

**'Catching the Flu':
A Supramolecular View on the
Interaction of Viruses at Interfaces"**

Jurriaan Huskens



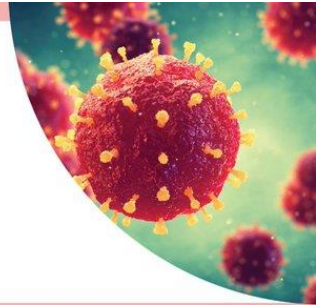
Influenza

Is the flu a relatively innocent disease?

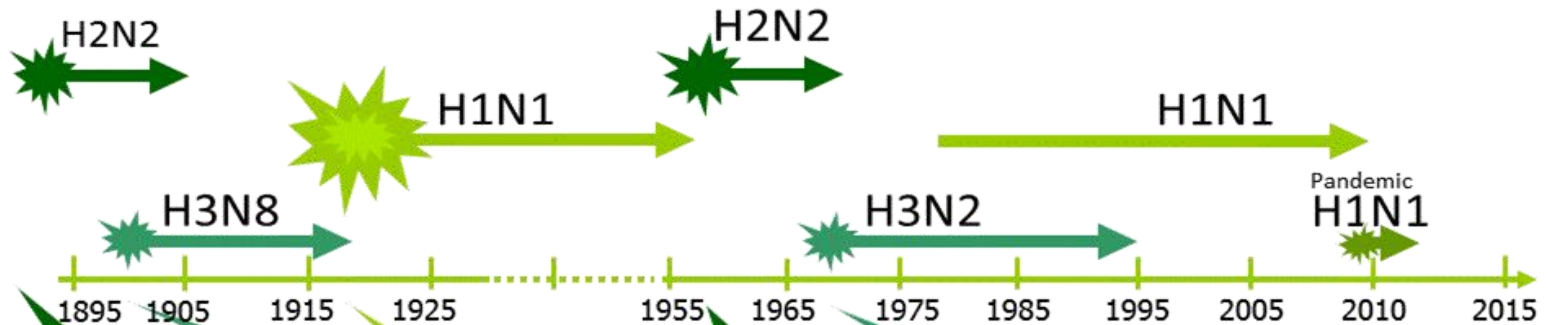
Some statistics (WHO):

- 10% of world population gets infected yearly
- associated with 250,000 – 500,000 deaths, in particular in young children, elderly, and people with other diseases

The world is not ready for a fast-moving airborne pandemic that could kill up to 80 million people, wipe out 5% of the global economy and create social chaos.



A WORLD AT RISK



1889
Russian
influenza
H2N2

1900
Old Hong Kong
influenza
H3N8

1918
Spanish
influenza
H1N1

1957
Asian
influenza
H2N2

1968
Hong Kong
influenza
H3N2

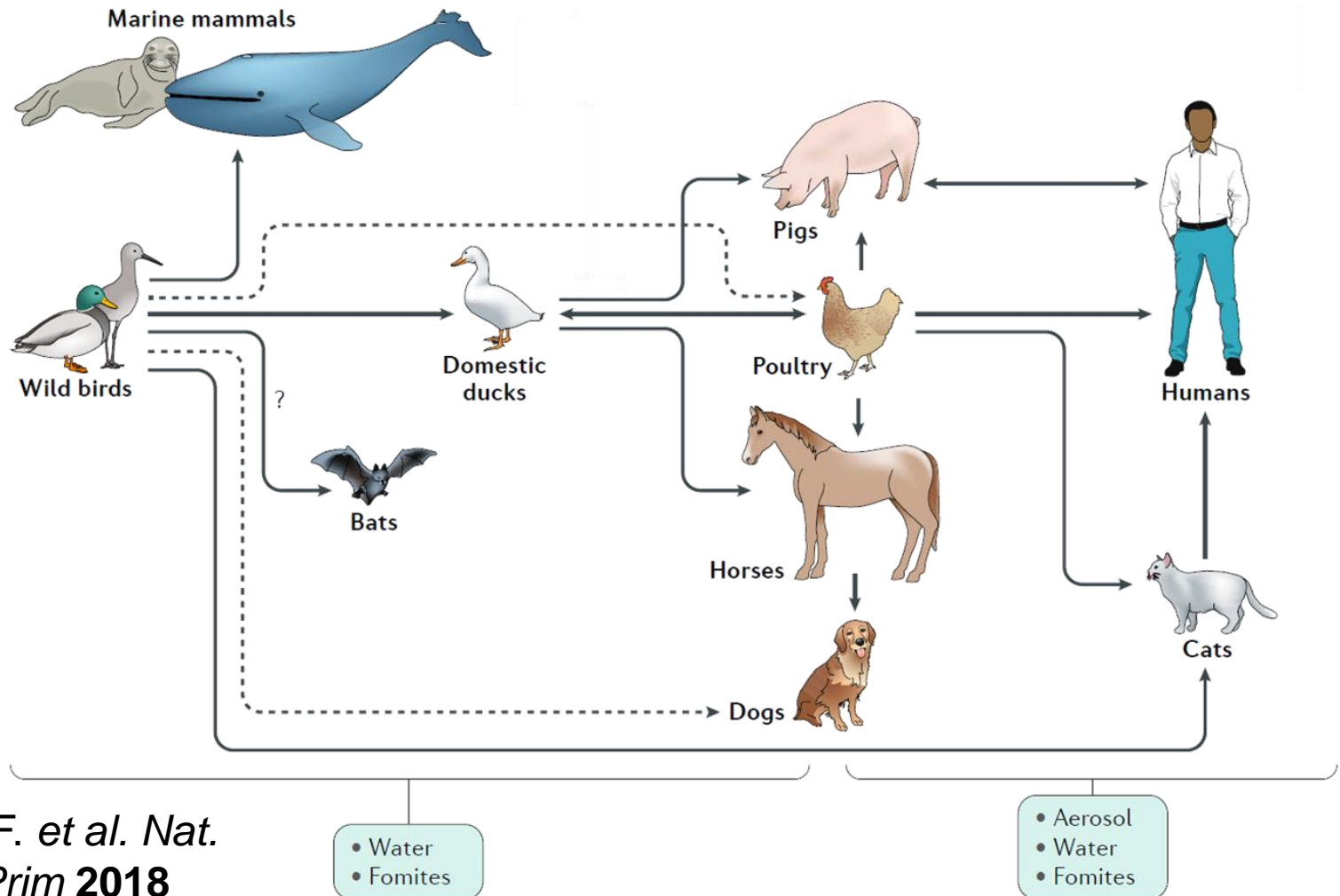
2009
Pandemic
influenza
H1N1

New avian influenzas



Influenza

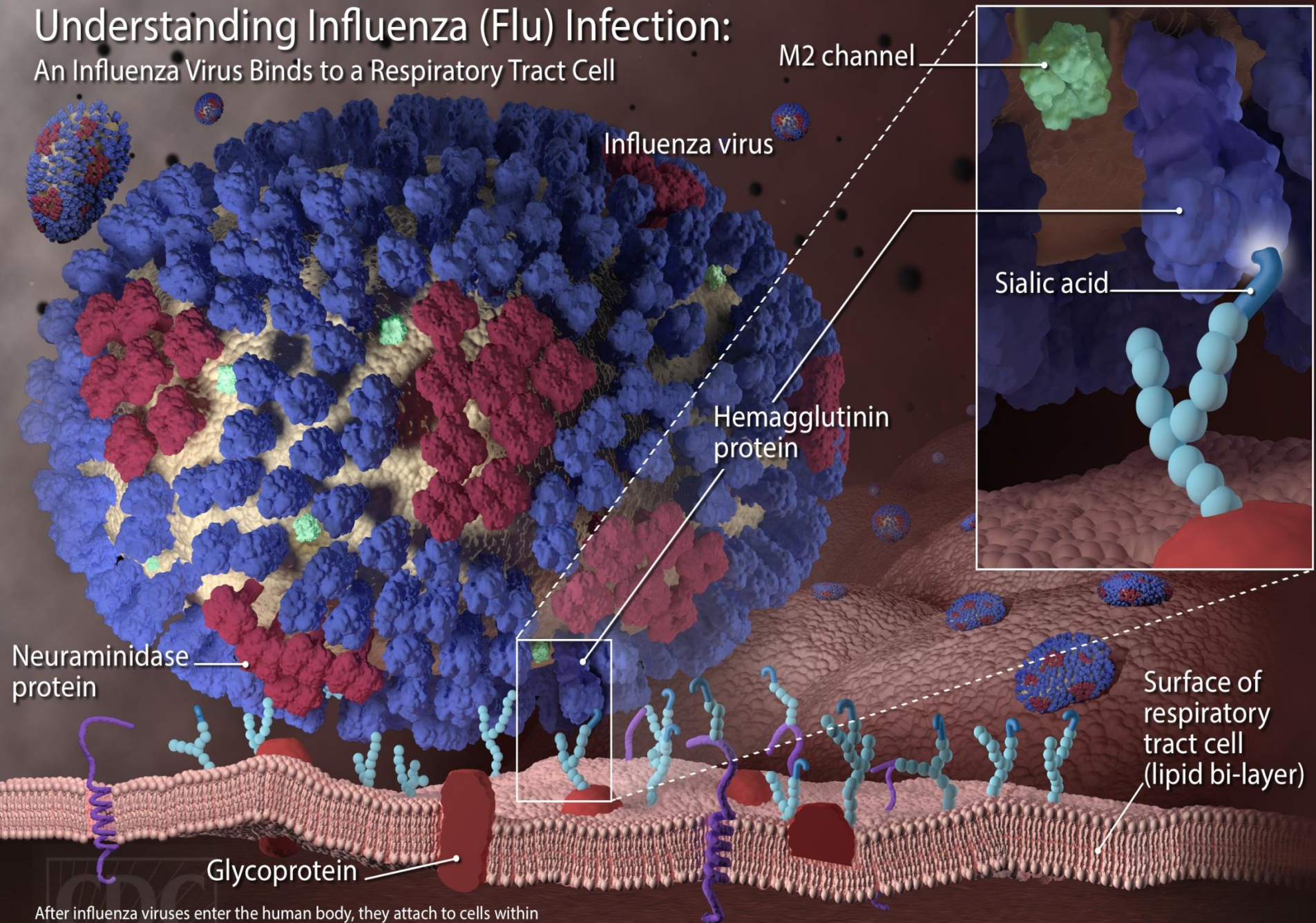
Is the flu a relatively innocent disease?
Mutations cause **zoonosis**



