



School of Computing, Computational PDEs Unit

<http://www.comp.leeds.ac.uk/cpde/>

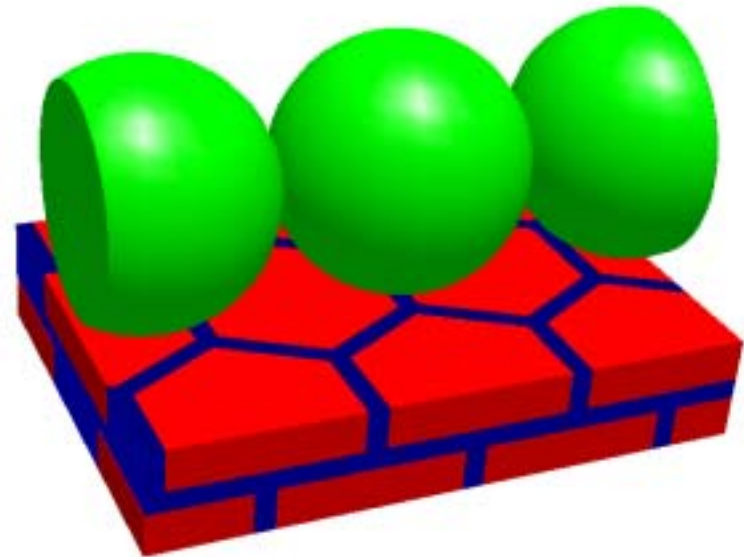
# Mathematical Modelling of Dermal Absorption

## Part II

Chris Goodyer

# Why model the Stratum Corneum?

- The heterogeneous structure of the stratum corneum is important to its barrier function and mathematical models that include these structures are needed.
- Models that include heterogeneous structures in the stratum corneum could be used to explore the cause of differences in barrier function:
  - Between species (e.g. human vs. rat)
  - Between human skin and human skin equivalents
  - Between normal and diseased skin
  - How spatially distributed sources differ from those with a uniform distribution in the vehicle?



# **Skin modelling - What do we need?**

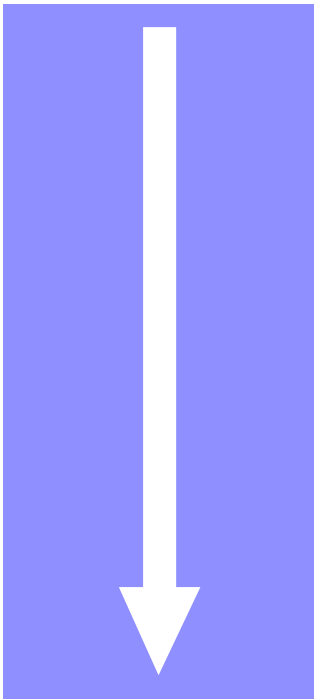
We have the following requirements from the model we are producing:

- The equations defining the absorption are given
- Corneocyte alignment will be variable
- Lipid properties are very important
- Input parameters must be as wide as could be envisaged
- Results obtained from calculations must be accurate

The main question for modelling work is now:

How much detail do we need to accurately model dermal absorption?

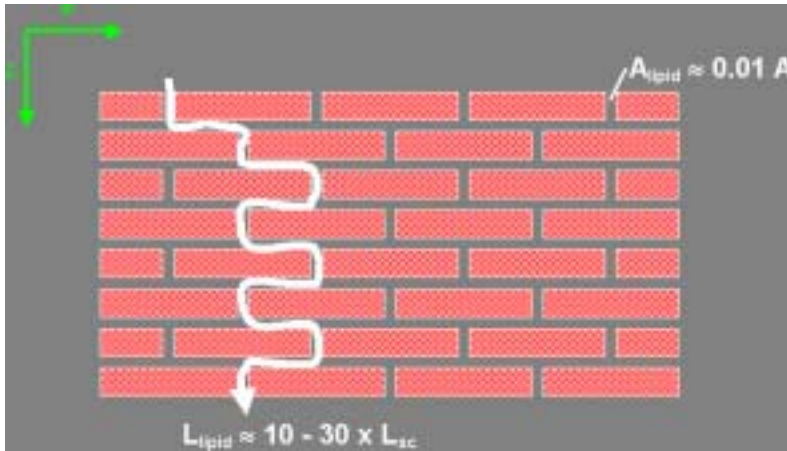
## Skin modelling - Why not 1d?



If skin is modelled as a 1d pseudo-homogenous membrane then:

- All chemical diffusion would be straight down
- Details about the differences between the corneocytes and the intercellular lipids are not necessary
- Many 'real world' effects of true skin would be lost, e.g.:
  - variation in corneocyte arrangement
  - effects of vehicle only partly covering the skin surface

## Skin modelling - Why not 2d?



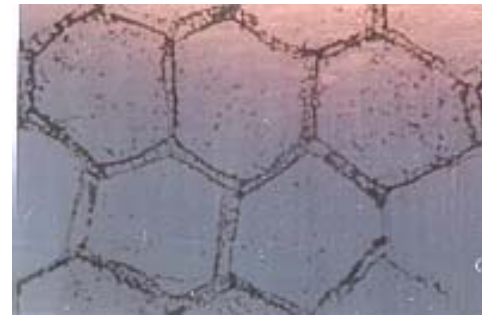
- *Brick and mortar* representations of corneocytes add a large measure of realism into the calculations
- Diffusivity pathways are now variable based on the alignment of the corneocytes
- 2d representations of complex 3d geometries are, perhaps, too simplistic...

