Superspreader Mitigation
&
A Synthetic Biology for Epidemics

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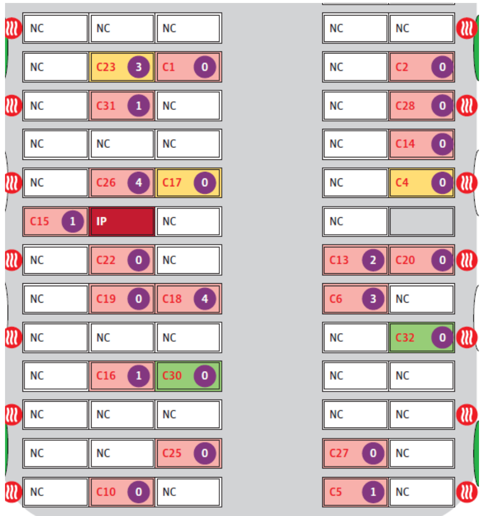
Talk at Nordita, 2023

Summary: Distributions (of virus load) Matters

Superspreaders & COVID-19

- Considerable **heterogeneity** in infectivity
  - 5-20% of infected population may cause 80% of infections (4 ``experimental/data analysis” papers before June 2020)



NC	NC	NC	NC	NC
NC	C23 3	C1 0	NC	C2 0
NC	C31 1	NC	NC	C28 0
NC	NC	NC	NC	C14 0
NC	C26 4	C17 0	NC	C4 0
C15 1	IP	NC	NC	
NC	C22 0	NC	C13 2	C20 0
NC	C19 0	C18 4	C6 3	NC
NC	NC	NC	NC	C32 0
NC	C16 1	C30 0	NC	NC
NC	NC	NC	NC	NC
NC	NC	C25 0	C27 0	NC
NC	C10 0	NC	C5 1	NC

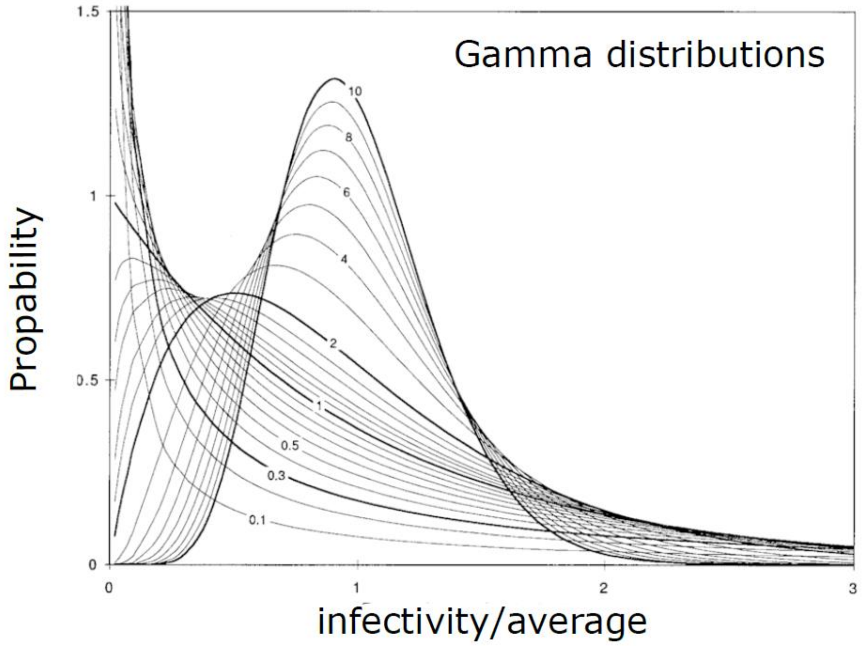
- Multiple reports of superspreading events
  - Choir in WA State: ~75% of 60 singers infected after 2.5 h practice
  - Bar hopper in S. Korea: ~60 cases one night
  - 1 person infect 23 on a 2 hour bus ride, + 7 on a following 2.5 hour ceremony +
  - 1 person infect 40 at wedding in Uruguai
  - An infected person only have p= 15% to infect to spouse.

Endo A, Abbott S, Kucharski AJ, Funk S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. Wellcome Open Res. 2020;5:67.

Miller D, Martin M, Harel N, Kustin T, Tirosh O, Sorek N, et al. Full genome viral sequences inform patterns of SARS-CoV-2 spread into and within Israel. Preprint [Internet]. 2020;May 22, 20. Available from: https://doi.org/10.1101/2020.05.21.20104521

Assumed Distribution of infectivity r:

$$P_I(r) \propto r^{k-1} \cdot exp(-kr/\mu)$$

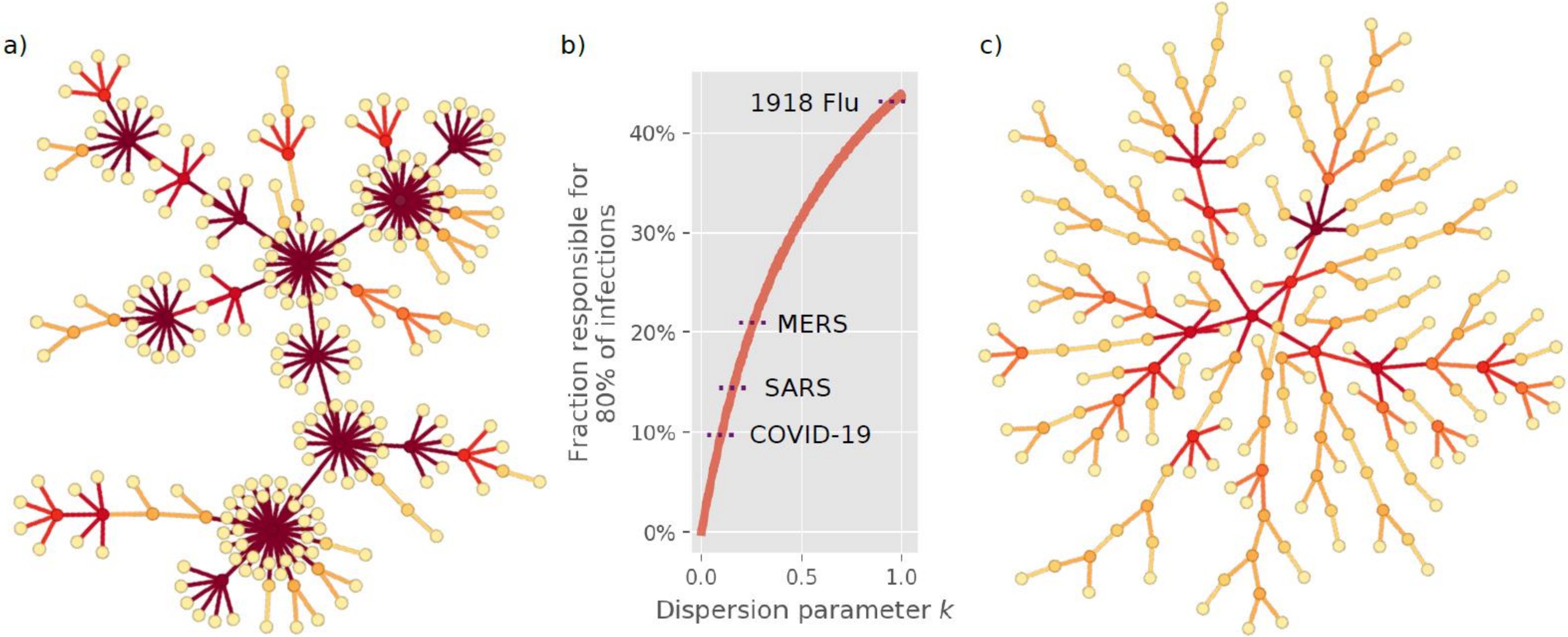


k=1, →exponential, seen for Influenza.

k<1, →for measles, SARS and covid-19, tuberculosis, many have r close to 1, few have r close to R0/k

…just mathematics, is a one parameter description of variability, *spread/man=1/sqrt(k)….*

Lloyd, Nature 2005

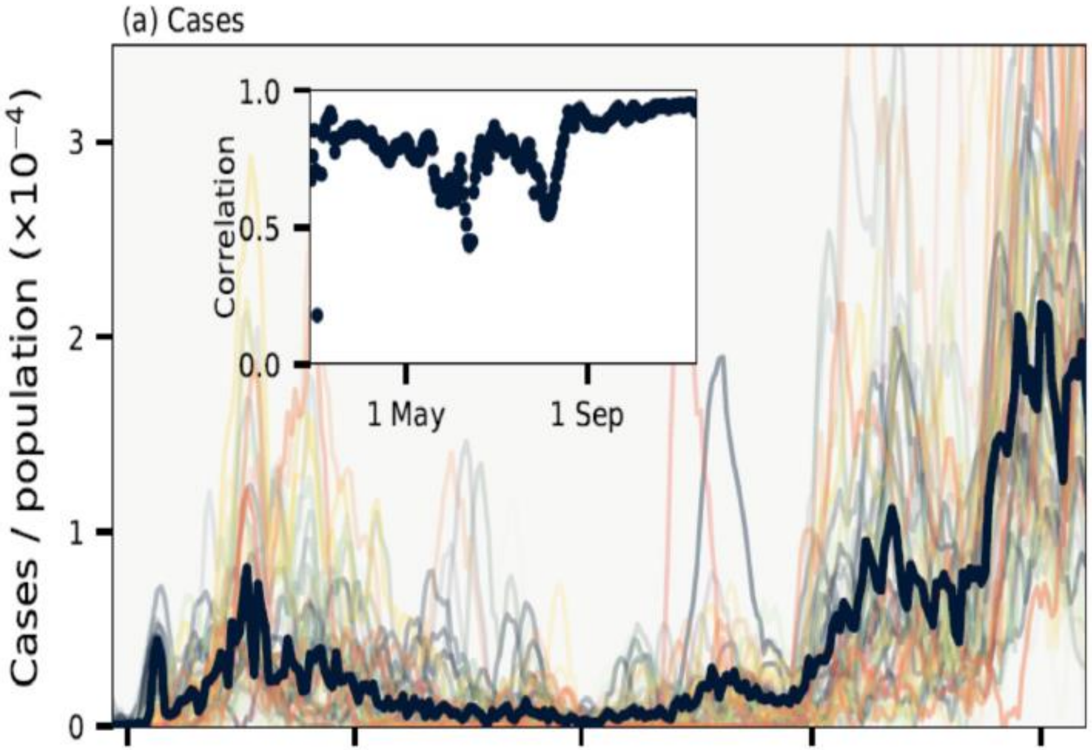


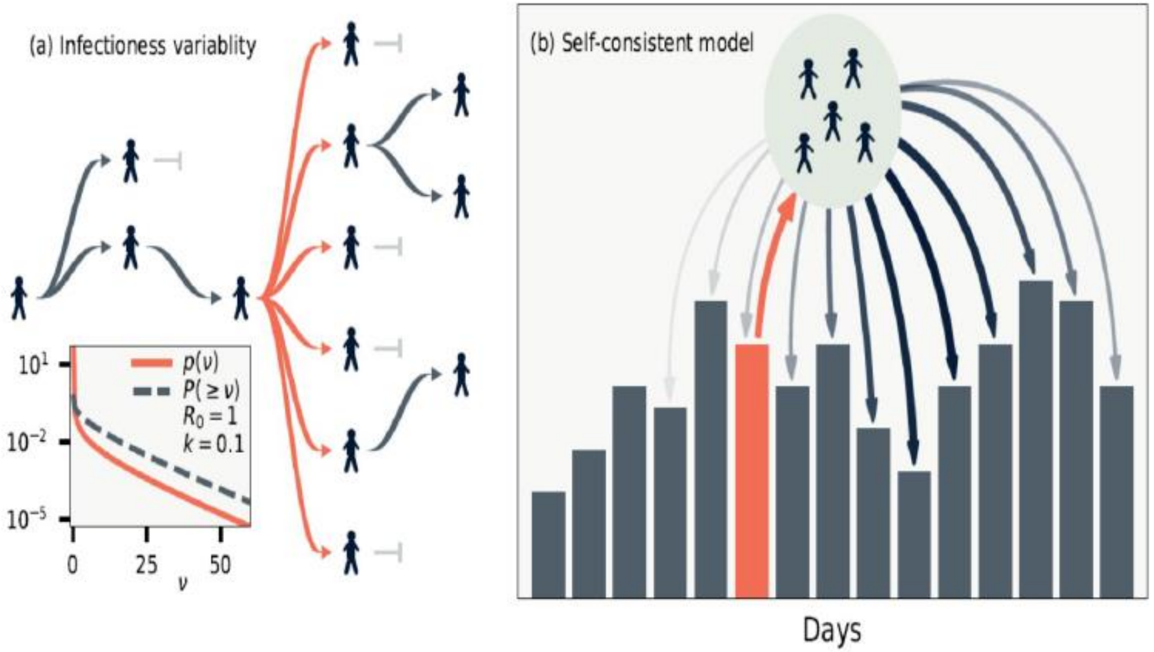
$$P(s)=s^{1-k}\ \exp(-k\ s/R)$$

Lloyd, Nature 2005

Nielsen, Bjarke Frost, Lone Simonsen, and Kim Sneppen. "COVID-19 superspreading suggests mitigation by social network modulation." *Physical Review Letters* 126.11 (2021): 118301.

Measuring *k*… from burstiness: 99 ``kommuner” in Denmark:

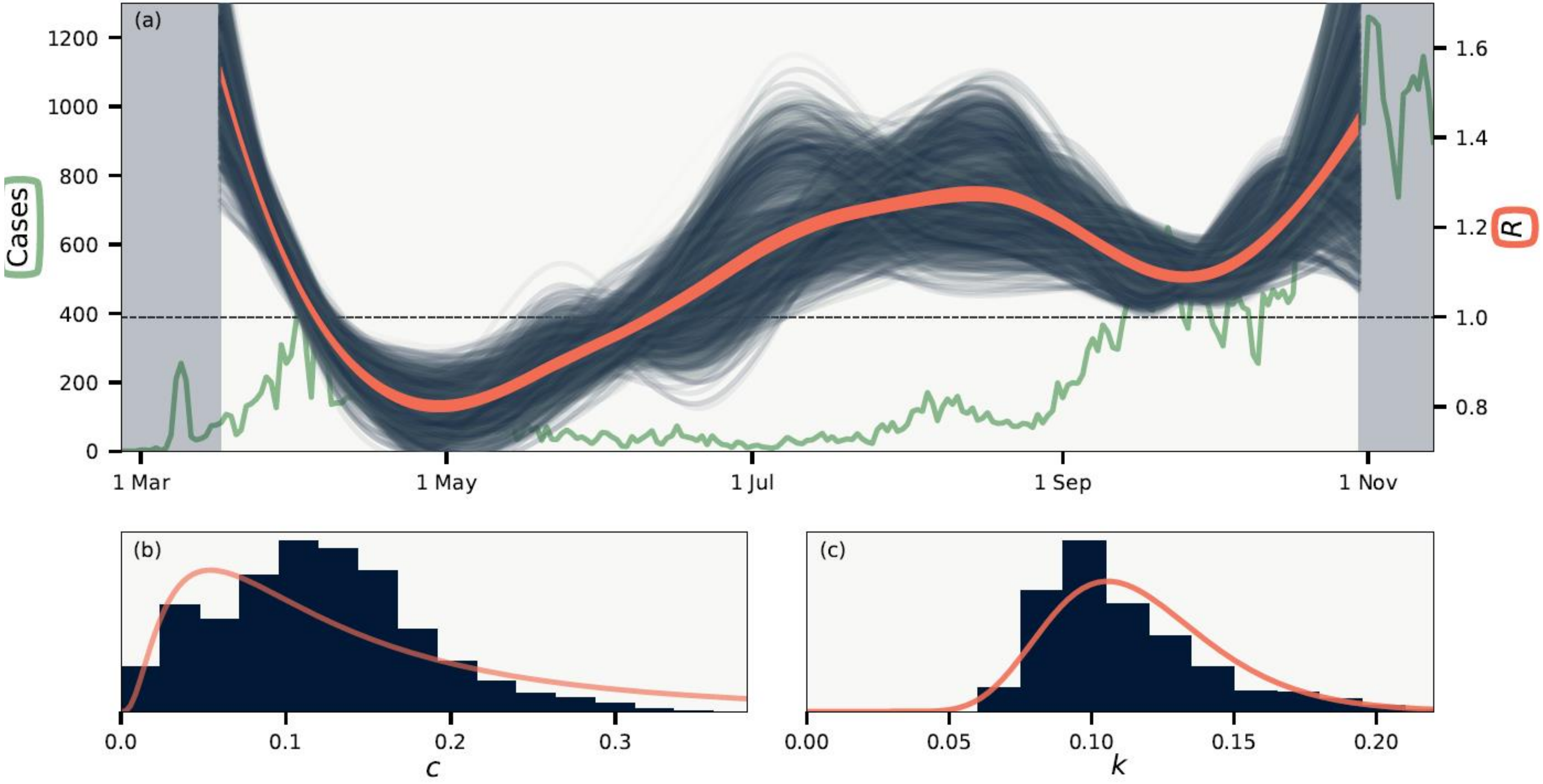




Variability of Individual Infectiousness
Derived from Aggregate Statistics of COVID-19

