Physics of viruses

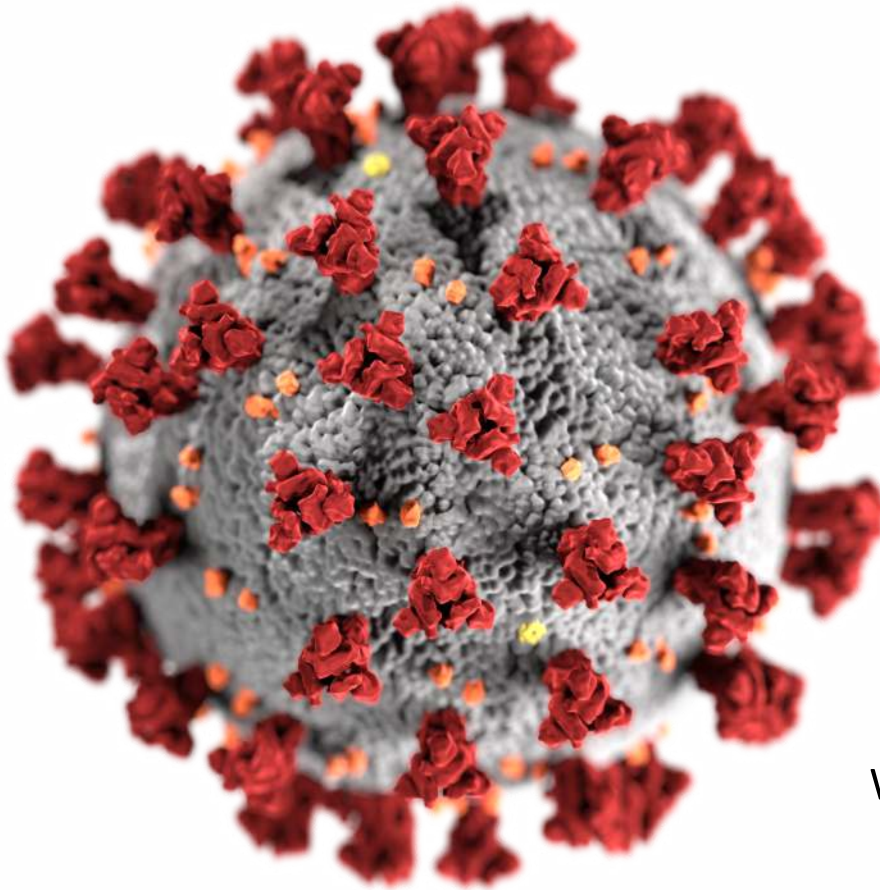
Ulrich Schwarz and Frederik Graw

seminar summer term 2020

introduction April 22 2020

update May 16 2020

SARS-CoV-2



Wikipedia

Very little is known about this new virus, but SARS-CoV is similar and well characterized due to the SARS-outbreak in 2003.

Gallery of icosahedral viruses

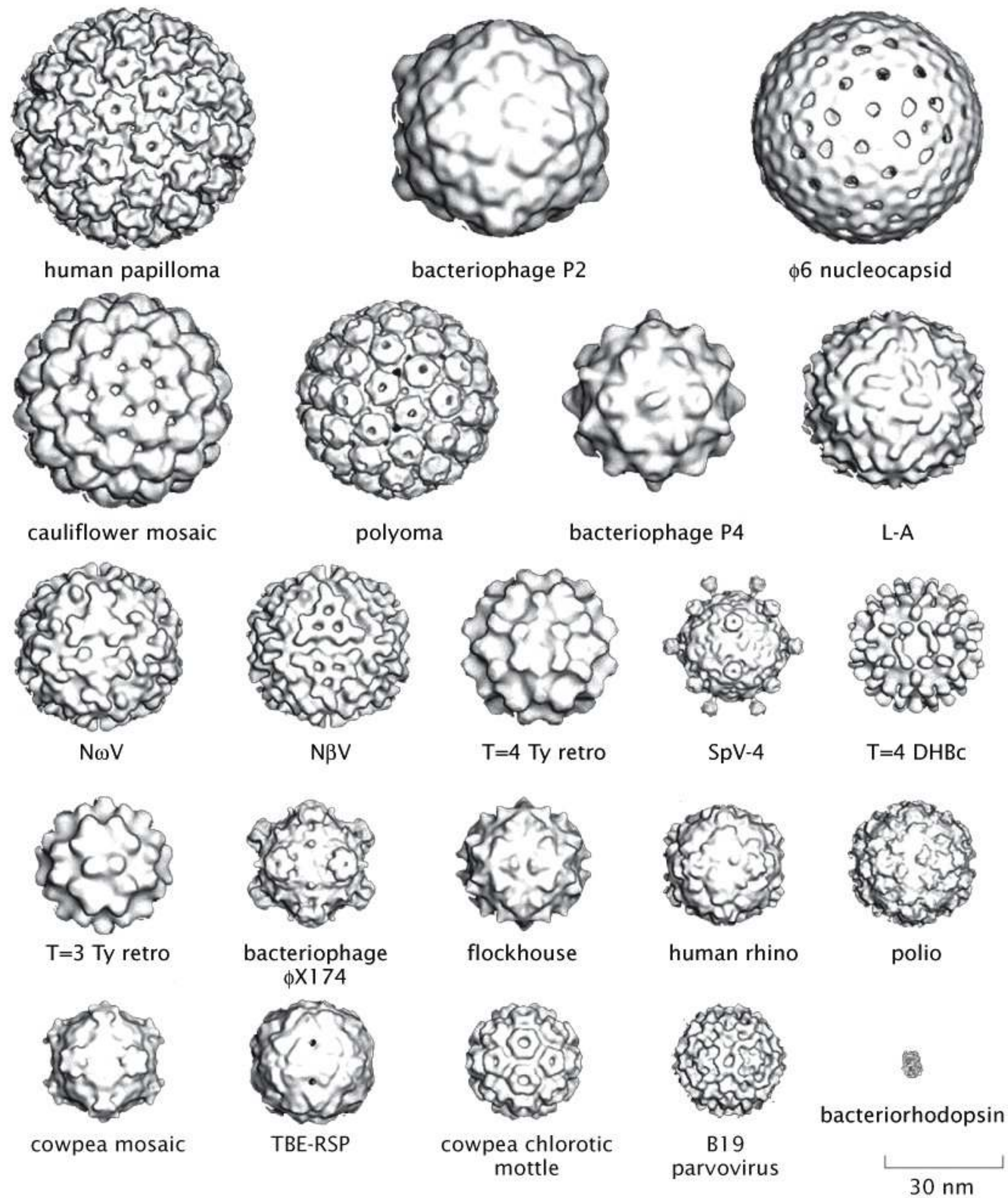
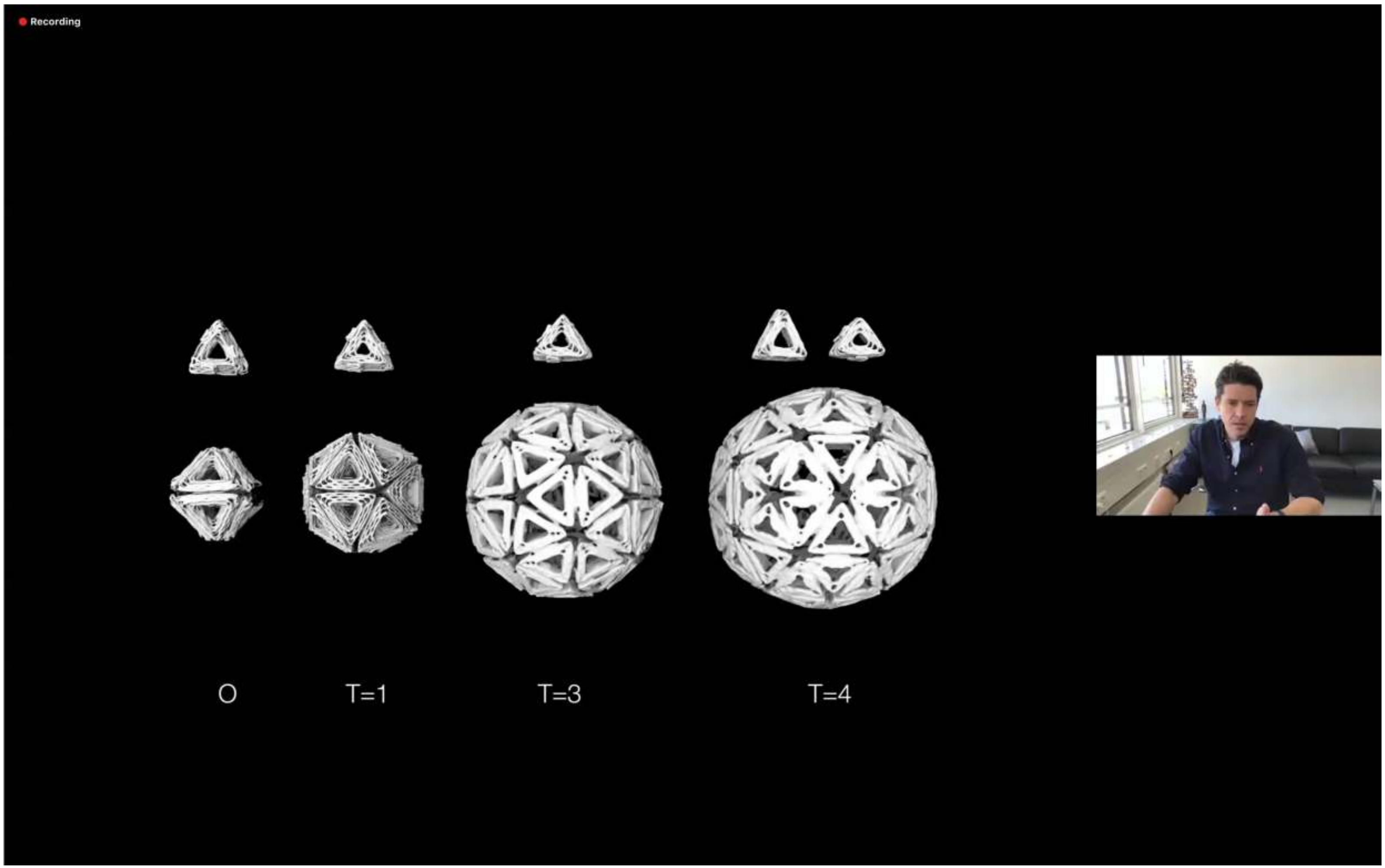


Figure 2.29 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

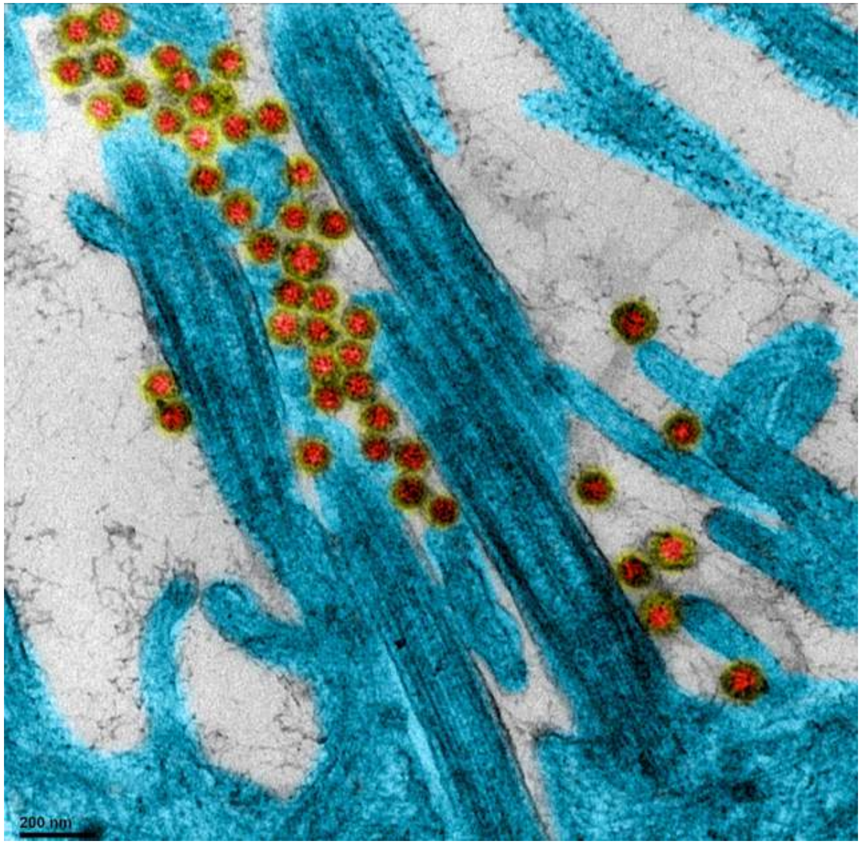
Resolution limit optical microscopy 250 nm – these viruses can only be seen in electron microscopy

Designing viruses with DNA-origami



Hendrik Dietz, TUM, zoom presentation at Matter to Life Lecture Series, April 22 2020

COVID-19



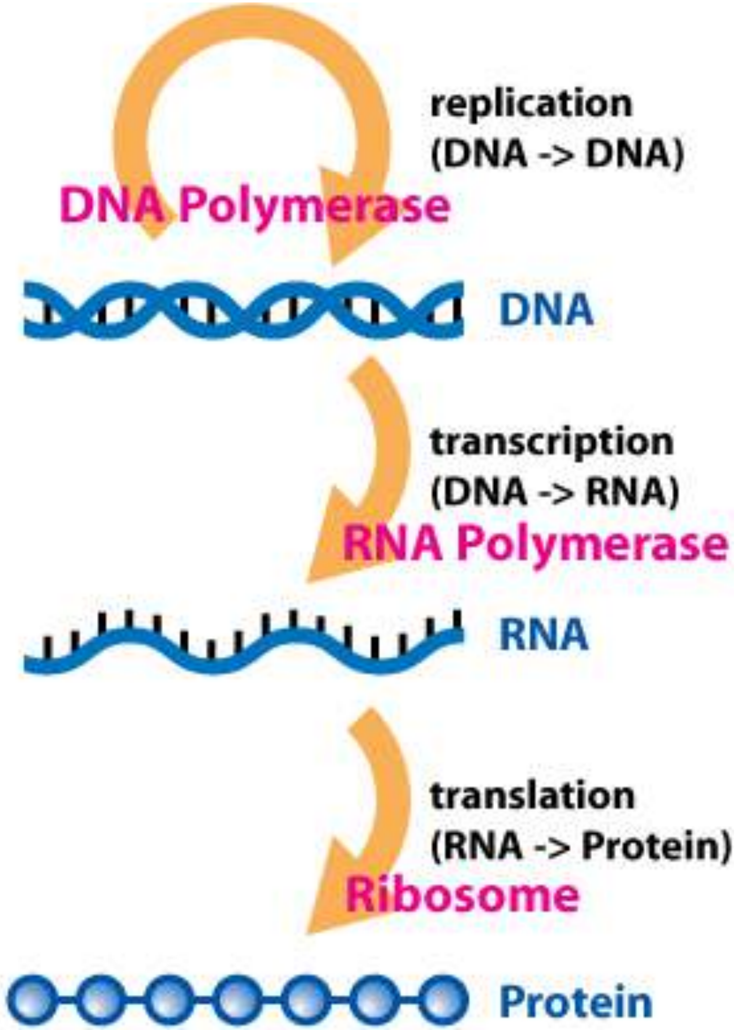
Coloured electron microscopy: SARS-CoV-2 viruses binding to ciliated lung cells

Many aspects of this disease are mysterious, esp. why it affects different individuals so differently. The entry receptor is ACE2 in lung epithelium (drug target for heart patients).

