

Thoughts on Epidemic Compartment Models and their Markovian Origin

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Introduction

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6001967/>

- Epidemics have been around since the beginning of recorded history:
 - “Spanish” flu epidemic of 1918–19 caused more than 50,000,000 deaths worldwide.
 - The Black Deaths (probably bubonic plague) spread from Asia throughout 1346-1666, and is estimated to have caused the death of as much as one-third of the population of Europe between 1346 and 1350.
 - Modern flu’s: Birdflu (Avian) 2013 , Pigflu
 - Corona: SARS (2003), MERS (2012), CoVID-19

Introduction

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6001967/>

- Epidemic models:
 - Bernoulli D. 1766. Essai d'une nouvelle analyse de la mortalité causée par la petite vérole. Mem. Math. Phys. Acad. Roy. Sci. Paris. – life expectancy
 - In 1906 W.H. Hamer proposed that the spread of infection should depend on the number of **susceptible individuals and the number of infective individuals** ([Hamer, 1906](#)). He suggested a mass action law for the rate of new infections, and this idea has **been basic in compartmental models since that time.**
 - COVID-19-CTRL: DTU, AAU, Novo Nordisk

Agenda

- Introduction
- Model types
- Derivation of models
- Comparison examples
- Conclusion

Analysis tools for epidemic spread

- CTMC: State dimension = number of disease states ^{population size}
- Aggregated CTMC = population size ^{number of disease states}
- Compartment models: SIR, SEIR, SIS, SIRS ... **(SI)**

Differential equations: ODE -> mean value evolution

- Compartment models with Poisson process noise (TK)

SDE - > variance analysis

- Agent based simulation (KDH)

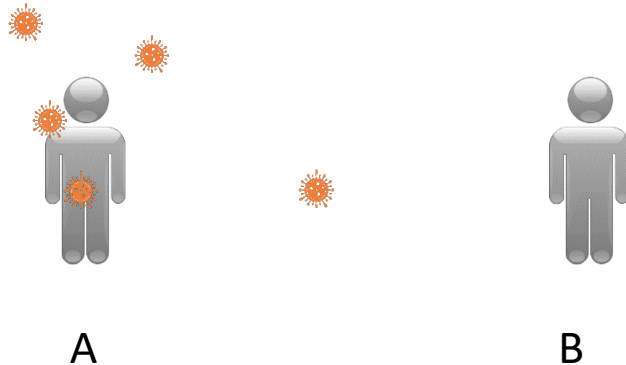
Monte Carlo simulation, full CTMC

Elementary dynamics

- Consider two individuals x and y , where y is infected and x is susceptible.
- Within a time interval $[t, t+dt]$ the 2 individuals are within *infection range* and the probability that infection happens is assumed to be

$$b \, dt$$

(smooth, memoryless, time-invariant, CTMC)



Elementary dynamics

- Consider a susceptible individual x within a group of I infected individuals all within infection range.
- The probability that infection happens within $[t, t+dt]$ is for small dt (disregarding multiple infection)

$$I * b \, dt$$

- Next consider a group of S susceptible individuals all within the same infection range with a group of I infected individuals.
- The probability that one or more susceptibles are infected within the interval is

$$1 - (1 - I * b * dt)^S \sim b * S * I * dt$$

- The probability that 1 susceptible is infected within $[t, t+dt]$ is

$$b * S * I * dt$$

- The probability that more than 1 susceptibles are infected is therefore at most $O(n^2)$

Elementary dynamics

- A group of S susceptible individuals all within the same infection range with a group of I infected individuals.
- The probability that 1 susceptible is infected within $[t, t+dt]$ is

$$b * S * I * dt$$

- The probability that more than 1 susceptibles are infected is therefore at most $O(n^2)$
- Considering conditional expectations (inf generator) we have

$$E[I(t + dt) - I(t) | I(t)] = b * S * I * dt$$

$$\lim_{dt \rightarrow 0} \frac{E[I(t+dt)] - E[I(t) | I(t)]}{dt} = b * S * I$$

- Taking expectations (Dynkin)

$$\frac{d}{dt} E[I](t) = b * E[S * I] \sim b * E[S] * E[I]$$

Example – 2 families

- 2 families each with M members

$$d/dt E[I_1] \sim b * E[I_1] * E[S_1] = b * E[I_1] * (M - E[I_1])$$

$$d/dt E[I_2] \sim b * E[I_2] * E[S_2] = b * E[I_2] * (M - E[I_2])$$

- Assume $E[I_1] = E[I_2]$, then with $I = I_1 + I_2$,

$$d/dt (E[I_1] + E[I_2]) = b * E[I_1] * (M - E[I_1]) + b * E[I_2] * (M - E[I_2]) = 2 * b * E[I_1] * (M - E[I_1]) \Rightarrow$$

$$d/dt E[I] = b * E[I] * (M - E[I]/2)$$

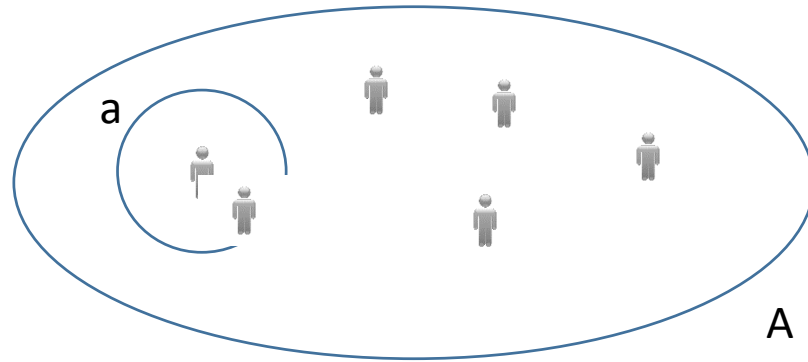
- Merge now the 2 families into a single family with 2M members, we have

$$d/dt E[I] \sim b * E[I] * (2M - E[I]) = 2 * b * E[I] * (M - E[I]/2)$$

- The overall *infection pressure* (rate) is $d/dt E[I]$
- **Thus, the infection rate is doubled by merging the families. !!**
- Underlying assumption is that everybody are within infection range.