Julius B. Kirkegaard and Kim Sneppen

→Result of best fit:

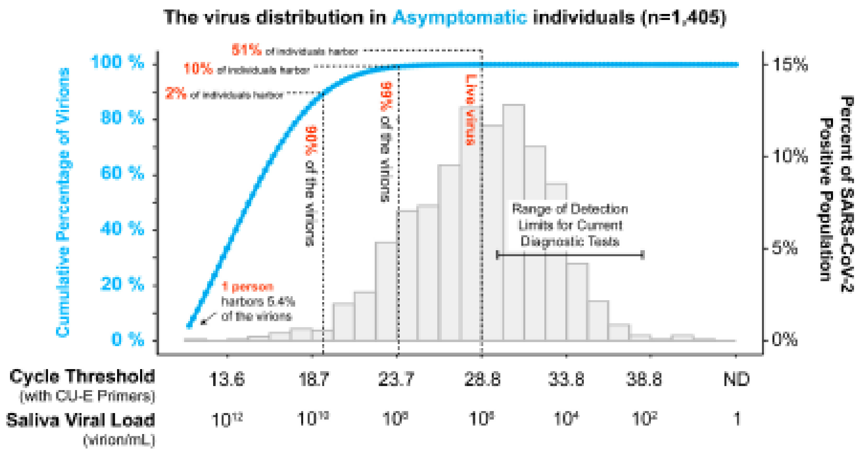


Variability of Individual Infectiousness
Derived from Aggregate Statistics of COVID-19

Julius B. Kirkegaard and Kim Sneppen

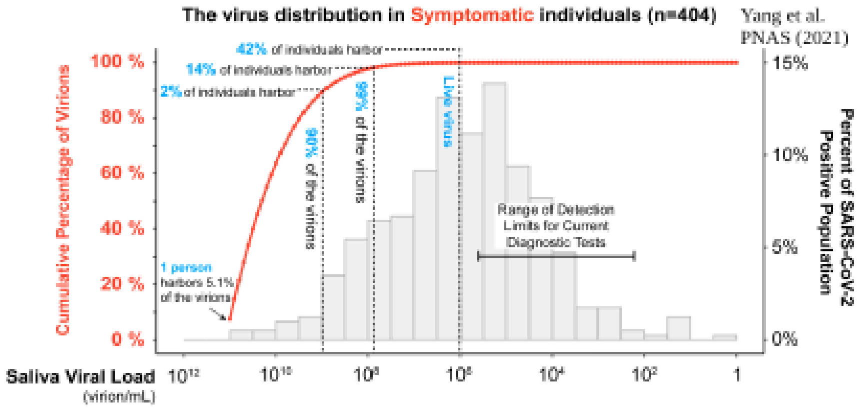
Supershedders in (wt) covid:

- Main argument: 2% carries 90% of virus



The virus distribution in Asymptomatic individuals (n=1,405)

- Only 17% household infections
  (however more like 30-40% for Delta).



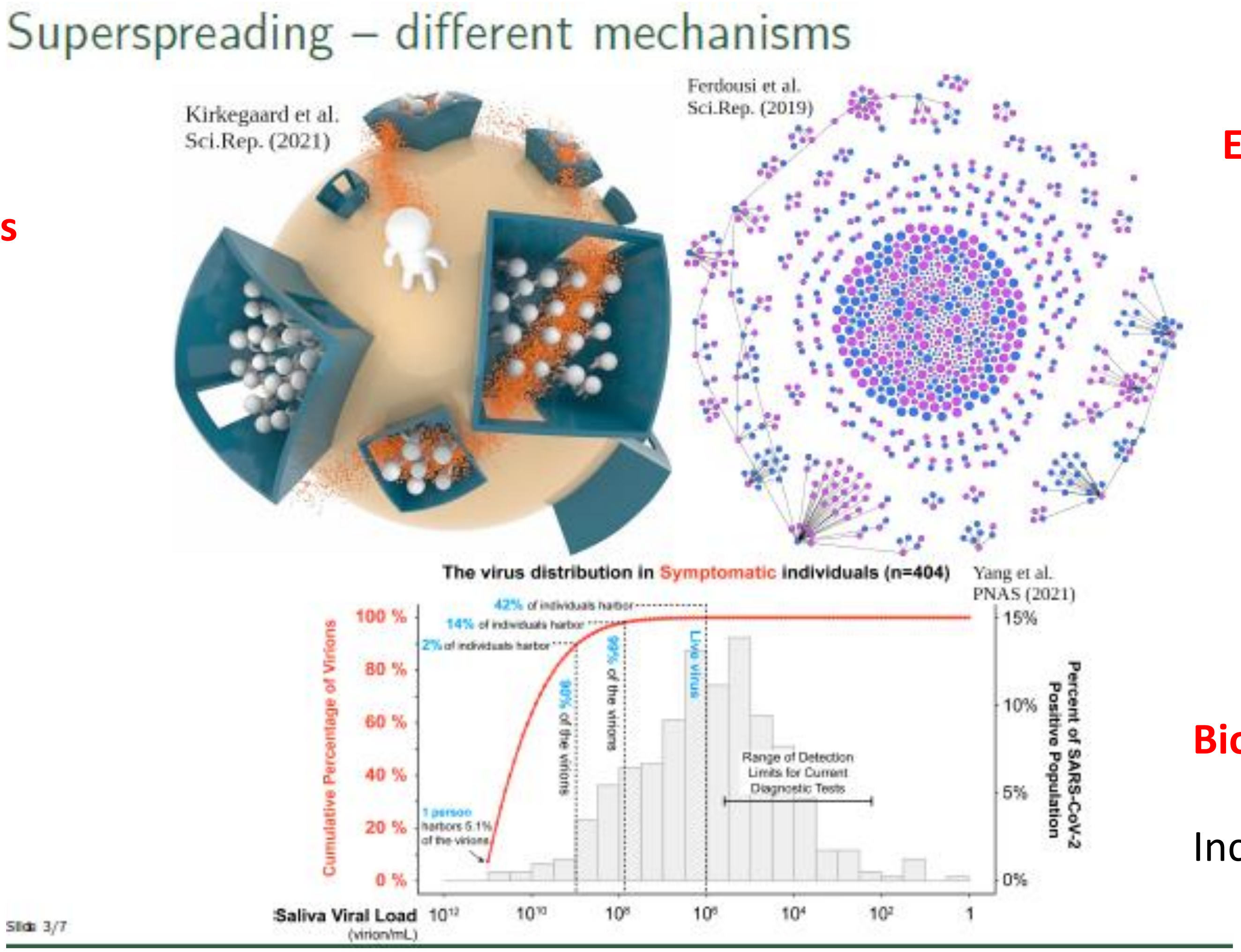
The virus distribution in Symptomatic individuals (n=404)

Yang et al. PNAS (2021)

- →It get important to think about
  Duration of contacts, Diversity of contacts & infectivity.

Other (next pandemics X?) may have:

Aerosol→social superspreaders



Superspreading – different mechanisms

Kirkegaard et al. Sci.Rep. (2021)

Ferdousi et al. Sci.Rep. (2019)

Yang et al. PNAS (2021)

Extreme beavior→social superspreaders

Biological variation→ superspreaders

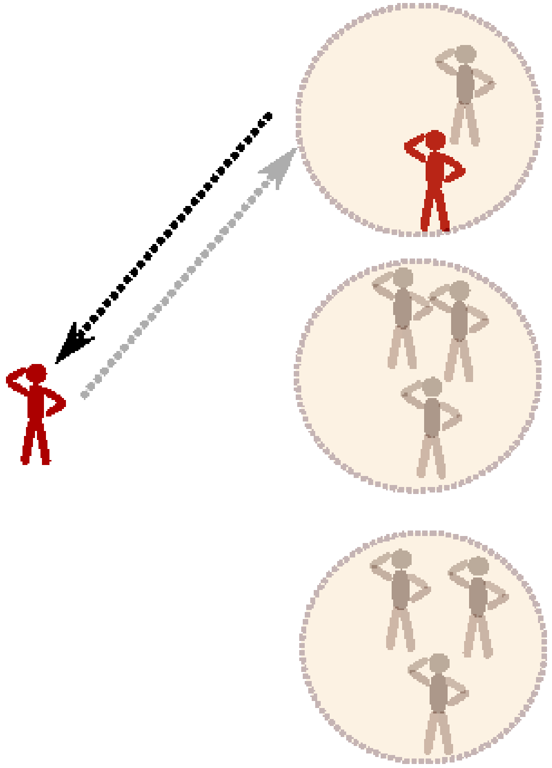
Includes Tuberculosis

SIR models wrong:

Disease spreading needs Infectability and Opportunity

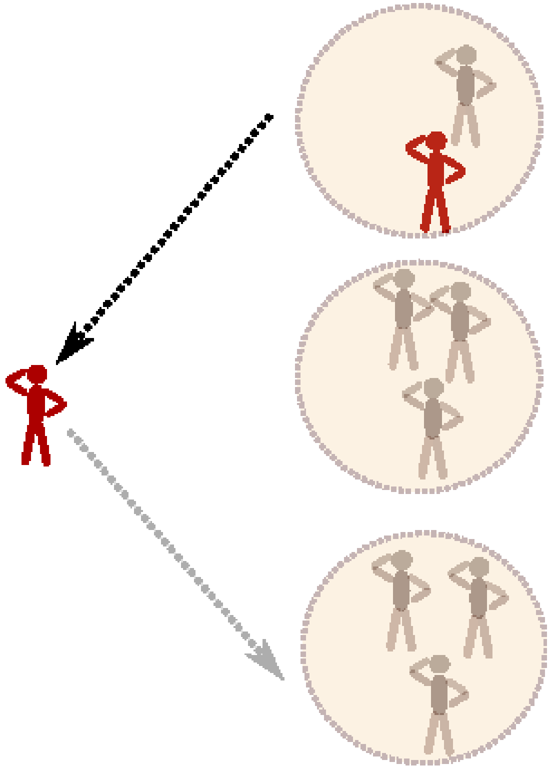
The latter nearly unlimited in SIR /compertemental models

Reality: Each man return
to same home every day



Here can only infect up to 2
new susceptibles

SIR simplification: Each man return
to a new home every day



Here he has unlimited infection
potential (one for each timestep)

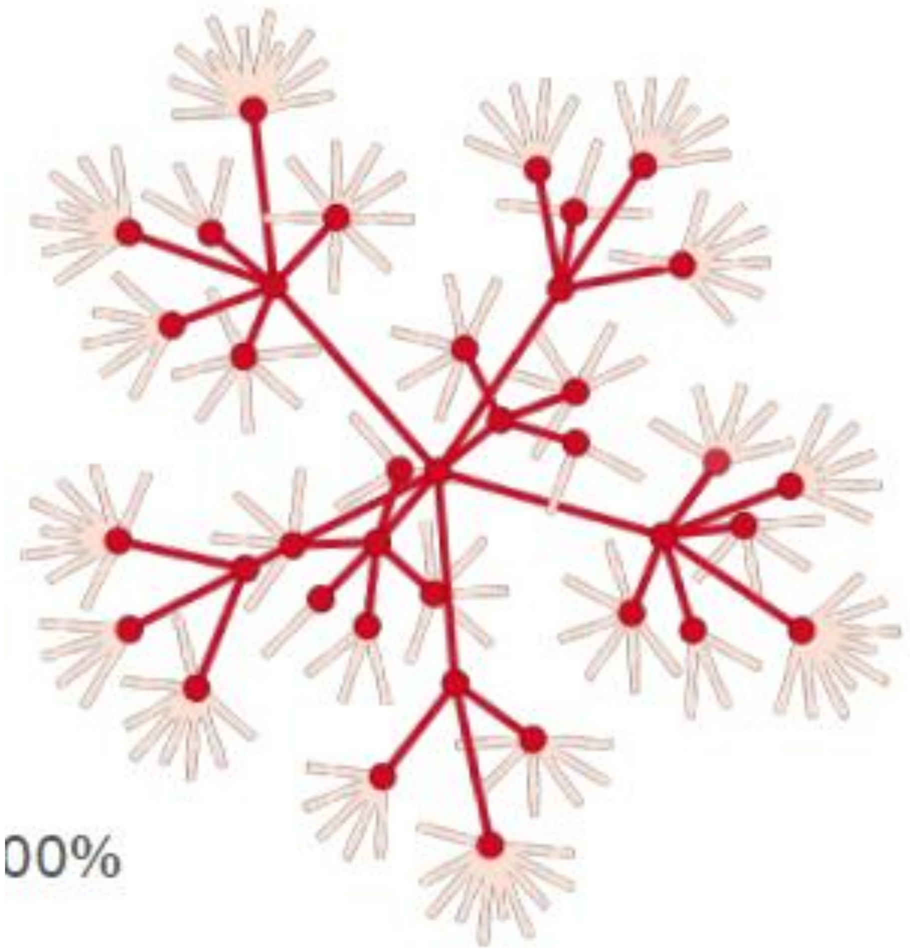
Agent based model:

- Follow individuals as nodes in a network:
- Can give people real homes & work, don’t give them a new family every evening (as done in SEIR models)
- Can give people individual properties….`` Quenched noise”

- **DOES NOT NEED TO BE COMPLICATED!!!!**

……………….e.g. same 2 basic parameters as SIR model

Put people on a network:



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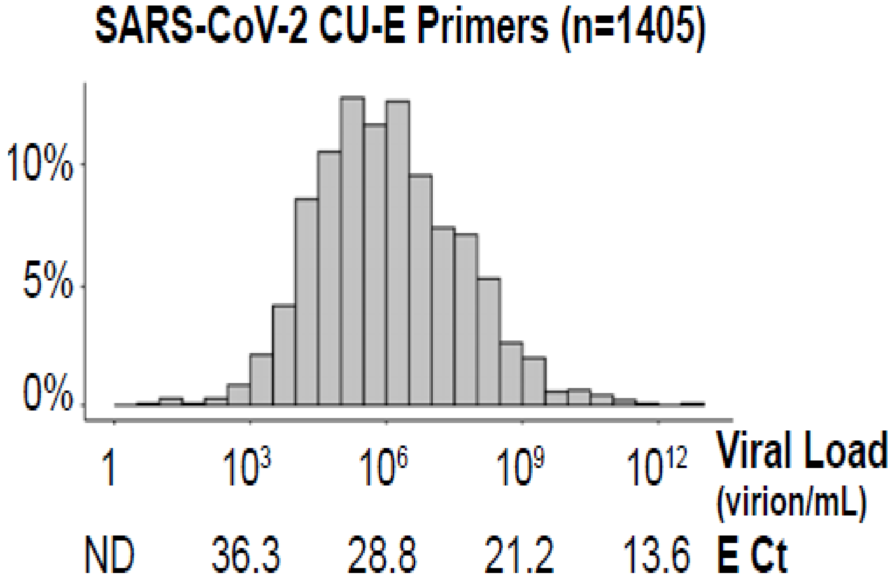


Main idea: you cannot Infect more that you are connected to

Agent based:
Disease on a social network:

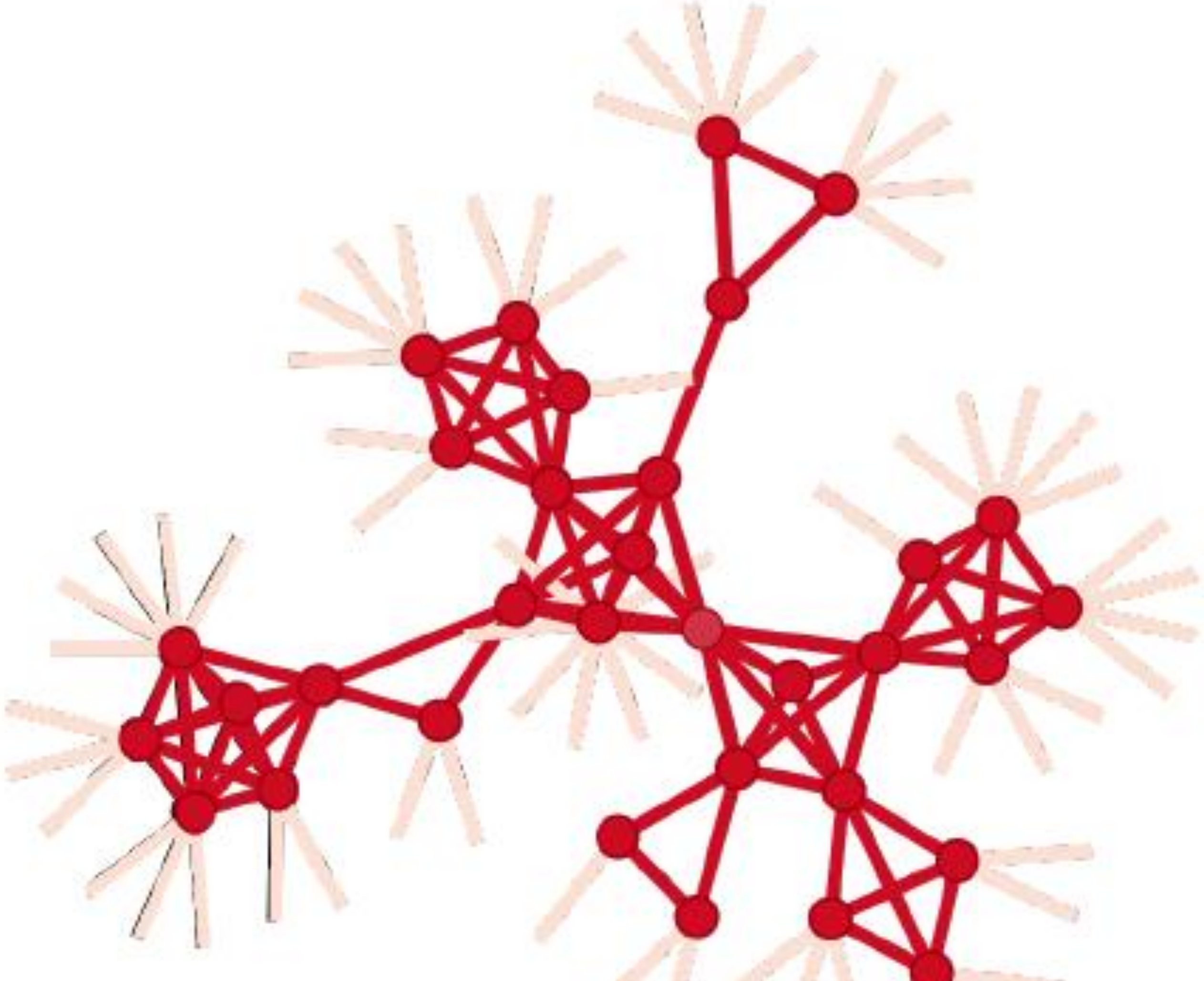
Repeat N times:

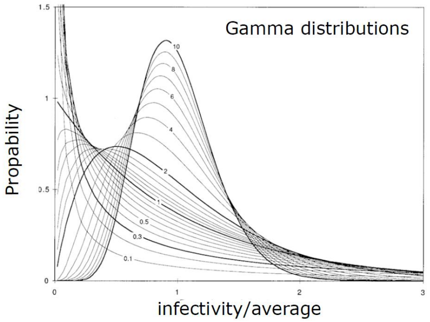
Take random agent *i*.

If in ***I***-state, take one of its neighbors. If this is in S-state then it is infected with probability = β*i* · dt

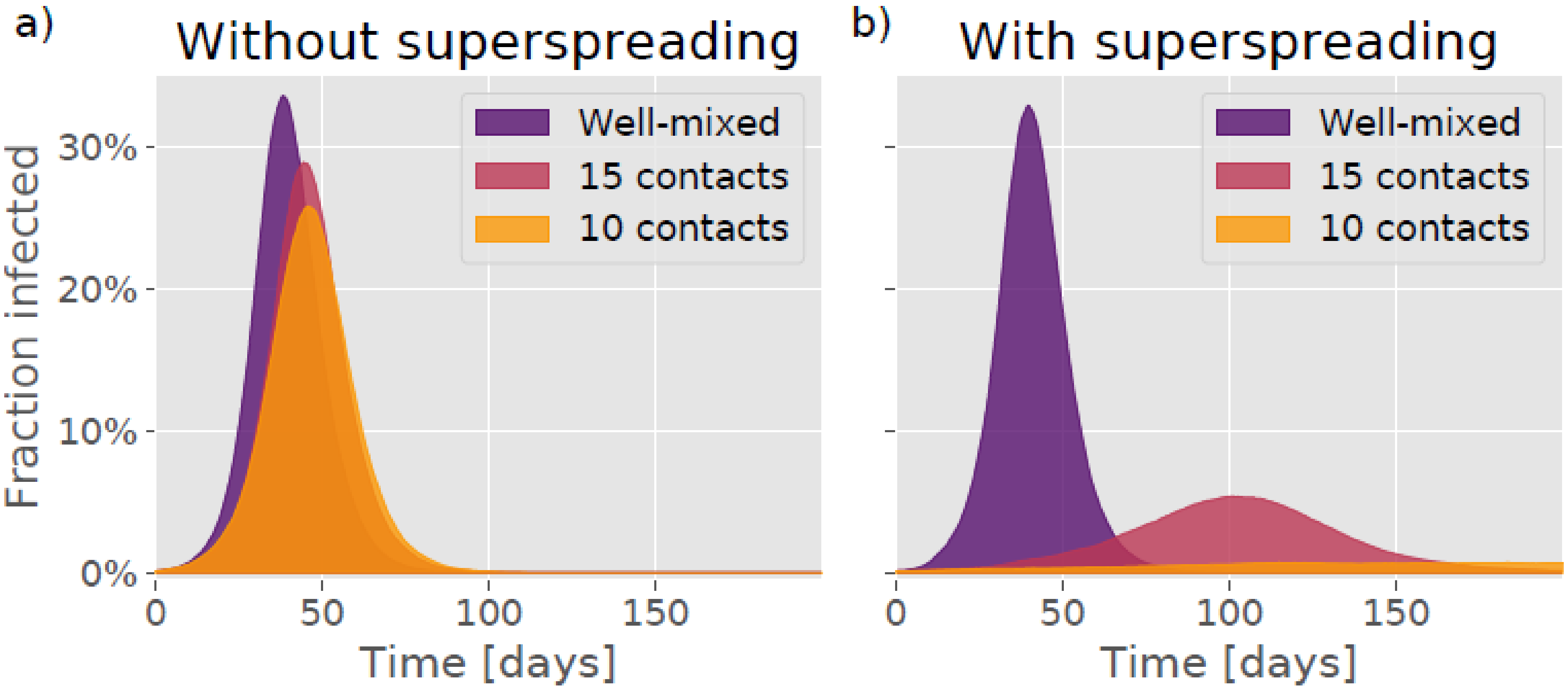
For each sites in state ***I*** convert it to state R with Probability = dt/τ   (duration of in ***I***-state)

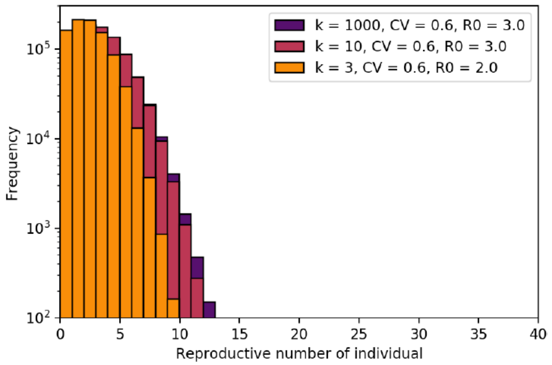
…NB: Notice each person assigned a different = β*i*… that is different infectivity, that is selected from a gamma distribution with form factor k



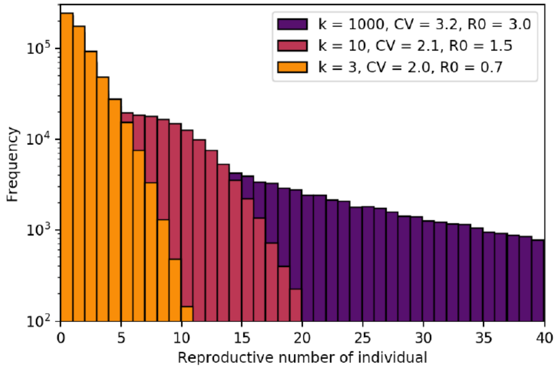


Bjarke Nielsen, Lone Simonsen & KS

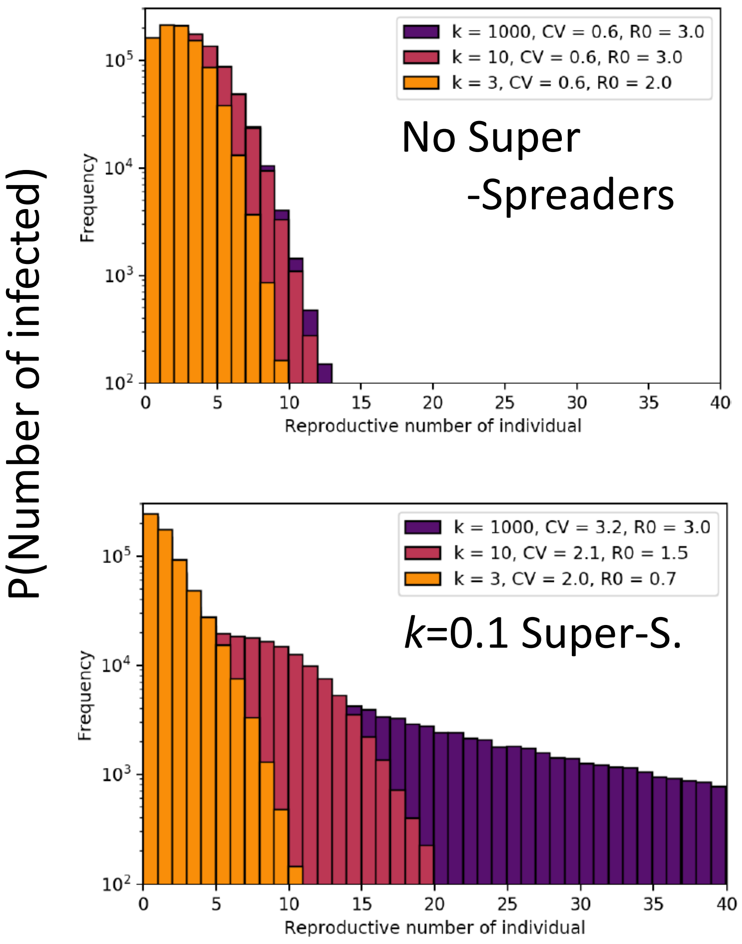




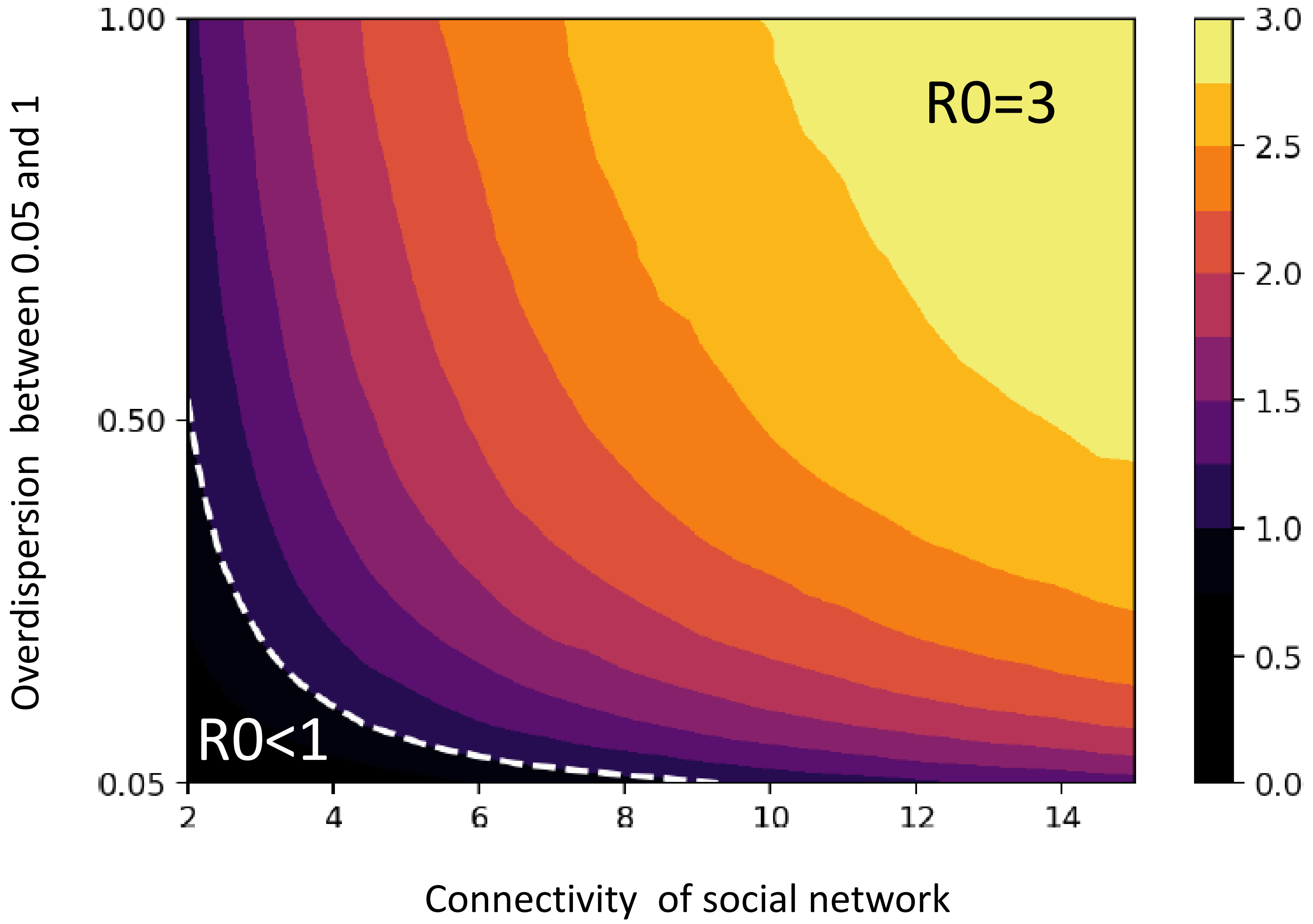
Nielsen, Bjarke Frost, Lone Simonsen, and Kim Sneppen. "COVID-19 superspreading suggests mitigation by social network modulation." *Physical Review Letters* 126.11 (2021): 118301.