Illustrations by David Goodsell

Some basic biology facts

Central dogma of molecular biology

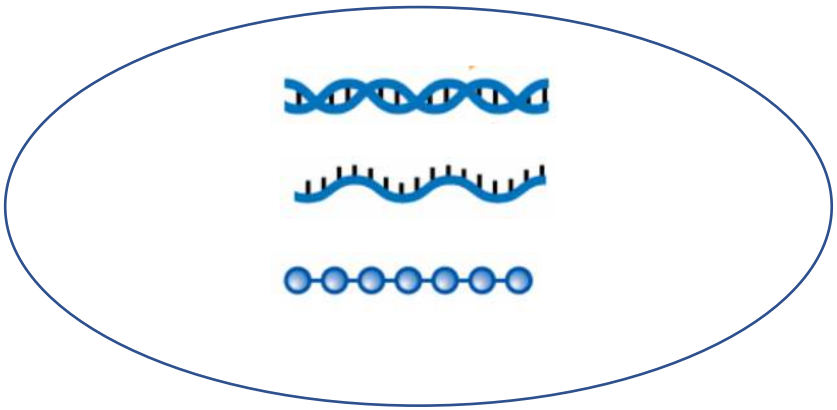


DNA stores the genetic information

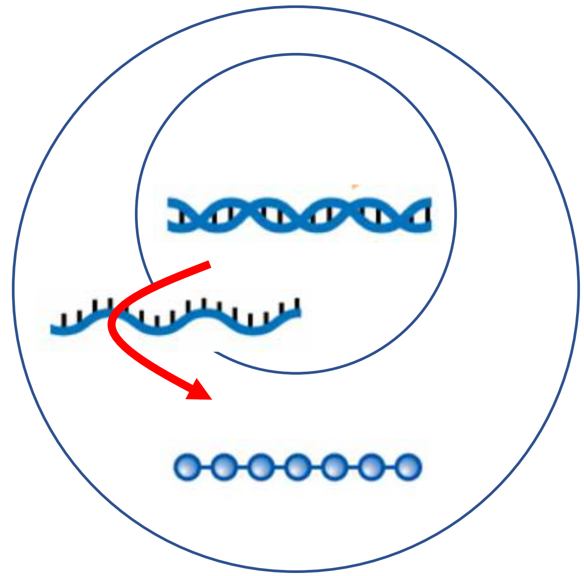
RNA transports the genetic information

Proteins go to work

Two types of cells ...

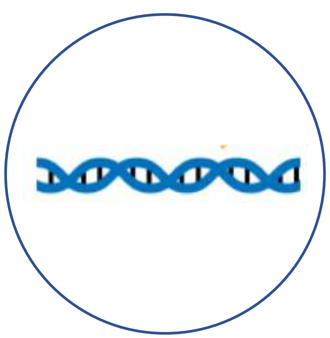


Prokaryotes (bacteria and archae)

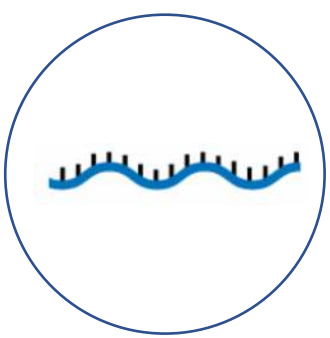


Eukaryotes (protists, algae, fungi, plants, animals, etc)

... and two types of viruses



DNA-virus



RNA-virus

Major classes of biomolecules

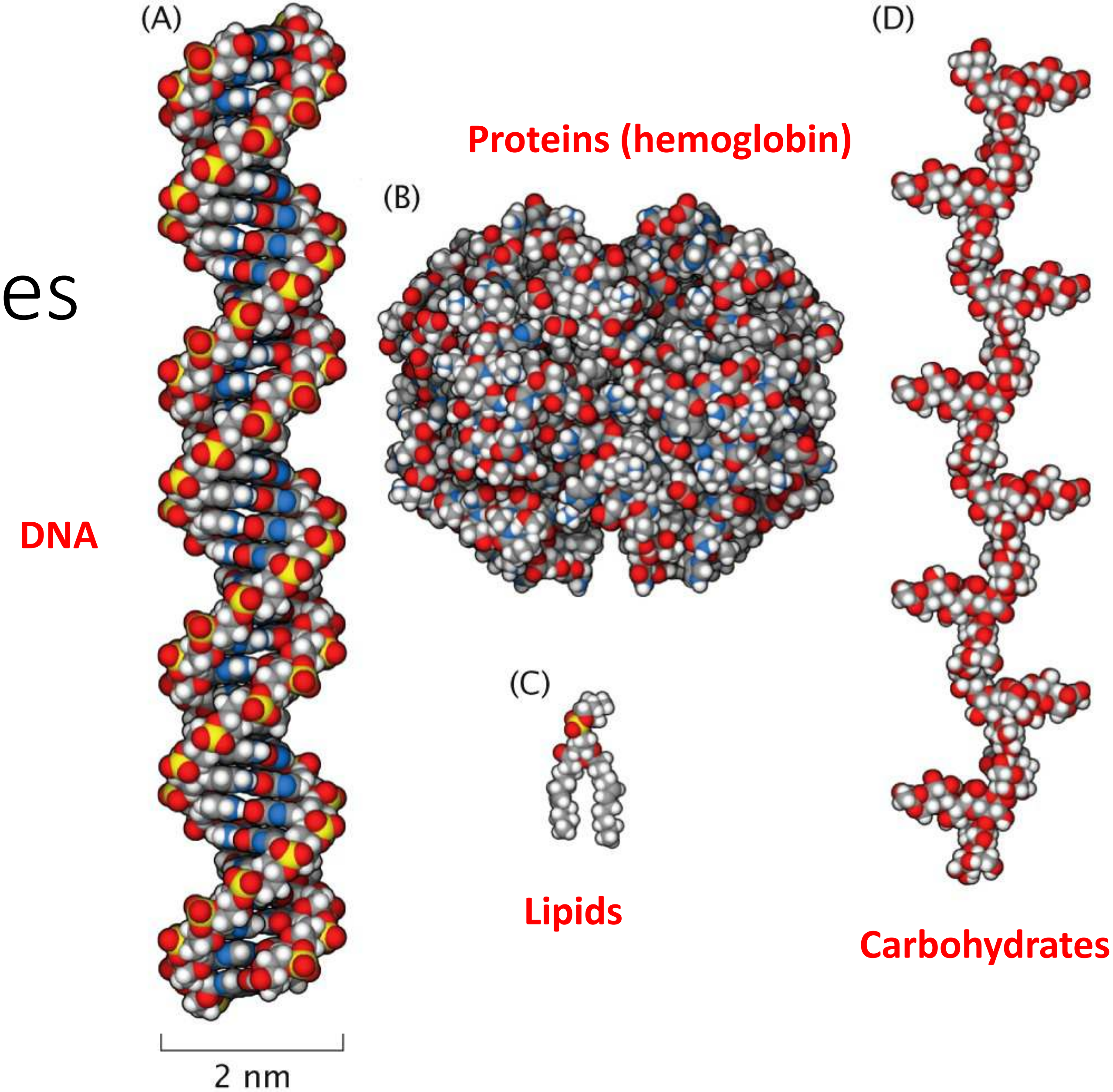


Figure 1.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Different representations of proteins (here an enzyme called triose phosphate isomerase)

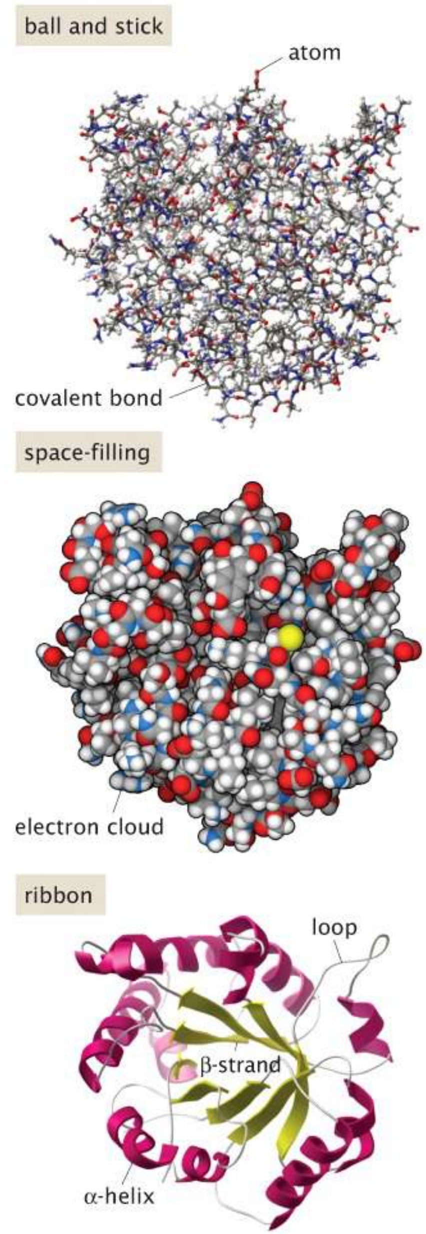
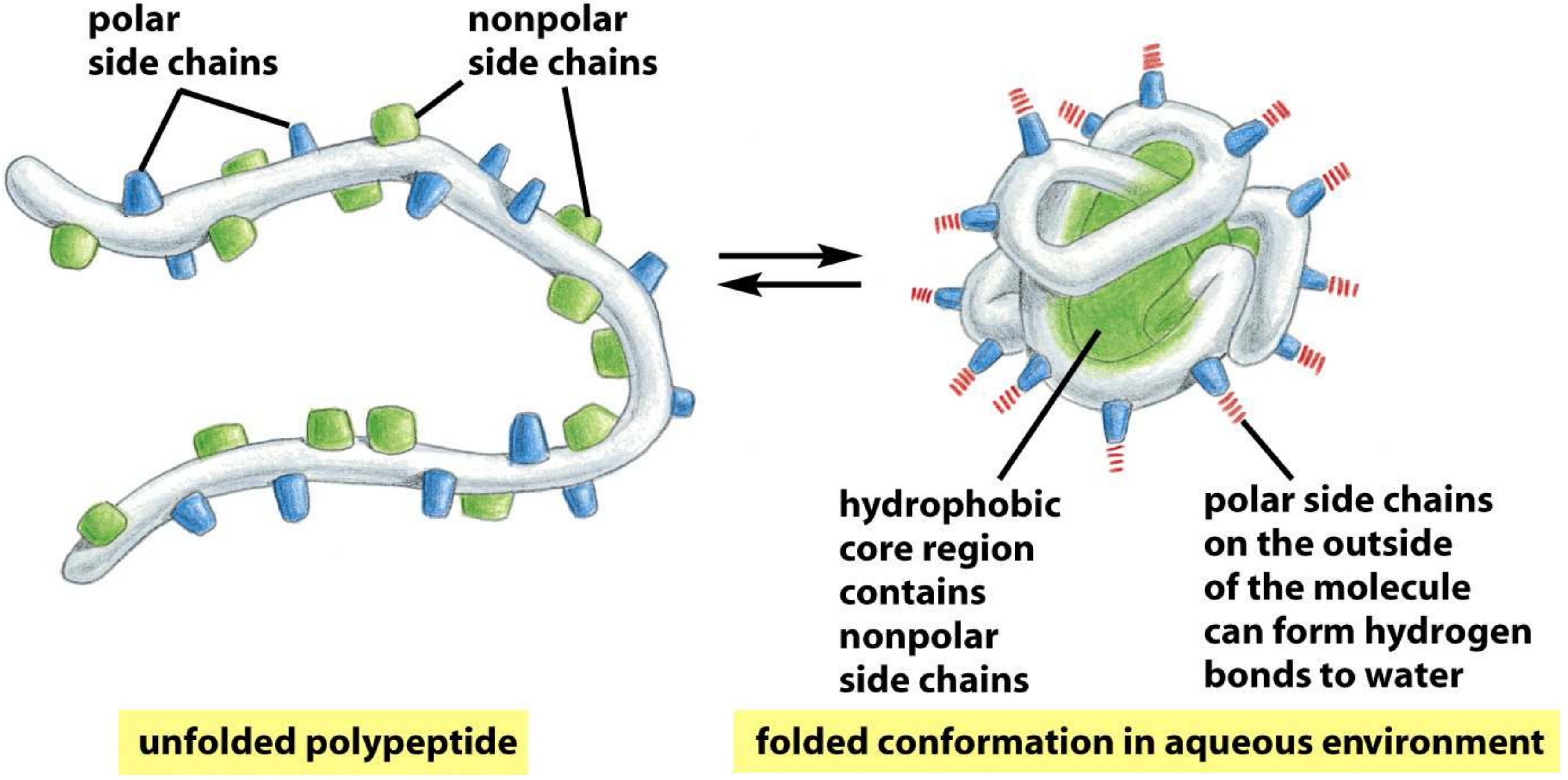
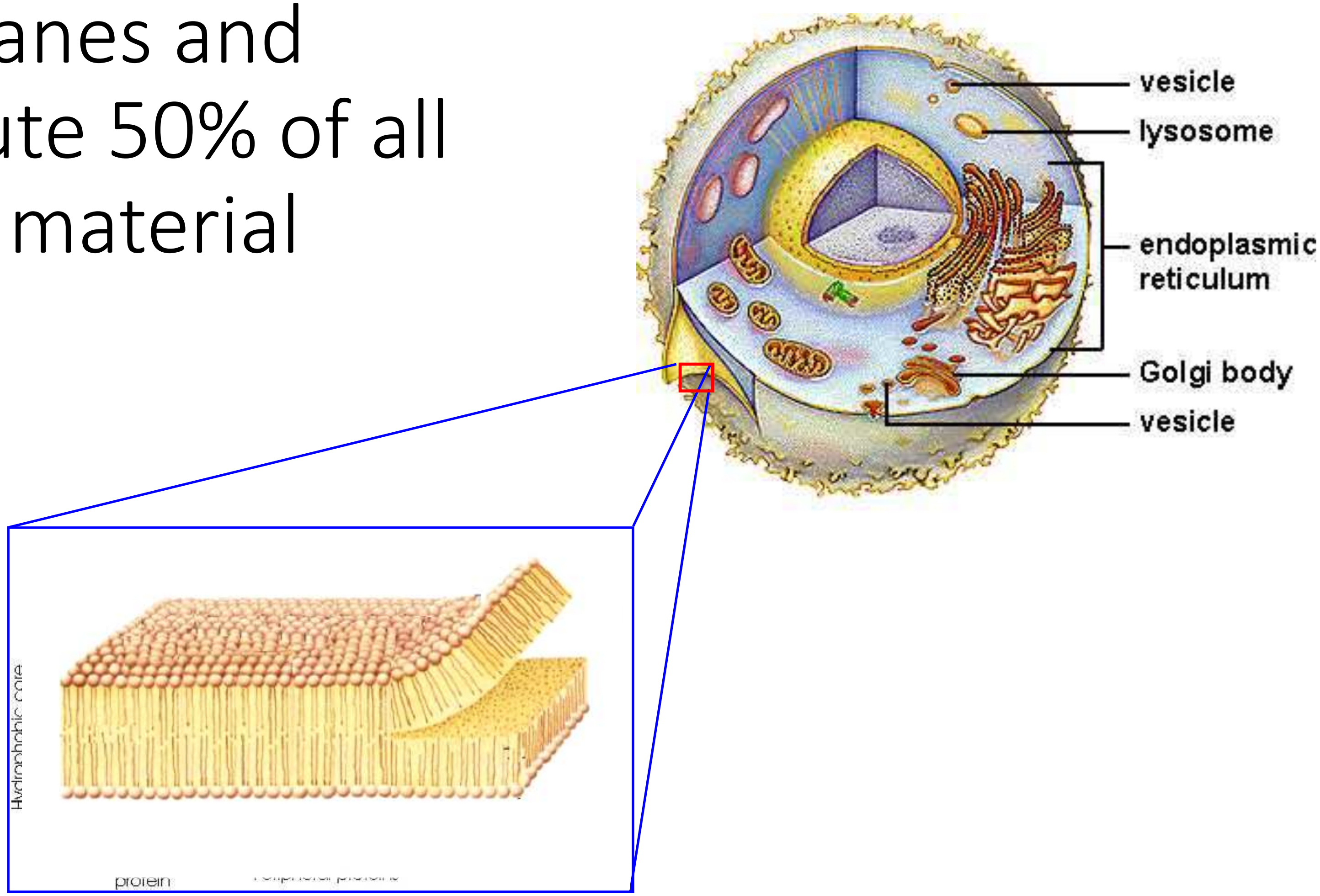


