Prediction of Immune Strength: A Mathematical Prognosis

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Outline

1. Biology
   - T cell - APC immunology
   - Our Problem: Immunological Synapse (IS)
2. Mathematical Modelling
   - A membrane model: fluctuation across a threshold
   - Continuous Probability Distributions - CDF & PDF
   - PDF: Statistical persistence (first passage probability)
3. Average spatial patch size: start of IS
4. Average time of contact: start of IS
5. Ongoing works & future directions

Viral Infection: Our Defence Mechanism

Relies on appropriate cell signalling to develop or proliferate **viral immunity** :

- Antibodies: When the human (i.e. vertebrate) immune system encounters a virus, it produces *specific* antibodies that connect to the the virus through cell-signalling. The target is to render the virus non-infectious either for a few weeks (**IgM**) or indefinitely over long periods (**IgG**).

- Coreceptor cells: By involving body immune cells, called T cells and B cells. They create a chemical bond to define alternative pathways to kill the *host antigen cells* through proliferation of *specific* killer-T cells.

Why AIDS is so destructive then?: Because HIV plays a hide-and-seek with the immune system by continuously changing the amino acid sequence of the APCs thereby avoiding both forms of protection!

Our Interest: T Cell Proliferation and Interaction

Key Players

Primary generators of T cells: Thymus
Primary generators of B cells: Bone marrow
Our focus: Protein antigens $\Rightarrow$ T cells

A TCR (T Cell Receptor) couples with an APC (Antigen Presenting Cell) through a MHC (Major Histocomptability Complex)

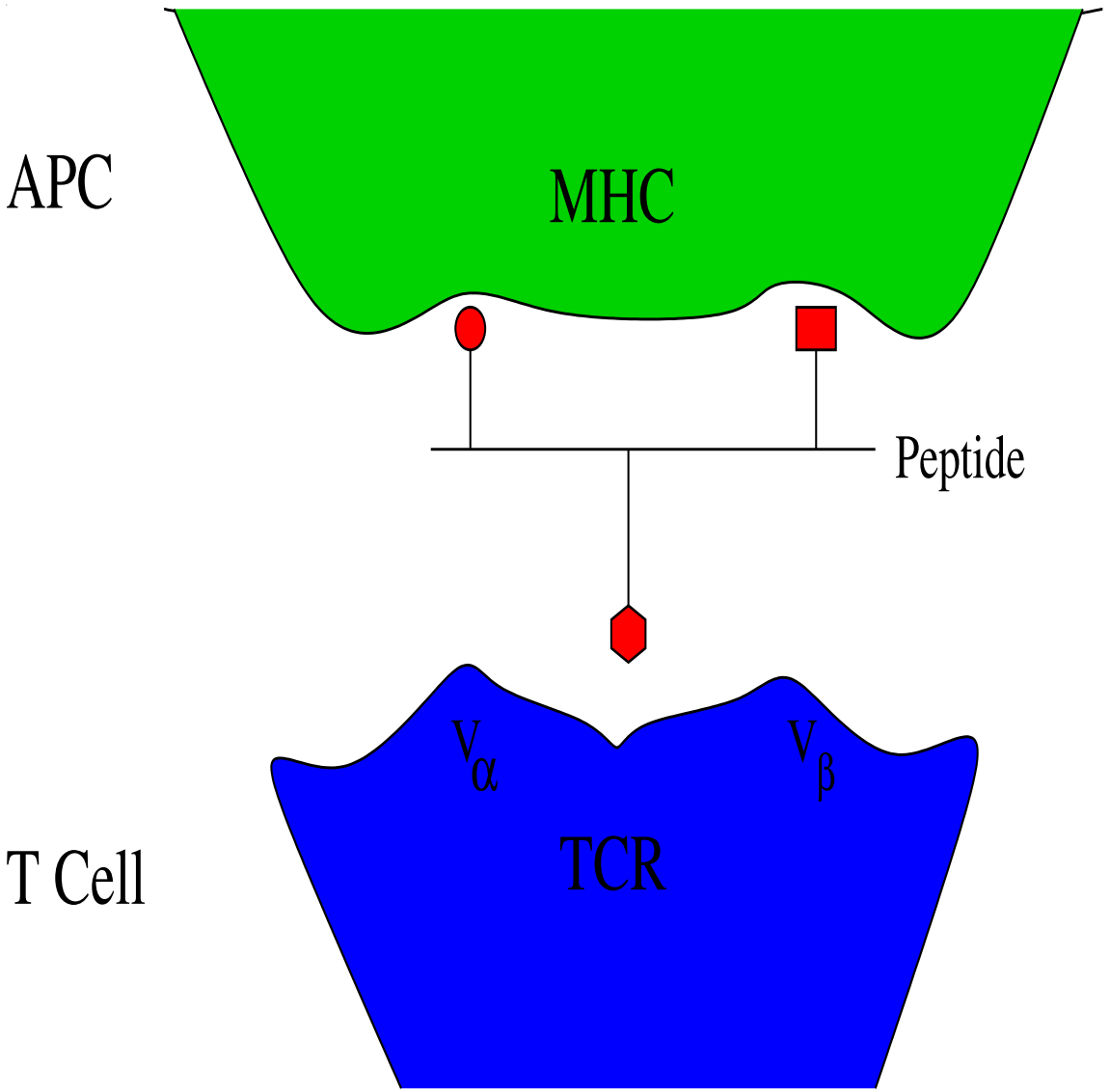
APC - MHC mechanism:

The MHC (I & II) are bound to the APC and are responsible for presenting antigens to the TCRs. The TCRs actually bind to the peptide molecules which are coupled to the surface of the MHC.