Systematics of social network constraints on superspreaders

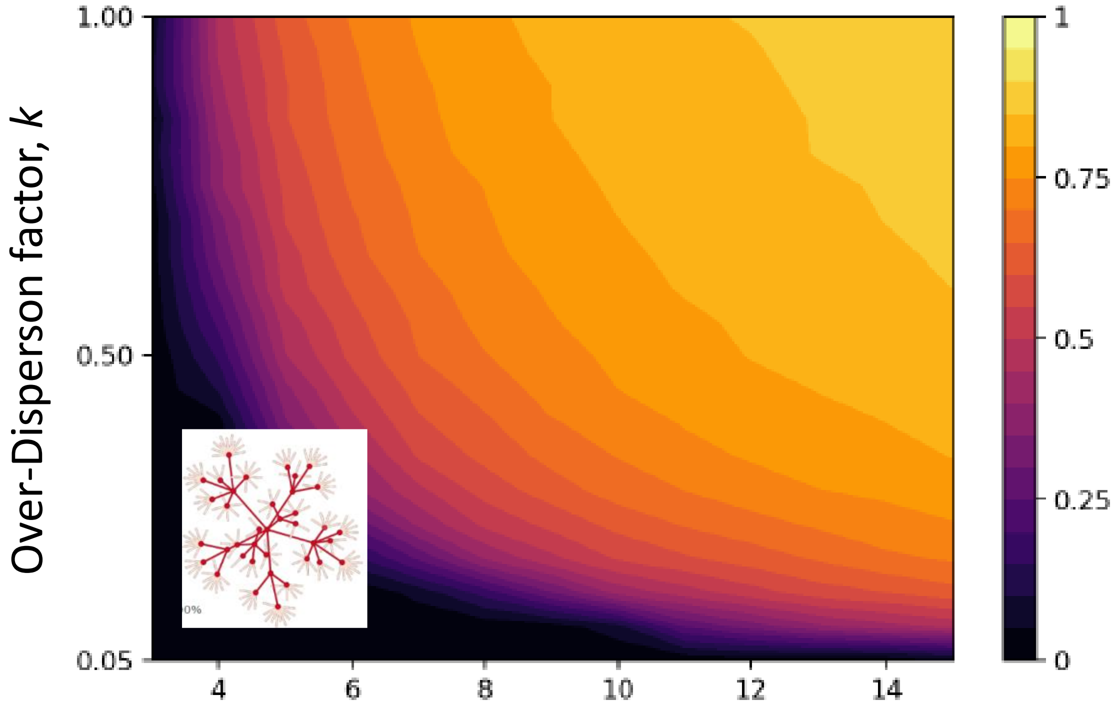


$P(s)=s^{k-1}\exp(-k\,s/3)$

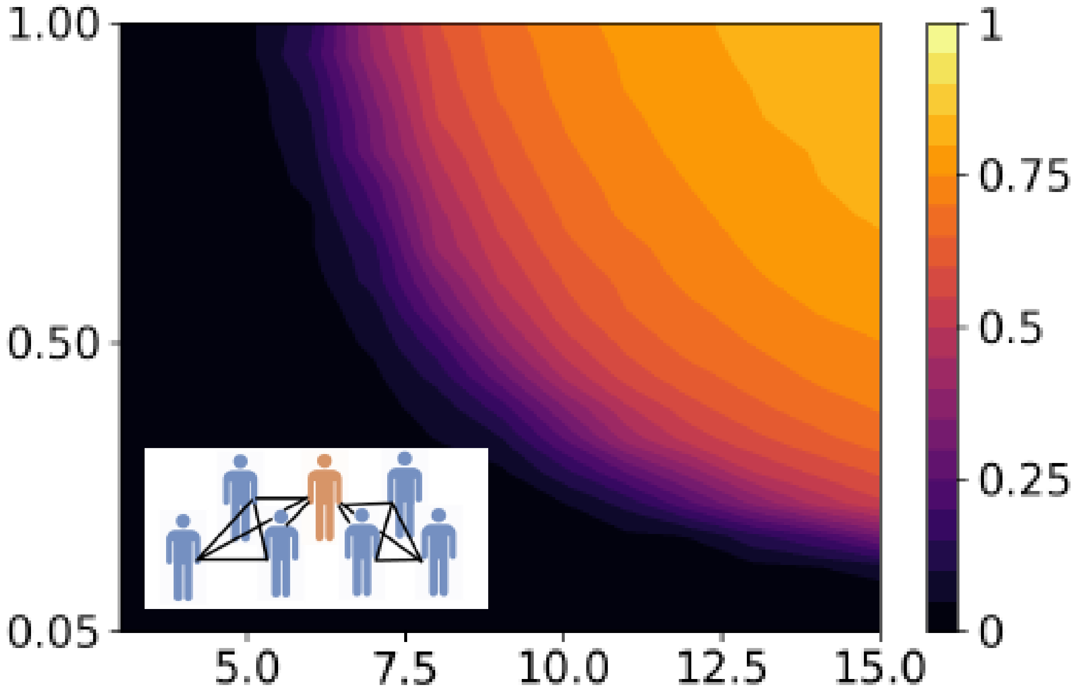


Main idea: Limit connectivity on your network stops the epidemic… already a limit of 10 works fairly well

Attack rate for superspreades (*k*=0.1):



Erdös-Renyi

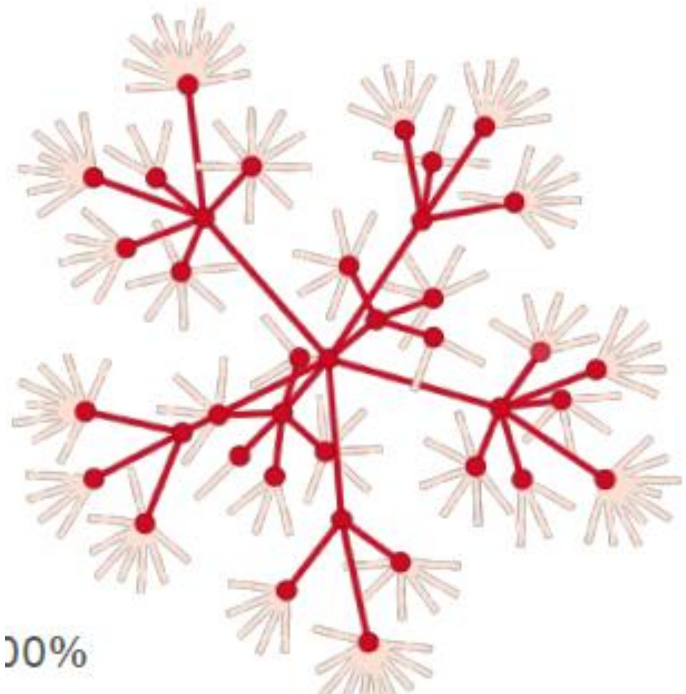


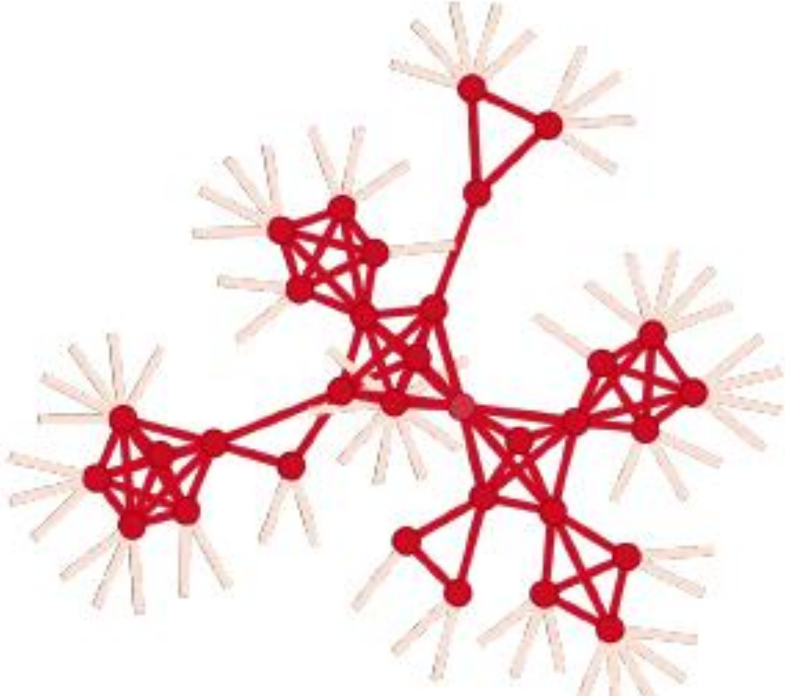
Group network

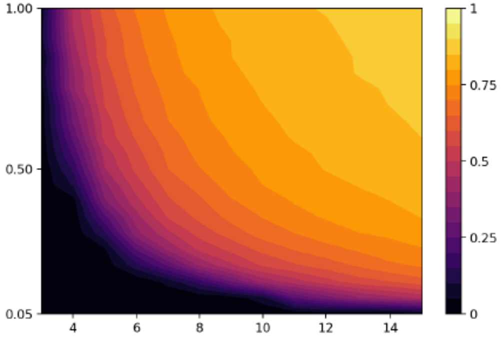
→Limits on propagation much higher if people you connect to connect to each other (cluster network)

…………….local saturation, if you are infected, most of your surroundings are already infected.

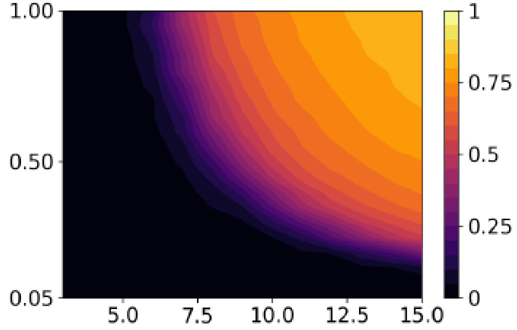
Social bubbles easier to mitigate than ``open” networks





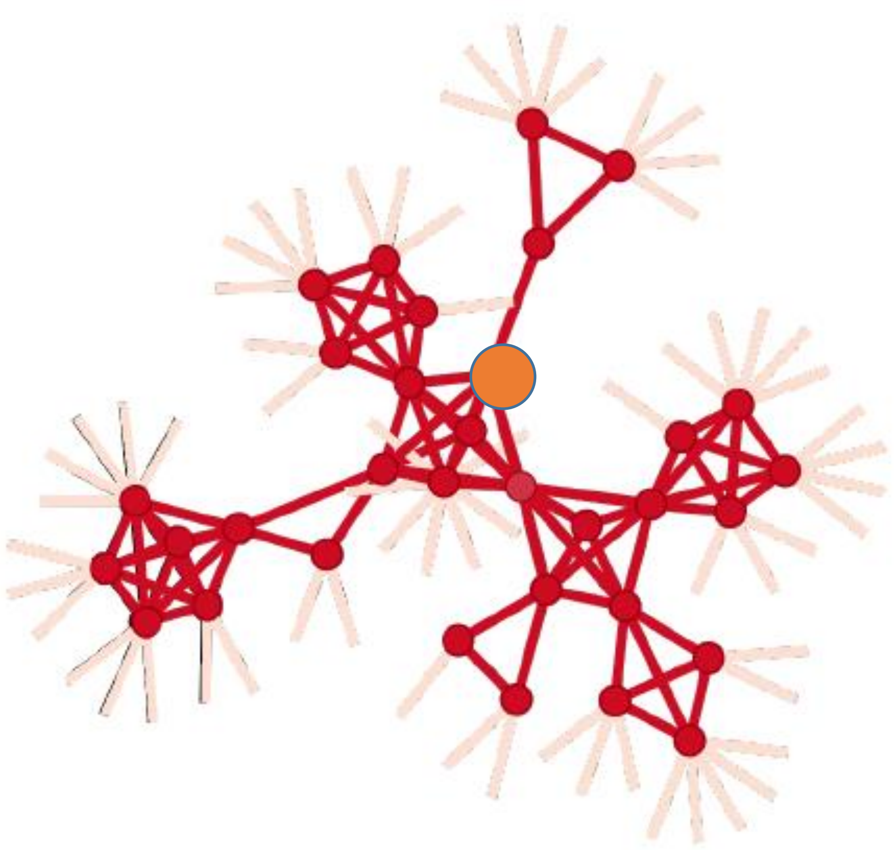


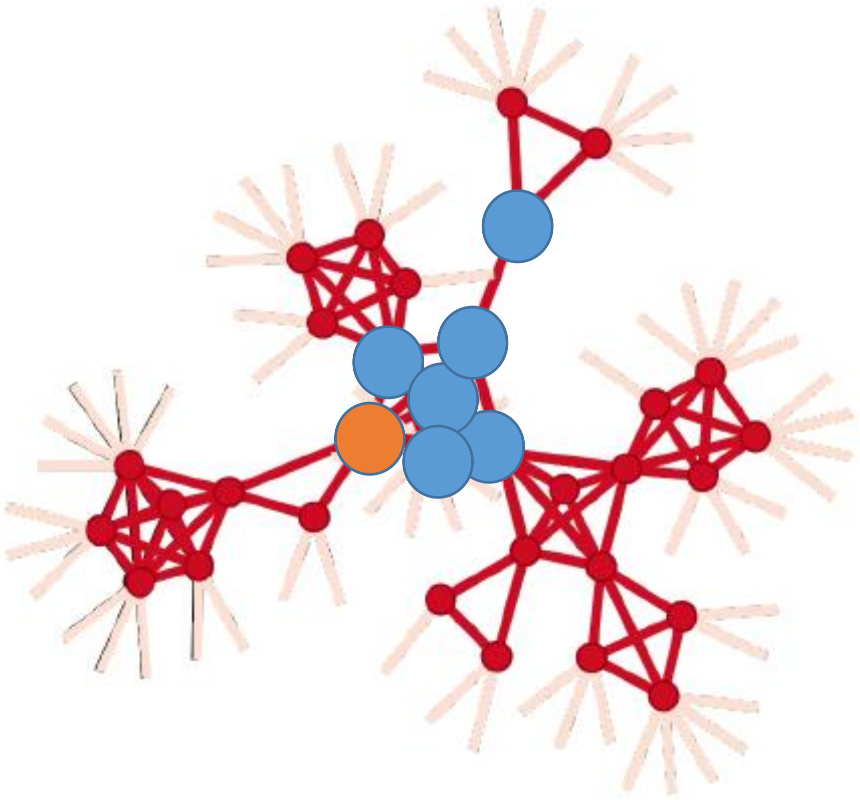
Erdös-Renyi



Group network

Diseases on networks, beta high → Local Saturation





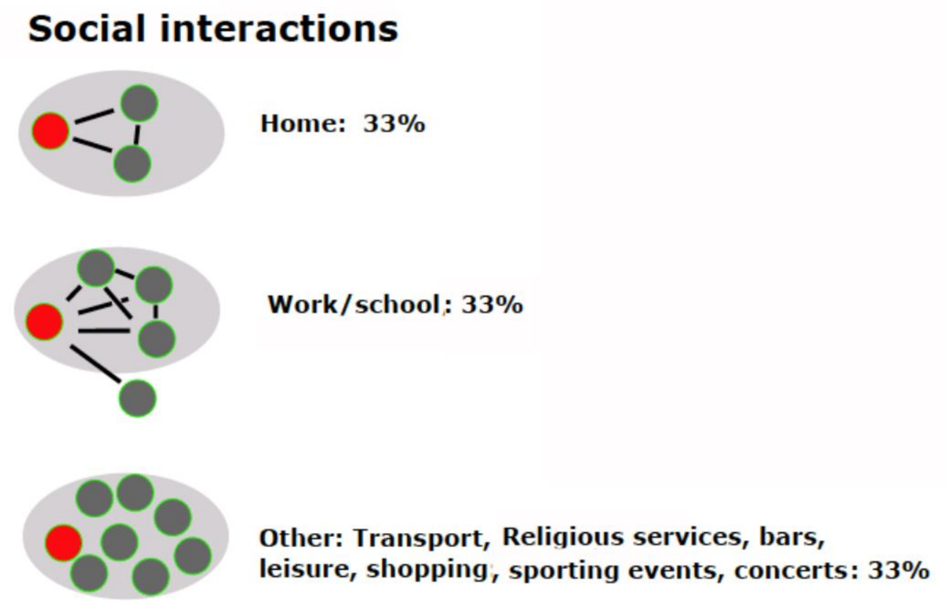
Mechanism of bubble battles:

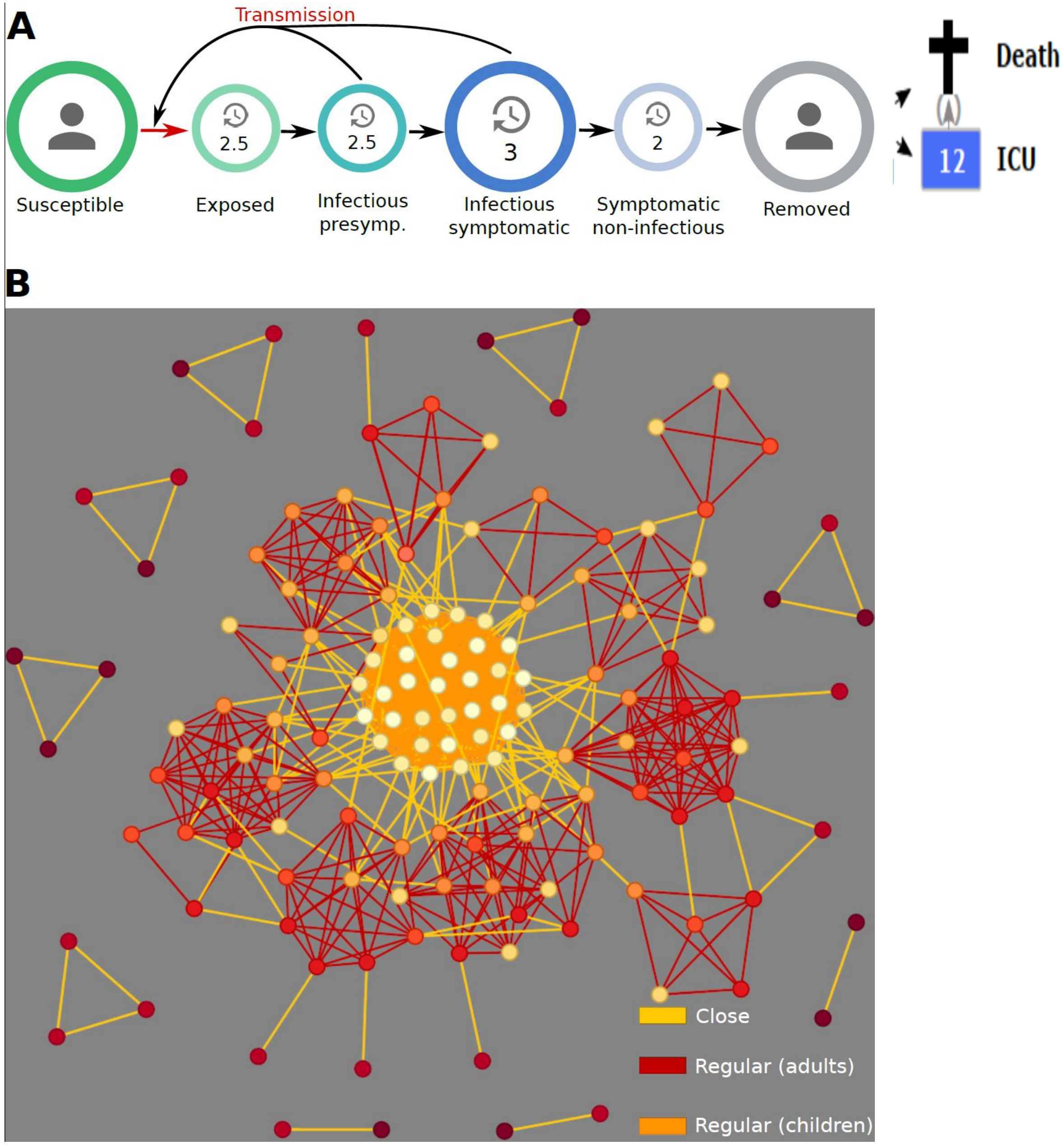
- With social bubbles, like your workplace, then when you get infected, most likely other also got it, and you thus cannot spread more at that workplace.
- When you get disease from a single contact, on the other hand, no local ``micro-herd” immunity.

