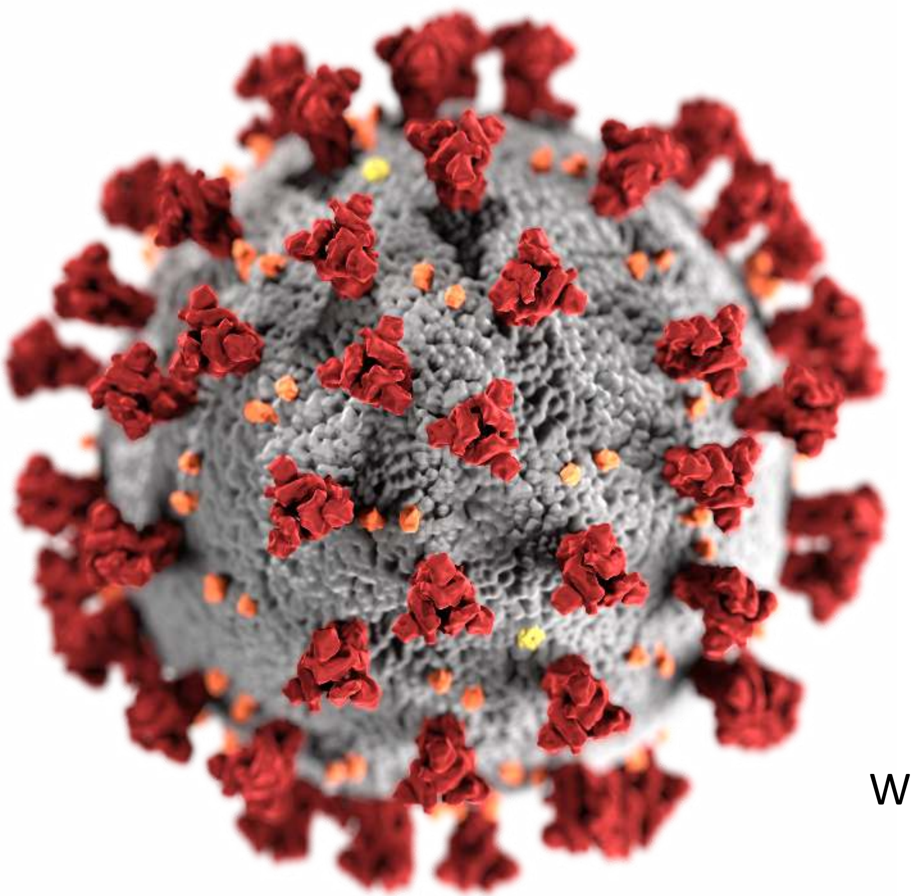
Physics of viruses

Frederik Graw, Ulrich Schwarz and Falko Ziebert

block seminar summer term 2021

introduction April 14 2020

SARS-CoV-2

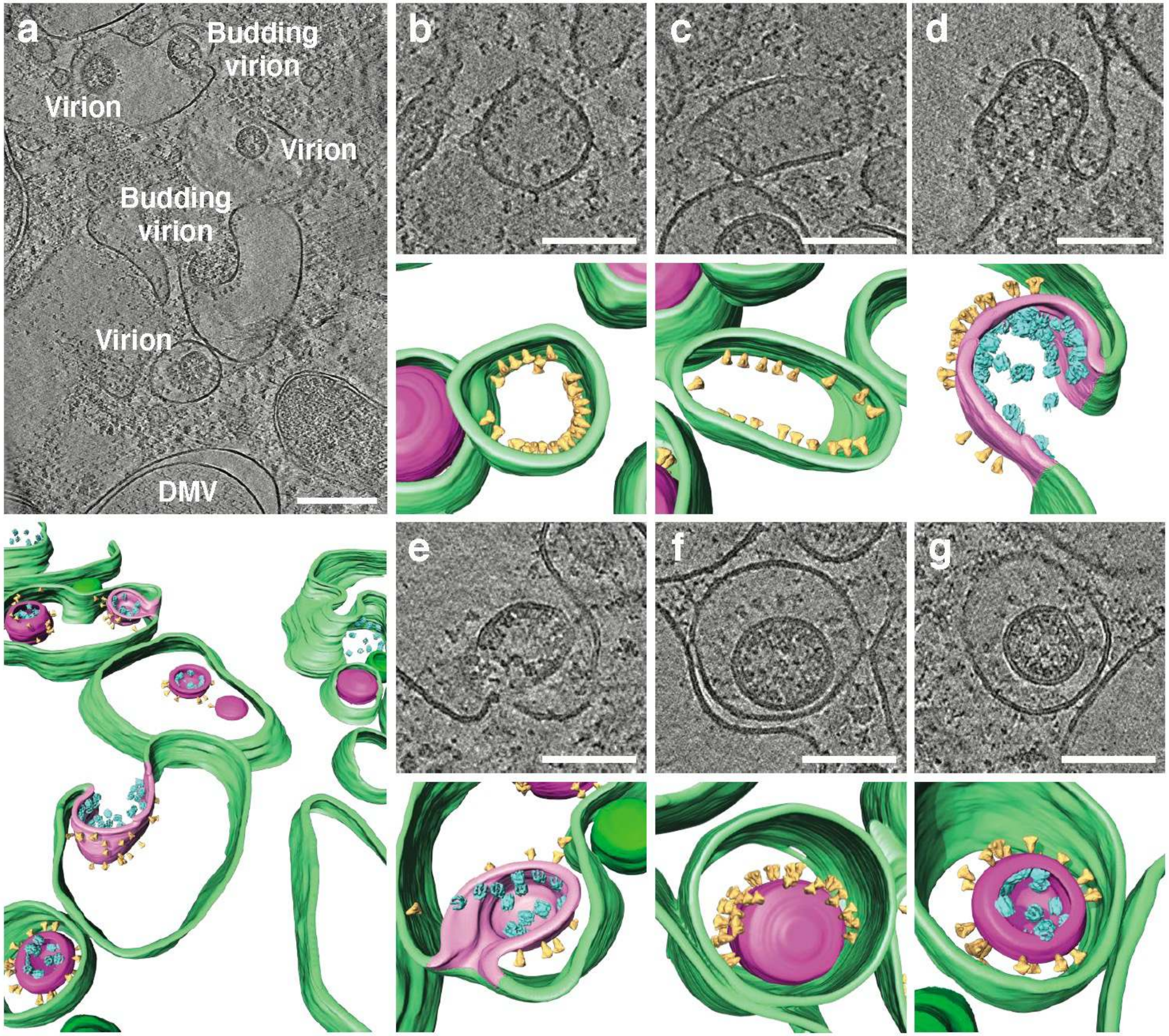


Wikipedia

Never before in the history of mankind has science reacted so quickly and so successfully to a new virus. 1.5 years after its appearance we know a lot about it and we have very successful vaccines targeting the spike proteins.

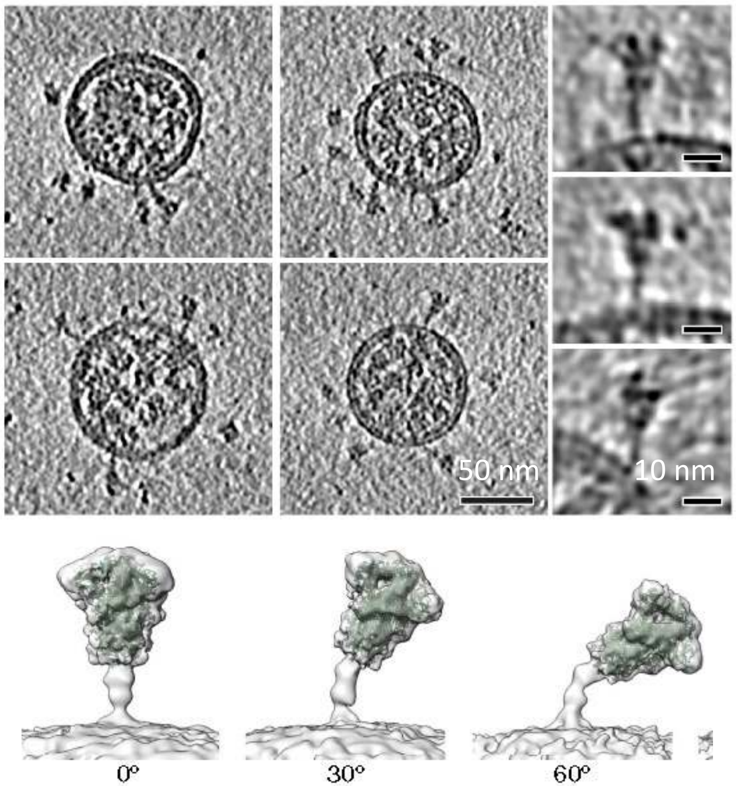
Illustrations by David Goodsell

In situ cryo-EM of SARS-CoV-2

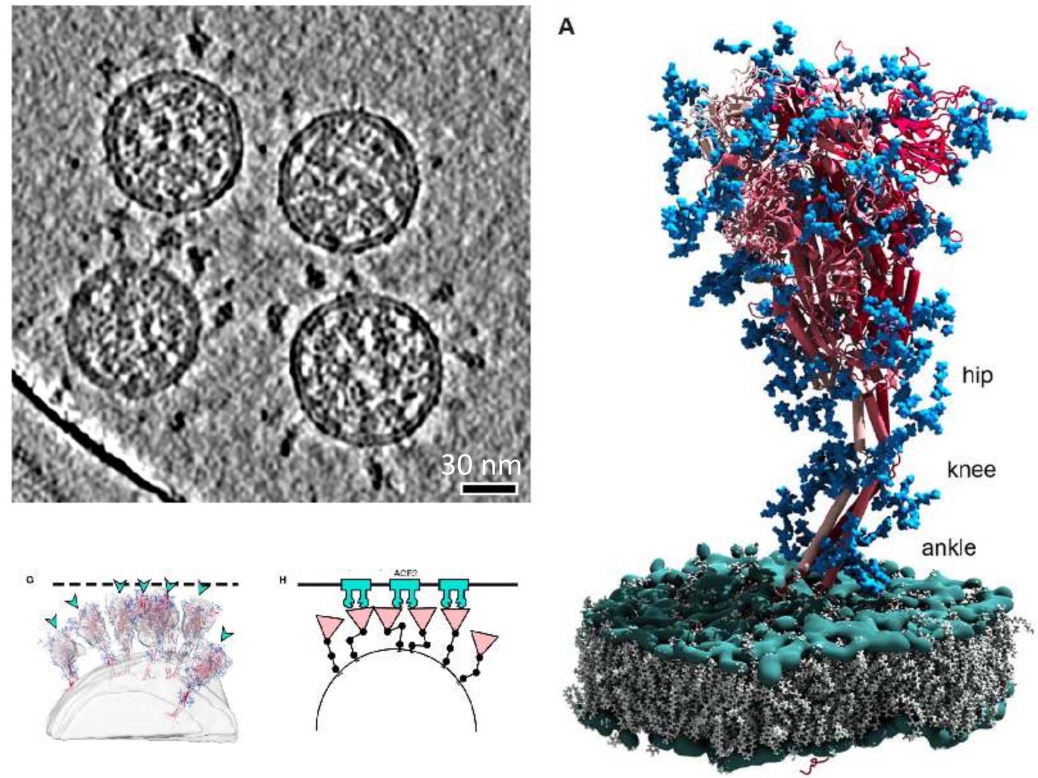


Chlandra group Nature Communications 19.11.2020
Cf. Bartenschlager group Cell Host Microbe 12.11.2020

Cryo-EM of SARS-CoV-2 spikes



Briggs group Nature 17.8.2020

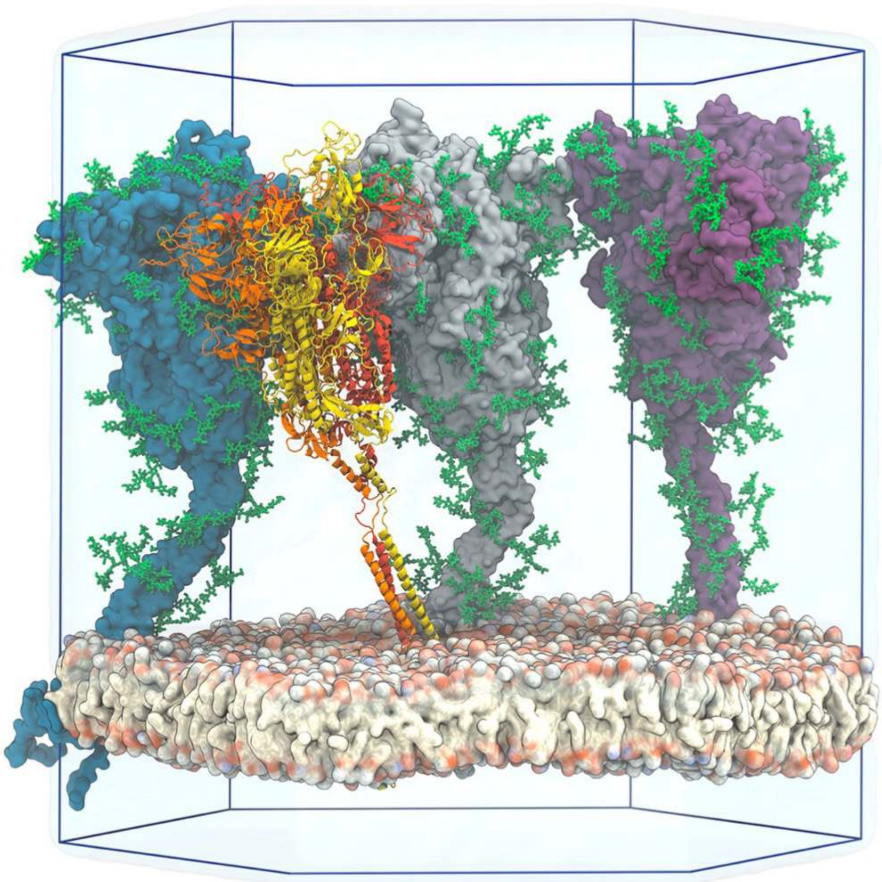


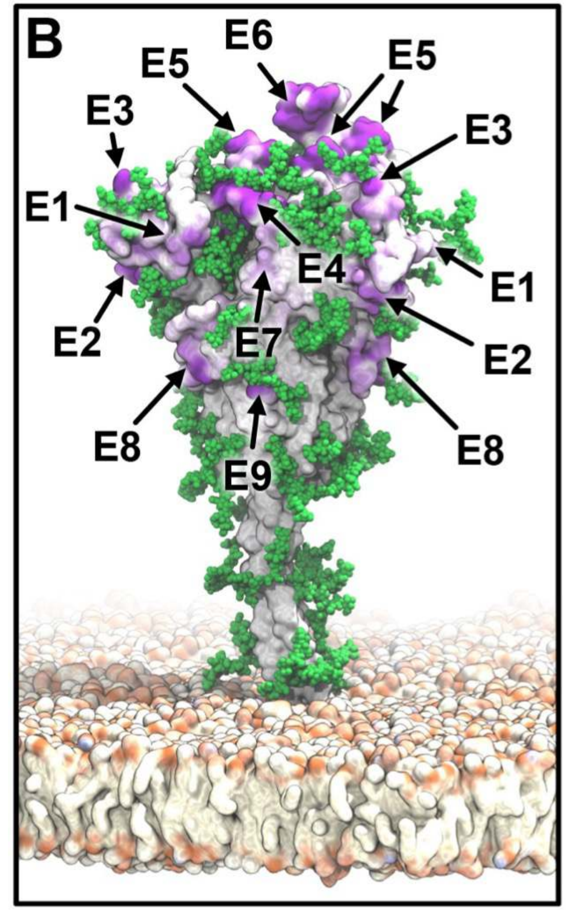
Beck group Science 18.8.2020

Viruses are round, membrane diameter 90 nm, > 20 spikes, each with three hinges, presumably facilitating binding to entry receptor ACE2