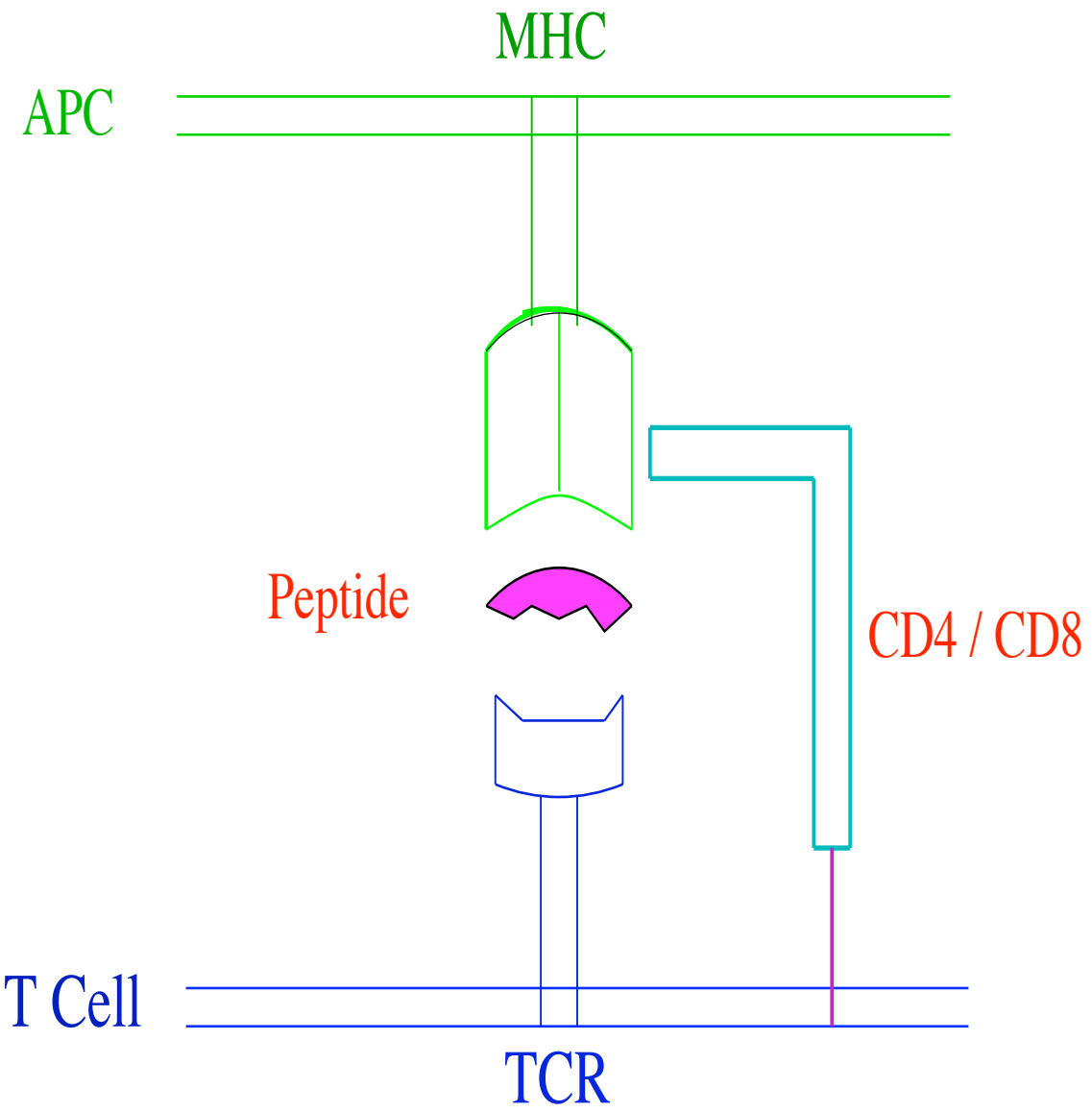
IS Movie (In Vitro)

(In vitro)

TCR-APC cartoon



A T cell receptor close to an antigen presenting cell



Immunological Synapse

The area of contact between an APC-MHC complex and an activated T cell is known as the immunological synapse (IS). This is a **chemical bond** formed between two cells and activated by numerous other *coreceptor* cells.

When a TCR comes close to the MHC, the following sequences appear:

- Within seconds, a native TCR is activated by the kinases Fyn and Lck through the co-receptors CD3 and CD4 leading to an initial aggregation of the adhesion molecules LFA1-ICAM1 $\rightarrow$ multiple length scales: TCR-APC bond $\sim$ 14-18 nm; LFA1-ICAM1 $\sim$ 41-45nm
- After 1-5 minutes, the aggregated adhesion molecules segregate to an outer ring. The central region is now occupied by the TCR-MHC complex.