Elementary dynamics

- Consider S susceptible within a group of I infected confined to an area A .
- We denote the area around x within infection range as a .



- Thus, the expected number of infected within a is not $E[I]$ but $E[I] \frac{|a|}{|A|}$
- This gives the following mean value dynamics

$$\frac{d}{dt} E[I](t) \sim b * E[S] * E[I] \frac{|a|}{|A|}$$

Elementary dynamics

- Consider S susceptibles within a group of I infected
- Assume that for a relevant range of population-densities the number of people within the infection range of any susceptible is fixed to L .
- Then the mean value dynamics become (with $N=S+I$)

$$\frac{d}{dt} E[I](t) \sim b * E[S] * E[I] \frac{L}{N} = \frac{b * L}{N} * E[S] * E[I] = \frac{\beta}{N} * E[S] * E[I]$$

- Normalizing $I = N * i$, $S = N * s$ leads to

$$\frac{d}{dt} E[i](t) = \beta * E[s] * E[i]$$

Example – 2 families

- 2 families each with M members

$$d/dt E[I_1] \sim \frac{\beta}{M} * E[I_1] * (M - E[I_1])$$

$$d/dt E[I_2] \sim \frac{\beta}{M} * E[I_2] * (M - E[I_2])$$

- Assume $E[I_1] = E[I_2]$, then with $I = I_1 + I_2$,

$$d/dt (E[I_1] + E[I_2]) = \frac{\beta}{M} * E[I_1] * (M - E[I_1]) + \frac{\beta}{M} * E[I_1] * (M - E[I_1]) = 2 * \frac{\beta}{M} * E[I_1] * (M - E[I_1]) \Rightarrow$$

$$d/dt E[I] = \frac{\beta}{M} * E[I] * (M - E[I]/2)$$

- Merge now the 2 families into a single family with 2M members, we have

$$d/dt E[I] \sim \frac{\beta}{2M} * E[I] * (2M - E[I]) = 2 * \frac{\beta}{2M} * E[I] * (M - E[I]/2) = \frac{\beta}{M} * E[I] * (M - E[I]/2)$$

- **Thus, the infection rate is unchanged by merging the families. !!**
- Underlying assumption is that a fixed number of people is within infection rate.

2 different models

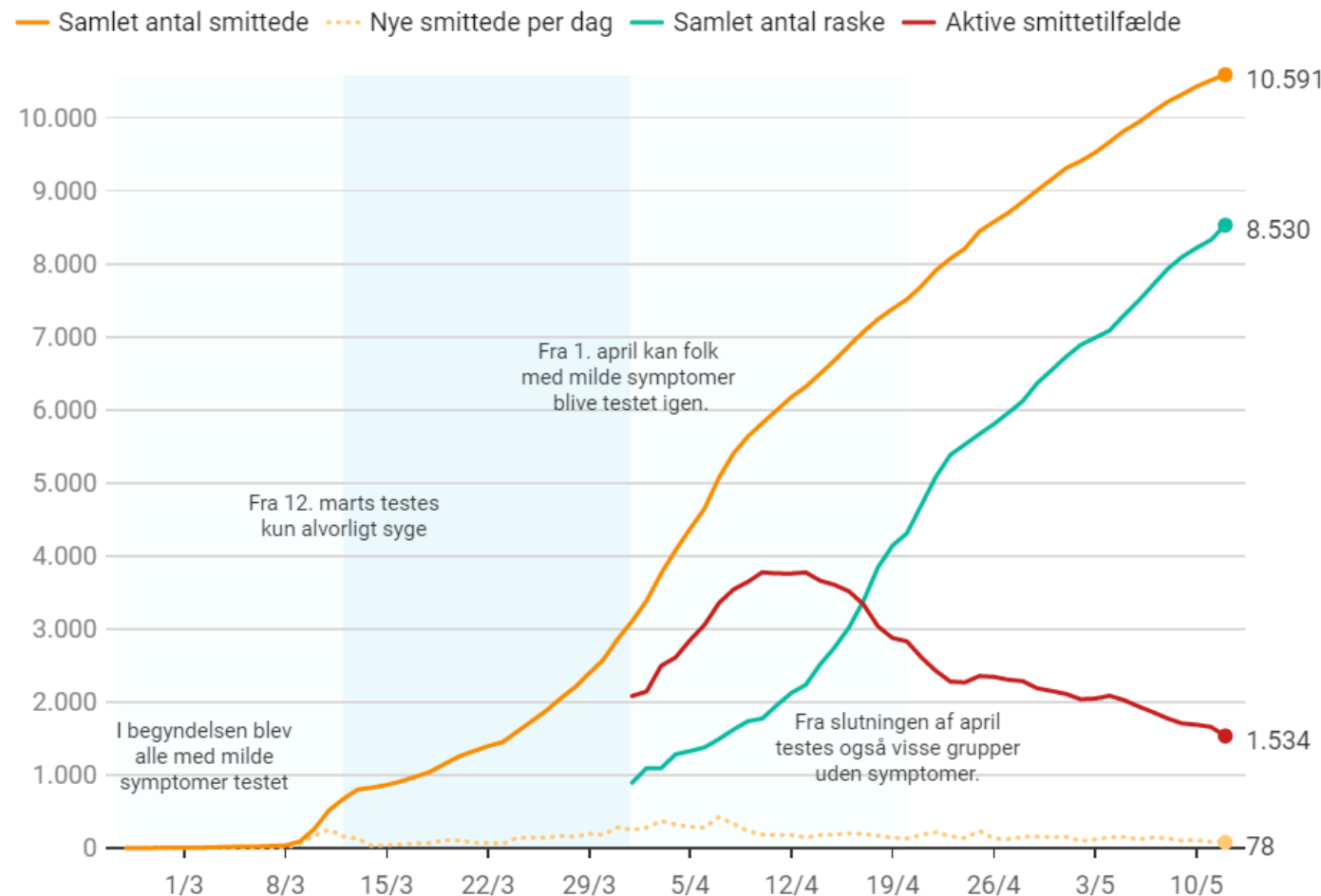
- Which model is correct ?
- Which model should be used in various situations:
 - The entire DK population
 - Herning warm blood stallion show (HWSS)
 - Families
 - Schools
 - ...
- Combined model

$$\beta = b * (L + \alpha \rho)$$

Claim

- 5 day event – 70.000 participants
- HWSS is just merging $12.000/5 = 2400$ families
- With the 1st model the infection rate is multiplied by 2400 !!!
- The number of people within infection range is not higher at HWSS than in a common family ..
- Thus merging 2400 families does not make a change
- Which is true ?