Compare also Yao et al., Cell 183, 730–738, October 29, 2020

MD-simulations of spike proteins

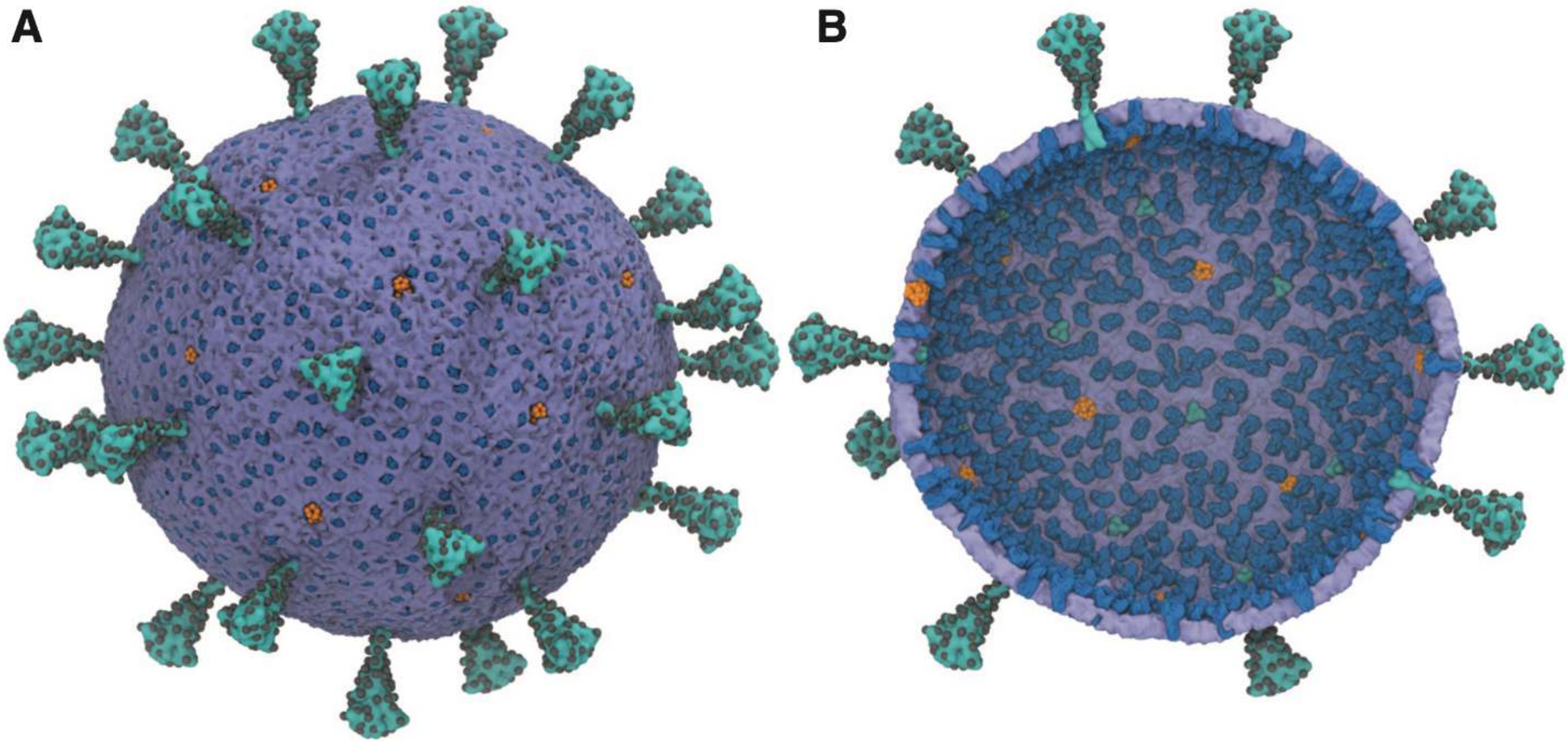




Molecular dynamics (MD) simulations are used for simulating the spike proteins, including their glycan shields (green). This allows prediction of all possible binding sites for potential vaccines („epitopes“).

[Hummer group PLOS Comp Biology 1.4.2021]

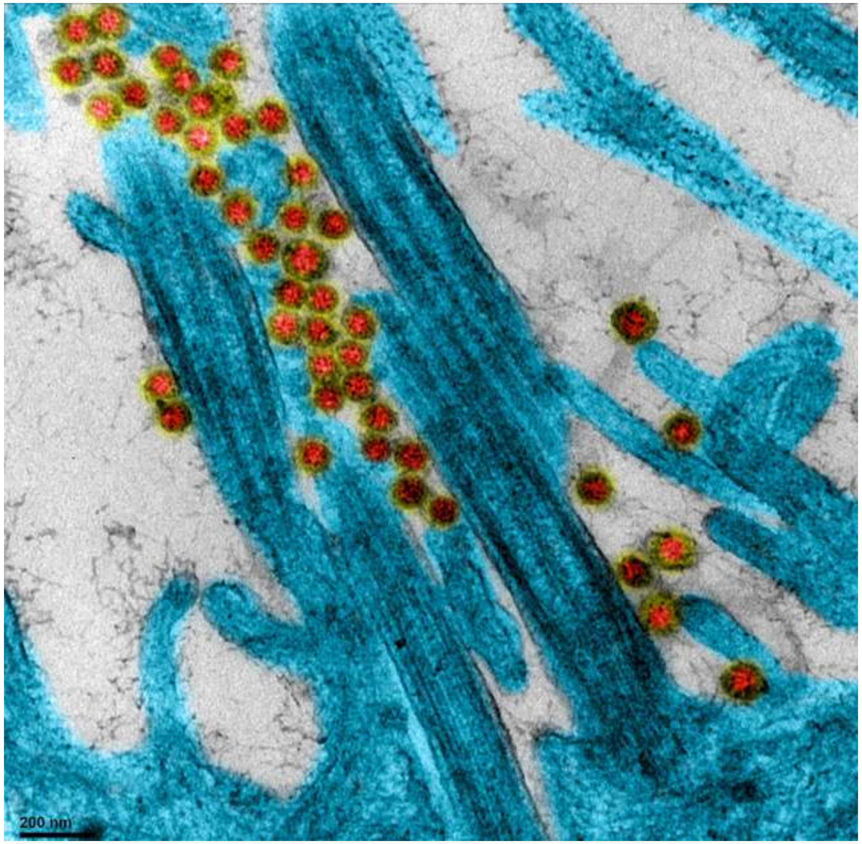
Coarse-grained computer model



The coarse-grained model includes representations of the four structural proteins: the spike (S, green), membrane (M, blue), nucleocapsid (N, not shown here) and envelope (E, orange, ion channels) proteins.

[Amaro and Voth groups, BPJ March 2021]

COVID-19

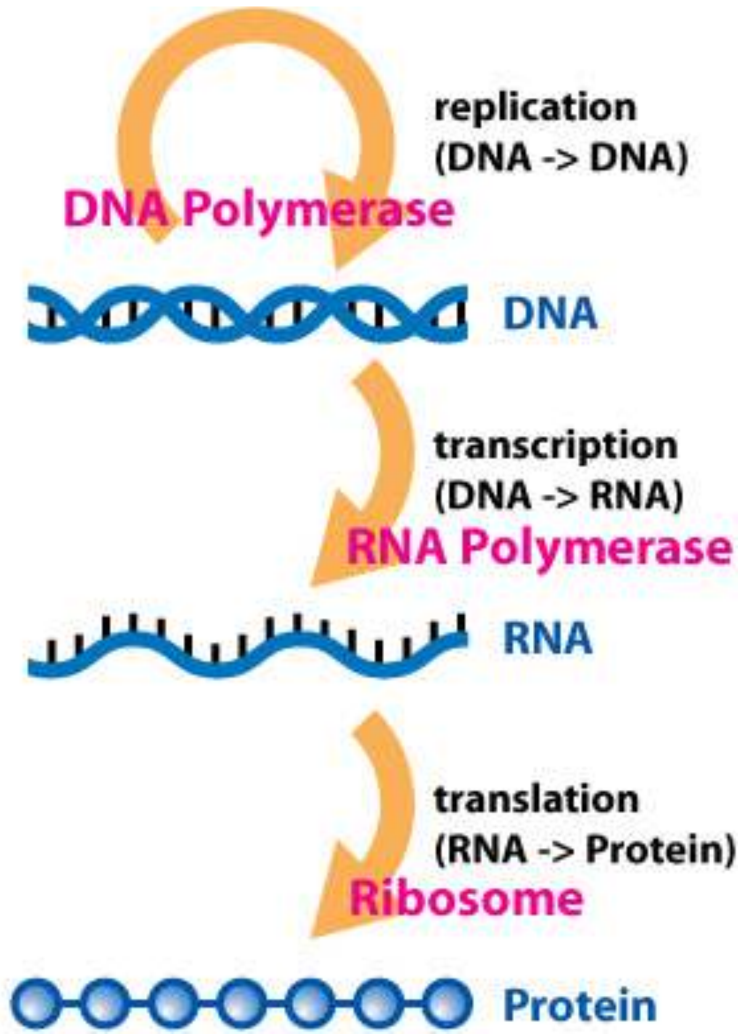


Coloured electron microscopy: SARS-CoV-2 viruses binding to ciliated lung cells

Although the virus itself is now well investigated, there are still many open questions regarding the corresponding disease, e.g. the risk factors of individual patients and the long-term consequences.

Some basic biology facts

Central dogma of molecular biology

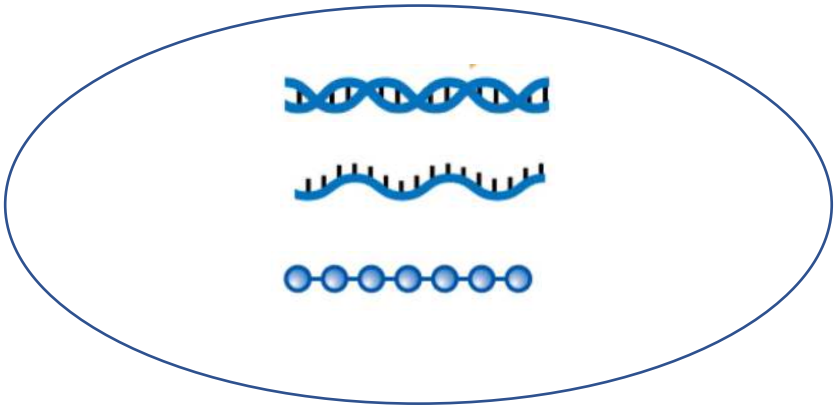


DNA stores the genetic information

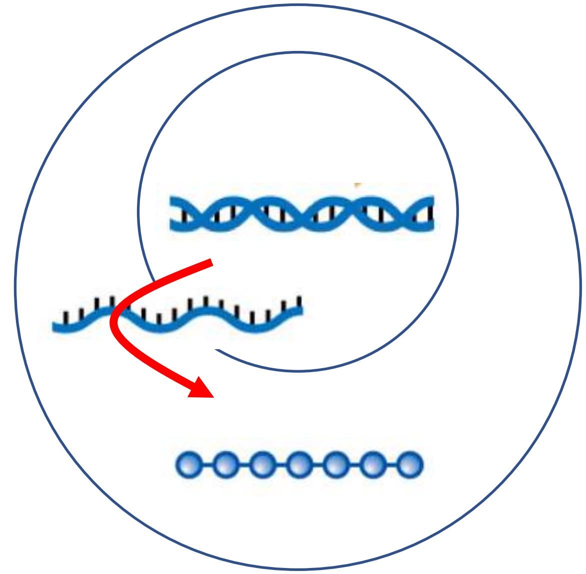
RNA transports the genetic information

Proteins go to work

Two types of cells …

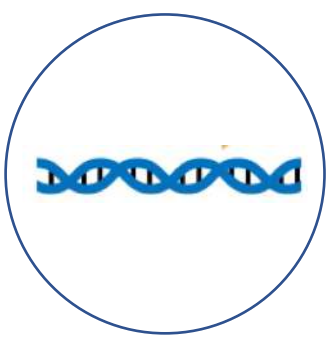


Prokaryotes (bacteria and archaea)

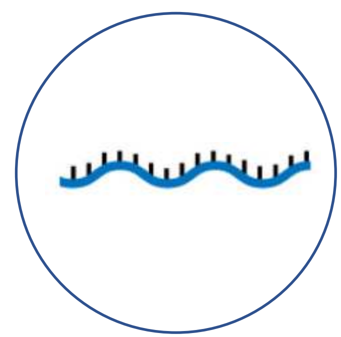


Eukaryotes (protists, algae, fungi, plants, animals, etc)