Work by Heisig *et al.* (Pharm. Res. **13**(3) 421–426) has made a start in this area.

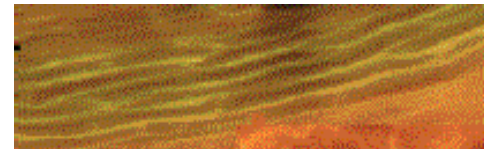
# True corneocyte alignment and implications

A hexagonal representation of the corneocytes makes tiling of the layers very easy, and more accurately represents the true nature of skin.

- The minimum path length through the s.c. is governed by the alignment
- Corneocytes in mice are very aligned, whereas in humans are not
- Most random corneocyte alignments will give very tortuous routes for particles
- Diffusion along individual layers of corneocytes may be more likely than diffusion between layers



Human corneocytes  
(plane view)



Human corneocytes  
(cross section)



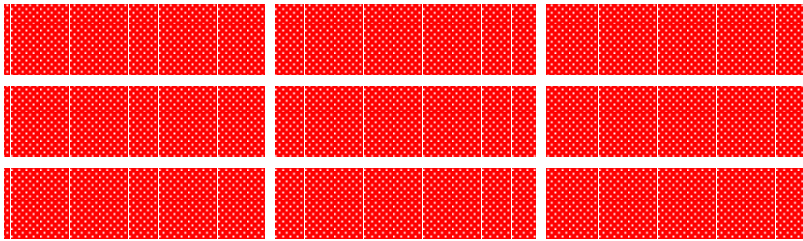
Mouse corneocytes  
(cross section)

# Skin modelling

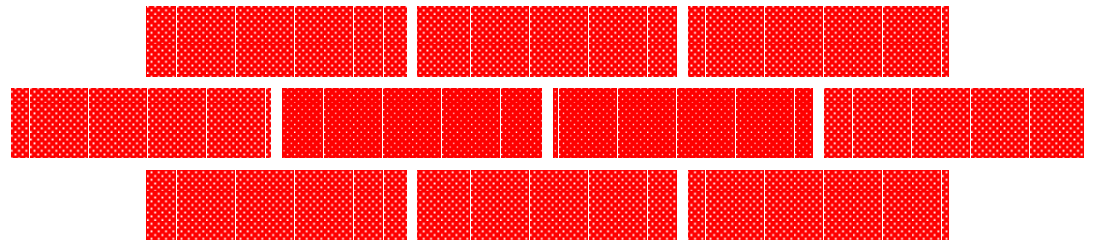
In two dimensions the alignment is governed only by the relative displacement of one layer from the others. We will consider regular repeating arrangements.

There are two extremes to this situation:

Fully aligned



Fully staggered.

