# Collaborative Bio-Inspired Algorithms
# Lecture 8: Immune System Modelling

Prof Jon Timmis

October 29, 2010

# Outline

# Complex systems

- Complex systems are a collection of component systems
  - Components interact through environmental media
  - Components may be very simple or very complex
  - E.g. the immune system ...
- Potential for emergent behaviours
  - Behaviours that are not simply the sum of the outputs of the component systems
- We are dealing with homogeneous complex systems
  - Very large number of components e.g. cells
  - Small number of sorts of component
  - Example: the immune system

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# Modelling

- Models are an abstraction to aid understanding or description
- Biologists and software engineers use diagrams to describe static structures and patterns of interaction
- For a whole complex system, models need to describe features of component systems, high-level system, and environment

# Simulation

- Simulations:
  - Execution of the model components, many times, in parallel
  - Explicitly provide time, space and environment
  - Key features of the (dynamic) environment provide the context for component behaviour and interaction
- Simulation issues:
  - A significant concern in complex systems is the *validity* of simulation
  - Poor choice of variables can give spurious equivalence giving little insight in to mechanisms and behaviours
  - The chosen components and environment has a significant effect on the simulation outcomes

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# Lymphocyte Entry to the Lymph Node through HEV

- Blood-borne lymphocytes enter functional tissue of lymph node through walls of high endothelial venules (HEV)
- During an immune response
  - HEVs dilate
  - The number of lymphocytes in lymph node increases
- Does dilation account for the increased numbers?
- Under what conditions is migration optimised?

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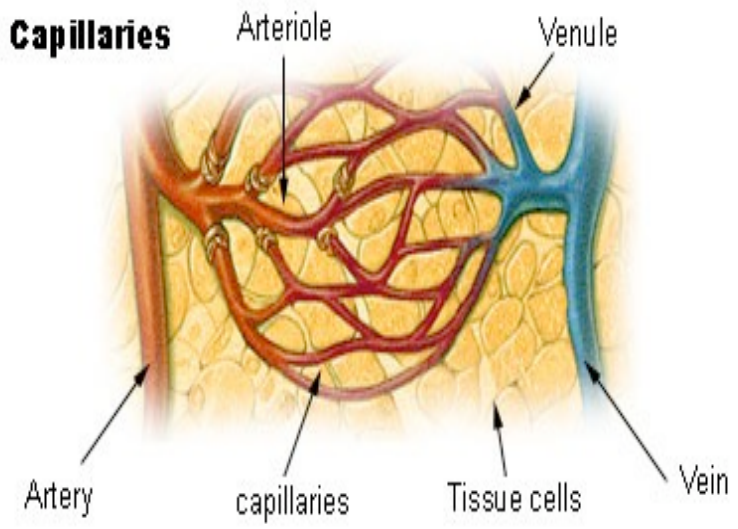
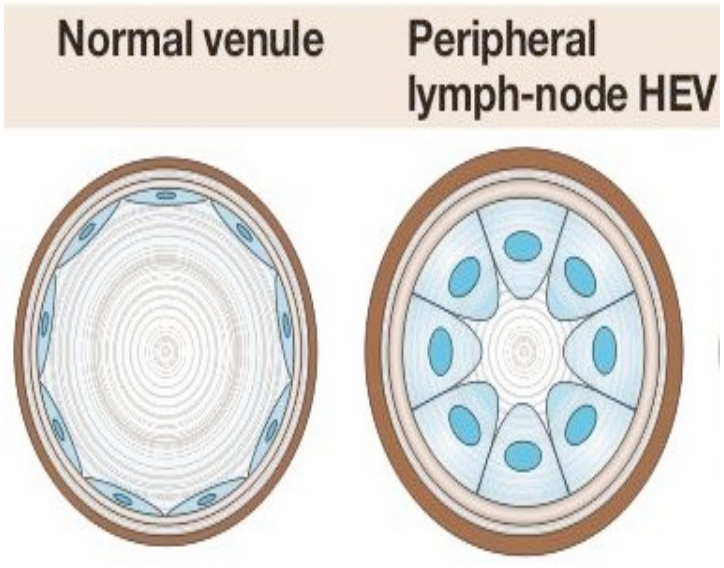
# HEV's




(a) Venules: small blood vessels that bring de-oxygenated blood to the veins form capillary bed

(b) High Endothelial Venules (HEV) which are characterised by plump endothelial cells