… and two types of viruses



DNA-virus



RNA-virus

Four major classes of biomolecules

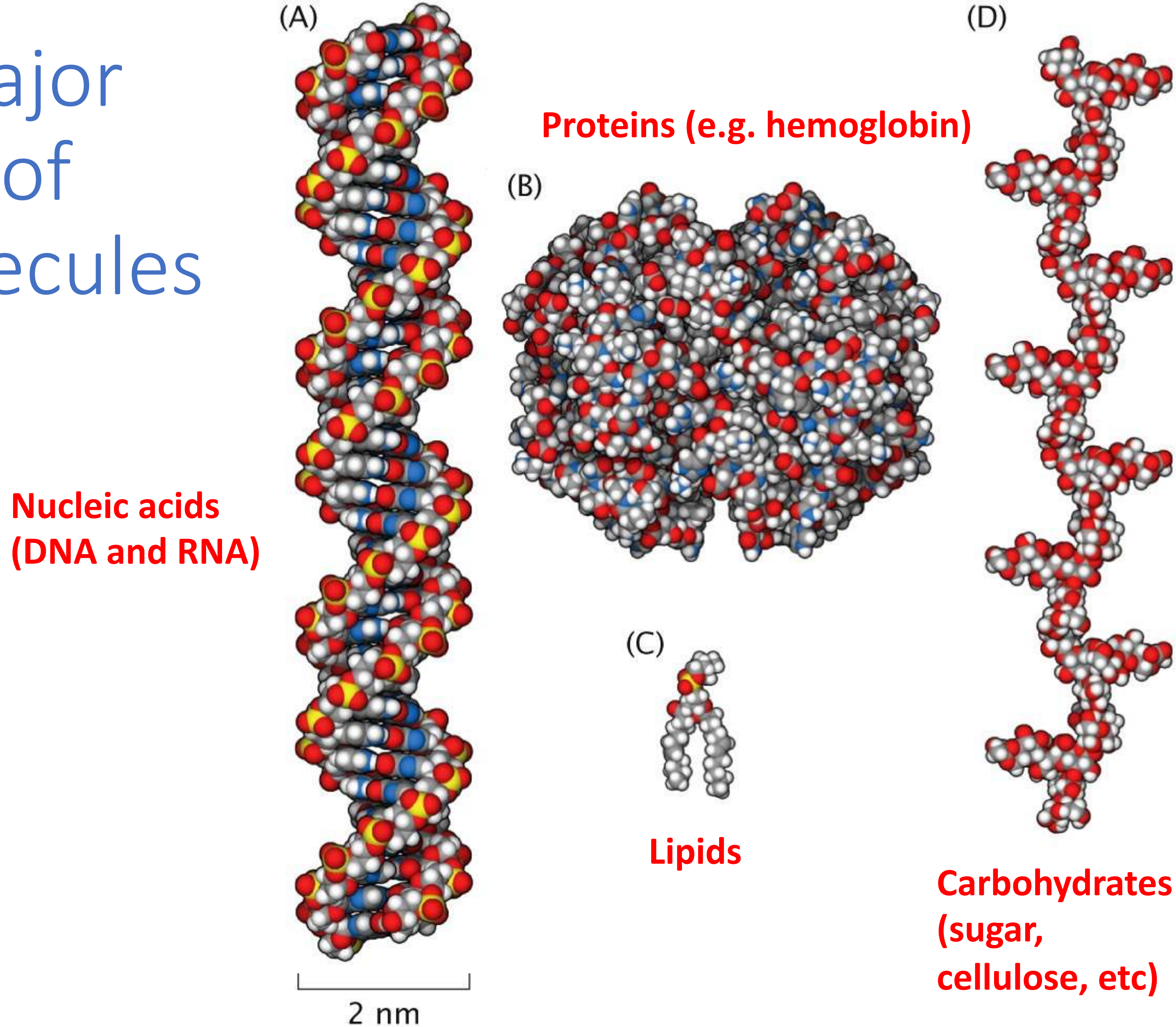


Figure 1.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

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

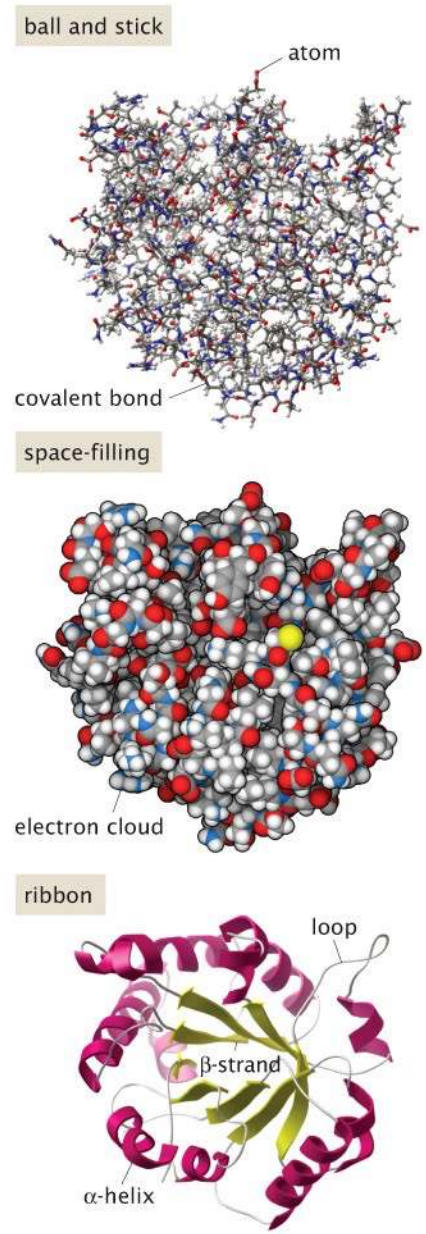
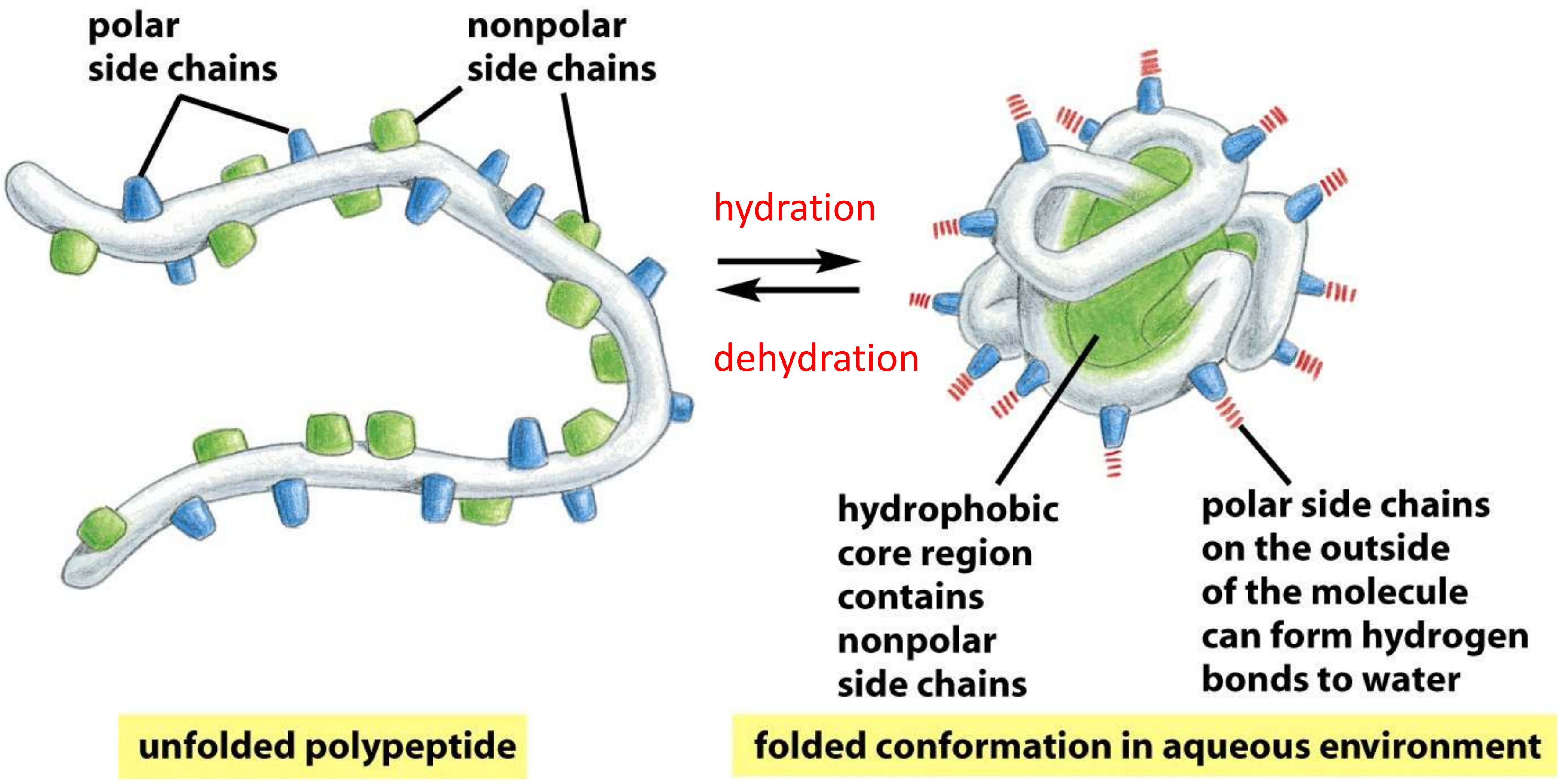
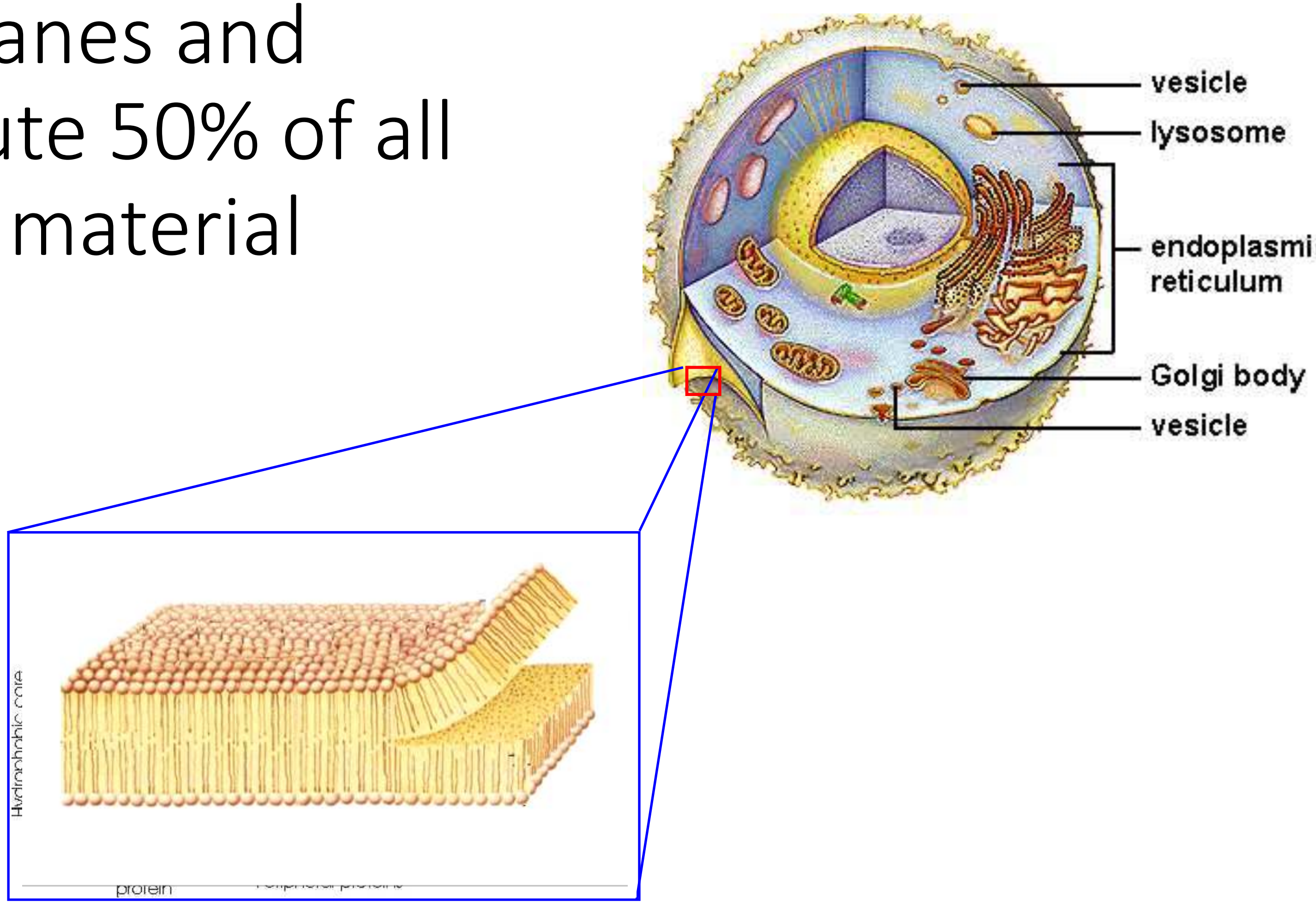


Figure 2.32 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Protein folding



Lipids form membranes and constitute 50% of all cellular material



Molecular content of E. Coli

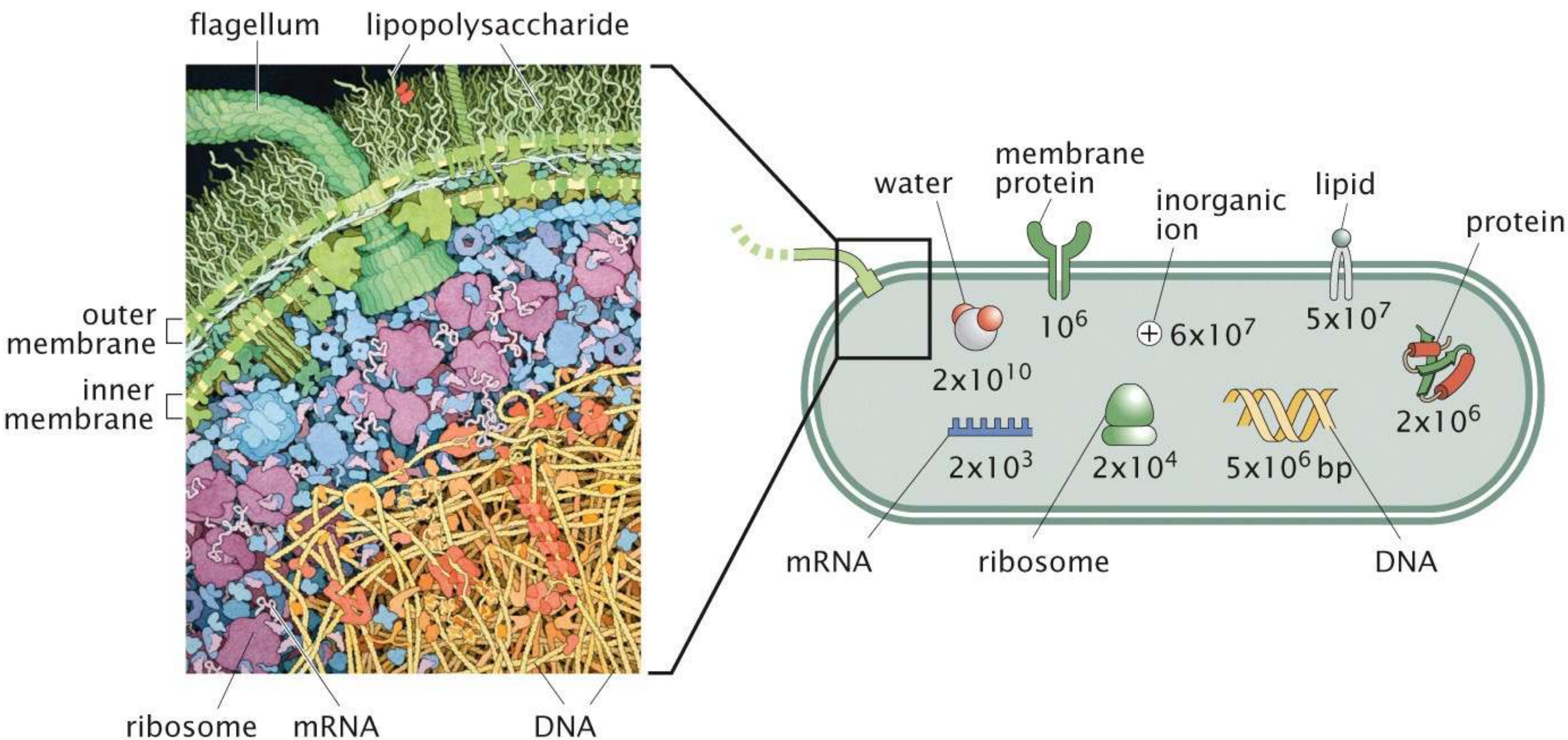
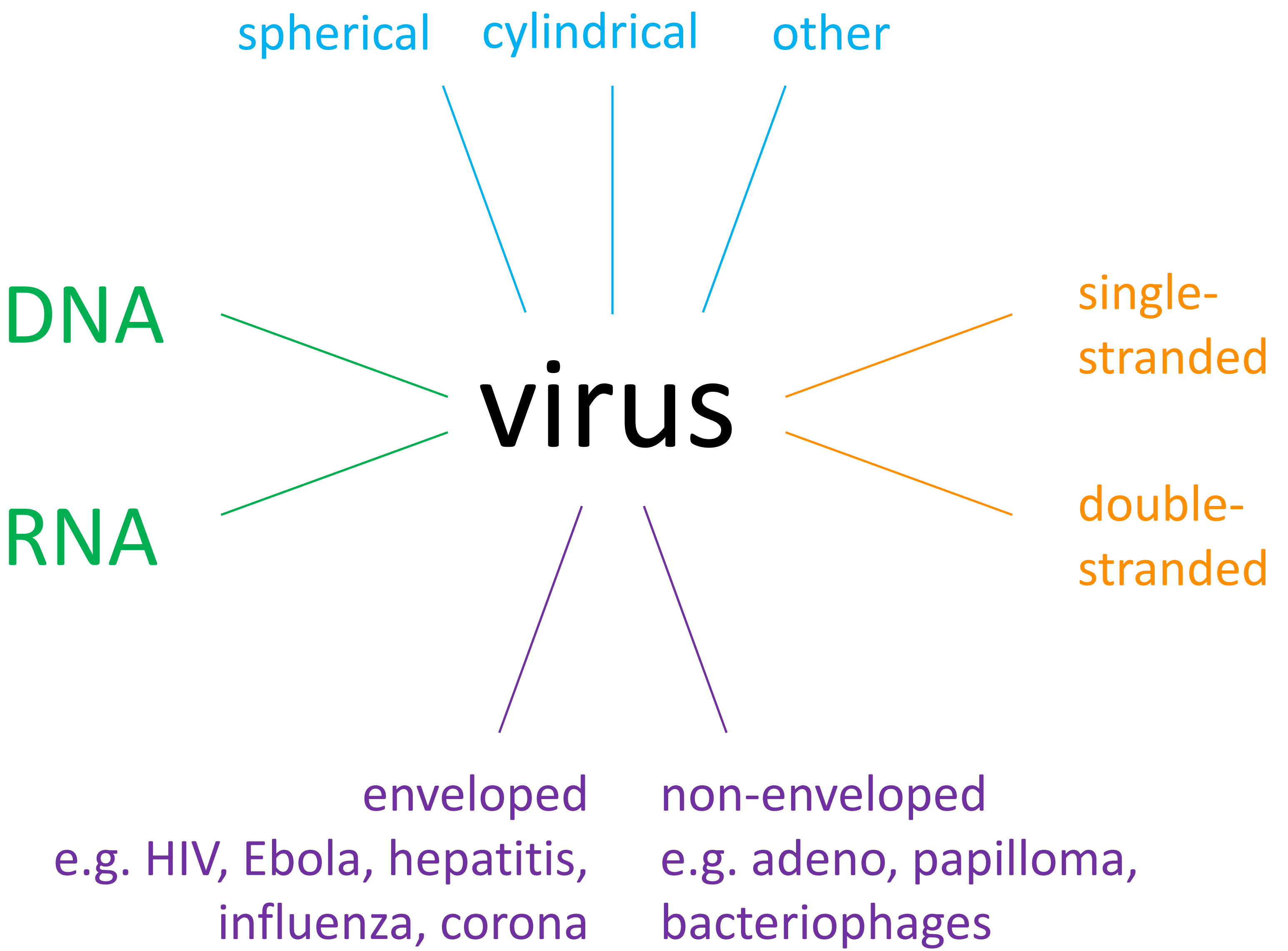