Smittede i Danmark



Det er ikke alle smittede, der har opsøgt lægehjælp eller er blevet testet. Langt flere kan derfor reelt være eller have været smittet. // Raske er defineret ved at være personer, som ikke er hverken indlagt eller døde, 14 dage efter de fik konstateret COVID-19 // Aktive smittetilfælde er det samlede antal registrerede smittede fratrukket raske og døde // Tallene for det seneste døgn er muligvis ikke endelige. Der kan komme nye og højere tal senere på dagen.

Grafik: Videnskab.dk • Kilde: [Statens Serum Institut](#) • [Hent data](#) • [Lavet med Datawrapper](#)

Sanity check 1st model

- Newly infected per day in DK: 100-200 (tested)
- Infection rate pr capita (DK): $150/6e6 = 2.5e-5$ (pr day)
- Infection rate pr capita (HWSS): $2400 * 2.5e-5 = 0.06$ (pr day)
- Expected no of infected in Herning pr day: $14000 * 0.06 = 840$!!

Sanity check 2nd model

1.4 Antal testede, smittede, indlagte og dødsfald fordelt på region

Region	Testede	Bekræftede COVID-19 smittede	Indlagte*	Dødsfald**
Nordjylland	34.205	421	99	21
Midtjylland	64.607	1.544	275	69
Syddanmark	61.810	921	228	29
Hovedstaden	125.135	5.958	1.082	303
Sjælland	47.484	1.689	448	105
I alt	333.241	10.533	2.132	527

- Density or meeting different people seems to matter

More precise SIR model for low N

- State: $x(t) = \{s_1, \dots, s_N\} \in X$
- $s_i \in \{SS, II, RR\}$
- State space: $X = \{SS, II, RR\}^N$ (large - 3^N elements)
- $S_x(t) = \#\{s \in x(t) \mid s = SS\}$
- $I_x(t) = \#\{s \in x(t) \mid s = II\}$
- $R_x(t) = \#\{s \in x(t) \mid s = RR\}$

Markovian property

- $X_t = \{ f: [0, t] \rightarrow \{SS, II, RR\} \}$
- $y, x_t \in X_t, x_t(\tau) = x(\tau) \text{ for } \tau \in [0, t]$

$$P(x(t+dt)=\{s_1, \dots, s'_i, \dots, s_N\} \mid x_t = y) = \Gamma(x(t)) = \\ P(x(t+dt)=\{s_1, \dots, s'_i, \dots, s_N\} \mid x(t)=\{s_1, \dots, s_i, \dots, s_N\})$$

Transition probabilities

- $P(x(t+dt)=\{s_1, \dots, s'_i, \dots, s_N\} \mid x(t)=\{s_1, \dots, s_i, \dots, s_N\})$
- $P(x(t+dt)=\{s_1, \dots, ll, \dots, s_N\} \mid x(t)=\{s_1, \dots, SS, \dots, s_N\}) = b/N * I_x(t) * dt$
- $P(x(t+dt)=\{s_1, \dots, RR, \dots, s_N\} \mid x(t)=\{s_1, \dots, ll, \dots, s_N\}) = \alpha * I_x(t) * dt$

Aggregate model

- State space: $X = \{SS, II, RR\}^N$ (large - 3^N elements)
- $A_{s,i,r} = \{x \in X \mid S_x(t) = s, I_x(t) = i, R_x(t) = r\}$
- $X_A = \{A_{s,i,r}\}$ is a partition of X with $\frac{N^2}{2} + 2N + 1$ elements
- $N=5 \rightarrow 3^N = 243, \quad \frac{N^2}{2} + 2N + 1 \sim 34$

Transition probabilities

- (1) $P(x(t + dt) = k \mid x(t) = p) = (g + b * i) * dt$
for $p \in A_{s,i,r}$ and $k \in A_{s-1,i+1,r}$
- (2) $P(x(t + dt) = k \mid x(t) = p) = \alpha * dt$
for $p \in A_{s,i,r}$ and $k \in A_{s,i-1,r+1}$

Transition probabilities – Infection

- $P(x(t+dt) \in A_{s-1,i+1,r} \mid x(t) \in A_{s,i,r}) =$
 $P(x(t+dt) \in A_{s-1,i+1,r} \ \& \ x(t) \in A_{s,i,r}) / P(x(t) \in A_{s,i,r})$