Nielsen, Bjarke Frost, Lone Simonsen, and Kim Sneppen. "COVID-19 superspreading suggests mitigation by social network modulation." *Physical Review Letters* 126.11 (2021): 118301.

More realism:

- Different type of social networks
- Also meet some people outside networks:



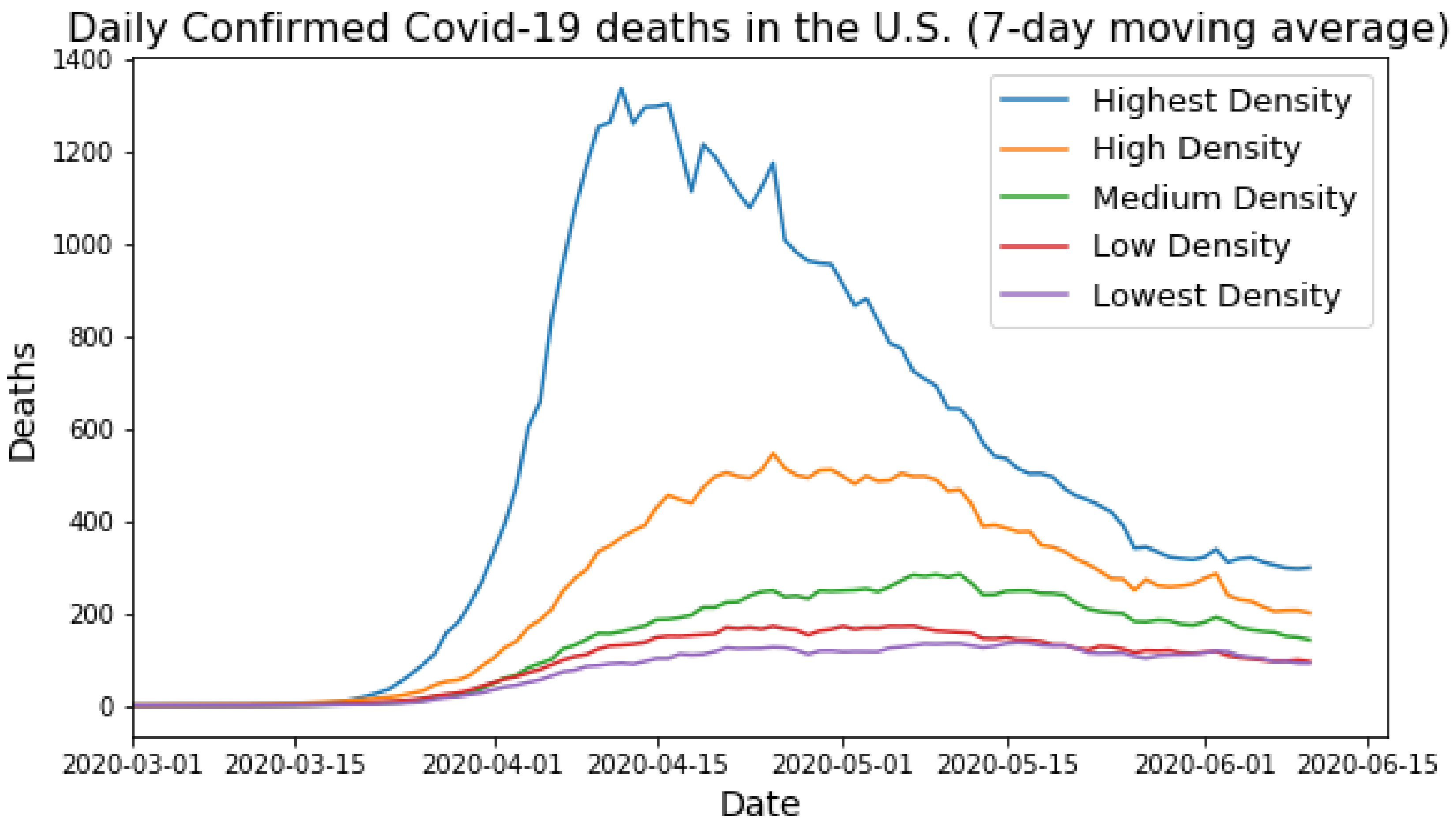


Sneppen, K., Nielsen, B. F., Taylor, R. J., & Simonsen, L. (2021). Overdispersion in COVID-19 increases the effectiveness of limiting nonrepetitive contacts for transmission control. *Proceedings of the National Academy of Sciences*, *118*(14).

Here we just remove 1 of 3 different sectors

→The only thing that matters is to remove the random connections = occasional encounters

Superspreading *potentially* explain why Covid-19 spreads more at high population density:

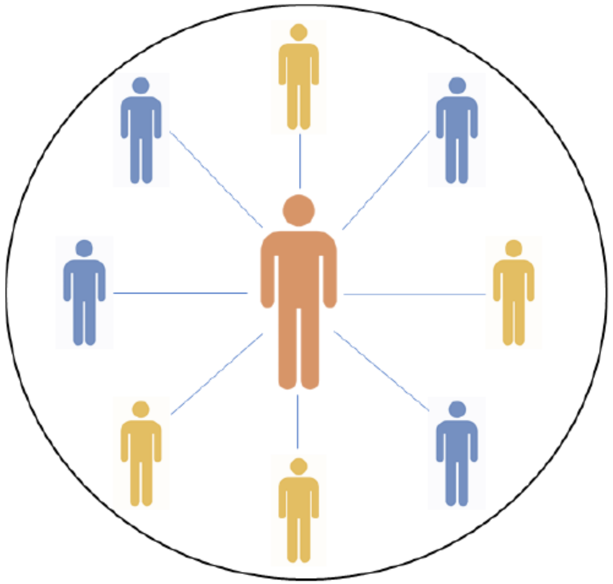


Eilersen, Andreas, and Kim Sneppen. "SARS-CoV-2 superspreading in cities vs the countryside." *Apmis* (2021).

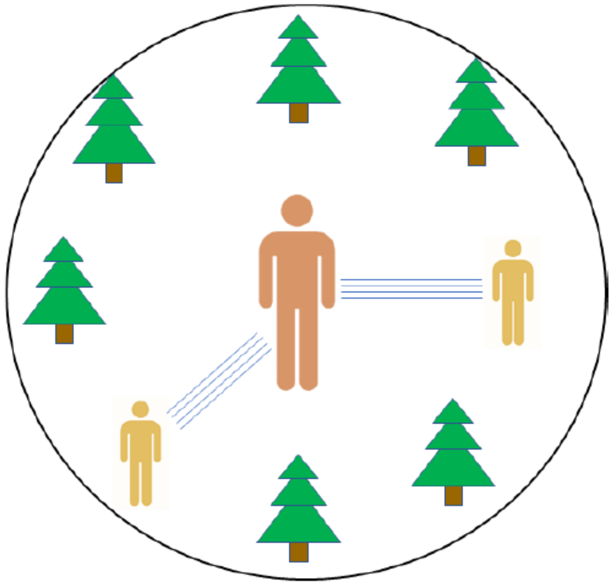
…..Influenza does not

Superspreaders and geography:

- 99% infection was indoors (in China, ref 1, 2))
- Few infections within households,→only visits facilitate spreading



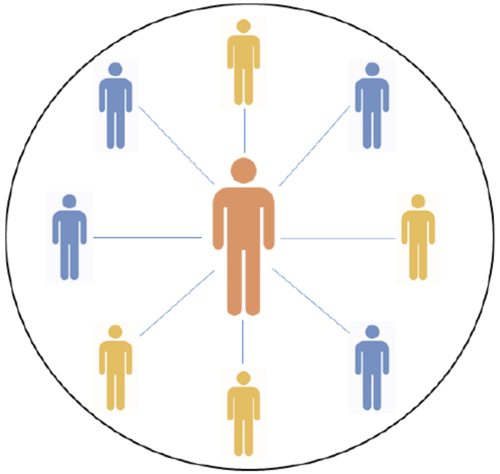
Superspreader in a city



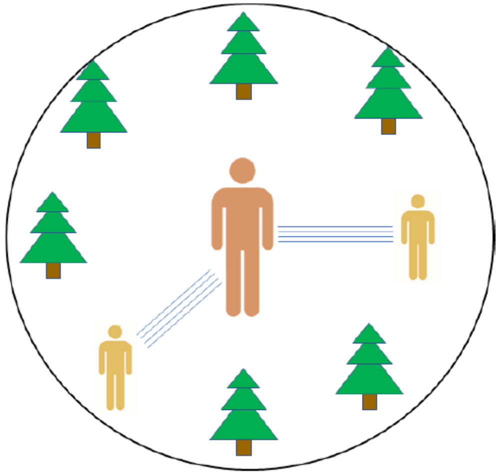
Superspreader outside the city

1) C. J. Carlson et al.
Species distribution modelsare inappropriate for covid-19, Nature Ecology & Evolu-tion4, 770 (2020).
2) H. Nishiura, et al.
Closed environments facilitate secondary transmission of coronavirus disease 2019 (covid-19),medRxiv (2020).
3) S. Y. Park et al. et al. Early release-coronavirus disease outbreak in call center,