Figure 2.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Viruses

Very simple taxonomy of viruses

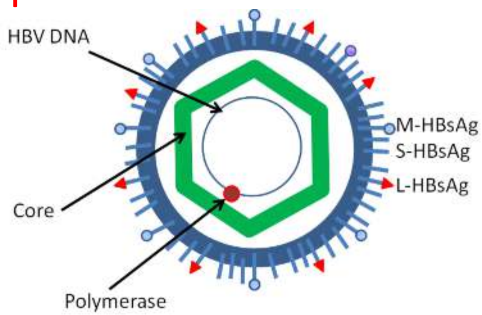


Classification of viruses

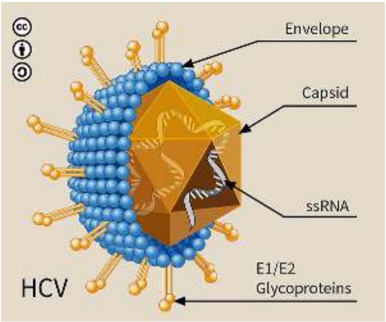
- Viruses are just a genome (RNA or DNA) protected by a protein shell (capsid); often they are in addition wrapped by a lipid bilayer membrane; in this case, sometimes the capsid is very weak
- Examples for enveloped: HIV, hepatitis B, Ebola, influenza, SARS-CoV-2
- Example for non-enveloped: adeno, papilloma, bacteriophages
- Example for RNA-viruses: HIV, influenza, SARS-CoV-2
- Examples for DNA-viruses: bacteriophages, herpes, smallpox
- SARS-CoV-2 is an enveloped RNA-virus with a very weak capsid (not connected to a full protein shell)

Enveloped viruses: genome + capsid + membrane

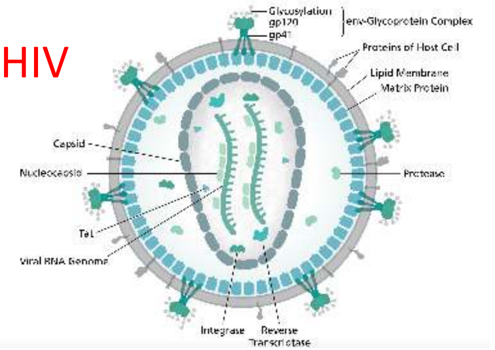
hepatitis B



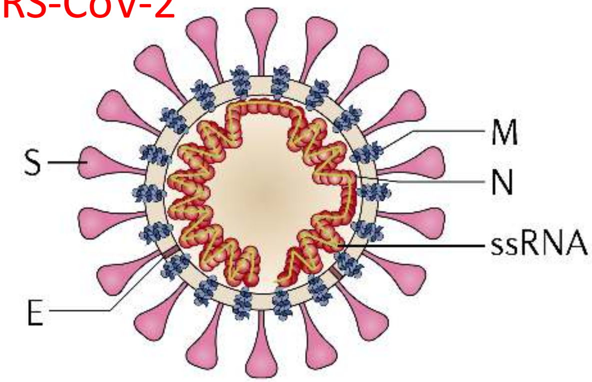
hepatitis C



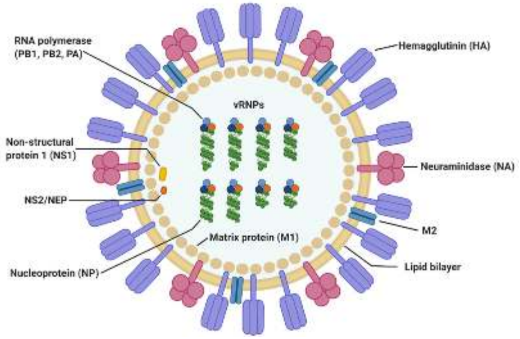
HIV

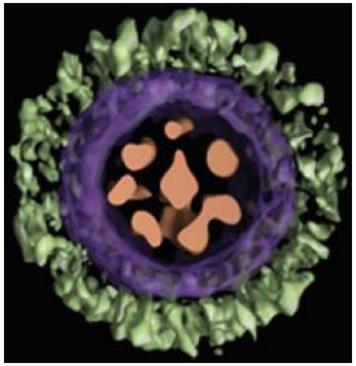


SARS-CoV-2

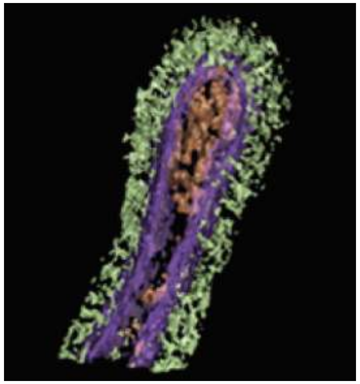


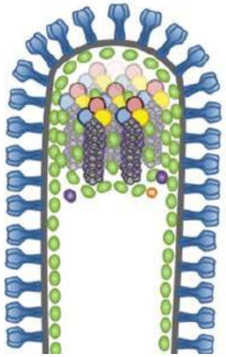
Influenza (lab strain)

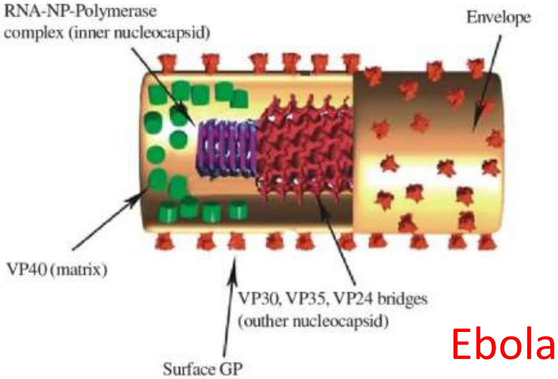




filamenteous influenza (natural strain)







Ebola

Gallery of non-enveloped icosahedral viruses

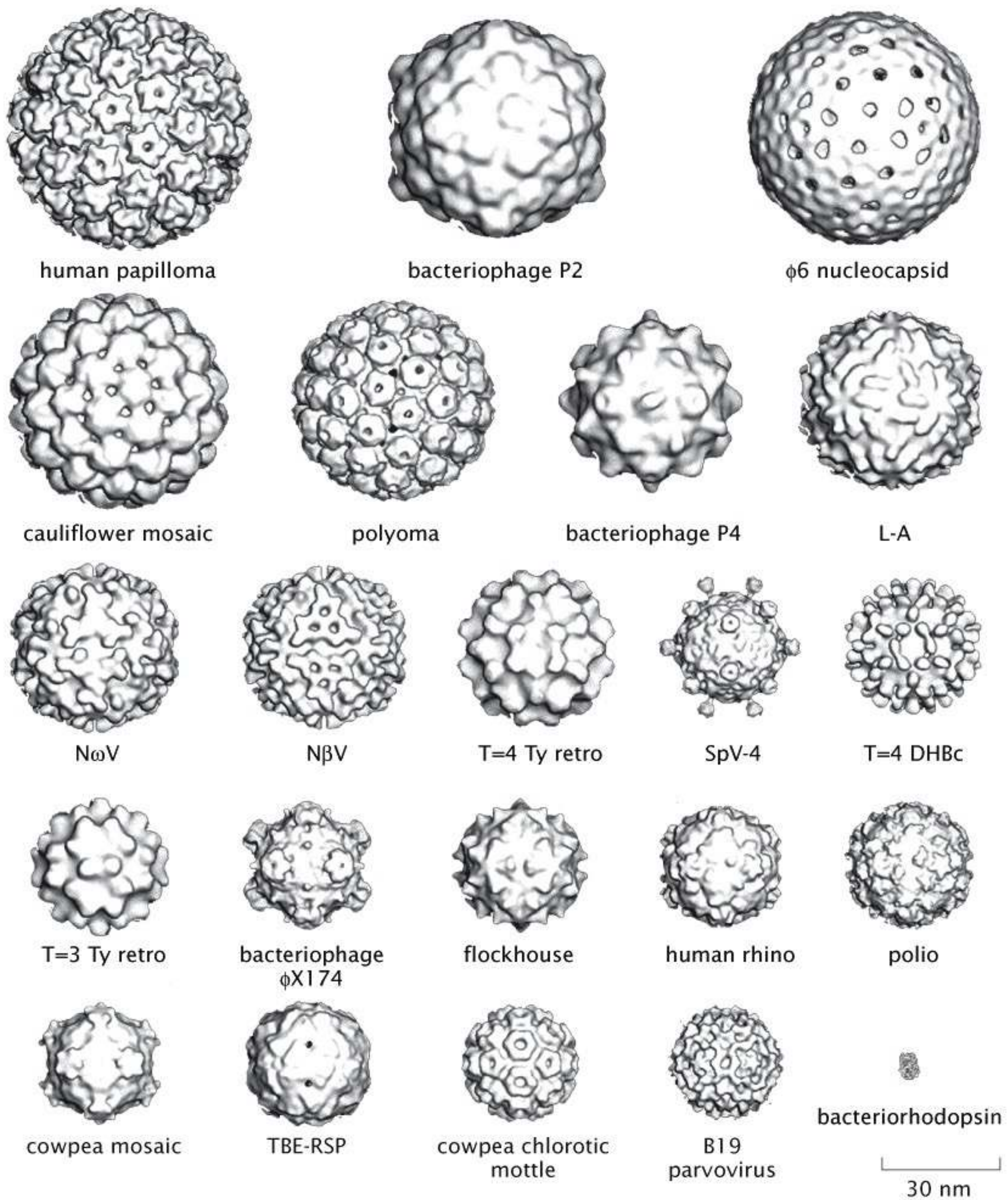
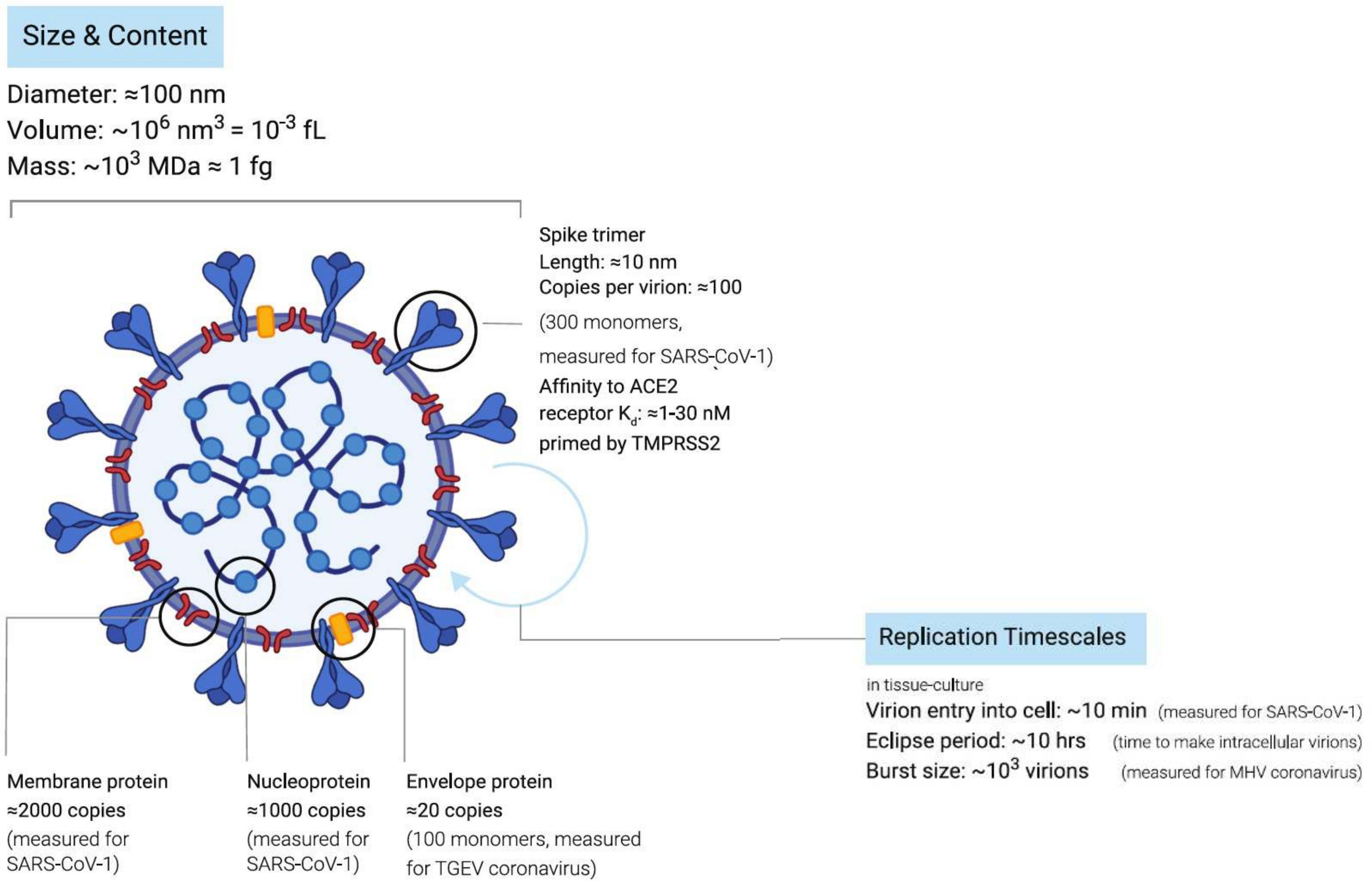


Figure 2.29 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

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

SARS-CoV-2 by the numbers

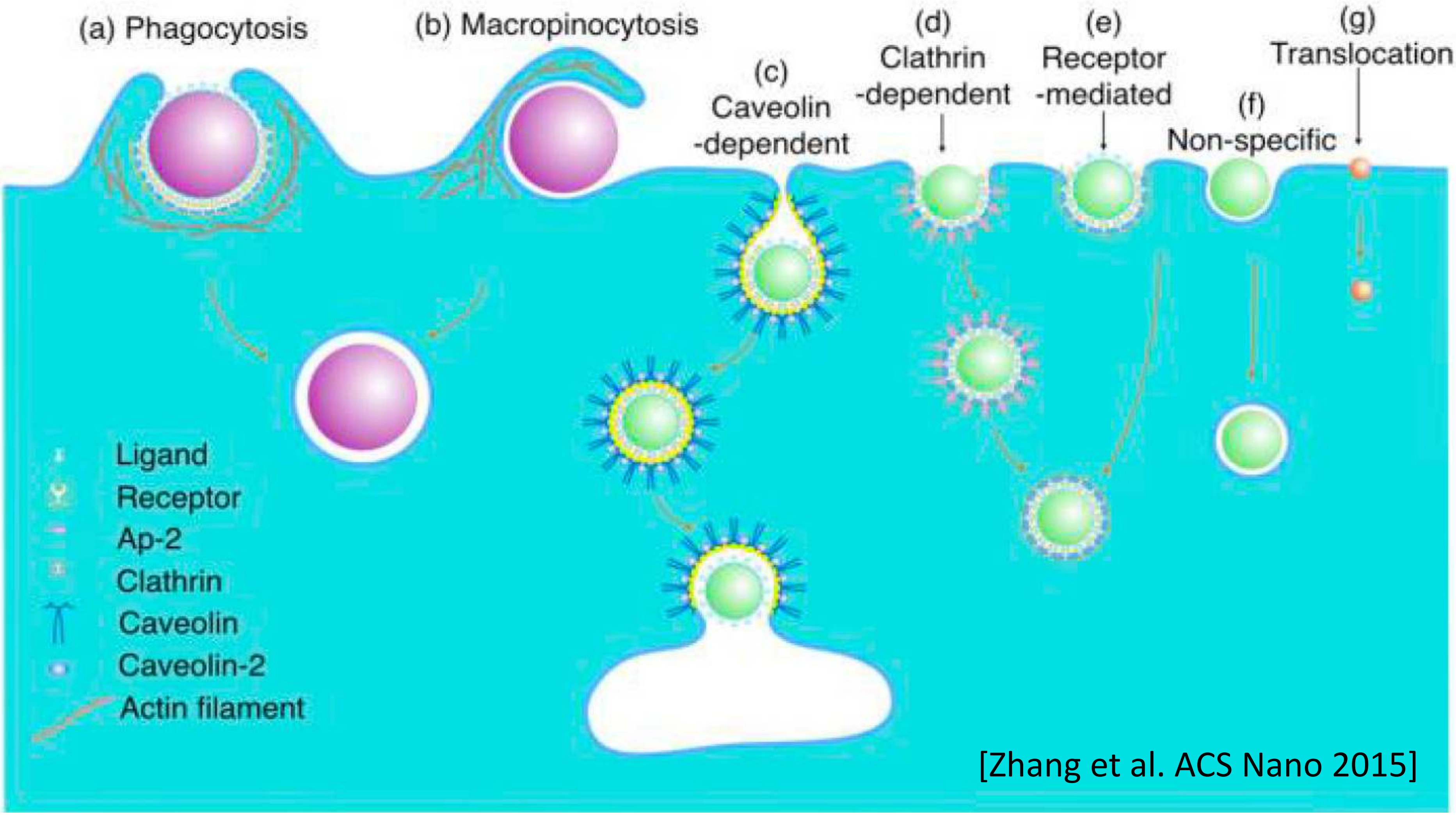


Bar-On, Flamholz, Phillips, Milo eLife 2020

Some more information

- SARS-CoV-2 is a beta-coronavirus whose genome is a single ≈ 30 kb strand of RNA (non-segmented). It codes for 10 genes ultimately producing 26 proteins, 4 of which are structural (S, M, E, N). Coronaviruses have the largest genomes of any known RNA viruses.
- The virus is detected by quantitative reverse-transcription polymerase chain reaction (RT-qPCR), that is the RNA is converted into DNA, this DNA is then multiplied (with temperature cycles) and finally detected (typically after 30 cycles).
- 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 (segmented virus, can evolve faster).
- Being a non-segmented virus, SARS-CoV-2 was expected to generate few mutants, but after having infected so many people in the world-wide pandemics, many new mutations emerged after all