Figure 2.32 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Protein folding



Lipids form membranes and constitute 50% of all cellular material



Molecular content of E. Coli

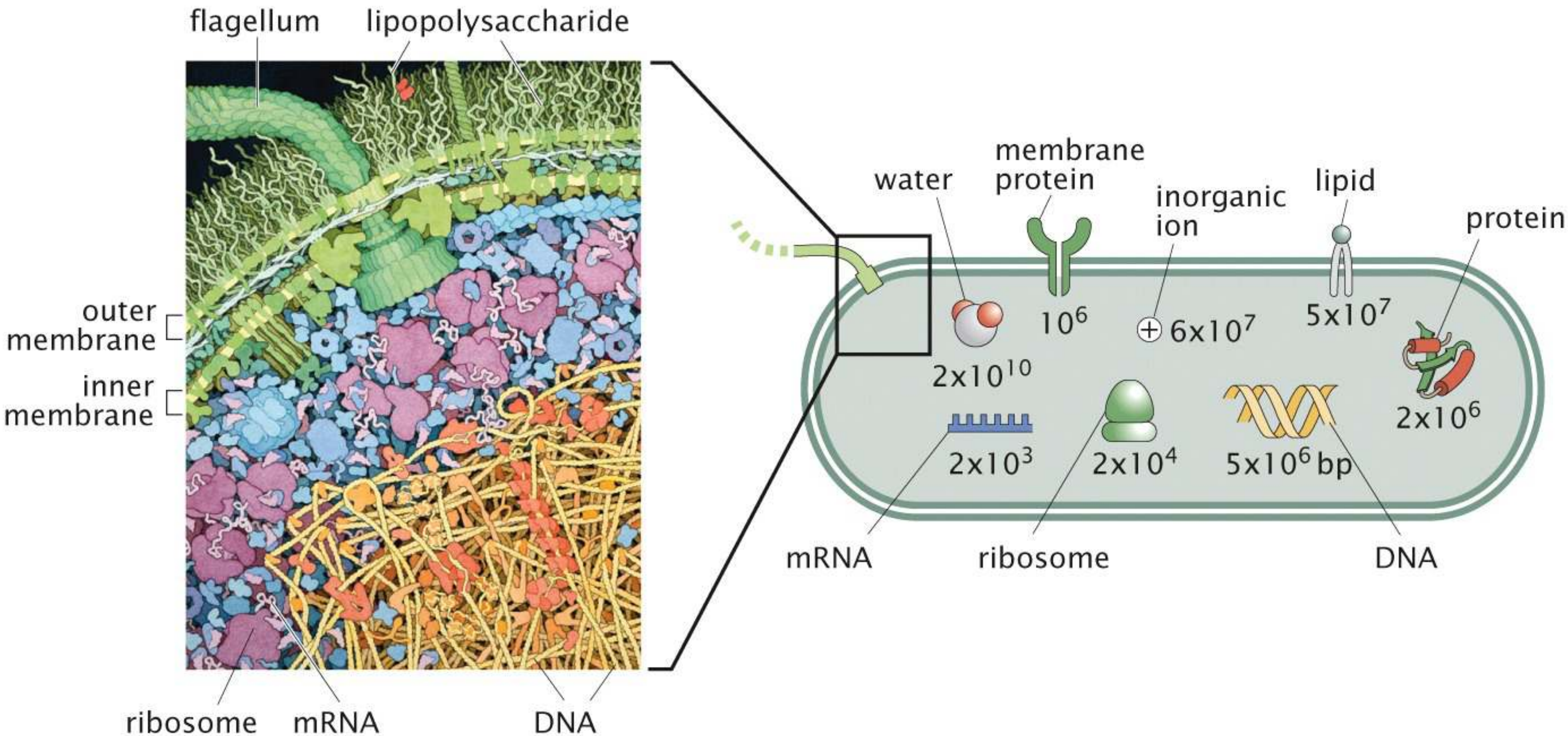


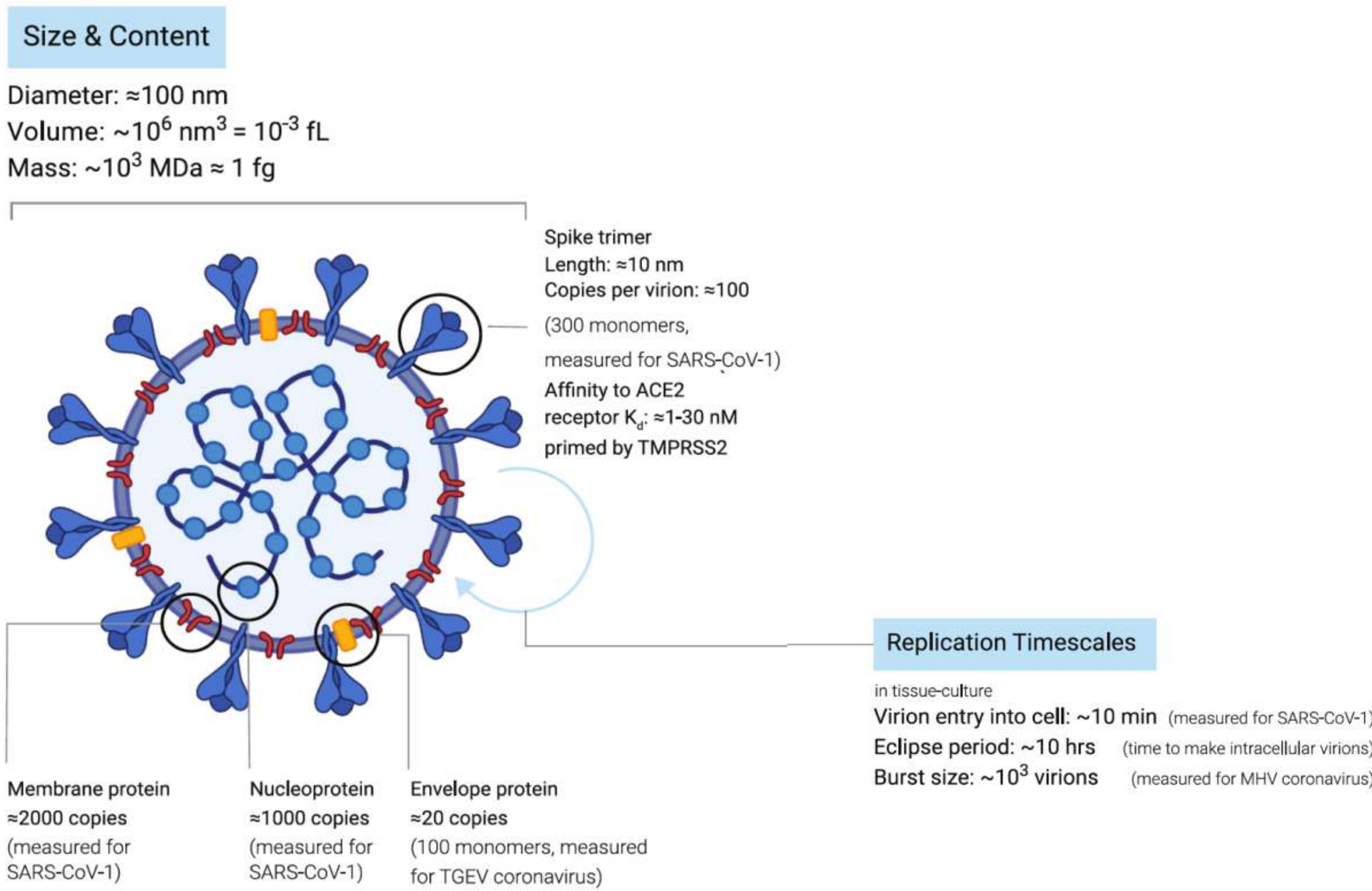
Figure 2.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Viruses

Classification of viruses

- Viruses are just a genome protected by a protein shell (capsid); sometimes they are in addition wrapped by a lipid bilayer membrane
- With lipid bilayer membrane (enveloped) or not (non-enveloped)
  - Examples for enveloped: HIV, hepatitis B, Ebola, influenza, SARS-CoV-2
  - Example for non-enveloped: adeno, papilloma, bacteriophages
- Genome RNA or DNA
  - Example for RNA-viruses: HIV, influenza, SARS-CoV-2
  - Examples for DNA-viruses: bacteriophages, herpes, smallpox
- The capsid of SARS-CoV-2 is not characterized yet and therefore usually not included in illustrations; will be done in the future with cryo electron tomography.

SARS-CoV-2 by the numbers



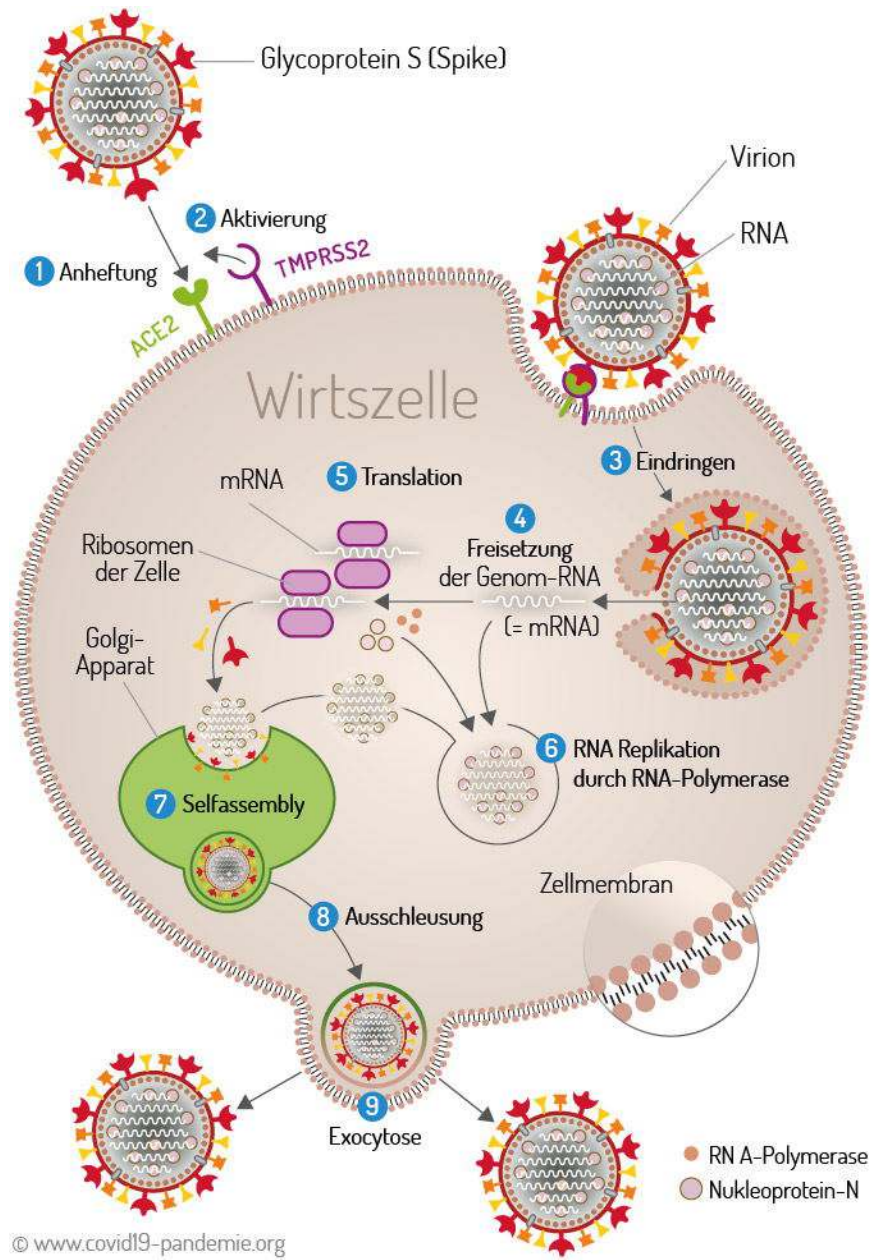
Bar-On, Flamholz, Phillips, Milo eLife 2020

Some more information

- SARS-CoV-2 is a beta-coronavirus whose genome is a single ≈ 30 kb strand of RNA. It codes for 10 genes ultimately producing 26 proteins. Coronaviruses have the largest genomes of any known RNA viruses.
- One long gene, orf1ab, encodes a polyprotein that is cleaved into 16 proteins by proteases that are themselves part of the polyprotein. This protease might be a good target for a drug / vaccine.
- The virus is detected by quantitative reverse-transcription polymerase chain reaction (RT-qPCR), that is the RNA converted into DNA, this DNA is then multiplied and detected.
- The flu is caused by an entirely different family of RNA viruses called influenza viruses. Flu viruses have smaller genomes (≈ 14 kb) encoded in 8 distinct strands of RNA.

Replication cycle

The entry receptor is ACE2. There is no evidence for fusion at the plasma membrane, so it is receptor-mediated endocytosis and endosomal fusion (but could depend on cell type). Replication cycle in the cell is typical for RNA-viruses (like influenza, but different from HIV).



Wikipedia

Lifecycle HIV

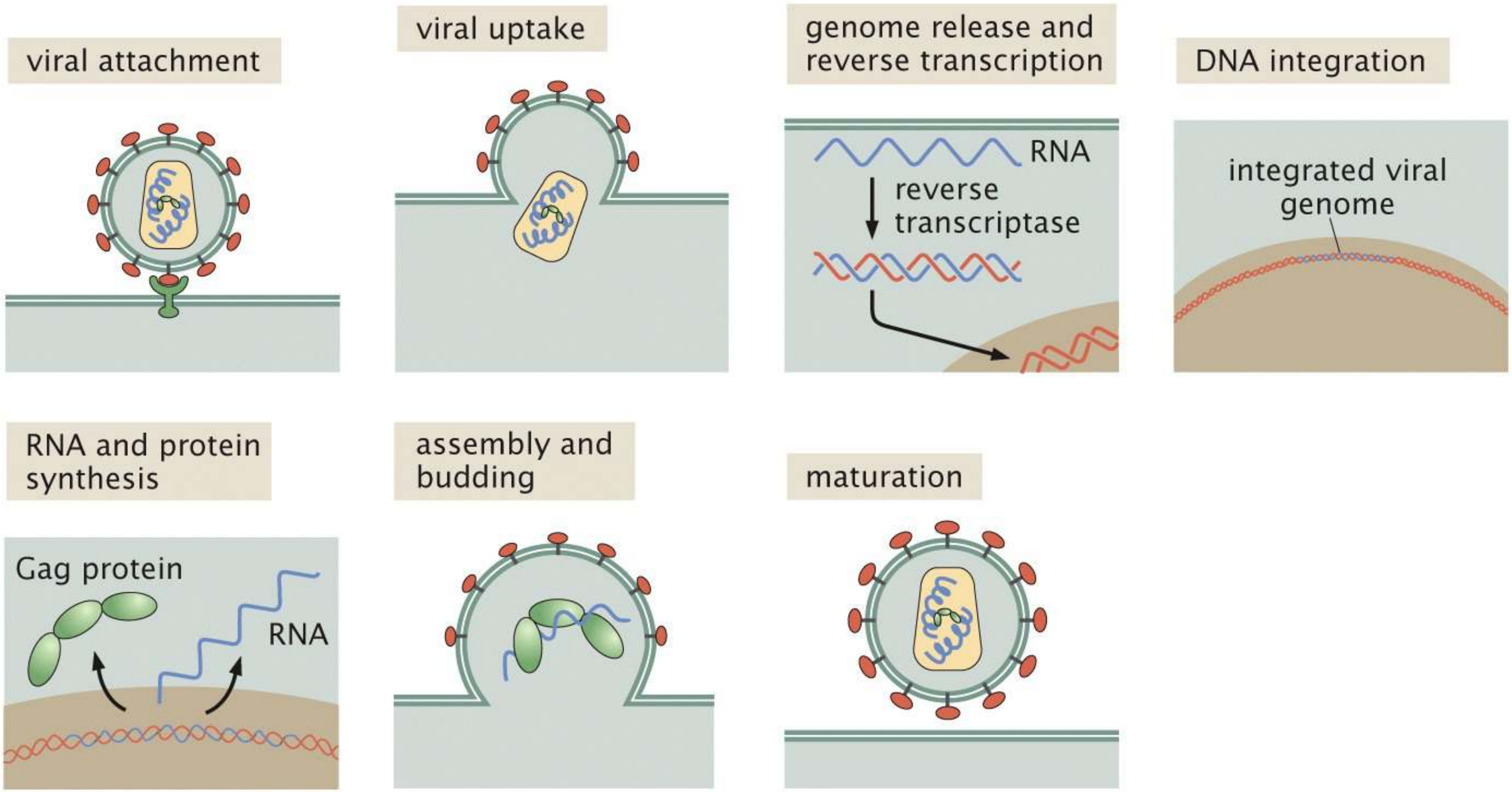


Figure 3.27 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Influenza uptake

