The Spreading Dynamics of COVID-19 and its Mitigation

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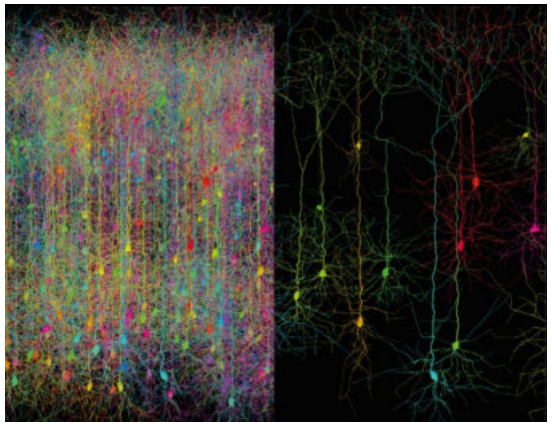
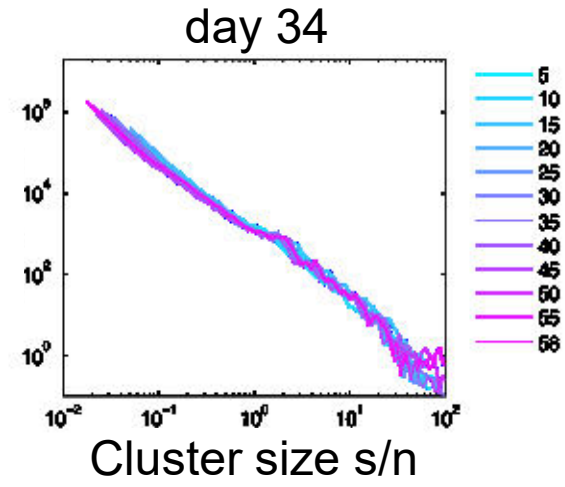
Overview

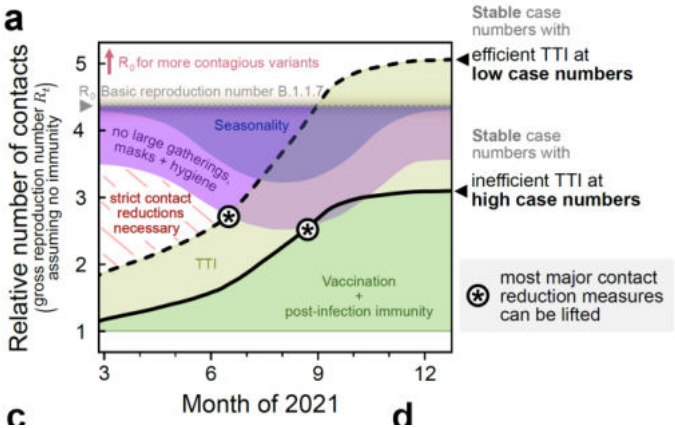
- **Large Scale Recordings & Subsampling:**
  How to infer collective properties and spreading dynamics from vastly under-observed systems

- **Subsampling Scaling:** Inferring avalanche distributions or degree distributions from subsampled networks

- **Mitigating the Spread of COVID-19:**
  - The effect of test-trace-isolate (TTI)
  - and of the vaccination progress

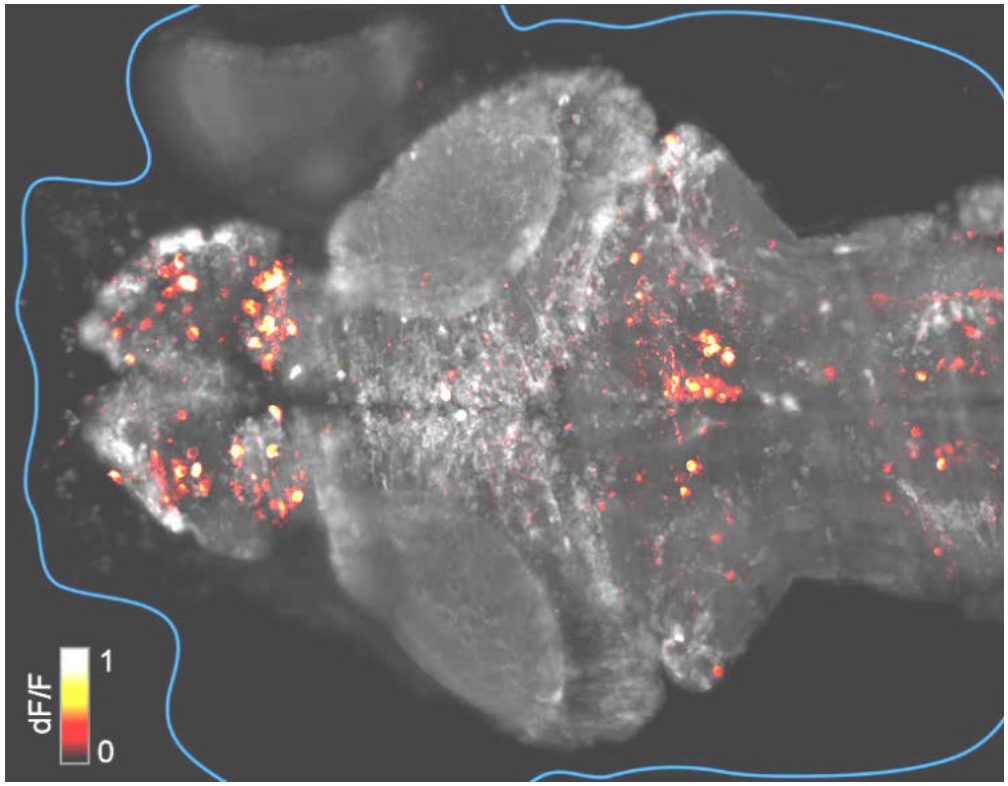






Collective Dynamics

Light sheet fluorescence imaging in a zebra fish larva



100.000 neurons (80bn in human)
10 – 10.000 connections/neuron

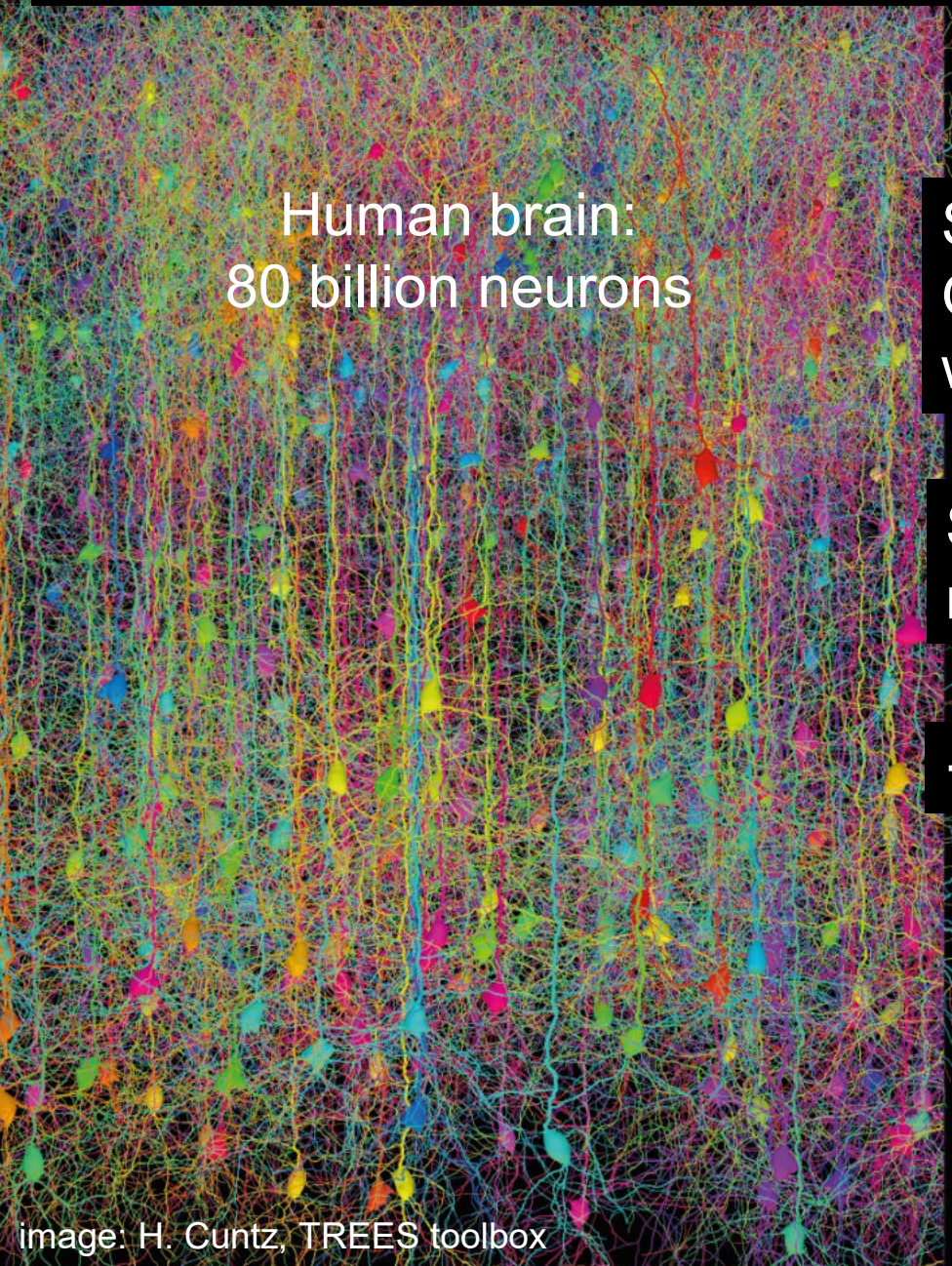
Interactions:

- pulse-like (“spikes“)
- directed
- time-delayed
- plastic (learning!)

High-dimensional topology
→ difficult to characterize collective properties

[Ahrens, Orger, Robson, Li, Keller; *Nat. Meth.,* 2013]

Subsampling Can Bias Inference



Sampling (experiment):
Only 100-1000 neurons
with sufficient precision

Subsampling bias leads to
misestimations

→ Bias-free inference

Neto, Spitzner & VP, arxiv
Wilting & VP, Cerebral Cortex, 2019
Wilting & VP, Nature Communications, 2018
Levina & VP, Nature Communications, 2017

image: H. Cuntz, TREES toolbox

Inferring the Spreading of Activity

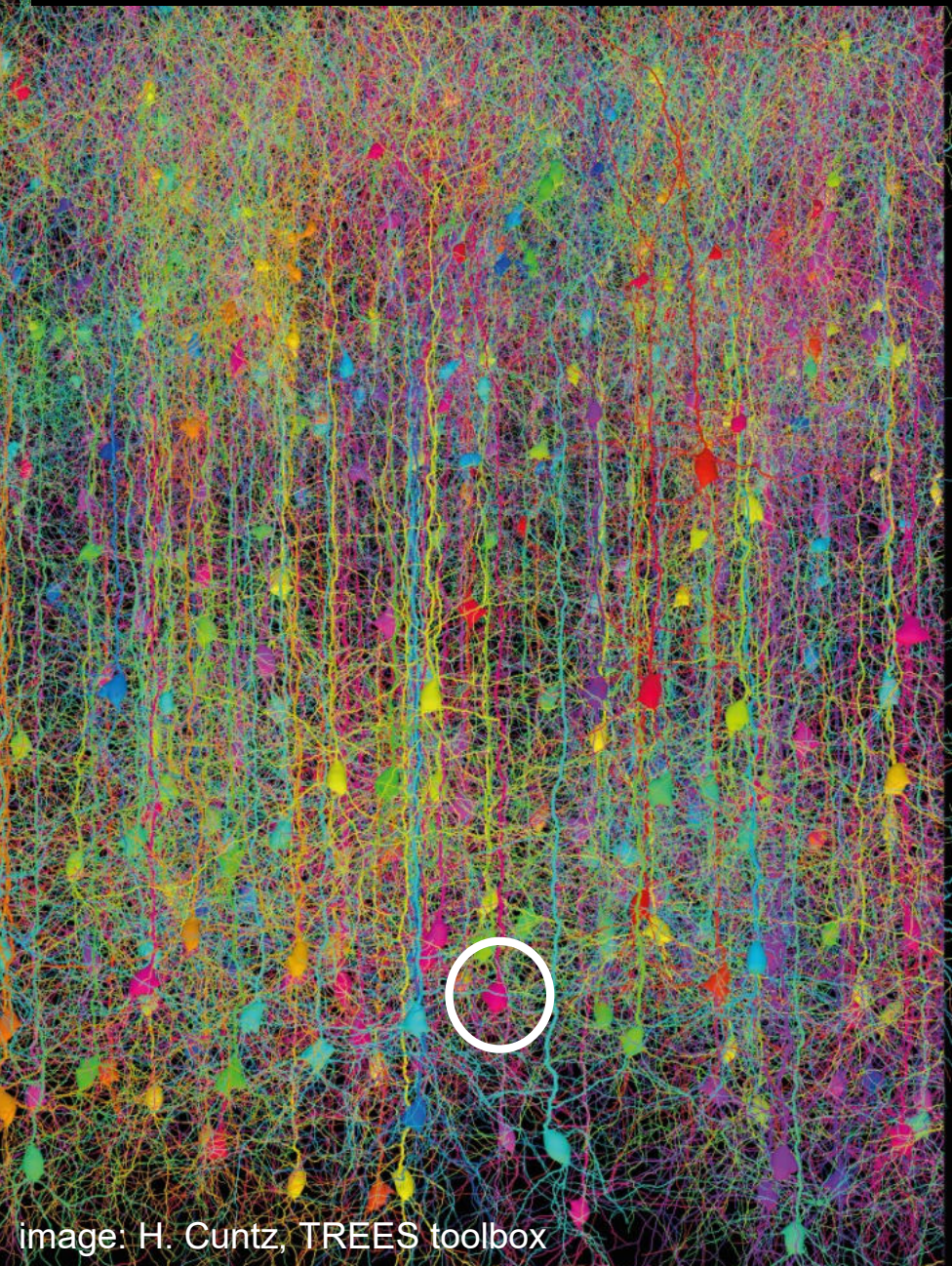


image: H. Cuntz, TREES toolbox

- What is the effect of a single spike?
- How well does activity propagate?
- How do neurons interact with others?