(Real experiment)

What are we after?

Estimate the Strength of the IS Bond: **How does the body organise its self-defence against viral invasions?**

What is **Definitely Known** about the IS Bond:

1. The IS bond is a **non-covalent bond**
2. Average sizes of T Cell - APC interaction patches define the IS bond strength
3. Average bonding time define the IS bond strength too

Our Interest is in Evaluating (2) and (3) Using Mathematical Modelling!

What have we got?

- We have a membrane that is driven by a stochastically fluctuating force (thermal or due to many body impact)
- We also have other coreceptor molecules that activate or deactivate the TCR:APC interaction like a switch.

MODEL:

Time rate of change of relative height between TCR:MHC membranes = -Membrane Rigidity term + Membrane diffusion term - Coreceptor switch term + Stochastic force

Linearised Membrane Model

Linear stability analysis of the RD model around the steady state gives

$$M\frac{\partial Z}{\partial t} = -B\nabla^4 Z + \gamma\nabla^2 Z - \lambda Z + M\eta$$

Membrane rigidity | Surface tension | Relaxation term | Stochastic fluctuation

$$< \eta(\vec{x},t)\eta(\vec{x}',t) >= 2D_0 M\delta^2(\vec{x}-\vec{x}')\delta(t-t') \rightarrow \text{ Gaussian White Noise,}$$

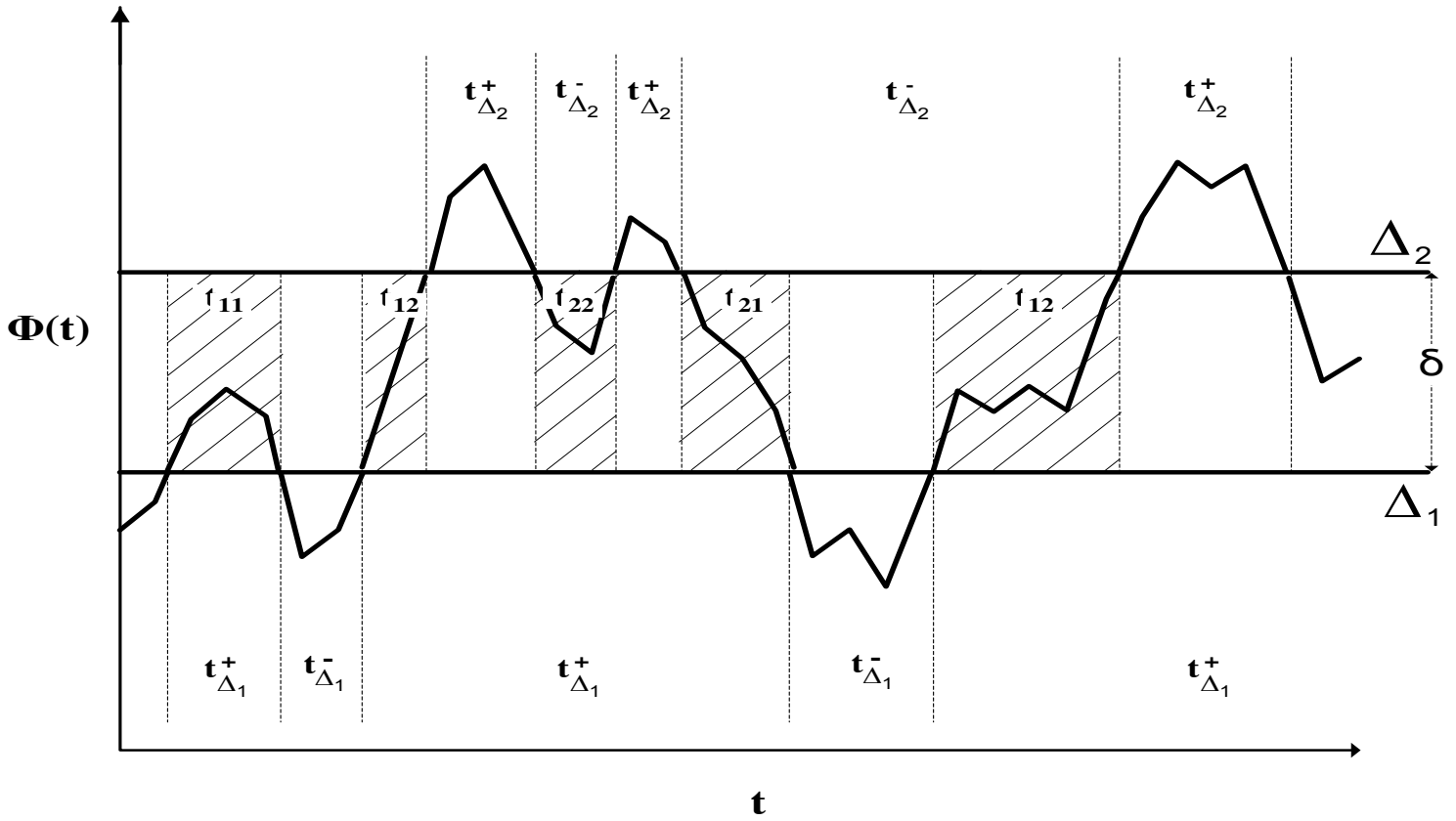
where $D_0 = k_B T_{eff}$ (energy units; k_B = Boltzmann's constant, T_{eff} = equilibrium temperature).

