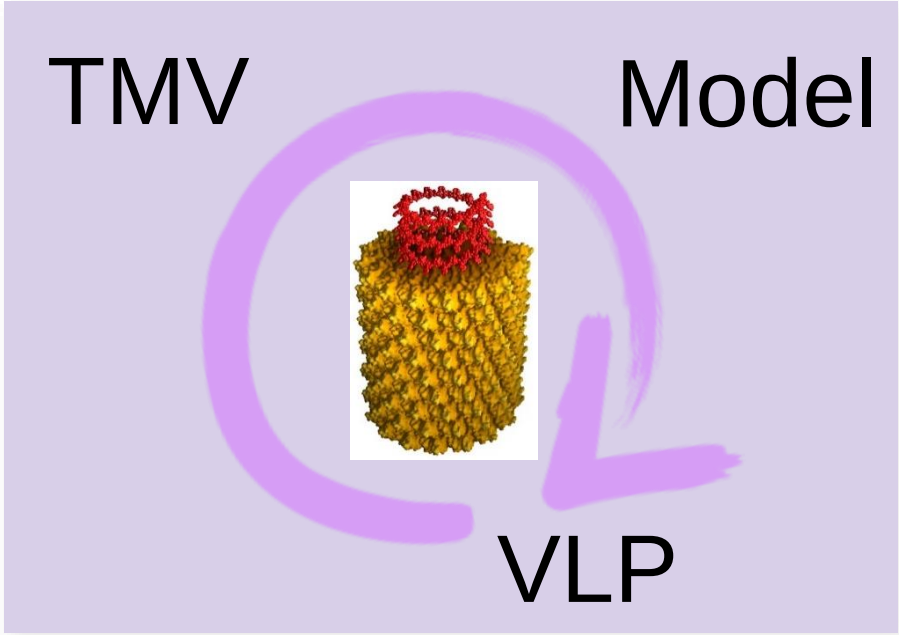
Self-Assembly Dynamics of Linear Virus-like Particles: Theory and Experiment



Paul van der Schoot

TU/e Technische Universiteit Eindhoven University of Technology

Universiteit Utrecht

Collaborators

Experiments

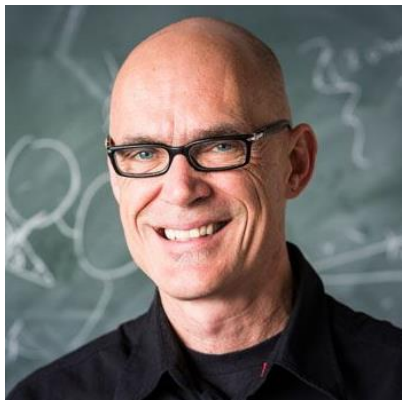
Theory

Armando Hernandez-Garcia

Renko de Vries

Daniela Kraft

Melle Punter



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Universiteit Utrecht

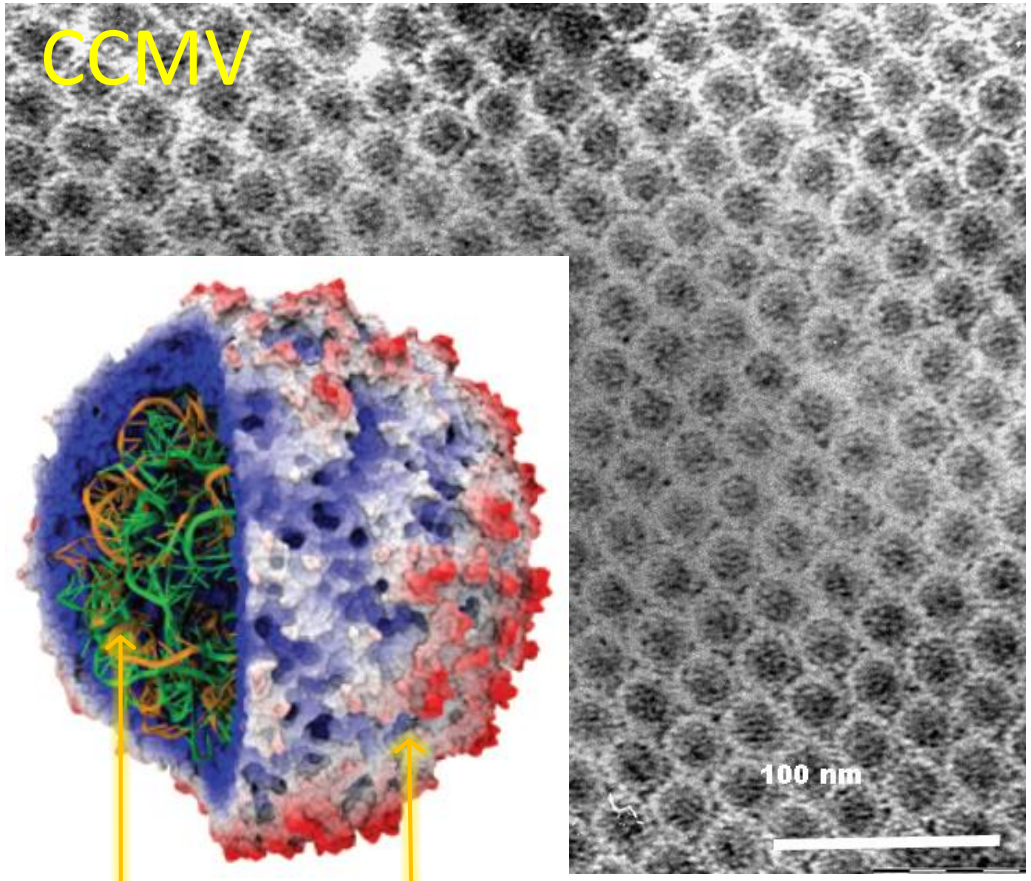
Funding:

NWO

DPI
DUTCH POLYMER INSTITUTE

HFSP

Simple viruses

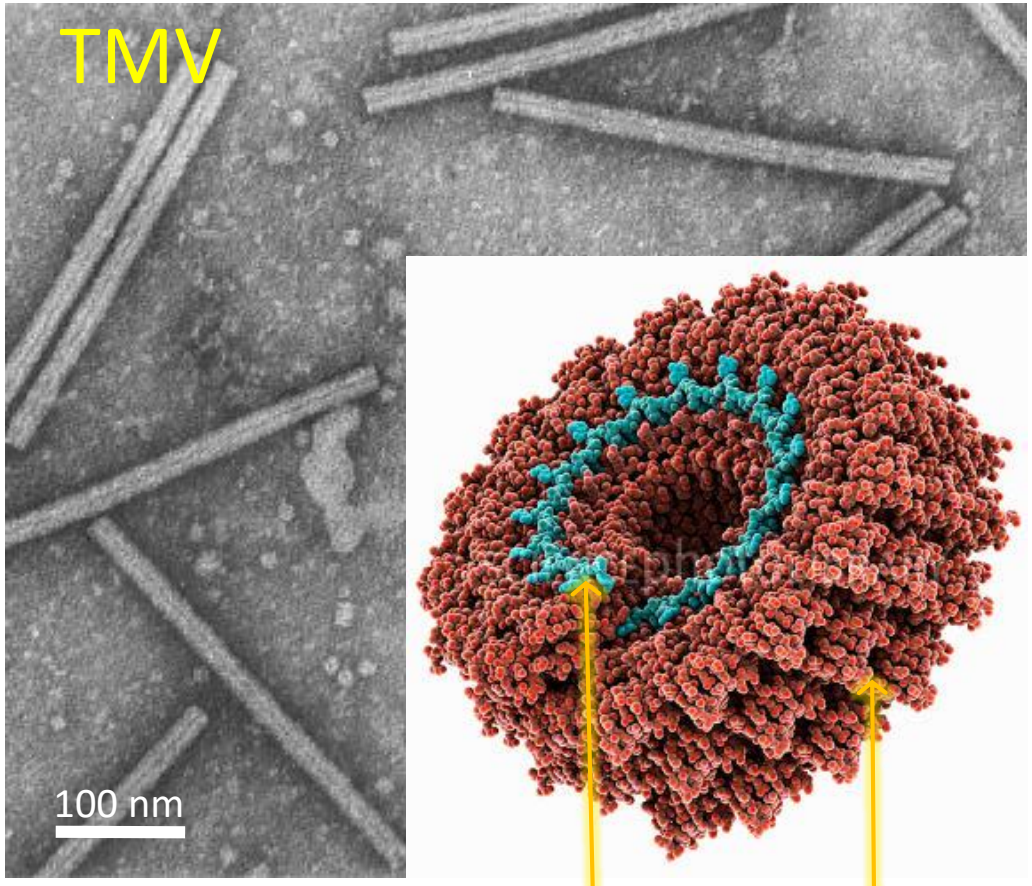


www.vcbio.science.ru.nl/en/fesem/tem/

ss RNA
(3000 nts)