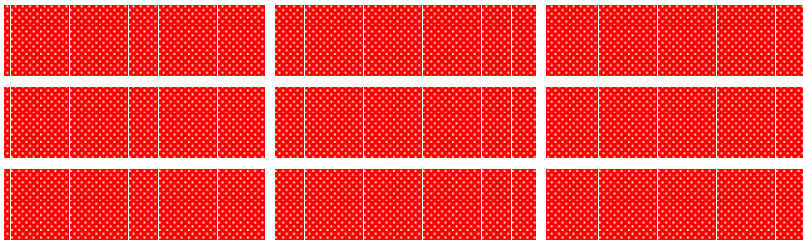


# Skin modelling

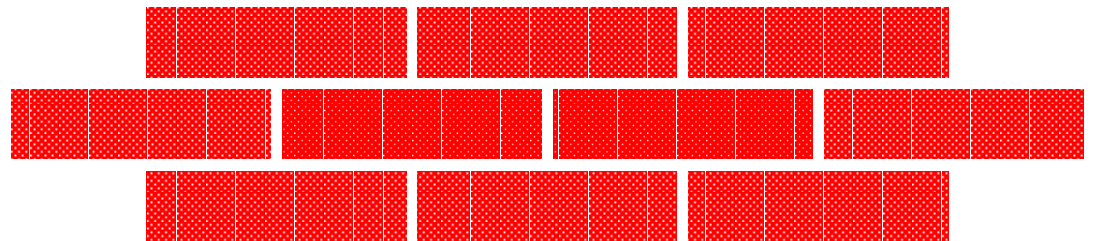
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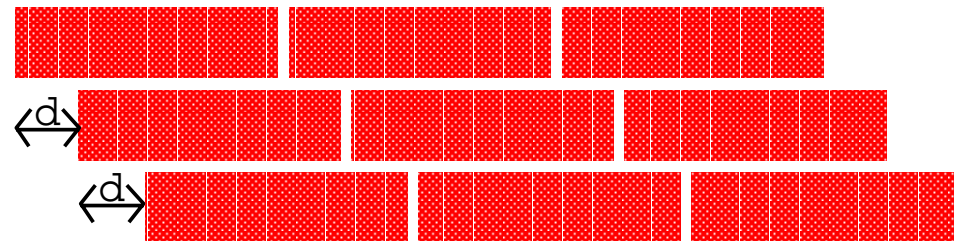
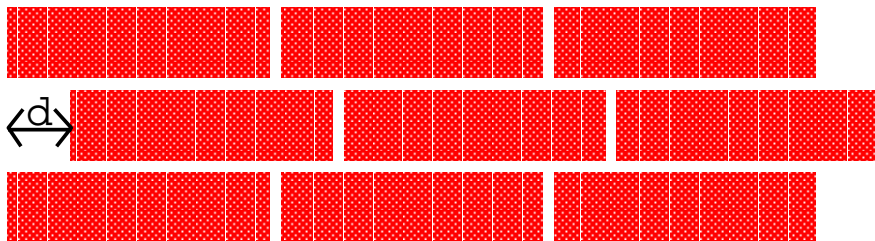
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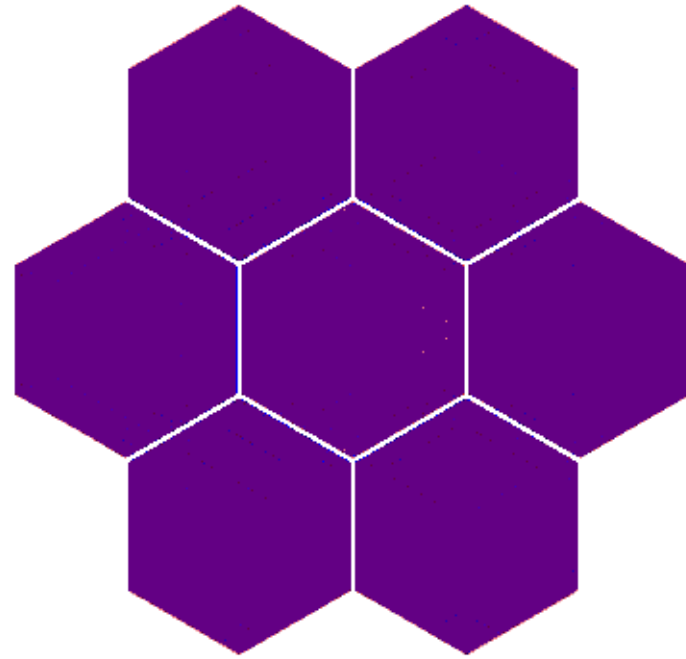
For other cases the translation may be in alternating directions or regular.



# Corneocyte Layer Alignment

In three dimensions the transformations become harder to categorise.

First, two fully aligned layers of corneocytes (hexagons) would look as follows:



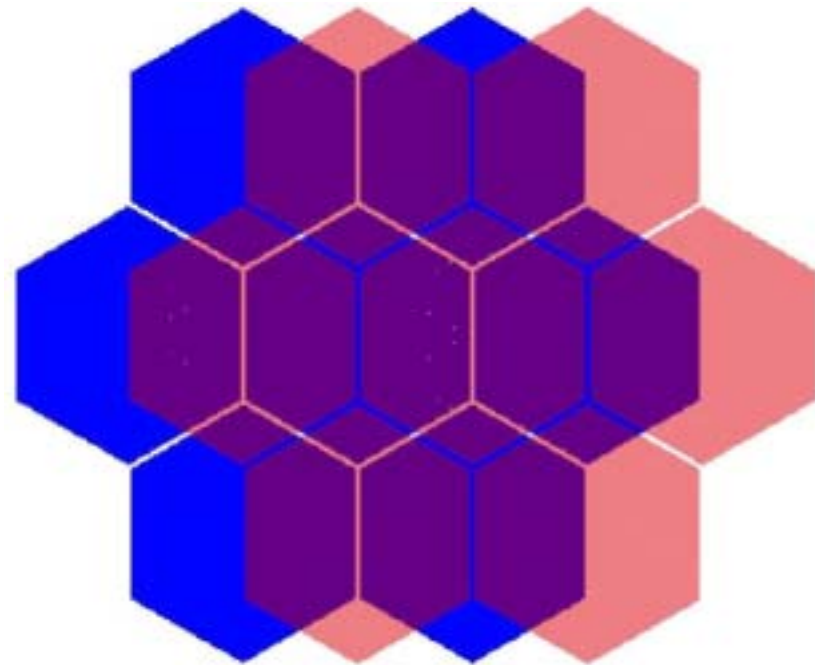
# Corneocyte Layer Translation

In three dimensions the transformations become harder to categorise.