Figure: Venules in and HEV

# HEVs in a Lymph Node

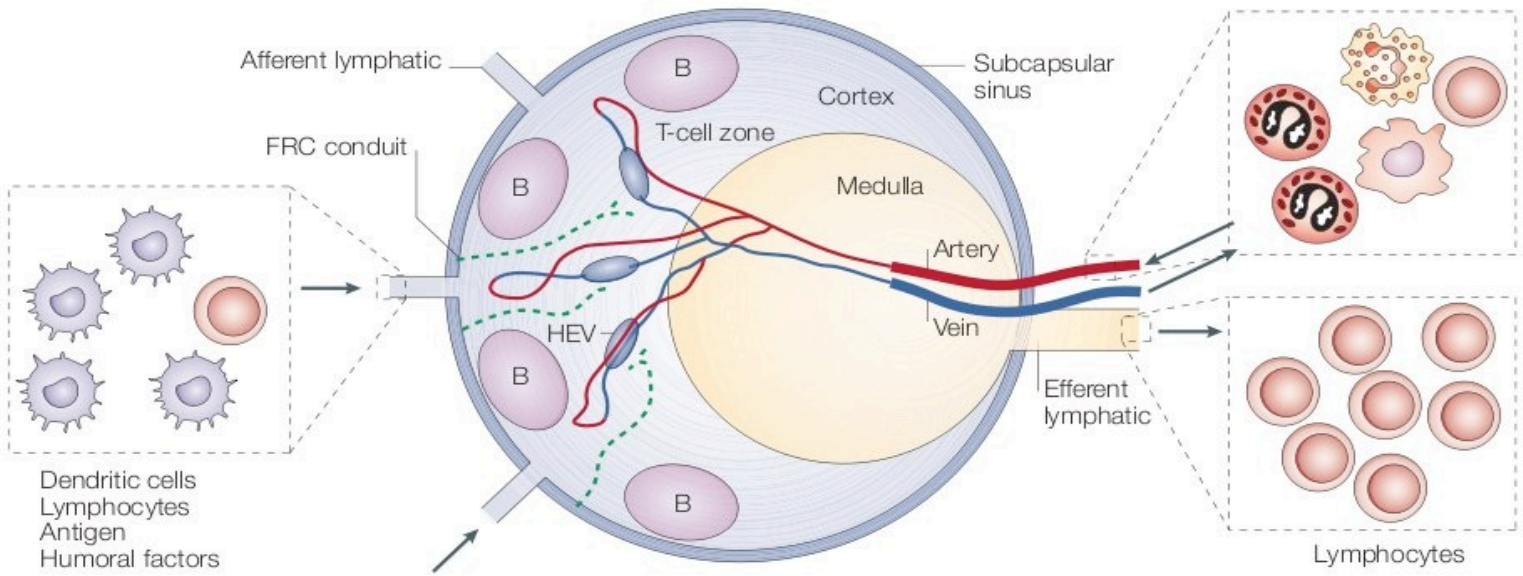



Figure: Many HEV's in the lymph node

# Pericytes

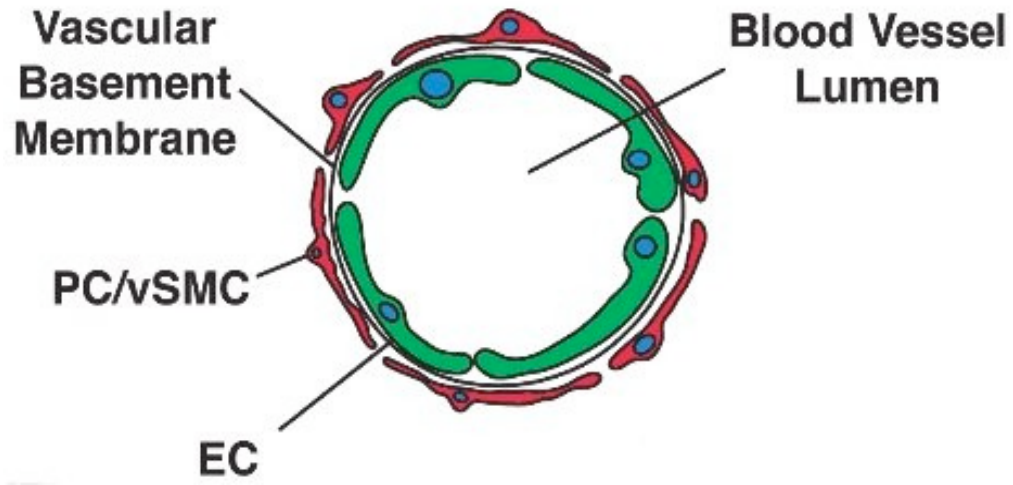



Figure: Cells that wrap around small blood vessels and act as a “scaffolding” around the blood vessel. Similar in nature to muscle cells.

# Lymphocyte Migration

- Lymphocytes enter lymph node through HEVs
  - Initiate in a rolling process
  - Under certain conditions, lymphocytes slow and squeeze though between endothelial cells
- Constriction and dilation regulates diameter and blood flow of vessel
- Rolling, slowing and migration mechanism controlled by cell surface molecules and receptors (selectins, integrins, chemokines)
- We have experimental data for amount of cells, time taken for rolling, sizes of vessels . . .