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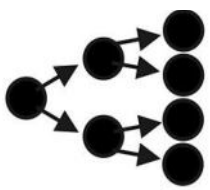
Propagating Activity as a Branching Process

control parameter *R*
expected number of "children"

$R < 1$ subcritical

$R = R_c = 1$ critical



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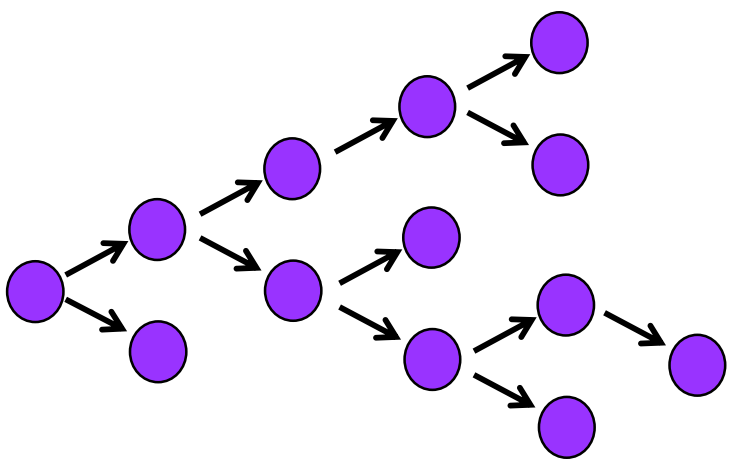

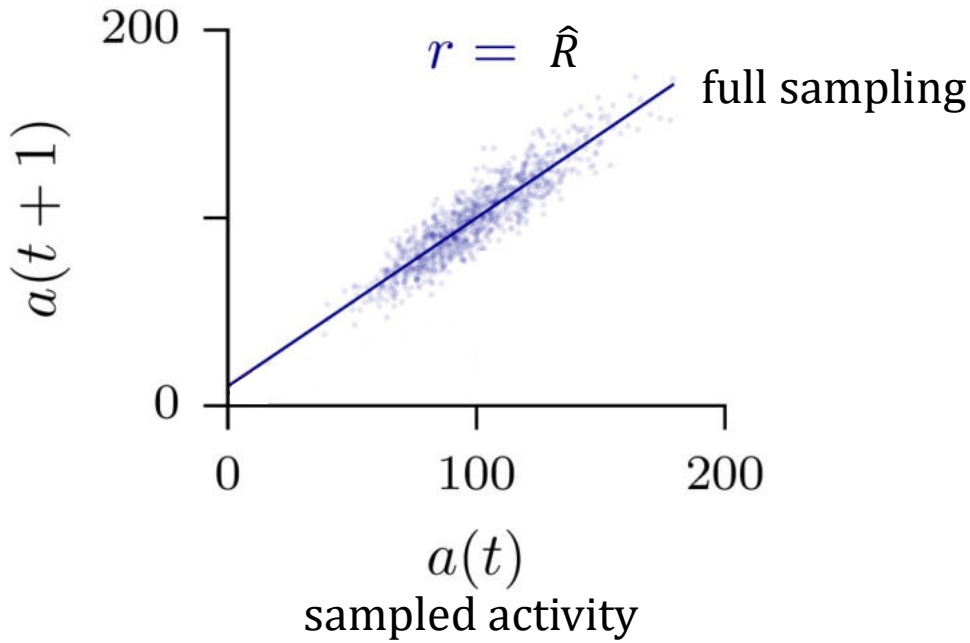

Branching process

activity $A(t)$ in system: $A(t) = \sum_{i=1}^{A(t-1)} Y_{i,t} + h_t$

h_t	external input (random variable)
Y	# activated units per active unit (r.v.)
$R = E[Y]$	mean # "children" per unit or eff. coupling strength

[Wilting & VP, Nature Communications, 2018]
[Levina & VP, Nature Communications, 2017]

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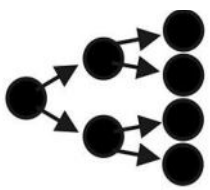

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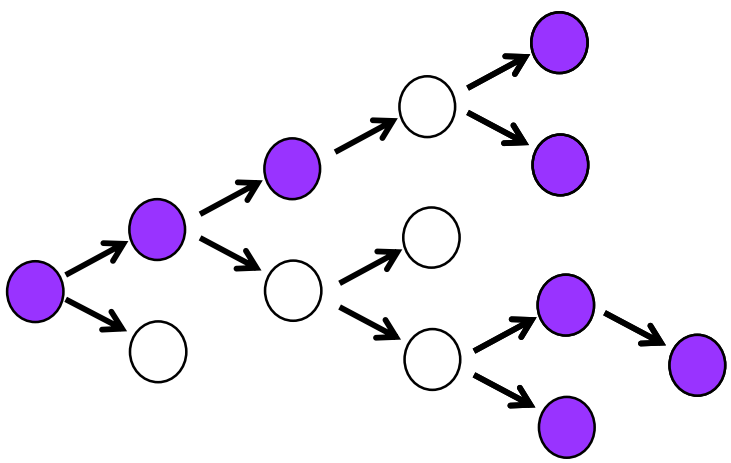

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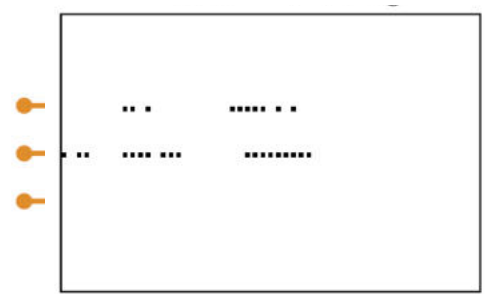
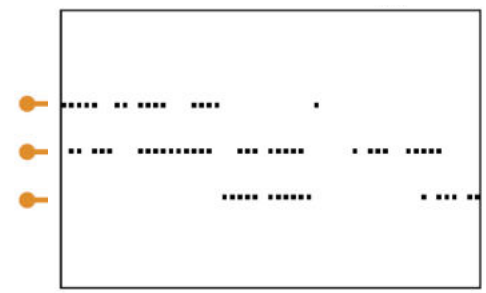
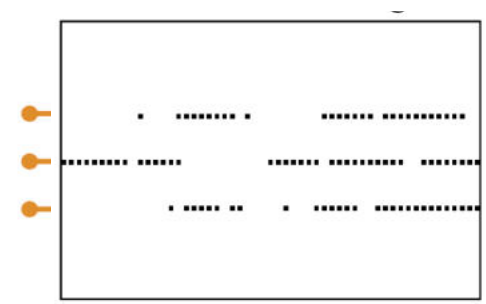


$R = 1$



$R > 1$



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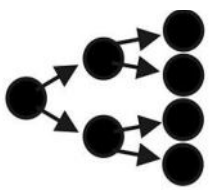

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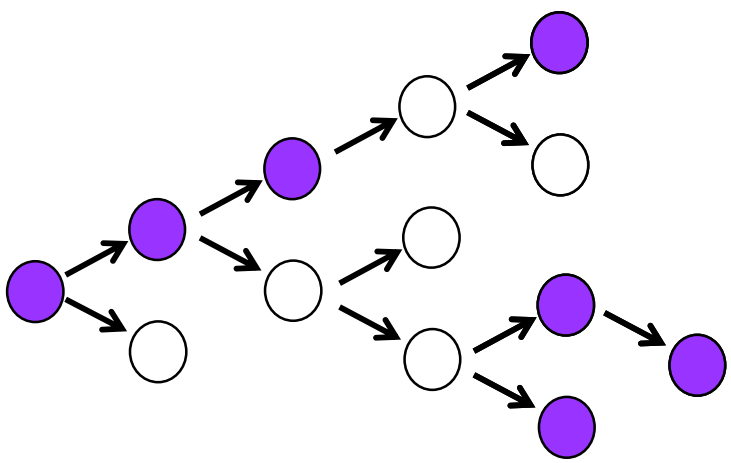

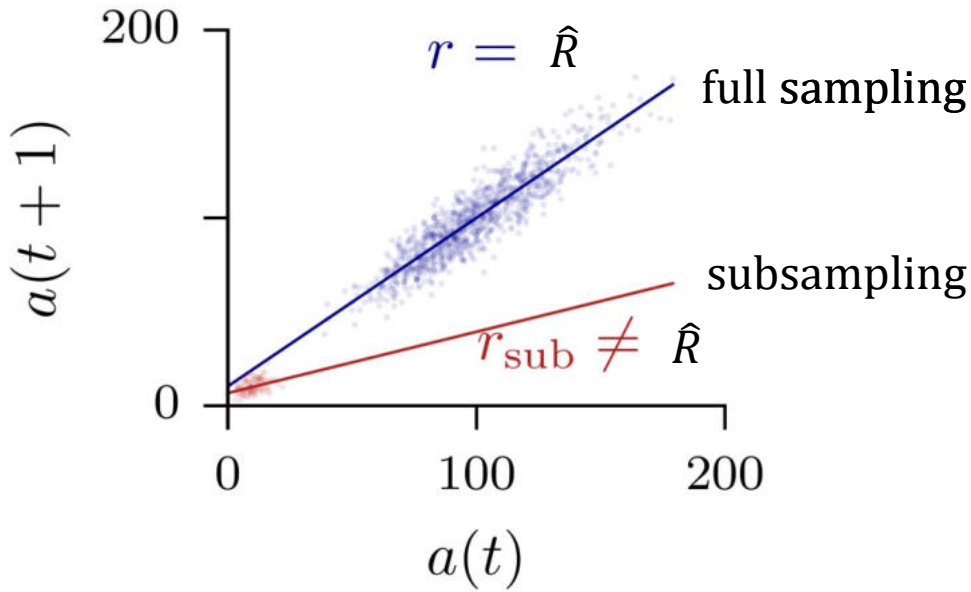

sampled activity

→ Correlation strength r
is biased under subsampling!

Ansatz:

- Generalizing estimator to any Δt:
  $r(a(t), a(t + \Delta t))$.
  Thereby we can partial out the bias

[Wilting & VP, Nature Communications, 2018]
[Levina & VP, Nature Communications, 2017]

Inferring Spreading Dynamics

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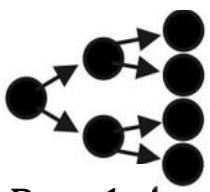

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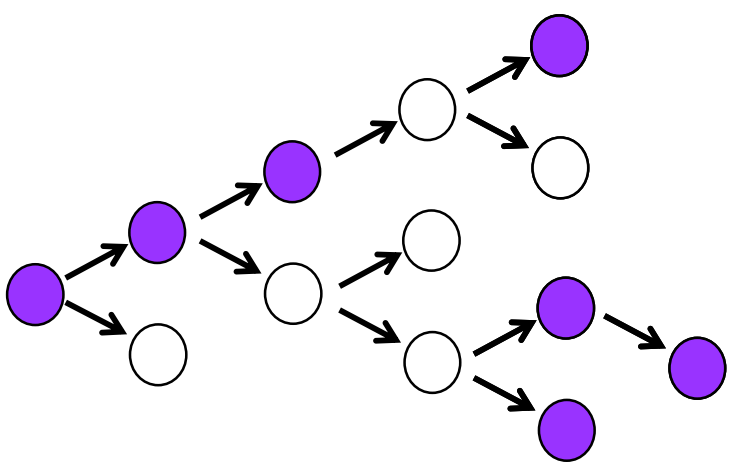


- returns the control parameter *R*, instead of a binary test for or against criticality

Efficient, precise, easily applicable:

- It only requires knowing a(t), i.e. the *sampled* activity at each time step
- It does not require knowing the system size N, the number of sampled units n, or any of the moments of the process.
- Ideal conditions: Estimation of control parameter from a single unit!

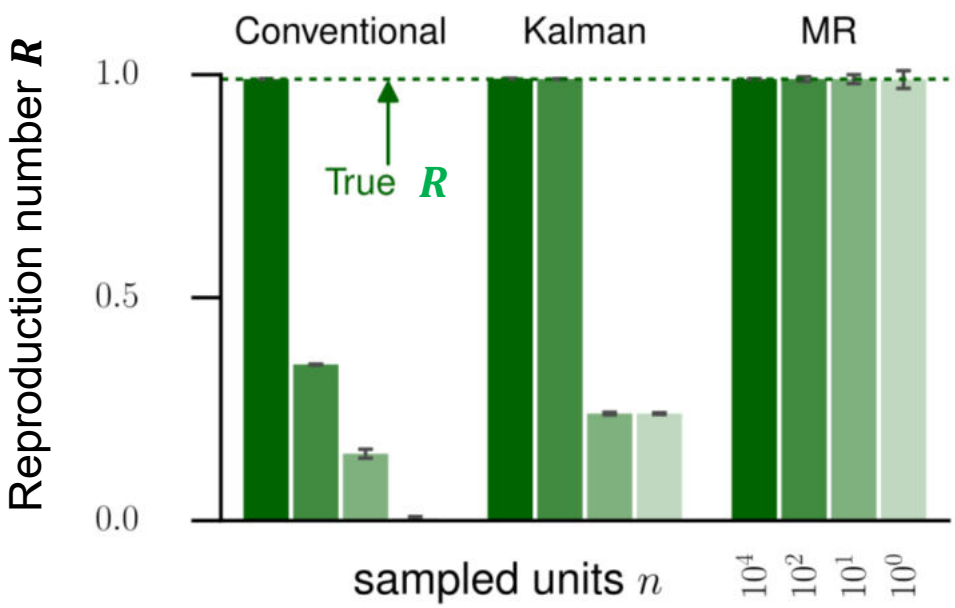
Adopted by: J.Beggs, K.Hengen, C.Butfering; e.g. Ma et al., Neuron, 2019

Python Toolbox: github.com/Priesemann-Group

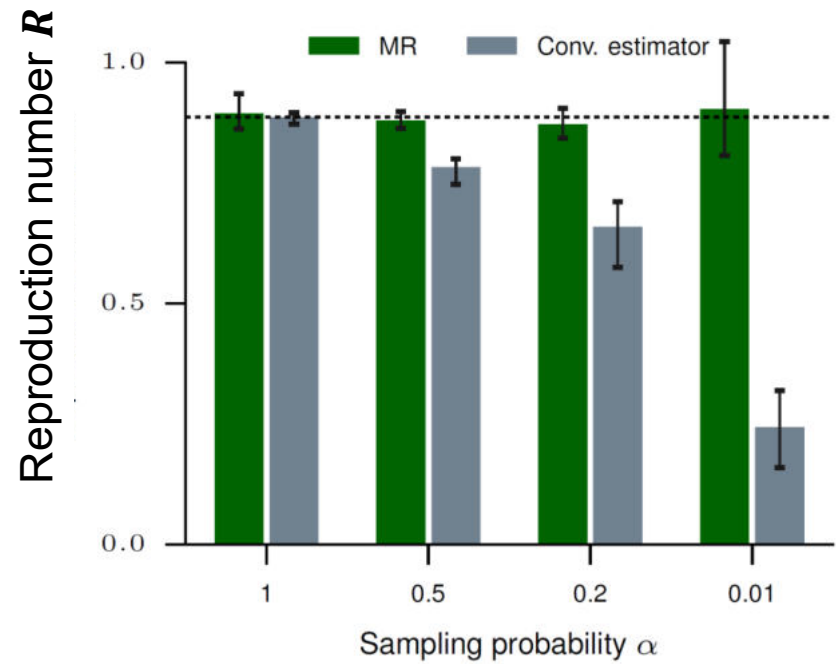
[Dehning et int. VP, Science, 2020]
[Wilting & VP, Nature Communications, 2018]
[Levina & VP, Nature Communications, 2017]

Overcoming the Subsampling Problem – to Assess Disease Spreading

Estimation of the reproduction number $\boldsymbol{R}$ in a model of 10.000 neurons



Estimation of the reproduction number $\boldsymbol{R}$ from measles case numbers



COVID-19:
[Contreras et int., VP, Nature Communications, 2021]
[Priesemann et a;., The Lancet, 2021a,b]
[Linden et int., VP, Dtsch. Arzteblt Int. 2020]
[Bauer et int., VP, arxiv; Contreras et int. VP, arxiv]

[Wilting & VP, Nature Communications, 2018]