Krammer, F. *et al.* *Nat. Rev. Dis. Prim* 2018

Understanding Influenza (Flu) Infection:

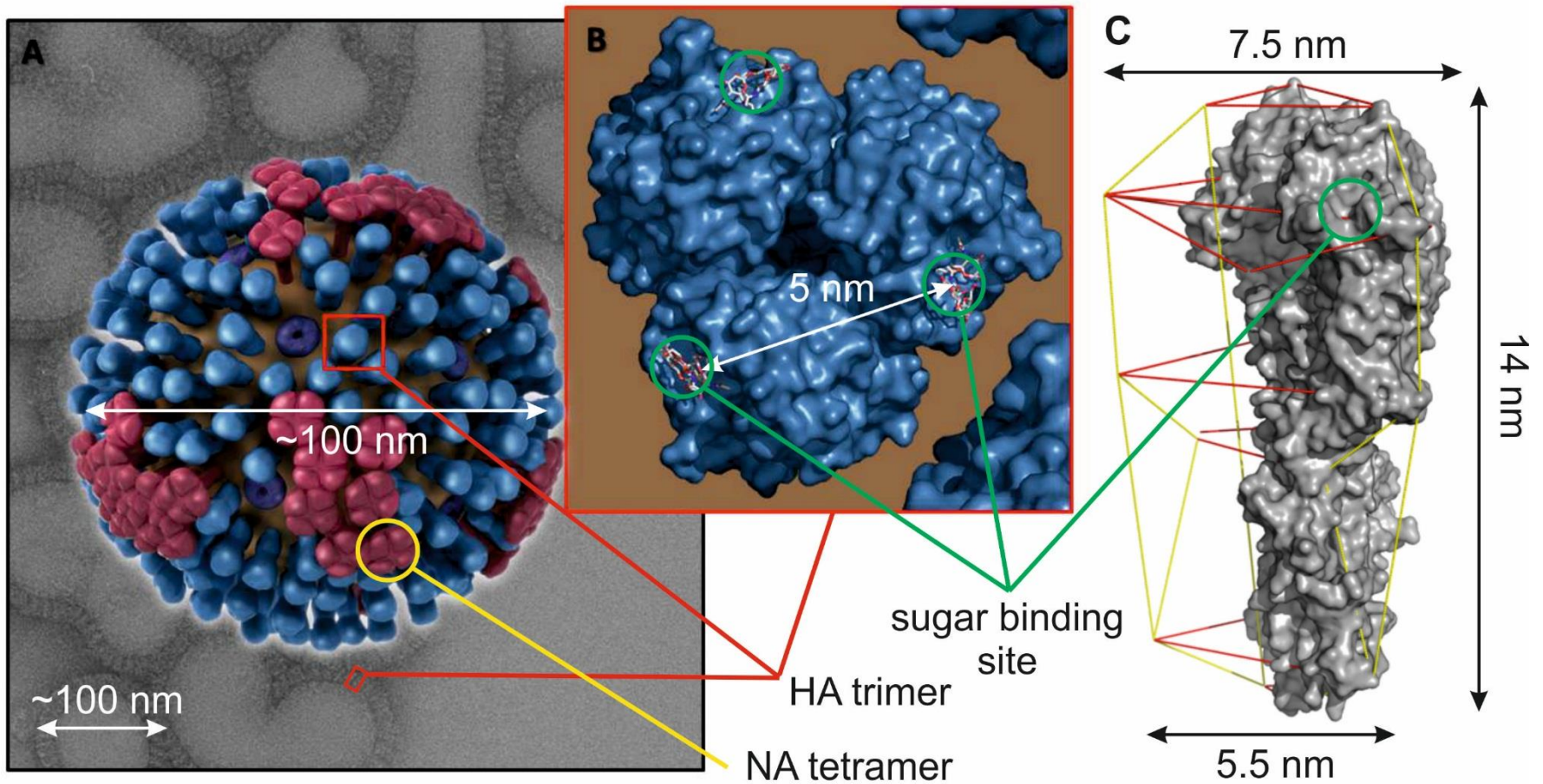
An Influenza Virus Binds to a Respiratory Tract Cell



After influenza viruses enter the human body, they attach to cells within the nasal passages and throat (i.e., the respiratory tract). The hemagglutinin (HA) surface proteins of the influenza virus bind to the sialic acid receptors on the surface of a human cell like a key to a lock. The influenza virus is then able to enter and infect the cell. This marks the beginning of a flu infection.

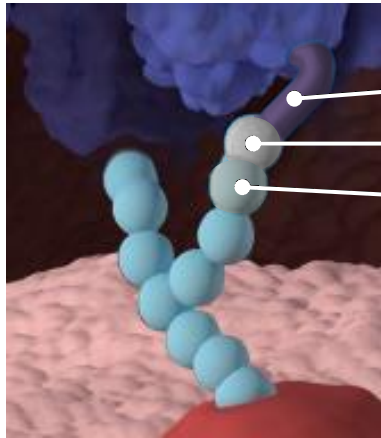
Influenza

Structure of the influenza virus:



Influenza

Basic motif of selectivity:

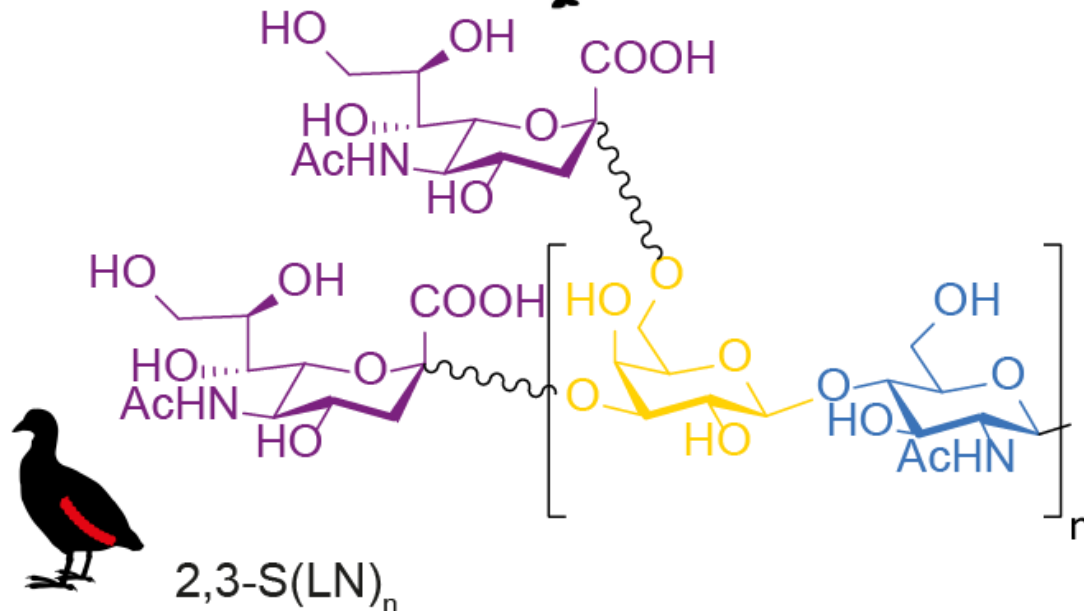


Sialic acid
Galactose
N-acetyl
glucosamine

HA affinity, in particular the **selectivity** for 2,6-SLN/2,3-SLN (human vs avian receptor) is a **good indicator** for bird to mammal **transmissibility**

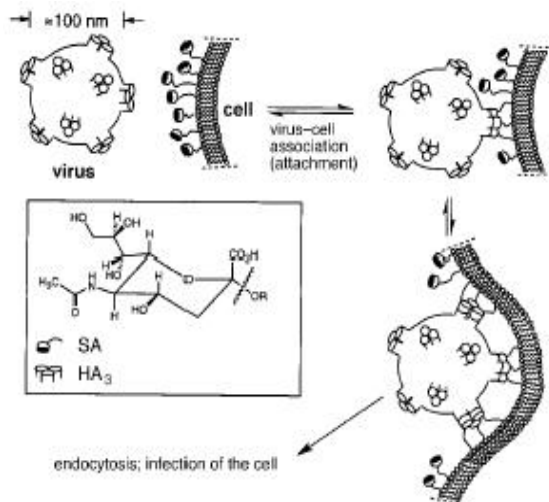
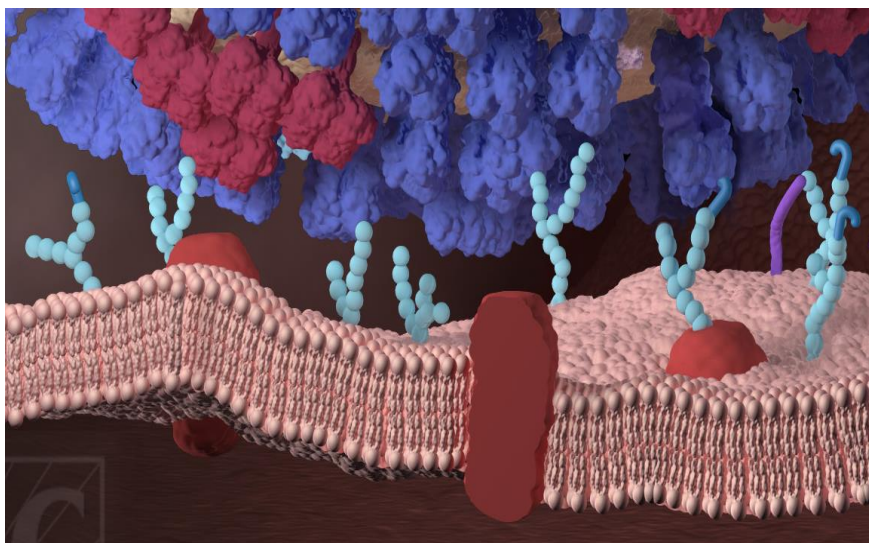


2,6-S(LN)_n



The molecular “picture”

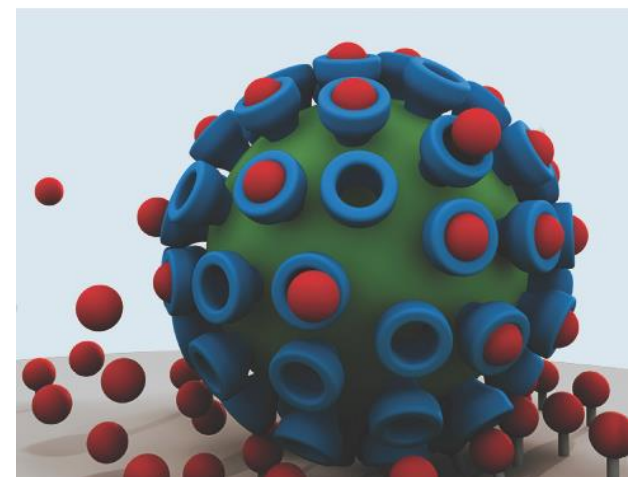
What can a chemist contribute to flu virology?
Viruses interact by **multivalent interactions**:



Edited by
Jurriaan Huskens
Leonard Prins
Rainer Haag
Bart Jan Ravoo

Multivalency

Concepts, Research & Applications



Mammen, Choi,
Whitesides, *Angew
Chem Int Ed* **1998**,
37, 2754

OBC **2004**, 2, 3409

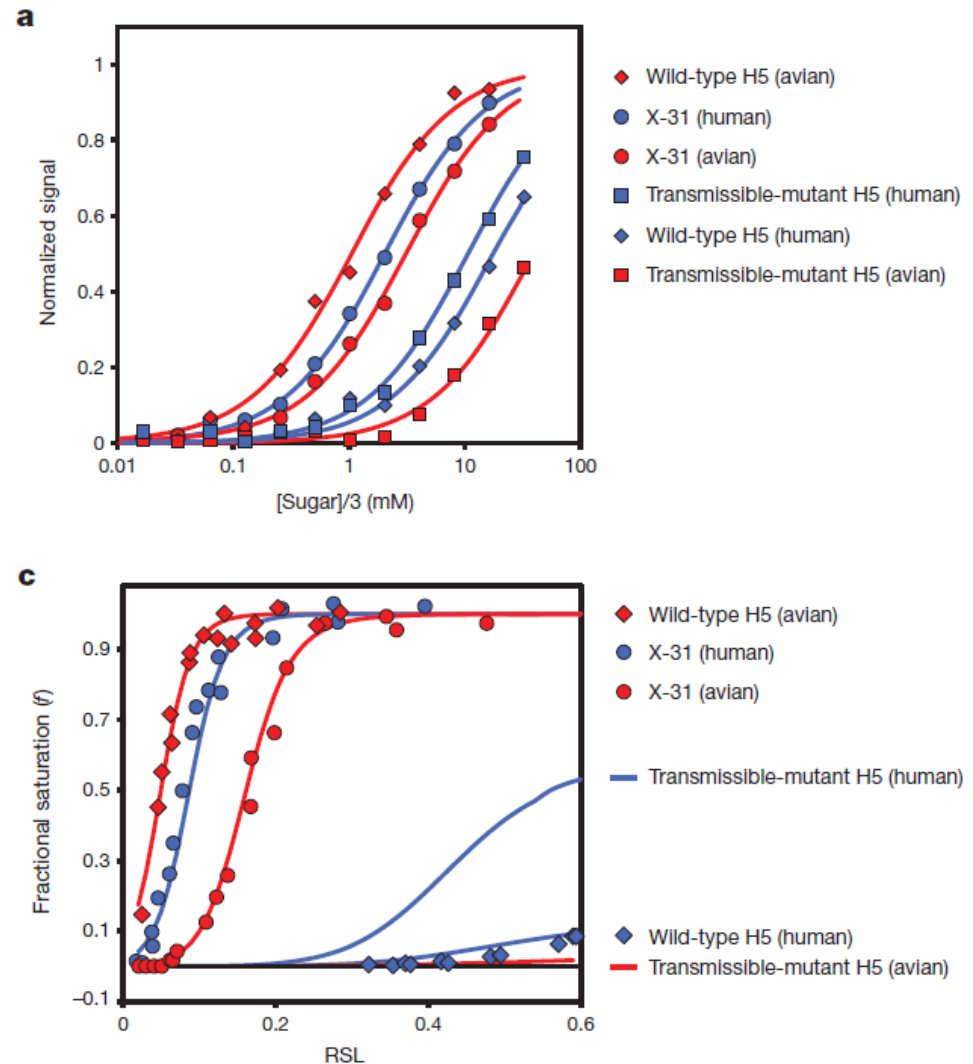
Chem Sci **2020**, 11, 27

The molecular “picture”

Monovalent vs multivalent:
Use of biolayer interferometry
(BLI):

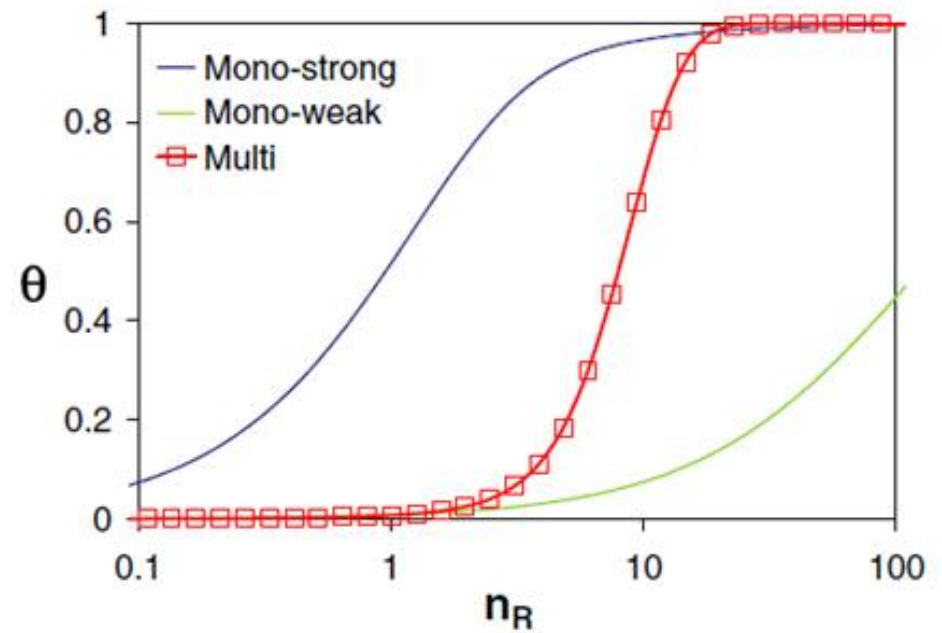
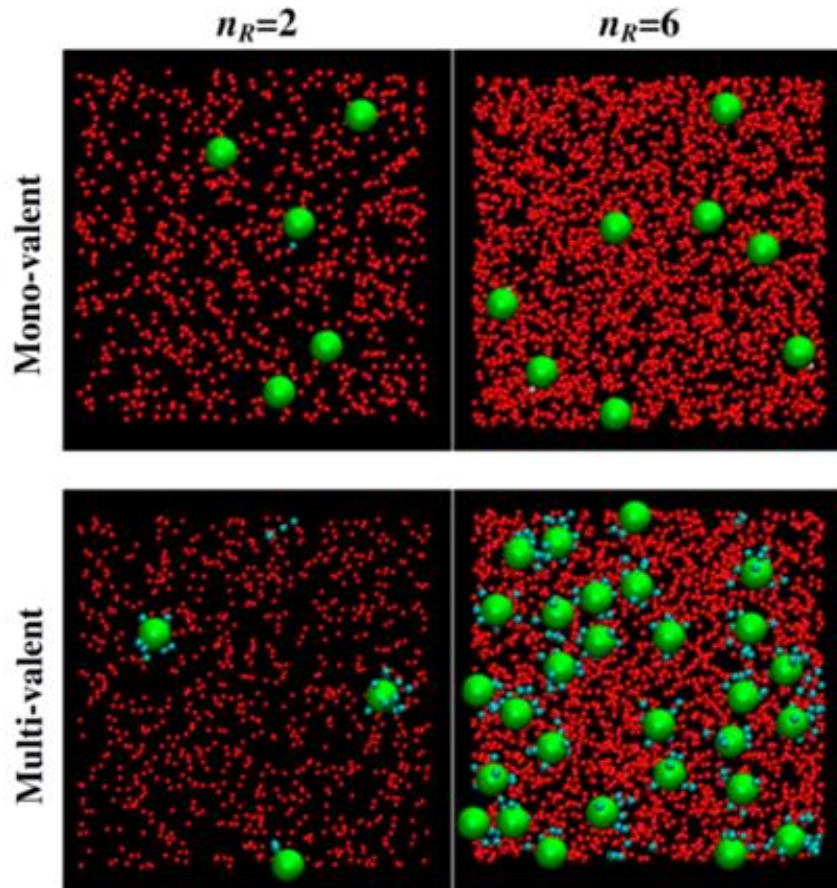
Monovalent affinities in the **mM range** and within 1 order of magnitude

Multivalent affinities differ by **orders of magnitude** and with a strong **dependence on receptor surface density**



Superselectivity

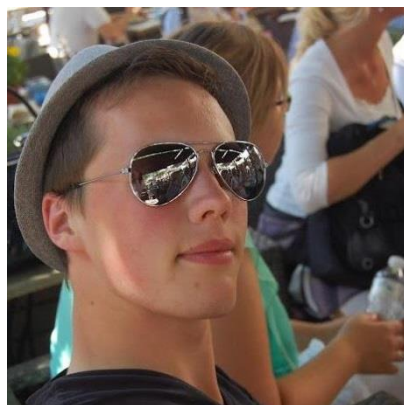
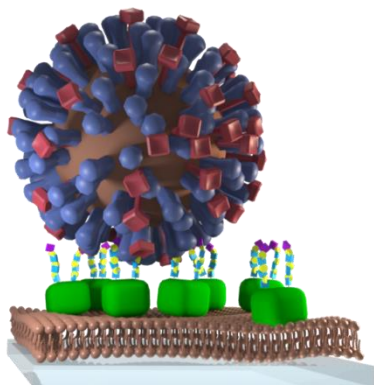
Superselectivity:



Multivalent Affinity Profiling



Direct visualization of superselective binding of influenza at surface gradients:



Nico Overeem



Erik Hamming



Erhard van der Vries



Robert de Vries



Geert-Jan Boons



Robert Woods

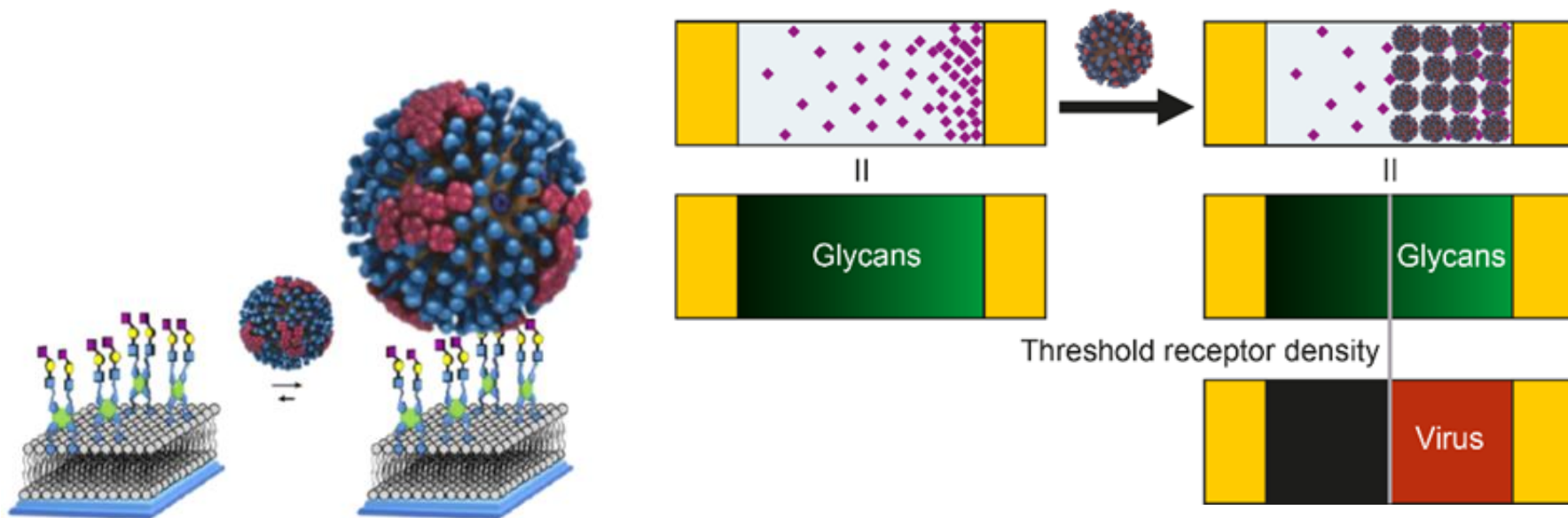


Nick Tito

Multivalent Affinity Profiling



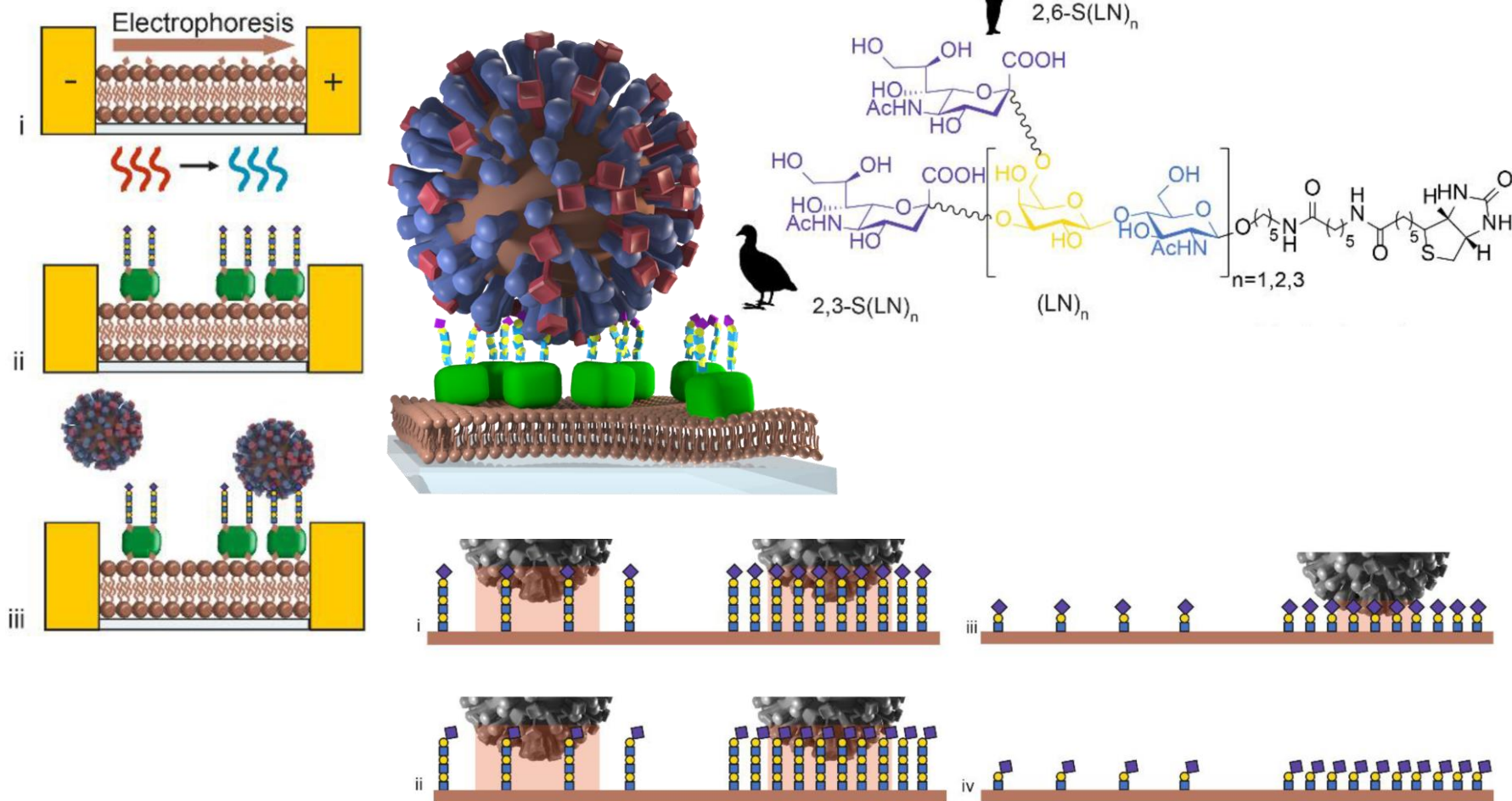
A multivalent sensing concept: Multivalent Affinity Profiling (MAP):



Multivalent Affinity Profiling

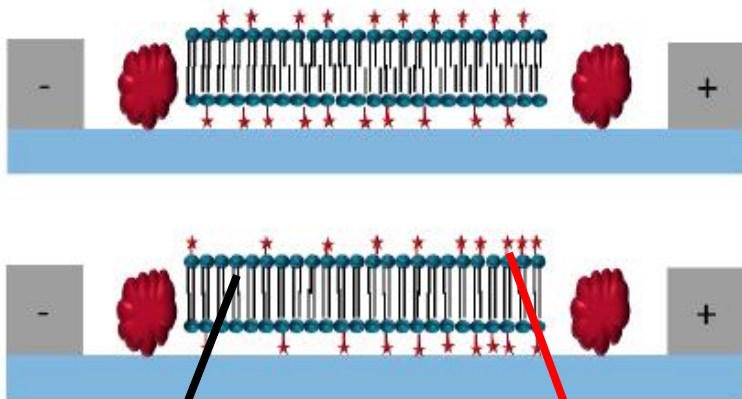


Multivalent Affinity Profiling: the platform:

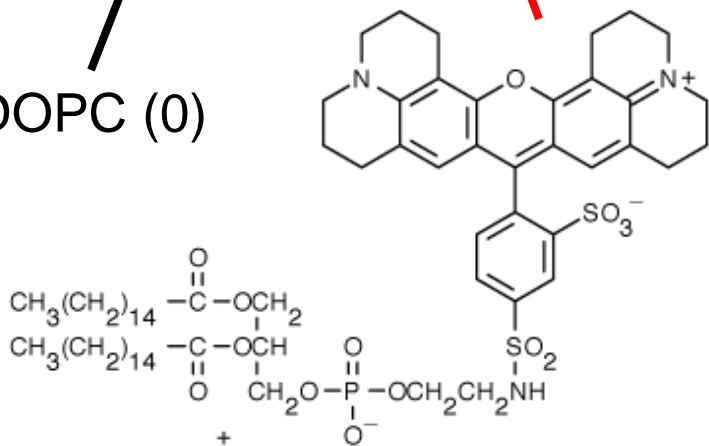


Gradients in lipid membranes

Experimental design: supported lipid bilayers (SLBs):

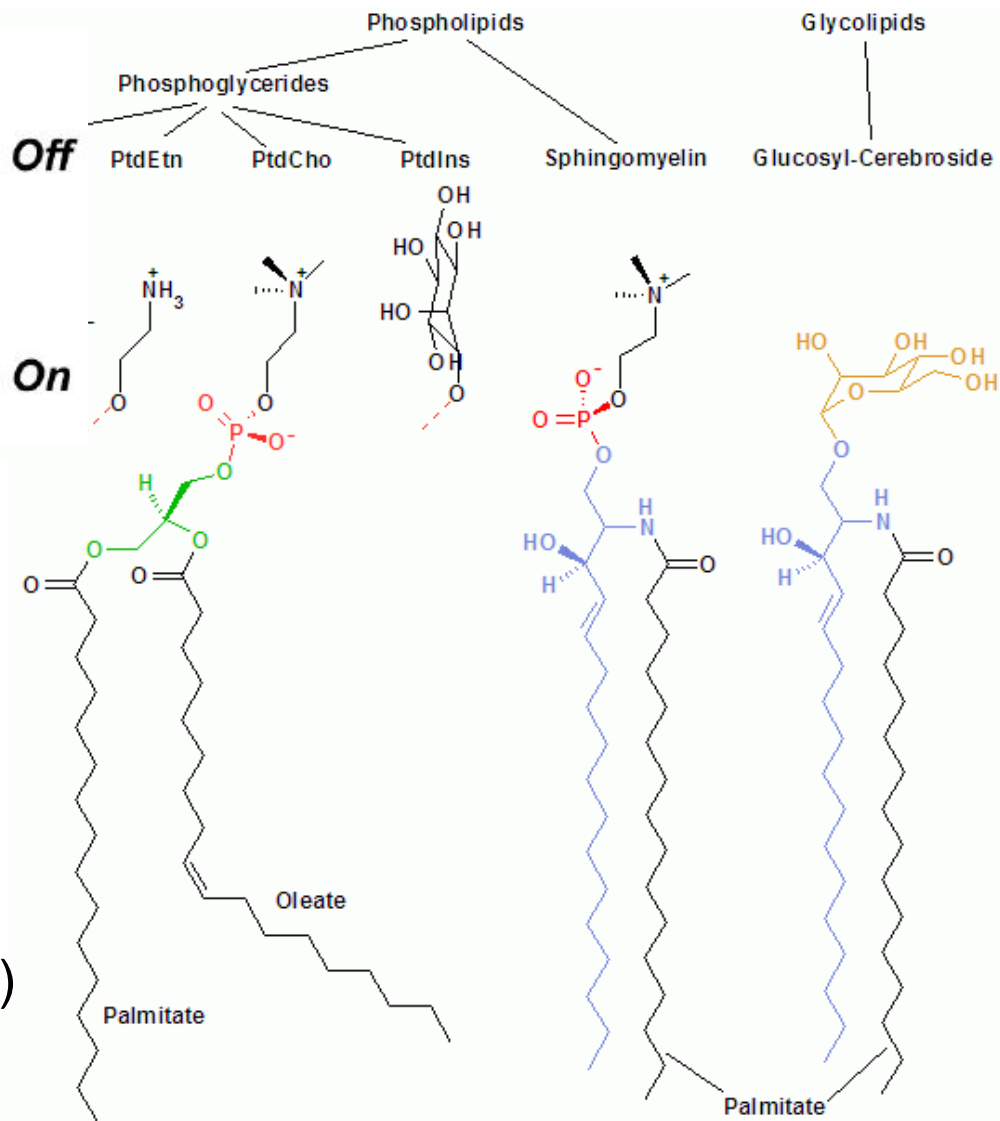


DOPC (0)