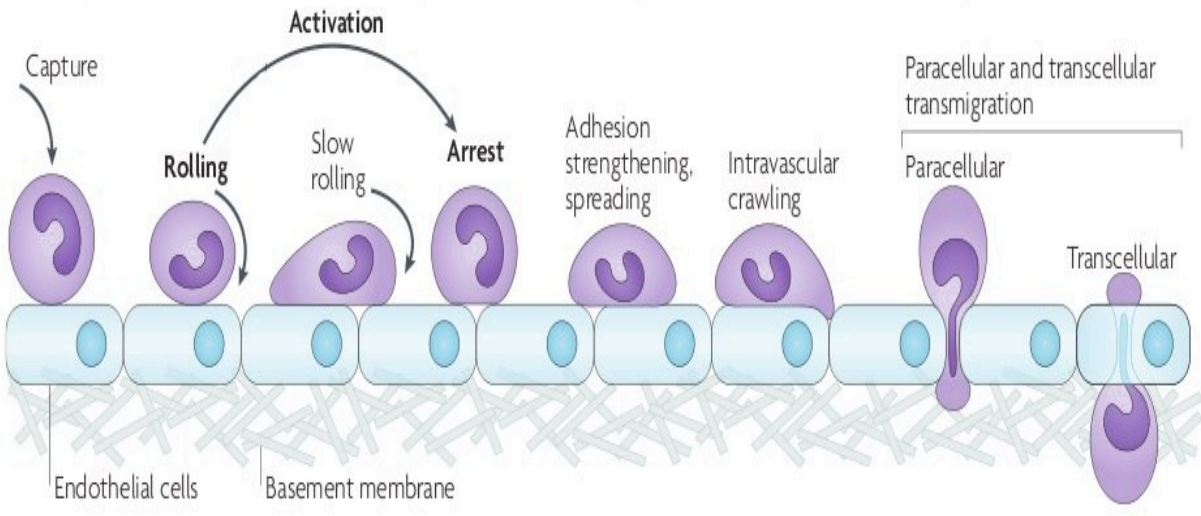
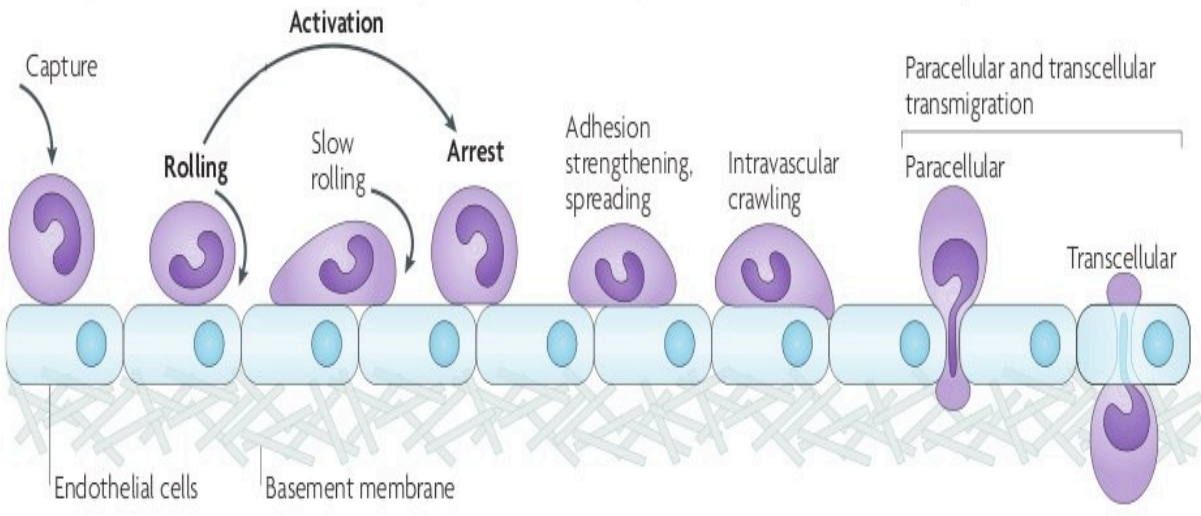



Figure: Rolling process of lymphocytes and their migration

The increase in lymphocyte numbers in lymph node during an immune response is a direct result of migration rather than proliferation of existing lymphocytes in the lymph node

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# A purpose for the simulation

- There should be a reason for what we are doing as it will effect our design and implementation
- In this case:
  - Implement something that is *biologically faithful*
  - Aid hypotheses testing
- Desired output:
  - Numerical data under different conditions
  - A format that allows insight into *in vitro* experimental data