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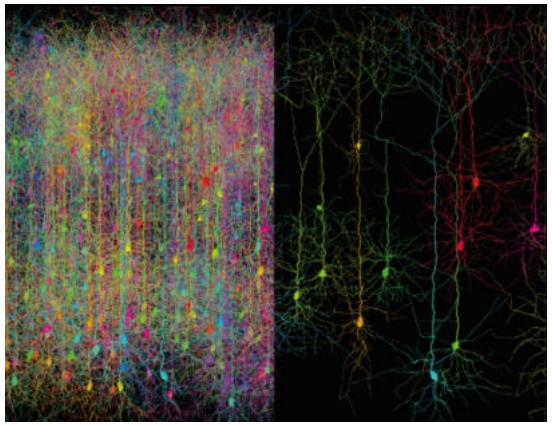
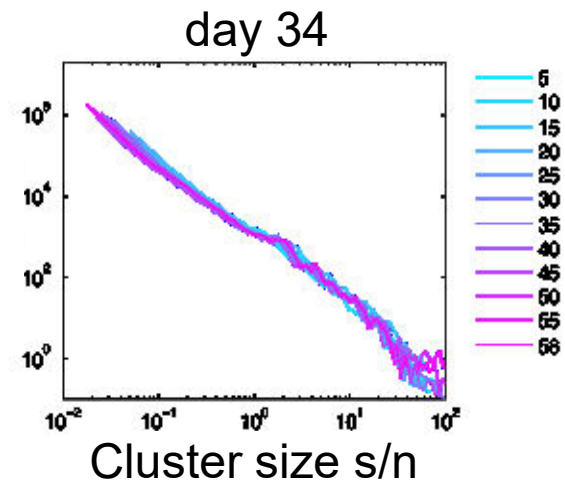
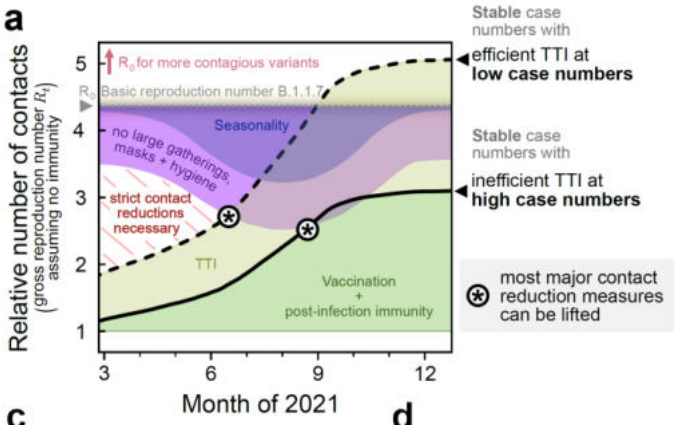
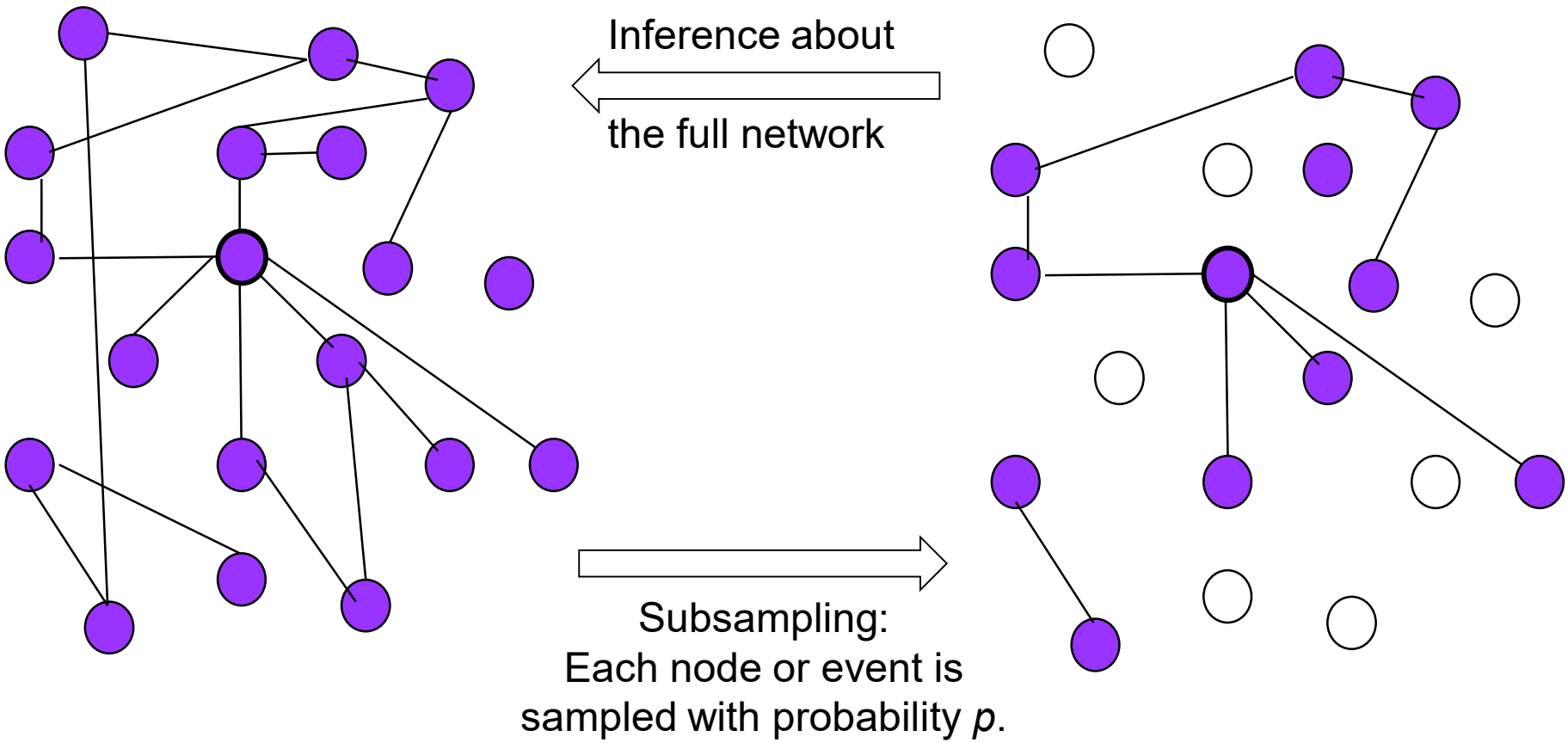






Subsampling Scaling Theory

Levina & Priesemann, Nature Comm, 2017



→ Subsampling Scaling: A theory about inference of collective properties from partly observed systems

Relation between P(s) under full and under subsampling

$$P_{\text{sub}}(s) = \sum_{k=s}^{\infty} P(k) \underbrace{\binom{k}{s} p^s (1-p)^{k-s}}_{\text{binomial sampling}}$$

$$\begin{aligned} G_{\text{sub}}(z;p) &= \sum_{s=0}^{\infty} z^s P_{\text{sub}}(s) \\ &= \sum_{s=0}^{\infty} z^s \sum_{k=s}^{\infty} P(k) \binom{k}{s} p^s (1-p)^{k-s} \\ &= \sum_{k=0}^{\infty} P(k)(zp + (1-p))^k \end{aligned}$$

probability generating function (PGF)

$$G(z) = \sum_{s=0}^{\infty} z^s P(s)$$

$$P(s=n) = \frac{G^{(n)}(z=0)}{n!}$$

$$G_{sub}(z;p) = G(\tilde{z};p) \qquad \text{with } \tilde{z} = zp + (1-p)$$

Scaling for Distributions with Cutoff

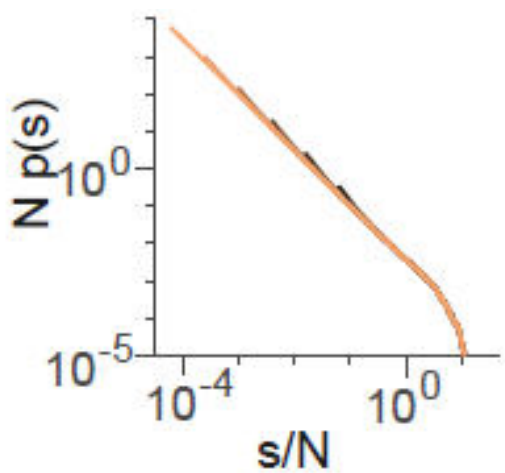
$$P(s) \sim s^{-\gamma}$$

$$P(s) \approx pP_{sub}(p \cdot s)$$

$$P(s) = C_\lambda e^{-\lambda s}$$

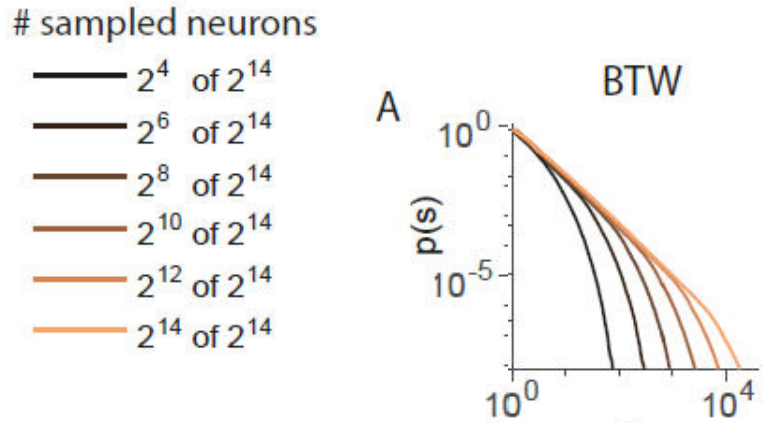
$$P(s) = \frac{e^{-\lambda_{\text{sub}}} + p - pe^{-\lambda_{\text{sub}}}}{p} P_{\text{sub}}\left(\frac{\ln\left(e^{\lambda_{\text{sub}}}p - p + 1\right)}{\lambda_{\text{sub}}} s\right)$$

$$P(s) \sim s^{-\gamma} e^{-\lambda s} \qquad \text{with } \lambda = 1/s_{max}$$



[Levina & Priesemann, Nature Comm. 2017]

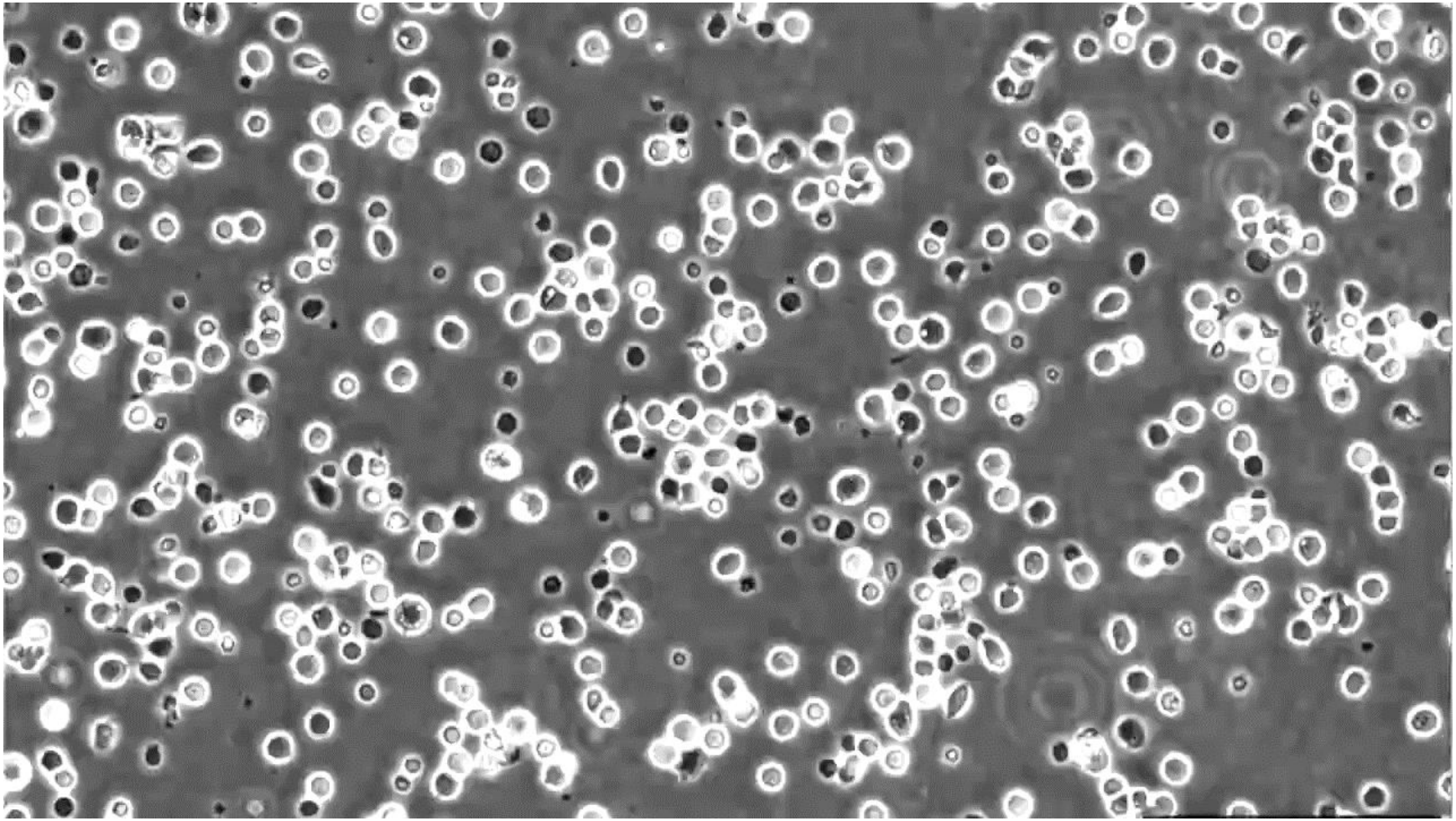
Subsampling in Models



Scale-free models from different universality classes

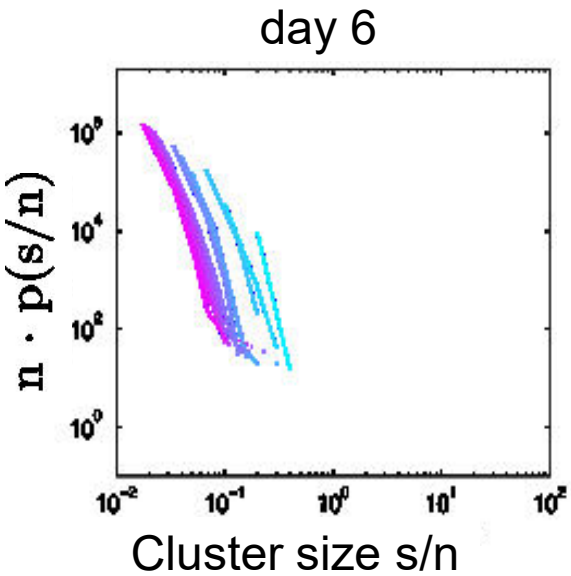
[Levina & Priesemann, Nature Comm. 2017]

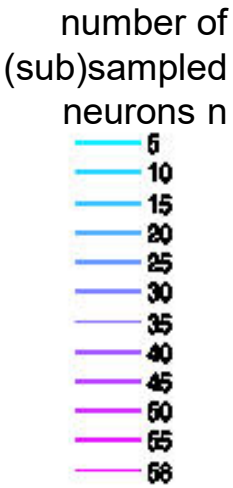
Developing Neural Network *in vitro*



see e.g. [Levina & VP, Nature Communications, 2017]

Developing Cortical Cultures
- Applying further subsampling to the recordings





[Levina & Priesemann, Nature Comm. 2017]

Summary

Subsampling Scaling

- reveals the “parent distribution”
- complementary to finite size scaling
- test for scale-free properties

[Levina & Priesemann, Nature Comm. 2017]

