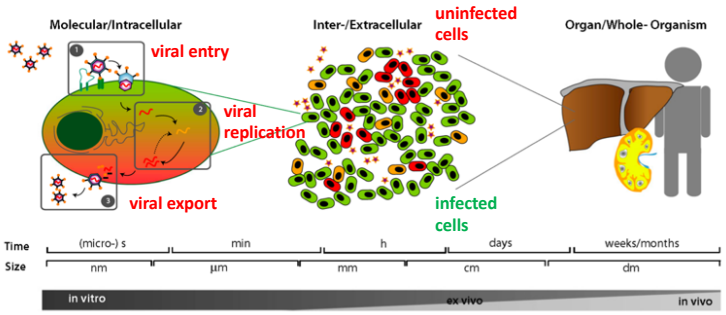
Dynamics of nanoparticle and virus uptake at cell membranes

Ulrich Schwarz

Heidelberg University
Institute for Theoretical Physics and BioQuant

Virus infection and spread are highly challenging multiscale problems



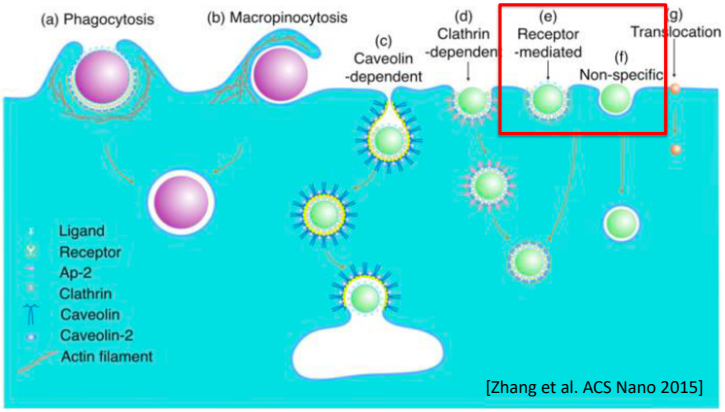
[Kumberger et al. FEBS Letters 2016]

Some general comments

- Viruses are probes of biological systems that might exploit unknown biological functions that we now can discover and understand
- Many aspects of viruses are accessible to biophysical analysis, including
  - Capsid structure, mechanics and assembly
  - Virus transport and barrier crossing
  - Population dynamics and epidemiology
- This talk:
  - What is the role of geometry and noise for virus uptake ?
  - How does HIV-1 spread in a complex environment ?

Analytical model for nanoparticle and virus uptake

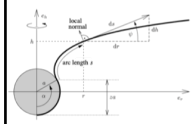
Nanoparticle uptake at the membrane



[Zhang et al. ACS Nano 2015]

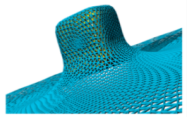
Different approaches to describe particle uptake at membranes

Analytical



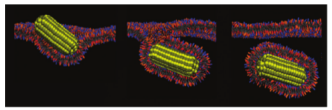
Markus Deserno, Physical Review E 2004

Numerical



Sabyasachi Dasgupta, Thorsten Auth and Gerhard Gompper, Nano Letters 2014

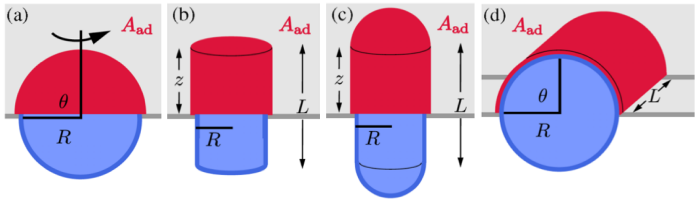
Computer simulations



Robert Vácha, Francisco J. Martinez-Veracoechea and Daan Frenkel, Nano Letters 2011

Here we take the analytical route and focus on the interplay between particle geometry and fluctuations.

Effect of particle shape and size



spherical | **normal cylinder (rocket)** | **spherocylinder** | **parallel cylinder (submarine)**

Viruses come in many different shapes and this will strongly affect the uptake dynamics. Also they often carry only 10s of adhesion receptors, potentially leading to stochastic effects.

[Frey, Ziebert and Schwarz PRL 2019]

Membrane Hamiltonian

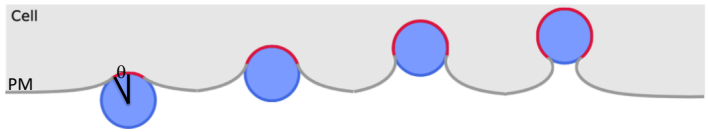
$$E_{\text{total}} = -\int_{A_{\text{ad}}} W dA + \int_{A_{\text{mem}}} 2\kappa H^2 dA + \sigma \Delta A$$

The energy gain due to adhesion energy density W has to overcome membrane bending (bending rigidity κ, mean curvature H) and surface tension σ.