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# The CoSMoS Process

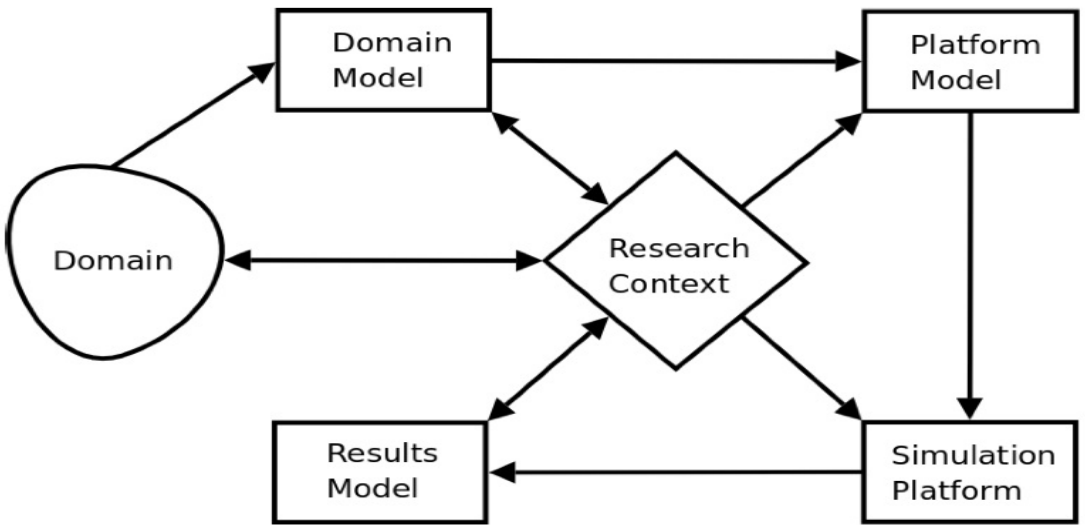


Figure: CoSMoS Modelling Process

# A domain model of the biology

- *Before* we construct a simulation, we identify the relevant *components* and *behaviours* in the form of a *domain model*
- Population of homogeneous lymphocytes interacting in an environment
- Environment:
  - Parts of the body with which the lymphocytes interact
  - Tube (HEV) consisting of HE cells and pericytes form of a tube
- Lymphocyte behaviour:
  - We model different environments lymphocytes pass through as *states*
  - *Transitions* occur when a lymphocyte moves between environments

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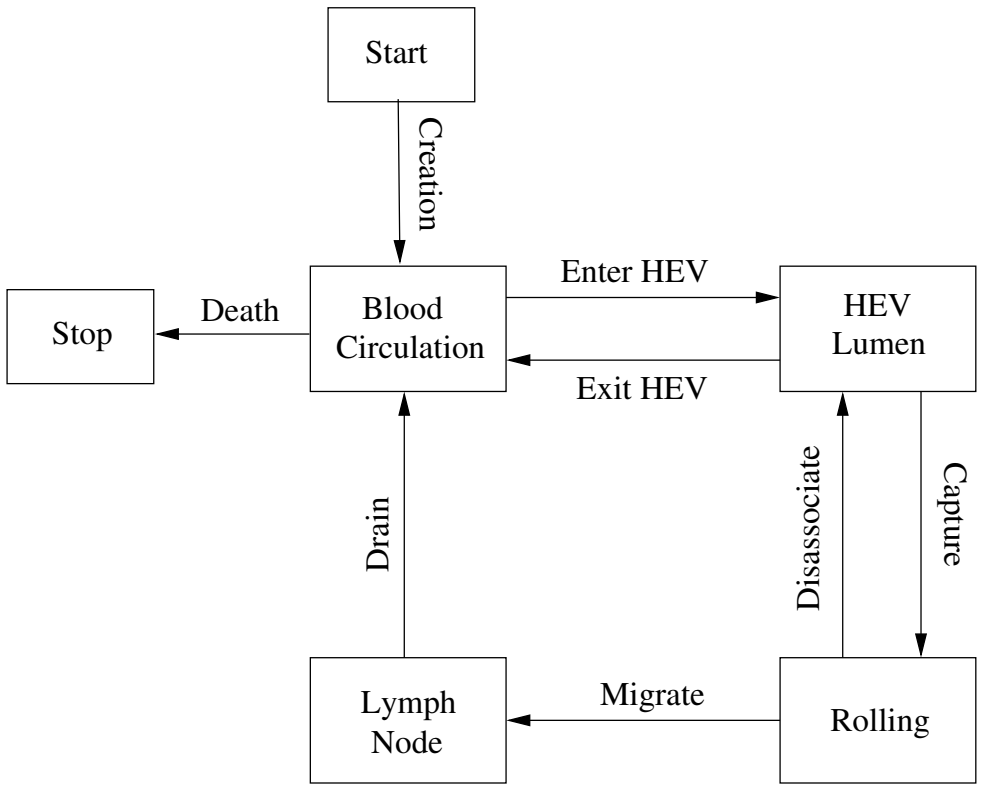
# State diagram model for a lymphocyte

**Start**: lymphocyte is 'born'

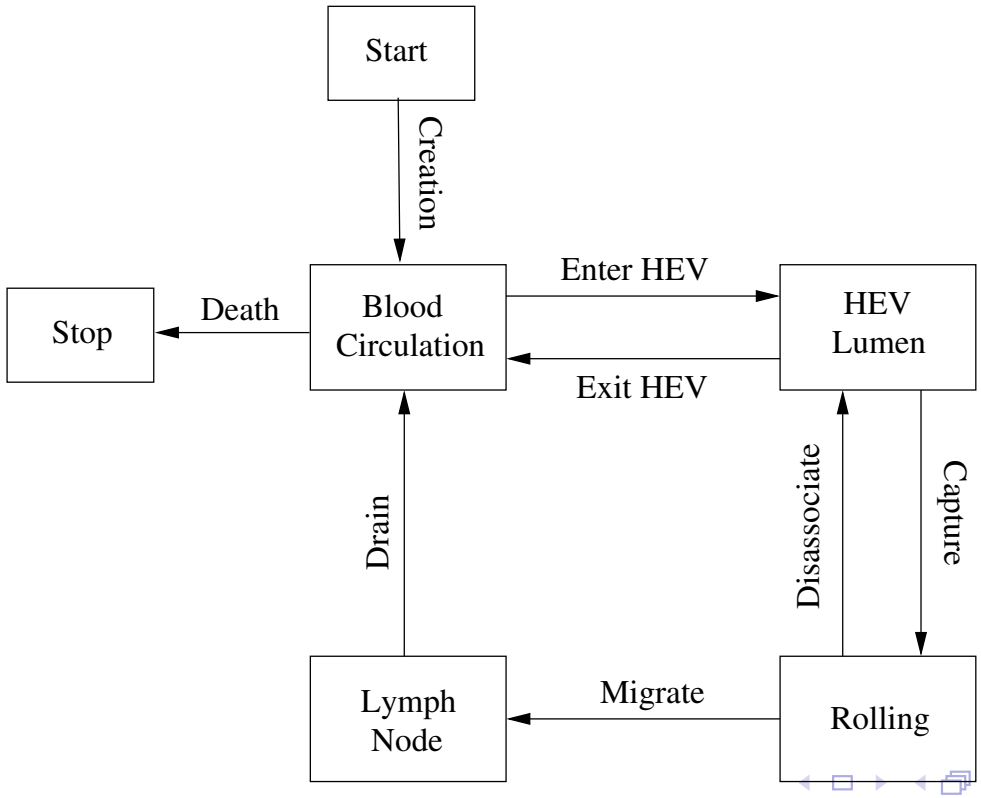
- *Creation* transits to **Blood circulation**