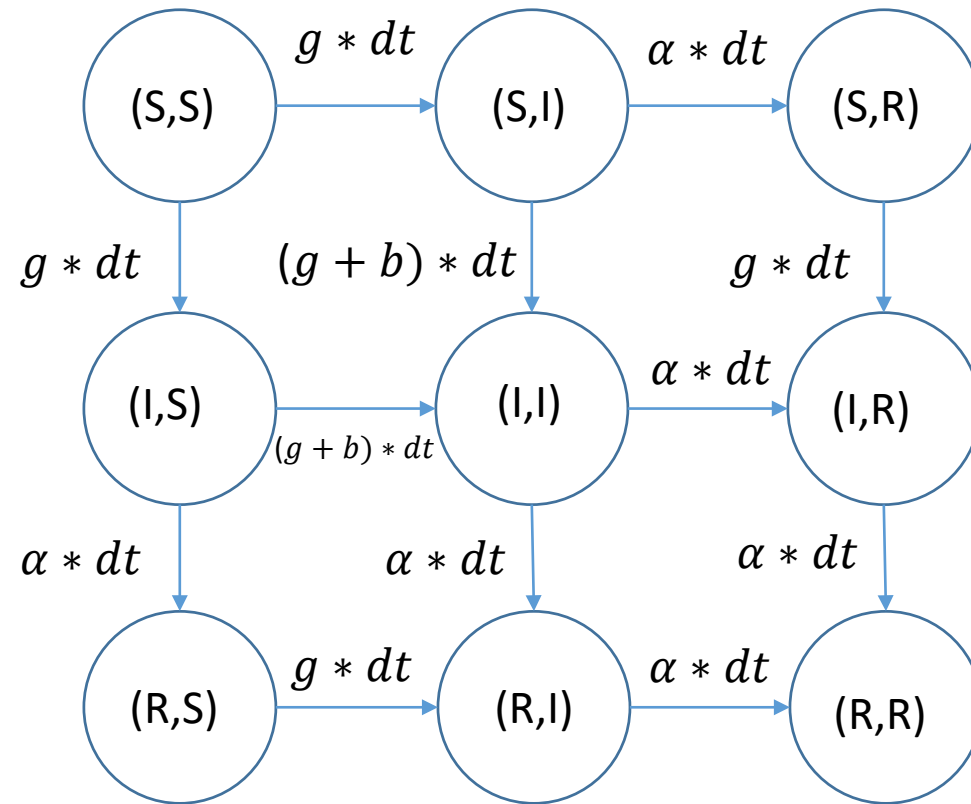
$$= \sum_{p \in A_{s,i,r}} \sum_{k \in A_{s-1,i+1,r}} P(x(t+dt) = k \mid x(t) = p) P(x(t) = p) / P(x(t) \in A_{s,i,r})$$
$$= \sum_{p \in A_{s,i,r}} \sum_{k \in A_{s-1,i+1,r}} (g + b * i) * dt * \delta_I(p, k) * P(x(t) = p) / P(x(t) \in A_{s,i,r})$$
$$= (g + b * i) * dt * \sum_{p \in A_{s,i,r}} P(x(t) = p) \sum_{k \in A_{s-1,i+1,r}} \delta_I(p, k) / P(x(t) \in A_{s,i,r})$$
$$= (g + b * i) * dt * P(x(t) \in A_{s,i,r}) * s / P(x(t) \in A_{s,i,r})$$
$$= (g + b * i) * dt * s$$

Transition probabilities - Recovery

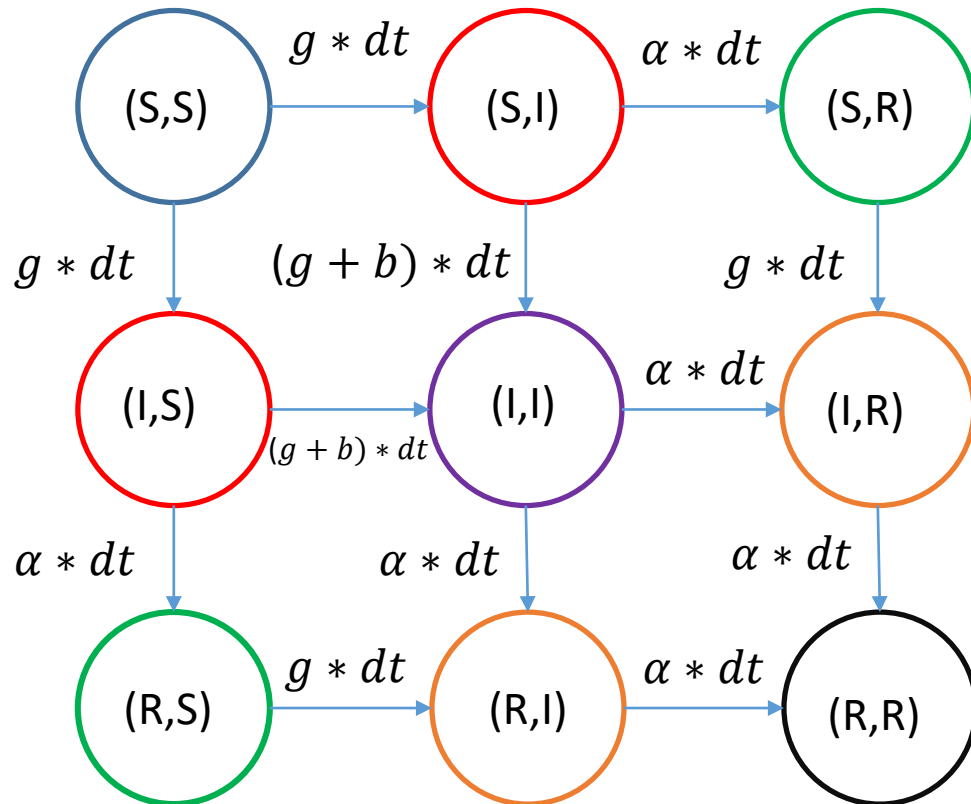
- $P(x(t+dt) \in A_{S,i-1,r+1} \mid x(t) \in A_{S,i,r}) =$
 $P(x(t+dt) \in A_{S,i-1,r} \ \& \ x(t) \in A_{S,i,r}) / P(x(t) \in A_{S,i,r})$

$$= \sum_{p \in A_{S,i,r}} \sum_{k \in A_{S,i-1,r+1}} P(x(t+dt) = k \mid x(t) = p) P(x(t) = p) / P(x(t) \in A_{S,i,r})$$
$$= \sum_{p \in A_{S,i,r}} \sum_{k \in A_{S,i-1,r+1}} \alpha * dt * \delta_I(p, k) * P(x(t) = p) / P(x(t) \in A_{S,i,r})$$
$$= \alpha * dt * \sum_{p \in A_{S,i,r}} P(x(t) = p) \sum_{k \in A_{S,i-1,r+1}} \delta_I(p, k) / P(x(t) \in A_{S,i,r})$$
$$= \alpha * dt * P(x(t) \in A_{S,i,r}) * i / P(x(t) \in A_{S,i,r})$$
$$= \alpha * dt * i$$

Example (N=2)