coat protein
(180 copies)

deskeng.com/articles/aaahnd.htm



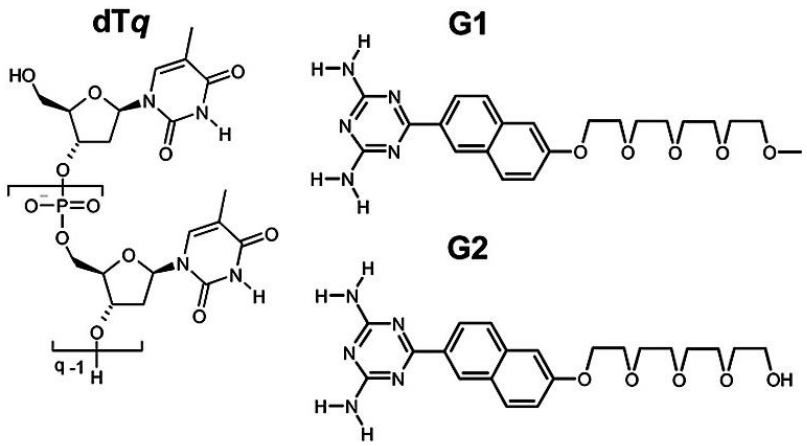
www.apsnet.org/edcenter/intropp/lessons/viruses/pages/tobaccomosaic.aspx

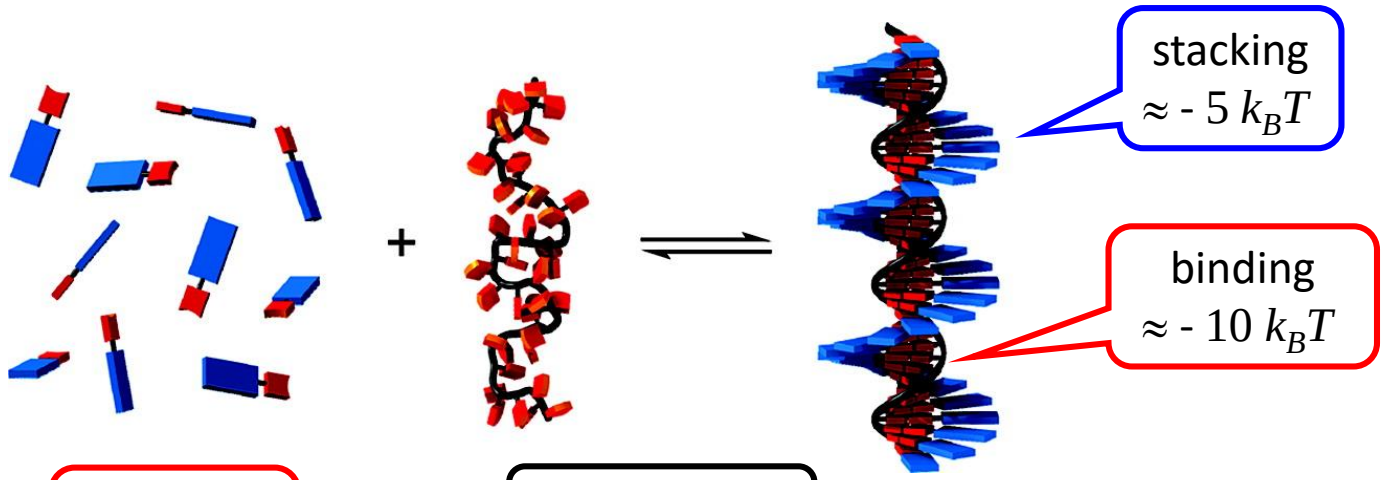
ss RNA
(6400 nts)

coat protein
(2100 copies)

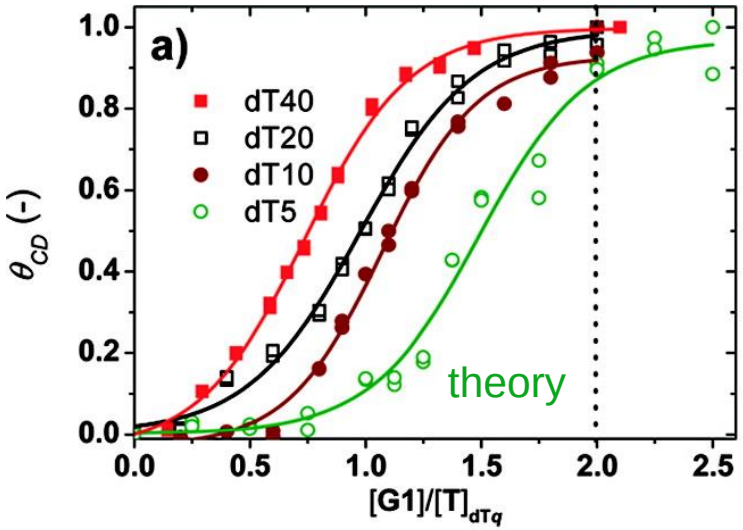
www.sweetpics.site/t/tobacco-mosaic-virus-model.html

Random templated assembly?

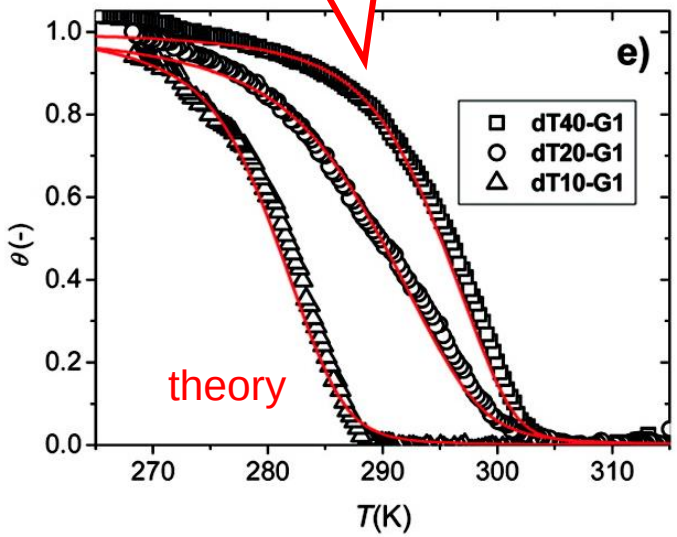




T = 263 K [dT*q*] = 0.25 mM

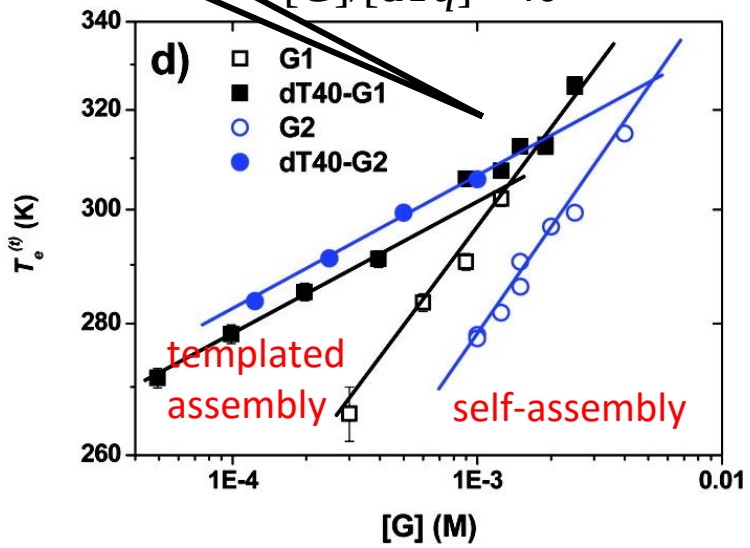


enthalpy
≈ - 20 k_BT



competition!