# State diagram model for a lymphocyte

**Blood Circulation**: parts of the body that the lymphocyte is in when it is not in the HEV or the lymph node tissue

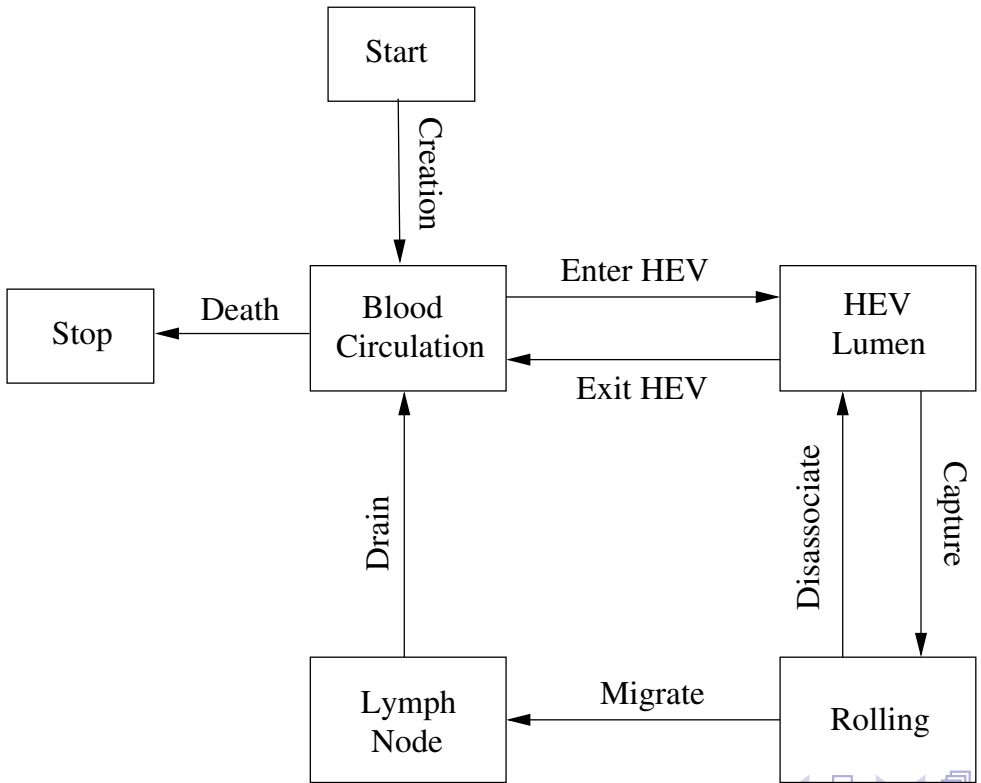
- *Enter HEV* transits to **HEV Lumen**
- *Death* transits to **Stop**



# State diagram model for a lymphocyte

**HEV Lumen**: lymphocyte when it is flowing freely in the lumen of a HEV

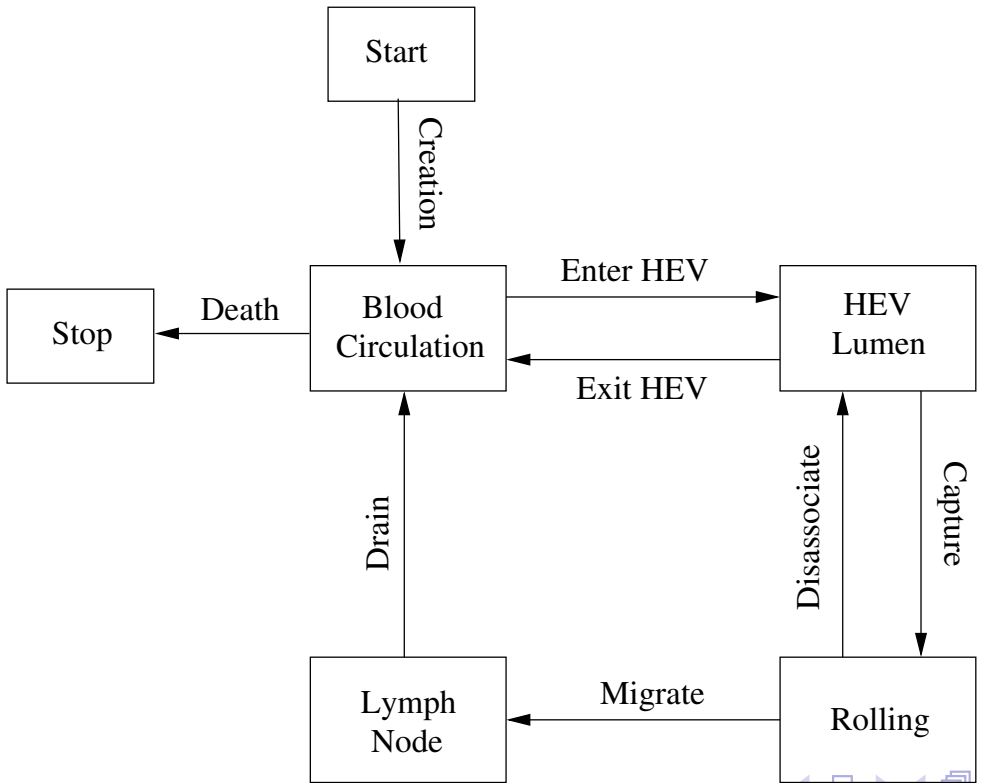
- *Exit HEV* transits to **Blood circulation**
- *Capture* transits to **Rolling**