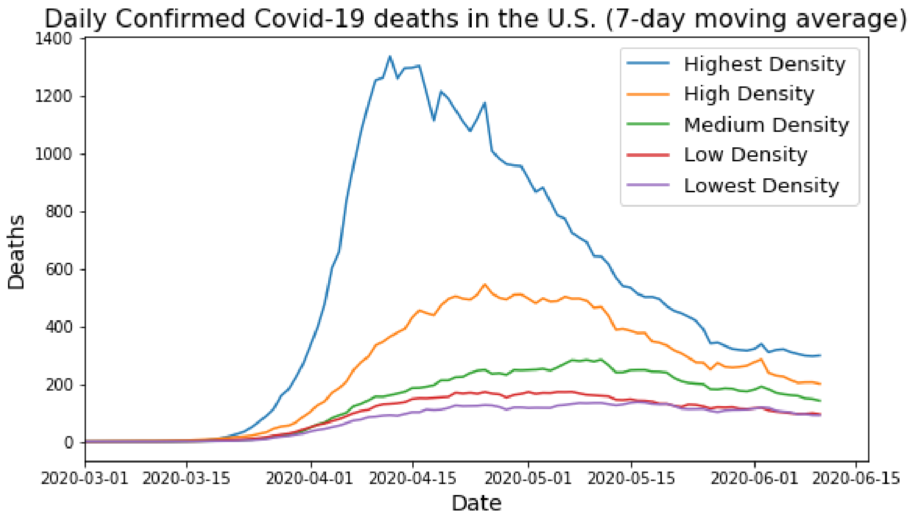
Superspreader &
City←→Countryside



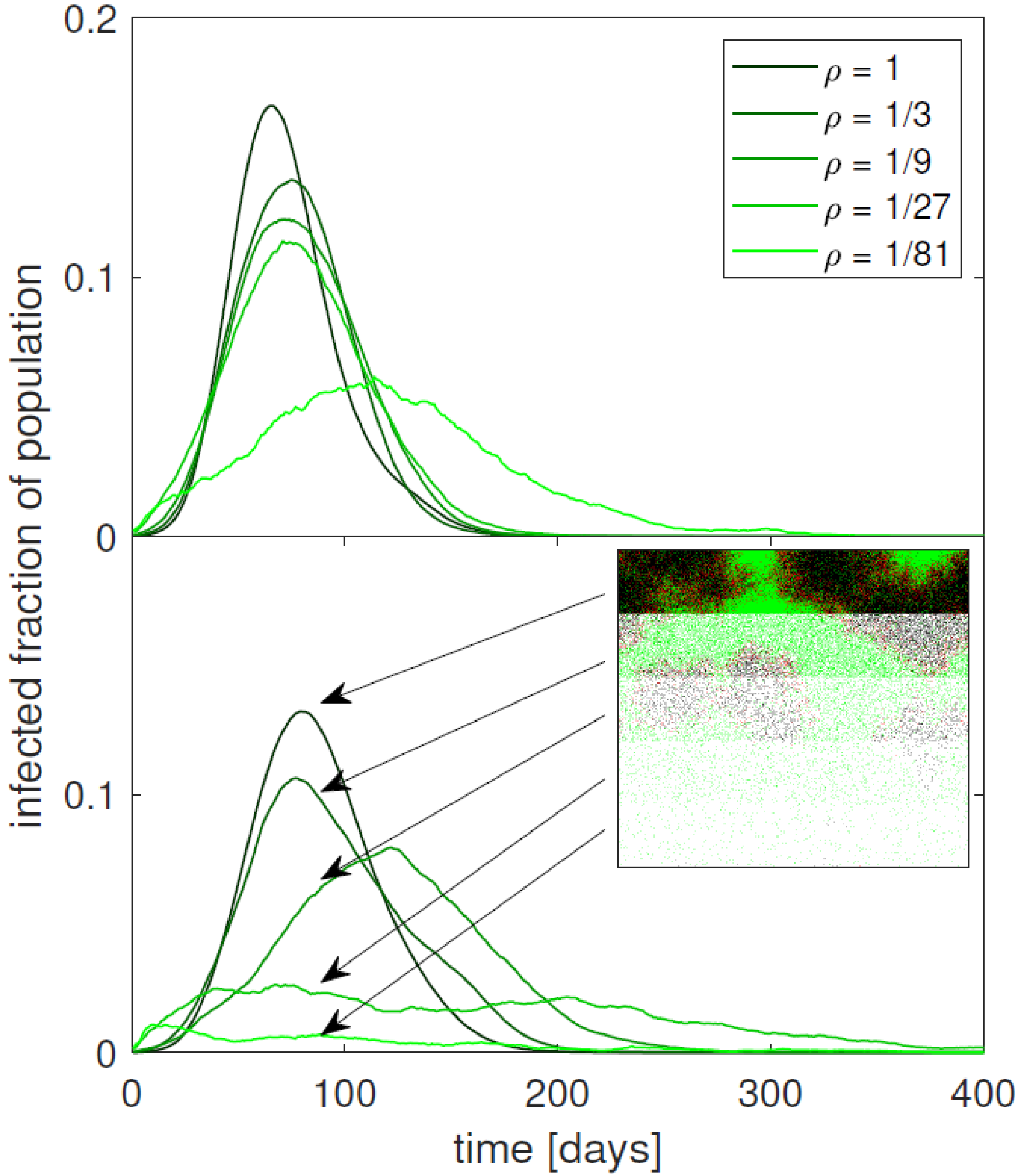
Superspreader in a city



Superspreader outside the city



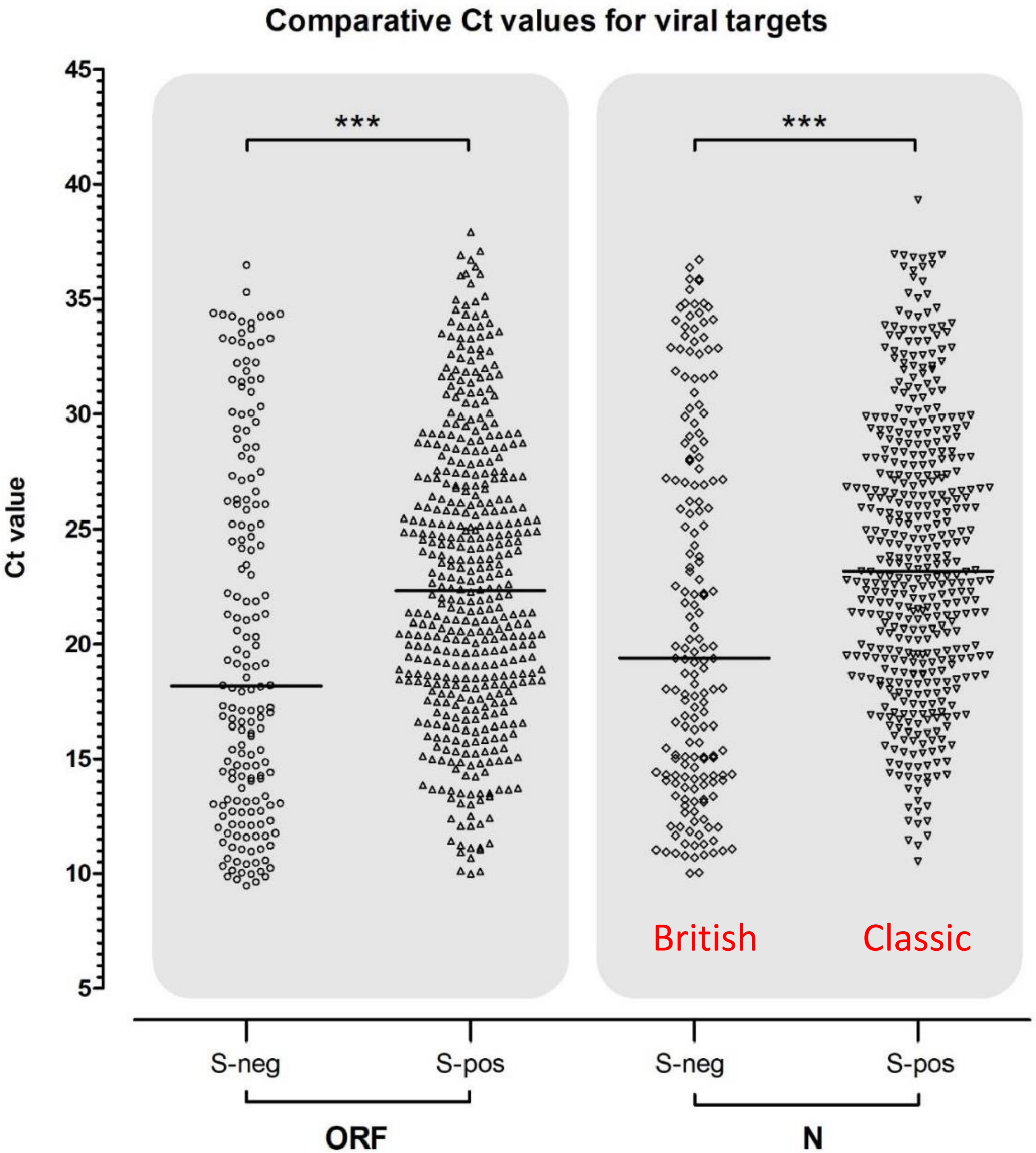
Daily Confirmed Covid-19 deaths in the U.S. (7-day moving average)

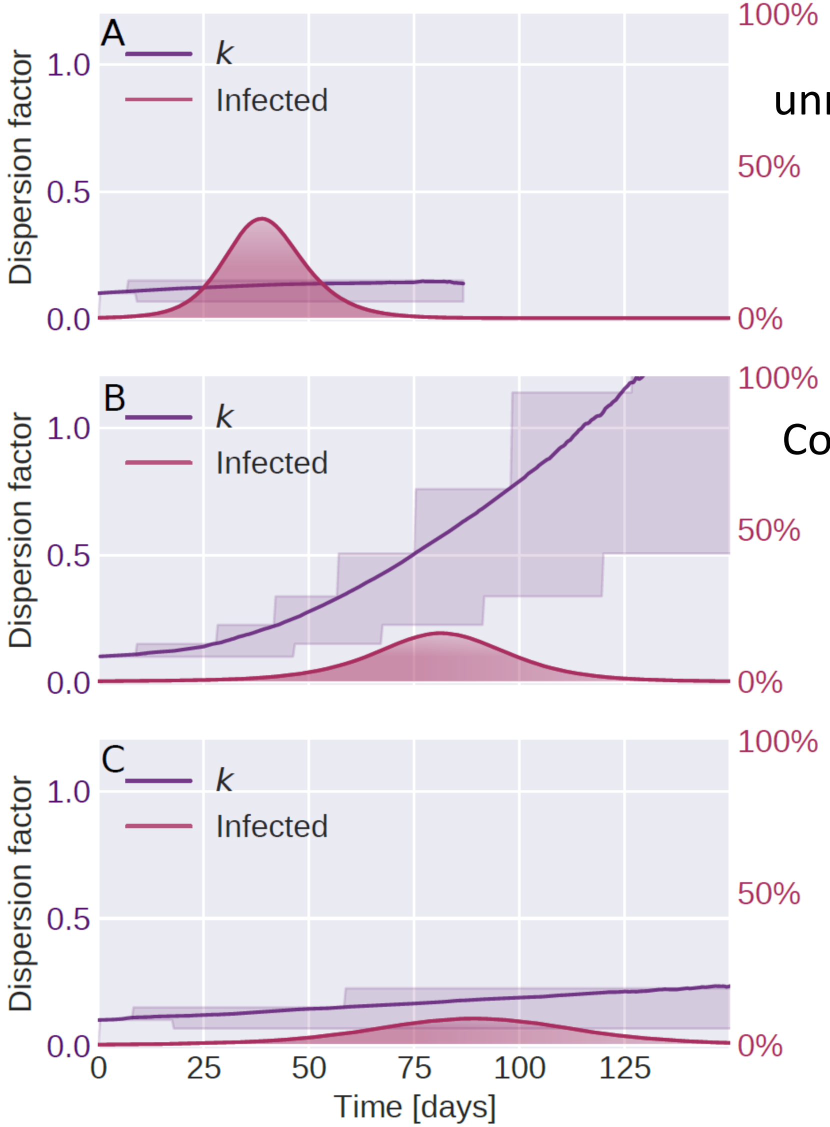


N. Mehdi.
June 2020.

→Evolution pressure: *k* should increase

(R of course also)





unrestrained

Contacts<10

Infectivity
Reduced
overall

Nielsen, B. F., Eilersen, A., Simonsen, L., & Sneppen, K. (2021). Lockdowns exert selection pressure on overdispersion of SARS-CoV-2 variants. *medRxiv*.

→ Shedding Summary:

- The more extreme the superspreader phenomenon, the easier it is to contain a COVID-19 epidemic !!!
- With 10%/75% superspredning, one can largely stop the Covid-19 epidemic by removing diffuse contacts
  - large events, public transportation, fitness centers etc
- And this will also be true in the middle of an epidemic!!!!!
- Consider heterogeneity when modelling COVID-19 mitigation
- Superspreading explain large initial contrast between city and countryside.

- **→→Stay with you friends….**

- **Delta variant worse! 1000 times more virus,…**
- **Omicron lighter, infect upper part of lungs…**

Thanks to:

- **Andreas Eilersen**
- **Mathias Heltberg**
- **Bjarke Frost Nielsen**
- **Julius Kirkegaard**
- **Joachim Mathiesen**
- **Lone Simonsen**
- **Robert Taylor**
- **Xu Xiaochan**

Publications:

Cost–benefit of limited isolation and testing in COVID-19 mitigation
Andreas Eilersen, Kim Sneppen, Scientific Reports 10.1 (2020): 1-7.

Overdispersion in COVID-19 increases the effectiveness of limiting nonrepetitive contacts for transmission control
K. Sneppen, BF. Nielsen, RJ Taylor, L. Simonsen, PNAS, 118.14 (2021): e2016623118.

Social network heterogeneity is essential for contact tracing
Bjarke Frost Nielsen, Kim Sneppen, Lone Simonsen, Joachim Mathiesen
The European Physical Journal B 94 (2021): 1-11.

Superspreading in cities vs the countryside.
Andreas Eilersen, Kim Sneppen, Apmis (2021) 2021, 129.7: 401-407.

Superspreading quantified from bursty epidemic trajectories.
Julius Kirkegaard & Kim Sneppen (2021). Scientific Reports, 11(1), 24124.

COVID-19 Superspreading Suggests Mitigation by Social Network Modulation
Bjarke Frost Nielsen, Lone Simonsen, Kim Sneppen, Phys. Rev. Letter 126.11 (2021): 118301.

Superspreading of airborne pathogens in a heterogeneous world
Julius B Kirkegaard, J. Mathiesen, Kim Sneppen, Scientific reports 11.1 (2021): 1-9

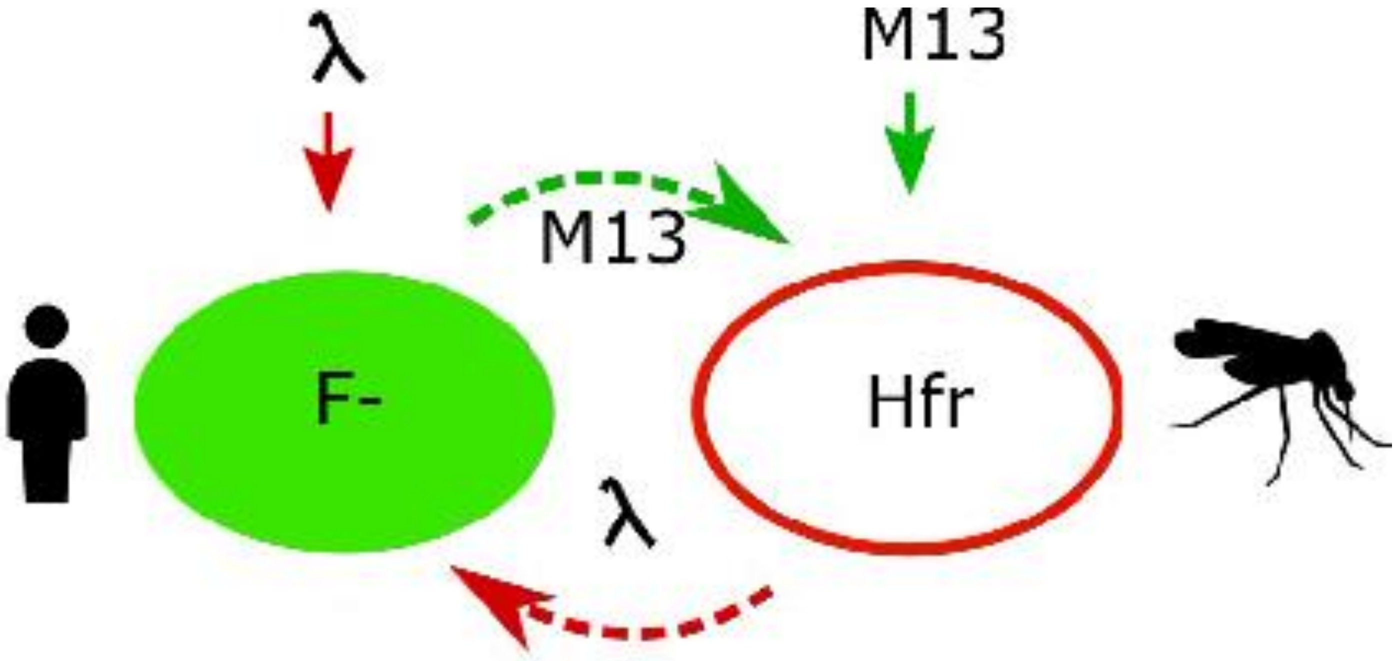
Lockdowns exert selection pressure on overdispersion of SARS-CoV-2 variants.
Nielsen, B. F., Eilersen, A., Simonsen, L., & Sneppen, K. Epidemics 40 (2022): 100613.

The timing of natural killer cell response in coronavirus infection: a concise model perspective.
Xu, X., & Sneppen, K. (2021). bioRxiv.

Synthetic Biology of Epidemics:

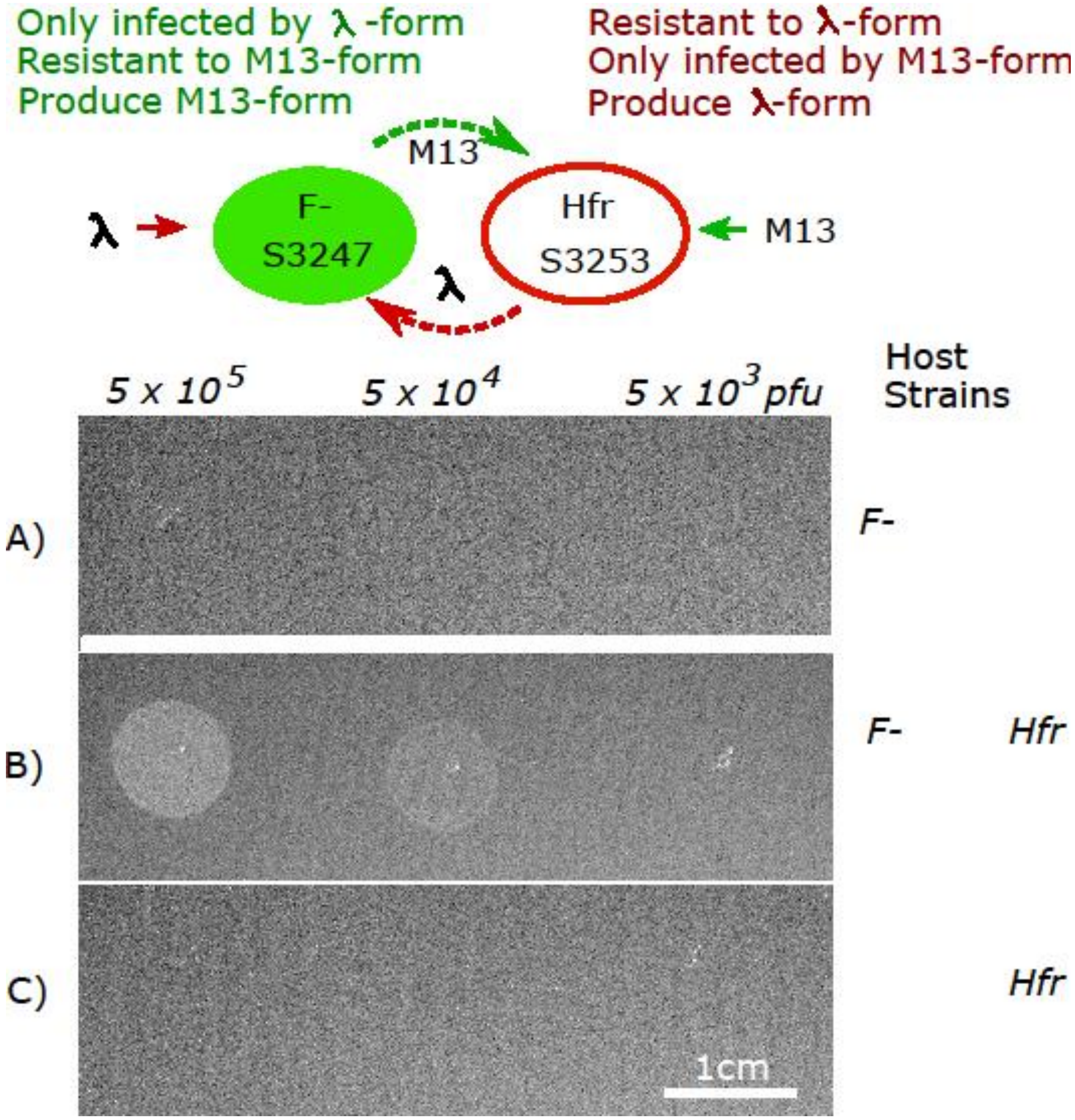
making lab models for exploring diseases X

Here of Vector borne diseases:



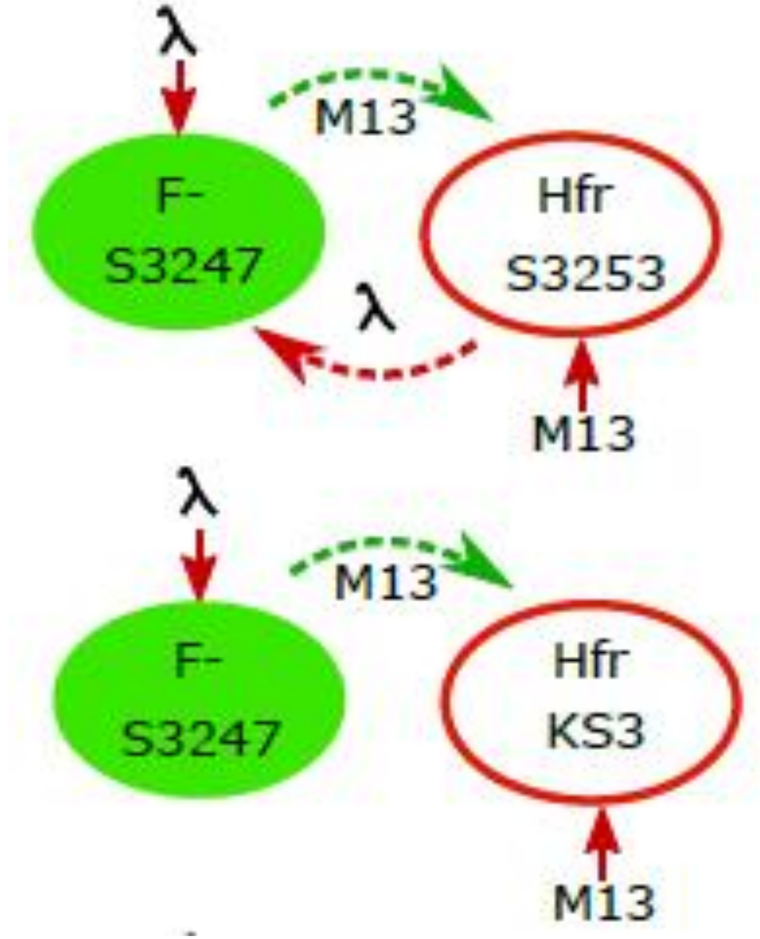
Done with bacterial constructed (gain of function) bacterial viruses & two mutant strains of E.coli