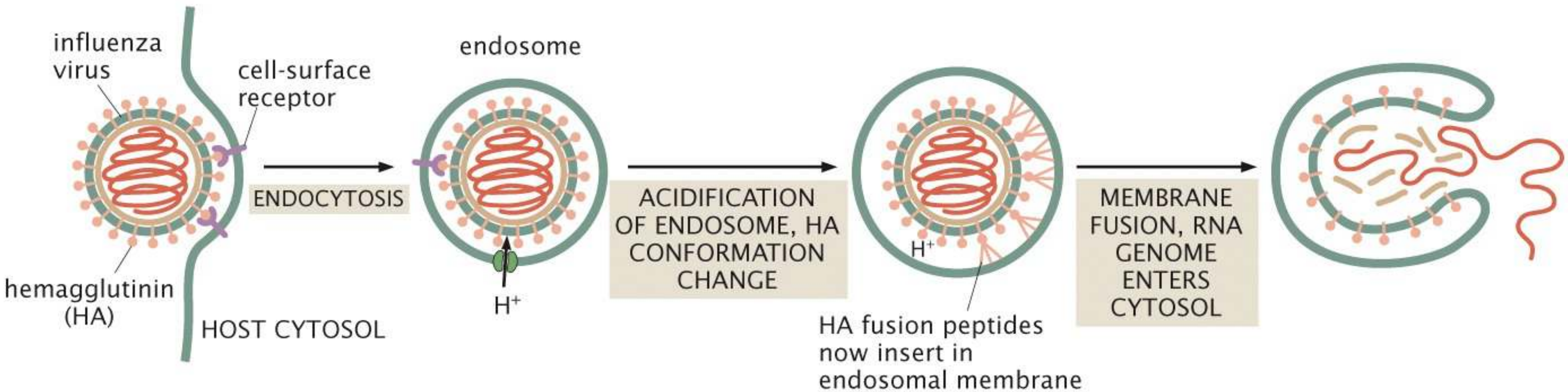


Figure 9.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Genome packing bacteriophages

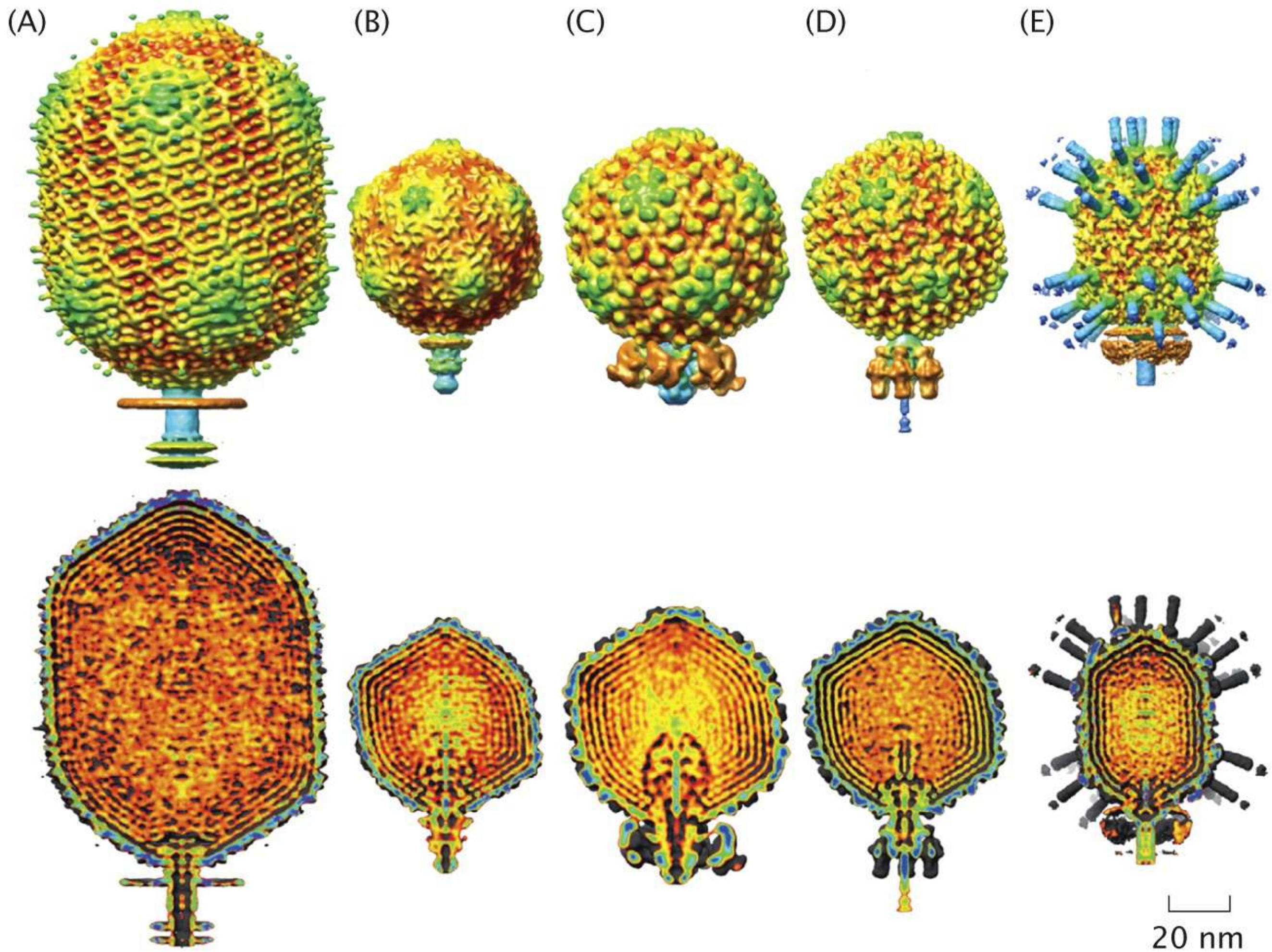
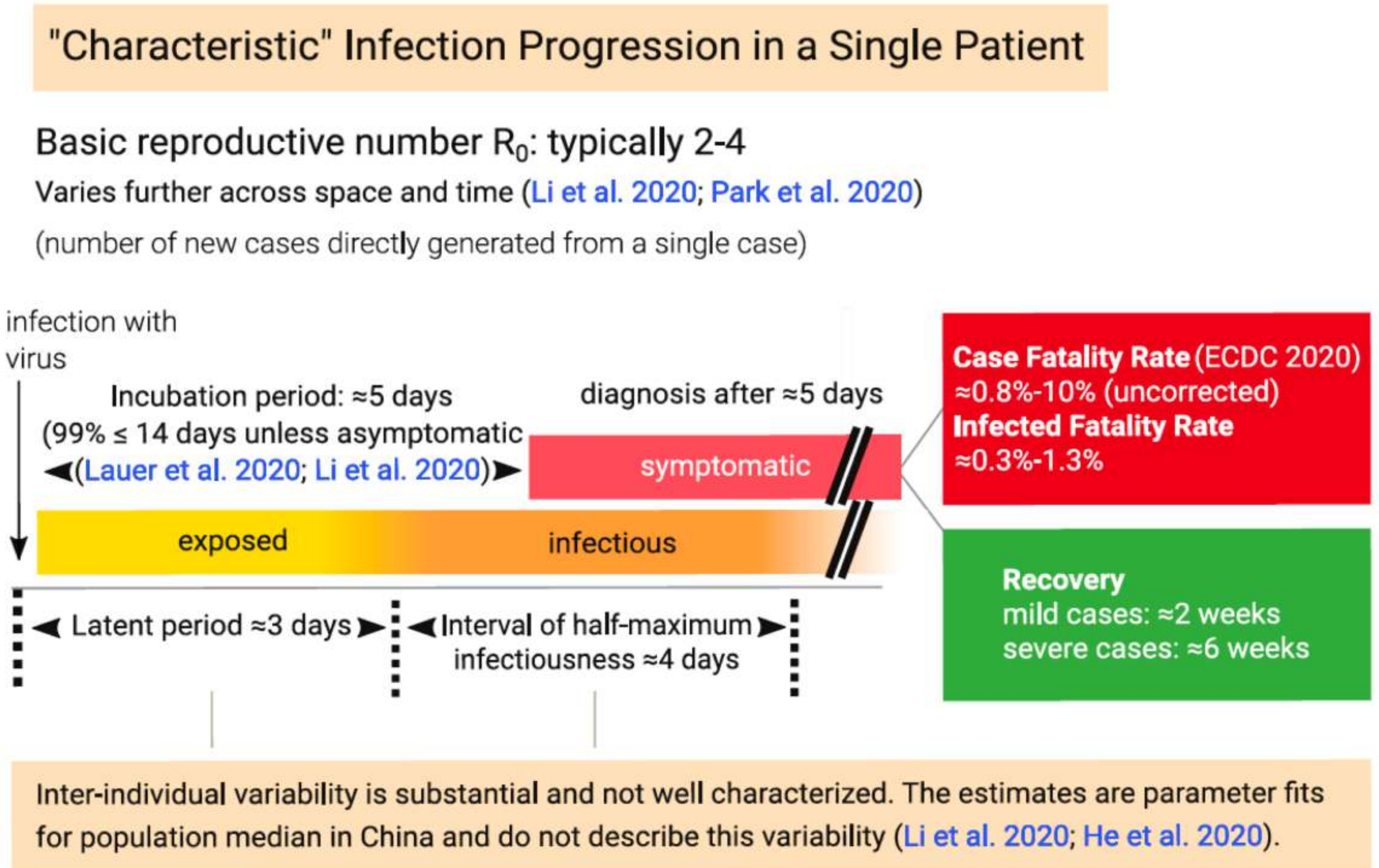


Figure 10.15 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Spread of infectious diseases

Time course COVID-19



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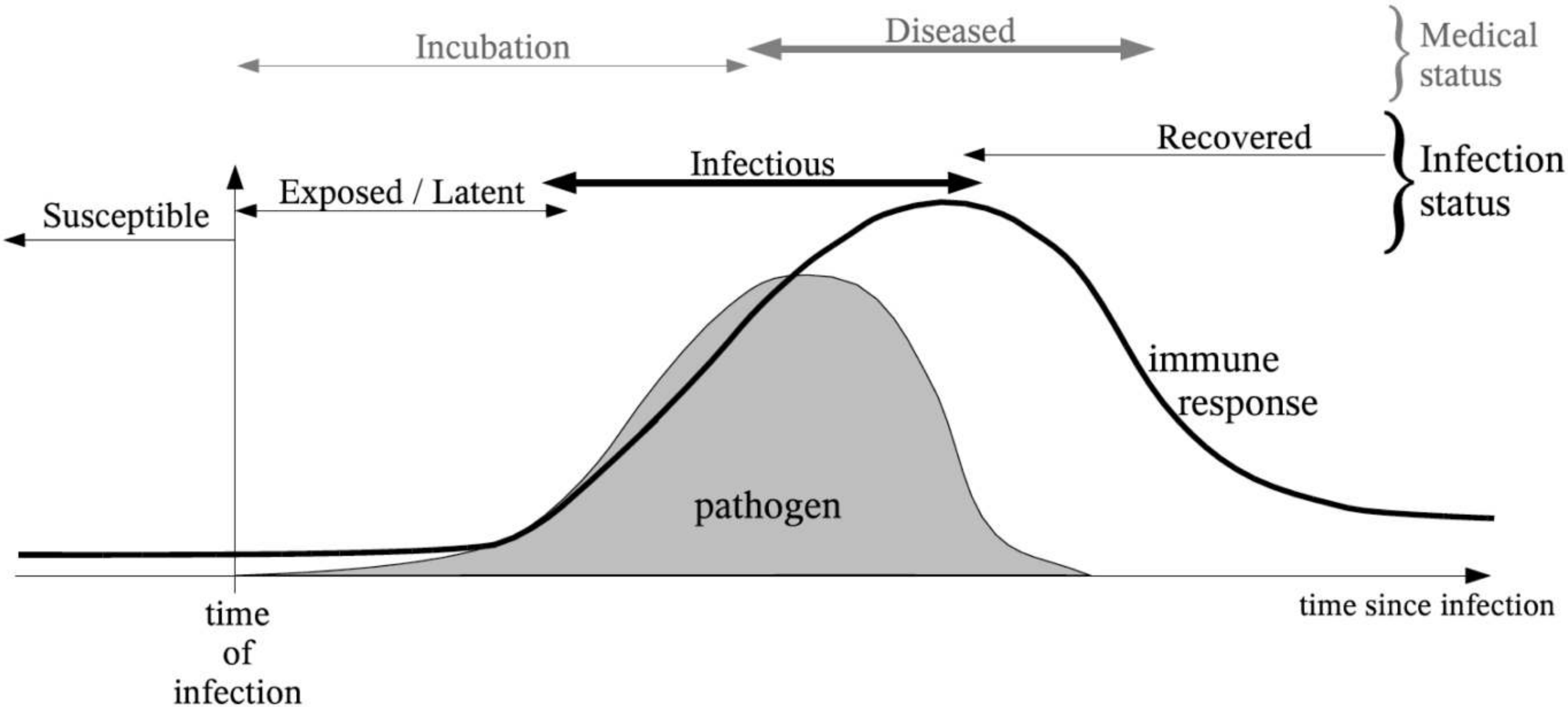
Infectious diseases

- Worldwide there are about 1,415 known human pathogens. Of these, around 15% are viruses and around 40% are bacteria.
  - Examples of bacterial infections (can be treated with antibiotics): plague (Pest), leprosy (Lepra), tuberculosis, typhus, syphilis
  - Examples of viral infections (cannot be treated with antibiotics): influenza, smallpocks, polio, measles, SARS-CoV-2
  - Malaria and sleeping sickness are caused by unicellular eukaryotes; drugs against these cells are usually not effective against bacteria or viruses
- Of the 1,415 known human pathogens, 60% are zoonotic (originated from animals) and can survive in an animal reservoir. Here only a few sources:
  - Plague: rats (Roman empire, middle ages), horses (East European steppe)
  - Leprosy: squirrels (in England)
  - Tuberculosis: seals (transmitting between Europe and the Americas)
  - Malaria, sleeping sickness: mosquitos (in Europe until 20th century)
  - Influenza: birds, pigs
  - HIV, Ebola, Zika: primates
  - COVID-19: bats, pangolins
- An epidemic with one of these pathogens usually has a very stereotypical time course.

Typical time course of an epidemic



Modeling infectious diseases in humans and animals, Matt J Keeling and Pejman Rohani, Princeton University Press 2008