[G]/[dT*q*]= 40

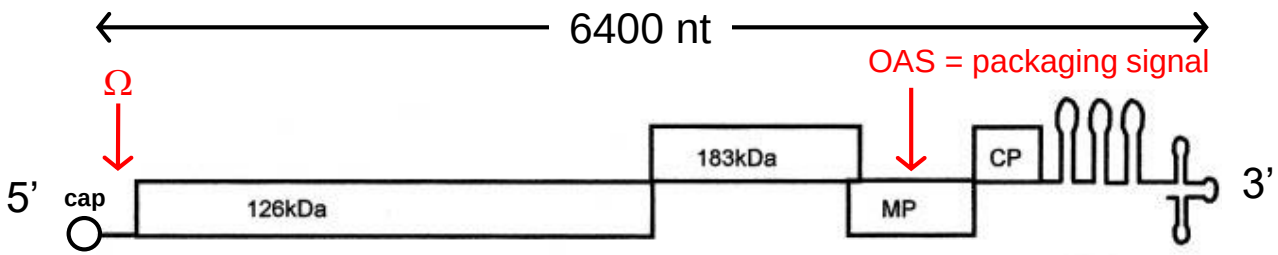


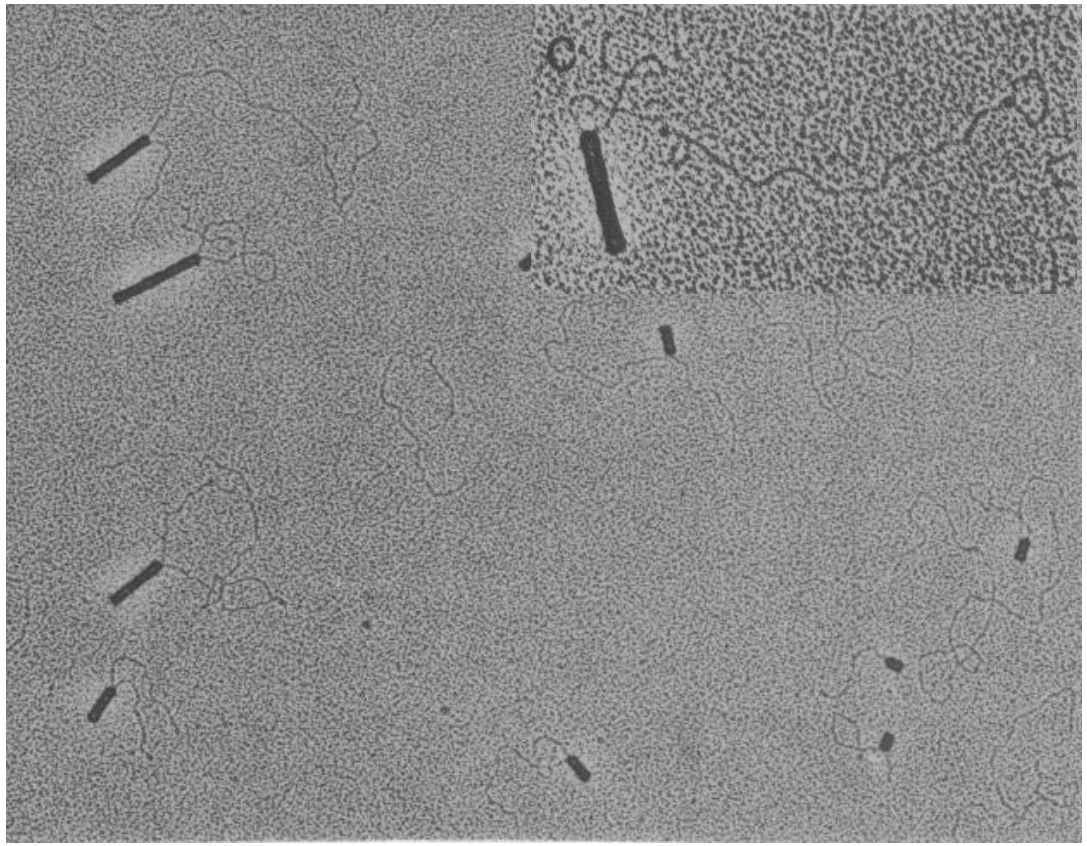
Janssen et al. *JACS* **131** (2009), 1222.

Jabbari et al. *Macromol.* **43** (2010), 5833.

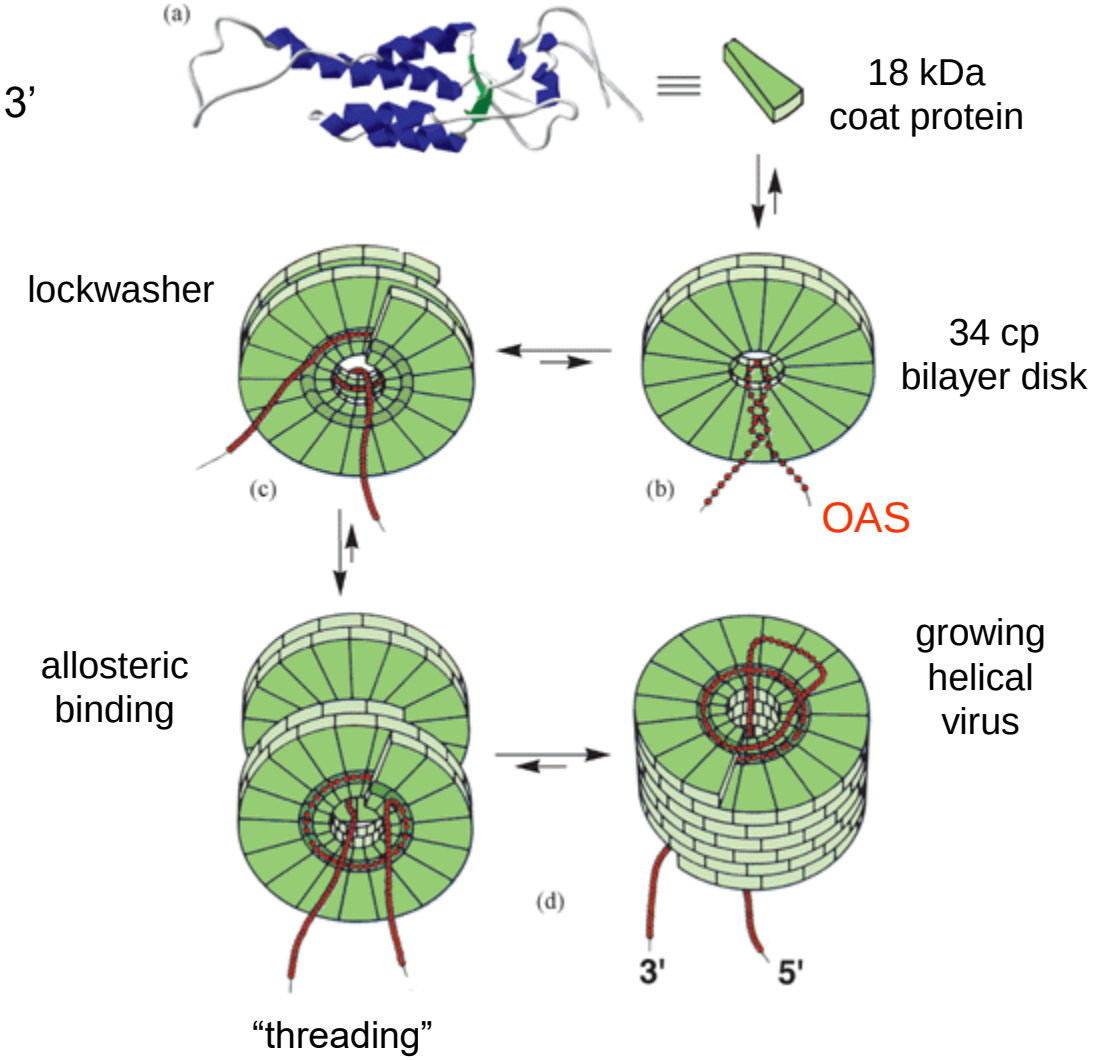
Directional self-assembly of TMV

PMV, CYMV, PRSV, TRV…





Lebeurier et al. *PNAS* **74** (1977), 149.



http://www.rsc.org/ej/CS/2001

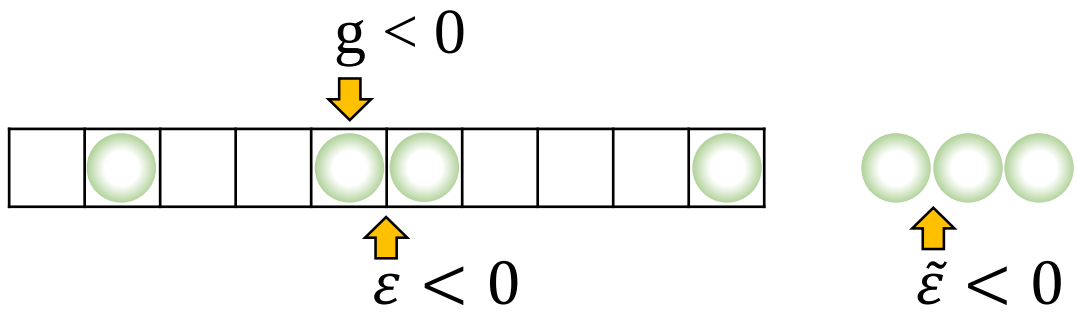
Chandrika et al. *Virol* 273 (2000) 198

Caspar *Biophys J* 32 (1980) 103

Koch et al. *Beilstein J. Nanotechnol.* **7** (2016), 613.