# State diagram model for a lymphocyte

**Rolling**: This state represents the lymphocyte when it is rolling on the interior surface of an HEV

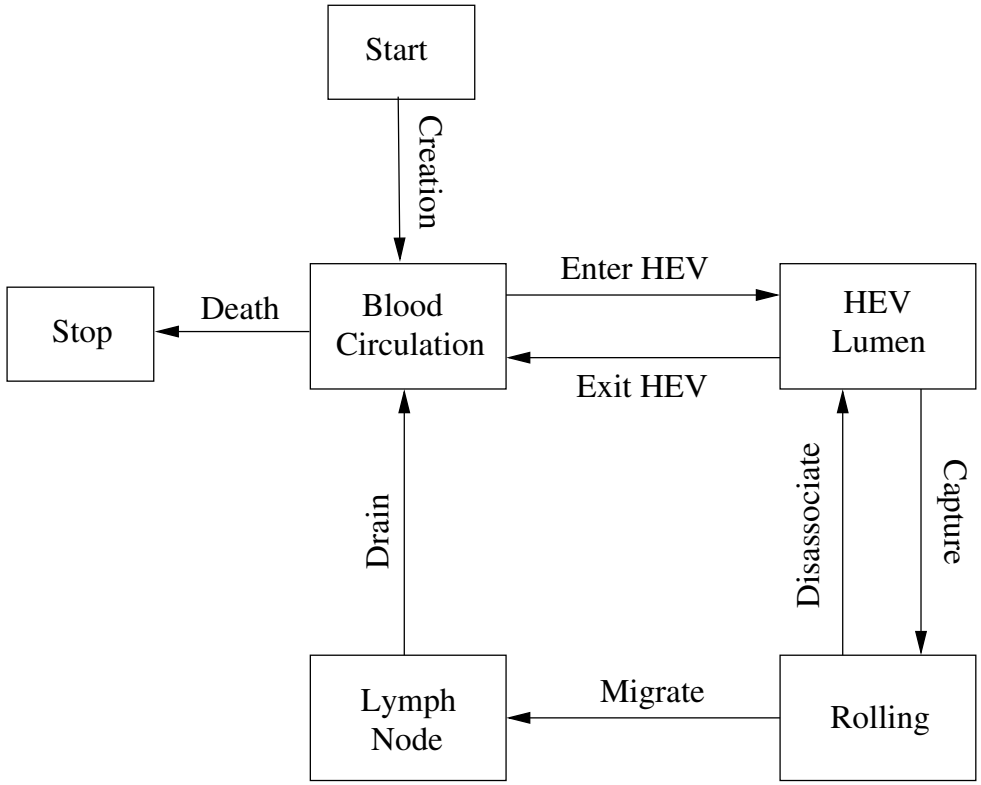
- *Disassociate* transits to **HEV Lumen**
- *Migrate* transits to **Lymph Node**



