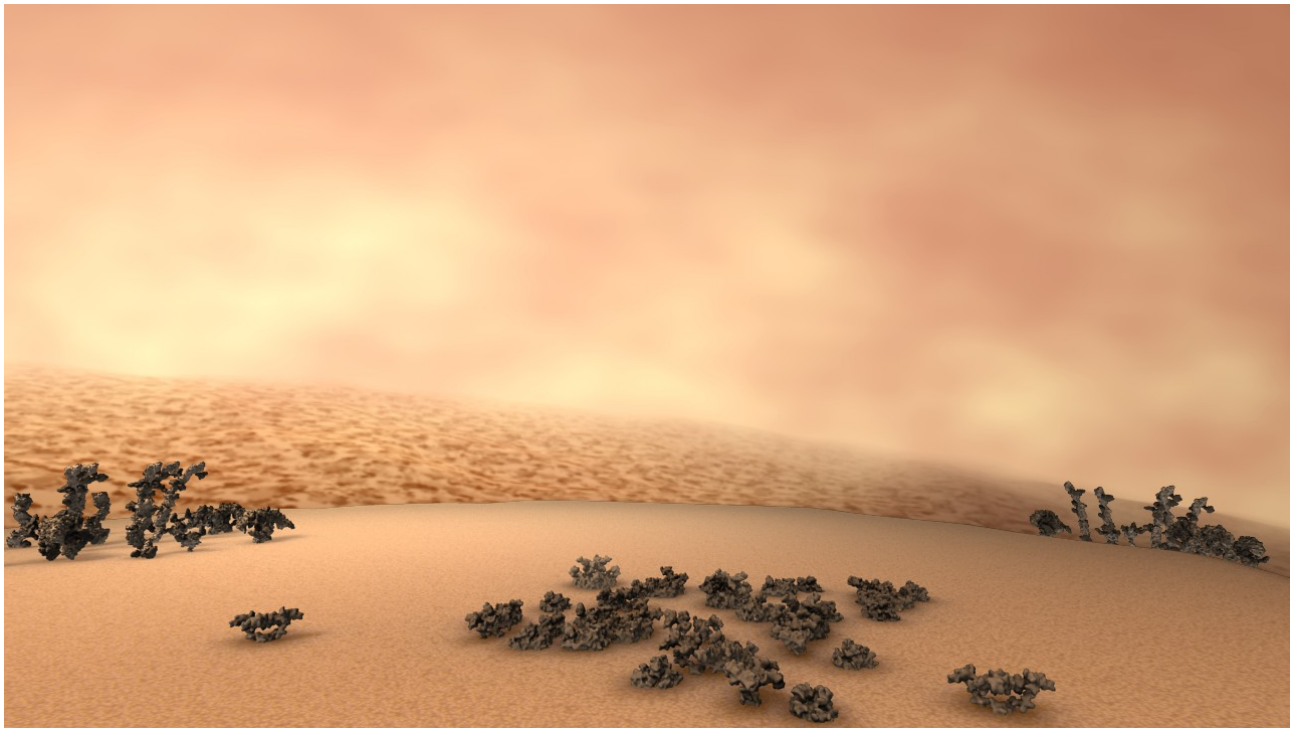
Explanatory Notes

The challenge of HIV research



In December 2012 Autodesk and the CgSociety launched a Visualization Challenge, in which entrants were provided with a package of information and tools with which they were going to produce a short animation. The aim of the animation was to sensitize people about HIV and the importance of research to find a cure.
Despite the fact that we at SciVis use a Computer Graphics program that is not distributed by Autodesk, we thought it would be interesting to test our own program, BioBlender, and our different approach to biological visualization for the challenge.

The final product, a short video that we titled 'The Challenge of HIV Research', was sent to the competition, and was ranked 4, winning a sum of 350 US $, which we delivered directly to the Blender Foundation.

Description of the scenes

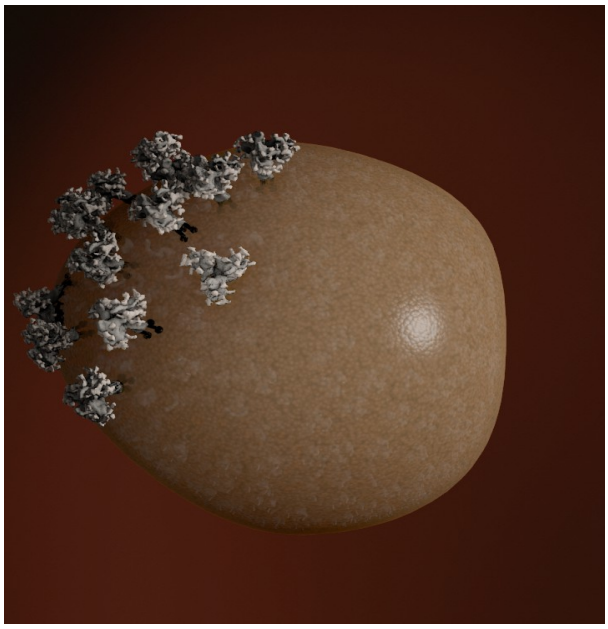
1. **Idyllic cell**
We see the surface of a white blood cell, with some of the proteins that are prominent of this kind of cell. A group on the right includes several proteins that are found on most cells, of any kind. These are: Aquaporin (a roughly square protein, responsible for water permeation, pdb file 1FQY), Rhesus Antigen (a trimeric antigen, pdb 3HD6), Glut1 (the glucose transporter, pdb 1SUK), Glycophorin A (dimeric partial structure, derived from pdb file 1AFO), and Band 3 (a transporter protein, structure based on pdb 2A65).