What is the probability of finding $Z > \Delta$?

Typical numbers:
$M = 4.7 \times 10^6\ k_B T_{eff}$ sec $\mu m^{-4} \rightarrow$ membrane damping constant
$B = 11.76\ k_B T_{eff} \rightarrow$ membrane rigidity constant
$\gamma = 5650\ k_B T_{eff}\ \mu m^{-2} \rightarrow$ membrane diffusion constant
$\lambda = 6.0 \times 10^5\ k_B T_{eff}\ \mu m^{-4} \rightarrow$ membrane relaxation constant
$5 \text{ nm} \leq \Delta \leq 45 \text{ nm} \rightarrow$ average bond length of molecules

APC/MHC membrane fluctuation: Time Series Across Two Thresholds (TCR:APC & LFA1:ICAM1)

$\Phi(t) = Z(\mathbf{x} = \mathbf{x_0}, t)$, Δ_1 = Average TCR:APC bond-length, Δ_2 = Average integrin:ligand bond-length, $\delta = \Delta_2 - \Delta_1$:



Persistence

Persistence: **what is the probability that a non-equilibrium field $Z(x,t)$ has not changed its sign upto time t (or through distance x) starting from some initial time t_0 (or x_0)?**

Our problems:

- what is the probability that for large enough times (stationary state), the average value of spatial cuts around $Z = \Delta$ is equal to $< x_{\pm} >$?
- what is the probability that the average value of temporal intersections around $Z = \Delta$ is equal to $< t_{\pm} >$ when ensemble averaged over all x's?

Biological Relevance:

- $< x_{+} > \approx$ size of the TCR-MHC contact $= \frac{1}{2}(< x_{12} > + < x_{21} >)$.
- $< x_{-} > \approx$ distance between any two TCR-MHC contact $= \frac{1}{2}(< x_{11} > + < x_{22} >)$.
- $< t_{+} > \approx$ average contact time of the IS bond $= \frac{1}{2}(< t_{12} > + < t_{21} >)$.
- $< t_{-} > \approx$ average detachment time of the IS bond $= \frac{1}{2}(< t_{11} > + < t_{22} >)$.

"<>" indicates **statistical average** of the respective quantities over many stochastic realisations; e.g. $< t_{11} > = \int dt_1 \int \mathrm{PDF}(t_1, t_2) t_{11}\, dt_2$.

PDFs: Spatial & Temporal

- Spatial/Temporal 2-point autocorrelation function ($\Delta_1 < Z < \Delta_2$):
  $c_{12}(\mathbf{x_1}, \mathbf{x_2}) =< Z(\mathbf{x_1}, t)Z(\mathbf{x_2}, t) >$ and $c_{12}(t_1, t_2) =< Z(\mathbf{x}, t_1)Z(\mathbf{x}, t_2) >$.

- Steady state:
  $t \to \infty$ for $c_{12}(\mathbf{x_1}, \mathbf{x_2}) \to c_{12}(|\mathbf{x_2} - \mathbf{x_1}|)$ and
  either of t_1 or $t_2 \to \infty$ for $c_{12}(t_1, t_2) \to c_{12}(|t_2 - t_1|)$.

Some **not-so-elementary** algebra will lead you to

- $c_{12}(\mathbf{x}) = \frac{k_B T_{\text{eff}}}{(2\pi)^2 M} \int d^2k \frac{e^{-i\mathbf{k}.\mathbf{x}}}{\alpha(\mathbf{k})} = \frac{k_B T_{\text{eff}}}{(4\pi)\sqrt{\lambda B}} \frac{K_0(e^{-\xi/2}\hat{x}) - K_0(e^{\xi/2}\hat{x})}{\sinh\xi}$, where $\alpha(\mathbf{k}) = \frac{Bk^4 + \gamma k^2 + \lambda}{M}$,
  $\xi = \log(\frac{\gamma - \sqrt{\gamma^2 - 4\lambda B}}{2\sqrt{\lambda B}})$, $\hat{x} = (\frac{\lambda}{B})^{1/4} x$ and $|\mathbf{x_2} - \mathbf{x_1}| = |\mathbf{x}|$.
- $c_{12}(\tau) = \frac{k_B T_{\text{eff}}}{(2\pi)^2 M} \int d^2k \frac{e^{-\alpha(\mathbf{k})\tau}}{\alpha(\mathbf{k})}$, where $\tau = |t_2 - t_1|$.

Average Bond Length & Average Bonding Time

- Average Bond Length: If the Gaussian field (variable) Z lies within $\Delta_1 < Z < \Delta_2$ for a small spatial interval x, the **probability of crossing** either $Z = \Delta_1$ or $Z = \Delta_2$ will be $\frac{x}{<x_+>}$; hence the **probability of no crossing** will be $1 - \frac{x}{<x_+>}$.