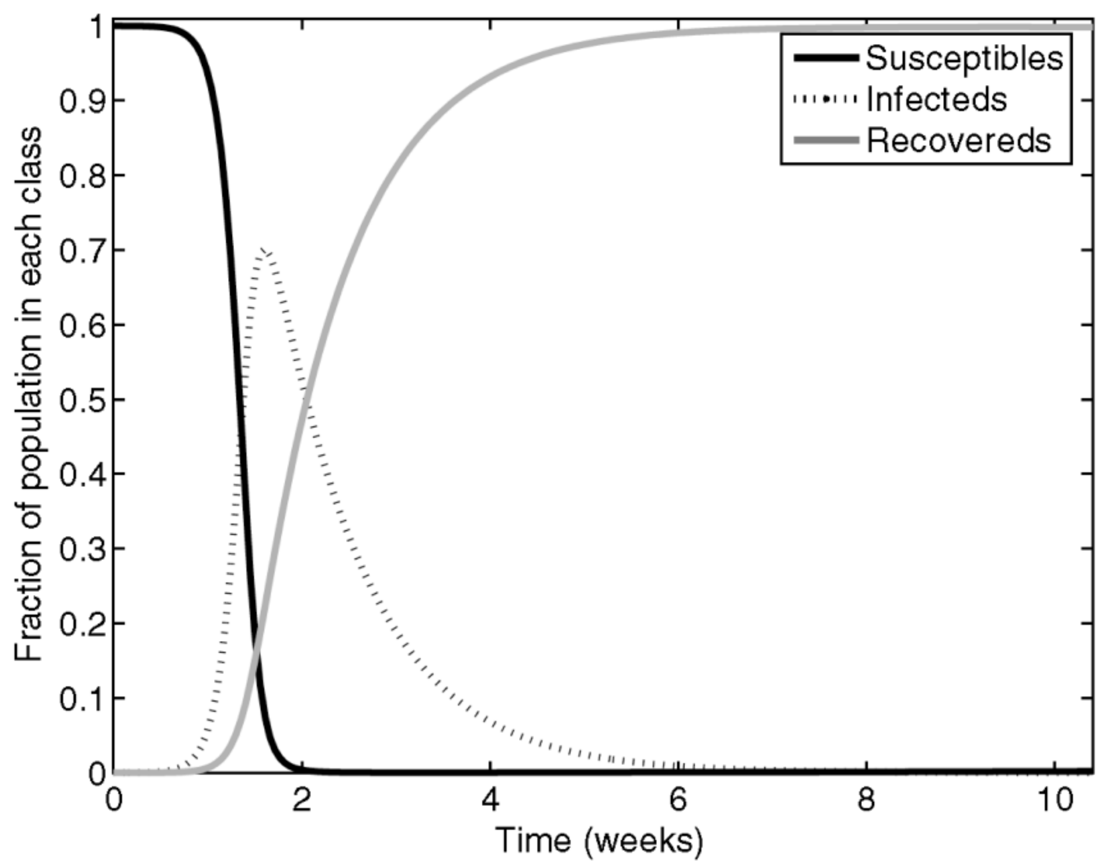
SIR-model

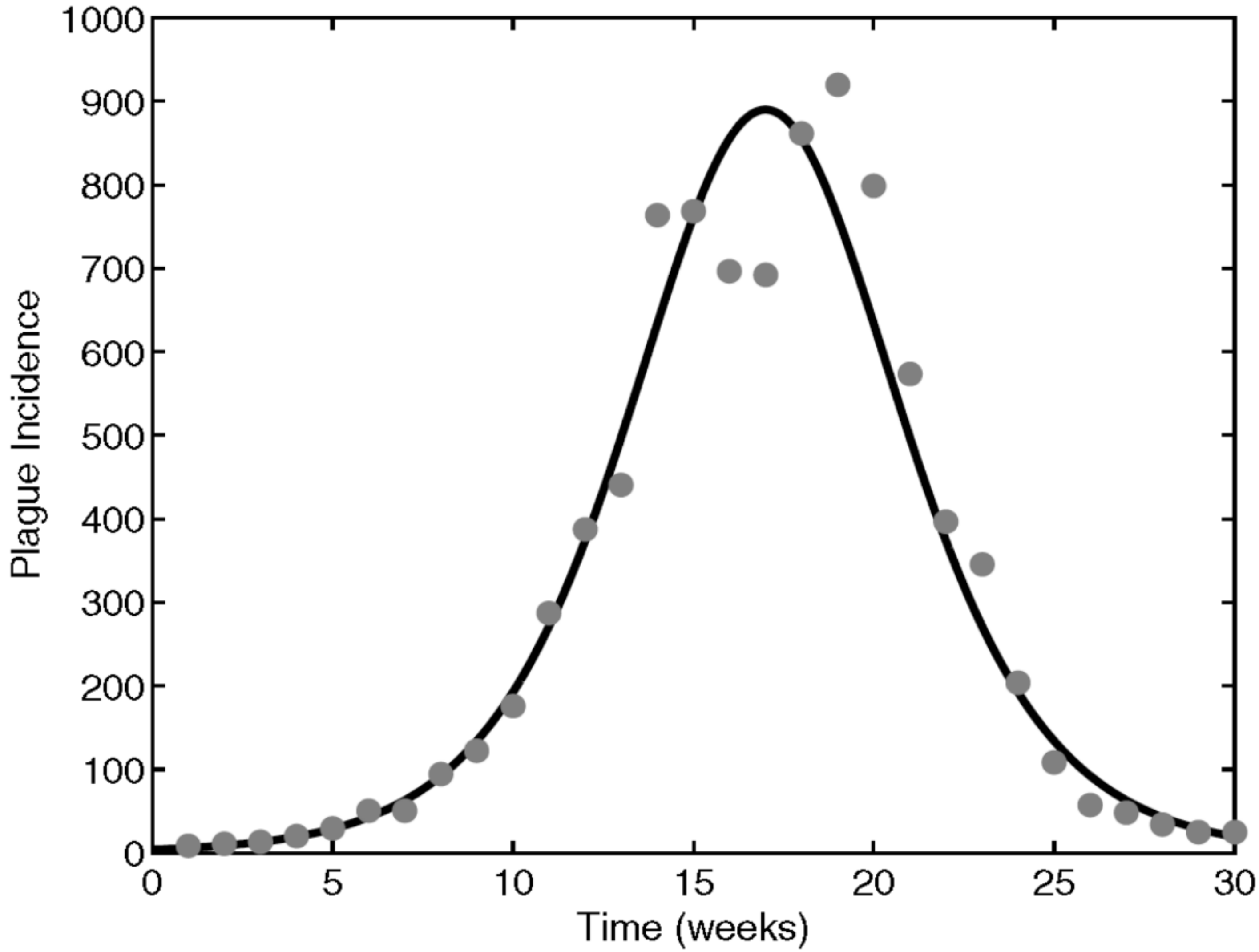
$$\frac{dS}{dt} = -\beta SI,$$

$$\frac{dI}{dt} = \beta SI - \gamma I,$$

$$\frac{dR}{dt} = \gamma I.$$

Kermack and
McKendrick 1927



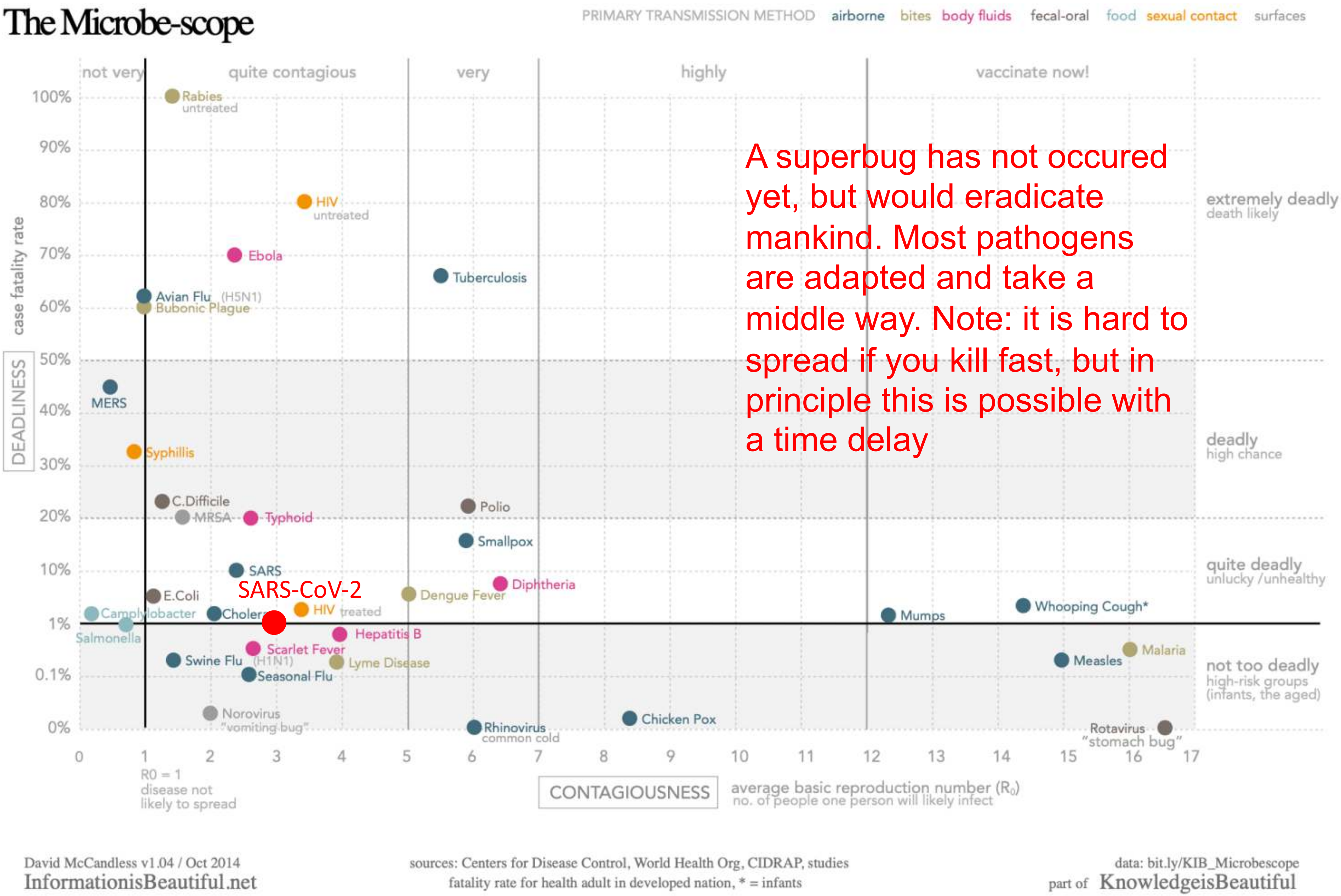


The epidemic curve. The filled circles represent weekly deaths from plague in Bombay from December 17, 1905 to July 21, 1906. The solid line is Kermack and McKendrick's approximate solution given by $dR/dt = 890 \operatorname{sech}^2(0.2t - 3.4)$.

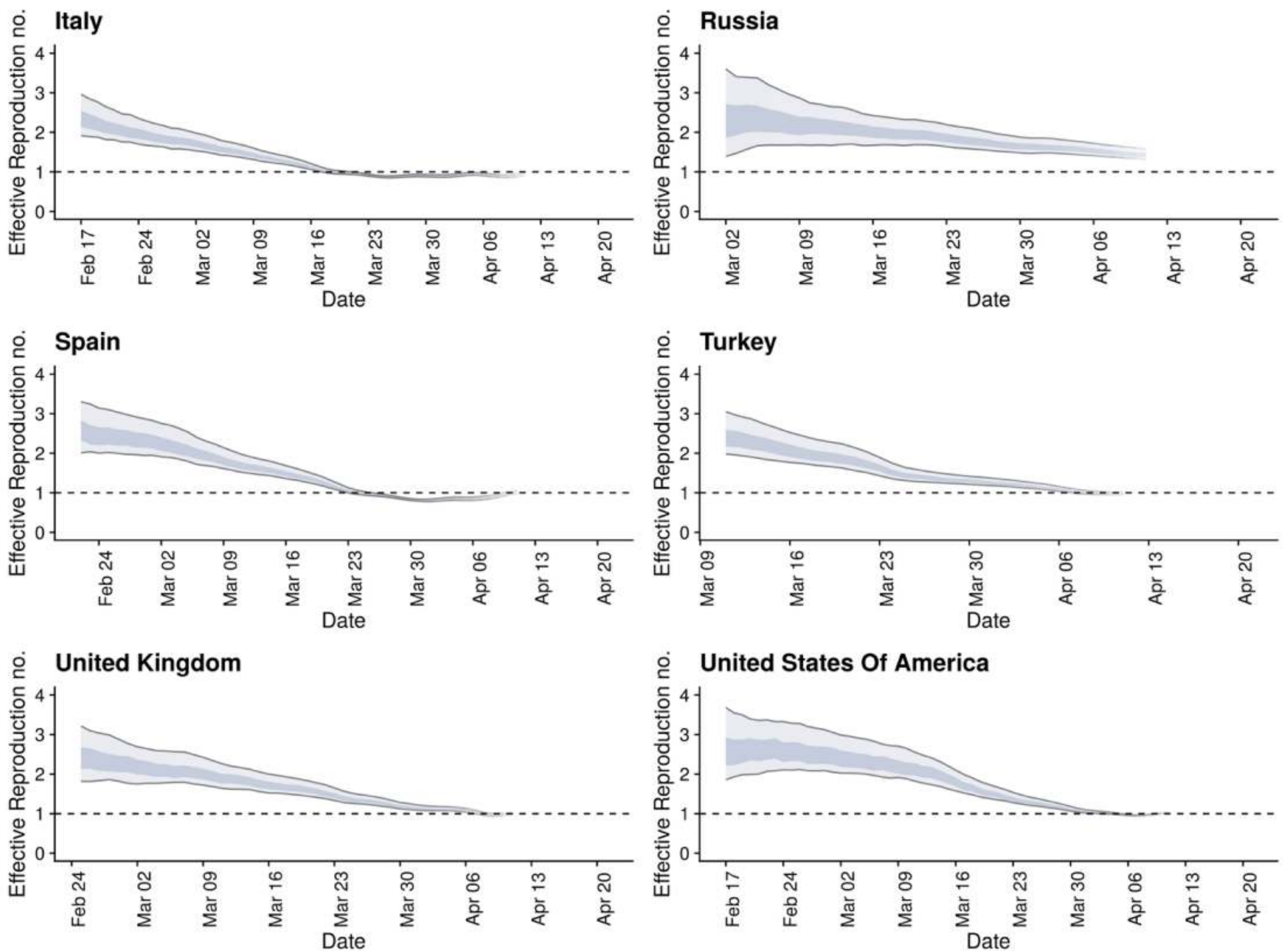
Basic reproductive number $R_0=\beta/\gamma$

Host	Disease	R_0	Data origin	Reference
Human	Measles	13-18	UK, USA, CAN	Anderson & May
	Pertussis	5-18	UK, USA, CAN	Anderson & May
	Scarlet Fever	5-8	USA	Anderson & May
	Mumps	7-14	USA, UK, NL	Anderson & May
	Polio	5-7	USA, NL	Anderson & May
	HIV	2-5	CH, UK	Anderson & May
	HCV	1.2-2.9	Africa, Asia	Pybus et al.
	Ebola	1.3-1.8	Congo, Uganda	Chowell et al.
	Influenza (1918)	3	USA	Mills et al.
	SARS	2-3	Hongkong	Riley et al.
Cattle	BSE	14	UK	de Koeijer et al.
Cattle	FMD	8	UK	Ferguson et al.
Canids	Rabies	1-2	Global	Hampson et al.