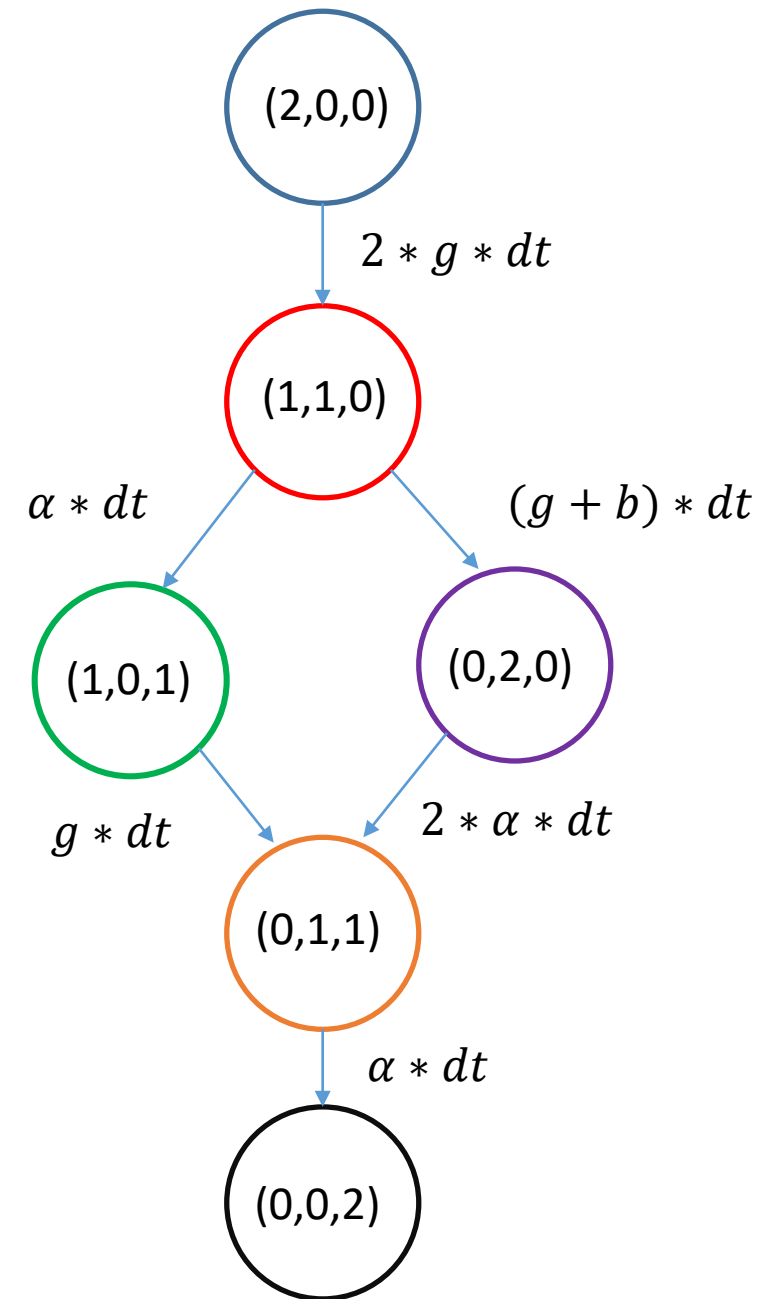
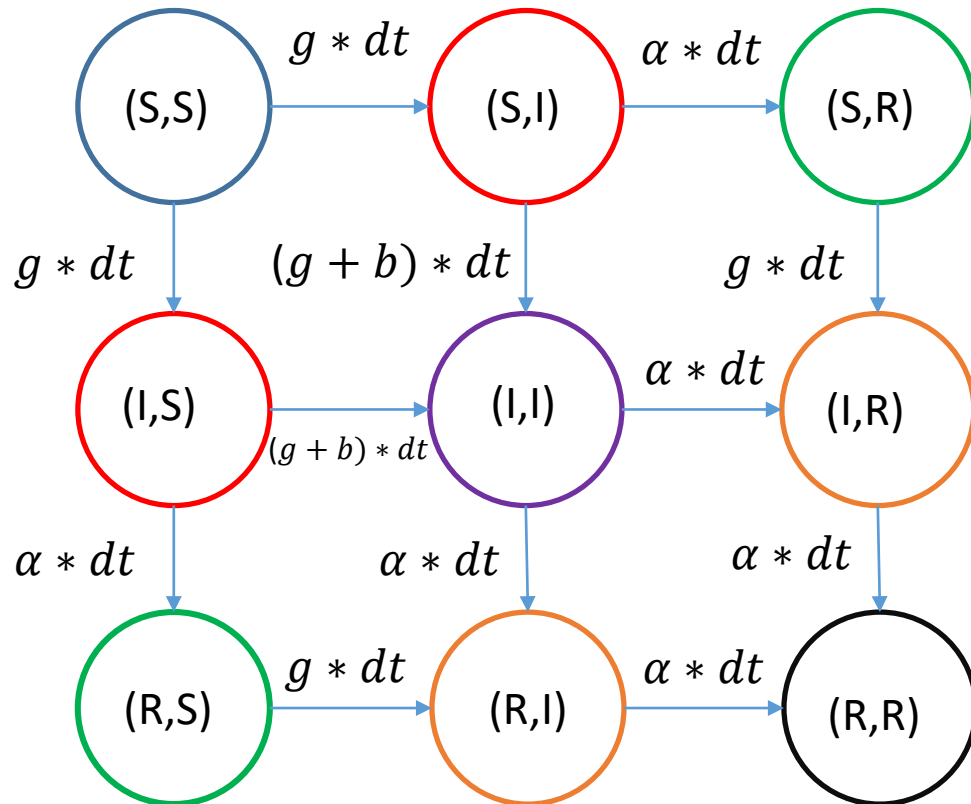


Example (N=2)