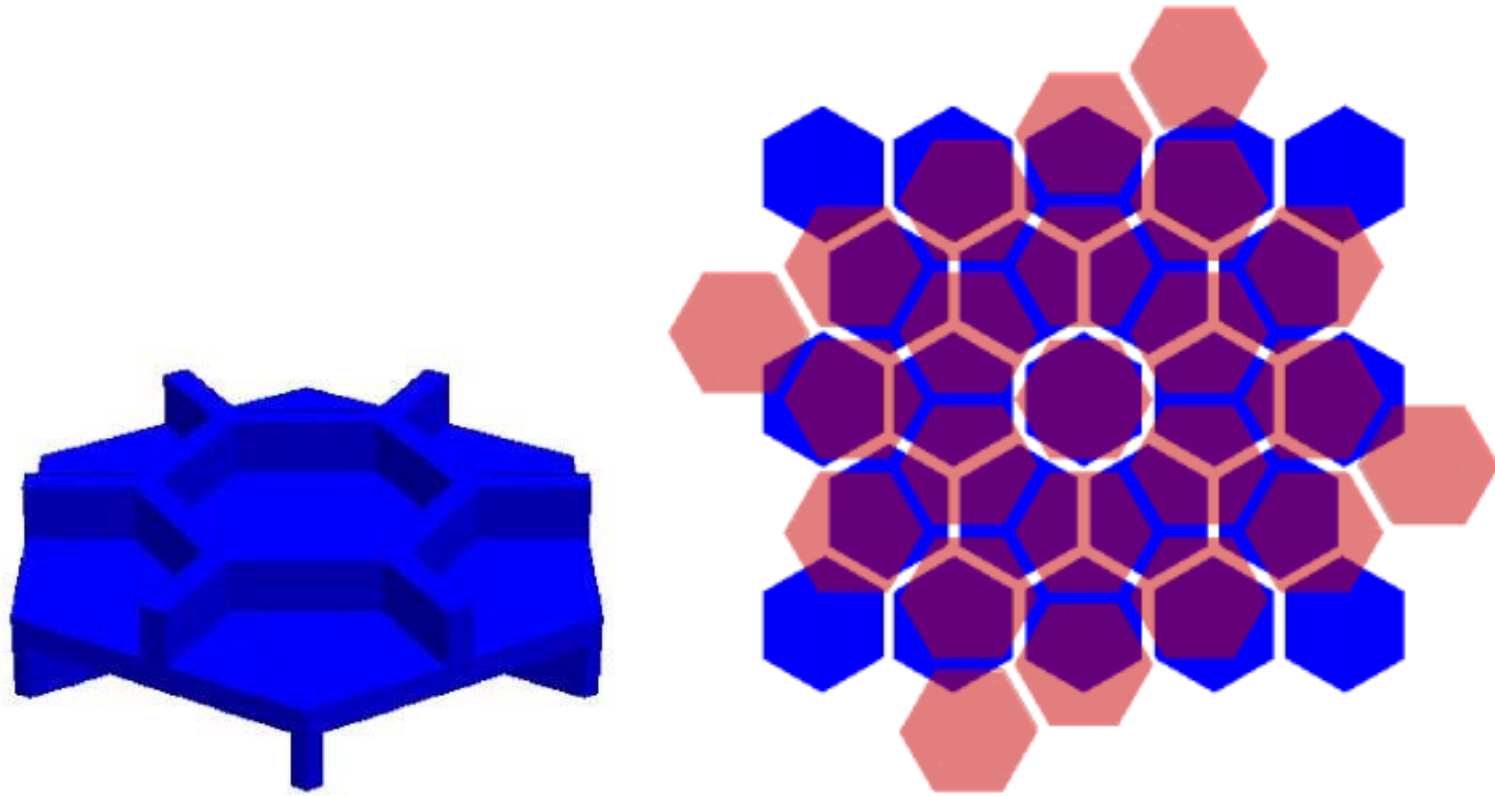
Each hexagon has two axes, a major and a minor.