On the left, another group of proteins, typically found on membrane rafts: TLR (Toll Like Receptor, with its characteristic shape, based on pdb 2Z7X), CD4 (the primary receptor of HIV, pdb 1WIO), Thy1 (pdb 2UX2) and I-CAM (the very tall protein, involved in cellular adhesion, based on pdb 1IAM for domains 1 and 2, and 1P53 for domains 3, 4 and 5).
All proteins were modelled on the basis of the reported PDB files, and completed by homology modelling and glycosylation when known. Proteins are not displayed by atomic or structural features, but by their surfaces, as calculated in BioBlender (using PyMOL) and with their texture determined by the lipophilic potential.

2. **Vein trip to emitting white cell**
The scene is composed with modelled Red blood cells (biconcave) flowing in a vein, whose walls are 'painted' using a real microscopy image of endothelial cells.
At the end of the scene we approach a white blood cell adhering to the vessel, and shedding a large number of particles (virions) from the surface.

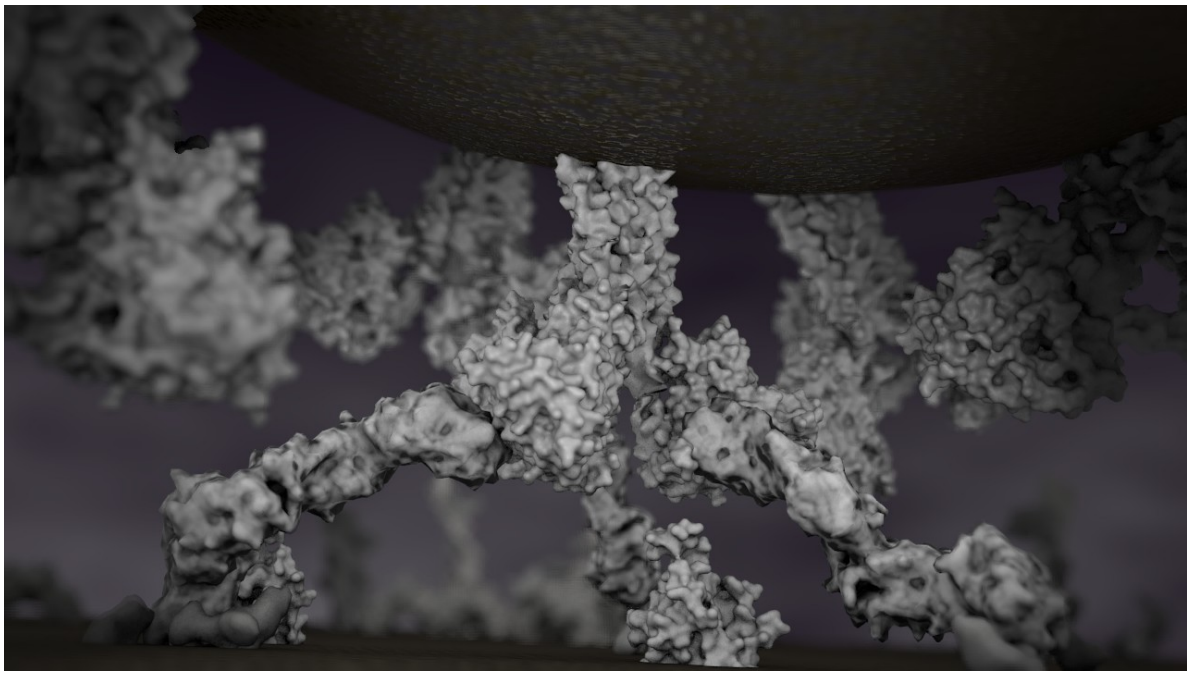
3. **White blood cell emitting virus**
The cell, seen from a close up, is clearly budding virions from its surface. The virions surrounded by a membrane derived from the cellular surface and are covered with viral spikes, the proteins used by the virus to adhere and gain access to new cells.

4. **Virions**
Of the many viral particles emitted by an infected cell, only a fraction is actually capable of infecting a new cell. Many are defective in one or more of their features. Here we see some virions in which the surface protein, called spike, and composed of 6 subunits (all derived form the *env* gene, 3 gp120 and 3 gp41) is either distributed inefficiently or (almost) absent from the surface.
The mature effective virions are believed to have an average of 15 spikes which are aggregated on one side of the particle.
The spike was modelled on the basis of data from several PDB files. gp120 was modelled on the basis of different X-ray structures (isolated, trimeric, bound to antibodies, bound to CD4), elaborated to include the variable loops (V1-V2 and V3), and several oligosaccharide chains. gp41, which is less visible, was based on pdb 3JWD.