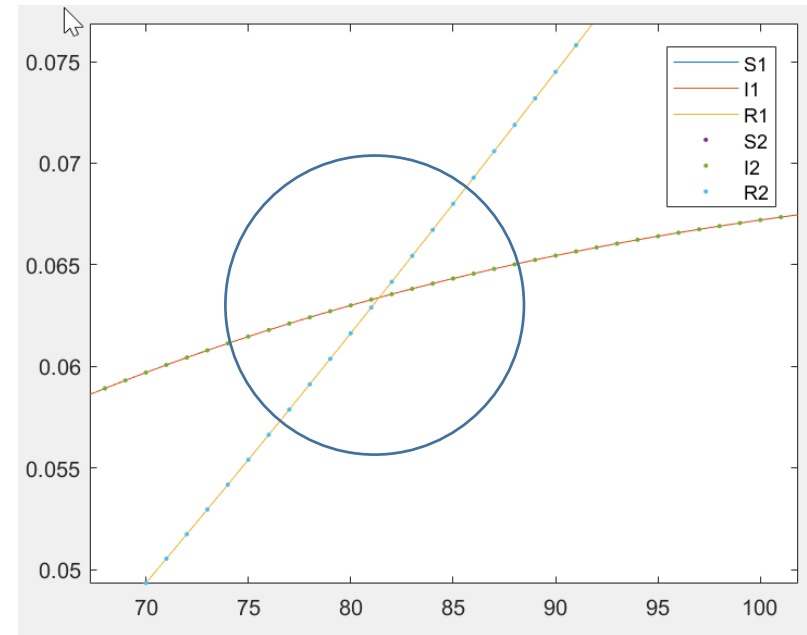
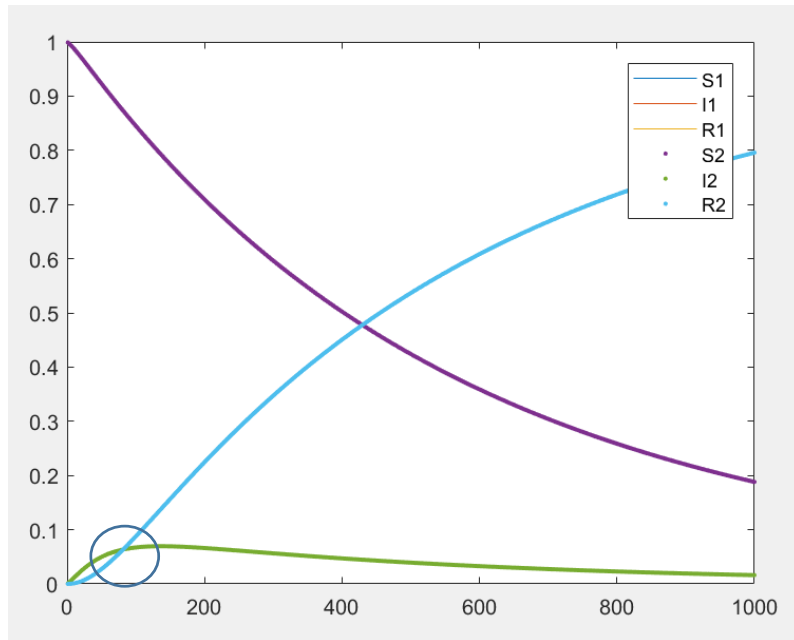


- $3^N = 3^2 = 9$
- $\frac{N^2}{2} + 2N + 1 = 7$

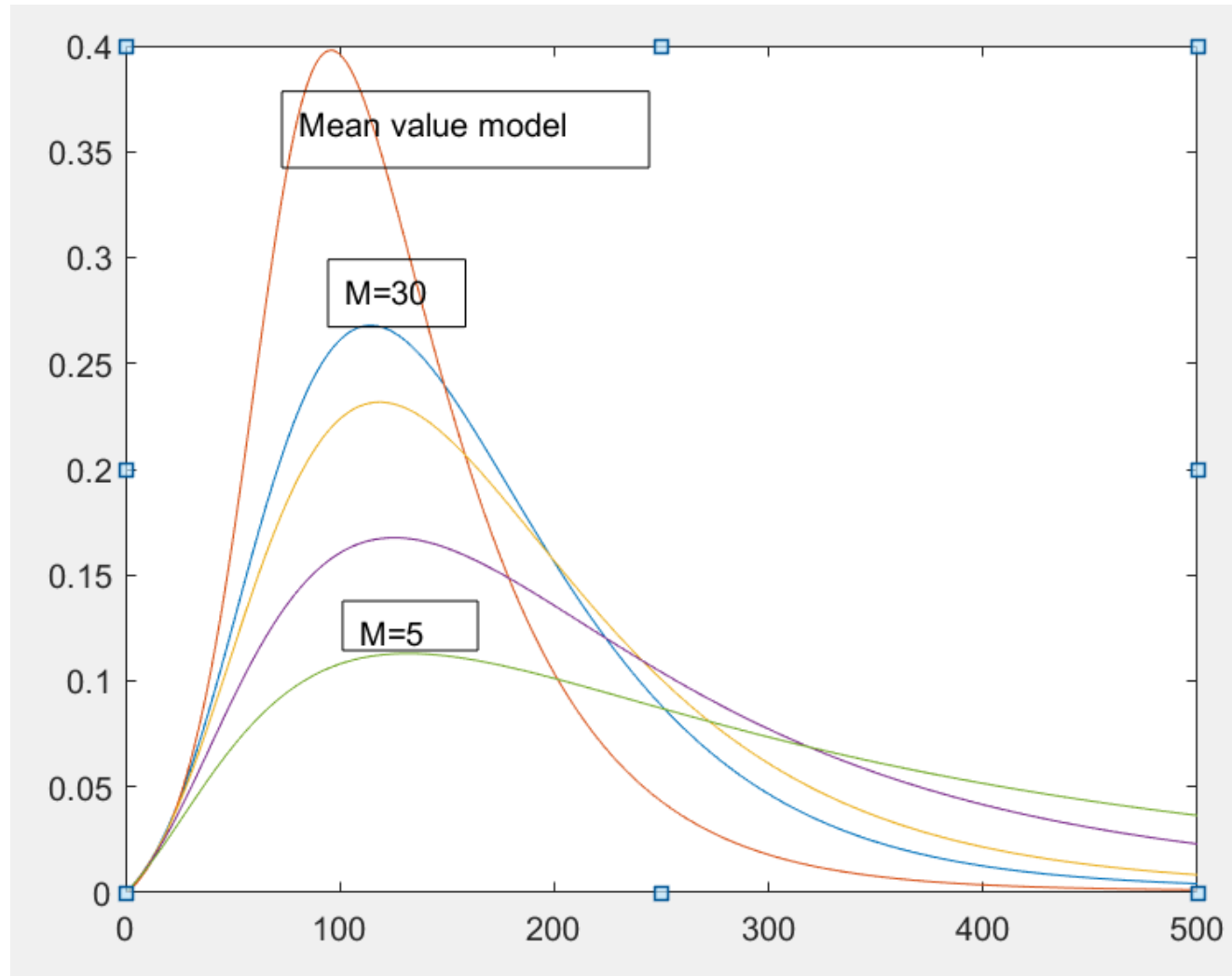
Example (N=2)