Engineering directional assembly

random templated assembly

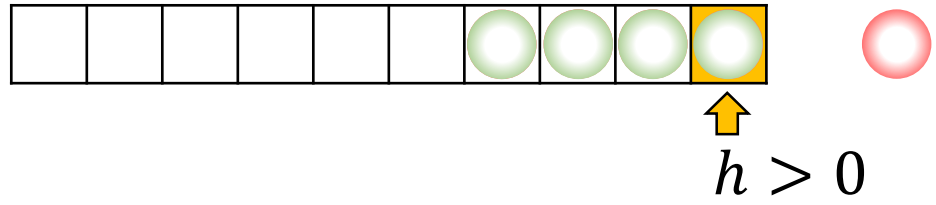


binding → templated assembly

interaction → co-operativity

→ self-assembly

directional templated assembly



switching → suppresses self-assembly

allostery → co-operativity

statistical mechanics

mass action → $S = \phi_P \exp[-\varepsilon - g] \equiv \phi_P / \phi_P^*$

stoichiometry → $\lambda = \phi_T / \phi_P$

co-operativity → $\sigma = \exp[-h + \varepsilon]$

→ equilibrium distribution $P(n)$

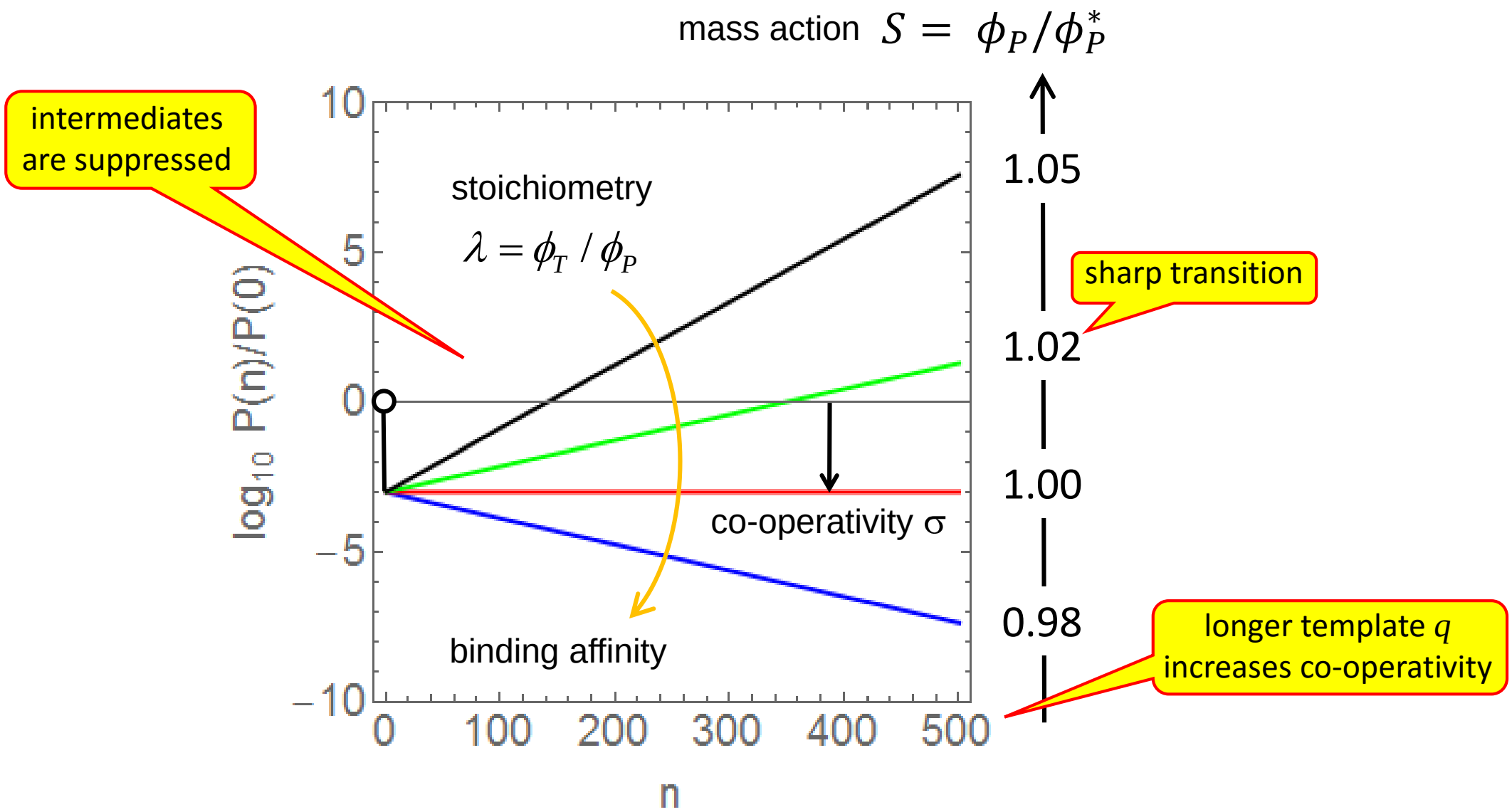
rate equations

$k_-(n) = k_+(n) \exp[g + \varepsilon + (h - \varepsilon)\delta_{n,1}]$

→ non-equilibrium distribution $P(n,t)$

Punter et al. *J Phys Chem B* **120** (2016), 6286.

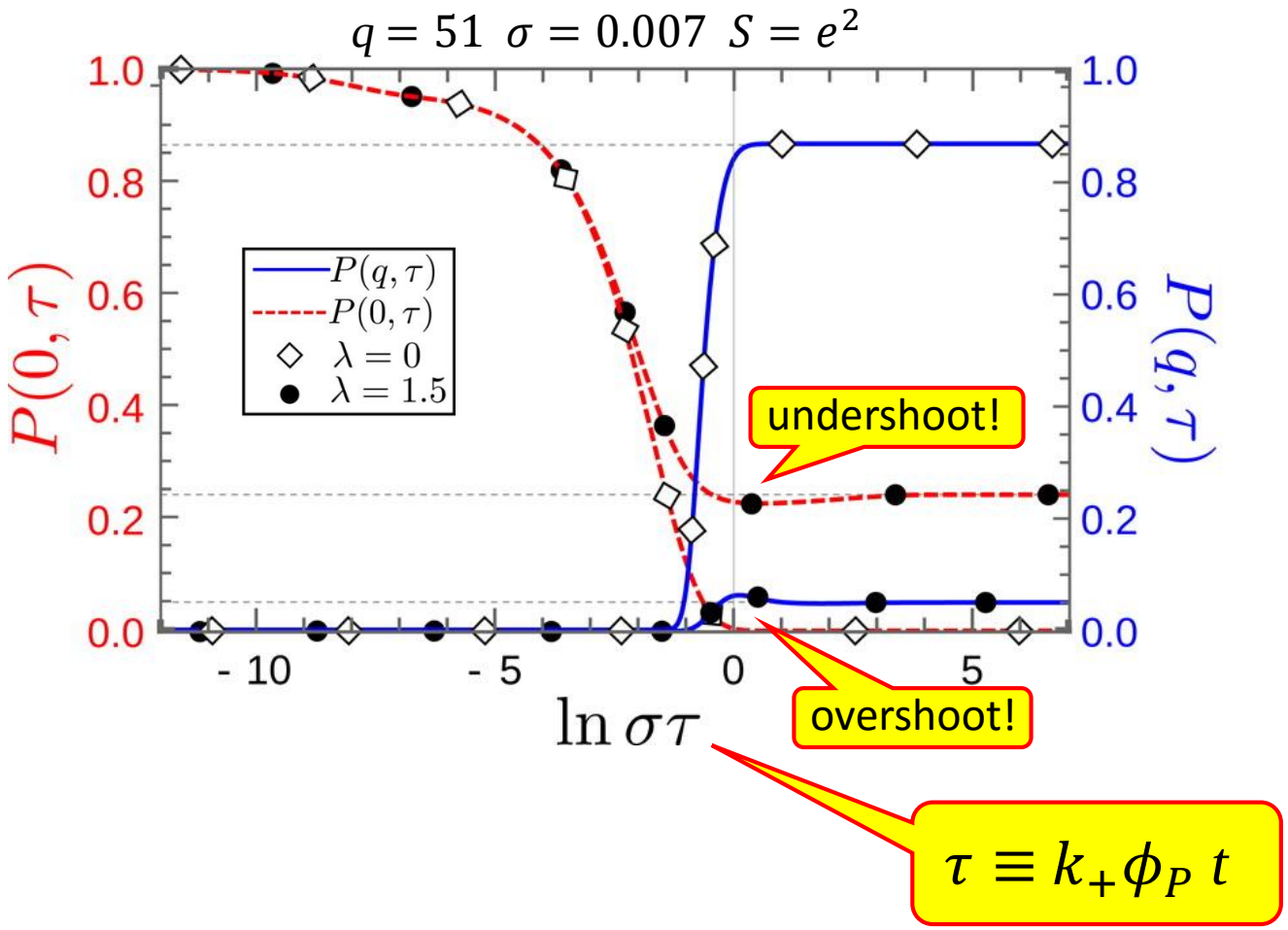
The advantages of zipping...