Balancing adhesion and bending for a sphere gives a critical minimal radius for uptake:

$$R_{crit} = \sqrt{\frac{2\kappa}{W}} = \sqrt{\frac{50\ kT}{10^{-4}\ J/m^2}} = 44\ \text{nm}$$

Membrane shape



Membrane shape can be calculated numerically from shape equations. For spheres, there are two limiting cases which can be solved analytically (Lionel Foret EPJE 2014).

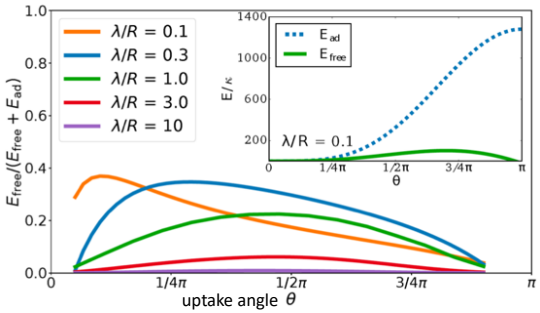
Typical membrane lengthscale: $\lambda = \sqrt{\frac{\kappa}{\sigma}} = \sqrt{\frac{25\ kT}{10^{-4} N/m}} = 32$ nm

1. Loose membrane, R << λ: bending dominates, minimal surface
2. Tense membrane, R >> λ: tension dominates, flat

With R=10-100 nm, many viruses are in the intermediate regime.

Membrane energy of free part for a spherical particle

[Frey, Ziebert and Schwarz arXiv:1905.01337]



The free part can contribute up to 20% to the total energy for λ/R=1 (green curve). This barrier can lead to partial uptake.

Equation of motion for sphere (without free membrane)

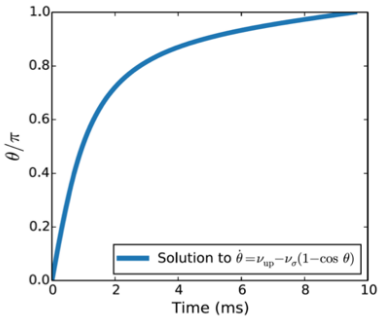
Timescale is assumed to be set by the membrane microviscosity η. As dynamical variable we take the opening angle θ(t):

$$\dot{\theta} = \nu_{\mathrm{up}} - \nu_\sigma(1 - \cos\theta)$$

with rates $\nu_{\mathrm{up}} = \nu_w - \nu_\kappa$ $\quad \nu_\kappa = 2\kappa/(R^3\eta)$

$\nu_\sigma = \sigma/(R\eta)$ $\quad \nu_w = W/(R\eta)$

Analytical solution: $\theta(t) = 2\arctan\left(\frac{\sqrt{\nu_{\mathrm{up}}}\tan\left(\frac{1}{2}t\sqrt{\nu_{\mathrm{up}}^2 - 2\nu_{\mathrm{up}}\nu_\sigma}\right)}{\sqrt{\nu_{\mathrm{up}} - 2\nu_\sigma}}\right)$



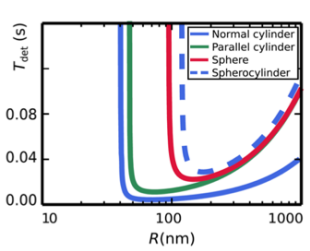
Deterministic uptake time:

$$T^{\circ}_{\mathrm{det}} \approx \frac{\pi}{\nu_{\mathrm{up}}\sqrt{1 - \frac{2\nu_\sigma}{\nu_{\mathrm{up}}}}}$$

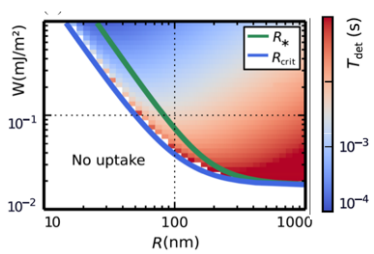
Critical radius: $R_{\mathrm{crit}} = \sqrt{\frac{2\kappa}{W - 2\sigma}}$

Optimal radius: $R_* = \sqrt{\frac{4\kappa(W-\sigma) + 2\kappa\sqrt{W^2 - 2\sigma W + 4\sigma^2}}{W(W - 2\sigma)}}$

Deterministic uptake times



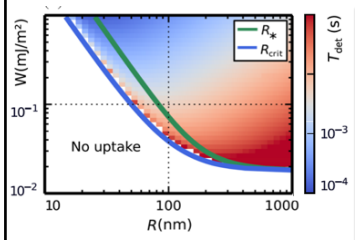
Similar calculations as for the sphere can also be done for the other geometries. Normal cylinder (rocket) performs best.