5. **Idyllic no more**
We return to the initial white blood cell. Now the virions are approaching and, although most of them will pass without effect, soon or later one of them will be able to get close enough to permit binding of its spike to the cellular protein that HIV uses as its principal receptor.

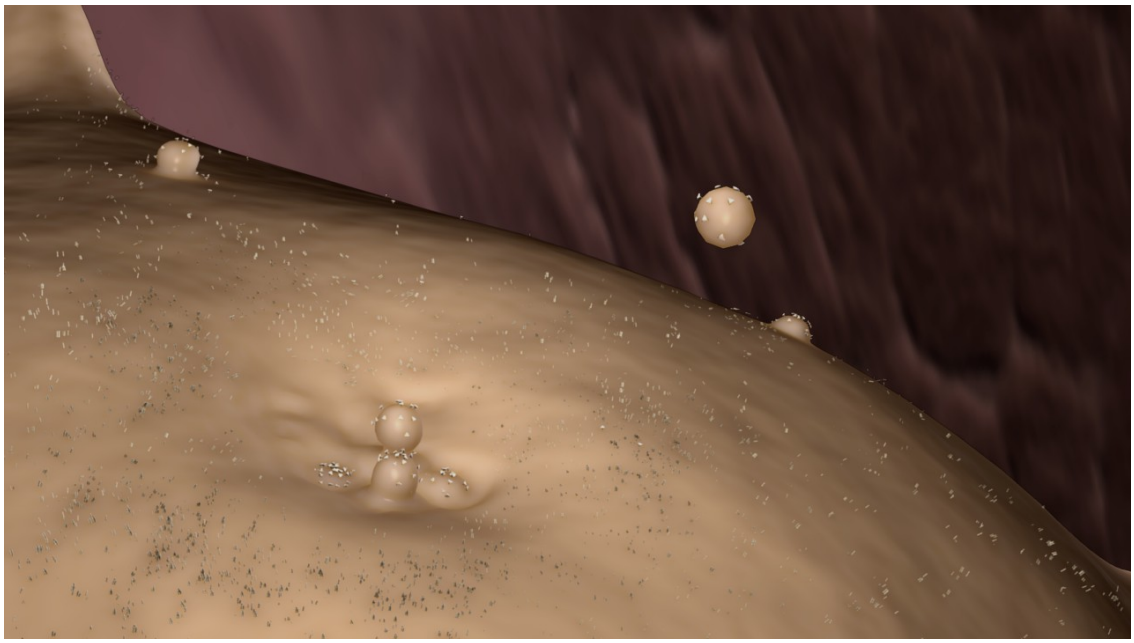
6. **Binding**
Entry of a viral particle into a new cell is mediated by the binding of its spike to two of the cellular proteins: first there is a contact between the three subunits of gp120 with 3 molecules of CD4, the primary receptor.
After one or more spikes are tightly bound to CD4, a conformational change in the trimer exposes another site that binds to the secondary receptor (in our case CCR5) and gets the viral membrane closer to the cellular membrane. At this point the virion can either be internalized by endocytosis or membrane fusion can occur, releasing the viral genome into the cell, which is now infected.



7. **Epilogue (not shown)**
Viral entry is not necessarily a condemnation to the cell: several cellular mechanism can impede the following steps of retro-transcription, nuclear entry, integration, transcriptional activation and more that can result in effective infection. All the mentioned steps can be ineffective for a number of reasons: the virion could be defective; or the cell can successfully activate its antiviral mechanisms, or the body can recognize the infected cell and destroy it before it starts emitting new virus.
The number of single viral particles, however, is often such that a sufficient number of them will escape cellular defence, and continue infection. In this case the best chance of contrasting the disease and its further spread is in the realm of pharmacological intervention.
The virus is highly mutable, and many drugs that are effective for some time will eventually become useless, once the specific target of the drug has been mutated in a way that renders it resistant.
For this reason it is always necessary to find new drugs, and new combinations of molecules that can keep infected people healthy and (most important) reduce the rate of infection.

Relevant sources - Websites
Blender www.blender.org
BioBlender www.bioblender.eu
Protein Data Bank www.pdb.org
Uniprot www.uniprot.
Wikipedia www.wikipedia.org

Literature - Spike structure
HIV-1 Envelope Glycoprotein Biosynthesis, Trafficking, and Incorporation. *J. Mol Biol.* 2011 410(4): 582-608
Structure of HIV-1 gp120 with gp41-interactive region reveals layered envelope architecture and basis of conformational mobility. *Prc. Natl.Acad.Sci.* 2010 107(3):1166-1171
Structure of an unliganded simian immunodeficiency virus gp120 core. *Nature* 2005 433:834-841



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