Comparison of infectious diseases

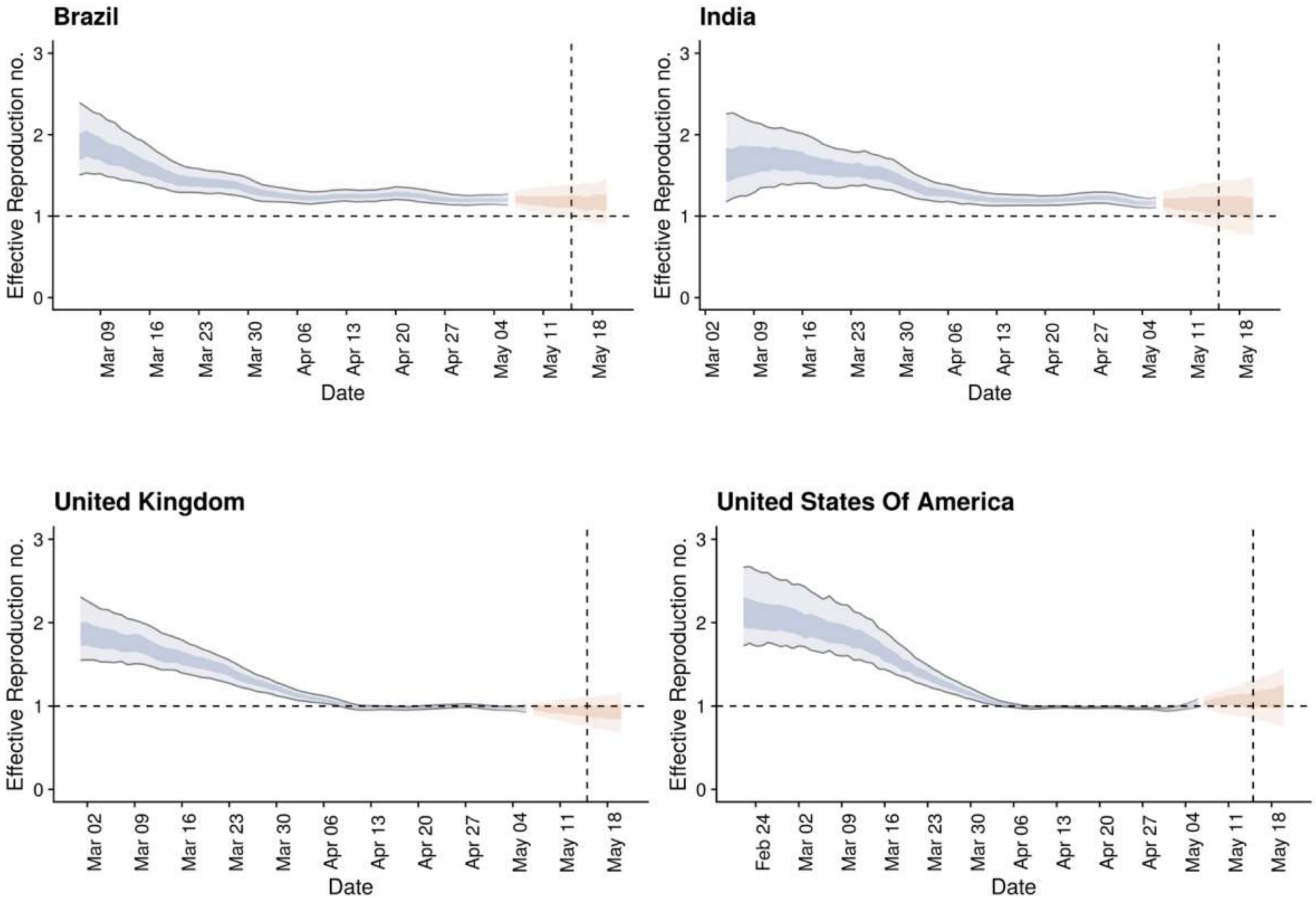


SARS-CoV-2 – reproductive number



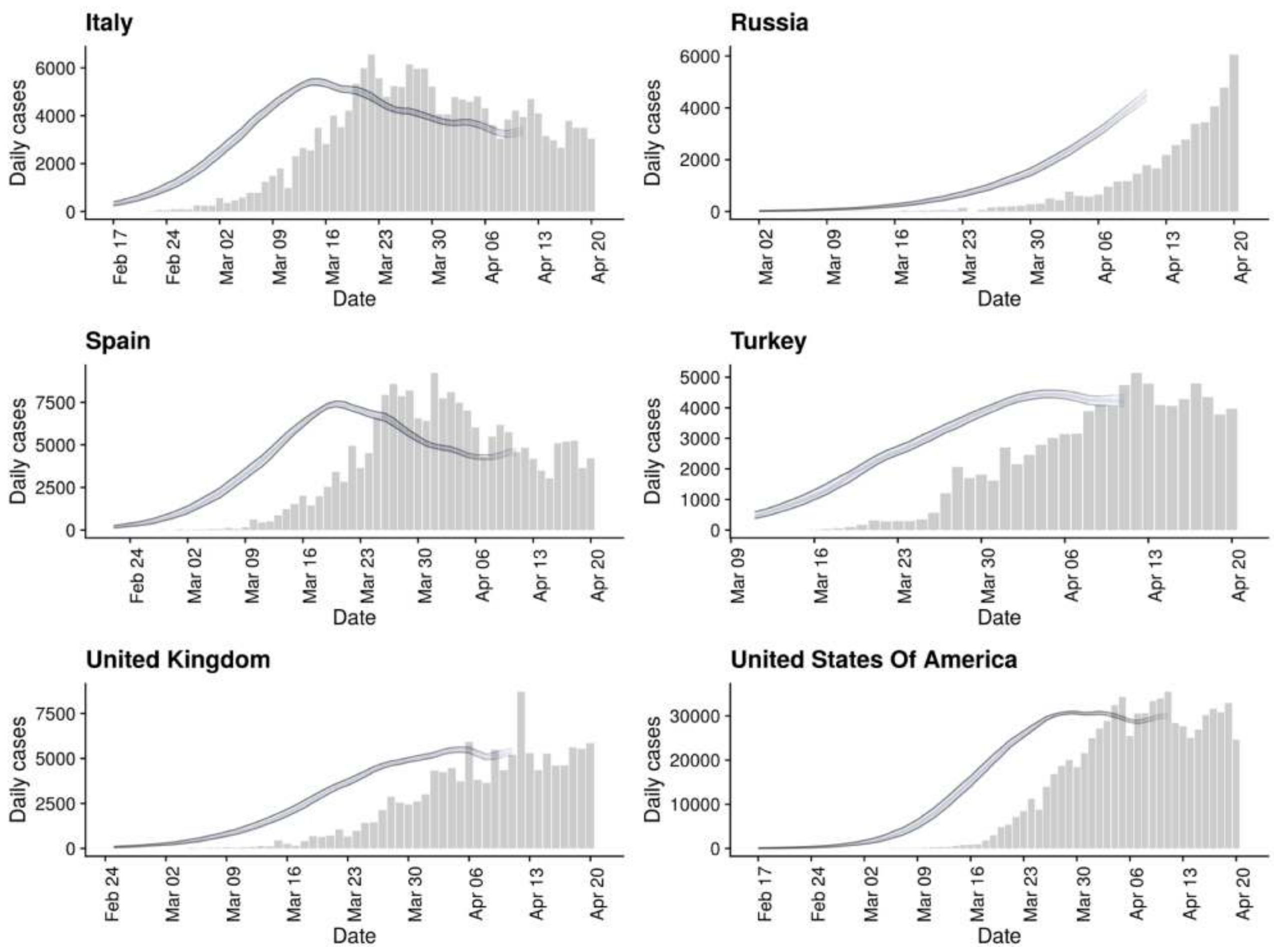
https://epiforecasts.io/covid/posts/global/, April 22 2020

SARS-CoV-2 – reproductive number



https://epiforecasts.io/covid/posts/global/, May 16 2020

SARS-CoV-2 – dates of infection



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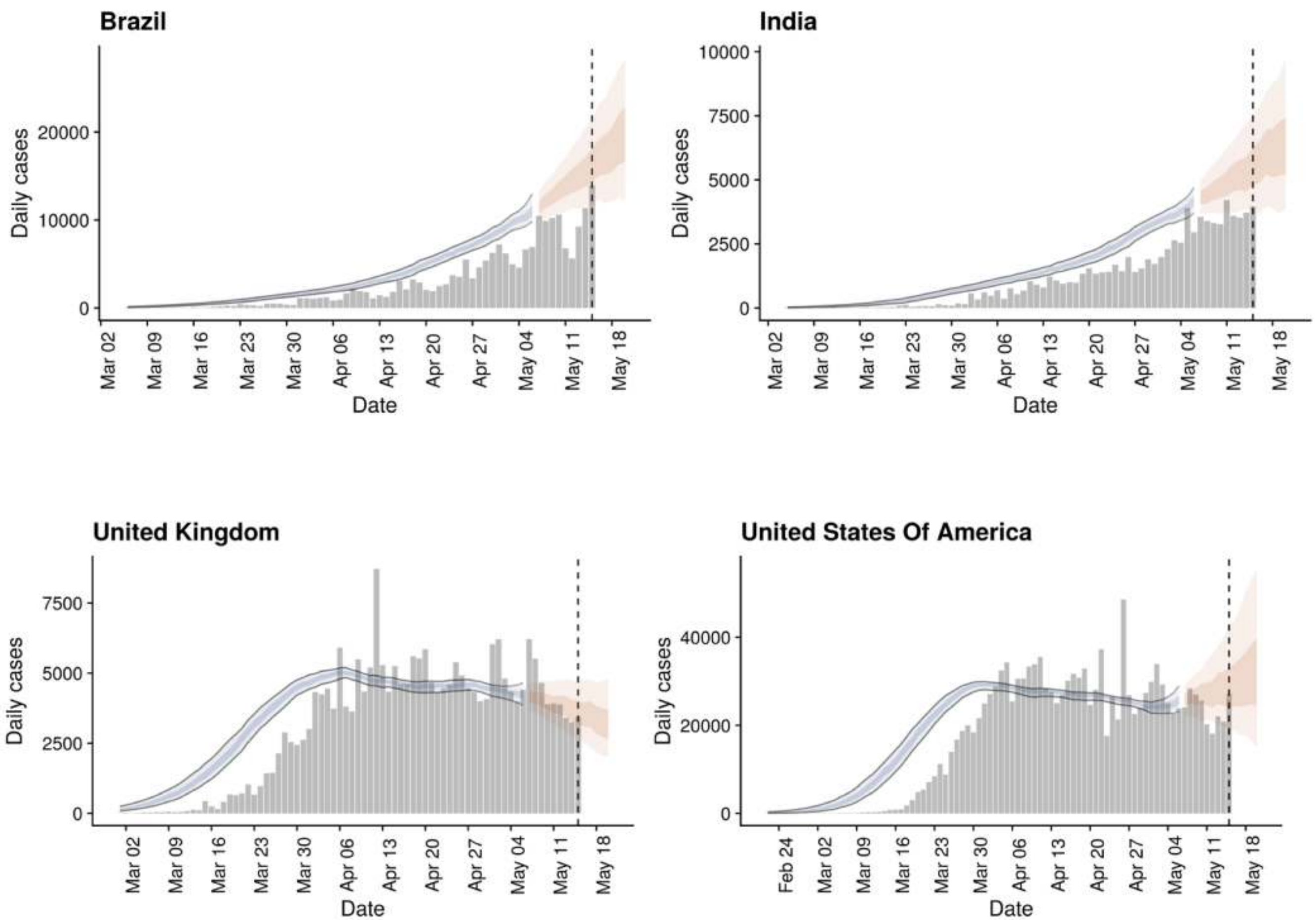
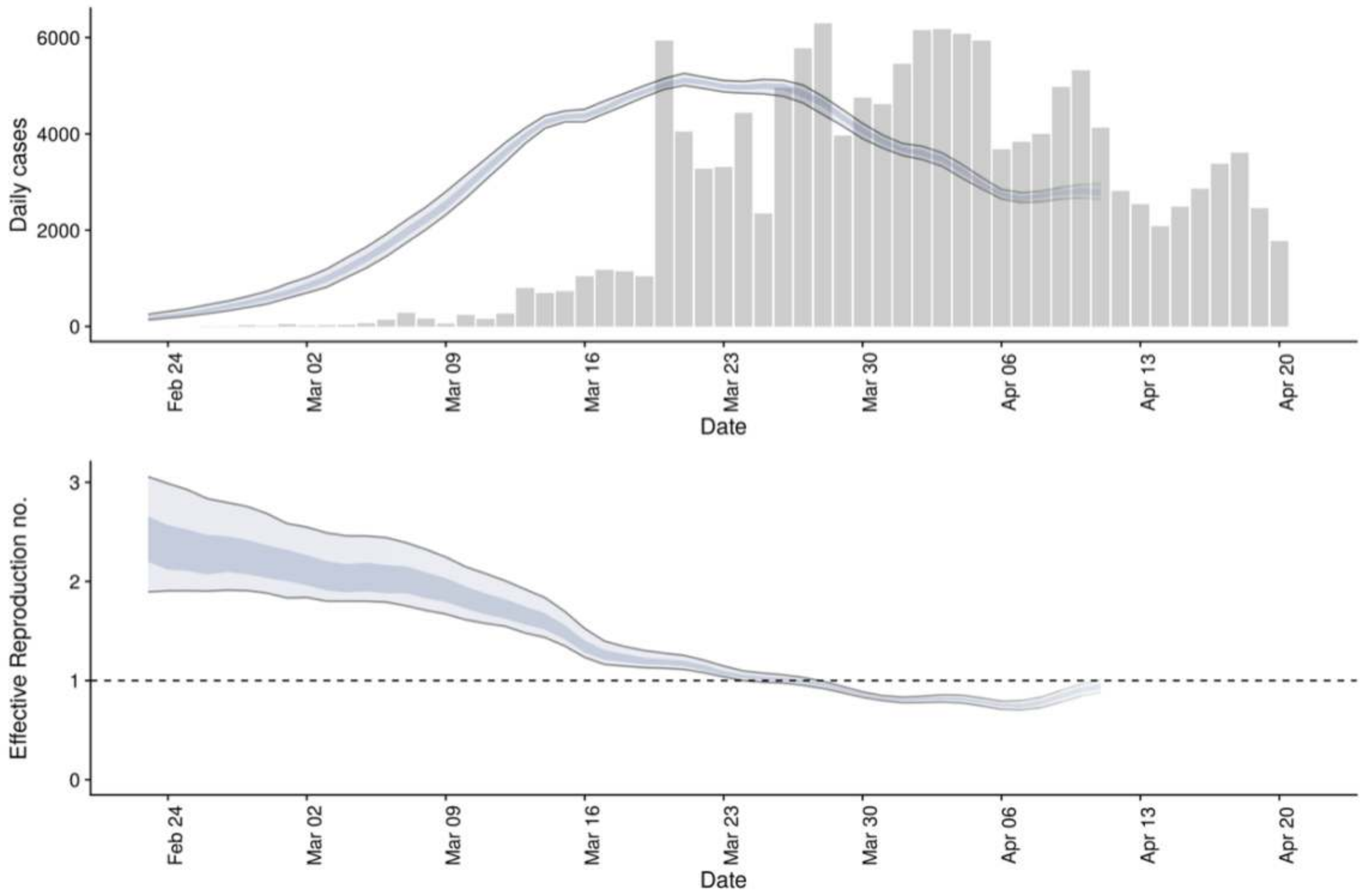
SARS-CoV-2 – dates of infection



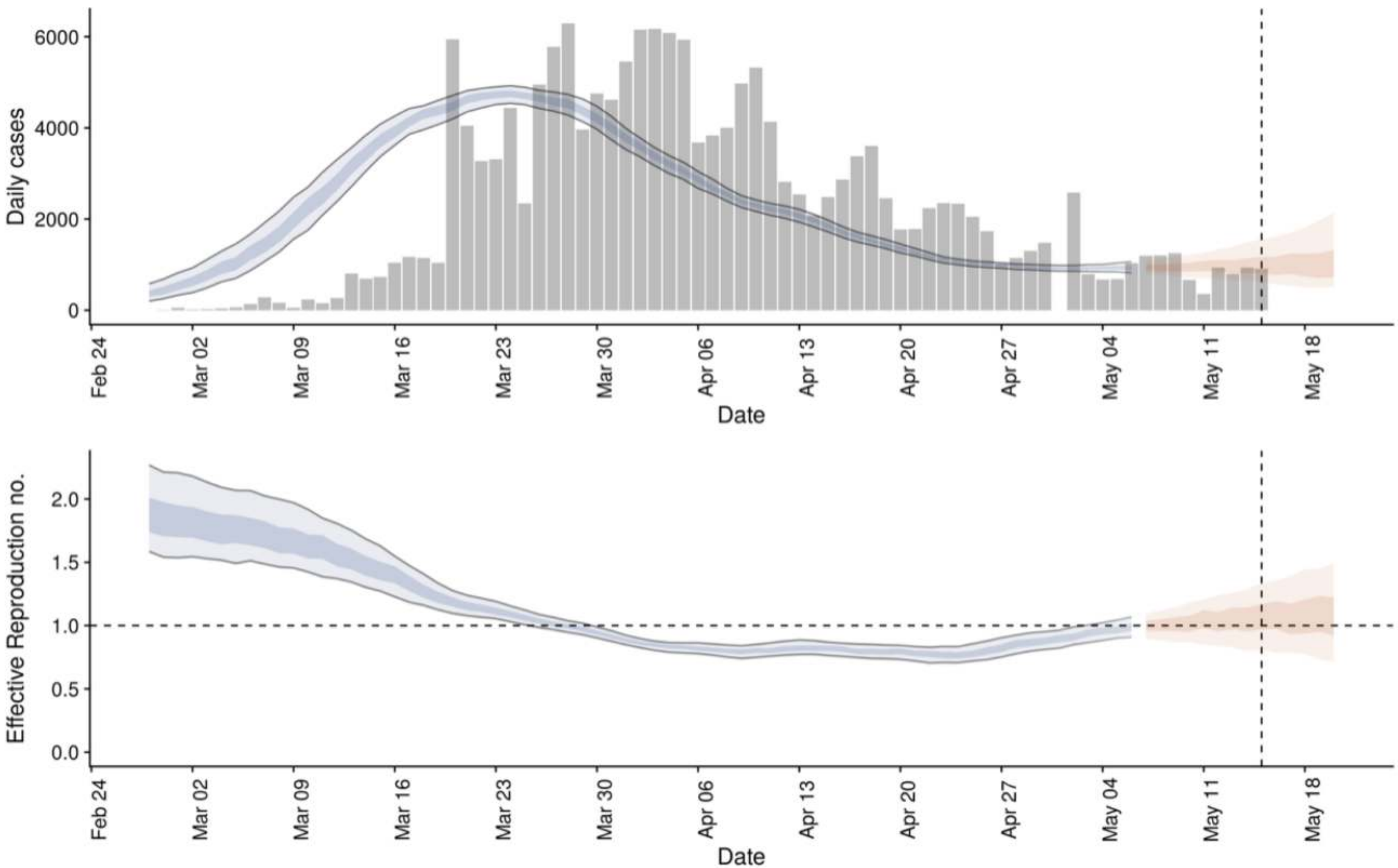
https://epiforecasts.io/covid/posts/global/, May 16 2020