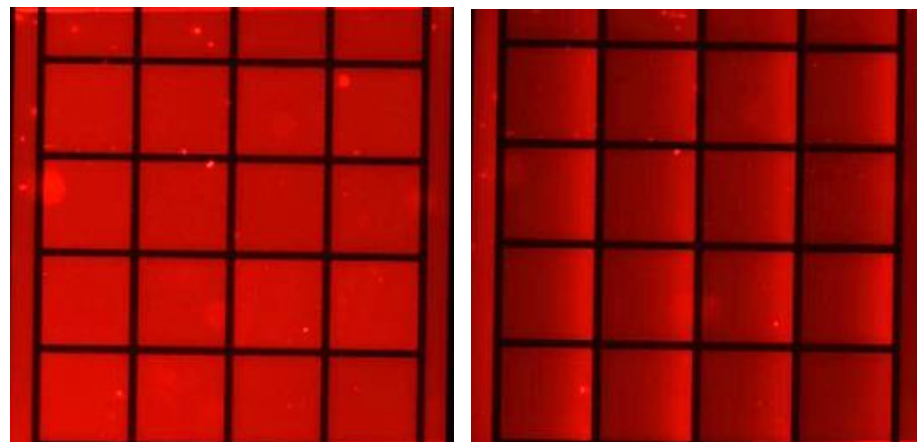
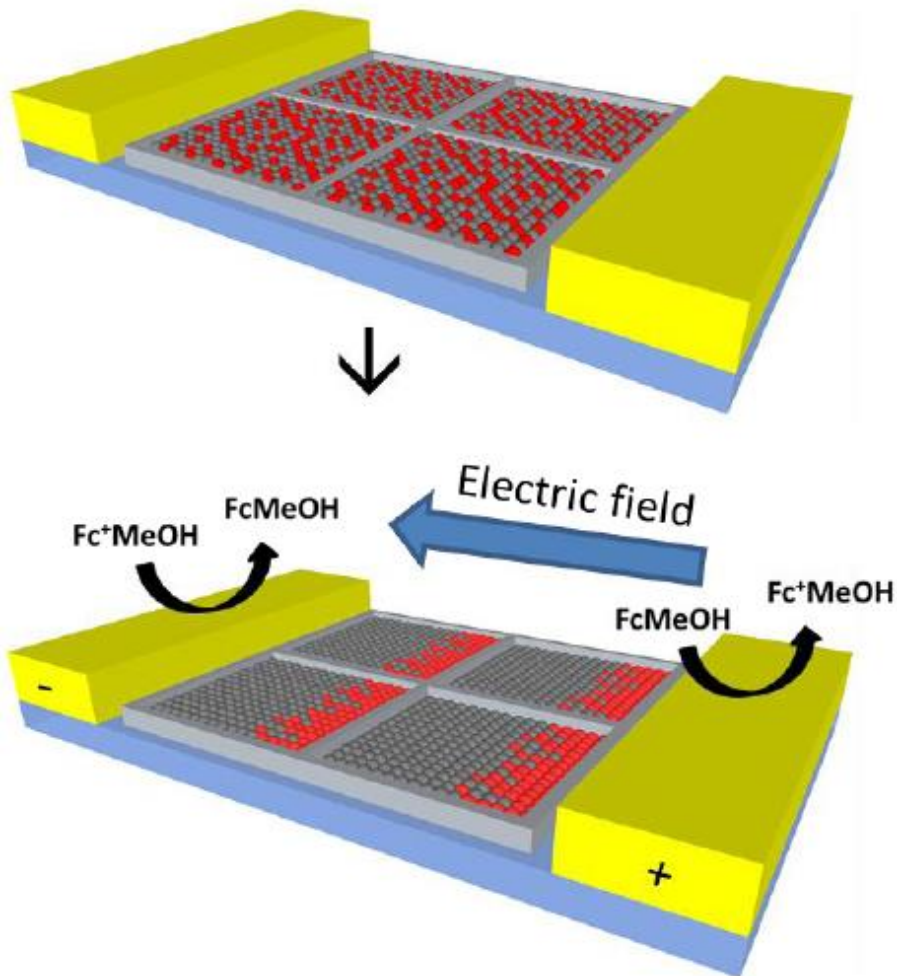
Texas red-DHPE (-)

JACS 2014, 136, 100



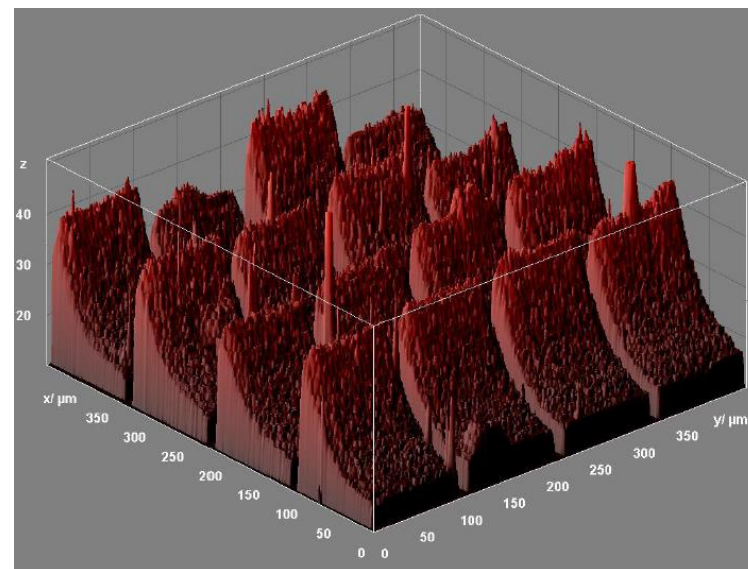
Gradients in lipid membranes

Experimental design & gradient formation:



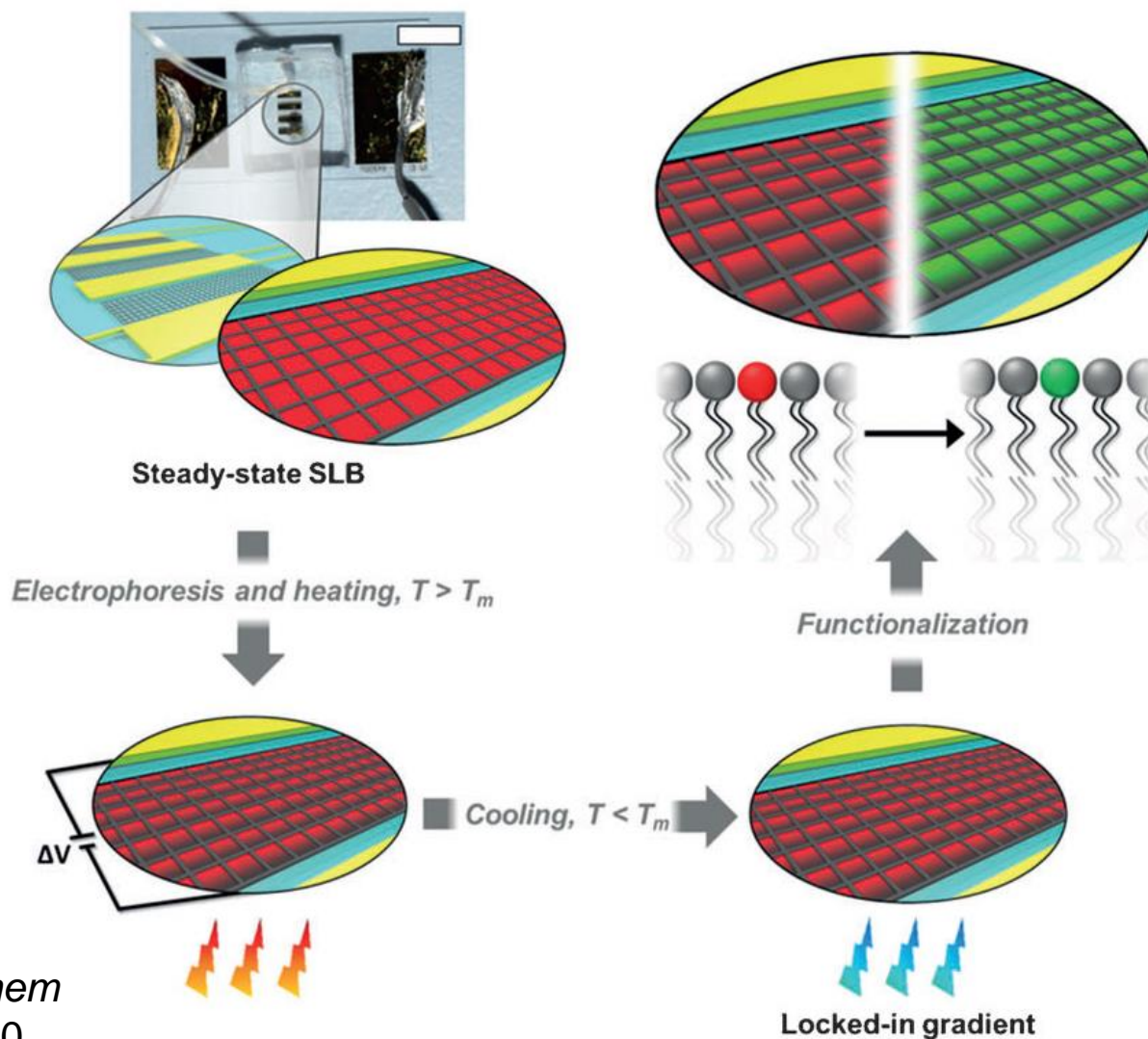
Before

1.2 V, 20 min



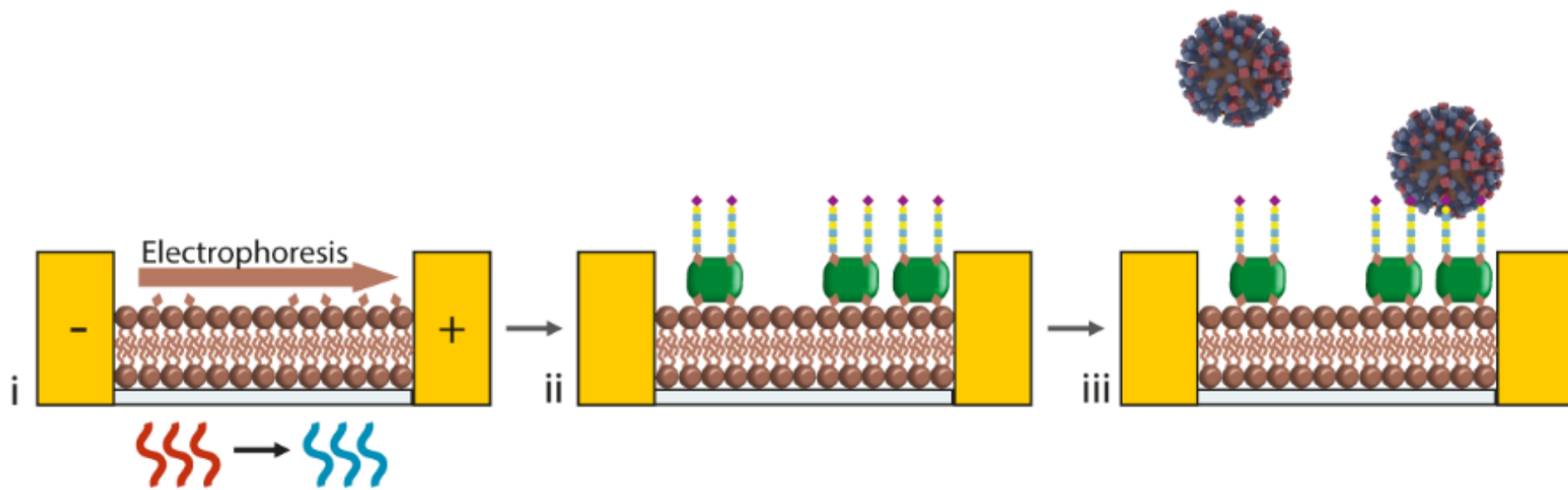
Gradients in lipid membranes

Fixation of the gradient in supported lipid bilayers:



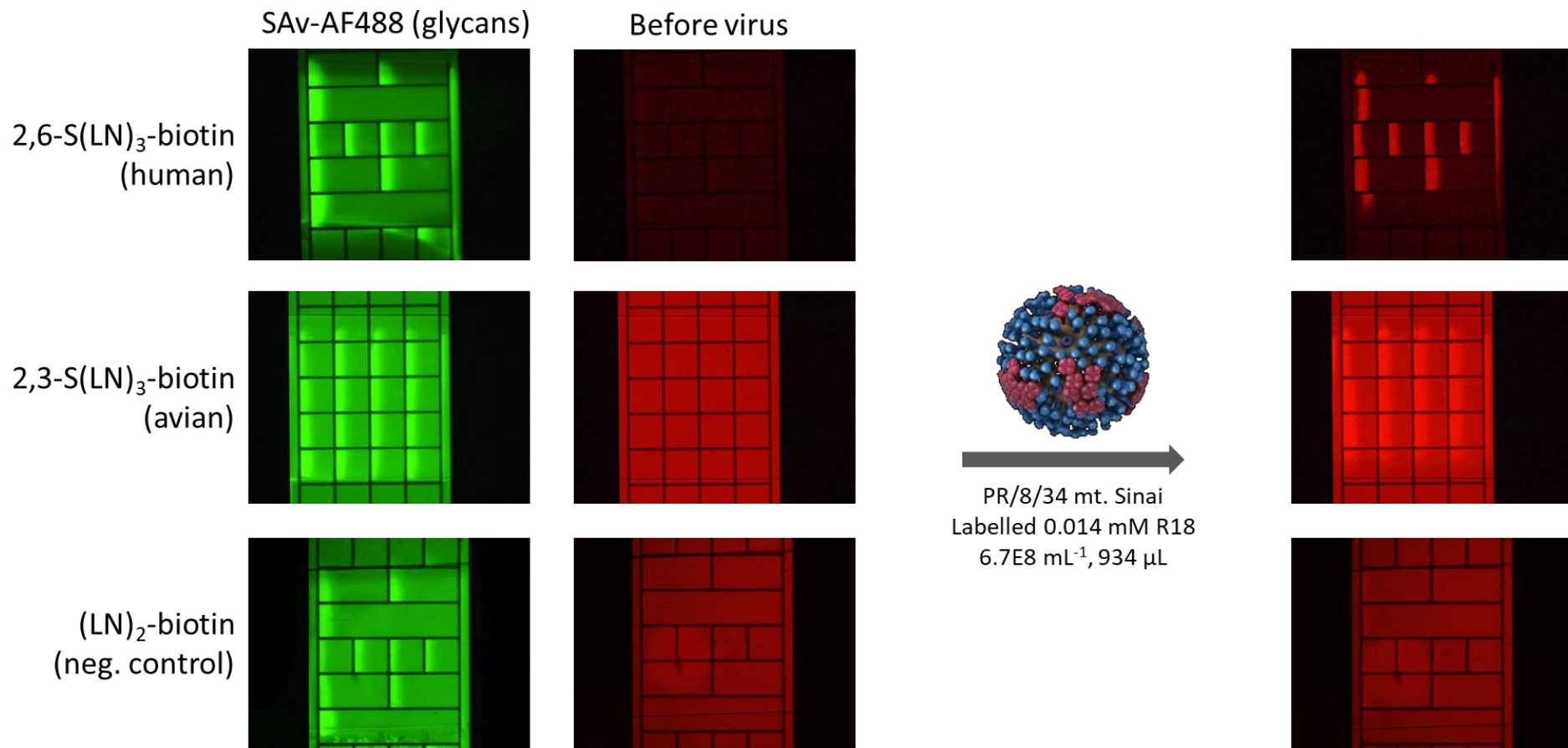
Multivalent Affinity Profiling

Influenza viruses at surface gradients:
Surface chemistry:



Multivalent Affinity Profiling

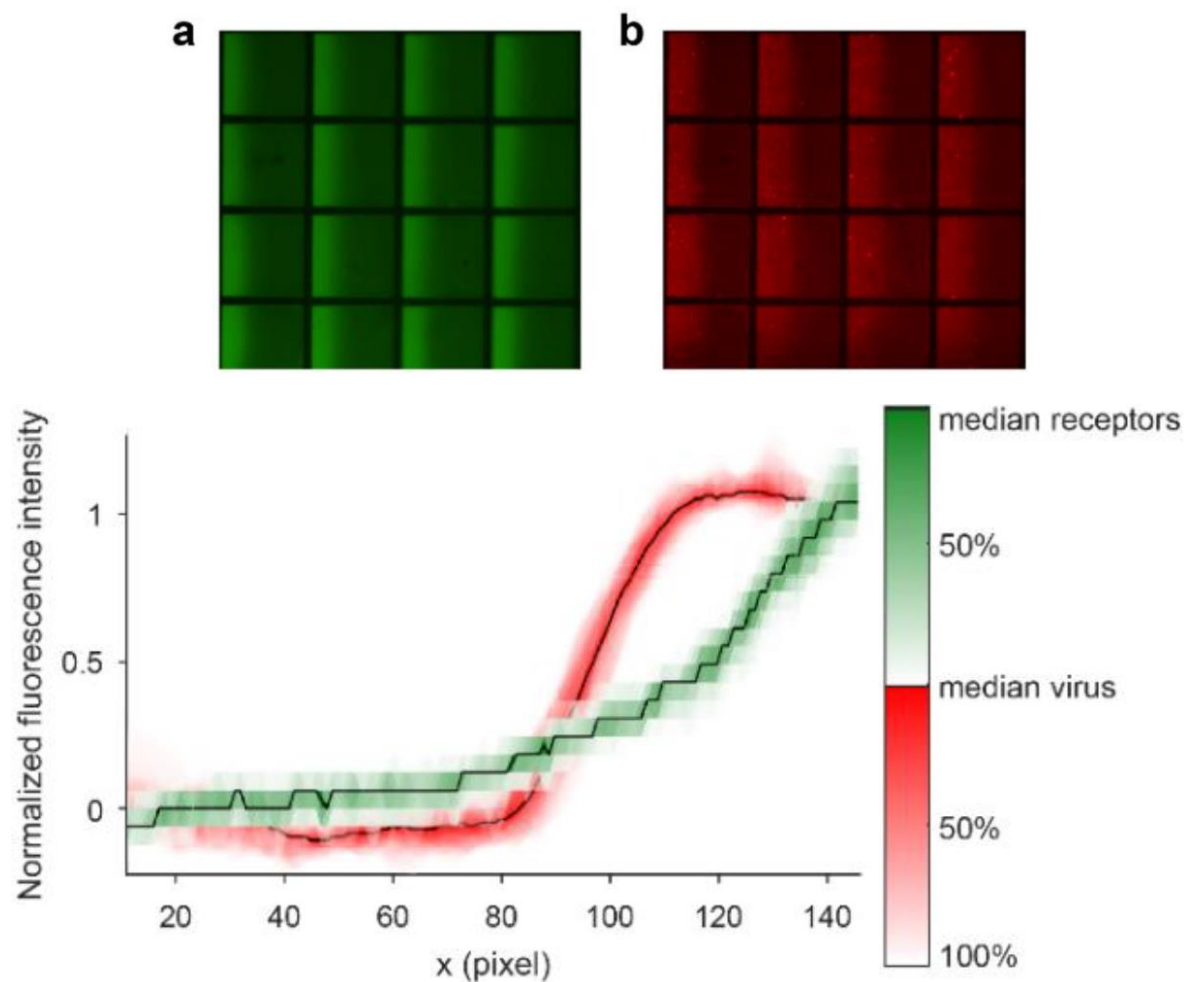
Influenza viruses at surface gradients:
Fluorescence detection of (labeled) virus binding:



Multivalent Affinity Profiling

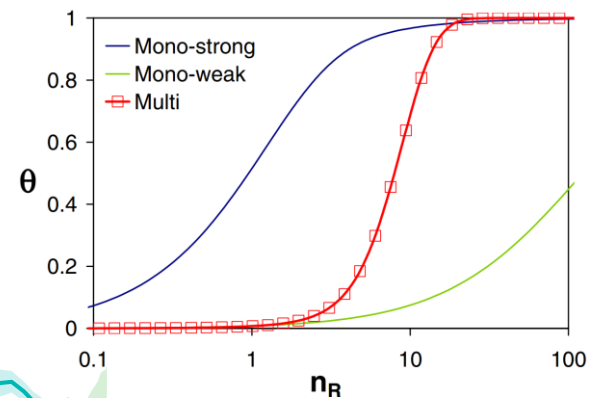
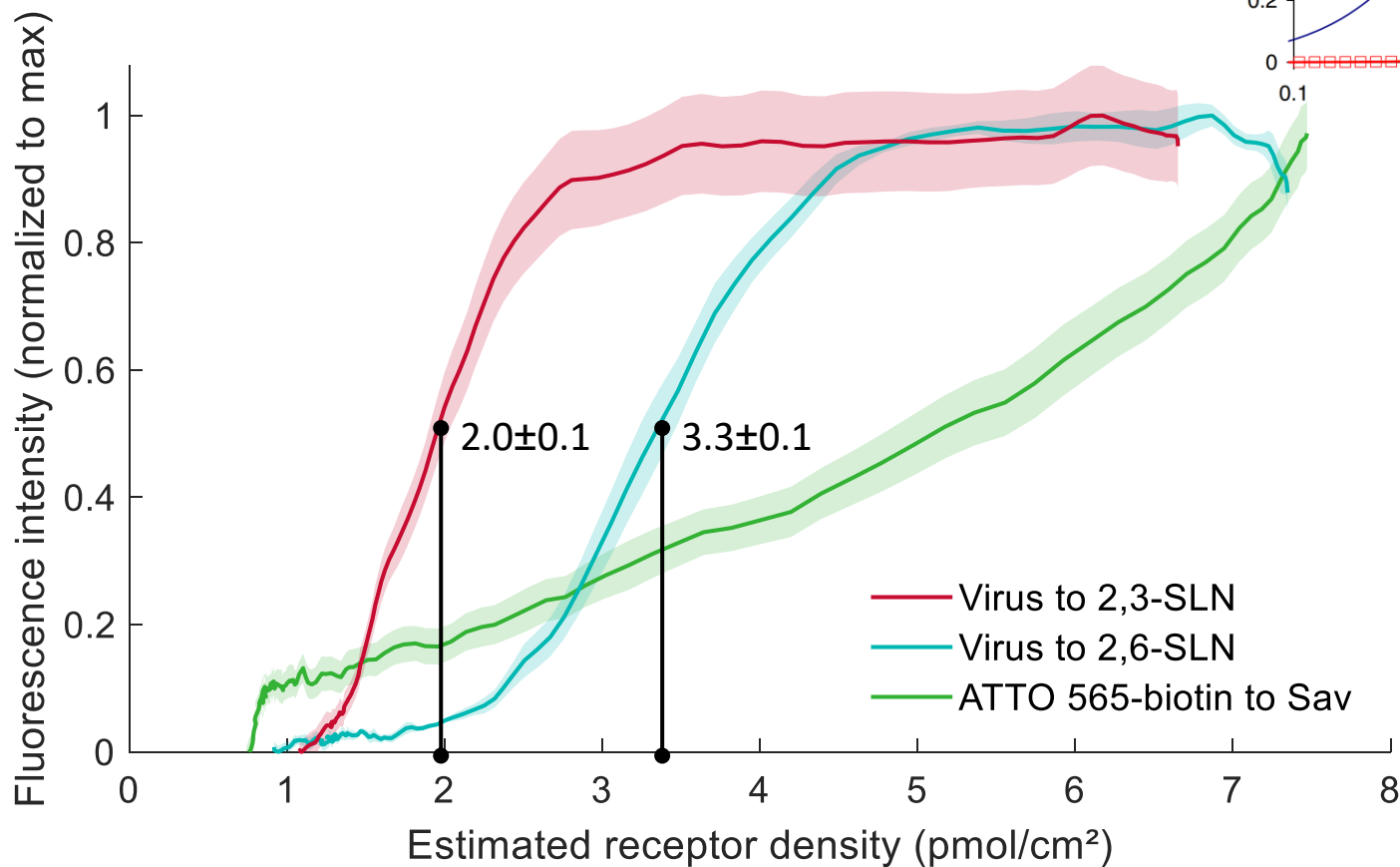


Multivalent Affinity Profiling: fluorescence microscopy:



Multivalent Affinity Profiling

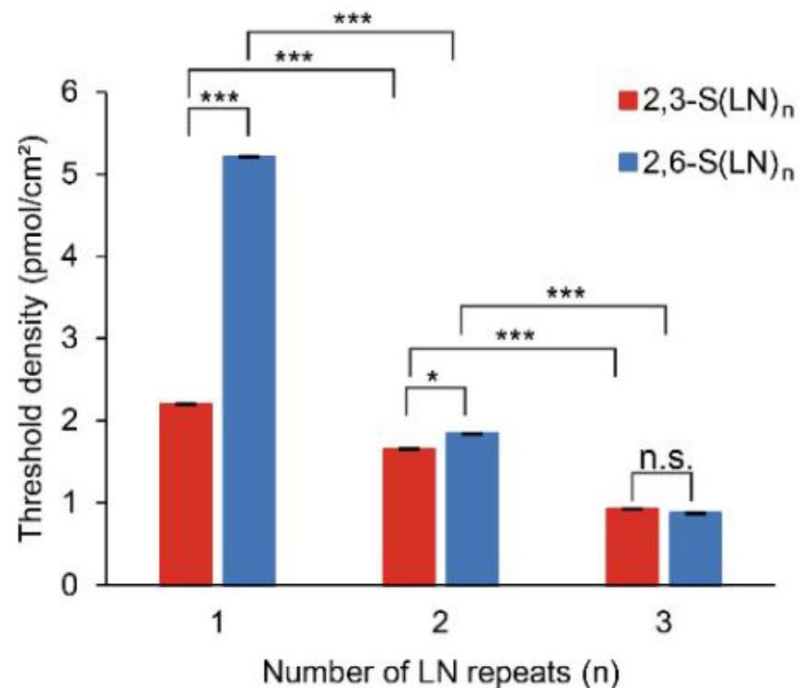
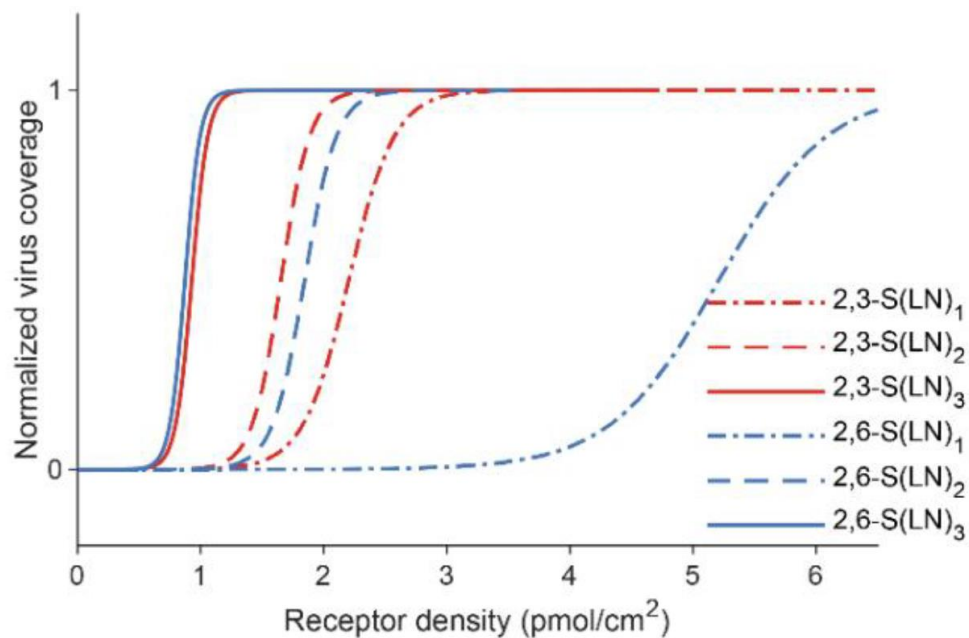
Influenza viruses at surface gradients:
Detection of threshold density:



Multivalent Affinity Profiling



Multivalent Affinity Profiling: threshold densities for different glycans:



Why is the binding more sensitive to glycan length for the 2,6-glycan??

