prod_{\nu=0}^{n-1}\frac{1}{I_{\nu+1}!}\frac{\partial^{I_{\nu+1}}}{\partial x^{I_{\nu+1}}}\left.\left(\frac{\frac{\gamma}{\tilde\beta}(x-1)\, e^{(\tilde\beta-\gamma)(t_{\nu+1}-t_\nu)} - \left(x-\frac{\gamma}{\tilde\beta}\right)}{(x-1)\, e^{(\tilde\beta-\gamma)(t_{\nu+1}-t_\nu)} - \left(x-\frac{\gamma}{\tilde\beta}\right)}\right)^{I_\nu}\right|_{x=0} \tag{35}$$

which can be maximised to get the most likely parameter values given the data. These parameter values can then be used to fit the actual data.

To maximize the likelihood function, we take the logarithm of it $\ell(\tilde{\beta},\gamma) := lnL(\tilde{\beta},\gamma)$ and from this the partial derivatives in respect to $\tilde{\beta}$ and γ to be zero. Hence we have

$$\frac{\partial \ell}{\partial \tilde{\beta}} = \sum_{\nu=0}^{n-1} \frac{\partial}{\partial \tilde{\beta}} ln \left(\frac{\partial^{I_{\nu+1}}}{\partial x^{I_{\nu+1}}} \left(\frac{\frac{\gamma}{\tilde{\beta}}(x-1)\, e^{(\tilde{\beta}-\gamma)(t_{\nu+1}-t_\nu)} - \left(x - \frac{\gamma}{\tilde{\beta}}\right)}{(x-1)\, e^{(\tilde{\beta}-\gamma)(t_{\nu+1}-t_\nu)} - \left(x - \frac{\gamma}{\tilde{\beta}}\right)} \right)^{I_\nu} \Bigg|_{x=0} \right) =: F(\tilde{\beta},\gamma) \tag{36}$$

and

$$\frac{\partial \ell}{\partial \gamma} = \sum_{\nu=0}^{n-1} \frac{\partial}{\partial \gamma} ln \left(\frac{\partial^{I_{\nu+1}}}{\partial x^{I_{\nu+1}}} \left(\frac{\frac{\gamma}{\tilde{\beta}}(x-1)\, e^{(\tilde{\beta}-\gamma)(t_{\nu+1}-t_\nu)} - \left(x - \frac{\gamma}{\tilde{\beta}}\right)}{(x-1)\, e^{(\tilde{\beta}-\gamma)(t_{\nu+1}-t_\nu)} - \left(x - \frac{\gamma}{\tilde{\beta}}\right)} \right)^{I_\nu} \Bigg|_{x=0} \right) =: G(\tilde{\beta},\gamma) \tag{37}$$

with the maximum of the log-likelihood given by $F(\tilde{\beta},\gamma) = 0$ and $G(\tilde{\beta},\gamma) = 0$ simultaneously. Since already in simpler models [1] we have to apply Newton's method in two dimensions to obtain the simultaneous estimates for $\tilde{\beta}$ and γ, the derivative operator $\partial^{I_{\nu+1}}/\partial x^{I_{\nu+1}}$ can also be calculated numerically or by symbolic transformation computer programs. Numerically, we have for the I^{th} derivative the scheme

$$p(I,t) = \frac{1}{I!} \left. \frac{\partial^I f(x,t)}{\partial x^I} \right|_{x=x_0=0} = \lim_{h\to 0} \left(\frac{1}{I!} \sum_{k=0}^{I} (-1)^k \left(\begin{array}{c} I \\ k \end{array} \right) \frac{1}{h^I}\, f(x_0 - k\cdot h) \right) \tag{38}$$

which is easy to evaluate in our application because we only have to take the first few derivatives of the generating function f at point $x_0 = 0$ in the likelihood function.

Further approximations like the Poisson approximation [11] of constant transition rates, e.g. $\lambda := \tilde{\beta} S^* I_0$ in the master equation for $p(I,t|I_0,t_0)$ lead again to expressions as already described earlier [1], and become less and less accurate for longer integration time $\Delta t = t_{\nu+1} - t_\nu$, where our more accurate scheme still holds well. Again, numerical tests have to show the validity of such further approximations in application to the present data. These methods come closer and closer to complete numerical estimation of likelihood functions [12].

3 Summary

For the onset of an SIR epidemic process, which describes e.g. seasonal influenza outbreaks, we have given the master equation, calculated the charcteristic function, and from this we calculated the likelihood function. The approximation of abundantly many susceptibles captures the exponential onset of the epidemic well, as we see from the time dependent solution of the mean value of infected as derived from the generating function. Though the analytic expressions are much more complicated than in the previously treated examples [1] to describe the noise floor of influenza and the seond part of the epidemics, the analytic expressions obtained here can be treated in future numeric work similarly to the previously investigated cases.

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References

[1] S.P. van Noort and N. Stollenwerk, *From dynamical processes to likelihood functions: an epidemiological application to influenza*, Proceedings of 8th Conference on Computational and Mathematical Methods in Science and Engineering, CMMSE 2008, ISBN 978-84-612-1982-7 (2008).

[2] N. G. van Kampen, *Stochastic Processes in Physics and Chemistry*, North-Holland, Amsterdam, 1992.

[3] T. Tomé and M.J. de Oliveira, *Dinâmica estocástica e irreversibildade*, Editora da Universidade de São Paulo, São Paulo, 2001.

[4] J. Honerkamp, *Stochastic Dynamical Systems: Concepts, Numerical Methods and Data Analysis*, VCH Publishers, Heidelberg, New York, 1993.

[5] A.T. Bharucha-Reid, *Elements of the theory of Markov Processes and their applications*, McGraw-Hill, New York, 1960.

[6] Influenzanet, http://www.influenzanet.com/.

[7] R.L. Marquet, A.I. Bartelds, S. van Noort, C.E. Koppeschaar, J. Paget, F.G. Schellevis, and J. van der Zee, *Internet-based monitoring of influenza-like illness (ILI) in the general population of the Netherlands during the 2003-2004 influenza season,* BMC Public Health **6** (2006) 242 (8 p.).

[8] S.P. van Noort, J. Lourenço, H. Rebelo de Andrade, M. Muehlen, and M.G.M. Gomes, *Gripenet: An internet-based system to monitor influenza-like illness uniformely across Europe*, Eurosurveillance Monthly **12** (2007) 7–8.

[9] A. Rényi, *Wahrscheinlichkeitsrechnung*, VEB Deutscher Verlag der Wissenschaften, Berlin, 1962.

[10] R. Casagrandi, L. Bolzoni, S. A. Levin and V. Andreasen, *The SIRC model and influenza A*, Mathematical Biosciences **200** (2006) 152–169.

[11] L. Gustafsson, and M. Sternad, *Bringing consistency to simulation of population models - Poisson simulation as a bridge between micro and macro simulation*, Mathematical Biosciences **209** (2007) 361–385.

[12] N. Stollenwerk and K. M. Briggs, *Master equation solution of a plant disease model*, Physics Letters **A 274** (2000) 84–91.