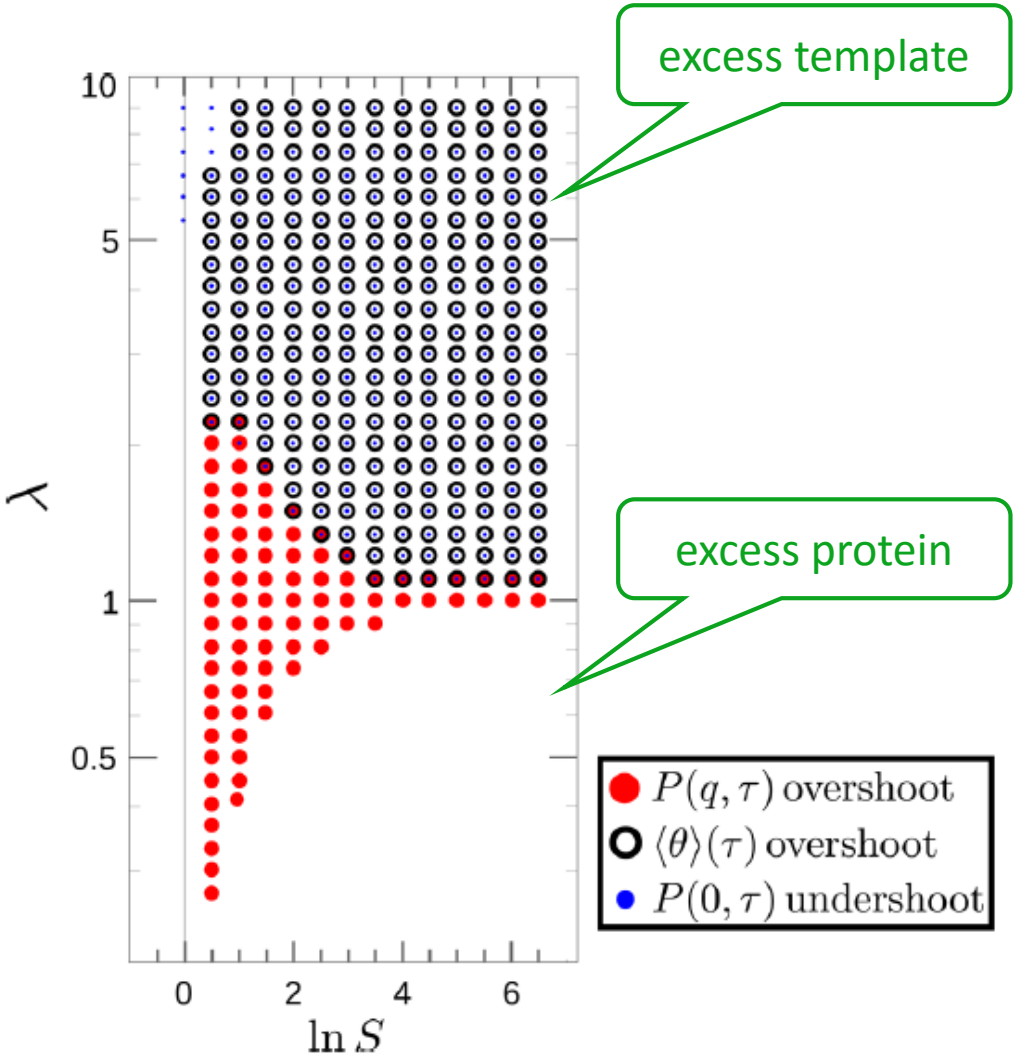


Kraft et al. *Biophys J* **102** (2012), 2845.

Punter et al. *J Phys Chem B* **120** (2016), 6286.

Zipper dynamics

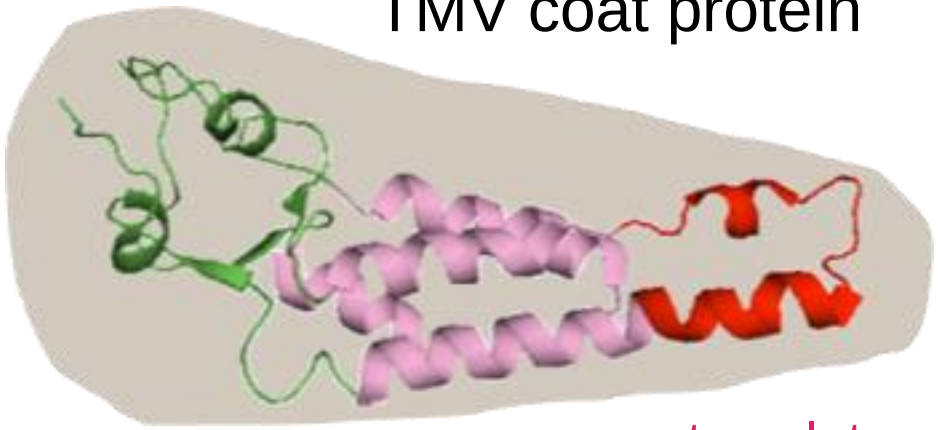




Punter et al. *J Phys Chem B* **120** (2016), 6286.