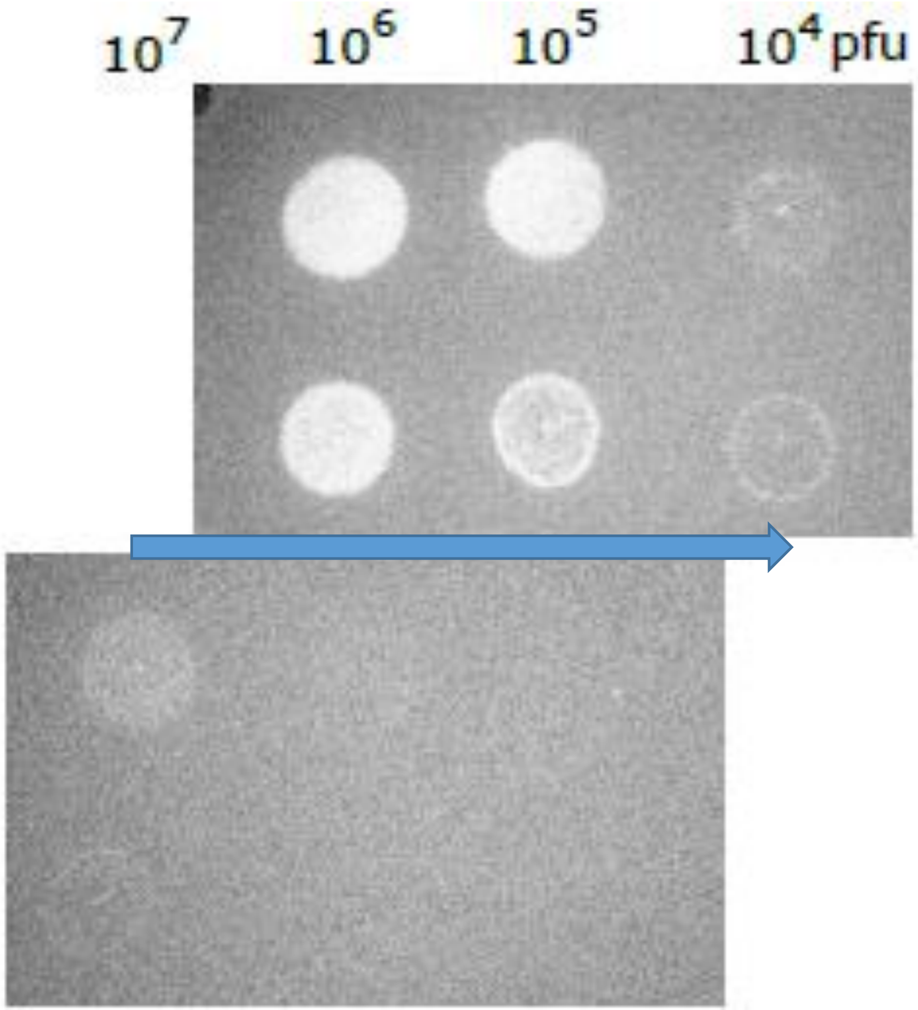
Proof Of Construction:



One cycle experiments:

1000-fold
less
spreading
if only
one cycle





Model & parameters:

S (prey)

$$\frac{df}{dt} = \Gamma_f \cdot f \cdot \mathcal{C} - \overbrace{\eta_\lambda \cdot P_\lambda \cdot f_{avai}}^{R} + \Gamma_{cure} \cdot f^* \cdot \mathcal{C}$$

E

$$\frac{df_1}{dt} = \eta_\lambda \cdot P_\lambda \cdot f_{avai} - f_1 \cdot \frac{n_m}{\tau_m} + \Gamma_f \cdot f_1 \cdot \mathcal{C}$$

$$\frac{df_i}{dt} = f_{i-1} \cdot \frac{k_m}{\tau_m} - f_i \cdot \frac{k_m}{\tau_m} + \Gamma_f \cdot f_i \cdot \mathcal{C} \quad , \quad i = 2, 3...$$

I
(predator)

$$\frac{df^*}{dt} = f_n \cdot \frac{k_m}{\tau_m} + \Gamma_f \cdot f^* \cdot \mathcal{C} - \Gamma_{cure} \cdot f^* \cdot \mathcal{C}$$

$$\frac{dP_m}{dt} = \Omega_m \cdot f^* \cdot \mathcal{C} - \eta_m \cdot P_m \cdot v_{abs} - Loss_m \cdot P_m$$

$$\frac{dv}{dt} = \Gamma \cdot v \cdot \mathcal{C} - \eta_m \cdot P_m \cdot v_{avai}$$

$$\frac{dv_1}{dt} = \eta_m \cdot P_m \cdot v_{avai} - v_1 \frac{k_\lambda}{\tau_\lambda}$$

$$\frac{dv_i}{dt} = v_{i-1} \cdot \frac{k_\lambda}{\tau_\lambda} - v_i \cdot \frac{k_\lambda}{\tau_\lambda} \quad for \;\; i = 2, 3, .., n_\lambda$$

$$\frac{dP_\lambda}{dt} = \beta \cdot \mathcal{C} \cdot v_{n_\lambda} \frac{k_\lambda}{\tau_\lambda} - \eta_\lambda \cdot P_\lambda \cdot f_{abs} - Loss \cdot P_\lambda$$

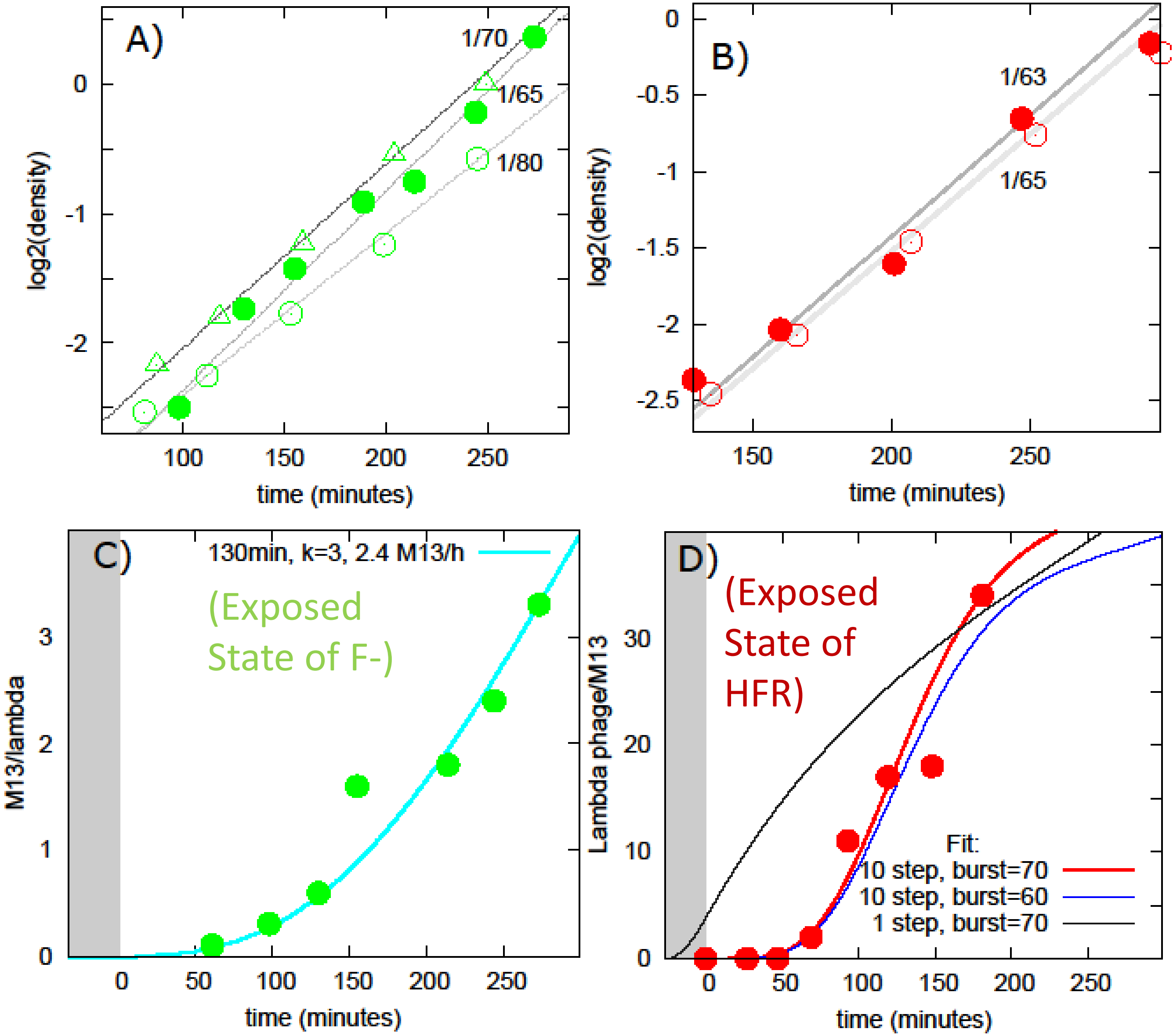
Colony Level Correction

$$v_{abs} = v_0 \cdot \left(\frac{v + v^L}{v_0} \right)^{1/3}$$

$$v_{avai} = v_{abs} \cdot exp \left(- \frac{\frac{v^L}{v_0}}{4 \cdot (\frac{(v+v^L)}{v_0})^{2/3}} \right)$$

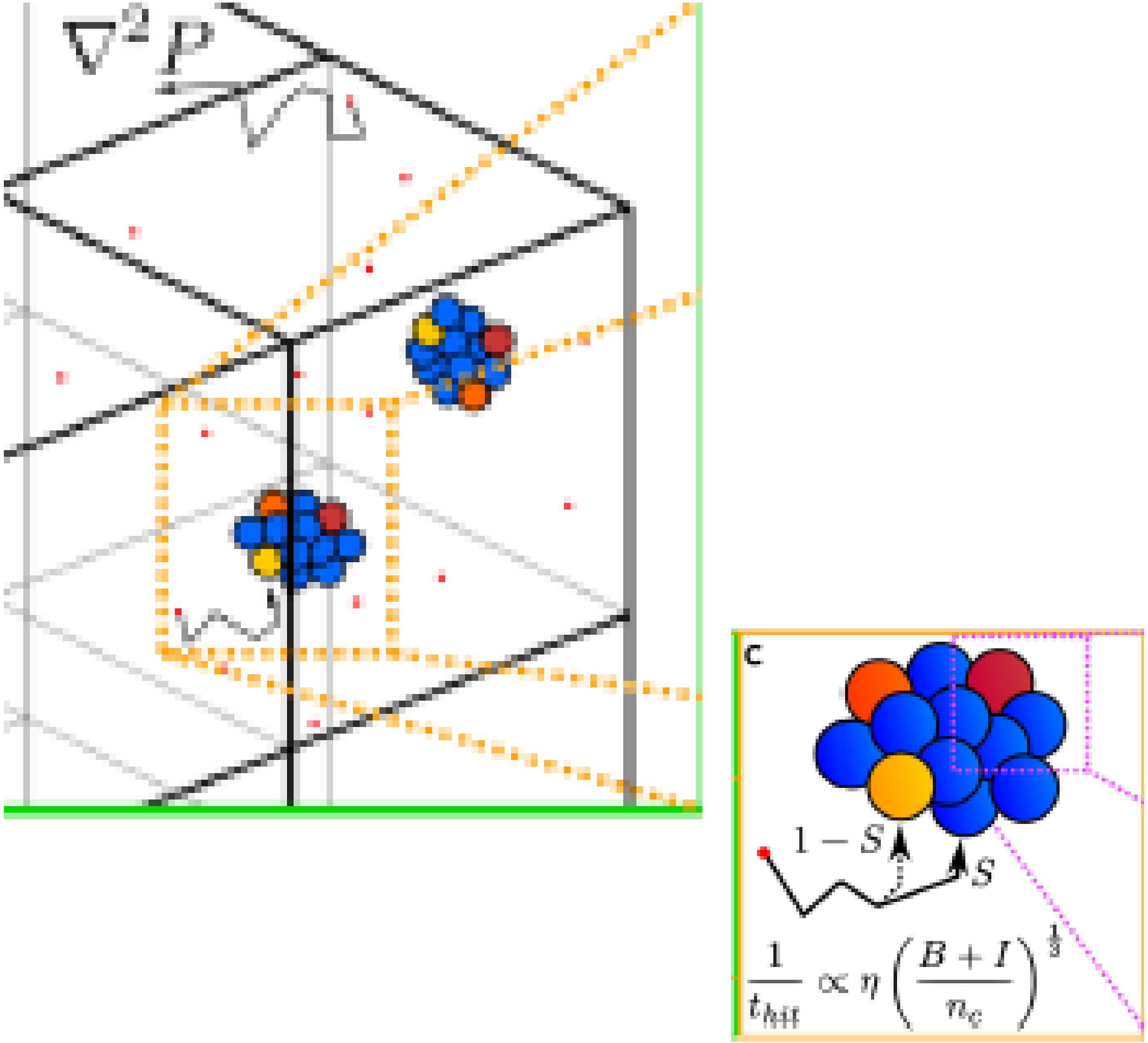
$$f_{abs} = f_0 \cdot \left(\frac{f + f^L + f^*}{f_0} \right)^{1/3}$$

$$f_{avai} = f_{abs} \cdot exp \left(- \frac{\frac{(f^L+f^*)}{v_0}}{4 \cdot (\frac{(f+f^L+f^*)}{v_0})^{2/3}} \right)$$



(Exposed
State of F-)

(Exposed
State of
HFR)



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Model & model parameters:

$$\frac{df}{dt} = \Gamma_f \cdot f \cdot \mathcal{C} - \eta_\lambda \cdot P_\lambda \cdot f_{avai} + \Gamma_{cure} \cdot f^* \cdot \mathcal{C}$$

$$\frac{df_1}{dt} = \eta_\lambda \cdot P_\lambda \cdot f_{avai} - f_1 \cdot \frac{n_m}{\tau_m} + \Gamma_f \cdot f_1 \cdot \mathcal{C}$$

$$\frac{df_i}{dt} = f_{i-1} \cdot \frac{k_m}{\tau_m} - f_i \cdot \frac{k_m}{\tau_m} + \Gamma_f \cdot f_i \cdot \mathcal{C} \ \ , \ i = 2, 3...$$

$$\frac{df^*}{dt} = f_n \cdot \frac{k_m}{\tau_m} + \Gamma_f \cdot f^* \cdot \mathcal{C} - \Gamma_{cure} \cdot f^* \cdot \mathcal{C}$$

$$\frac{dP_m}{dt} = \Omega_m \cdot f^* \cdot \mathcal{C} - \eta_m \cdot P_m \cdot v_{abs} - Loss_m \cdot P_m$$

$$\frac{dv}{dt} = \Gamma \cdot v \cdot \mathcal{C} - \eta_m \cdot P_m \cdot v_{avai}$$

$$\frac{dv_1}{dt} = \eta_m \cdot P_m \cdot v_{avai} - v_1 \frac{k_\lambda}{\tau_\lambda}$$

$$\frac{dv_i}{dt} = v_{i-1} \cdot \frac{k_\lambda}{\tau_\lambda} - v_i \cdot \frac{k_\lambda}{\tau_\lambda} \quad for \ \ i = 2, 3, .., n_\lambda$$

$$\frac{dP_\lambda}{dt} = \beta \cdot \mathcal{C} \cdot v_{n_\lambda} \frac{k_\lambda}{\tau_\lambda} - \eta_\lambda \cdot P_\lambda \cdot f_{abs} - Loss \cdot P_\lambda$$