# State diagram model for a lymphocyte

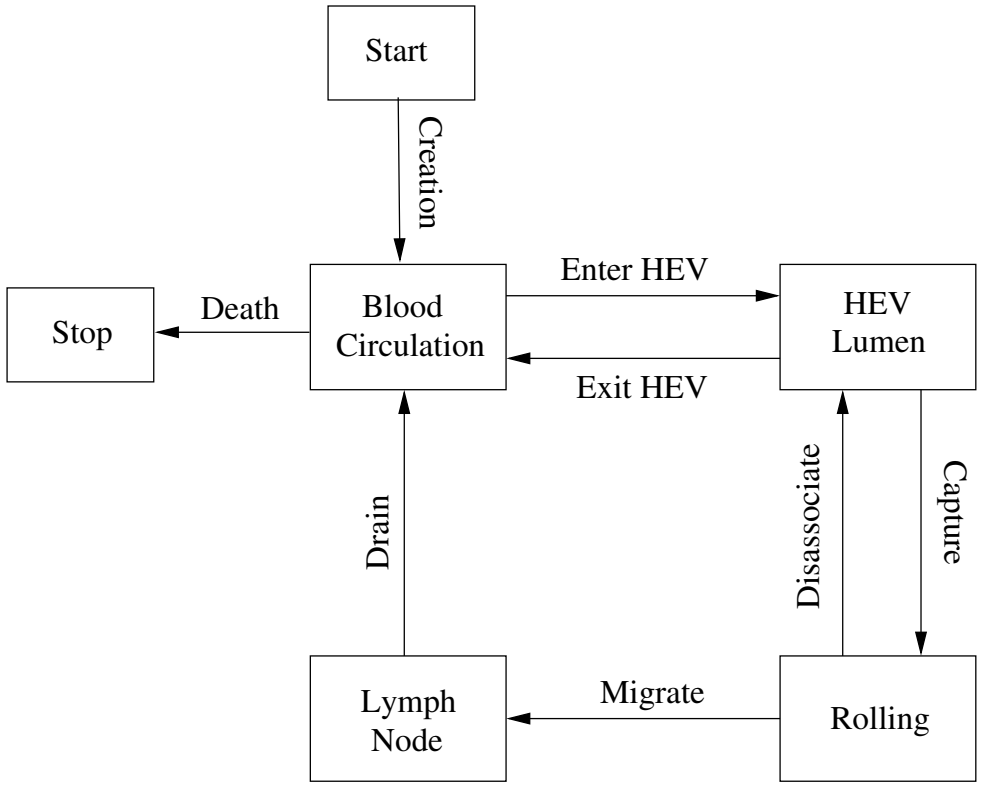
**Lymph Node**: This state describes the lymphocyte when it is present in functional tissue of a lymph node

- *Drain* transits to **Blood circulation**



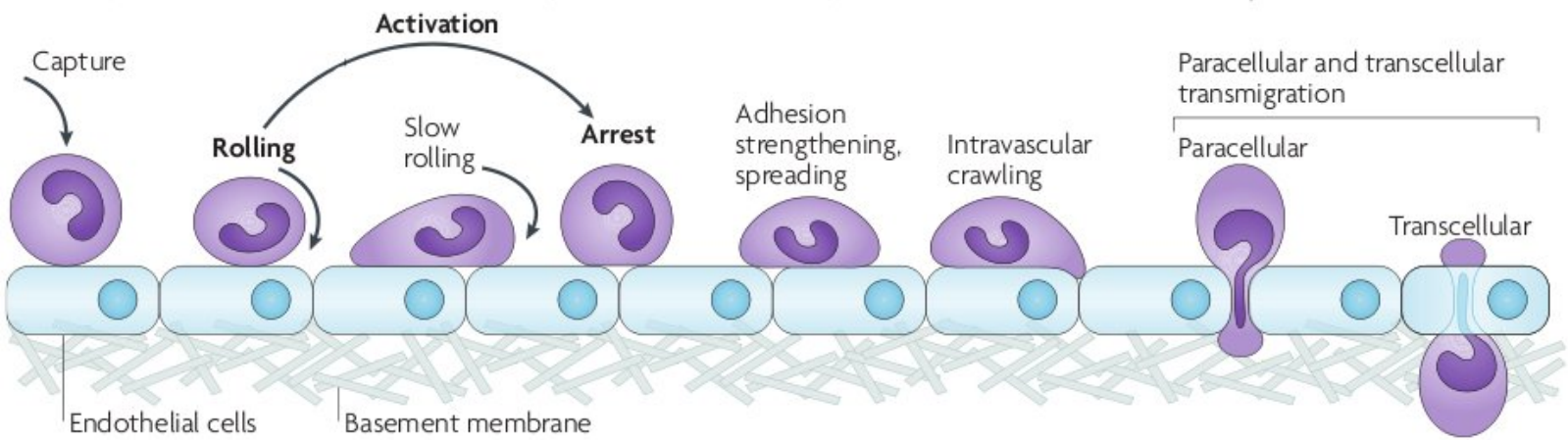
# State diagram model for a lymphocyte

**Stop**: lymphocyte ‘dies’



# Main simplification

- Reduced the multi-stage rolling and adhesion cascade down to two main steps
  1. Capture of lymphocytes on to the endothelial wall
  2. Migration after receiving the chemokine signal
- Other stages assumed to be either deterministic, or have such small probabilities of failing that they are insignificant



# Simulations

- Developed two simulations of the domain model
- *Migration-abstract*
  - No explicit co-ordinate system, only the four body locations
  - Each of these four state spaces can contain a number of lymphocyte agents
- *Migration-space*
  - 3-dimensional HEV tube made up of endothelial cells,
  - Supports visualisation of the HEV and of the lymphocytes migration
  - Simulation is “closer to the biology”(?)