Maximum translation along the minor axis is shown here

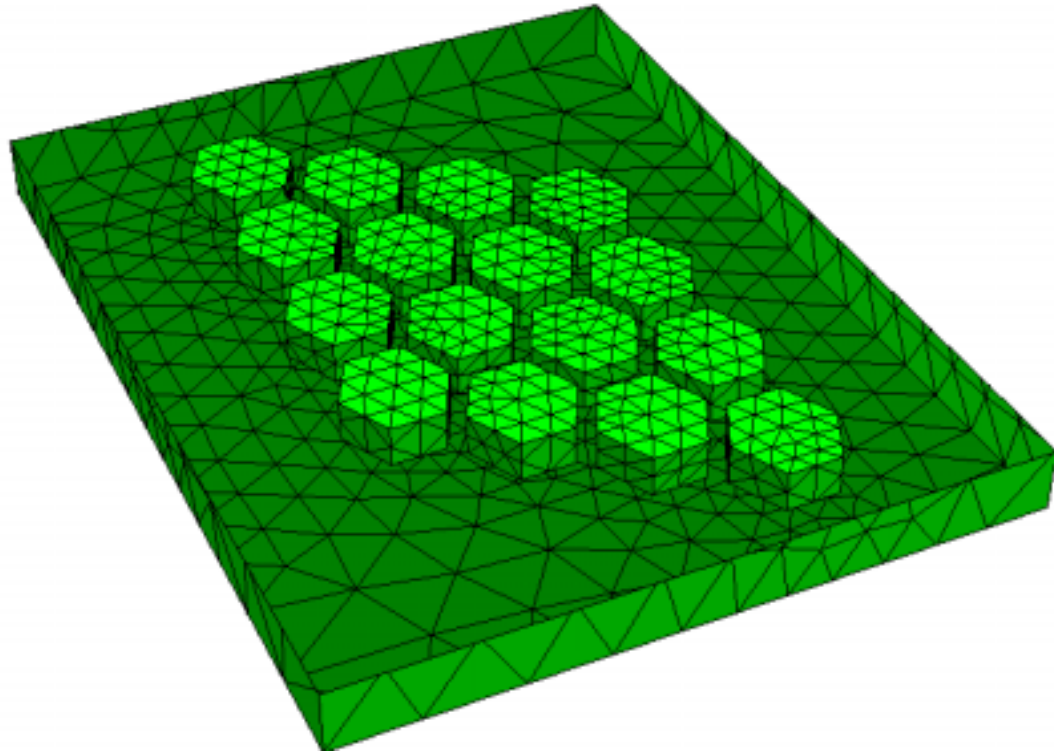
Note the ‘shoot through’ points are in the middle of the edges.