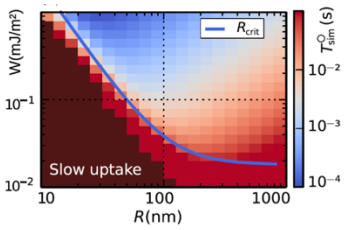
For the sphere, the optimal radius R_* (smallest uptake time) is close to the critical radius R_{crit} (no uptake at smaller radii).

One-step master equation

We map our deterministic model to a one-step master equation through $\dot{N} = (dN/d\theta)\dot{\theta}$. Simulation with the Gillespie algorithm gives a new phase diagram:



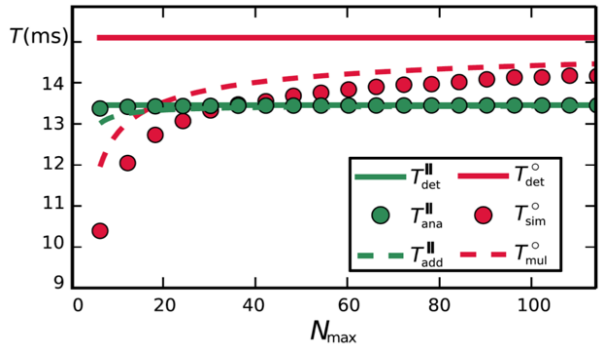
deterministic



stochastic

In the stochastic case, uptake is possible for all parameter values. It is also much faster now due to small system size.

Spherical particles profit from noise



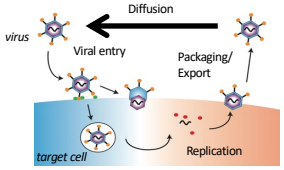
A spherical particle with R=180 nm and few surface receptors can be taken up faster than a cylindrical particle of equal volume due to the effect of noise.

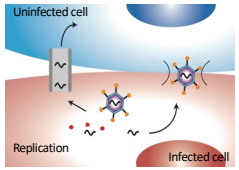
Why are so many viruses spherical ?

- Sphere has largest volume at given surface area, largest possible container for genome
- Caspar-Klug theory: icosahedral viruses need minimal coding for capsomer proteins due to quasi-equivalence
- Sphere has superior mechanical stability
- But: spheres are taken up slower then cylinders !
- We showed here that spheres can profit from stochastic noise in small systems

Virus spread in complex environments

Emerging new paradigm: viruses often spread through direct cell-cell contacts

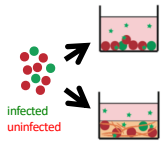




Traditional view: cell-free spread through virions in solution

Alternative: spread through cell-cell contacts, e.g. virological synapse or tunneling nanotube

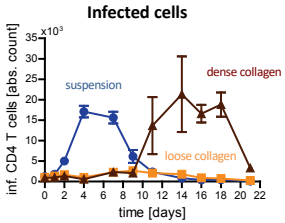
Spread of Human Immunodeficiency Virus-1 (HIV-1) in long-term 3D cell culture

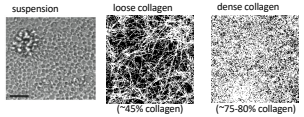


2D suspension culture

3D collagen culture

biosafety level 3

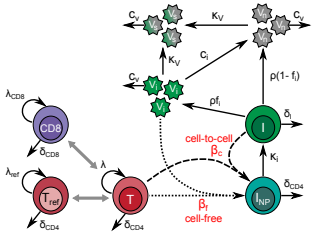




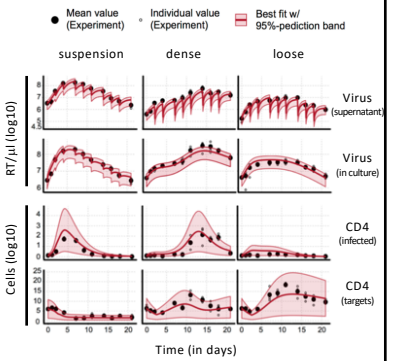
Dense collagen is most efficient but has a long time delay

[Imle et al. Nat Comms 2019]