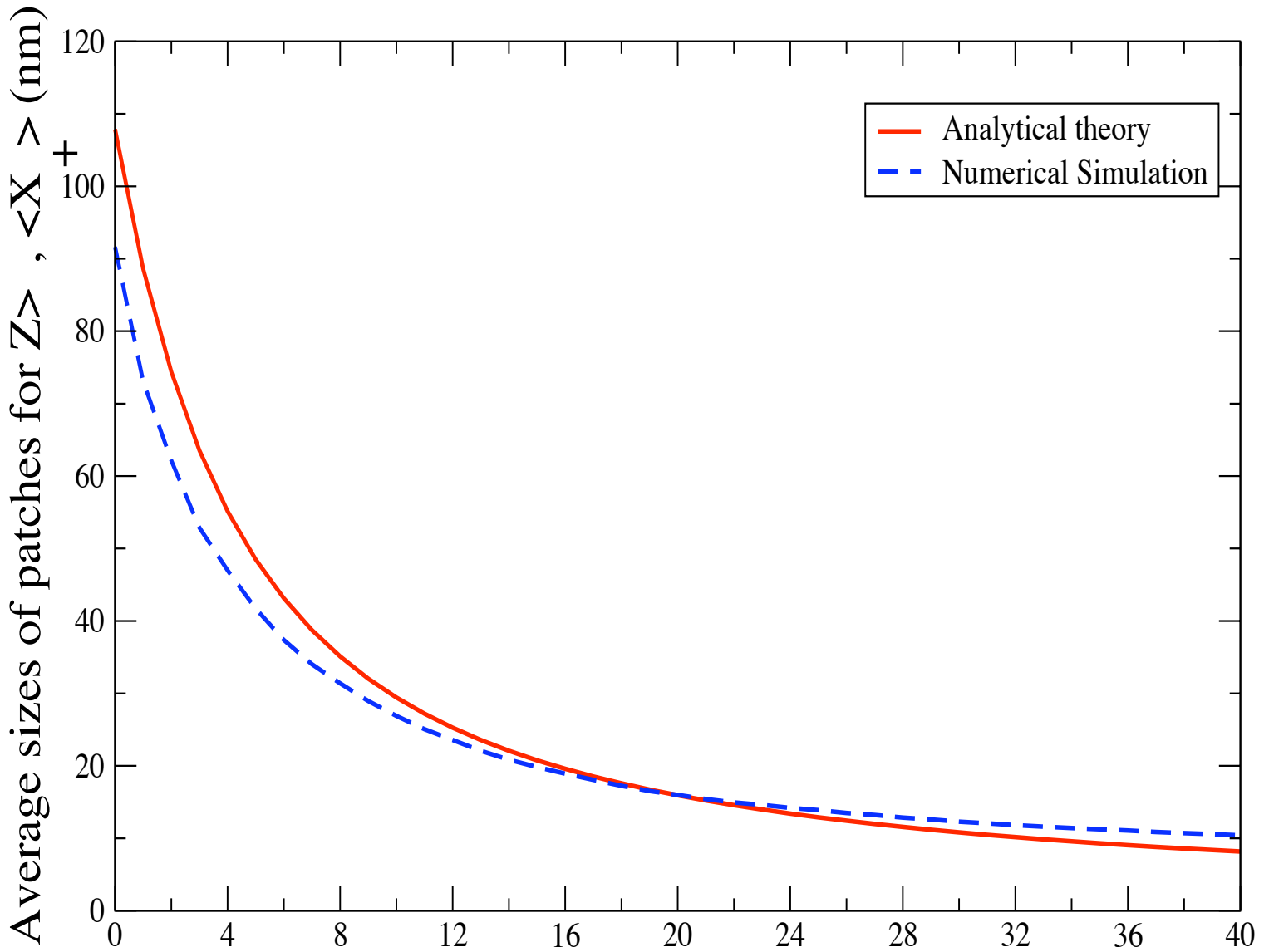
- Average Bonding Time: If the Gaussian field (variable) Z lies within $\Delta_1 < Z < \Delta_2$ for a small time interval τ, the **probability of crossing** either $Z = \Delta_1$ or $Z = \Delta_2$ will be $\frac{\tau}{<\tau_+>}$; hence the **probability of no crossing** will be $1 - \frac{\tau}{<\tau_+>}$.

Mathematical Results:

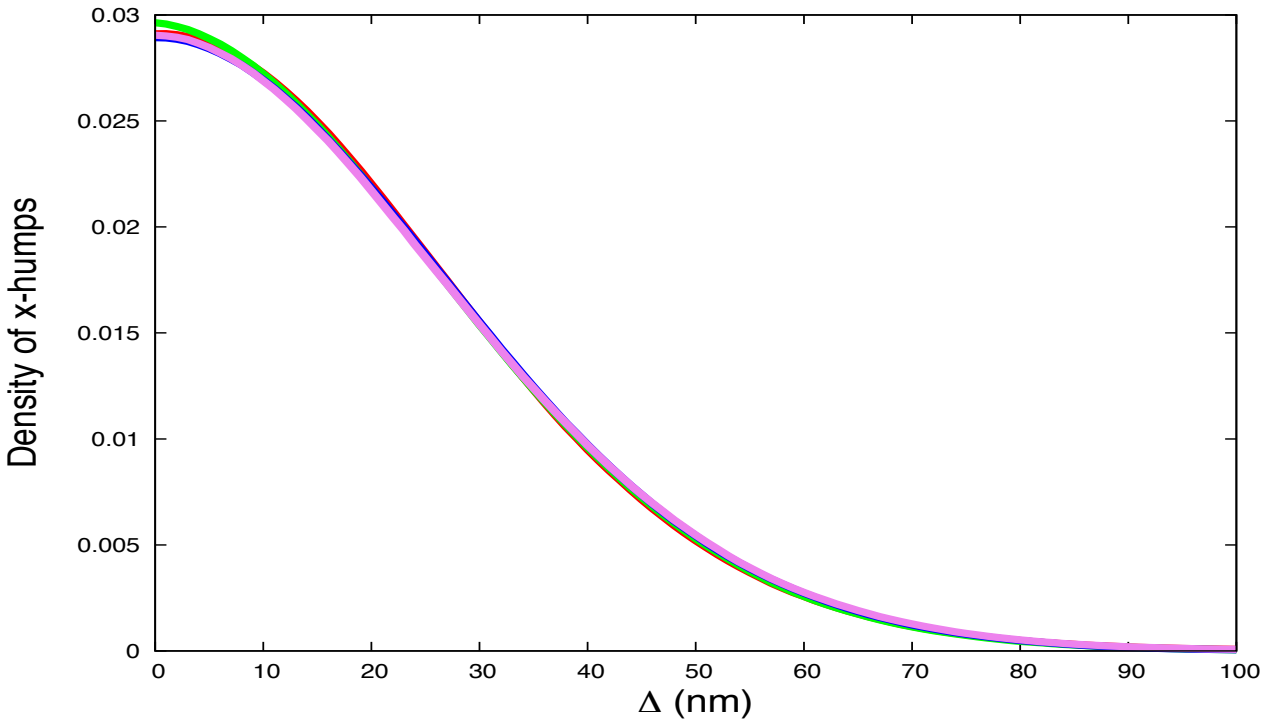
- If the conditional correlator $A_+ =< \mathrm{sgn}(Z(\mathbf{x_1}, t) - \Delta_i)\,\mathrm{sgn}(Z(\mathbf{x_2}, t) - \Delta_i) >$ (i=1,2) defines the probability of probability of **no spatial crossing** across $(= |\mathbf{x_2} - \mathbf{x_1}|)$, then
$$< x_+ >= -\frac{1}{\left(\frac{dA_+}{dx}\right)}$$

- If the conditional correlator $B_+ =< \mathrm{sgn}(Z(\mathbf{x}, t_1) - \Delta_i)\,\mathrm{sgn}(Z(\mathbf{x}, t_2) - \Delta_i) >$ (i=1,2) defines the probability of probability of **no temporal crossing** across τ $(=|t_2 - t_1|)$, then
$$< \tau_+ >= -\frac{1}{\left(\frac{dB_+}{d\tau}\right)}$$

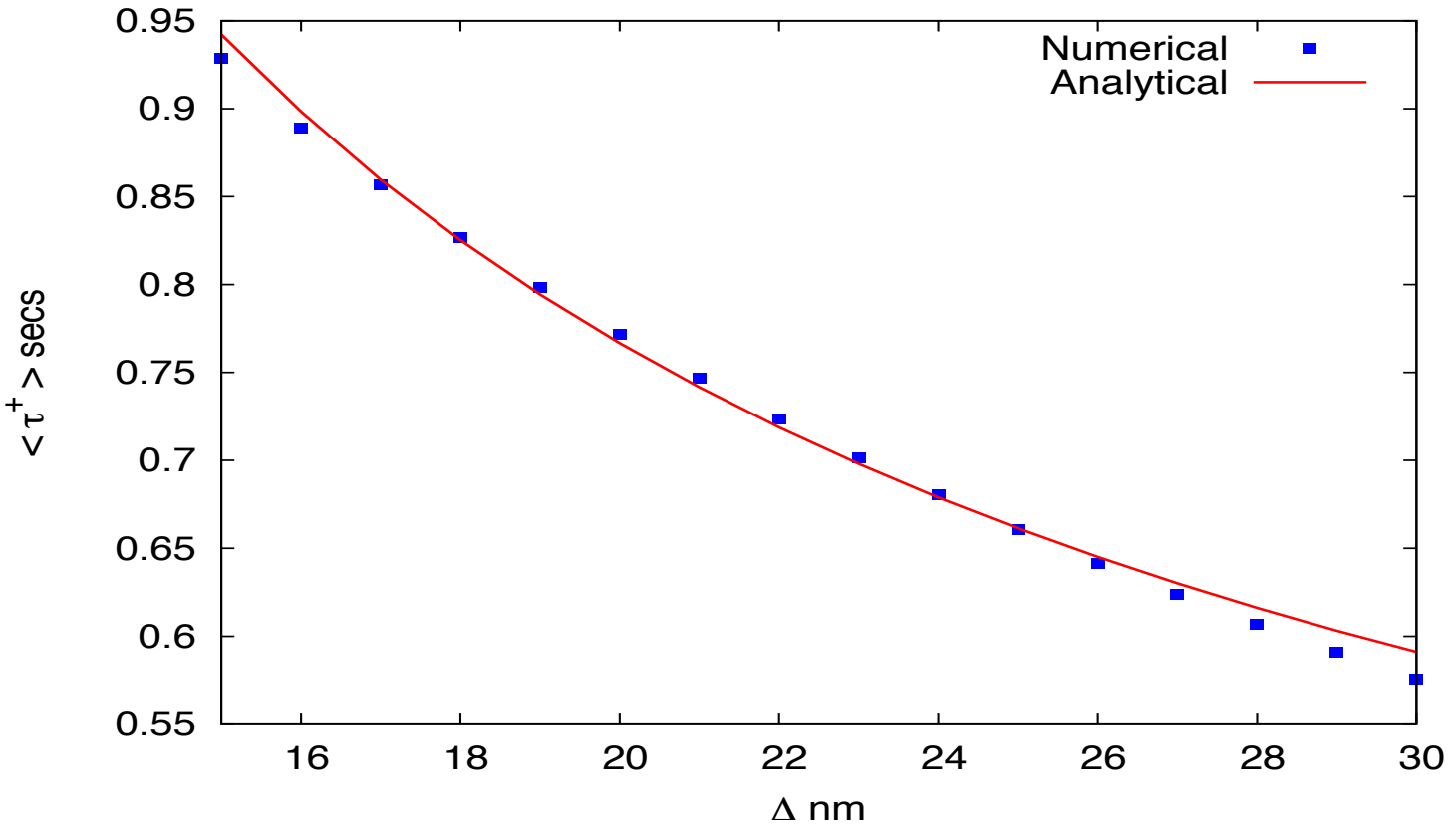
Average patch size varying with bond length for $Z > \Delta$