SARS-CoV-2 – Germany



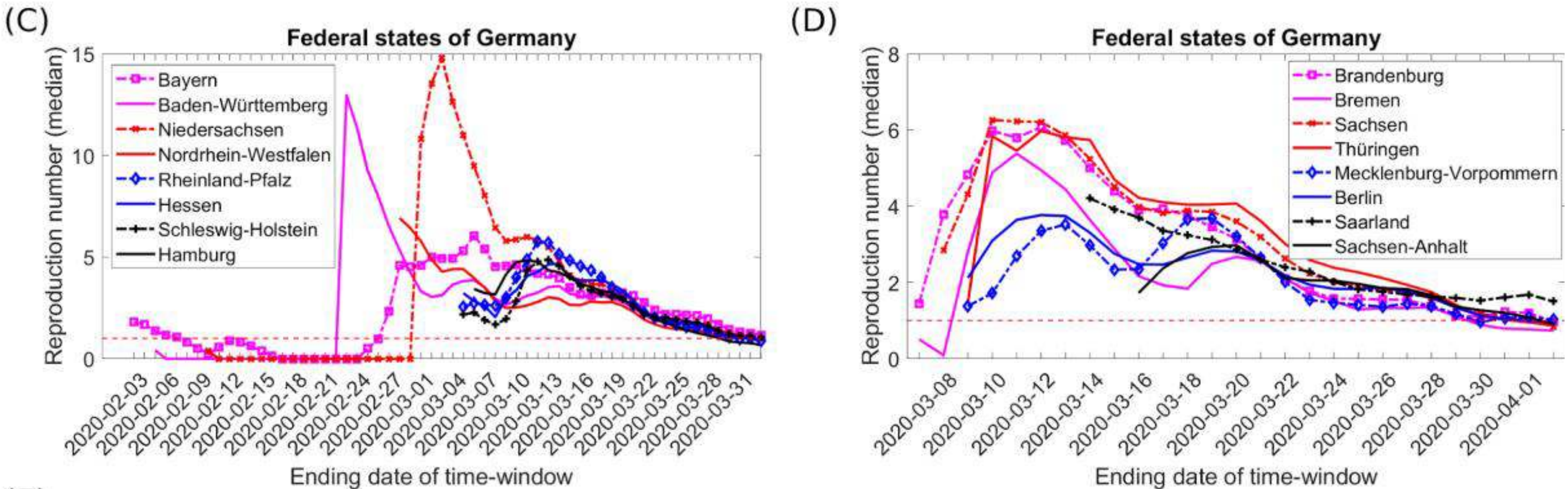
https://epiforecasts.io/covid/posts/global/, April 22 2020

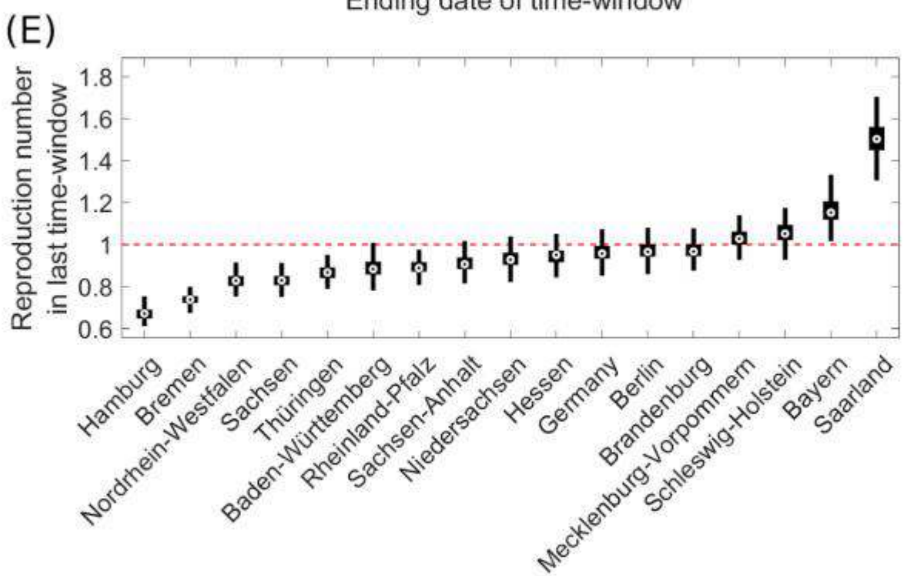
SARS-CoV-2 – Germany



https://epiforecasts.io/covid/posts/global/, May 16 2020

SARS-CoV-2 in German federal states

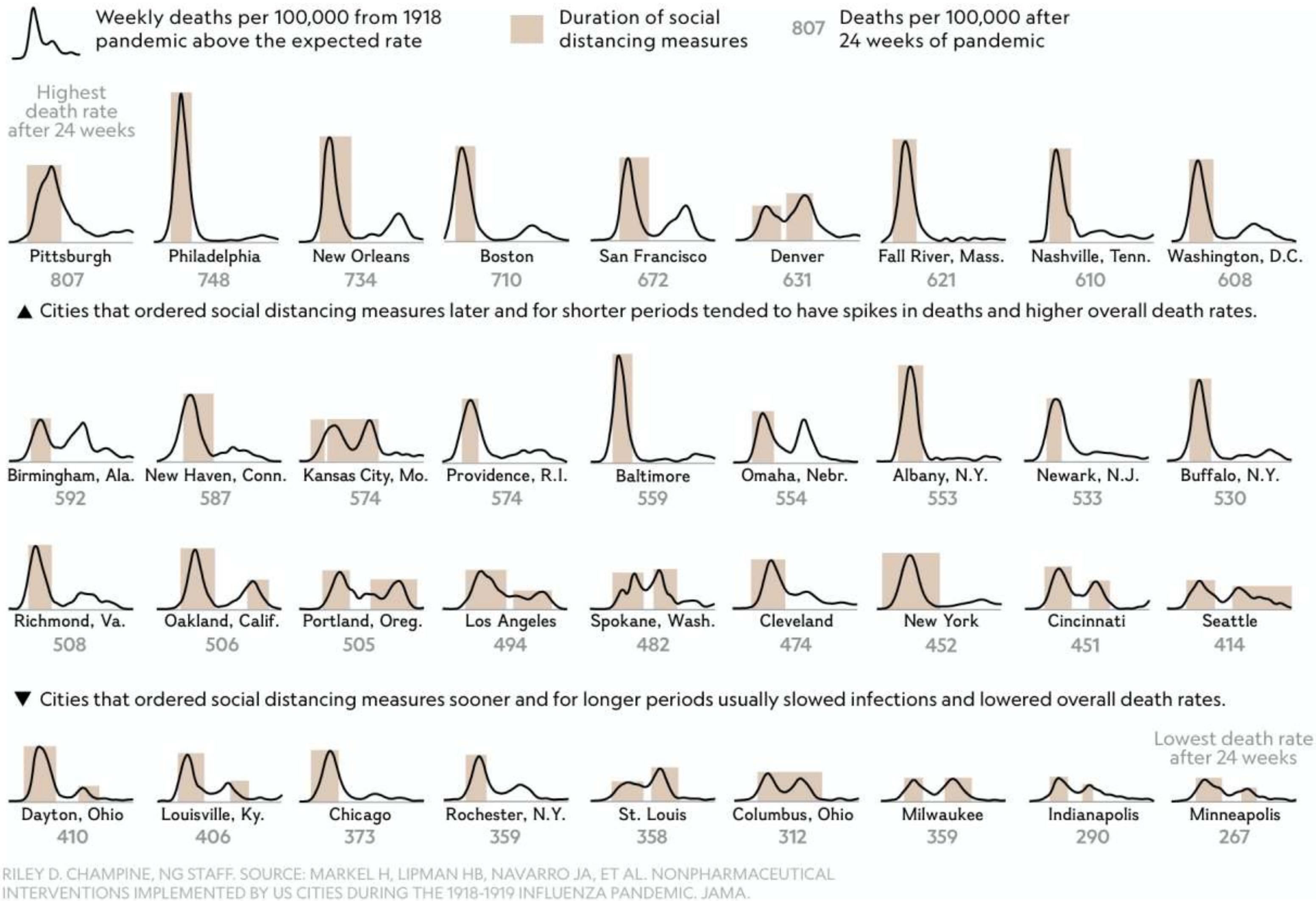




https://www.medrxiv.org/content/10.1101/2020.04.04.20053637v1

April 2020

The second wave



https://www.nationalgeographic.com/history/2020/03/how-cities-flattened-curve-1918-spanish-flu-pandemic-coronavirus/

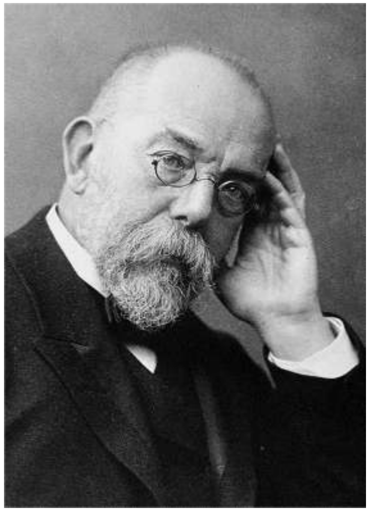
Some history

History of virology

- **Edward Jenner** in 1796 observed that milkmaids exposed to cowpox didn't contract smallpox (Pocken) and vaccinated children using the body fluid of infected patients. Smallpox remains the only disease to date that has been eradicated world-wide. No mechanistic insight yet.
- **Louis Pasteur** (1822–1895): germ theory of disease, vaccination against rabies (Tollwut) caused by the virus RABV, importance of hygiene and sterility
- **Robert Koch** (1843–1910): identified the bacteria causing tuberculosis, cholera and anthrax, importance of hygiene and sterility, Nobel prize 1905

Jenner

Pasteur

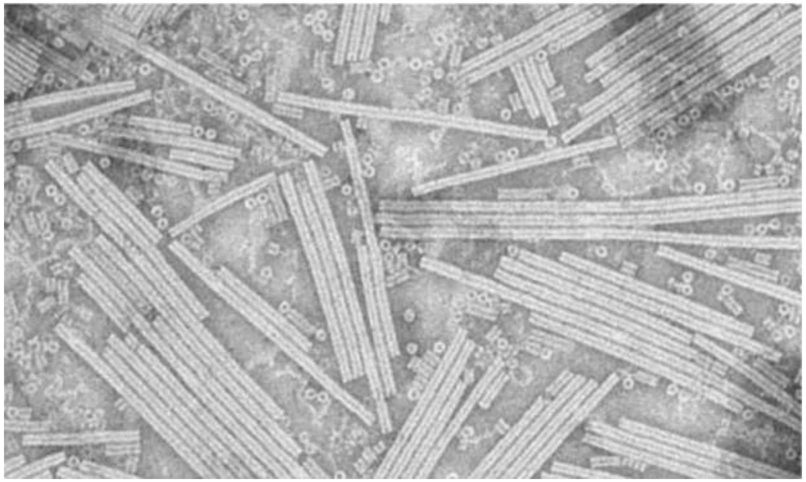


Koch

Wikipedia

Adolf Mayer 1882 realized that the tobacco mosaic disease is not caused by a bacterial or fungal agent. **Dimitri Ivanofsky** 1892 showed that it goes through the filters that retain bacteria. **Martinus Beijerinck** 1898 found that it replicated in plants, so it cannot be a toxin. He called it *contagium vivum luidum*, that is a contagious living liquid. The infectious agent was called *tobacco mosaic virus* (TMV), with „virus" just meaning „slimy liquid or poison" (for a long time also called „filterable agents"). 1935 TMV was crystallized for the first time; it was a rod containing proteins and RNA. The first electron micrograph of TMV was taken in 1939 (method invented by Ernst Ruska in Berlin 1937), finally proving directly that it is a particle and not a liquid. 1956 it was shown that the RNA in TMV is its genetic material (part of the revolution of molecular biology, discovery of the genetic code).

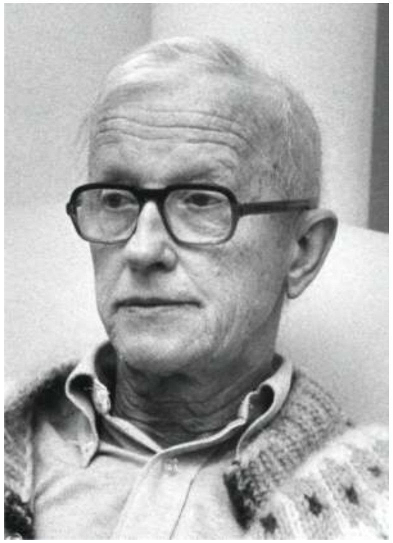
tobacco mosaic disease

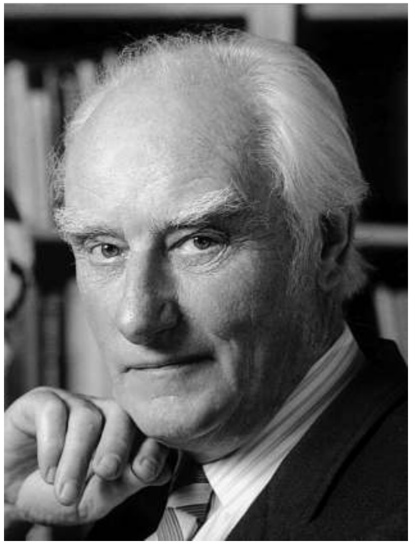


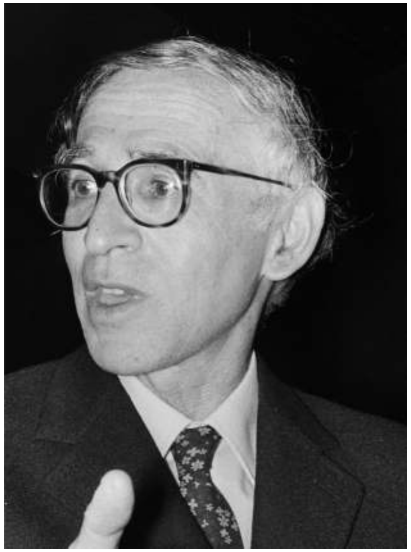
tobacco mosaic virus (TMV)

Wikipedia

- From 1900 onwards, many other viruses were identified, including the first **human virus** in 1901 (yellow fever virus). The 1918 influenza pandemics (Spanish flue, H1N1) killed 50 million people and demonstrated the role of social contacts.
- **Felix d'Herelle** had found in 1915 that some infectious agent (*bacteriophages*) can kill bacteria (phages are DNA-viruses attacking bacteria). Around 1940, the German theoretical physicist **Max Delbrück** and the Italian geneticist **Salvador Luria** started the phage group at Cold Spring Harbor Laboratory. In 1952 **Alfred Hershey** showed that the genetic material is DNA (the structure of DNA was solved in 1953 by Watson and Crick). Nobel Prize 1969 to Delbrück, Luria and Hershey.
- **Francis Crick** (a theoretical physicist) and **Jim Watson** 1956 suggest that virus capsids are made from one or a few species of identical protein subunits, explaining their spherical and cylindrical shapes. **Donald Kaspar** and **Aaron Klug** developed the crystallographic theory for spherical virus capsids and Aaron Klug verified it with electron microscopy and X-ray diffraction (Nobel Prize 1982).

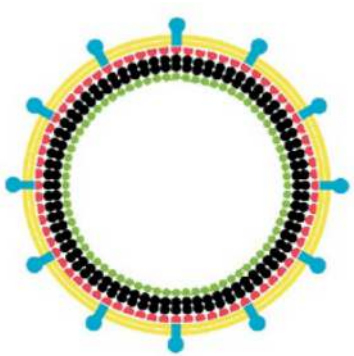

Delbrück

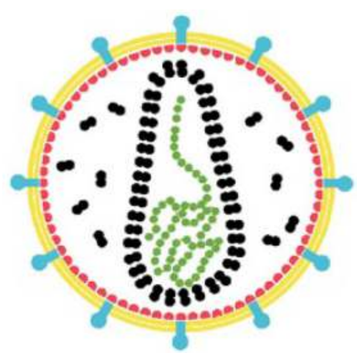

Crick

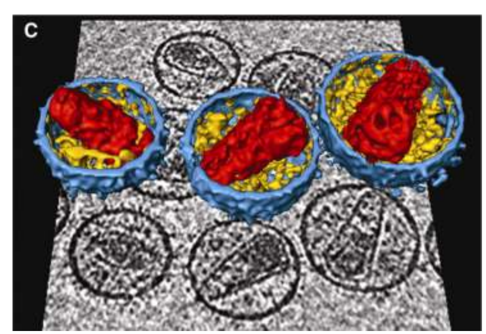

Klug

Wikipedia

- 1957 the anti-viral defense molecule **interferon** was discovered, showing that our immune system is in a constant fight against viruses. Some viruses lead to an overreaction of the immune systems (*cytokine storm)*, possibly also by SARS-CoV-2.
- 1981 the **AIDS-epidemics** scattered the world. 1983 HIV was discovered as its causative agent (Nobel prize 2008).
- 1982 **Stanley Prusiner** discovered infectious proteins (*prions*, Nobel Prize 1997), so infectious liquids do exist after all. Prions are the causative agents of e.g. mad cow disease and Creutzfeldt-Jakob disease.
- 1966-1977: WHO-program to eradicate **smallpox** (no animal reservoir, requires person-to-person contact for its spread). Also **polio** has been eradicated from most of the world, but is still active in Nigeria, Afghanistan and Pakistan.
- Viruses can cause **cancer**: e.g. Epstein-Barr virus, hepatitis B virus, papilloma virus (Nobel Prize **Harald zur Hausen** 2008, shared with the one for HIV)
- Most emerging infections represent **zoonotic infections**: e.g. HIV, severe acute respiratory syndrome (SARS), West Nile virus, chikungunya virus, Zika virus, Ebola virus, H1N1 influenza 2009, SARS-CoV 2013, SARS-CoV-2 2019.