Our model triblock coat protein C-S_n-B

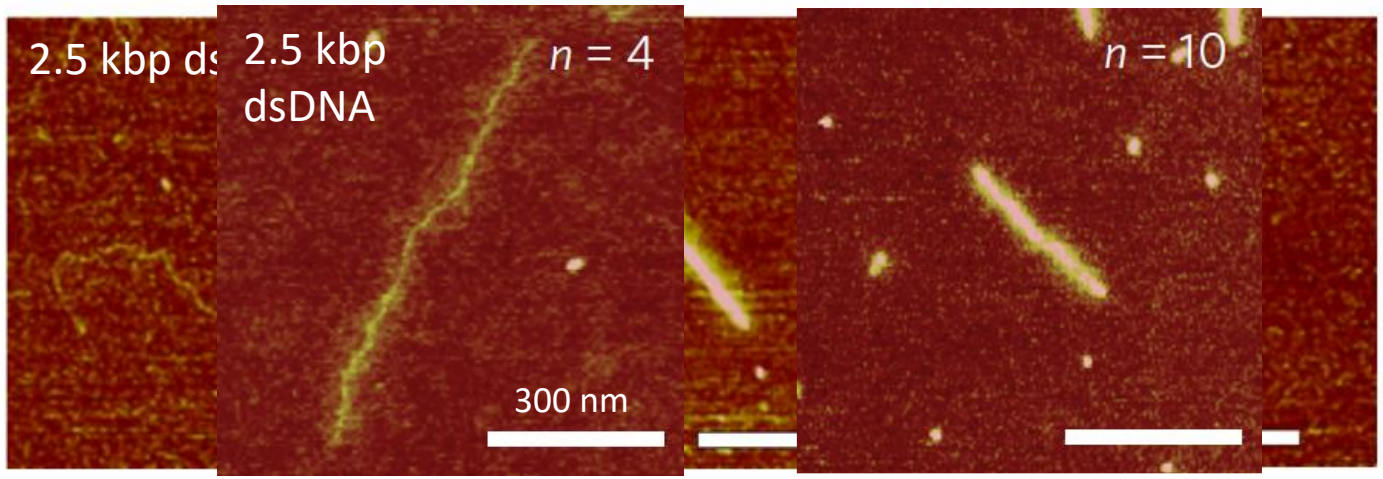
TMV coat protein

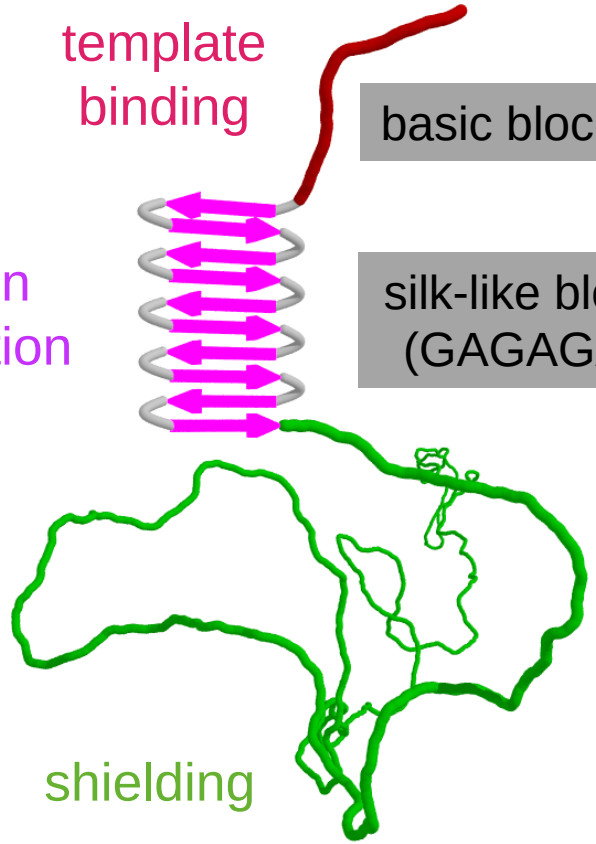


shielding

protein interaction

template binding





template binding

protein interaction

shielding

basic block B: K_{12}

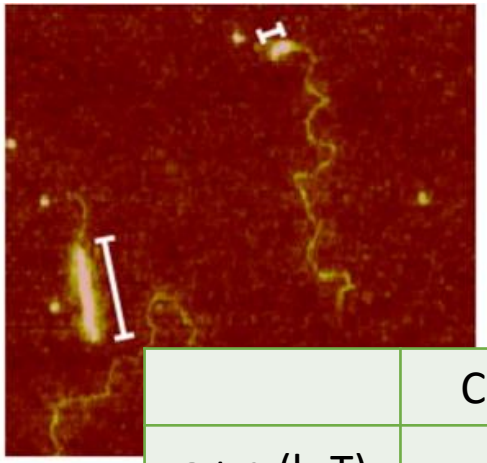
silk-like block S_n: $(GAGAGAGQ)_n$

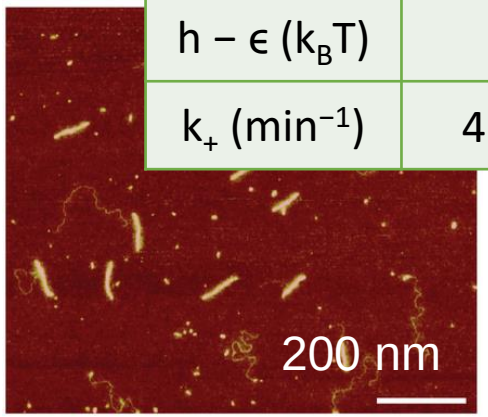
$n \geq 10$

collagen-like block C: hydrophilic random coil (400 amino acids)

Garcia-Hernandez et al. *Nature Nano* **9** (2014), 698.

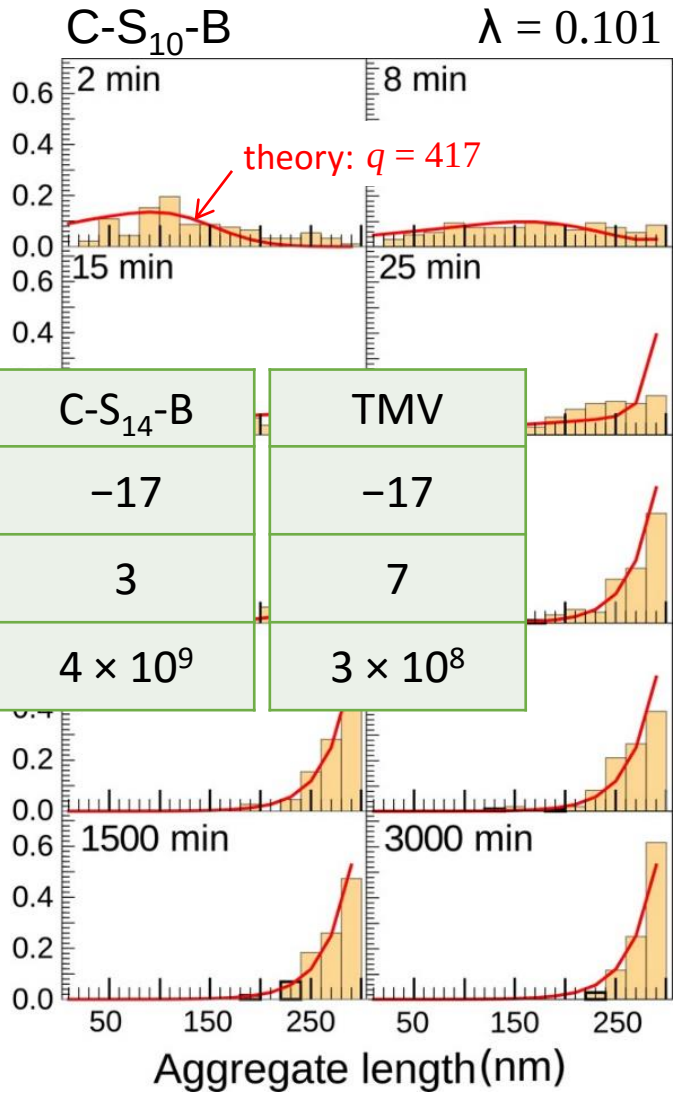
Comparison with experiments

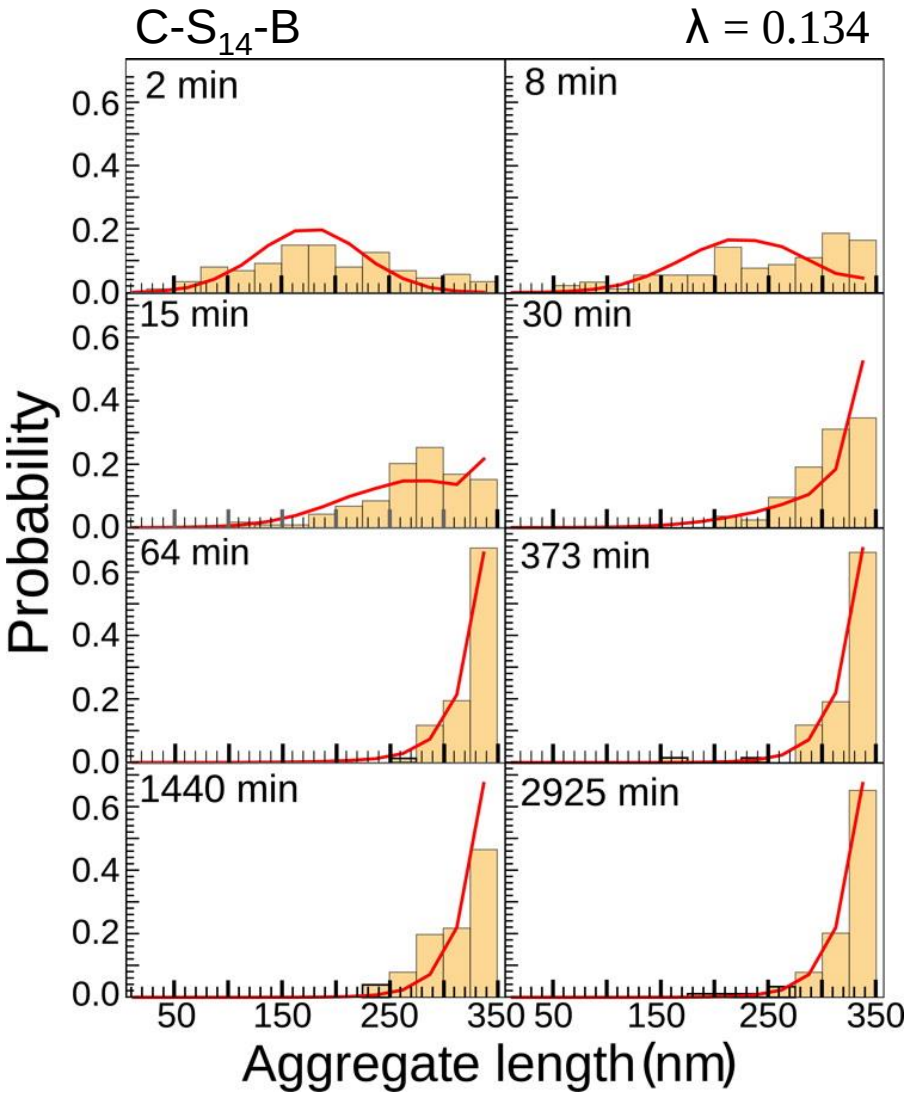




2.5 kDa DNA
c_{DNA} = 0.65 nM

	C-S_{10}-B	C-S_{14}-B	TMV
$\epsilon + g$ (k_BT)	−17	−17	−17
$h - \epsilon$ (k_BT)	6	3	7
k_+ (min^{-1})	4×10^9	4×10^9	3×10^8