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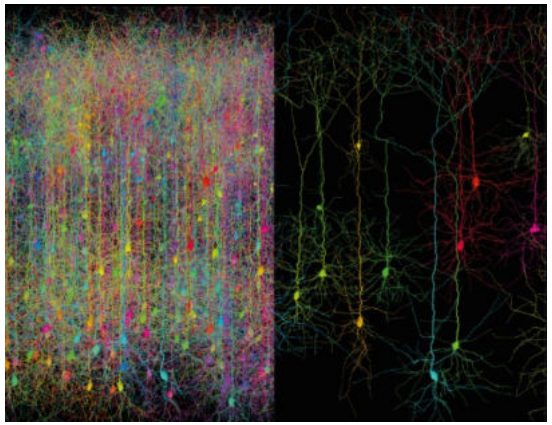
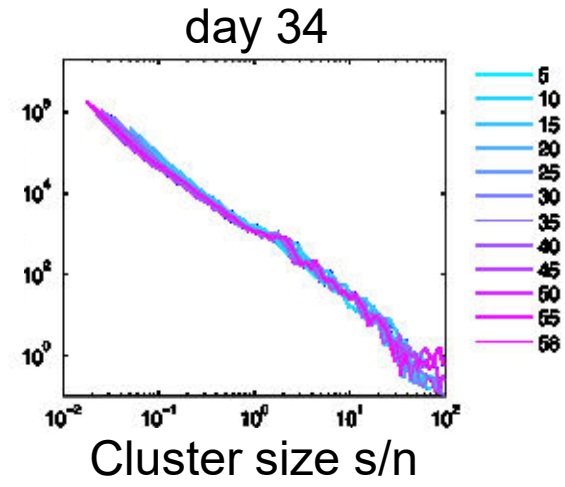
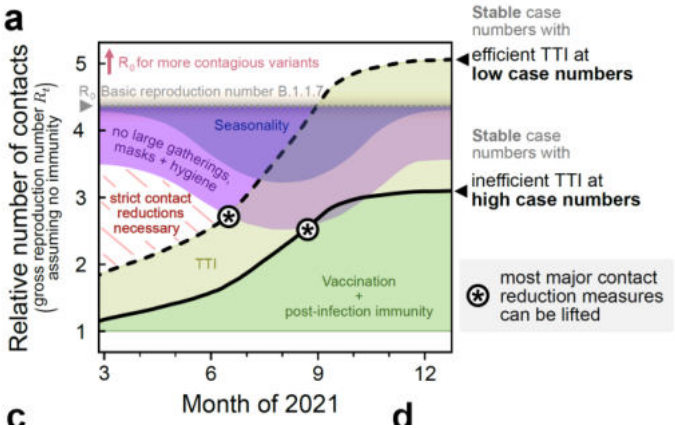
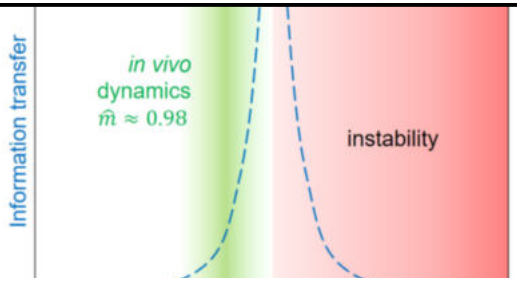






Physics of Neural Systems

Spreading Dynamics and Phase Transitions



VP et al., Plos Comp Biol., 2013
Wilting & VP, Cerebr. Ctx, 2019
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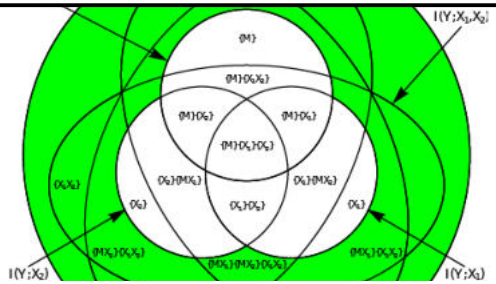
Neto, Spitzner & VP, arxiv; Spitzner et al., arxiv

Information Theory to Quantify & Design Computation



Wibral, Lizier & VP, Matter to Life, 2017
Wollstadt et al., Plos CB, 2017
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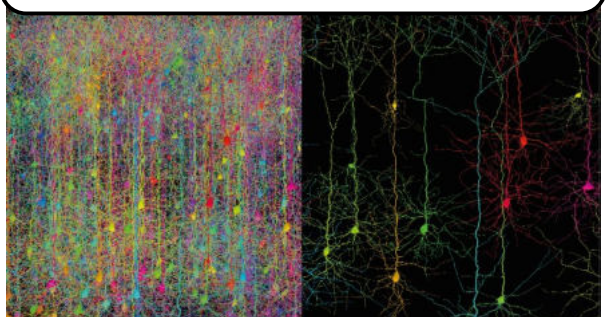
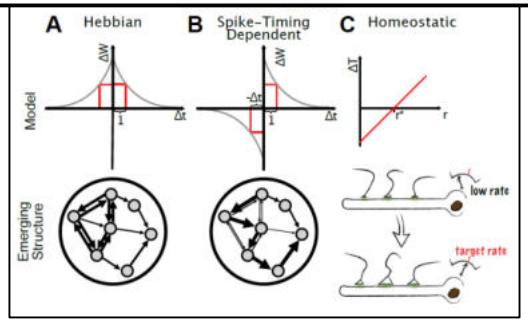
Rudelt, … VP, biorxiv, 2020

Subsampling Theory



VP et al., 2009, 2013, 2014
Levina & VP, Nat. Commun., 2017
Wilting & VP, Nat. Commun., 2018
de Heuvel et al., PRE & PRR, 2020

Local Learning Rules to Optimize Computation



Zierenberg, … VP, Phys Rev X, 2018
del Papa, VP & Triesch, 2017, 2019
Cramer, … VP, Nat Commun., 2020
Mikulasch, Rudelt & VP, arxiv; Loidolt et al., arxiv

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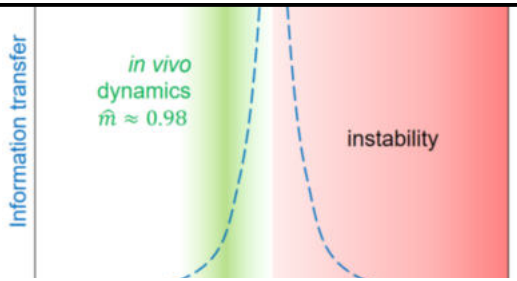

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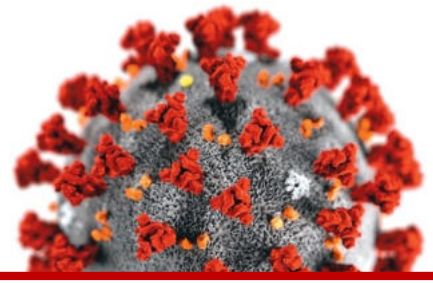

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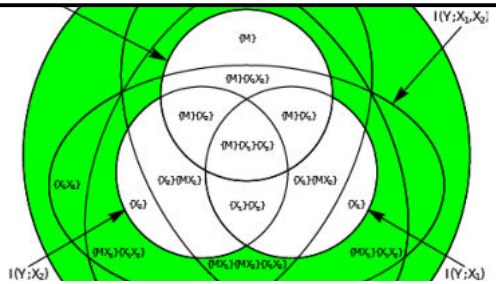

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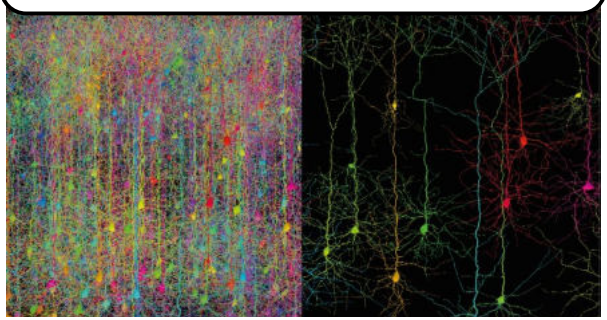
Subsampling Theory



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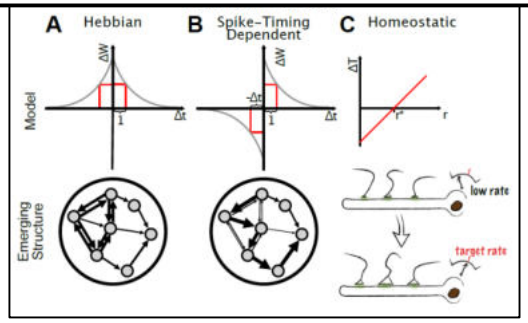

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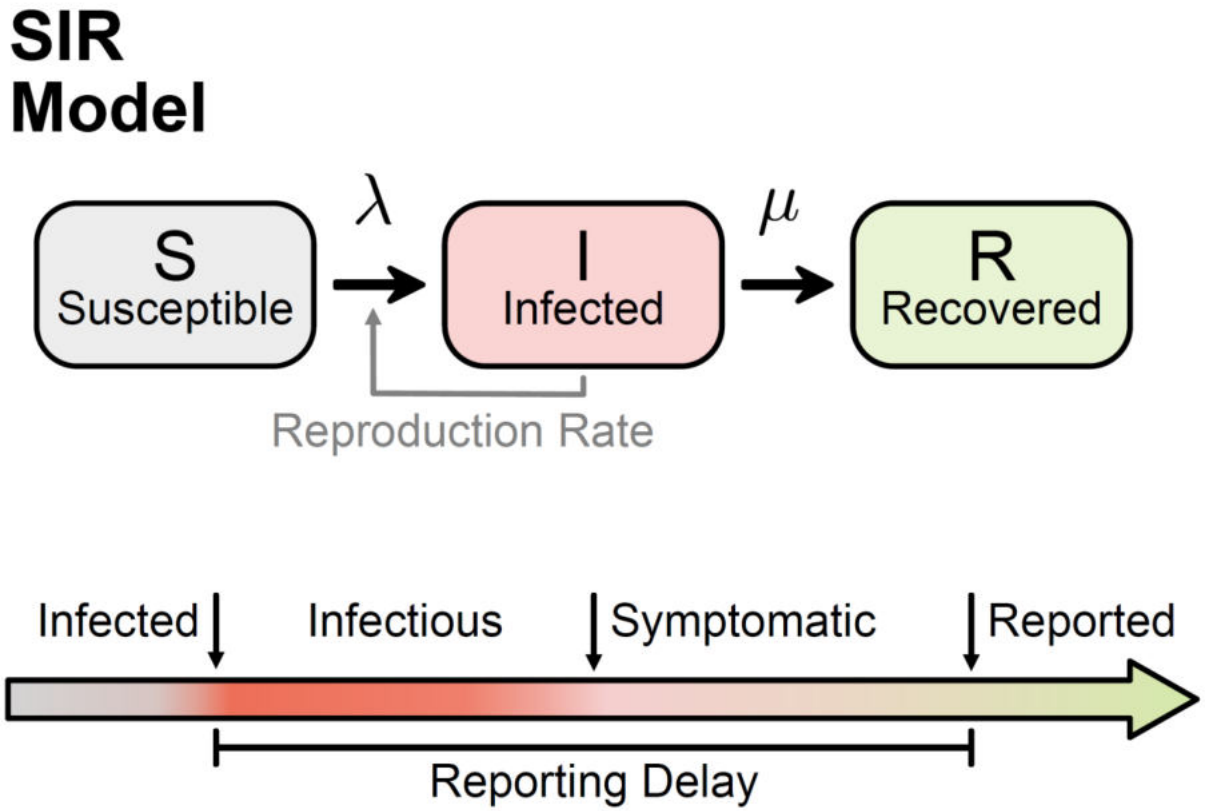
Mikulasch, Rudelt & VP, arxiv; Loidolt et al., arxiv

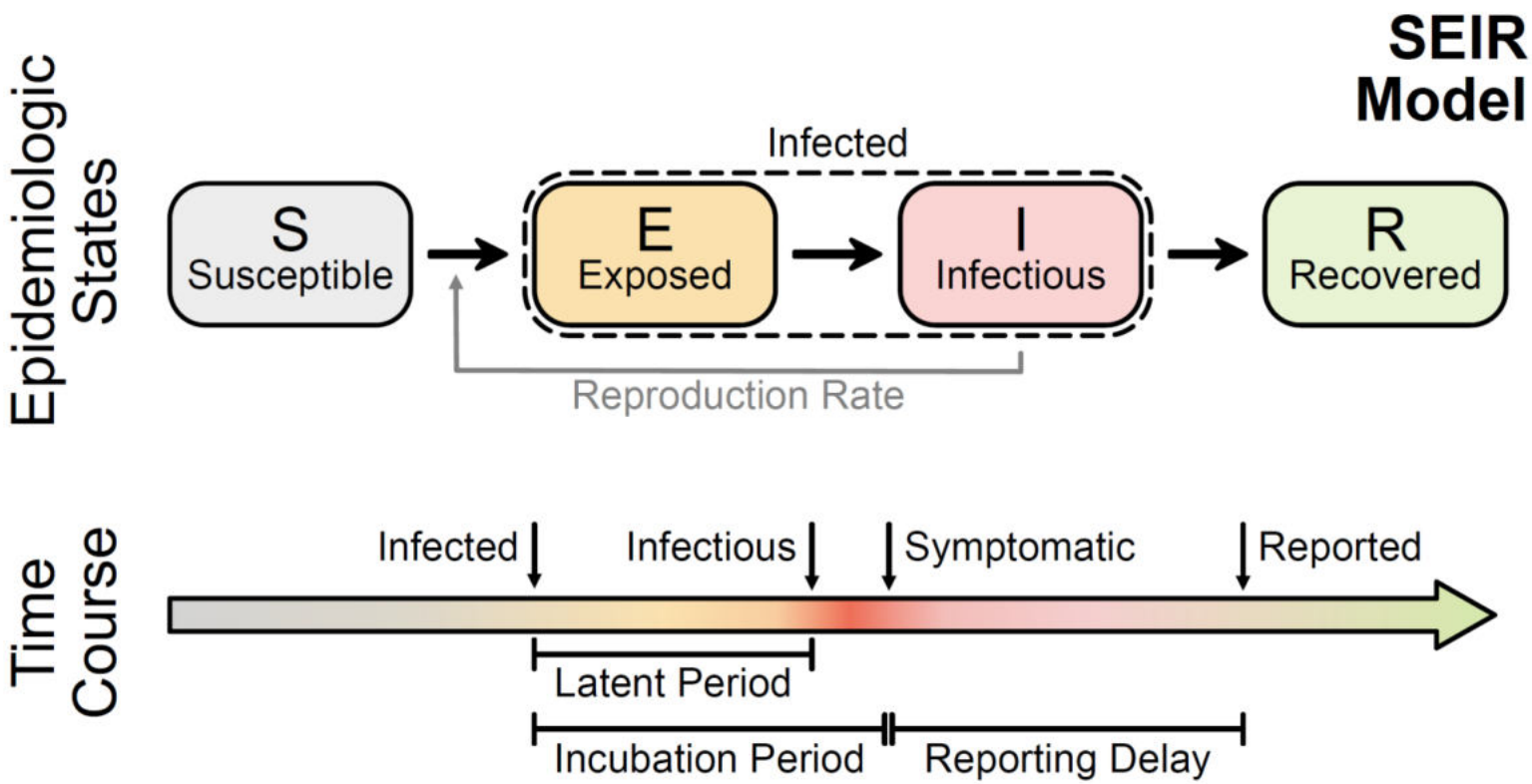
SIR: Susceptible-Infected-Recovered



$$\frac{dS}{dt} = -\lambda \frac{SI}{N}$$
$$\frac{dI}{dt} = \lambda \frac{SI}{N} - \mu I$$
$$\frac{dR}{dt} = \mu I$$

[Dehning et int., Priesemann, medRxiv]
https://www.medrxiv.org/content/medrxiv/early/2020/09/18/2020.09.16.20187484.full.pdf

SEIR: Susceptible-Exposed-Infected-Recovered



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  How to infer collective properties and spreading dynamics from vastly under-observed systems

- **Subsampling Scaling:** Inferring avalanche distributions or degree distributions from subsampled networks