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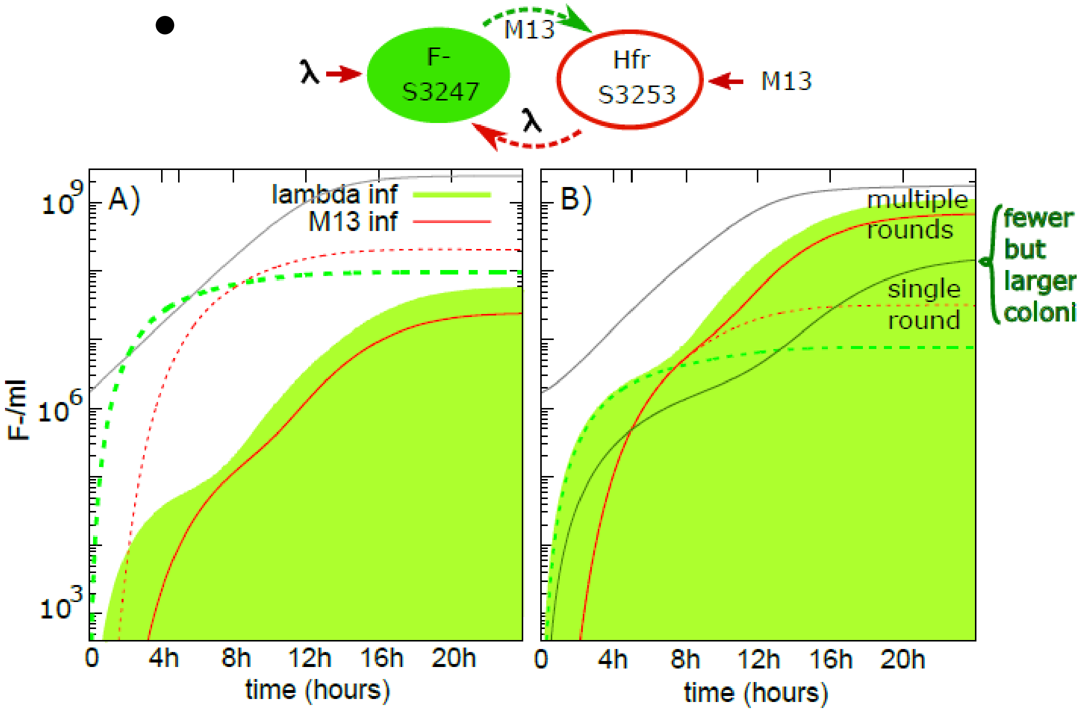
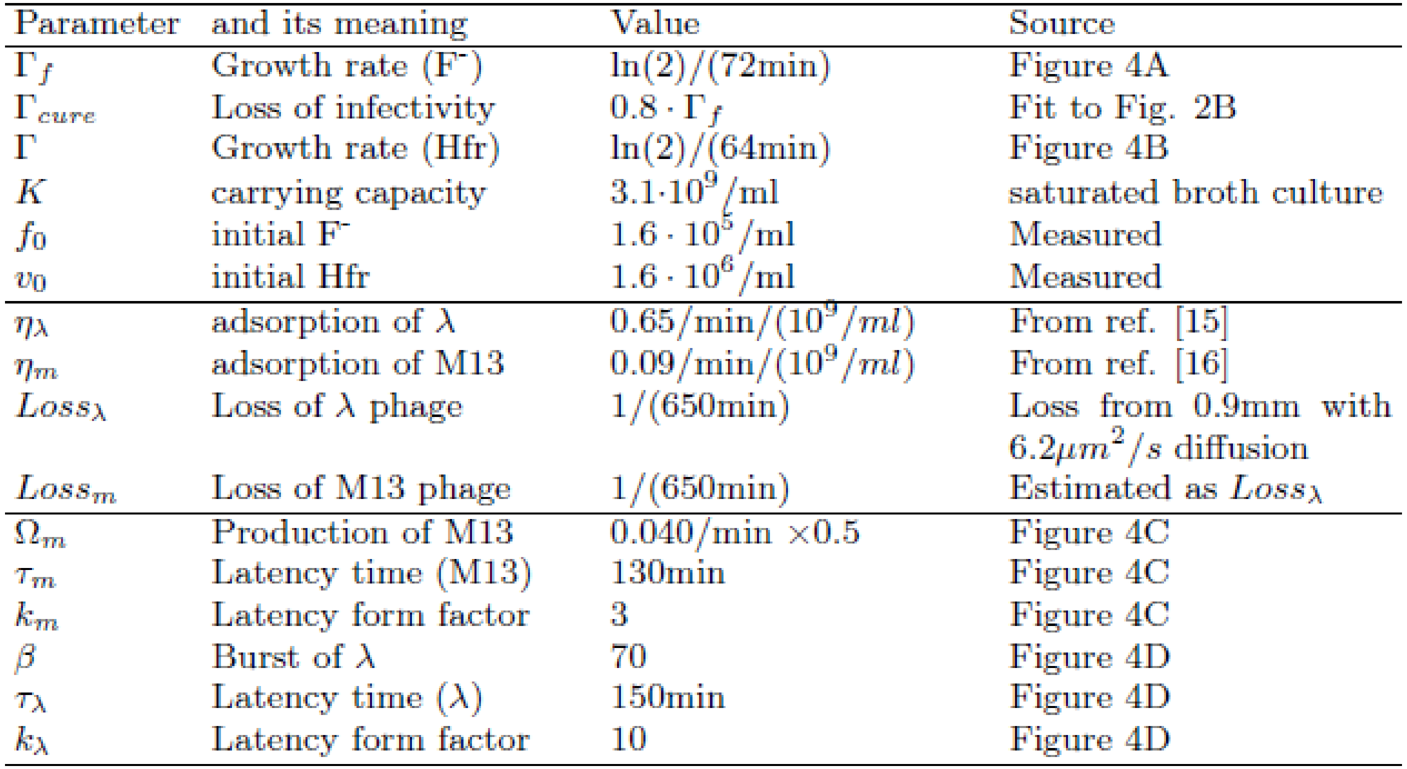
Parameter	and its meaning	Value	Source
Γ_f	Growth rate (F$^-$)	ln(2)/(72min)	Figure 4A
Γ_{cure}	Loss of infectivity	$0.8 \cdot \Gamma_f$	Fit to Fig. 2B
Γ	Growth rate (Hfr)	ln(2)/(64min)	Figure 4B
K	carrying capacity	$3.1 \cdot 10^9$/ml	saturated broth culture
f_0	initial F$^-$	$1.6 \cdot 10^5$/ml	Measured
v_0	initial Hfr	$1.6 \cdot 10^6$/ml	Measured
η_λ	adsorption of λ	$0.65/\text{min}/(10^9/ml)$	From ref. [15]
η_m	adsorption of M13	$0.09/\text{min}/(10^9/ml)$	From ref. [16]
$Loss_\lambda$	Loss of λ phage	1/(650min)	Loss from 0.9mm with $6.2\mu m^2/s$ diffusion
$Loss_m$	Loss of M13 phage	1/(650min)	Estimated as $Loss_\lambda$
Ω_m	Production of M13	0.040/min ×0.5	Figure 4C
τ_m	Latency time (M13)	130min	Figure 4C
k_m	Latency form factor	3	Figure 4C
β	Burst of λ	70	Figure 4D
τ_λ	Latency time (λ)	150min	Figure 4D
k_λ	Latency form factor	10	Figure 4D

Need to consider colony level heterogeneity to reproduce
Data with reasonable parameters (weakens phage to travel)

Model Simulations:

- 



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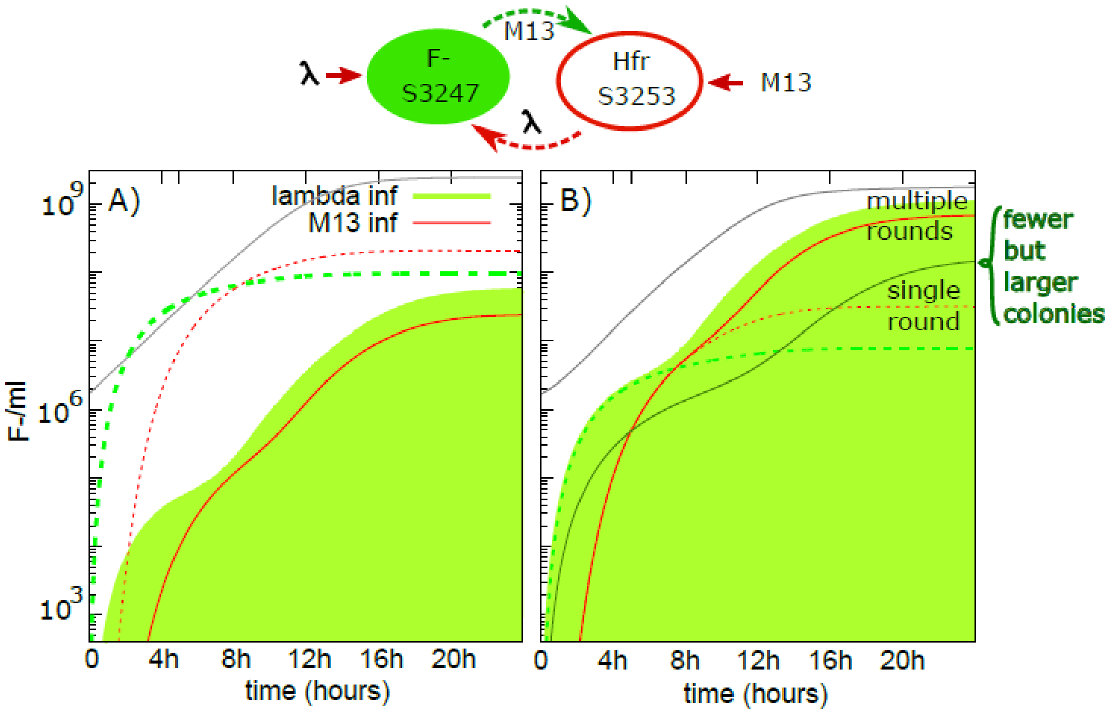
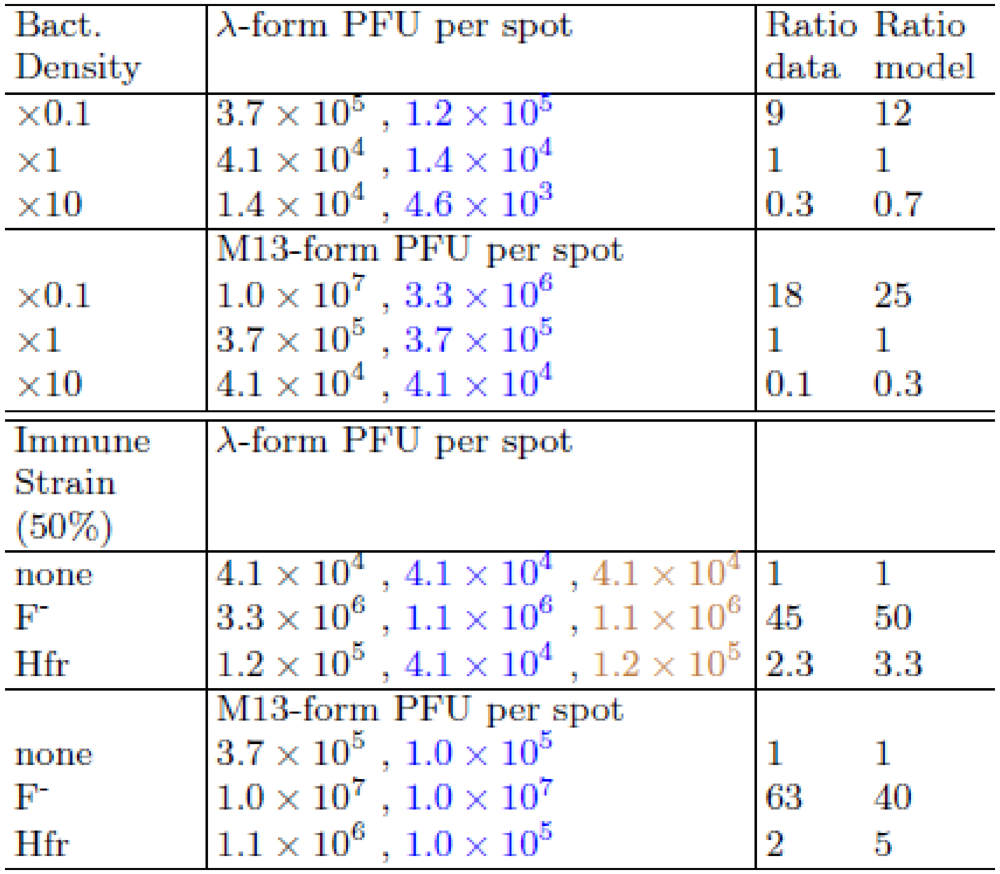
Reproducing data of (adjust Gamma_cure)
Single round experiment,
With 1000 fold larger MOI
(don’t fit dotted red line,
KS5 failure).

Model←→Experiment: Social Heterogeneity & Herd immunity….

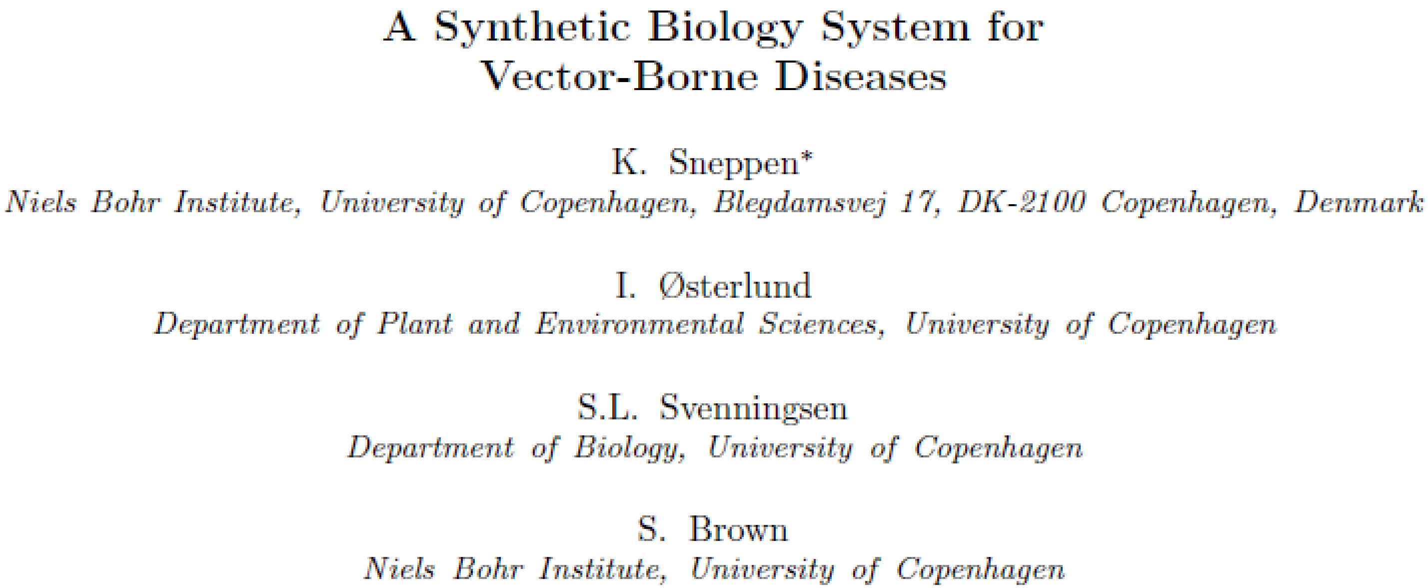




Bact. Density	λ-form PFU per spot	Ratio data	Ratio model
×0.1	3.7×10^5 , 1.2×10^5	9	12
×1	4.1×10^4 , 1.4×10^4	1	1
×10	1.4×10^4 , 4.6×10^3	0.3	0.7
	M13-form PFU per spot		
×0.1	1.0×10^7 , 3.3×10^6	18	25
×1	3.7×10^5 , 3.7×10^5	1	1
×10	4.1×10^4 , 4.1×10^4	0.1	0.3
Immune Strain (50%)	λ-form PFU per spot		
none	4.1×10^4 , 4.1×10^4 , 4.1×10^4	1	1
F^-	3.3×10^6 , 1.1×10^6 , 1.1×10^6	45	50
Hfr	1.2×10^5 , 4.1×10^4 , 1.2×10^5	2.3	3.3
	M13-form PFU per spot		
none	3.7×10^5 , 1.0×10^5	1	1
F^-	1.0×10^7 , 1.0×10^7	63	40
Hfr	1.1×10^6 , 1.0×10^5	2	5

Thanks to:

- Stanley Brown
- Sine Svenningsen
- Isabella Østerlund



A Synthetic Biology System for
Vector-Borne Diseases

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