## Rotation between corneocyte layers - $30^\circ$

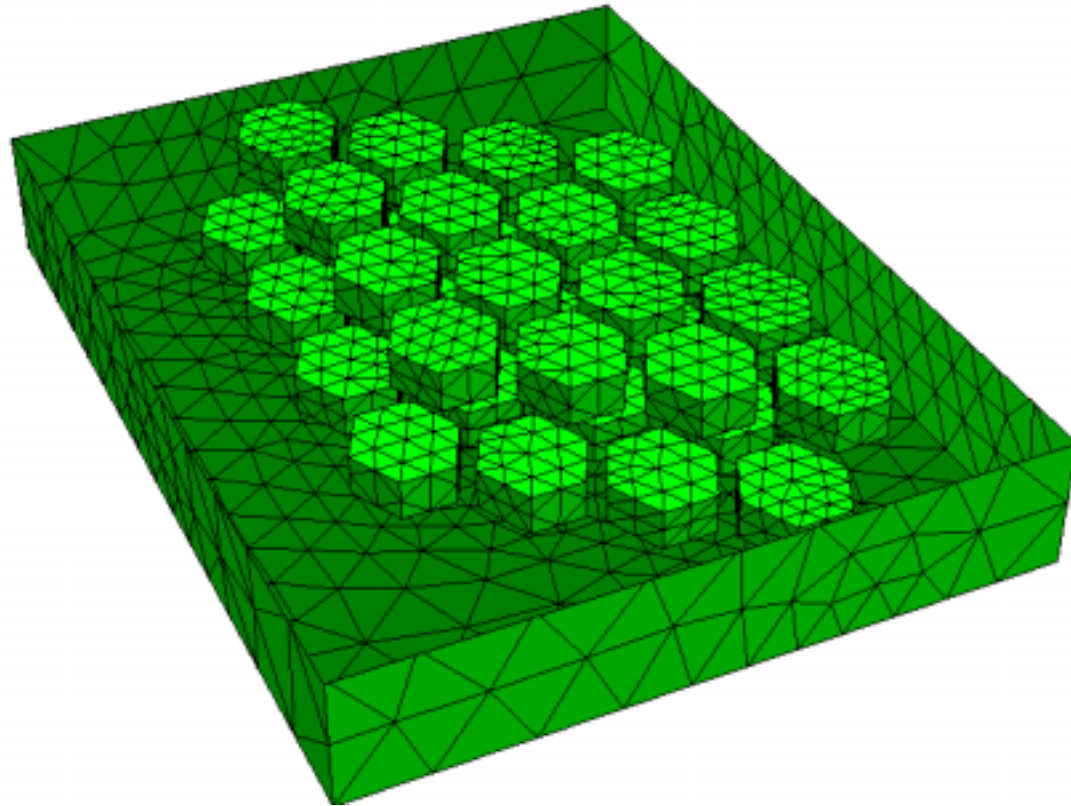


# Meshing around the skin geometry



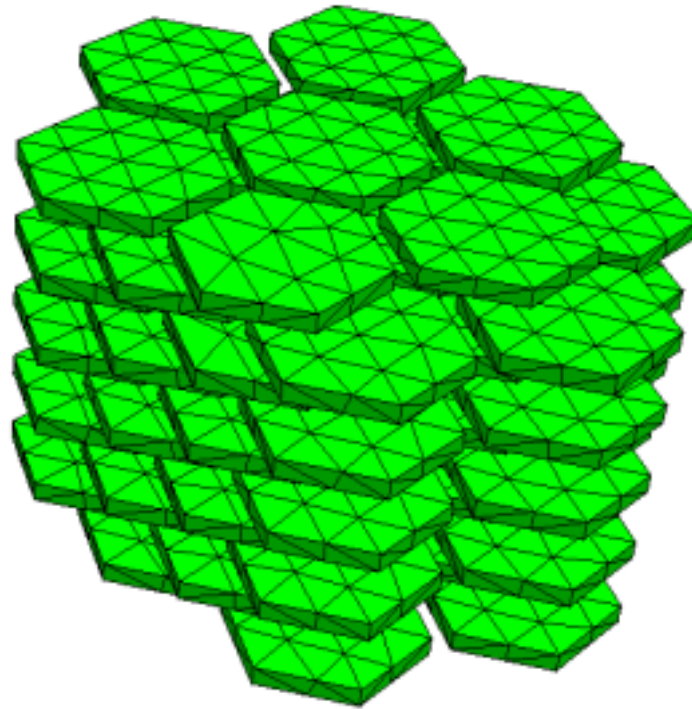
Meshing of the domain will use triangles on the faces of the corneocytes and tetrahedra filling the lipid.

# Meshing around the skin geometry



Meshing of the domain will use triangles on the faces of the corneocytes and tetrahedra filling the lipid.

# Meshing around the skin geometry



The s.c. geometries to be modelled will have a much greater volume of corneocytes!

If permeable corneocytes are to be used then each corneocyte will need an interior mesh in addition to the lipid mesh.

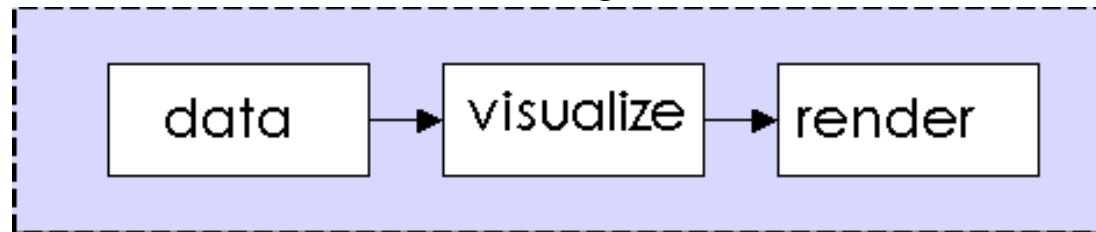
# Turning the solver into a tool

To be useful to skin researchers the package developed must be:

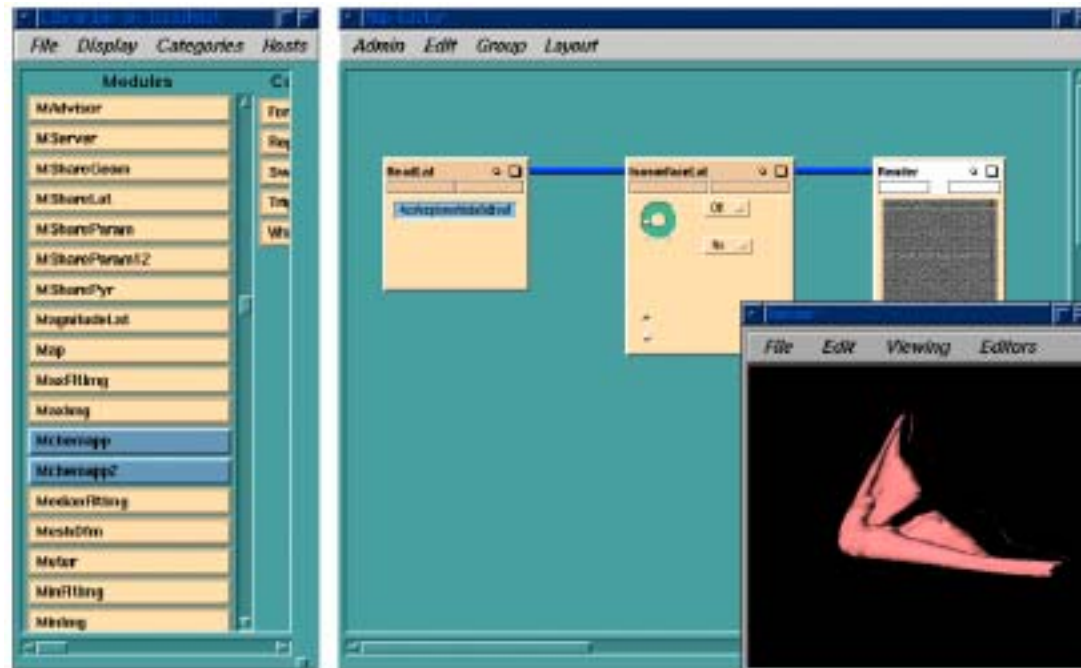
- Accurate
  - Every solution obtained must be worth having
- Quick
  - Access to high performance computers
- Simple
  - Users need not understand the details of the numerical solver
- Meaningful
  - The solver must produce meaningful solution visualisations
- Collaborative
  - Researchers in different locations can work together with shared data