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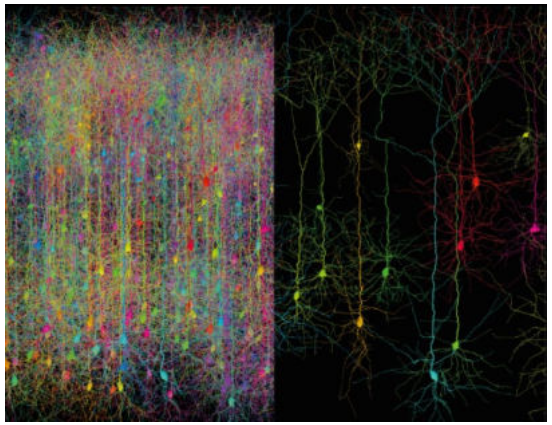
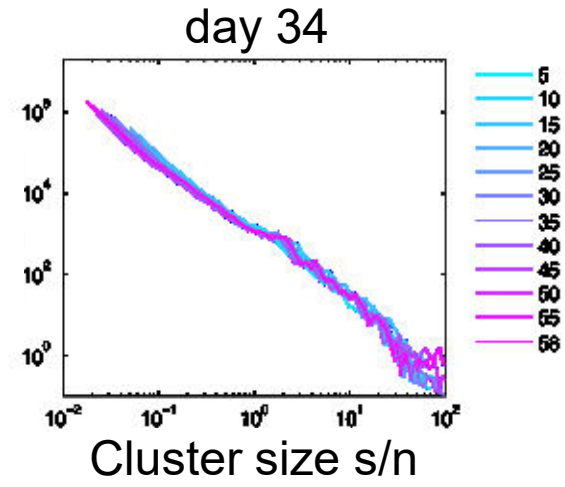
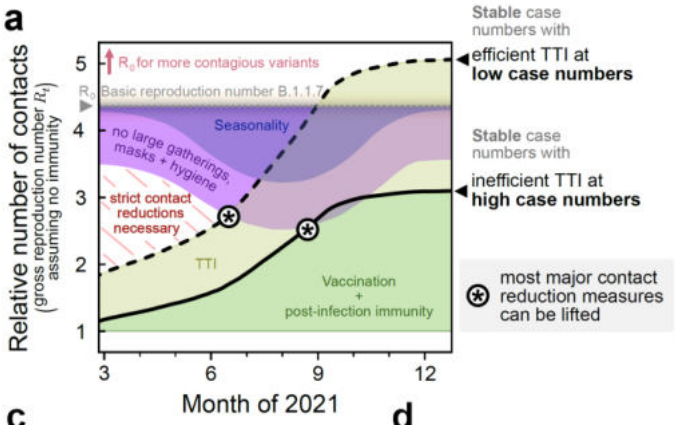
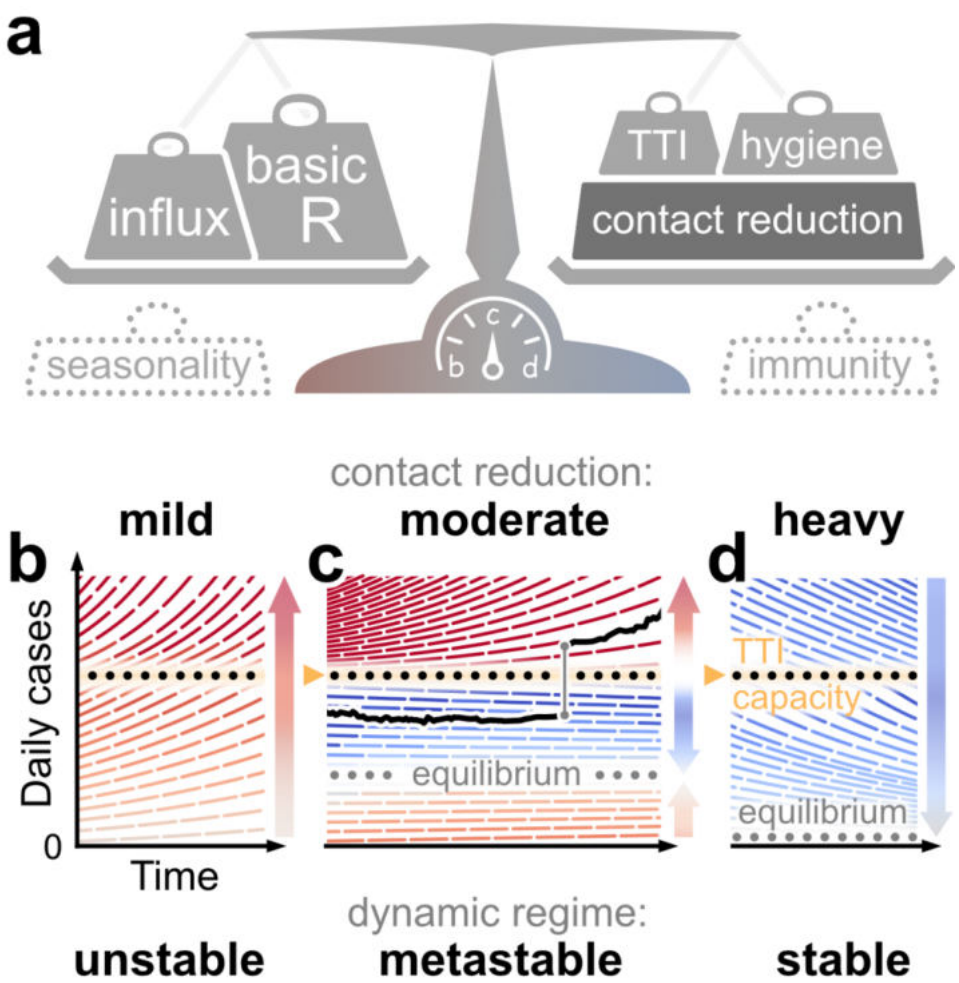
  - The effect of test-trace-isolate (TTI)
  - and of the vaccination progress







Combined measures to contain COVID-19



[Contreras et int., Priesemann, arxiv / under review]

nature COMMUNICATIONS

ARTICLE

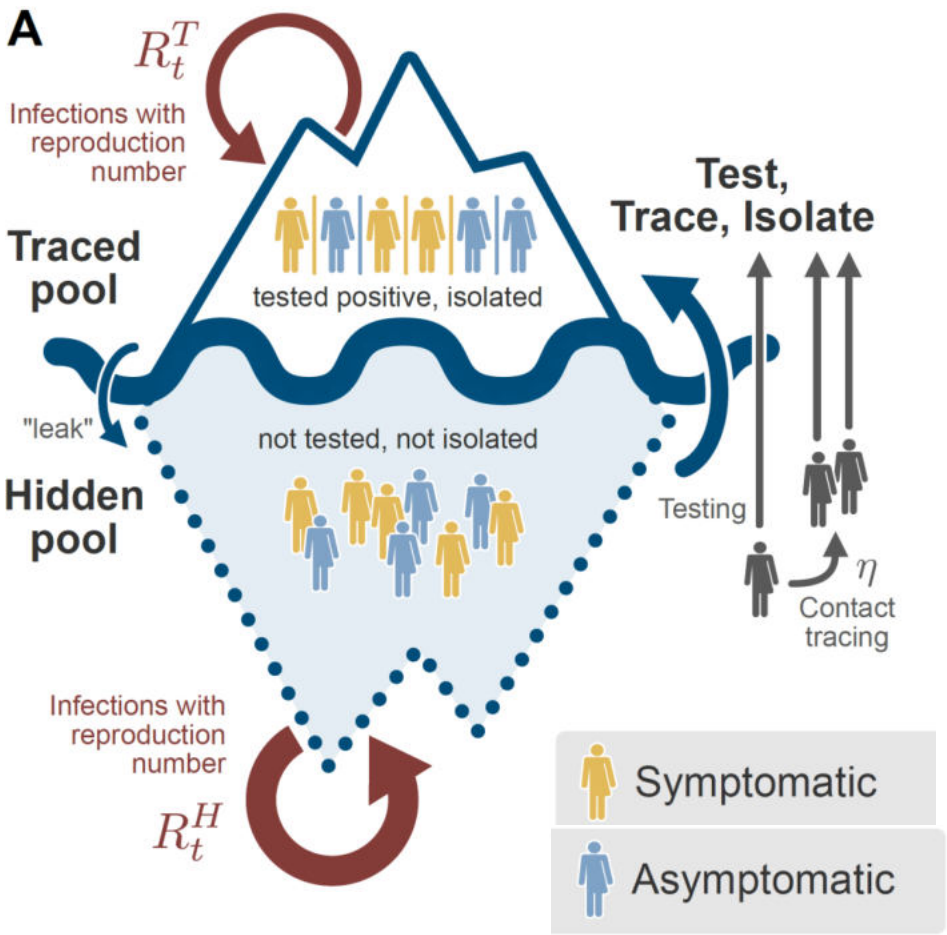
https://doi.org/10.1038/s41467-020-20699-8 OPEN

The challenges of containing SARS-CoV-2 via test-trace-and-isolate

Sebastian Contreras[1,2,5], Jonas Dehning[1,5], Matthias Loidolt[1,5], Johannes Zierenberg[1], F. Paul Spitzner[1], Jorge H. Urrea-Quintero[1], Sebastian B. Mohr[1], Michael Wilczek[1,3], Michael Wibral[4] & Viola Priesemann[1,3]✉

Without a cure, vaccine, or proven long-term immunity against SARS-CoV-2, test-trace-and-isolate (TTI) strategies present a promising tool to contain its spread. For any TTI strategy, however, mitigation is challenged by pre- and asymptomatic transmission, TTI-avoiders, and undetected spreaders, which strongly contribute to "hidden" infection chains. Here, we study a semi-analytical model and identify two tipping points between controlled and uncontrolled spread: (1) the behavior-driven reproduction number R_t^H of the hidden chains becomes too large to be compensated by the TTI capabilities, and (2) the number of new infections exceeds the tracing capacity. Both trigger a self-accelerating spread. We investigate how these tipping points depend on challenges like limited cooperation, missing contacts, and

Test-Trace-and-Isolate (TTI) contributes to containment



Test & isolated

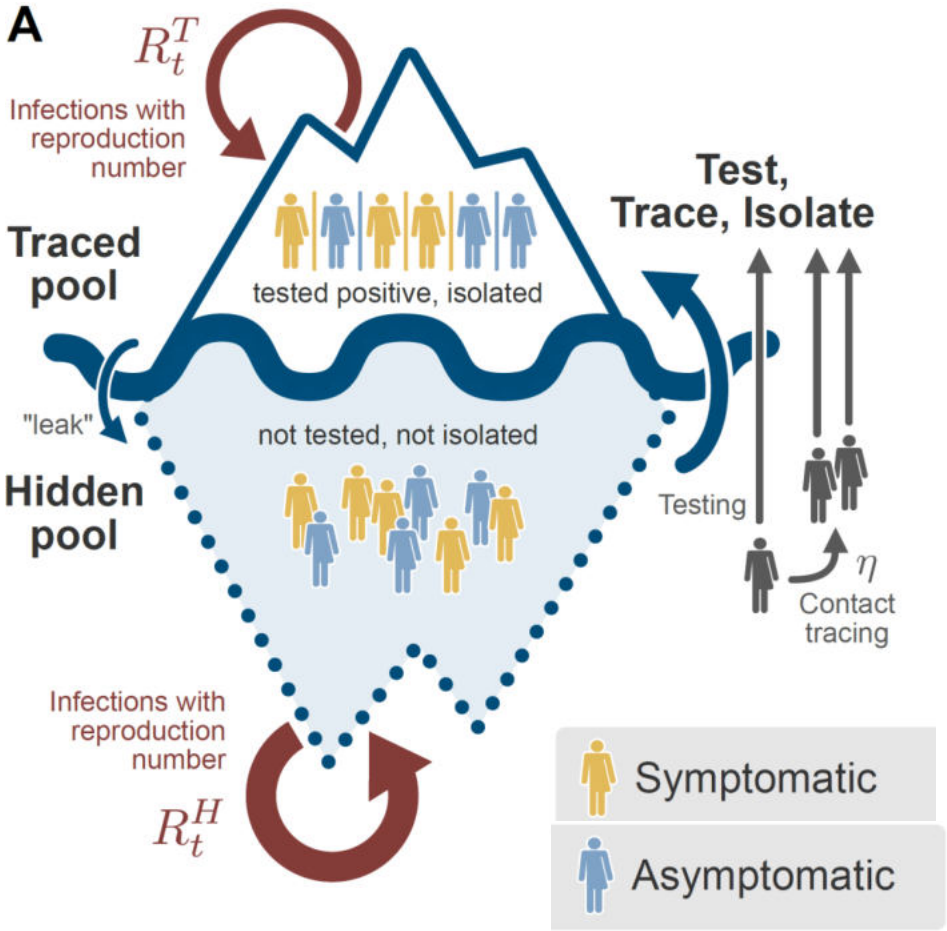
- Random (0)
- Symptoms (50 % of sympt., on average after 5 days)
- Test contact persons

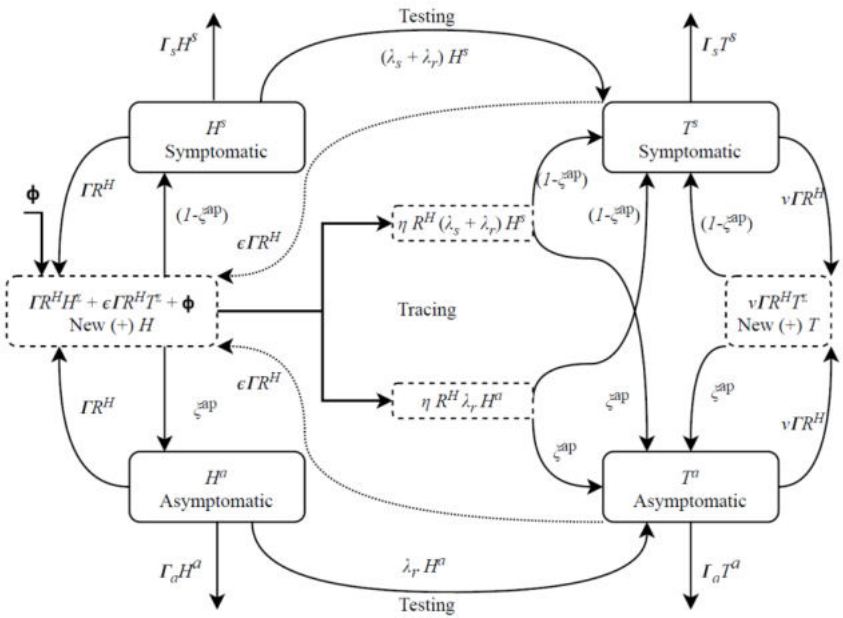
Contact tracing is difficult:

- Pre- und asymptomatic infection
- 1/3 of contacts are overlooked
- Quarantine is not perfect
- People who do not get tested (20%)
- Introduction of new infectious from abroad
- Limited capacities of health offices for testing and tracing

[Contreras et int., Priesemann, Nature Communications, in press]

Test-Trace-and-Isolate (TTI) contributes to containment

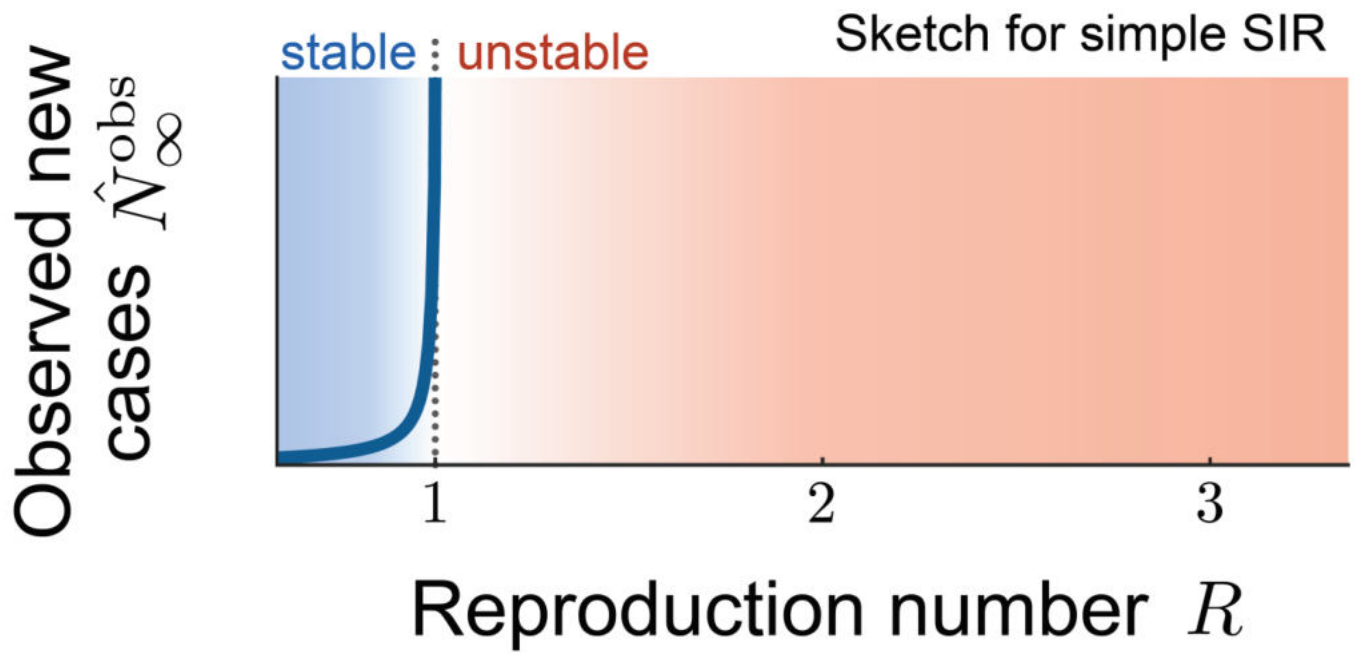


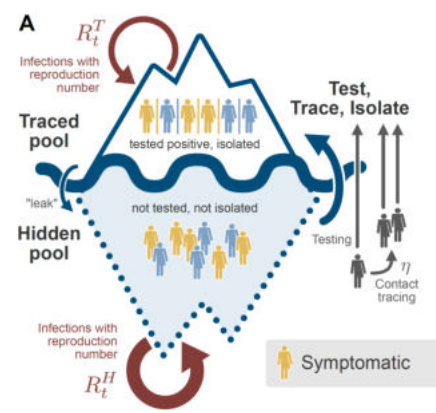


[Contreras et int., Priesemann, Nature Communications, in press]