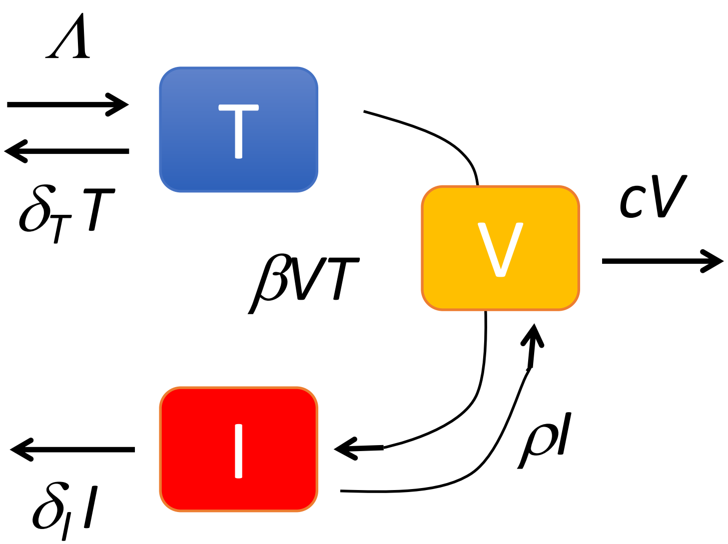
HIV-maturation – HG Kräusslich and J Briggs, Heidelberg

Mathematical methods and physical concepts in virology and infectious disease research

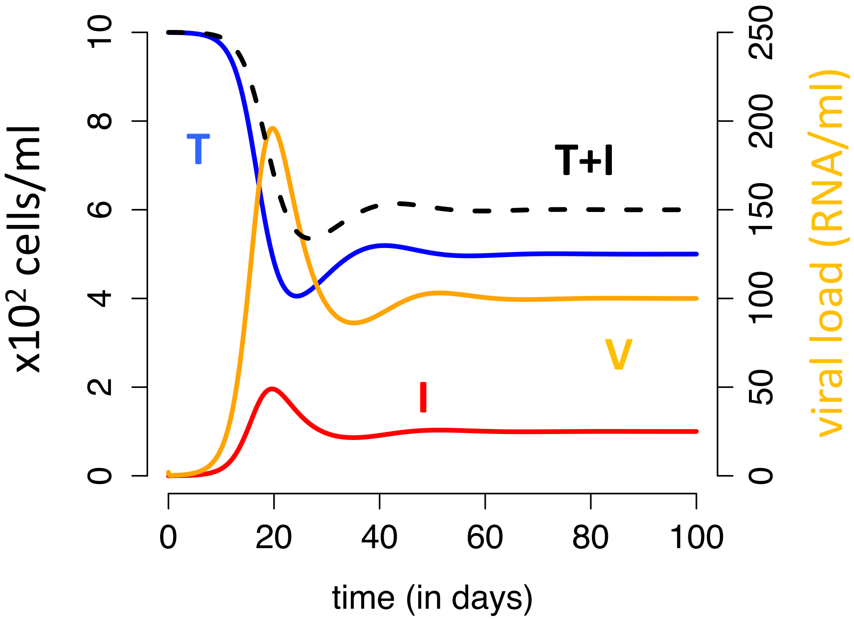
- **John Graunt** 1662 published "Natural and Political Observations on the Bills of Mortality", calculated mortality rates that correct for population sizes
- **Daniel Bernoulli** 1766, first mathematical model to investigate an infectious disease: Impact of variolation on smallpox mortality in France
- **William Heaton Hamer/ Roland Ross**, 1906/1908 – mass-action kinetics to describe the spread of infectious diseases. Mathematical description of the feedback of the infection on itself.
- **Kermack and Mc Kendrick** 1927, SIR-Model – Standard type of model to describe the spread of an epidemic. Various extensions have been developed.

The standard model of viral dynamics

The SIR-model within a patient



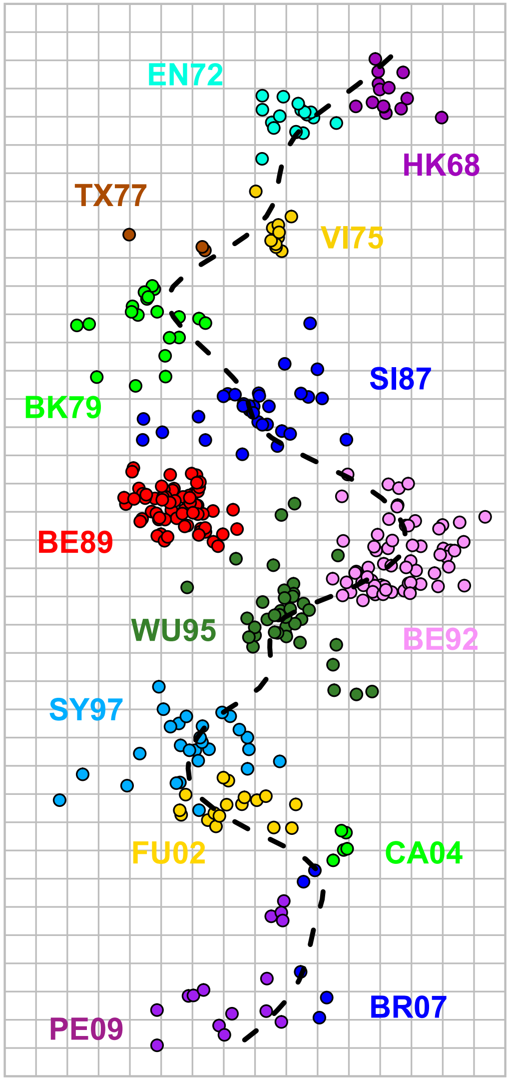
$$
\begin{aligned}
dT/dt &= \Lambda - \beta V T - \delta_T T \\
dI/dt &= \beta V T - \delta_I I \\
dV/dt &= \rho I - cV
\end{aligned}
$$



Translational research and application in clinical practice

- Identifying antiviral targets and predicting antibody binding affinities
- Prediction of viral evolution to determine vaccine strains for subsequent influenza seasons
- Determining timing and dosing of antiviral therapies
- Predicting the spread of epidemics and evaluating appropriate public health interventions

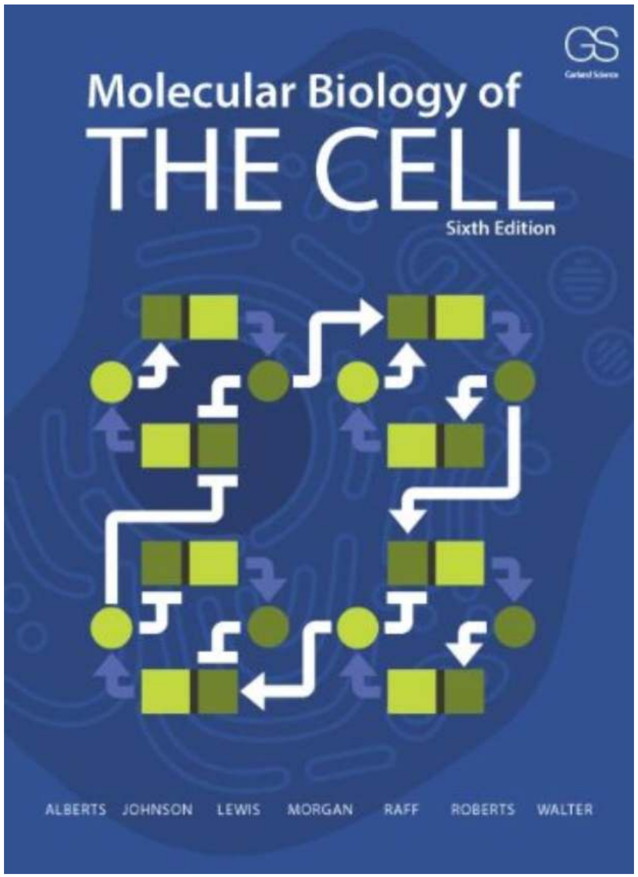
(Smith et al. Science 2005)



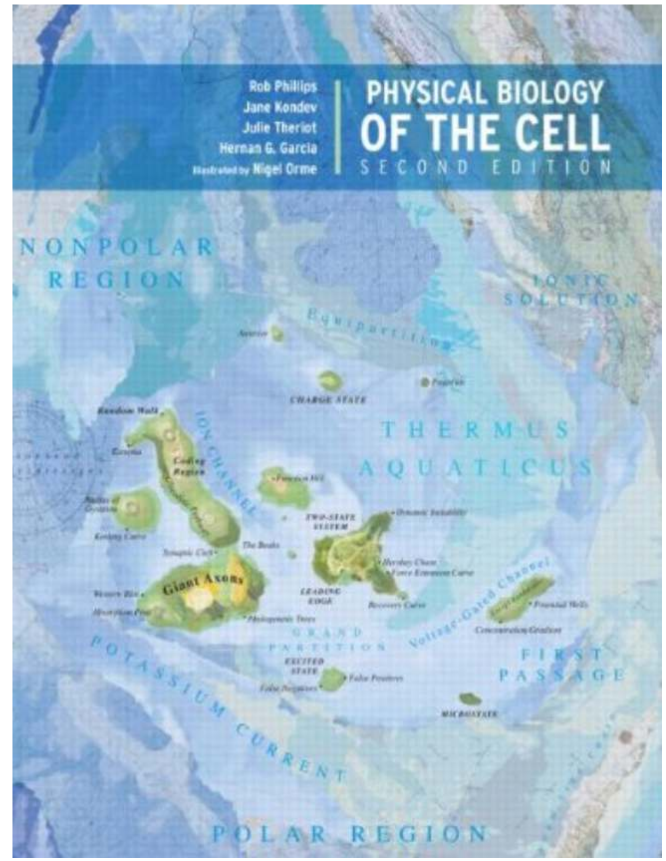
Evolution of Influenza A in antigenic space

Books

Recommended textbooks



Molecular Biology of the Cell,
Bruce Alberts et al., 6th ed.,
Garland 2014



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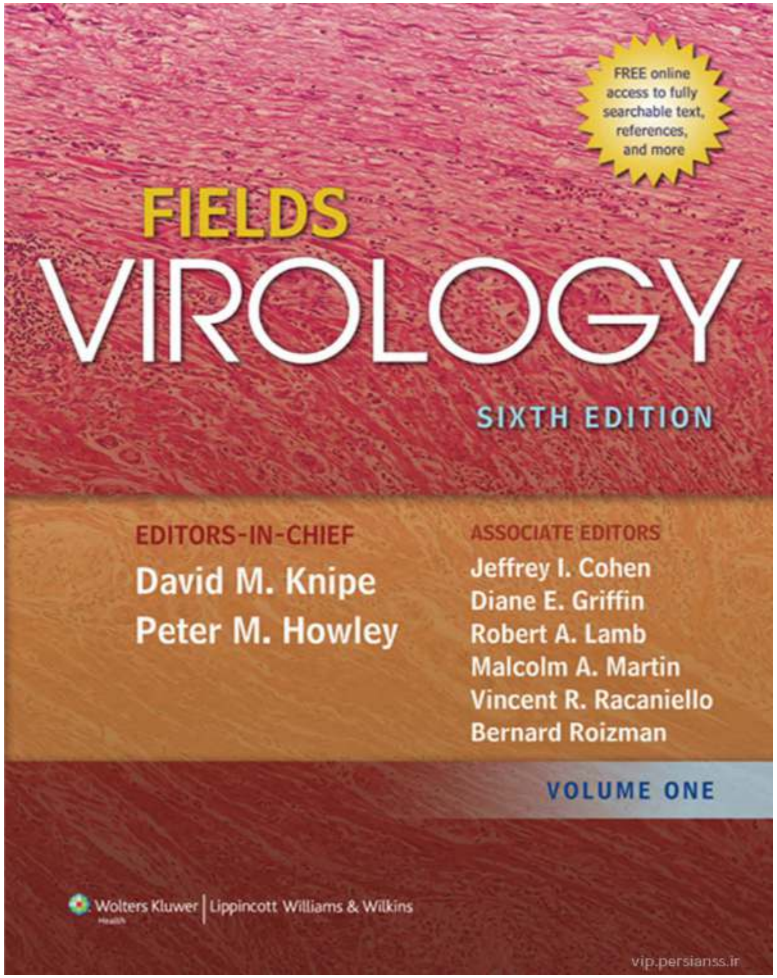

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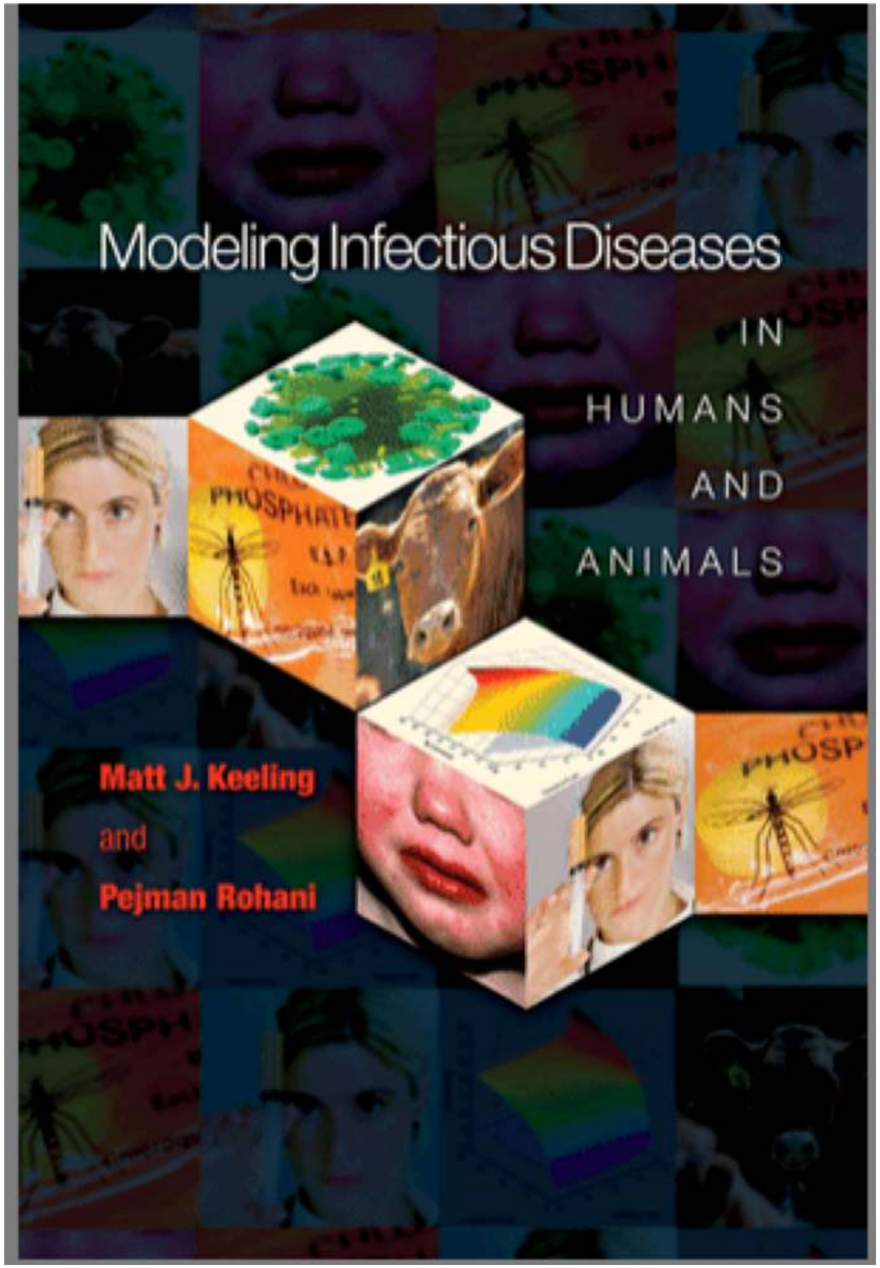

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The virus equations

non-enveloped virus
= genome + capsid

enveloped virus
= genome + capsid + membrane

genome

= (DNA or RNA) and (ss or ds)

protein production =
transcription + translation + folding