The host cell membrane is the main barrier for virus entry



[Zhang et al. ACS Nano 2015]

Influenza uptake

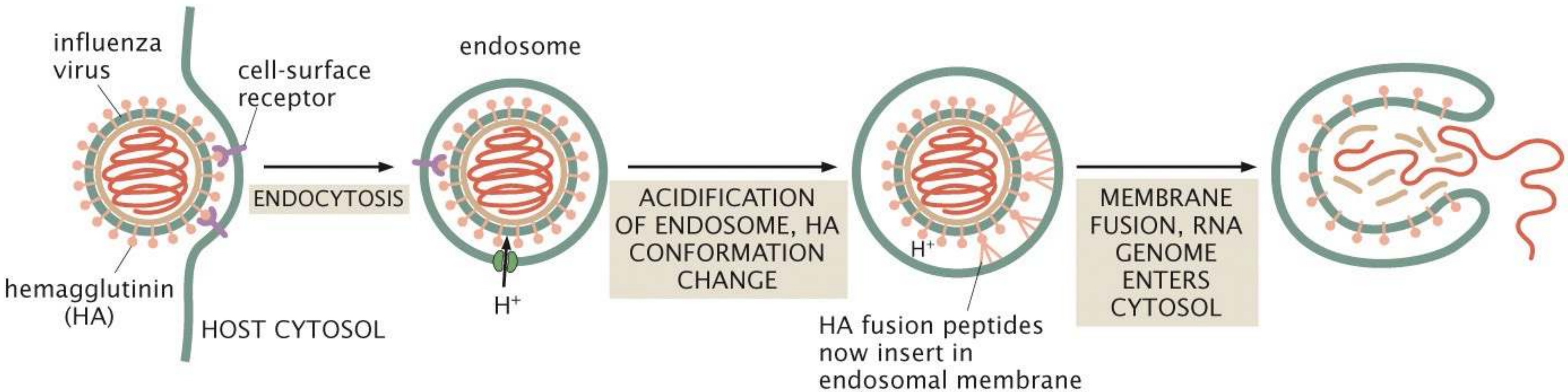
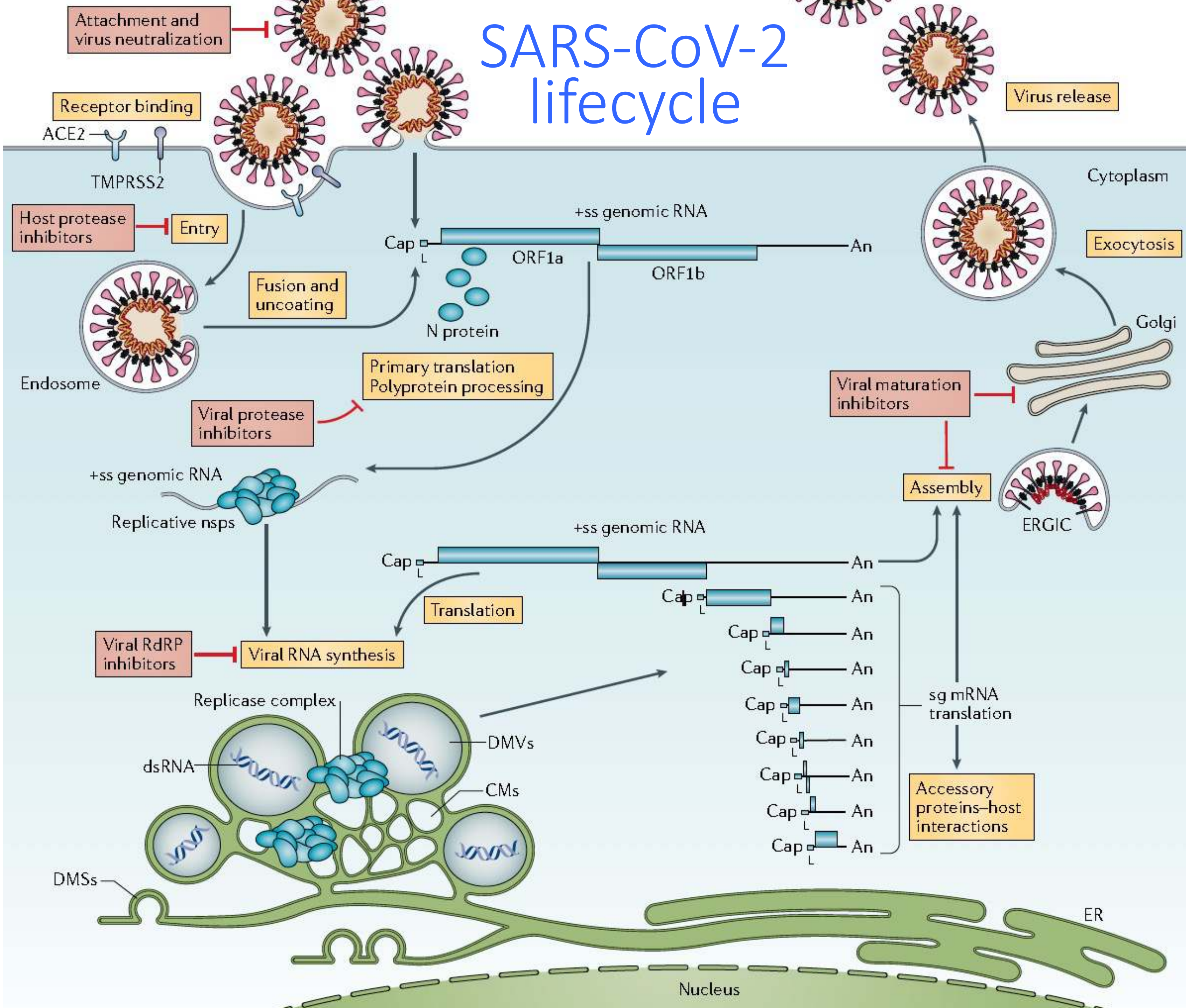


Figure 9.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

SARS-CoV-2 lifecycle



[K'kovski et al. Nat Rev Microbiol 2020]

Lifecycle HIV (retrovirus)

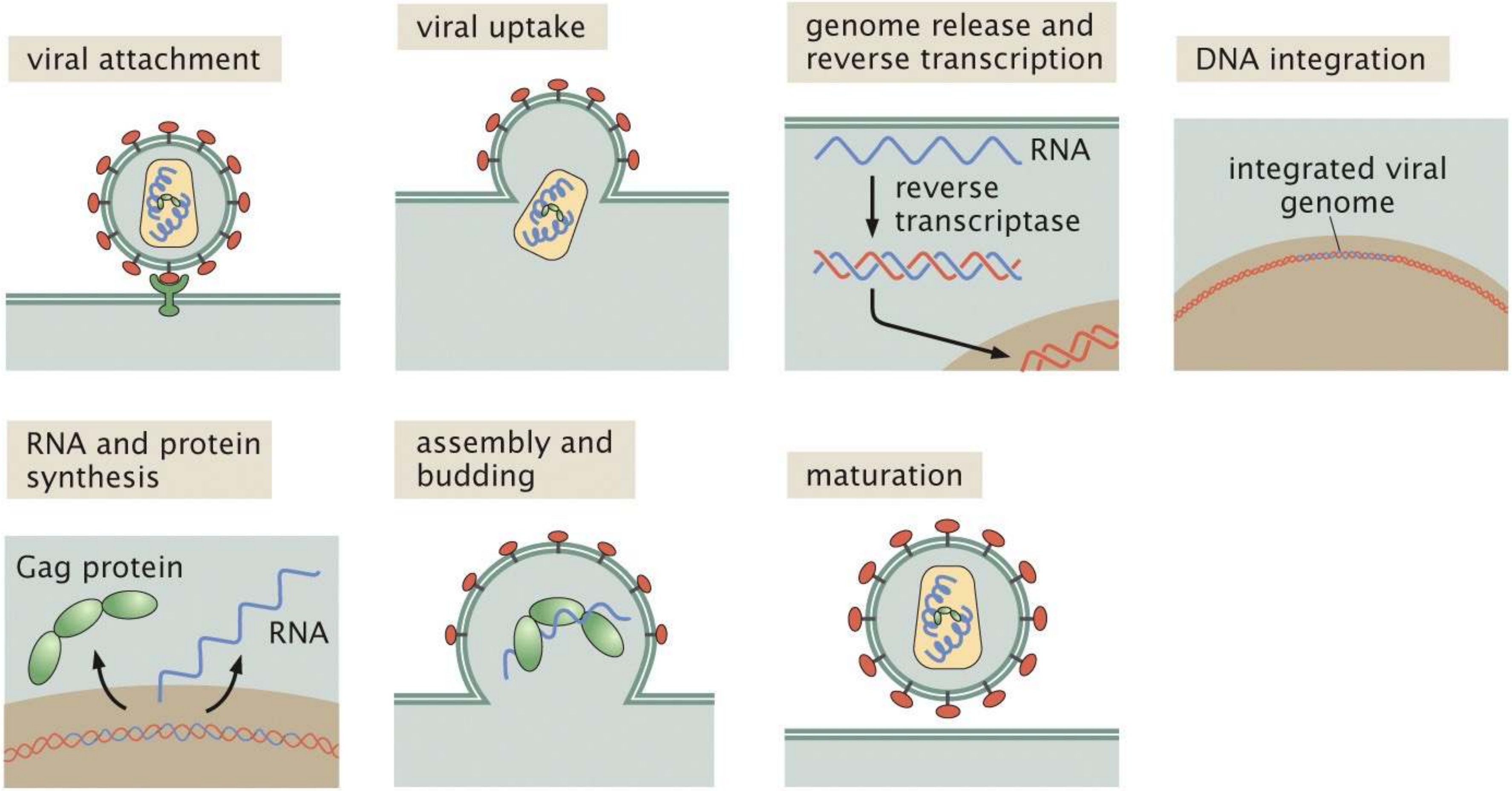


Figure 3.27 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Genome packing bacteriophages

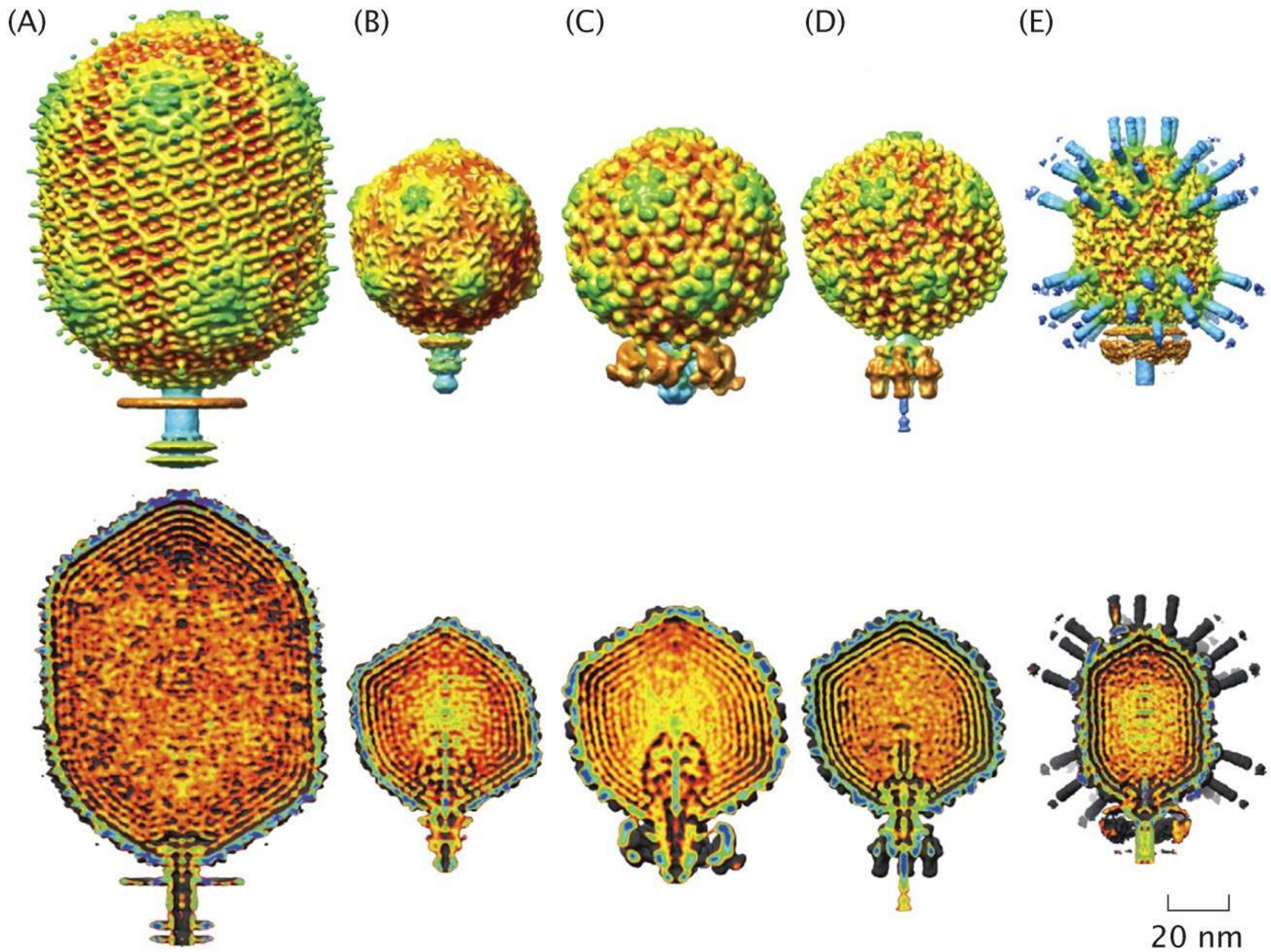
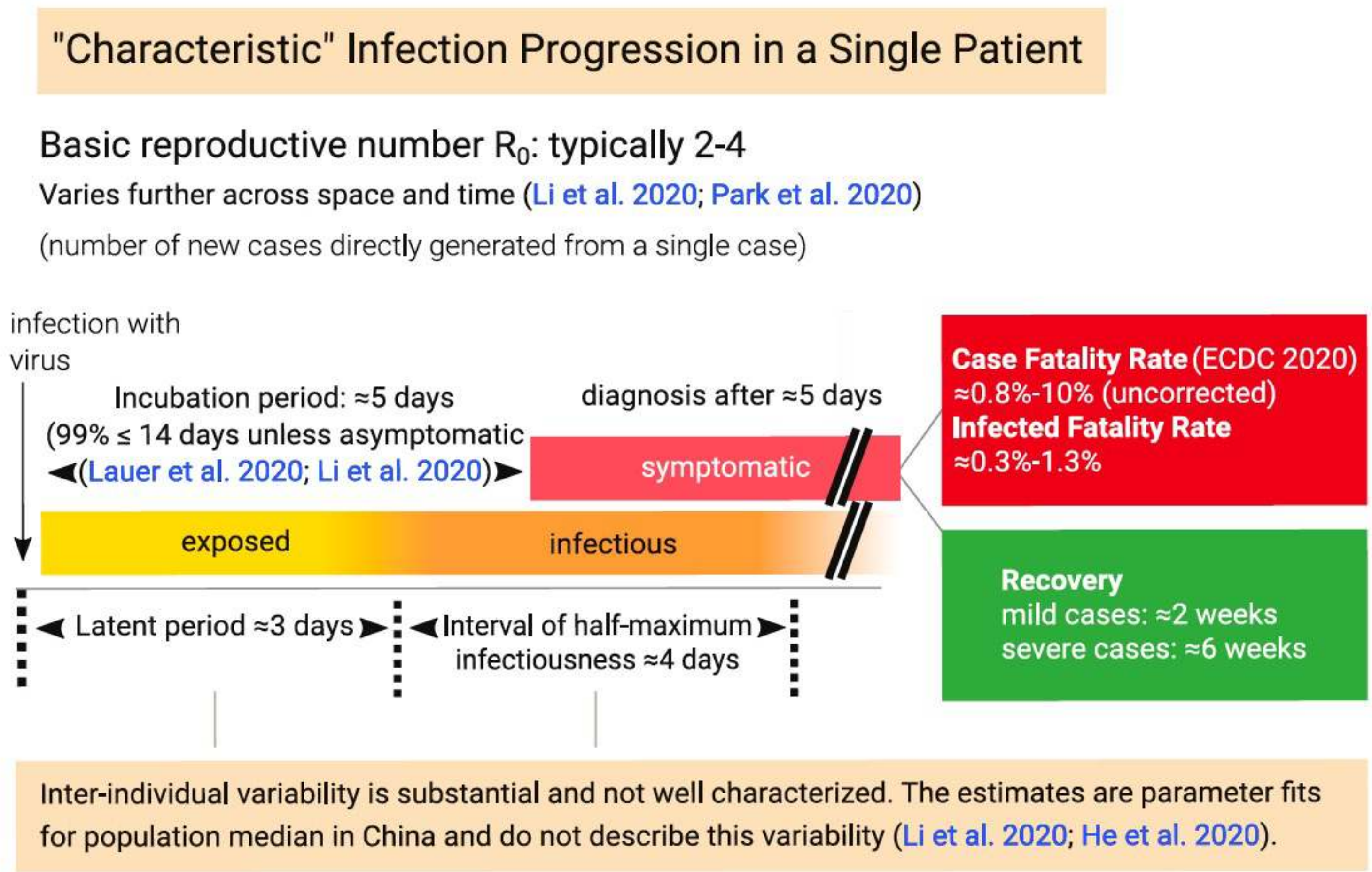