The reproduction number *R* and the external influx of new cases Φ determine the level of new infections *N*

$$N \approx \frac{\Phi}{R_c - R} = \frac{\Phi}{1 - R}\,, \qquad \text{for } R < 1$$

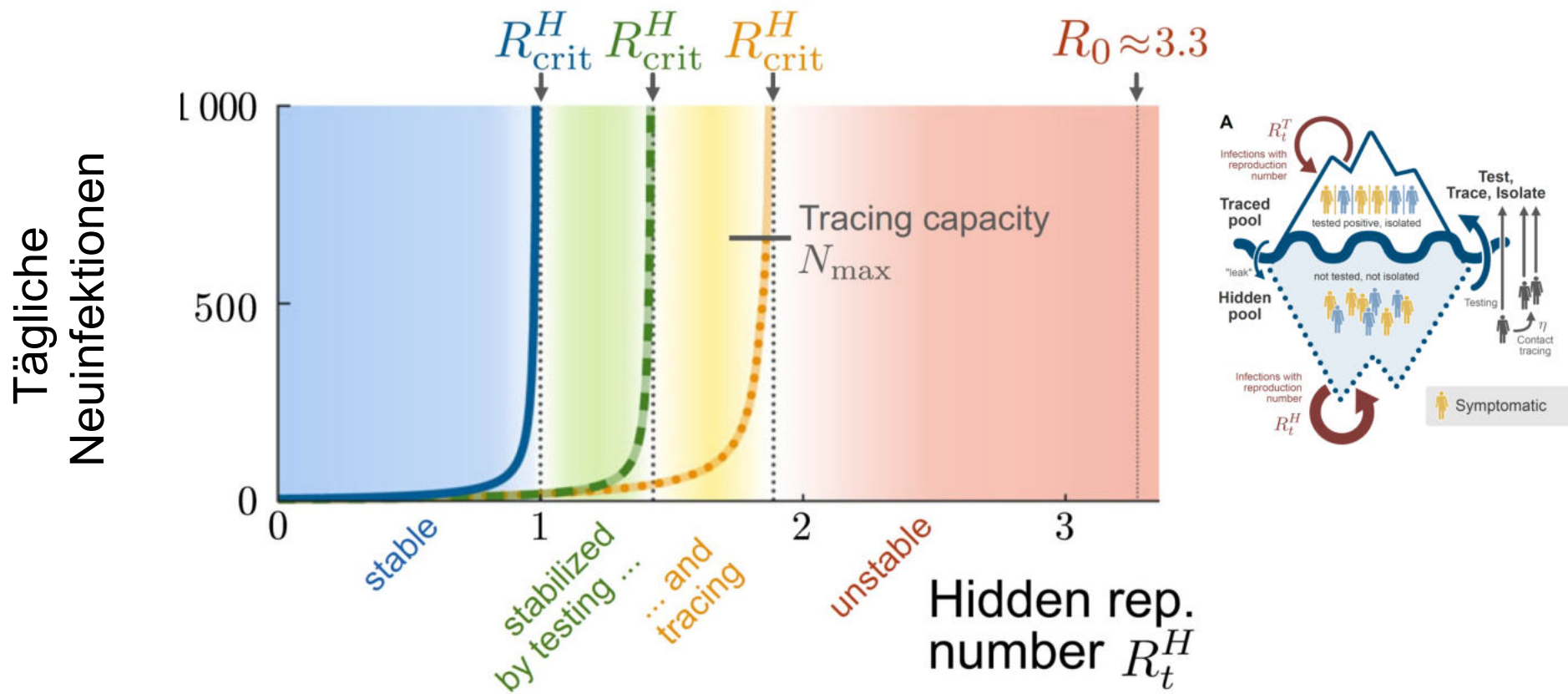




[Contreras et int., Priesemann, Nature Communications, in press]

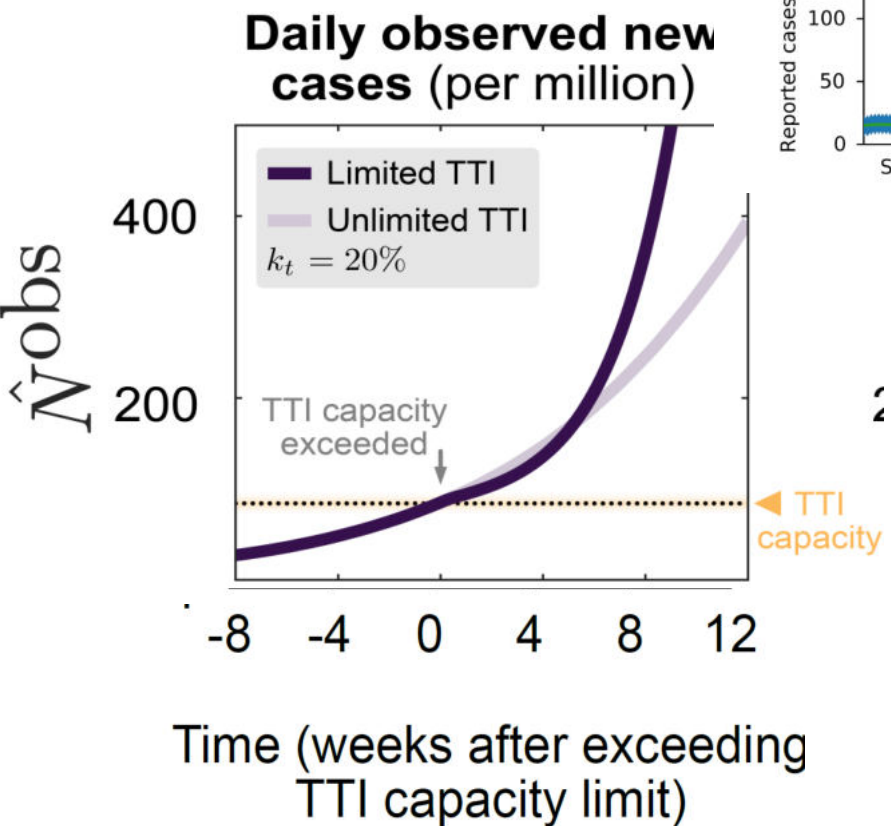
Test-Trace-Isolate (TTI) moves the stability limit:

Without TTI, R must be below 1
With TTI, R in the day to day life can be up to two

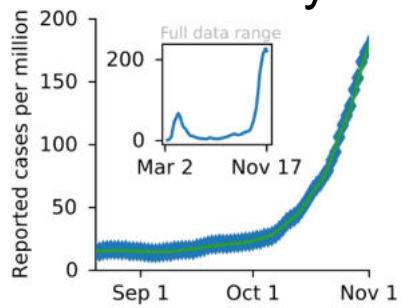


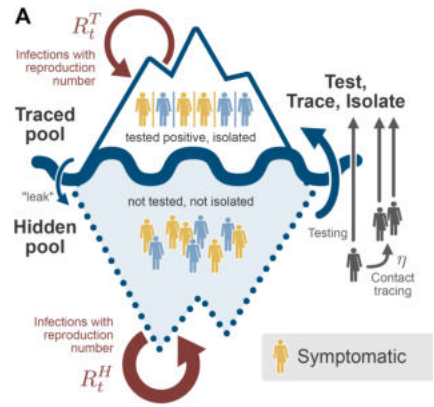
[Contreras et int., Priesemann, Nature Communications, in press]

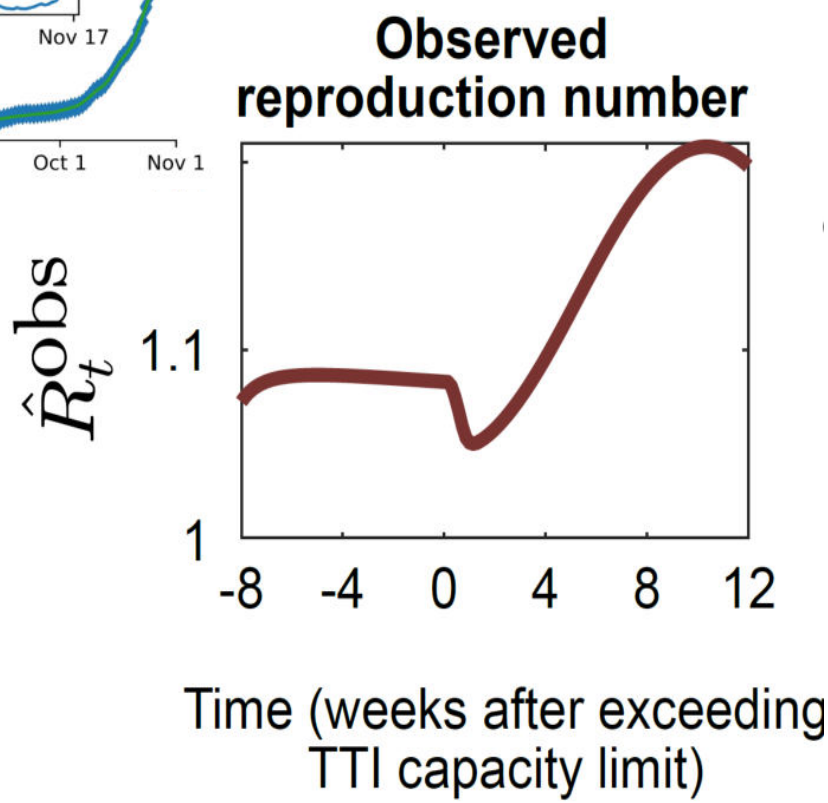
Crossing the TTI Limit: Case numbers grow faster than exponential



New infections Germany

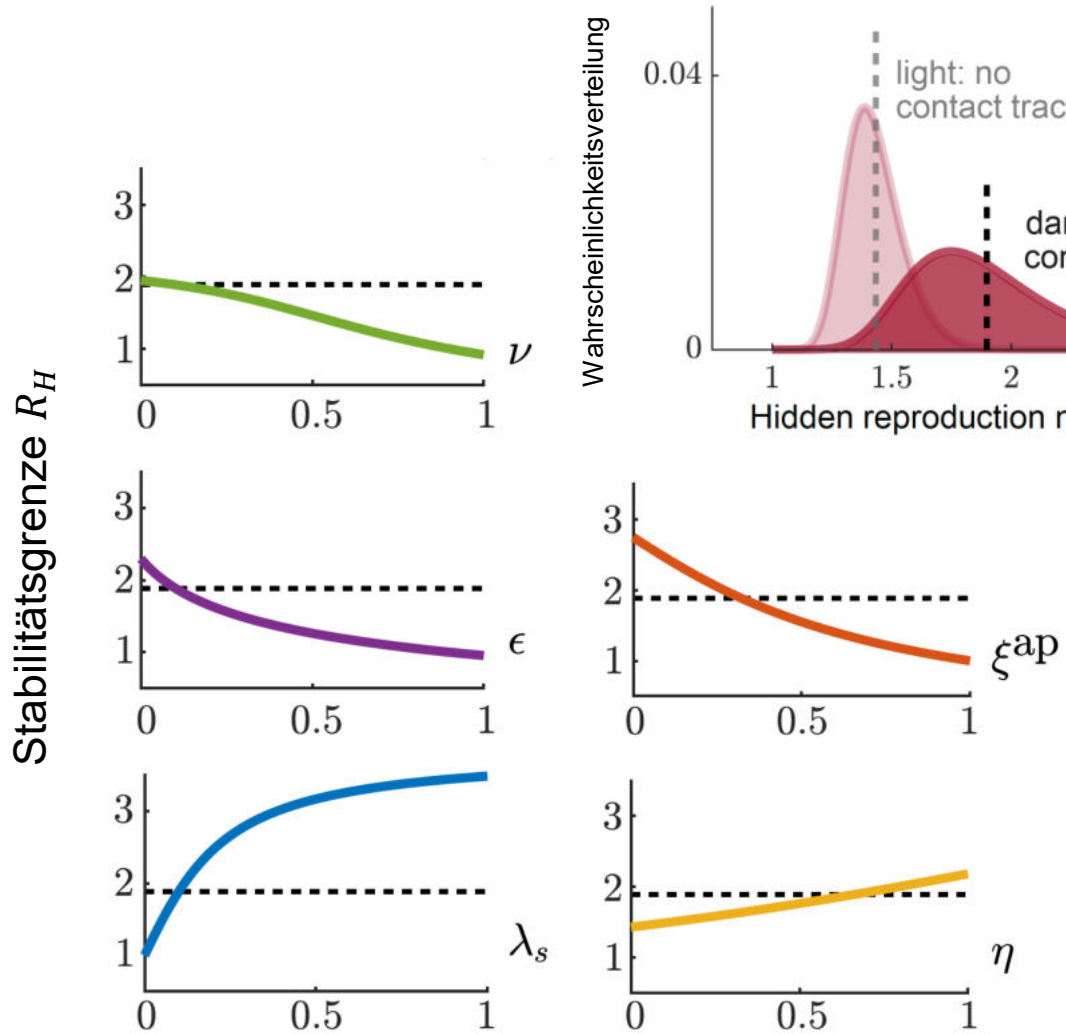


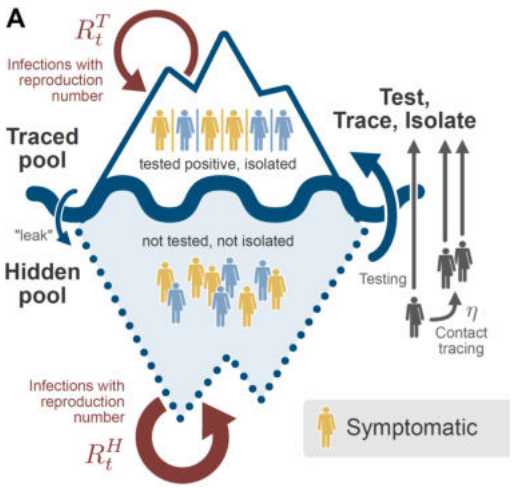




[Contreras et int., Priesemann, Nature Communications, 2021, and arxiv]

Sensitivity Analysis



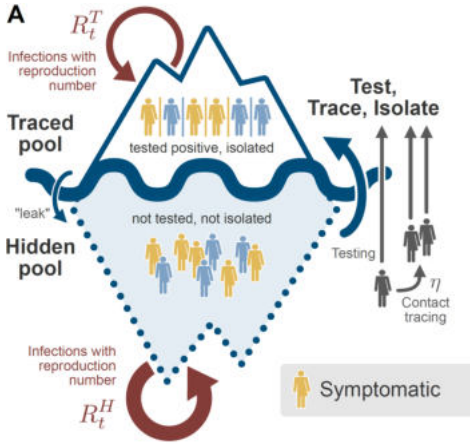


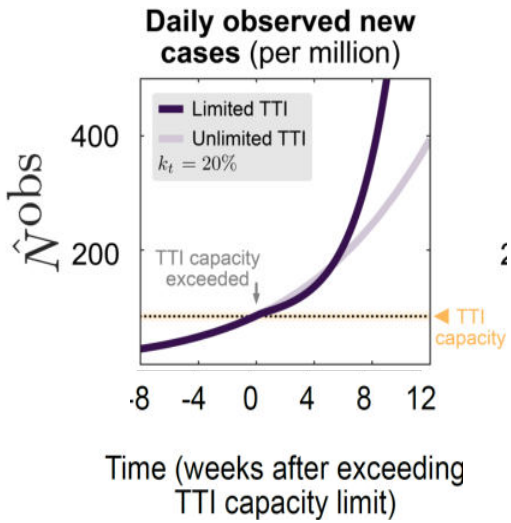
ν	Isolation factor
ϵ	"leak" factor
λ_s	Symptom-driven testing
ξ^{ap}	Apparent asymptomatic fraction
η	Tracing efficiency

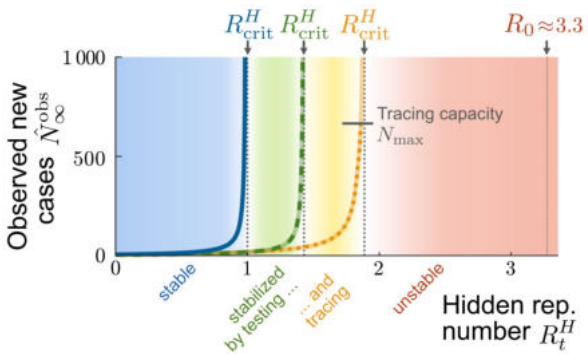
[Contreras et int., Priesemann, Nature Communications, in press]

Summary of the TTI strategy

Test-Trace-Isolate (TTI) contributes to containing COVID-19:







The undetected cases contribute most strongly to the spread

If the TTI capacity is surpassed, a tipping point is crossed, and growth self-accelerates.