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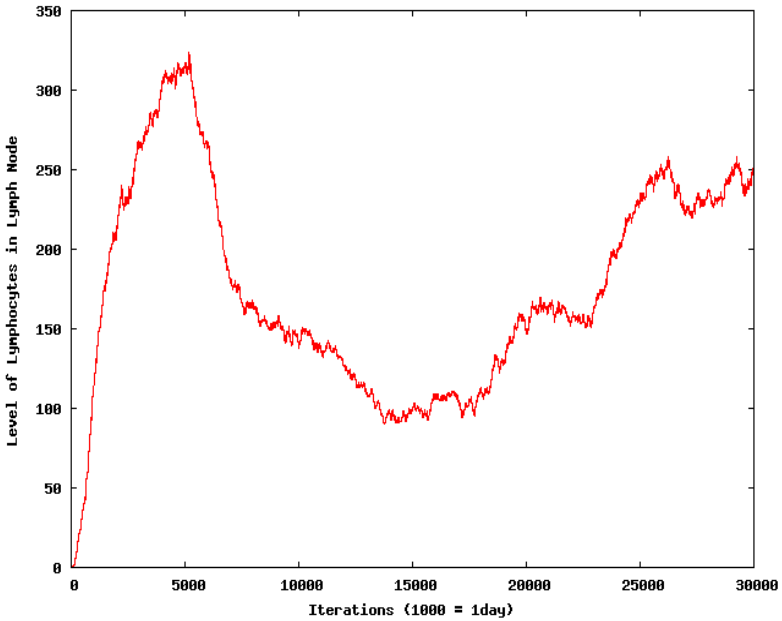
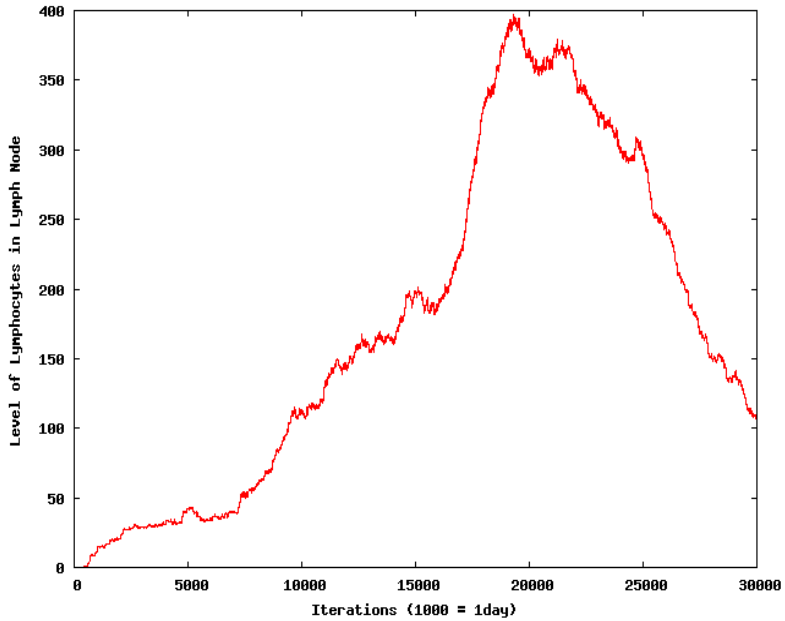
# Initial Simulation

# Results from Simulation




(a) Not taking into account a greater flow of lymphocytes through the HEV when the volume of the HEV expands




(b) Increasing the number of lymphocytes entering the HEV proportional to its volume: the number of lymphocytes in the lymph node increases.

# Immuno-Engineering

## immuno-engineering:

the abstraction of immuno-ecological and immuno-informatics principles, and their adaptation and application to engineered artefacts (comprising hardware and software), so as to provide these artefacts with properties analogous to those provided to organisms by their natural immune systems.

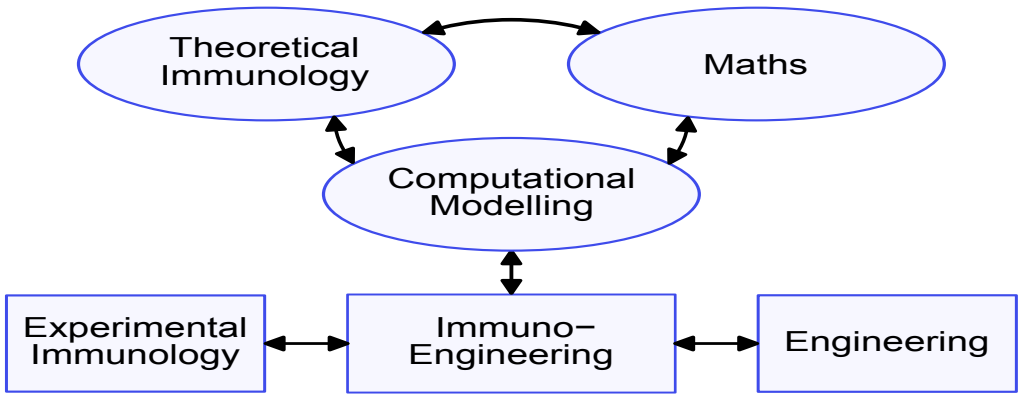



Figure: Immuno-engineering

# Bridging Immunology and Engineering

- Can all this feedback into Engineering?
  - Development of tools and methodologies for modelling complex systems (including the immune system)
  - Via “immuno-engineering” we can soundly abstract and apply immune-inspired ideas
  - Later in the lecture series we will look two examples of modelling feeding directly the development of algorithms (T cell signalling and chemical identification, then Granuloma formation and robotics)
- Can all this feedback into Immunology?
  - Models allow for *in-silco* experiments and drive *in-vitro* experiments
  - Develop a deeper understanding of the system under study