# Data Visualisation

Traditional data visualisation is done in stages

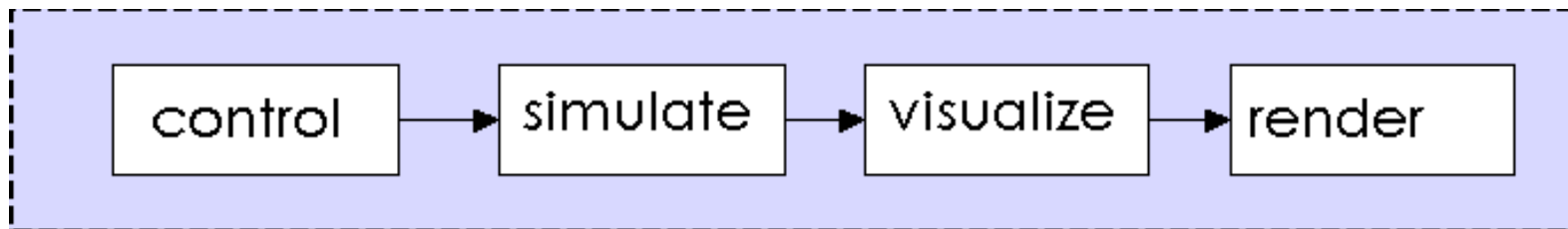


In a visual programming environment data follows a pipeline for rendering



# Problem Solving Environments

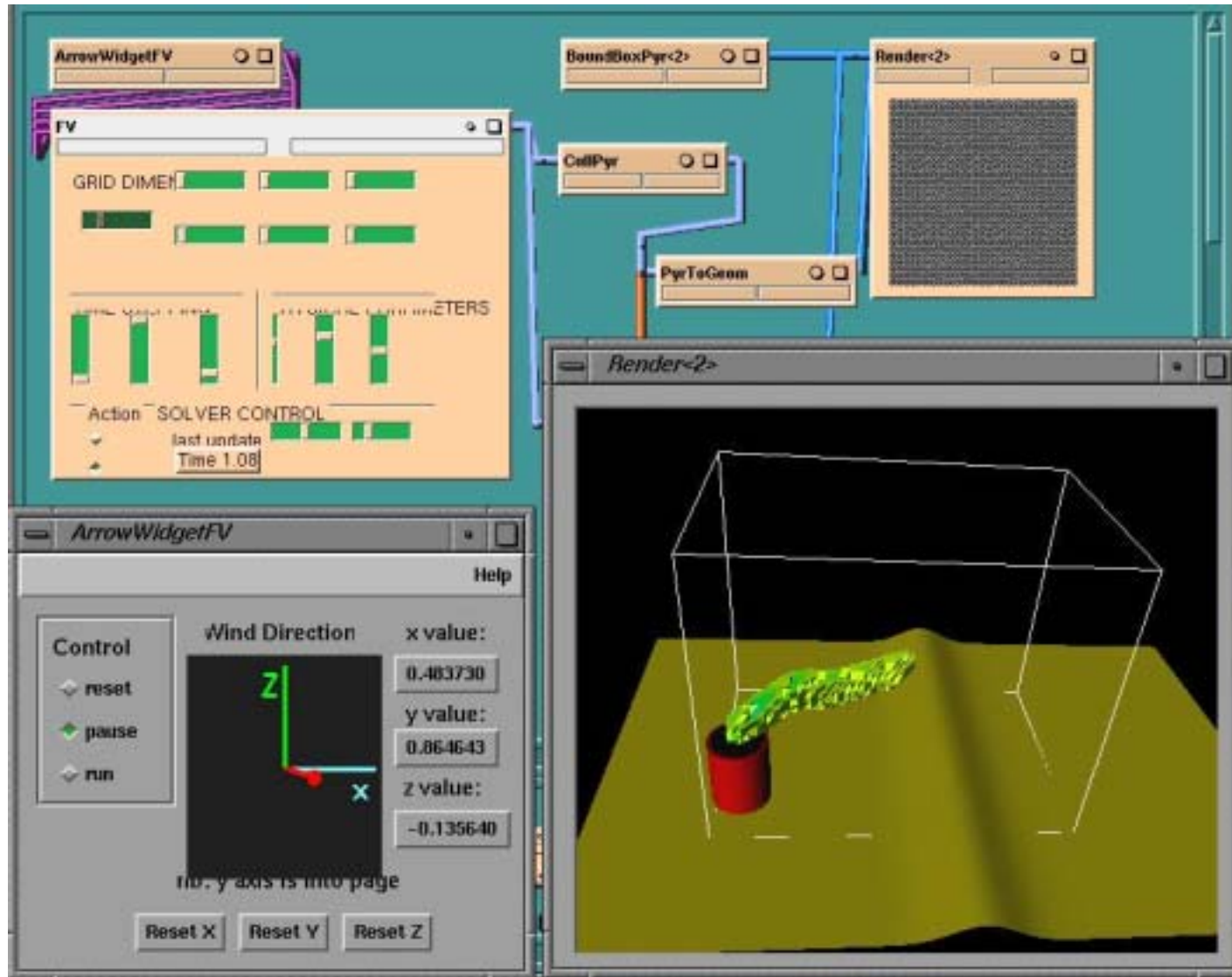
If the numerical simulation generating the output data to be visualised was included in the pipeline then we would get a Problem Solving Environment (PSE).