TTI enables every single person to have more contacts: Instead of one, about two persons can be infected → Compensaiton by TTI.

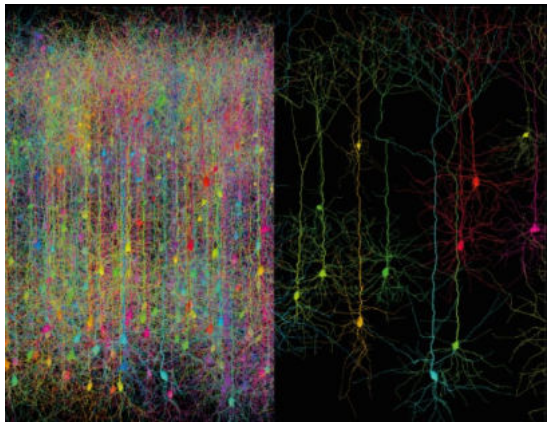
https://arxiv.org/pdf/2011.11413 [Contreras et int., Priesemann, arxiv]
https://arxiv.org/pdf/2009.05732 [Contreras et int., Priesemann, Nature Communications, in press]

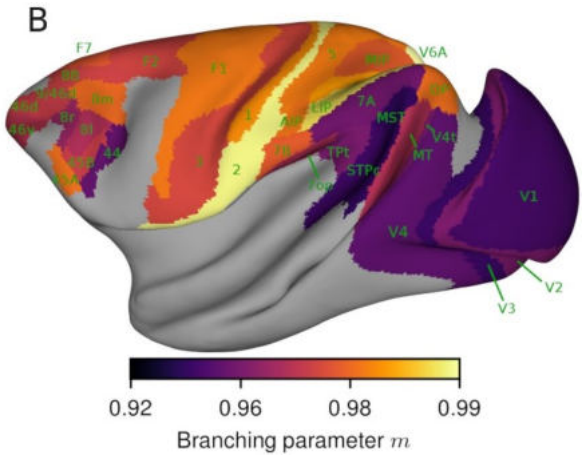
Overview

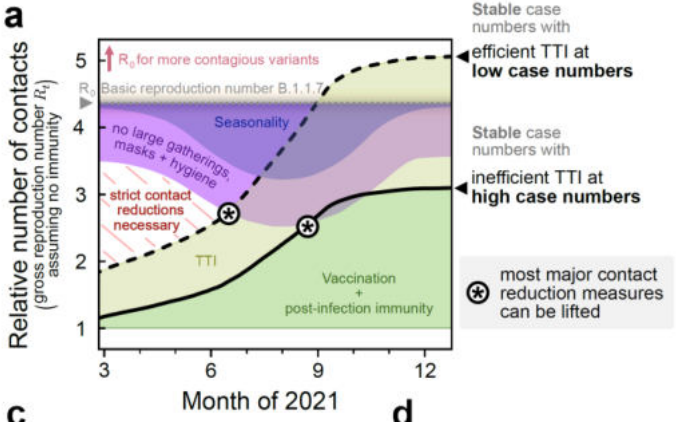
- **Large Scale Recordings & Subsampling:**
  How to infer collective properties and spreading dynamics from vastly under-observed systems

- **Spreading Dynamics & Information Transfer:** Tuning a network close to a second-order phase transition enablse rapid tuning to task requirements

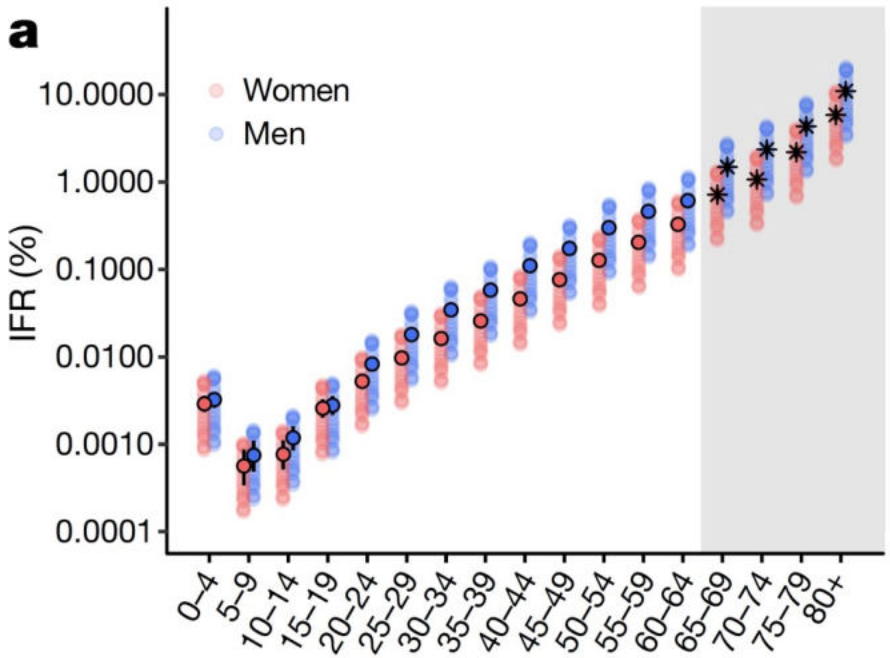
- **Mitigating the Spread of COVID-19:**
  - The effect of test-trace-isolate (TTI)
  - and of the vaccination progress







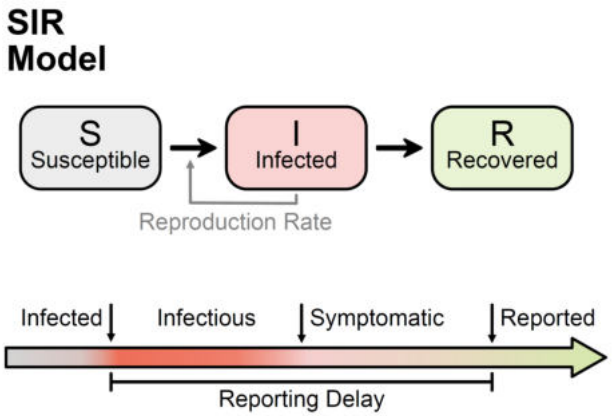
The age-dependent infection fatality Rate (IFR) of SARS-CoV-2

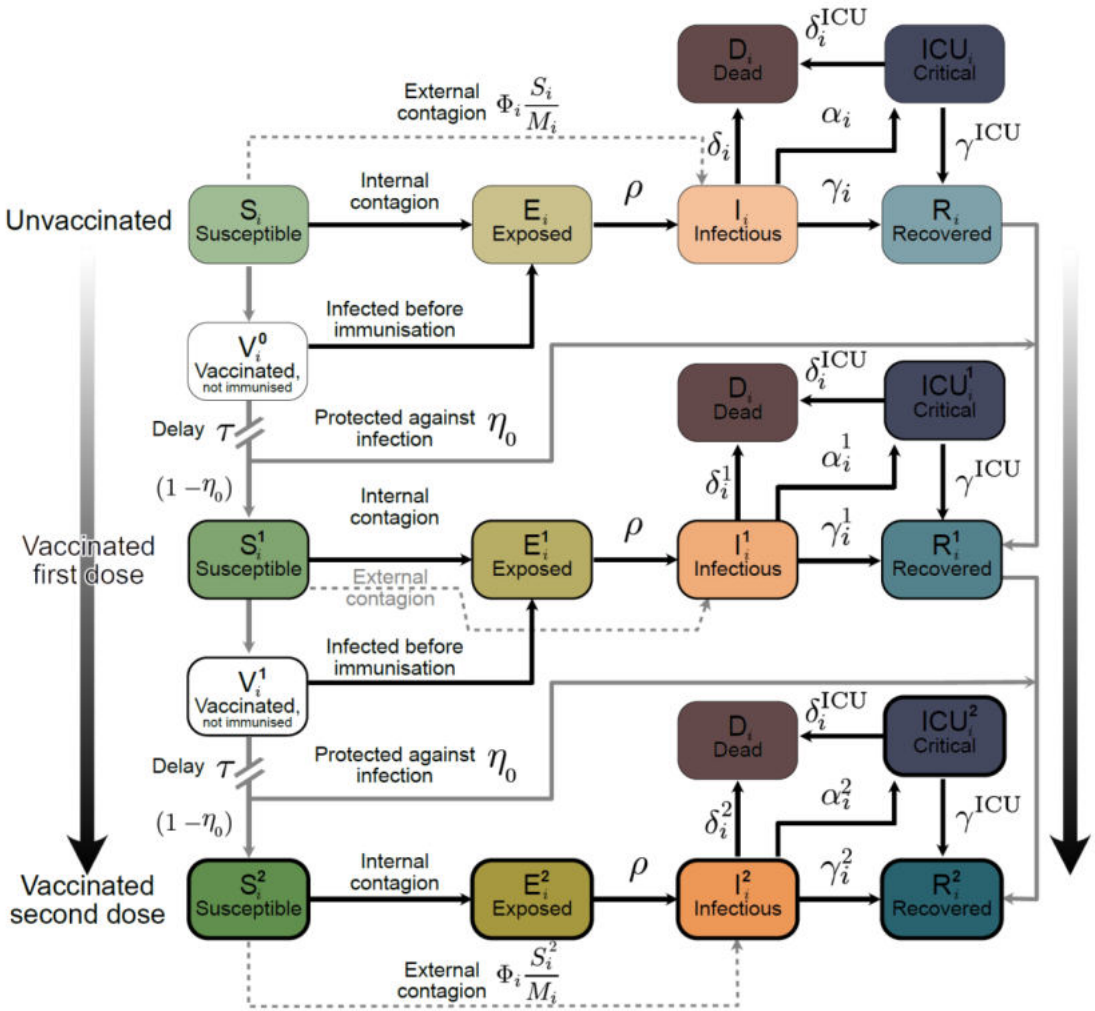


O'Driscoll et al., Nature, 2020; https://www.nature.com/articles/s41586-020-2918-0

Levin et al. Eur. J Infect. Disease, 2020;, https://link.springer.com/content/pdf/10.1007/s10654-020-00698-1.pdf [Bauer et al. 2020, arxiv]

Implementing Vaccination Progress





A model with compartments for

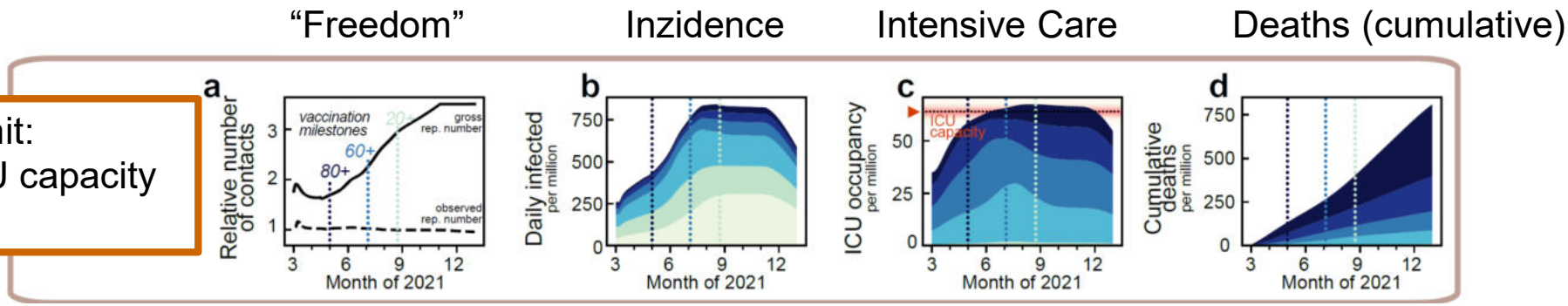
- SIRS (naturally infected)
- 1st vaccination dose
- 2nd vaccination dose
- Intensive care units
- Recovered / dead

Parameters of the current vaccination delivery plan for Europe

[Bauer et int., Priesemann, arxiv: https://arxiv.org/pdf/2103.06228]

The main determinant of lifting restrictions is the progress in vaccination

Limit:
ICU capacity



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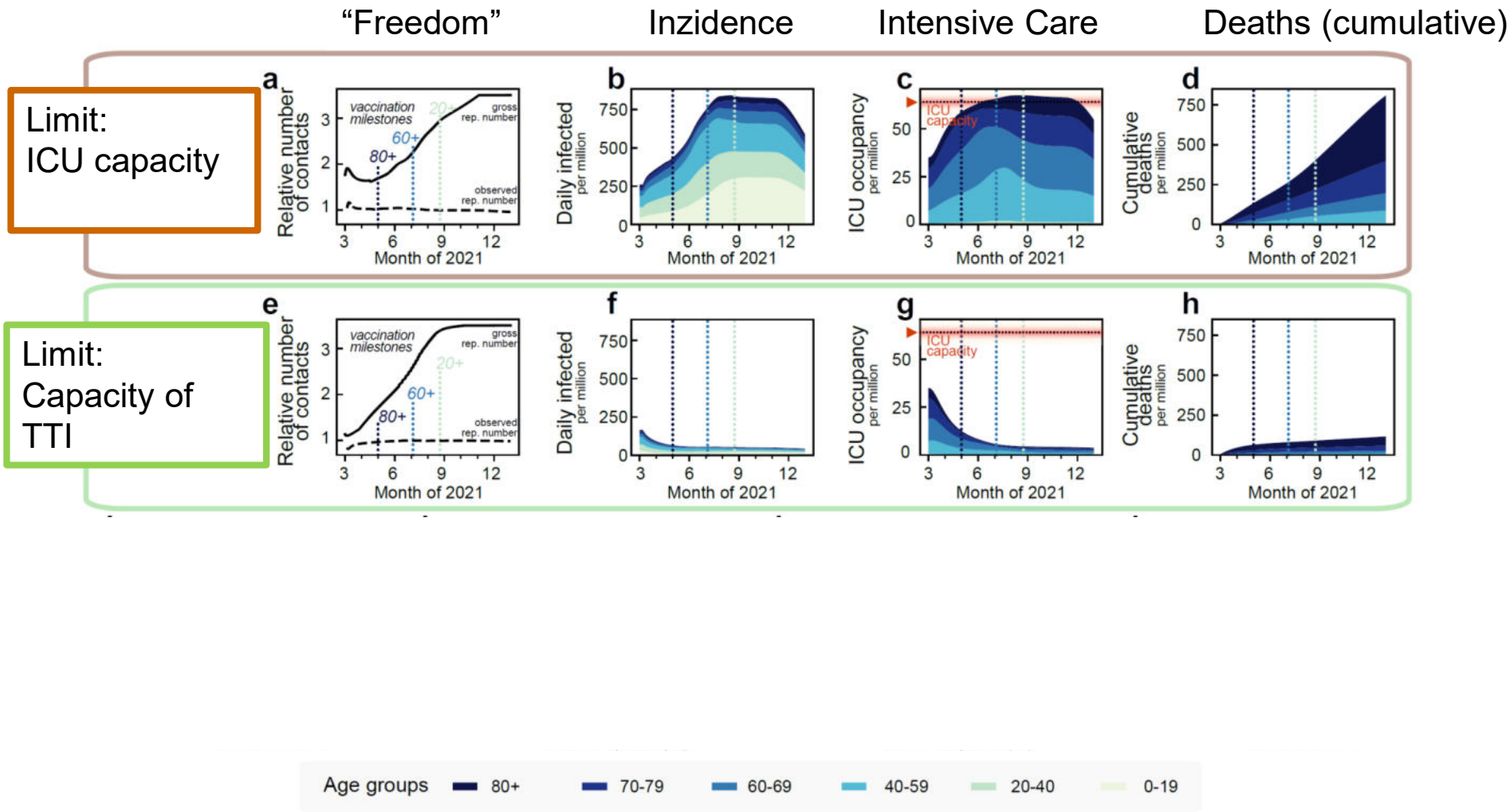