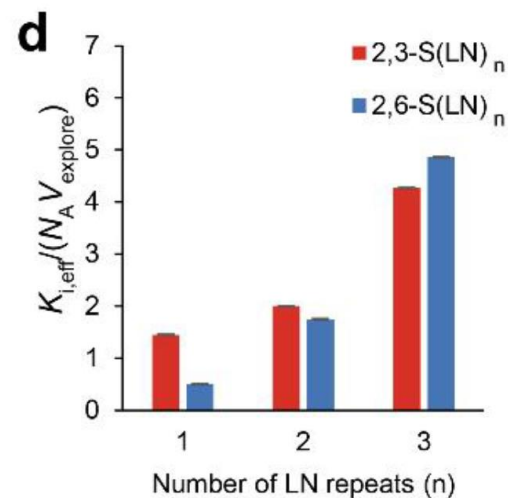
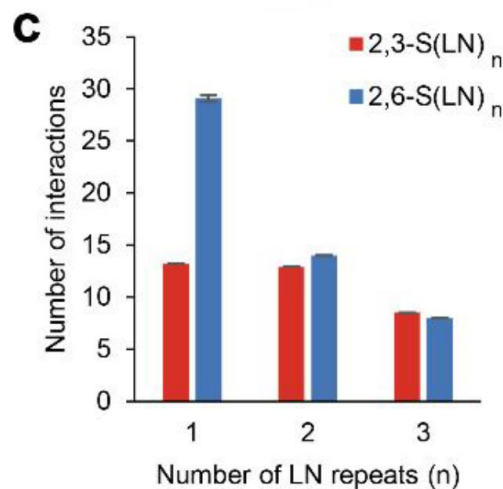
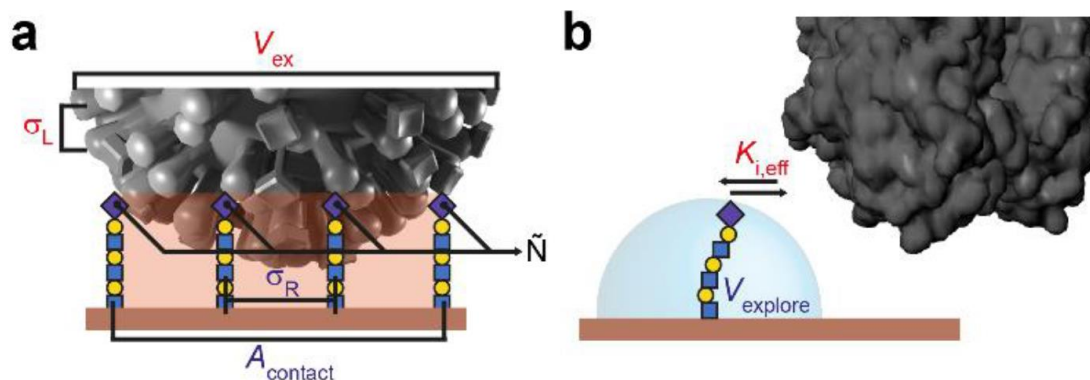
A multivalent model of influenza binding



Development of a multivalent thermodynamic model for influenza:

$$K_{av} = N_A V_{ex} \left(1 + \frac{K_{i,eff}}{N_A V_{explore}} \right)^{\tilde{N}}$$

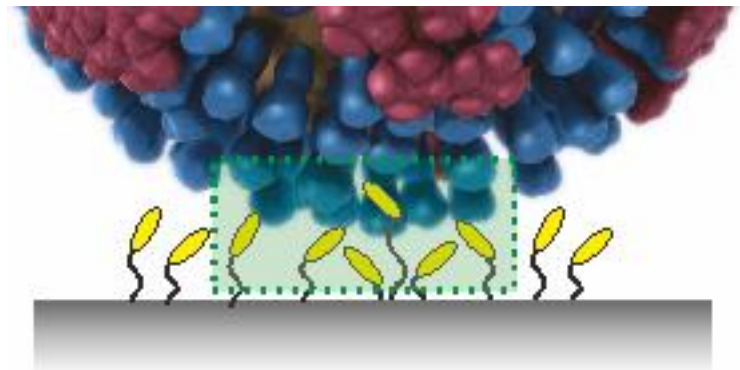
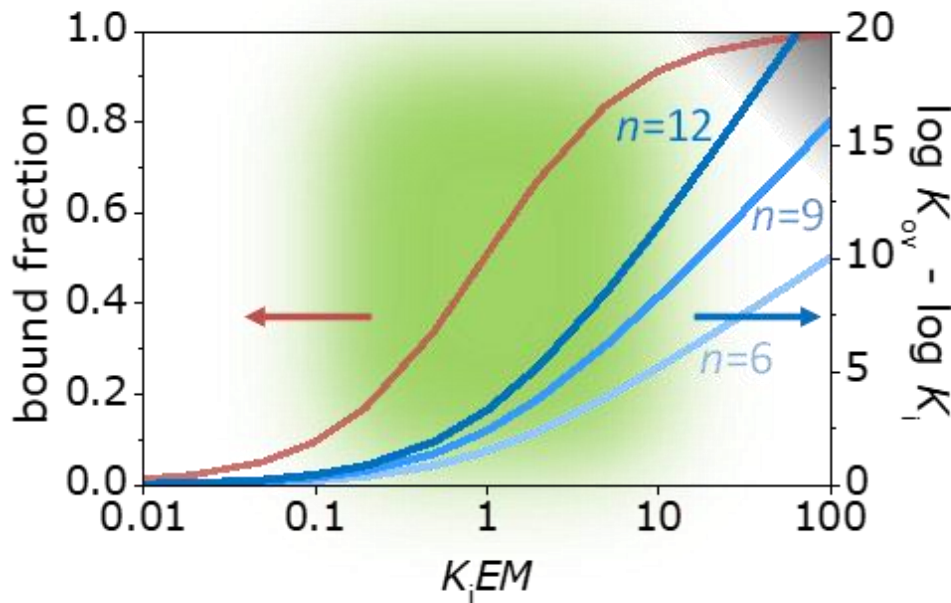
$$\tilde{N} = A_{contact} \cdot \min(\sigma_R, \sigma_L)$$



A multivalent model of influenza binding

Hypothesis:

Biological systems occupy a 'sweet spot' in the binding energy landscape !? **Weakly multivalent** !?



Interaction is **dynamic**:

- $K_i/N_A V = 2-10$
- each site is 10-20% of the time unbound
- bound & unbound lifetimes \sim ms

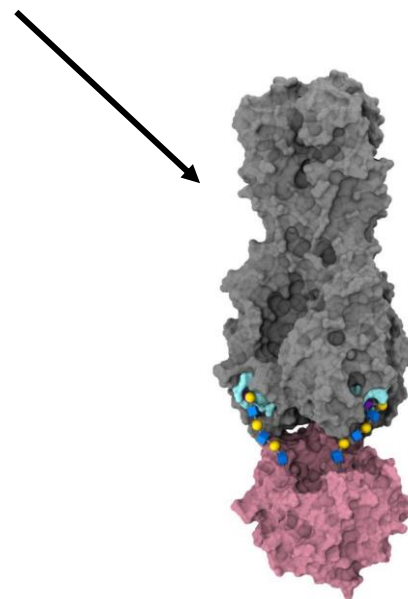
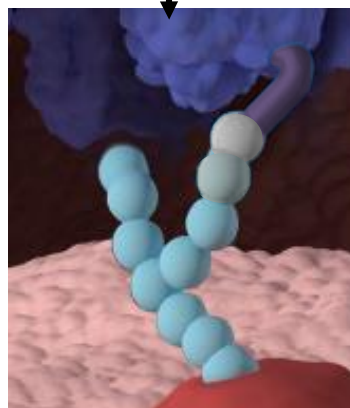
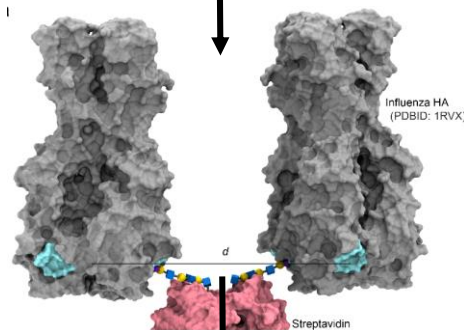
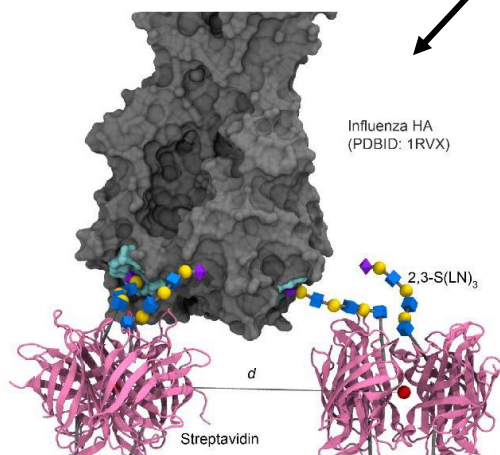
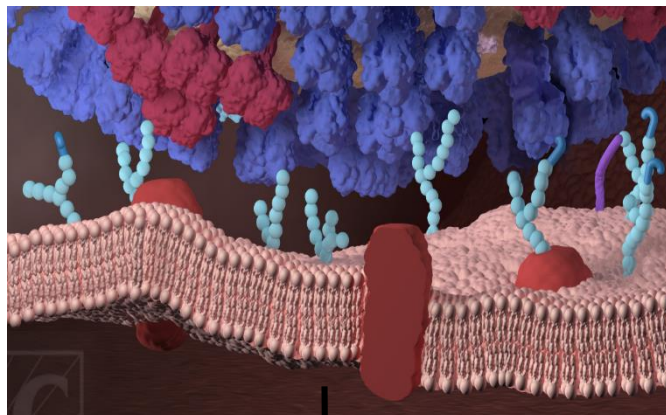
ACS Central Science **2020**, 6, 2311

ACS Nano **2019**, 13, 3413

A multivalent model of influenza binding



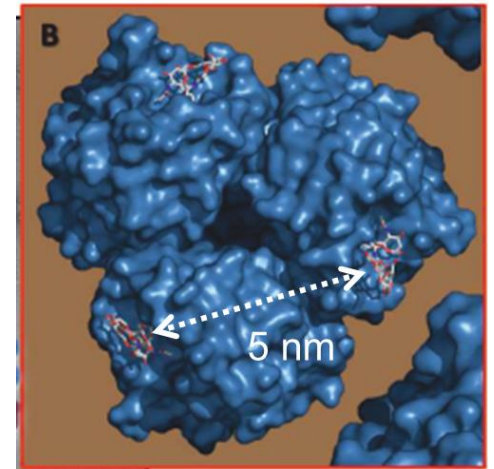
Hierarchical multivalent effects control influenza host specificity:



Influenza

Hypothesis:

Biological systems occupy a 'sweet spot' in the binding energy landscape !?
Weakly multivalent !?



New questions arise:

- Why are the binding sites of HA positioned so far apart? Does the resulting **low EM lead to an evolutionary advantage?**
- What is the **role of NA?** Reactivity (splitting off the terminal sialic acid) to reduce EM?
- What are the effects of HA and NA density and clustering on virus binding?
- What is the impact of **HA and NA mutations** on virus binding? And on crossing the inter-species barrier?
- Can we make **new small-molecule based virus inhibitors?**

Etc...

Small 2021, in press

UNIVERSITY OF TWENTE.

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MOLECULAR
NANO FABRICATION

Financial support:

MESA+

INSTITUTE FOR NANOTECHNOLOGY



Nederlandse Organisatie voor
Wetenschappelijk Onderzoek



MARIE CURIE ACTIONS

MULTI-APP



European
Commission

Horizon 2020
European Union funding
for Research & Innovation



VolkswagenStiftung



European Union



European Regional Development Fund

ULTRAPLACAD