All inputs to the model being solved would then be available through an intuitive interface rather than by writing and compiling code.

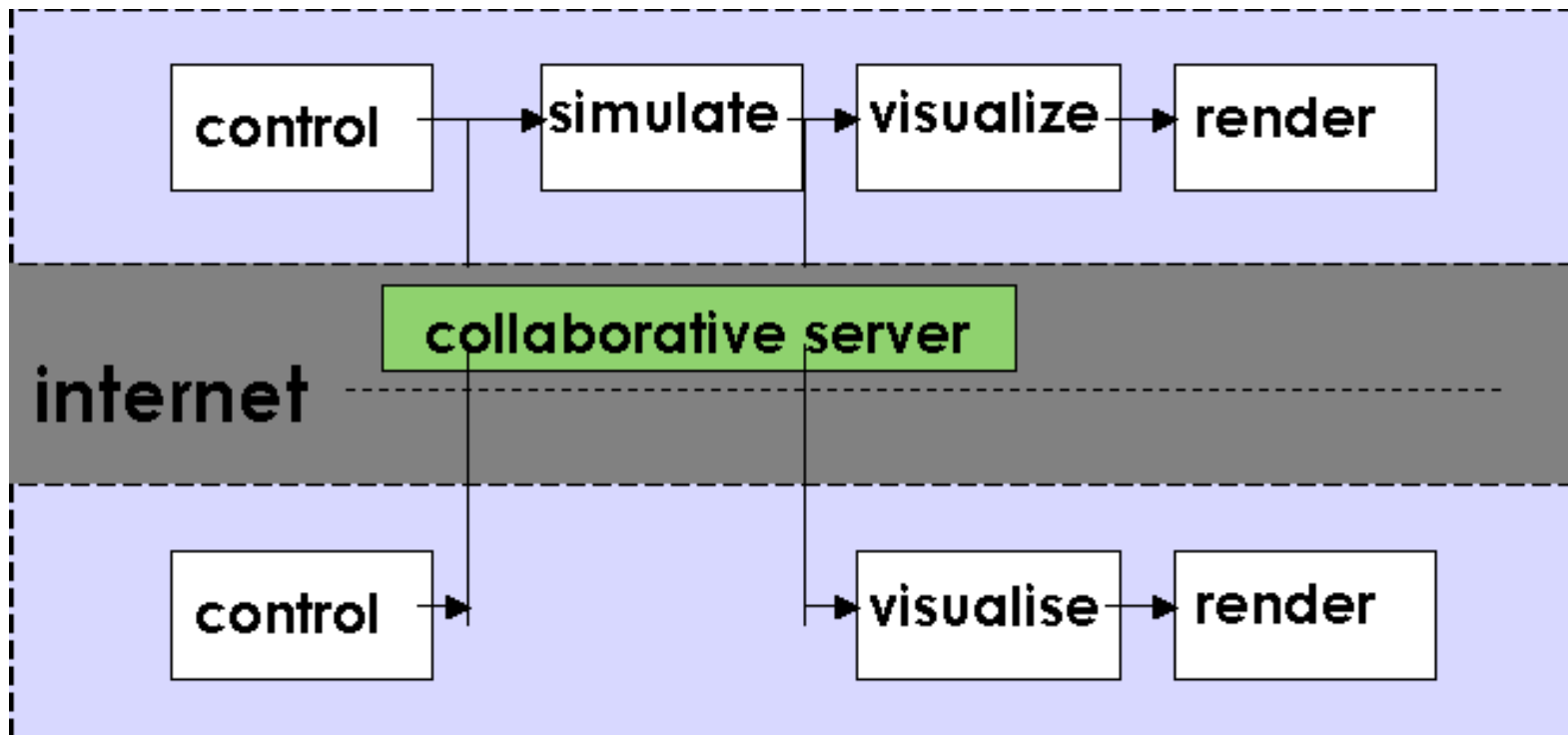
Results generated throughout the computation can be visualised immediately and changes made to the problem being solved through *computational steering*.

# Example PSE - A Pollution Plume



# Collaboration in a PSE

- Researchers on a project are often located at geographically separate locations
- Interactive sharing of expertise is facilitated by sharing access to both input parameters and output results through a PSE
- Different users may visualise different parts of the solution set if desired



## Where to now?

- Develop numerical solver for the skin geometry
- Develop a suitably useful Problem Solving Environment
- Discover answers from the numerical model and compare against experimental results
- Extend the model used, e.g. permeability of corneocytes

Applications for funding are being made to both EPSRC and NSF.