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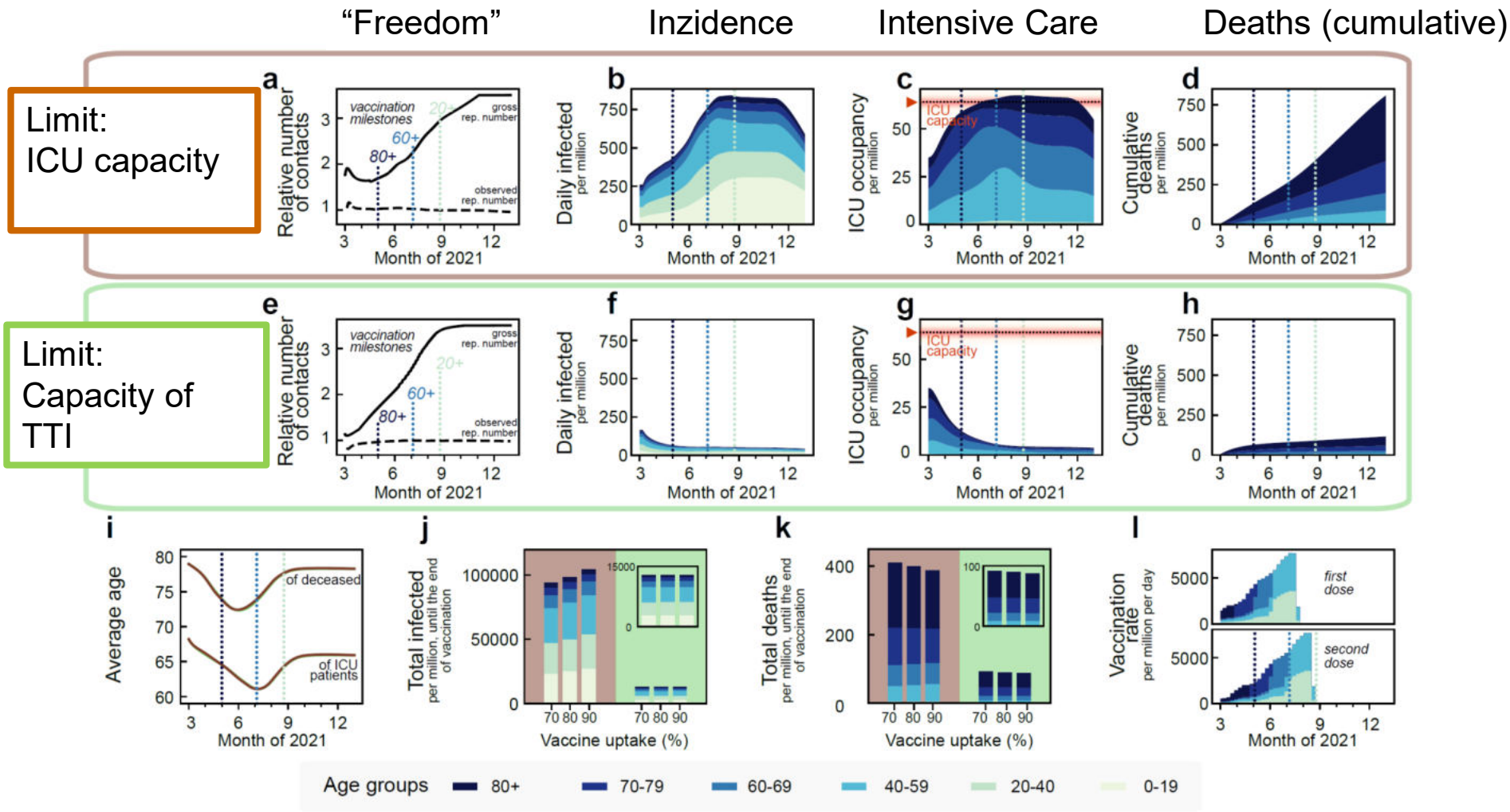

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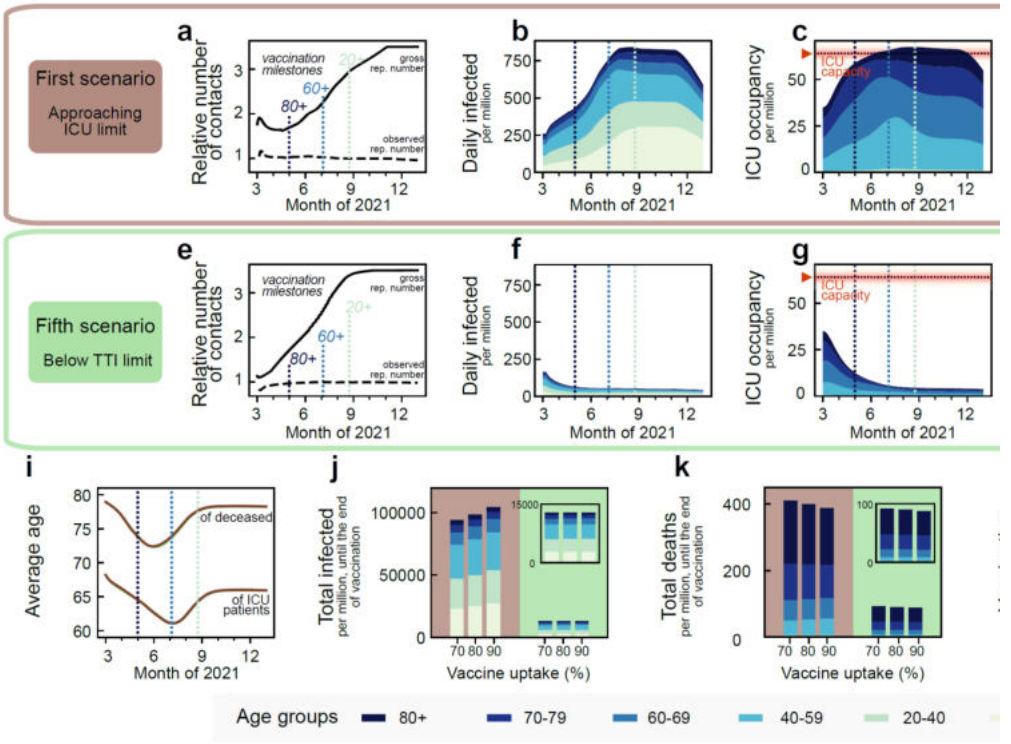
Policy Goals
Not overwhelming the ICU capacity
or
Low Incidence and Control

- Intensive care units can still be full for several weeks.
- The number of infections, deaths and long-term consequences (Long-COVID) are very different
- In both cases, the average age of ICU patients and deaths decreases
- The number of contacts ("freedom") increases in a very similar manner for both policy goals



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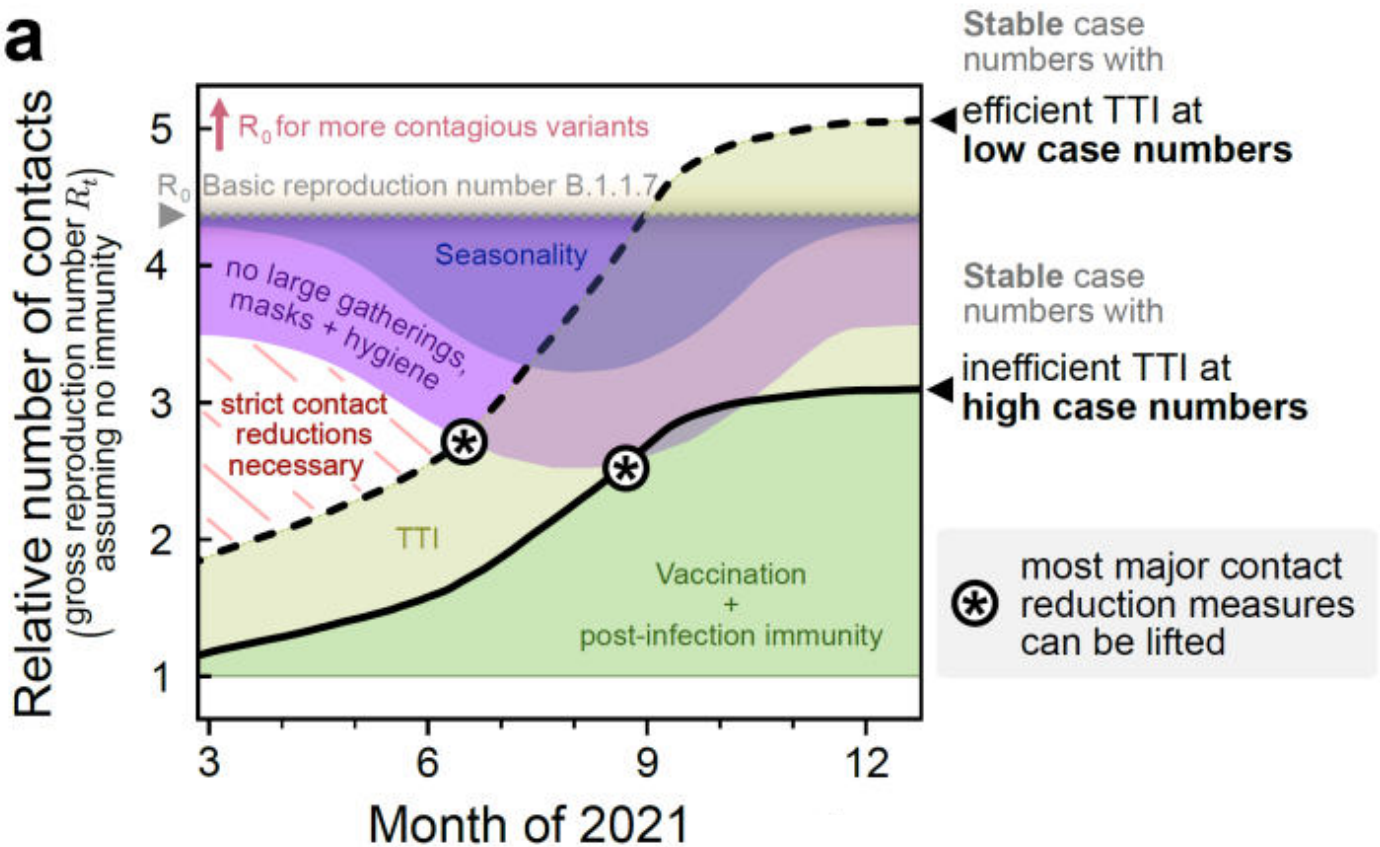
At low case numbers, the lifting of restrictions can be faster, because TTI contributes to containment

“Freiheit”



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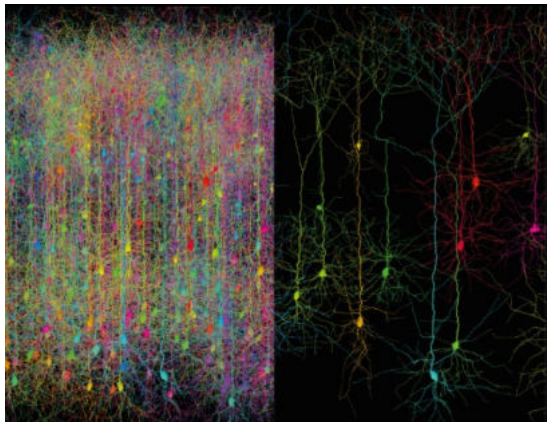

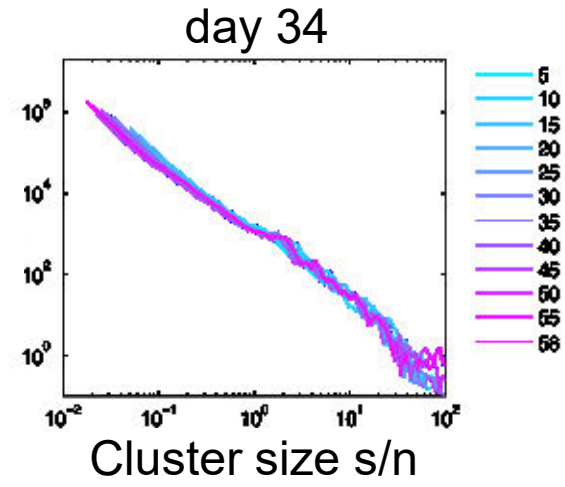

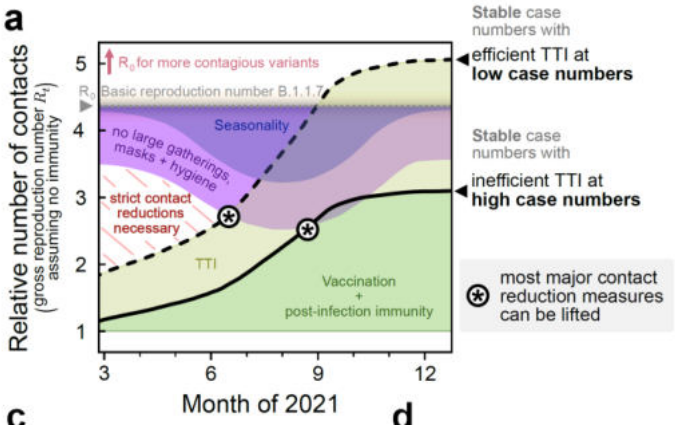

Thank you!

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Matthias Linden
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Henrik von der Emde (Cambridge)
Mathias Sogorski (PSI, Berlin)
Moritz Layer (Cambridge)
Victor Brasch (EPFL)

MAX-PLANCK-GESELLSCHAFT

Discussions on COVID within the Göttingen Campus and beyond:
Heike Bickeböller, Philip Bittihn, Eberhard Bodenschatz, Wolfgang Brück, Alexander Ecker, Andreas Leha, Theo Geisel, Ramin Golestanian, Helmut Grubmüller, Stephan Herminghaus, Gerald Haug, Reinhard Jahn, Jürgen Jost, Norbert Lossau, Vladimir Zykov, Michael Meyer-Hermann, Iris Pigeot, Simone Scheithauer, Anita Schöbel, Fredi Schüth, **Michael Wibral & Michael Wilczek**

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