Figure 10.15 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Spread of infectious diseases

Time course COVID-19

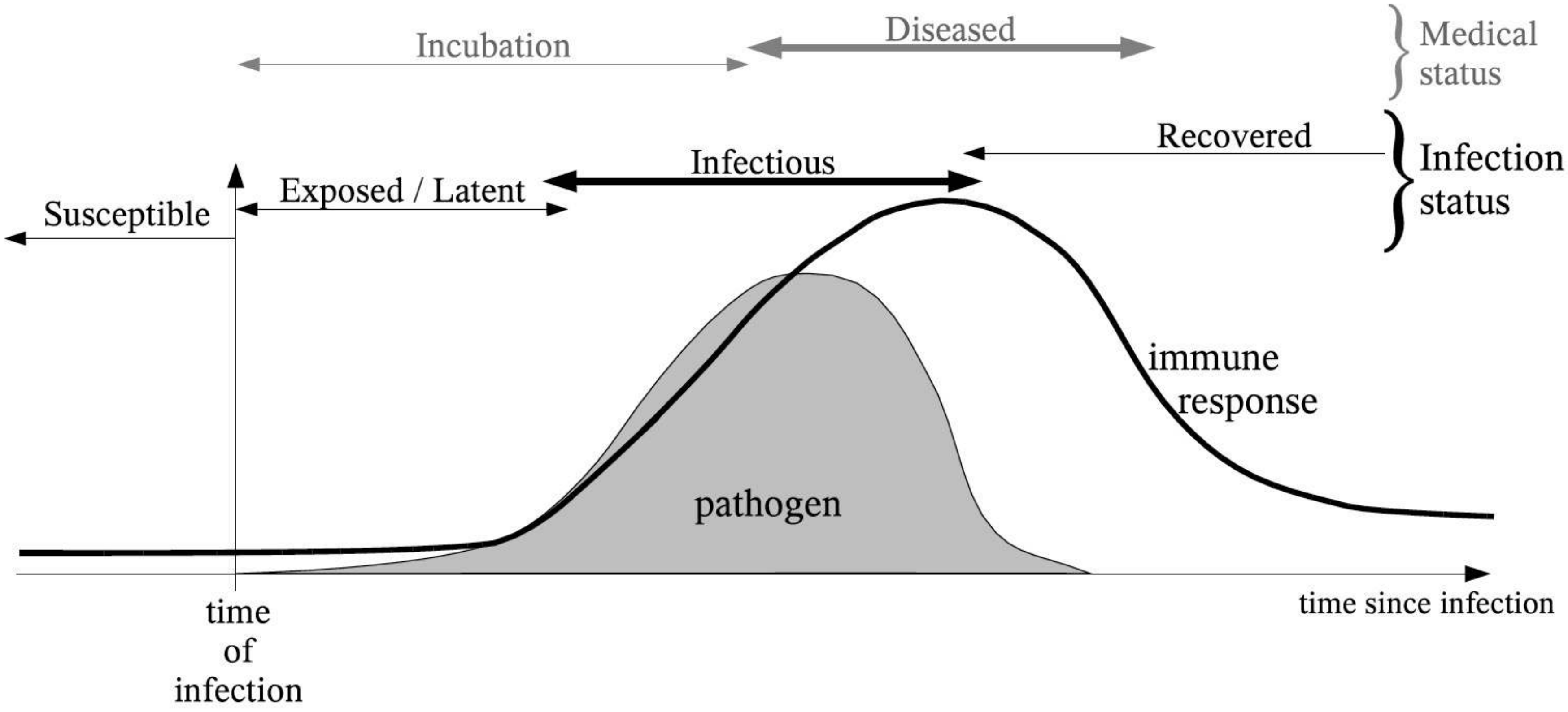


Bar-On, Flamholz, Phillips, Milo eLife 2020

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

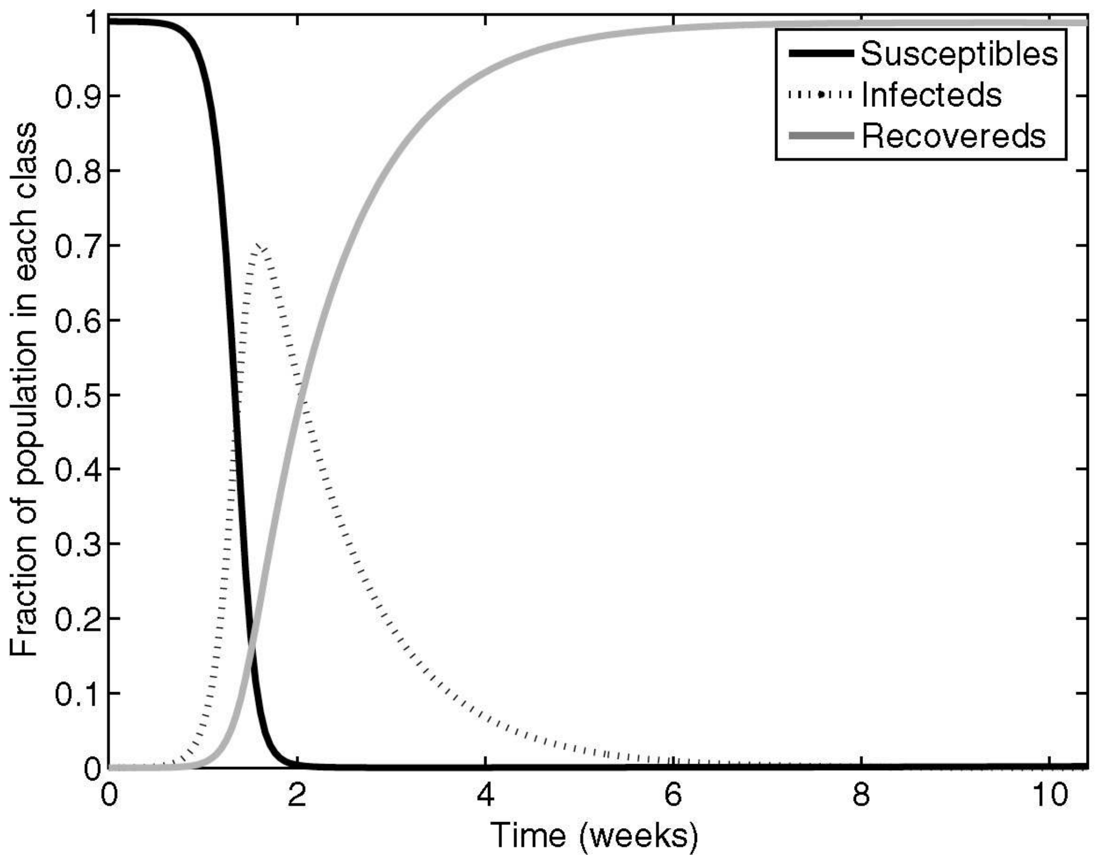
SIR-model

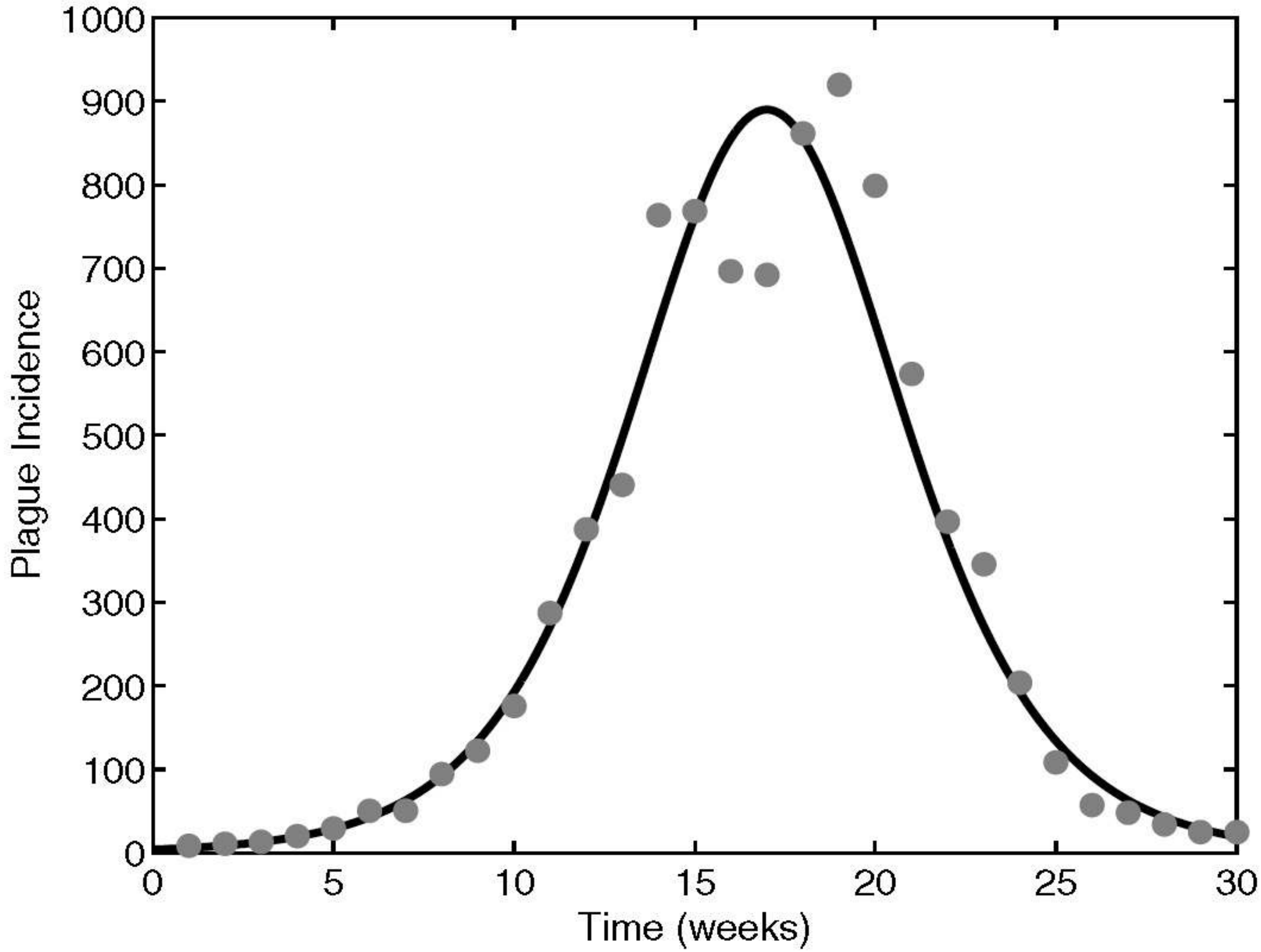
$$\frac{dS}{dt} = -\beta SI,$$

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

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

Kermack and McKendrick 1927



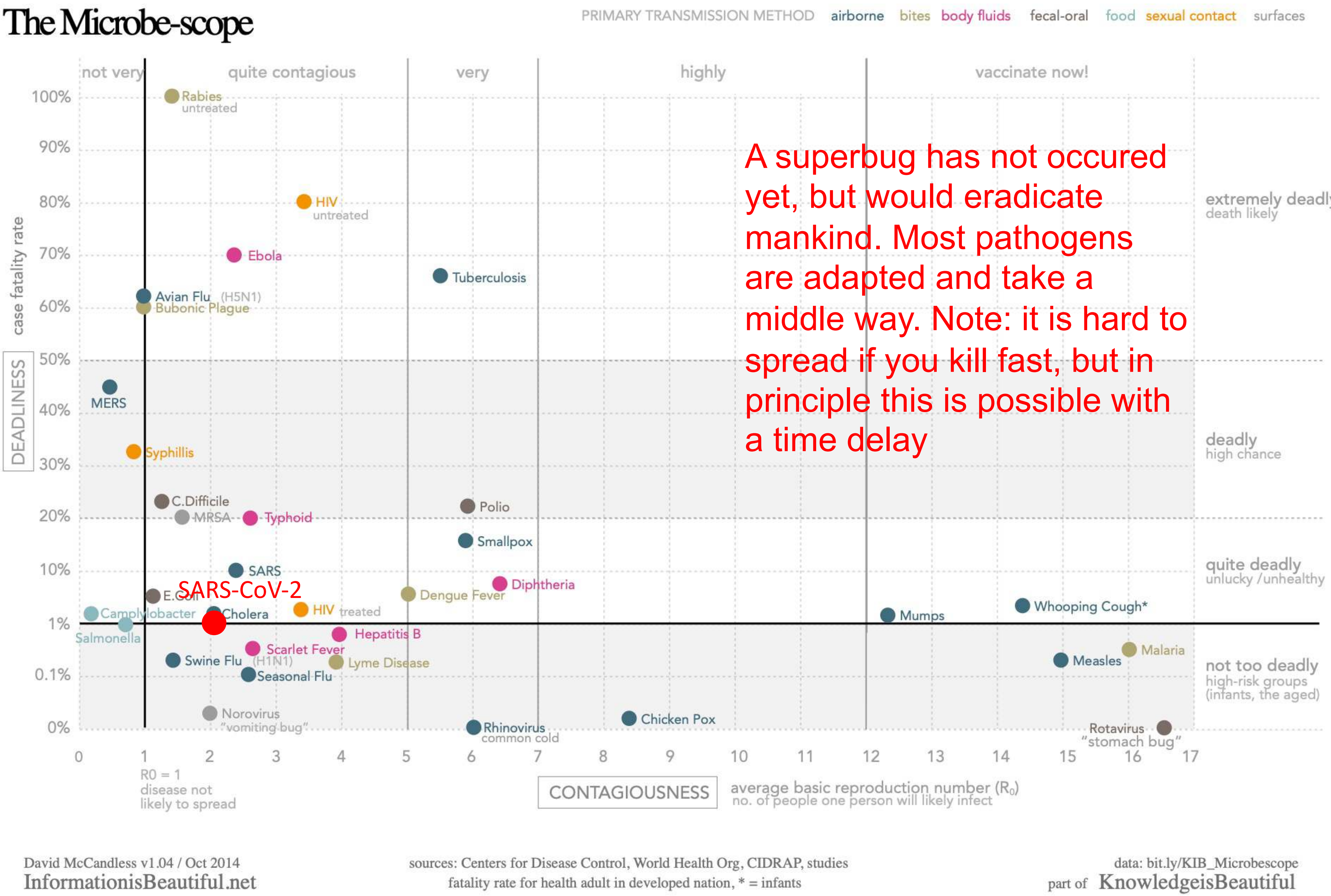


The epidemic curve. The filled circles represent weekly deaths from plague in Bombay from December 17, 1905 to July 21, 1906. The solid line is Kermack and McKendrick's approximate solution given by $dR/dt = 890 \text{ sech}^2(0.2t - 3.4)$.