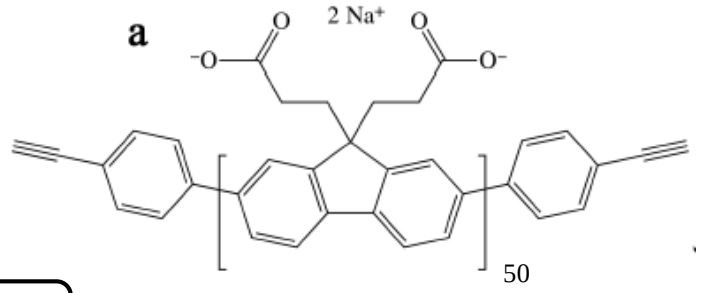


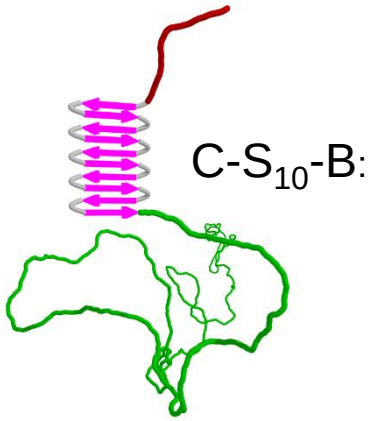
Punter et al. *J Phys Chem B* **120** (2016), 6286.

Kraft et al. *Biophys J* **102** (2012), 2845.

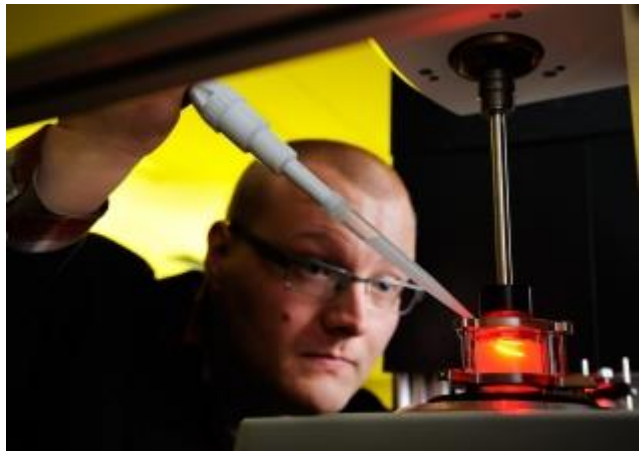
Things get yet more complicated...

polyfluorene: optomechanical proxy genome





C-S_{10}-B:



Joris Sprakel

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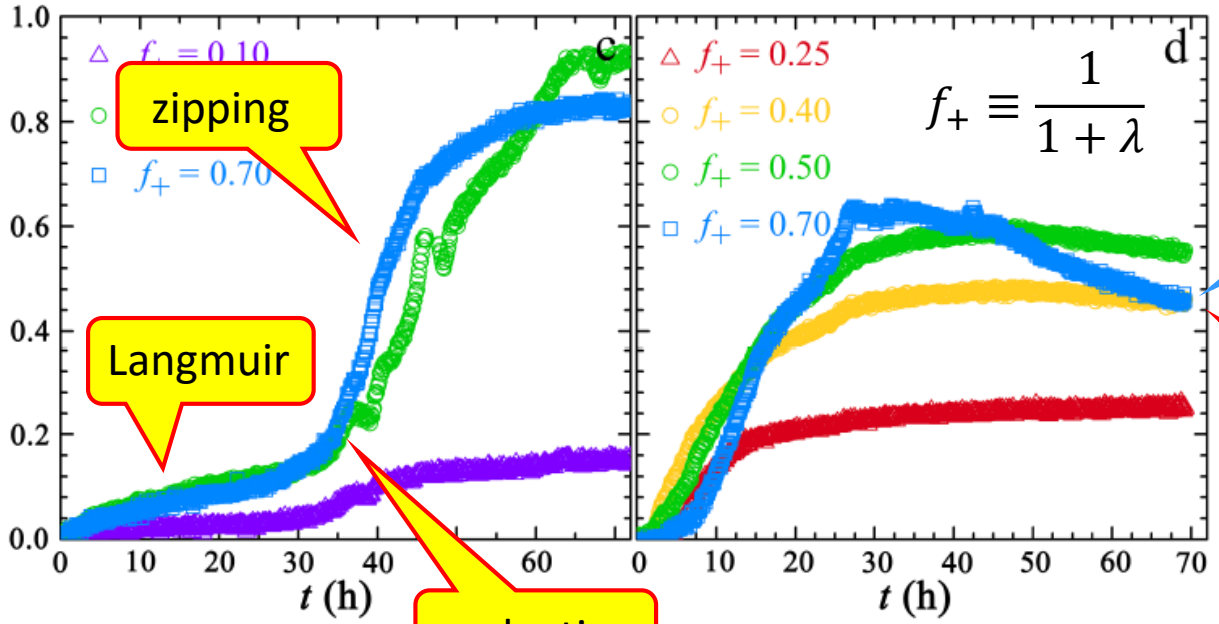
WAGENINGEN UR

fraction taut

ϕ_T = 0.06 μM

ϕ_T = 0.6 μM



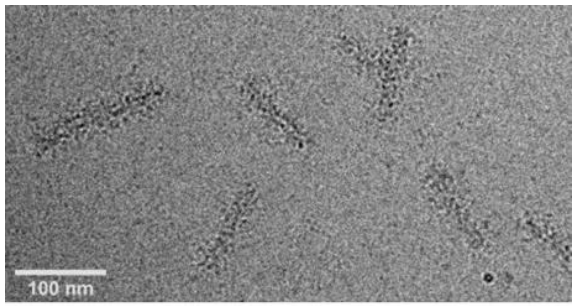
zipping

Langmuir

nucleation

excess protein!

Garcia-Hernandez et al. *Nature Nano* **9** (2014), 698.

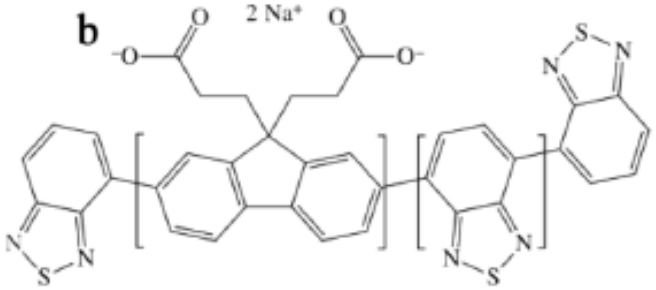


- parasitic self-assembly
- co-assembly templates

Cigil et al. *J. Am. Chem. Soc.* **139** (2017), 4962

Things get yet more complicated...

polyfluorene: optomechanical proxy genome



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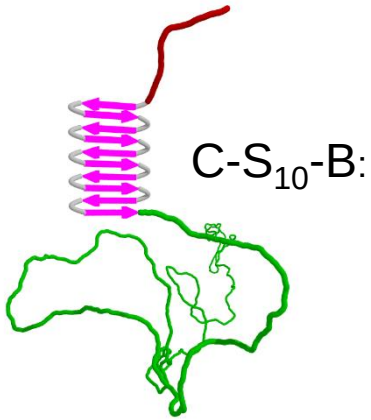
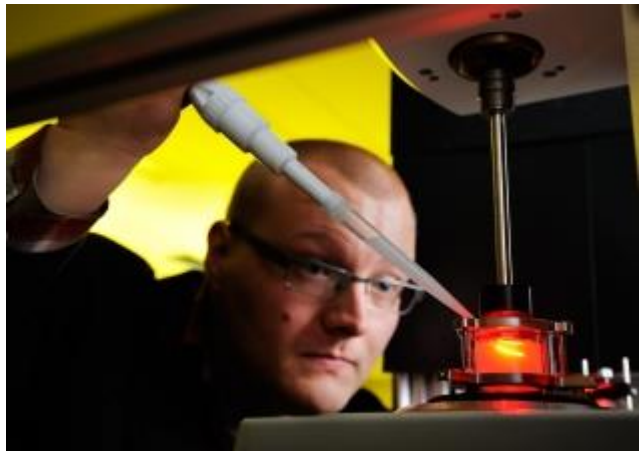