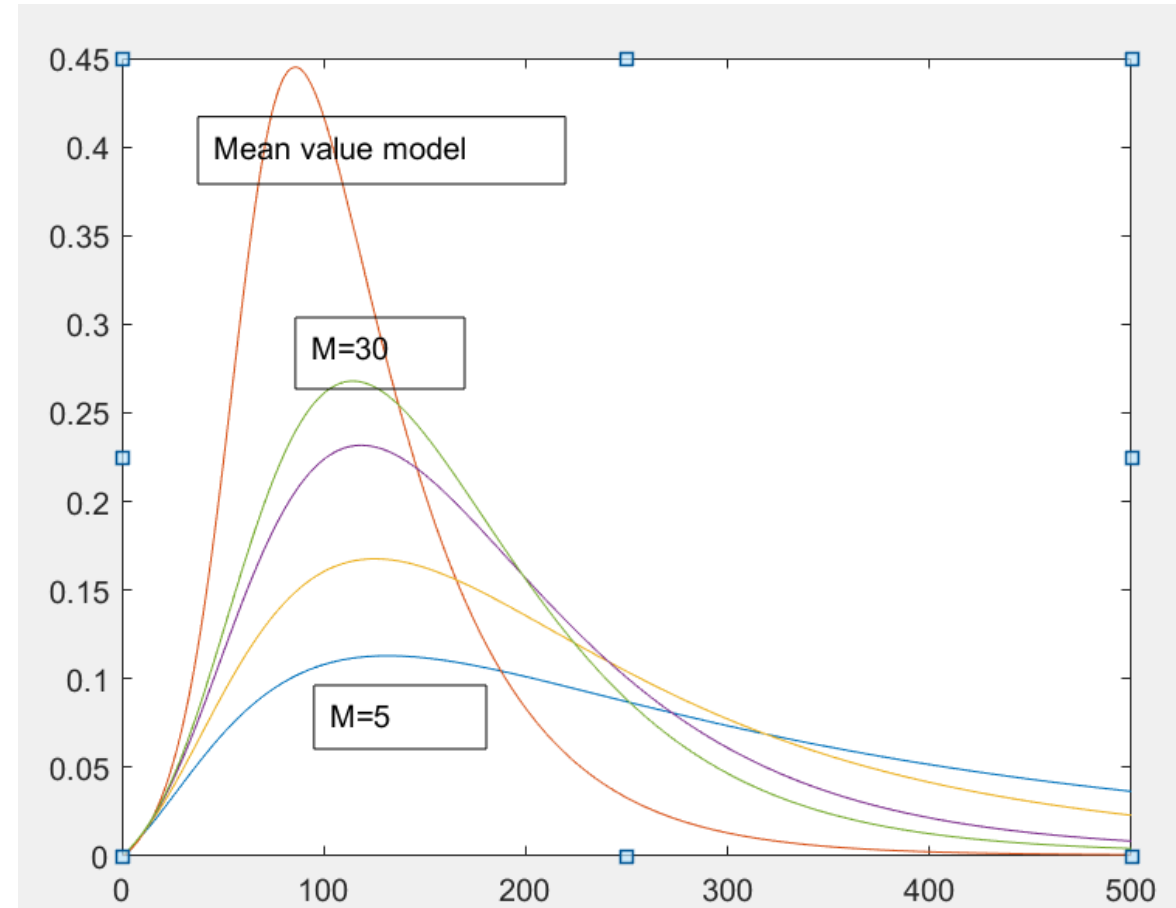
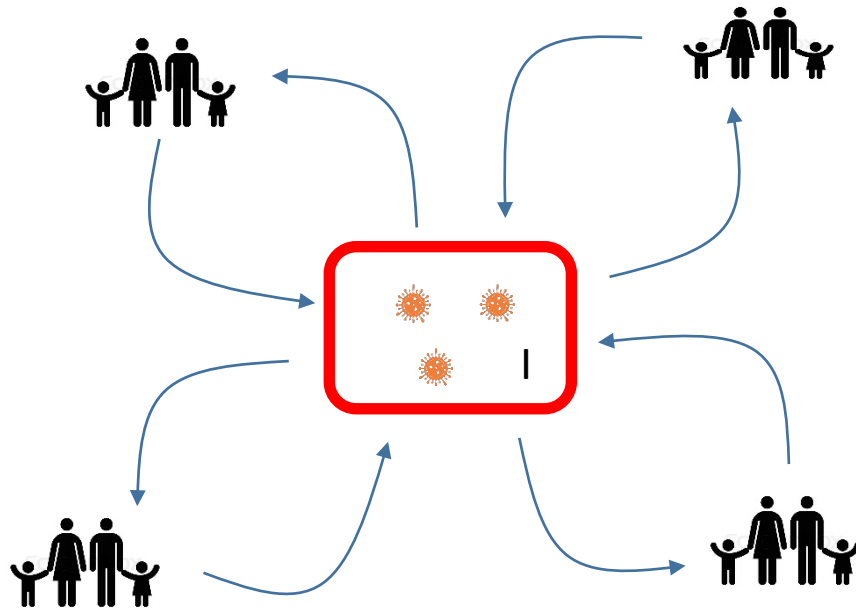
Comparison



Mean value model vs aggregated model



Mean value model vs aggregated model with FeedBack



Conclusions

- For mean value models infection rate heavily depends on model assumption – especially the number N of people within infection rate
- Model with proportional N gives highly exaggerated results for large assemblies
- Model with scaled N gives counter-intuitive results for small groups
- For small groups both mean-value models overestimate infection rate
- Feedback seems to amplify the model discrepancy