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

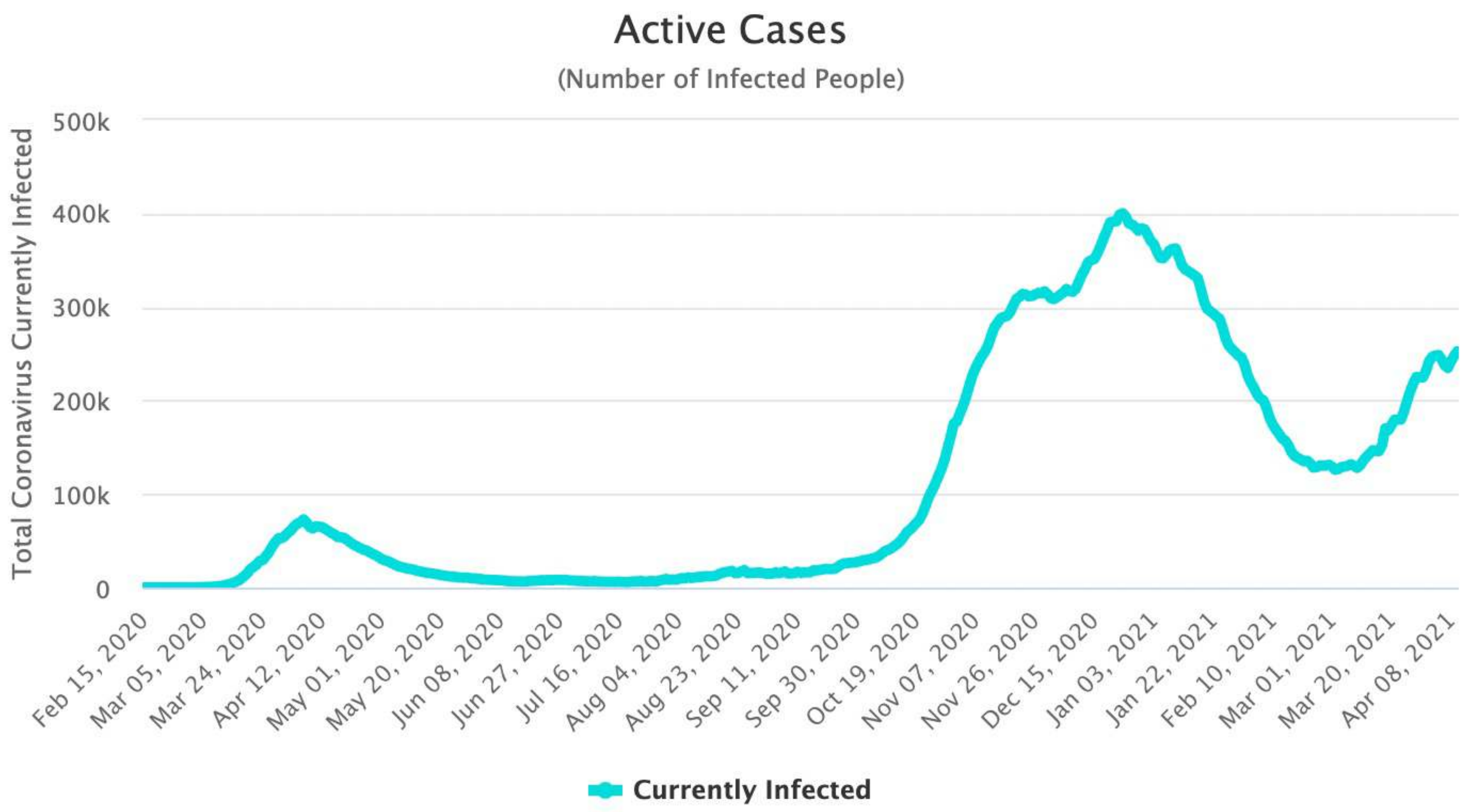
Host	Disease	R_0	Data origin	Reference
Human	Measles	13-18	UK, USA, CAN	Anderson & May
	Pertussis	5-18	UK, USA, CAN	Anderson & May
	Scarlet Fever	5-8	USA	Anderson & May
	Mumps	7-14	USA, UK, NL	Anderson & May
	Polio	5-7	USA, NL	Anderson & May
	HIV	2-5	CH, UK	Anderson & May
	HCV	1.2-2.9	Africa, Asia	Pybus 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



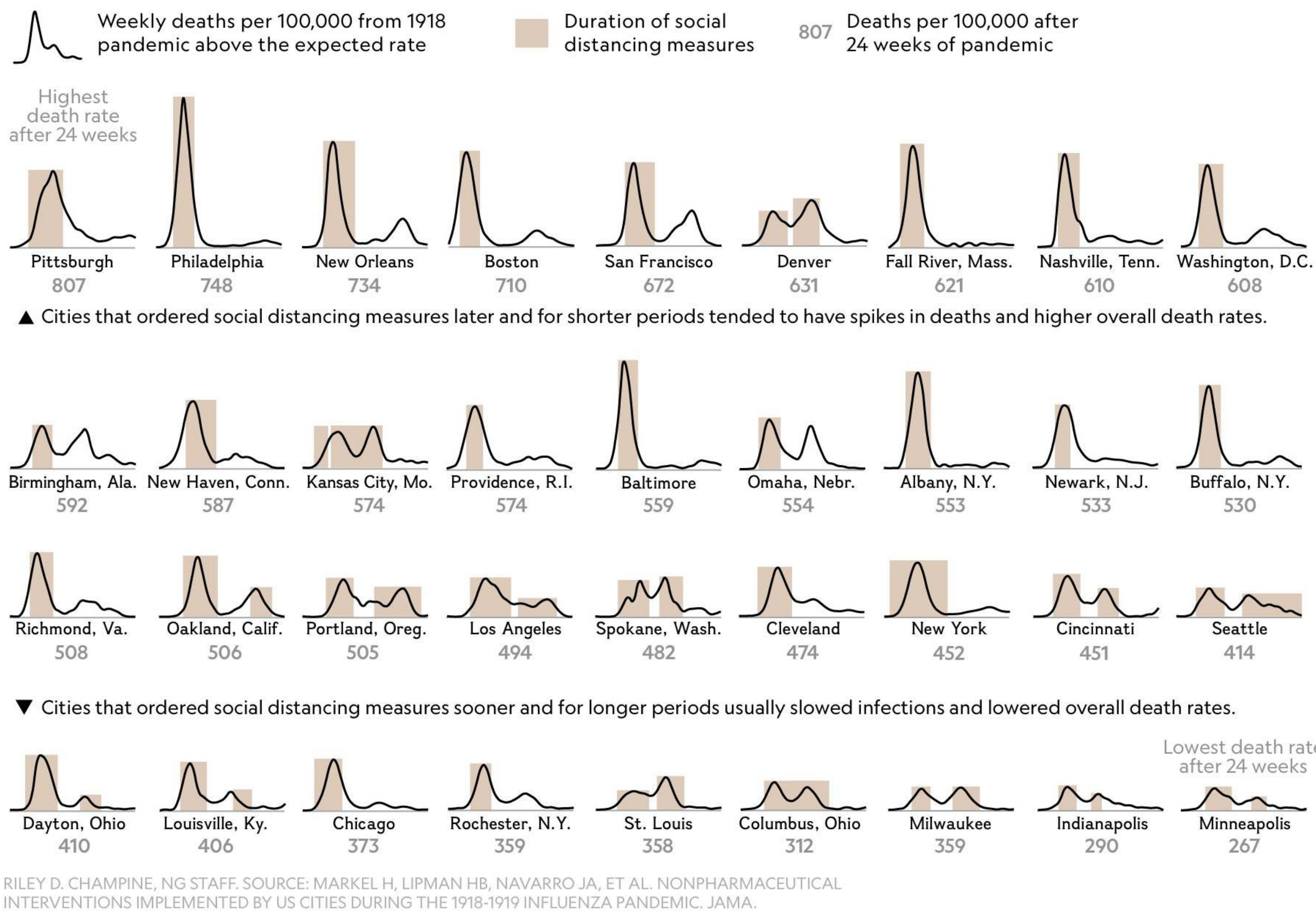
A superbug has not occured yet, but would eradicate mankind. Most pathogens are adapted and take a middle way. Note: it is hard to spread if you kill fast, but in principle this is possible with a time delay

Active Cases in Germany



https://www.worldometers.info/coronavirus/country/germany/

The Spanish flue



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

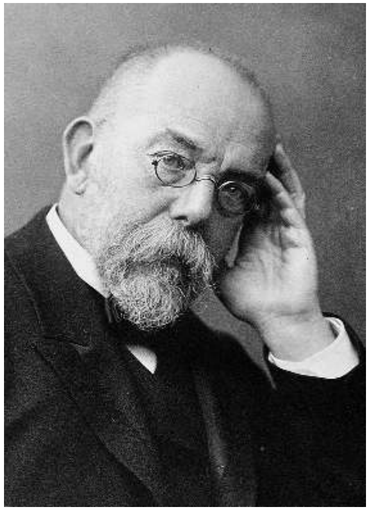
Some history

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

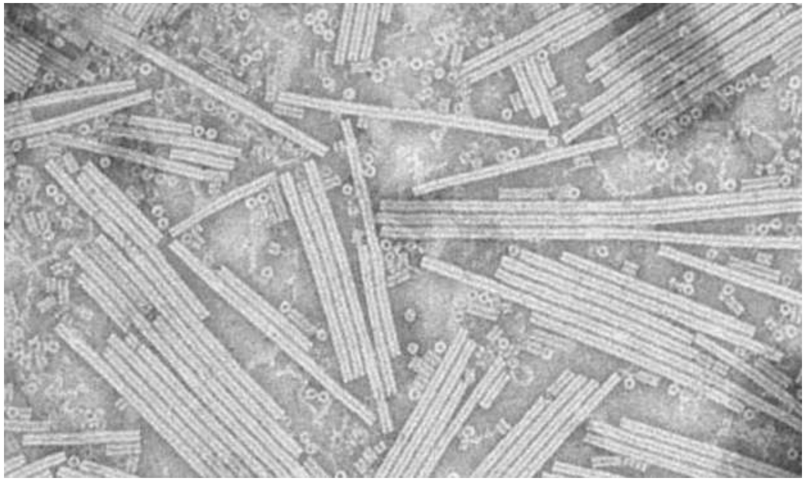

Pasteur


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).

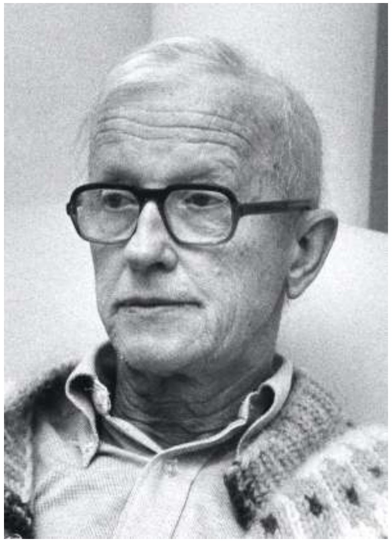
tobacco mosaic disease



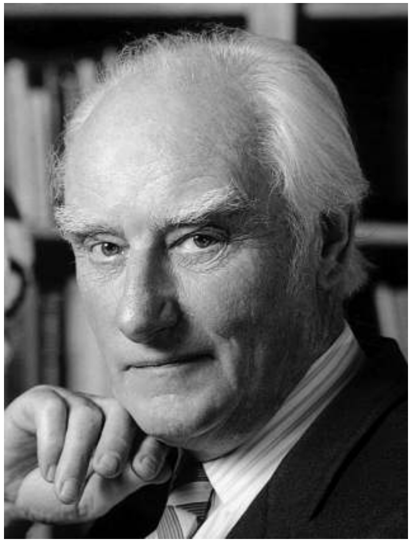
tobacco mosaic virus (TMV)

Wikipedia

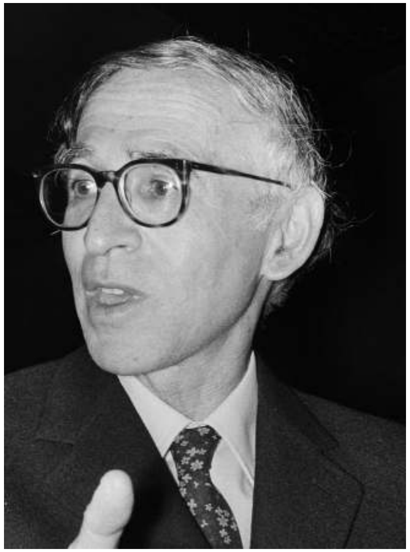
- From 1900 onwards, many other viruses were identified, including the first **human virus** in 1901 (yellow fever virus). The 1918 influenza pandemics (Spanish flue, H1N1) killed 50 million people and demonstrated the role of social contacts.
- **Felix d'Herelle** had found in 1915 that some infectious 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



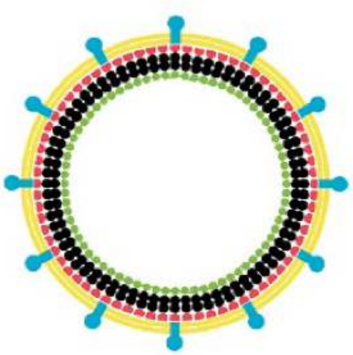
Crick

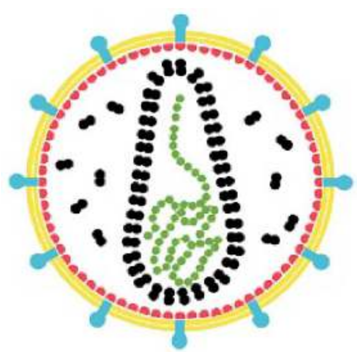


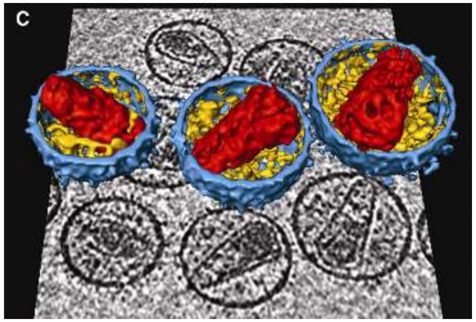
Klug

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.