C-S_{10}-B:



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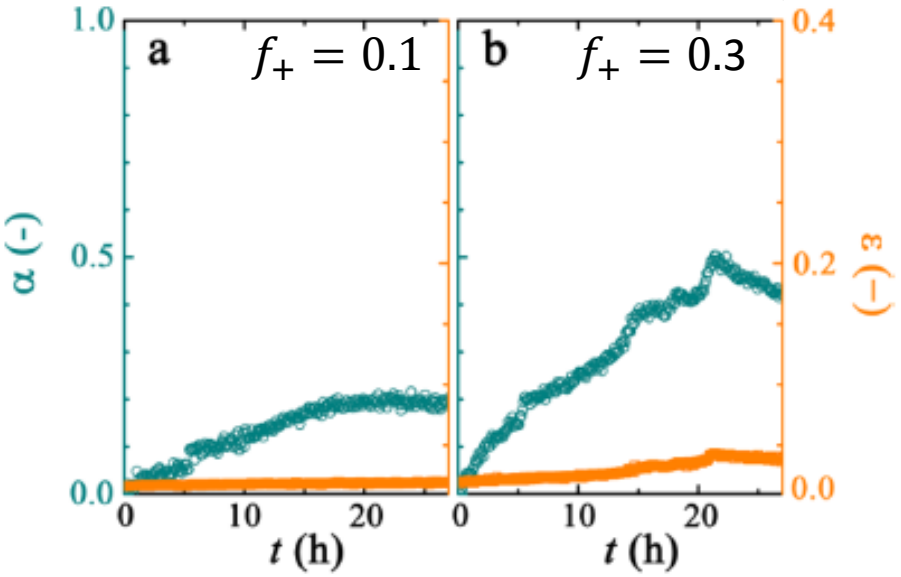
fraction taut

FRET efficiency

excess protein!

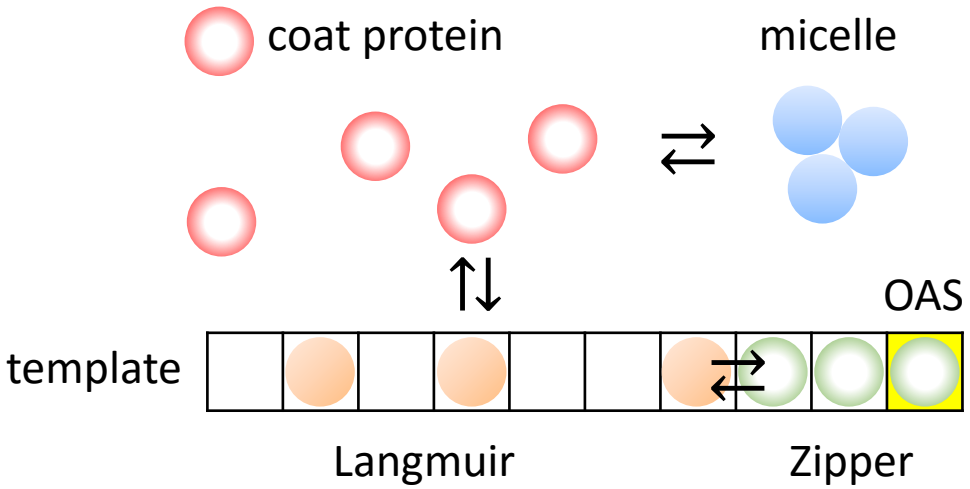


self-assembly

co-assembly

Cigil et al. *J. Am. Chem. Soc.* **139** (2017), 4962

Langmuir, Zipper & Micelle dynamics...



Sander Kuipers
Universiteit Utrecht

critical concentrations

$$\phi^*_{P,Z} = e^{-12}$$
$$\phi^*_{P,L} = e^{-11}$$
$$\phi^*_{P,M} = e^{-9}$$

mass action

$$\phi_P / \phi^*_{P,Z} = e^2$$
$$\lambda = 0.2$$

excess protein!

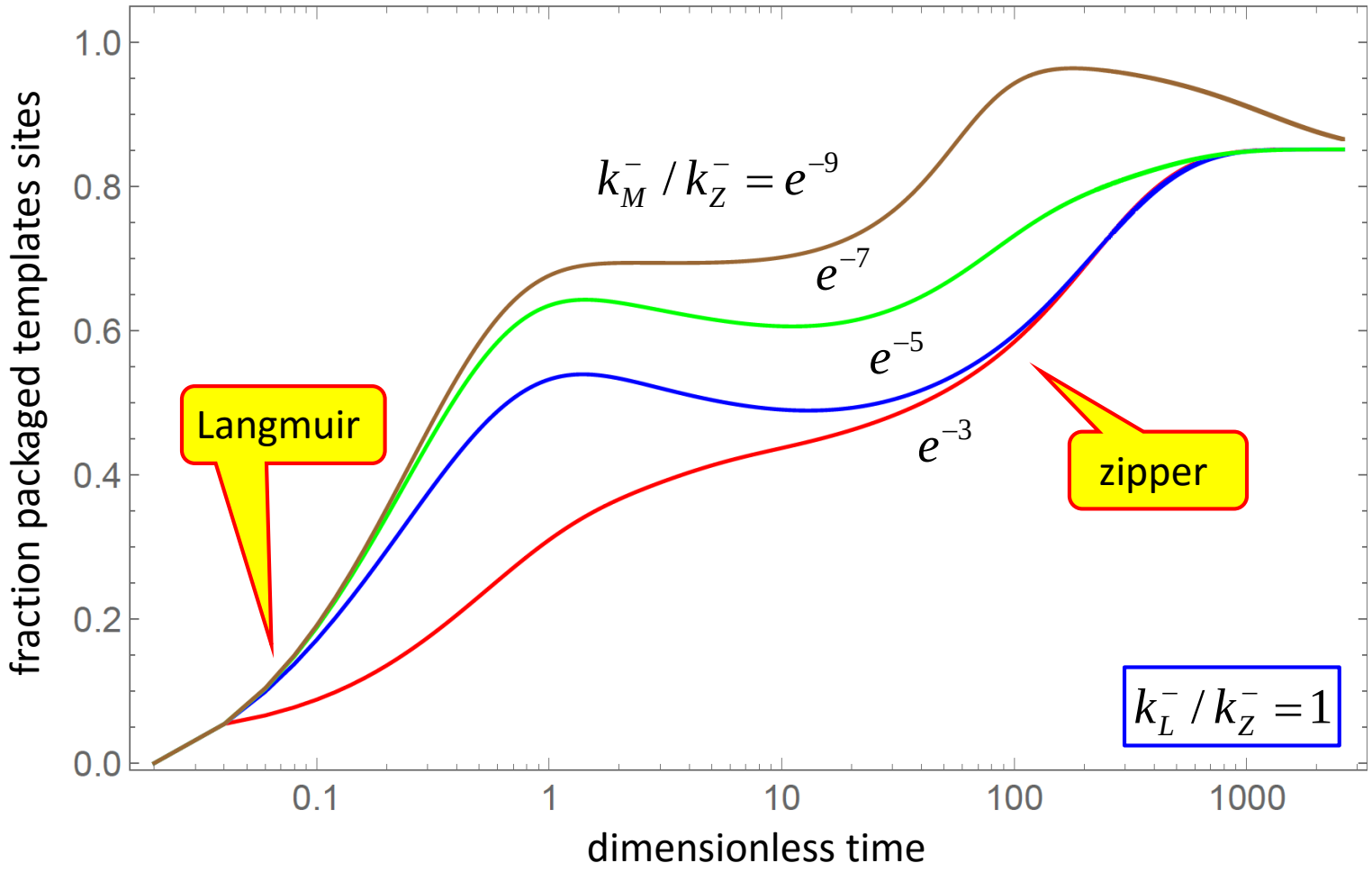
aggregate sizes

$$q_T = 50$$
$$q_M = 5$$

co-operativity

$$\sigma = 0$$

Langmuir, Zipper & Micelle dynamics...



Sander Kuipers
Universiteit Utrecht

Kuipers, bachelor thesis (Utrecht U, 2017)

Conclusions

- Protein polymers can be designed to mimic coat proteins of linear viruses
- Our model triblock protein co-polymer successfully encapsulates DNA
- Allostery and directional assembly seem crucial ingredients
- The kinetic zipper model describes the time evolution of the encapsulation of DNA
- We predict over- & undershooting under conditions of excess DNA
- Overshooting under conditions of excess of protein may occur in competition with micellisation