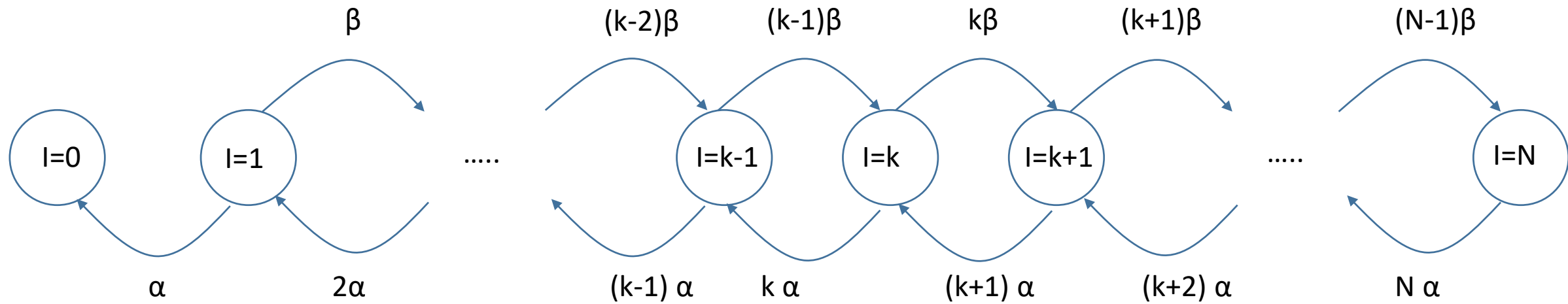
Simpler model for Epidemic birth- and infant-death

- The number S of susceptibles is large and approximately N
- The number I of infected is small $\ll N$
- Infected are spread so IL/N within infection range
- SIR model
- Transition probabilities

$$P(x(t+dt)=\{s_1, \dots, II, \dots, s_N\} \mid x(t)=\{s_1, \dots, SS, \dots, s_N\}) = b \frac{L}{N} * I_x(t) * dt = \beta * I_x(t) * dt$$

$$P(x(t+dt)=\{s_1, \dots, RR, \dots, s_N\} \mid x(t)=\{s_1, \dots, II, \dots, s_N\}) = \alpha * I_x(t) * dt$$

Chain for only I



Measurement model

- Sequencing performed on a sample of positives p .
- $c5$ found among this

$$P(c5 \& p) = P(c5 | p) P(p) = P(c5) \Rightarrow$$

$$P(c5 | p) = P(c5)/P(p)$$

- $P(c5) \sim$ no of $c5$ / no of tests (maybe X 2 for dark cases)
 $\sim 1 / 6e6$
- $P(p) \sim 1.4 \%$

Measurement model

- Probability of k observations of $c5$ given $I = m$

- $P(c5 \mid p) = \frac{P(c5)}{P(p)} = \frac{\frac{m}{6e6}}{1.4\%}$

- $P(k \text{ obs of } c5 \mid I = m) = \text{binom}(k, P(c5 \mid p))$

- $P(0 \text{ obs of } c5 \mid I = m) = \text{binom}(0, P(c5 \mid p)) = (1 - P(c5 \mid p))^k$

Bayesian Filter

- Markovian dynamics

$$P(x(1) = i(1), \dots, x(N) = i(N)) = \\ P(x(1) = i(1)) P(x(2) = i(2) | x(1) = i(1)) \dots P(x(N) = i(N) | x(N-1) = i(N-1))$$

- Independent observation model

$$P(x(1) = i(1), \dots, x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N)) = \\ P(x(1) = i(1)) P(x(2) = i(2) | x(1) = i(1)) \dots P(x(N) = i(N) | x(N-1) = i(N-1)) \\ P(y(1) = j(1) | x(1) = i(1)) \dots P(y(N) = j(N) | x(N) = i(N))$$

Bayesian Filter

- $$\begin{aligned}
 &P(x(1) = i(1), \dots, x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N)) = \\
 &\quad P(x(1) = i(1)) P(x(2) = i(2) | x(1) = i(1)) \dots P(x(N) = i(N) | x(N-1) = i(N-1)) \\
 &\quad P(y(1) = j(1) | x(1) = i(1)) \dots P(y(N) = j(N) | x(N) = i(N)) \\
 &= P(x(1) = i(1)) H(i(1), i(2)) \dots H(i(N-1), i(N)) G(i(1), j(1)) \dots G(i(N), j(N))
 \end{aligned}$$

$$P(x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N))$$

$$\begin{aligned}
 &= \sum_{i(N-1)} \dots \sum_{i(1)} P(x(1) = i(1), \dots, x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N)) \\
 &= G(i(N), j(N)) \sum_{i(N-1)} H(i(N-1), i(N)) G(i(N-1), j(N-1))
 \end{aligned}$$

$$\sum_{i(N-2)} \dots \sum P(x(1))$$

Bayesian Filter

$$P(x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N))$$

$$= \sum_{i(N-1)} \dots \sum_{i(1)} P(x(1) = i(1), \dots, x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N))$$

$$= G(i(N), j(N)) \sum_{i(N-1)} H(i(N-1), i(N)) G(i(N-1), j(N-1))$$

$$\sum_{i(N-2)} \dots \sum_{i(1)} P(x(1) = i(1)) H(i(1), i(2)) \dots H(i(N-2), i(N-1)) G(i(1), j(1)) \dots G(i(N-1), j(N-1))$$

$$= G(i(N), j(N)) \sum_{i(N-1)} H(i(N-1), i(N)) G(i(N-1), j(N-1)) \\ P(x(N-1) = i(N-1), y(1) = j(1), \dots, y(N-1) = j(N-1))$$

Bayesian Filter – conditional by normalization

$$P(x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N)) =$$

$$G(i(N), j(N)) \sum_{i(N-1)} H(i(N-1), i(N)) G(i(N-1), j(N-1)) \\ P(x(N-1) = i(N-1), y(1) = j(1), \dots, y(N-1) = j(N-1))$$

$$P(x(N) = i(N) \mid y(1) = j(1), \dots, y(N) = j(N)) = \\ P(x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N)) / \sum_{i(N)} P(x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N))$$

Bayesian Filter – observation Likelihood by summation of joint distribution

$$P(x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N)) =$$

$$G(i(N), j(N)) \sum_{i(N-1)} H(i(N-1), i(N)) G(i(N-1), j(N-1)) \\ P(x(N-1) = i(N-1), y(1) = j(1), \dots, y(N-1) = j(N-1))$$

$$P(y(1) = j(1), \dots, y(N) = j(N)) = \sum_{i(N)} P(x(N) = i(N), y(1) = j(1), \dots, y(N) = j(N))$$