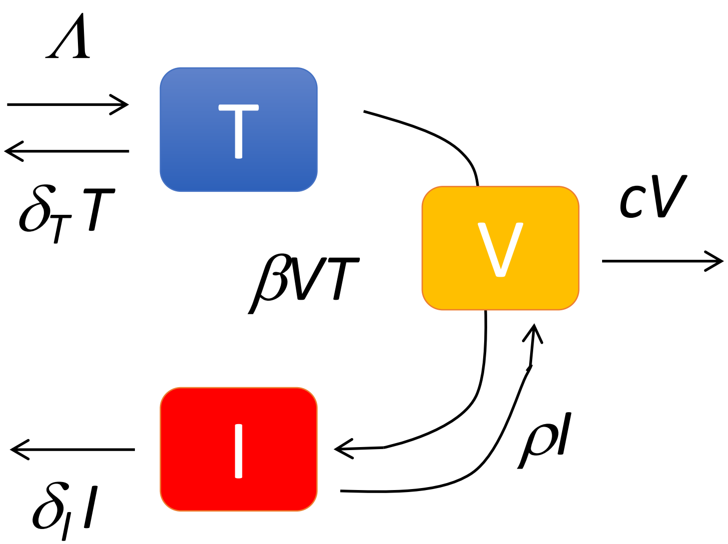
HIV-maturation – HG Kräusslich and J Briggs, Heidelberg

Mathematical methods and physical concepts in virology and infectious disease research

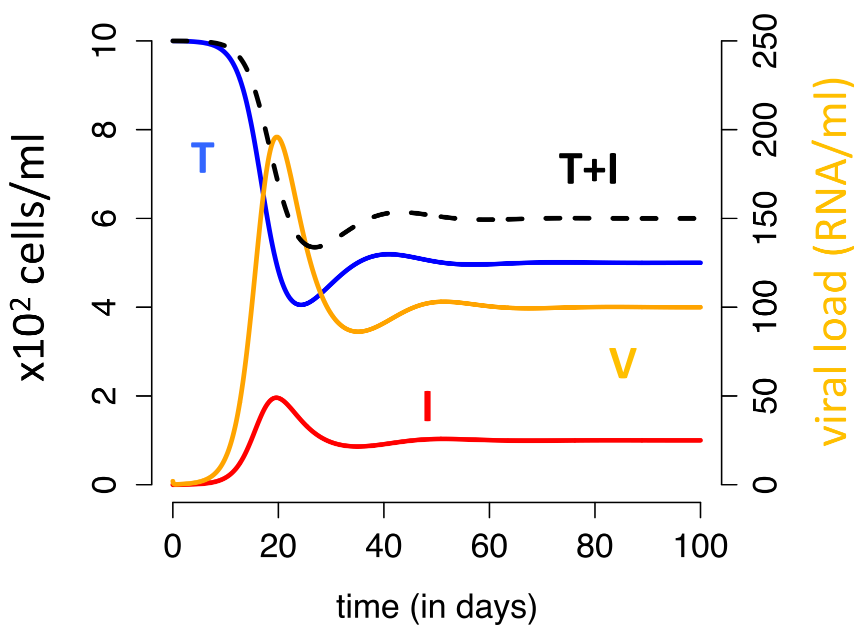
- **John Graunt** 1662 published “Natural and Political Observations on the Bills of Mortality”, calculated mortality rates that correct for population sizes
- **Daniel Bernoulli** 1766, first mathematical model to investigate an infectious disease: Impact of variolation on smallpox mortality in France
- **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



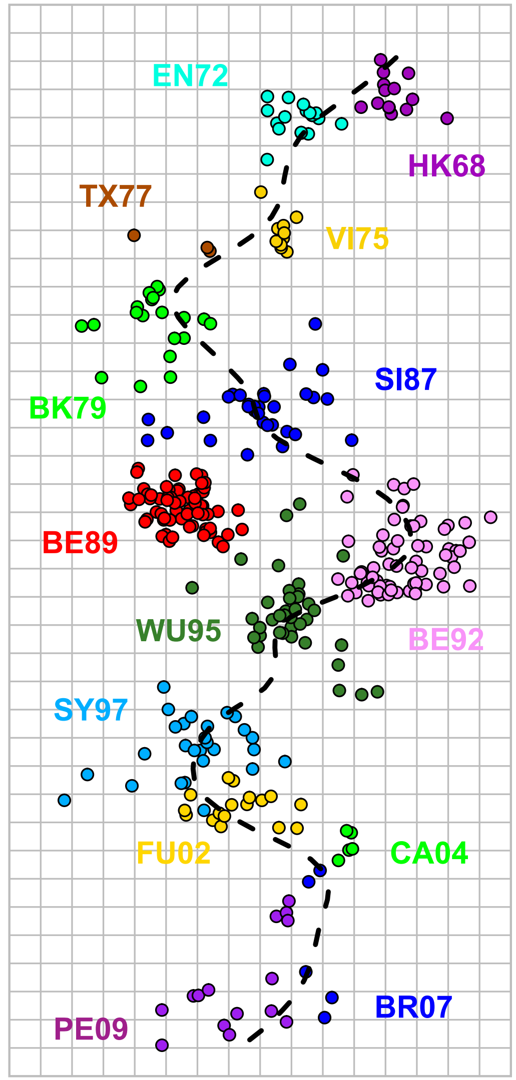
$$
\begin{aligned}
dT/dt &= \Lambda - \beta V T - \delta_T T \\
dI/dt &= \beta V T - \delta_I I \\
dV/dt &= \rho I - c V
\end{aligned}
$$



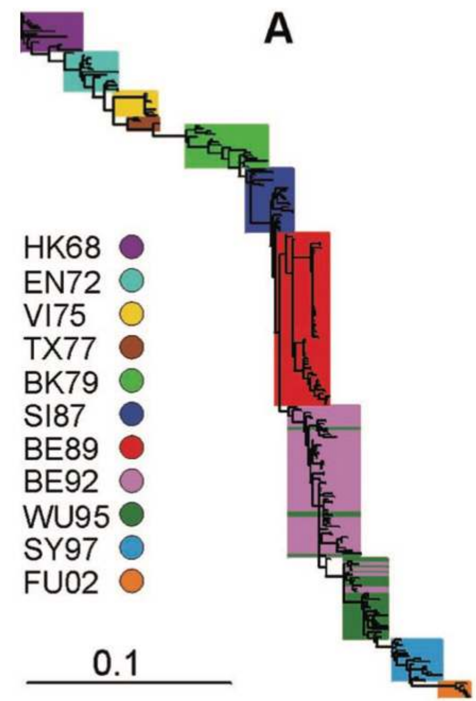
From evolution to translation

- 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)

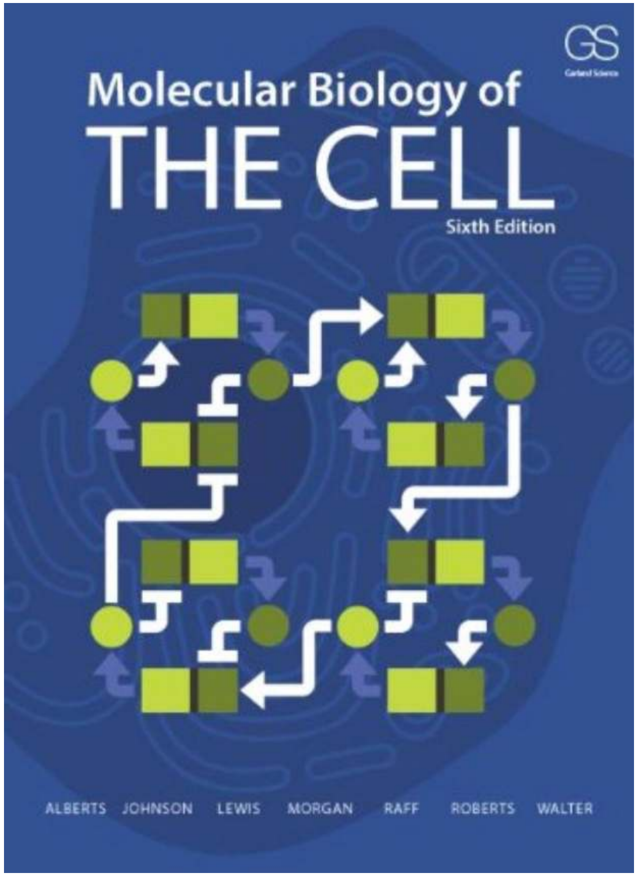


Tracking of antigenic and genetic evolution

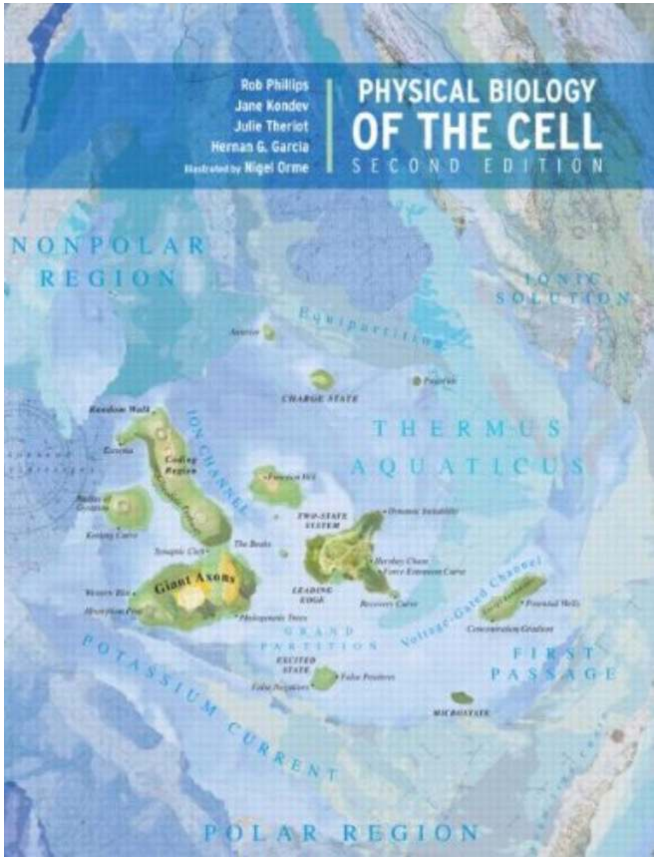


Books

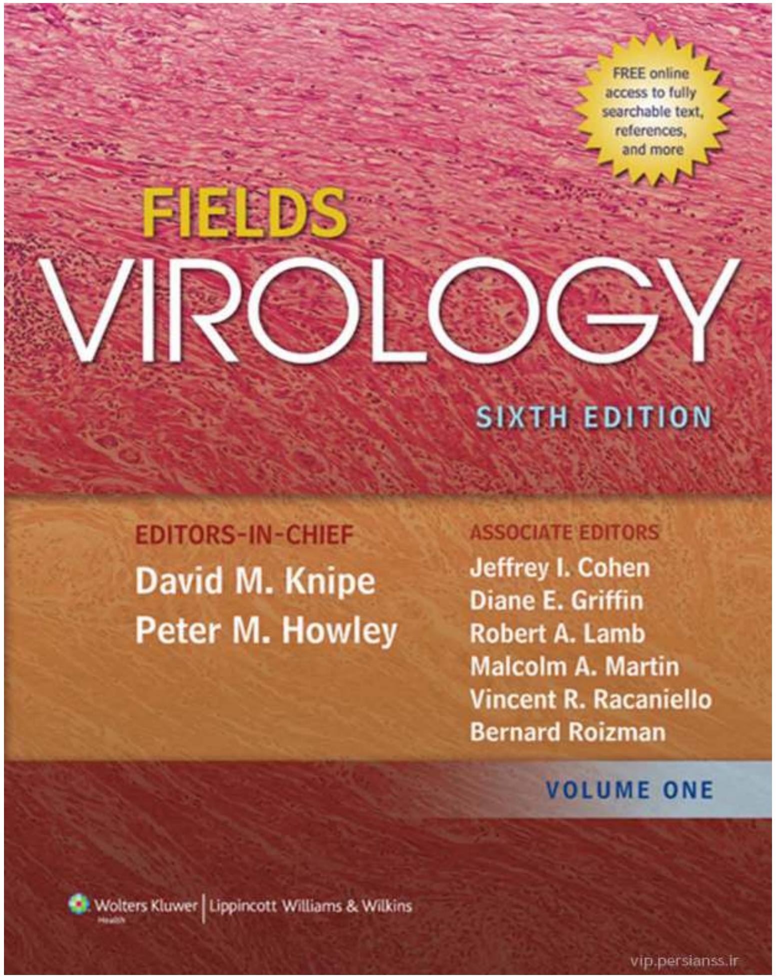
Recommended textbooks



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



Physical Biology of the Cell,
Rob Phillips and coworkers
Taylor and Francis 2nd ed 2012



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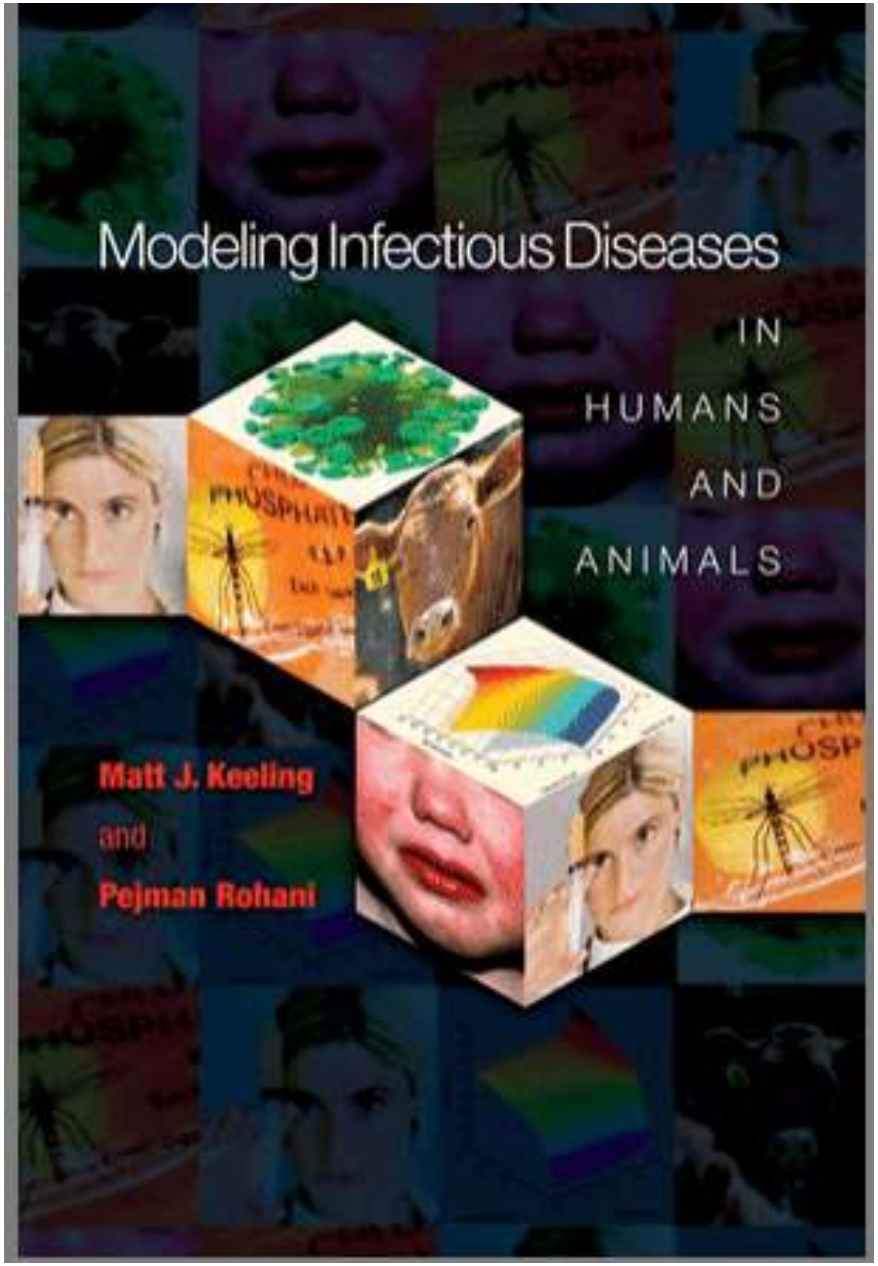
standard textbook on virology



Modeling infectious diseases in humans and animals

Matt J Keeling and Pejman Rohani, Princeton University Press 2008

Computer code available at http://www.modelinginfectiousdiseases.org

standard textbook on modelling

Reviews

- Peter Kumberger, Felix Frey, Ulrich Schwarz and Frederik Graw. "Multiscale modeling of virus replication and spread." *FEBS letters* 590.13 (2016): 1972-1986.
- Perelson, Alan S. "Modelling viral and immune system dynamics." *Nature Reviews Immunology* 2.1 (2002): 28-36.
- Roos, W. H., R. Bruinsma, and G. J. L. Wuite. "Physical virology." *Nature physics* 6.10 (2010): 733-743.
- R. Bruinsma, G.J.L. Wuite, W.H. Roos, “Physics of viral dynamics”, Nature Reviews Physics **3:** 76–91(2021)
- Zhang, Sulin, Huajian Gao, and Gang Bao. "Physical principles of nanoparticle cellular endocytosis." *ACS nano* 9.9 (2015): 8655-8671.
- Perlmutter, Jason D., and Michael F. Hagan. "Mechanisms of virus assembly." *Annual review of physical chemistry* 66 (2015): 217-239.