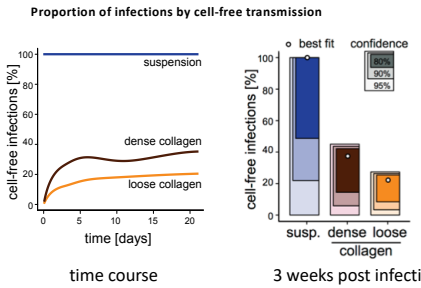
Kinetic model



- Variant of the SIR-model adapted to our experiments
- 39 unknown parameters
- nearly all identified by model-experiment iterations



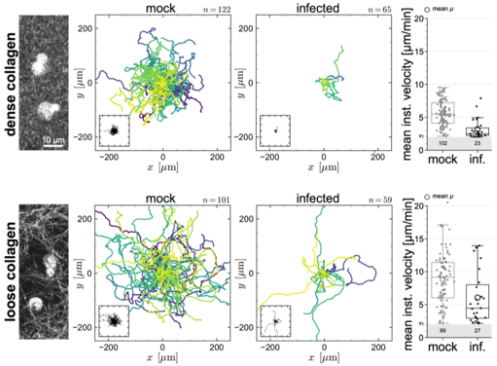
Model result: in collagen transmission occurs mainly through cell-to-cell mode



time course | 3 weeks post infection

7- and 4-fold higher probabilities for cell-to-cell transmission in loose and dense collagen, respectively, compared to suspension

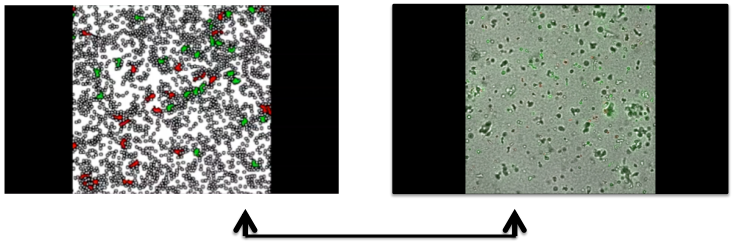
HIV-1 infected cells show very different motilities at different collagen densities



Both infection and dense collagen reduce motility.

Cellular Potts Model can represent different collagen densities

Cellular Potts Model | Live-cell microscopy



Infected cell

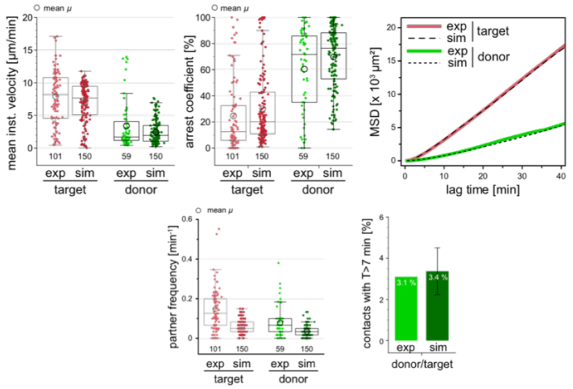
target cell

- pyABC: distributed likelihood-free inference method
- 16 unknown parameters
- Runtime ~ 1 week

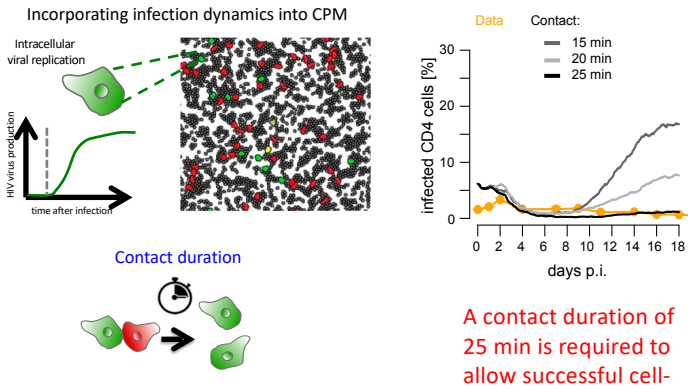
CPM can recapitulate all microscopic observations on motility

Measurements:

- Velocity
- Arrest coefficient
- Mean squared displacement
- Turning angle
- Straightness coefficient
- Contact frequency
- Contact duration



Full model combines infection kinetics with CPM and predicts contact times



A contact duration of 25 min is required to allow successful cell-to-cell spread

Conclusions

- **Analytical model for virus uptake:** spherical viruses might be taken up faster than cylindrical ones due to stochastic effects
- **HIV-1 spread in 3D collagen:** cell-cell contact is the main mode of virus transmission in complex cell environments like lymph nodes

Acknowledgments

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Funding

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