Probability Density of X-Humps against Threshold Δ

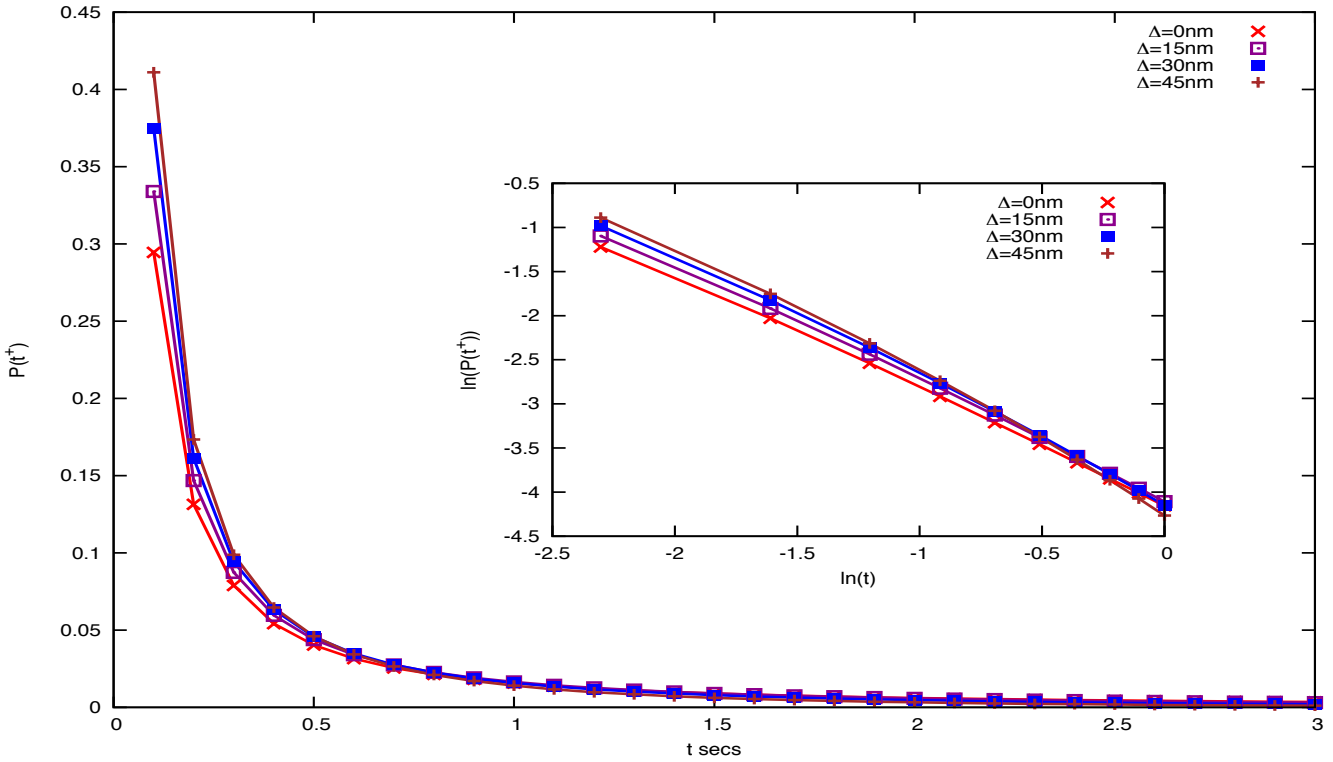


Time persistence for different thresholds, $< \tau^+ >$ vs Δ_i

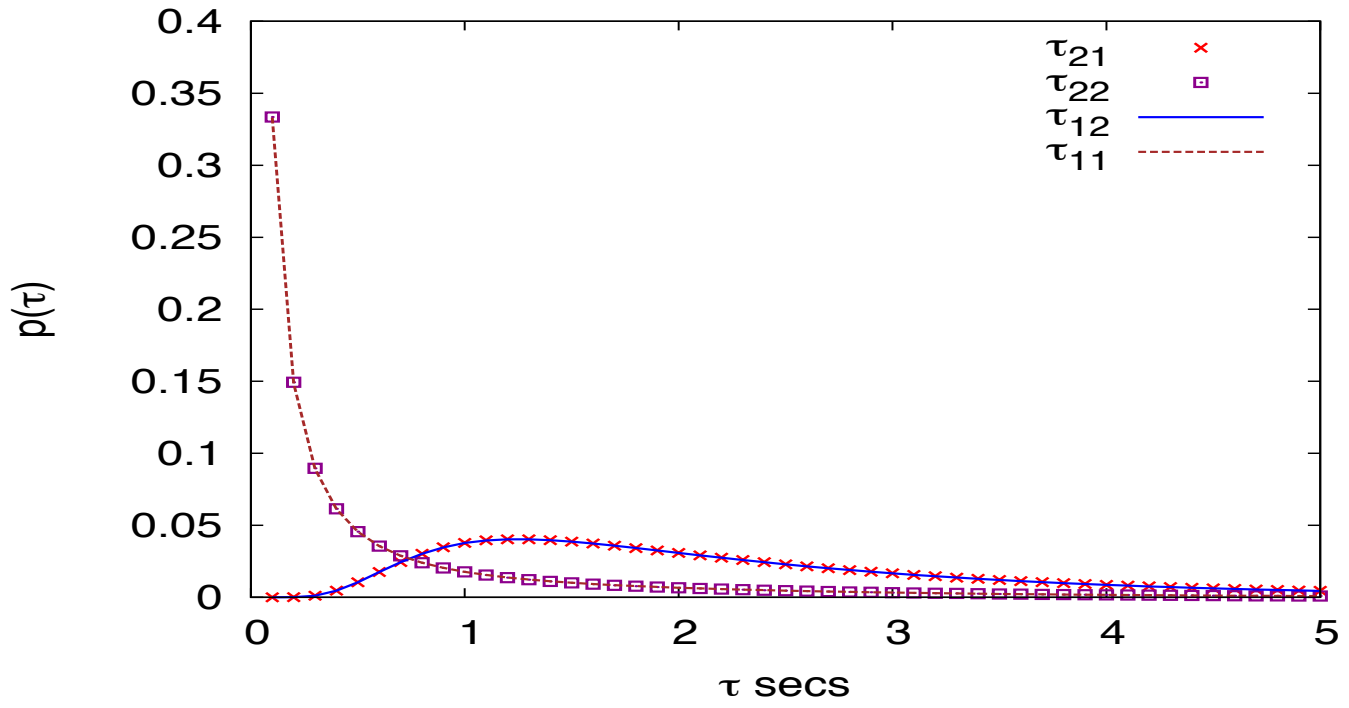


Probability density function for t^+, about various Δ

Power law predicted: confirms the **first passage distribution hypothesis**.



Probability Density $p(\tau)$ between two thresholds for the τ_{11}, τ_{12}, τ_{21} and τ_{22} cases



Summary

- We now know that the average size of the TCR-APC patches: < 100 sq. nm.
- We also know the average time needed for an immature TCR-APC contact to form at the start of the IS: $\sim$ 2-5 seconds
- As Δ increases, both $< X_+ >$ and $< t_+ >$ decrease indicating that more energy (equivalent to larger separation) will be needed for longer IS bonding. This indirectly confirms that only the TCR:APC bond is the strongest under the given time and length scales.
- As the distance between the threshold δ increases, the average bonding time for an *immature bond* initially increases but then saturates reconfirming the existence of two dominating length scales in the system.
- The spatial probability distribution of TCR-APC patches decreases as Δ increases both for time and spatial distributions.
- The first passage distribution statistics (related to average bonding time) clearly follows a power-law statistics but unlike in conventional models, **the power-law exponent is a non-universal one** indicating the model dependence of the statistics, as expected biologically.

Future Directions

- Evaluating average sizes of contacts and times for fully matured IS bonds. This necessitates a non-linear model.
- Calculating the force of interaction between a TCR and an APC membrane under the simultaneous presence of the other (kinase, phosphatase, etc) molecules for the actual non-linear reaction-diffusion model.
- Effect of memory in immunological synapse and in neurological synapse
- Studying the role of nascent TCRs in already formed IS bonds

For the more interested ones

- AKC and N. J. Burroughs, *Close contact fluctuations: The seeding of signalling domains in the immunological synapse* - EPL **77**, 48003 (2007)
- AKC - *Fluctuations in membrane models: thermal versus non-thermal* - PRE **84**, 032101 (2011)
- AKC & D. R. Bush - *Contact time periods in Immunological Synapse* - submitted
- AKC, *Time persistence exponent: The survival threshold* - manuscript under preparation

All relevant publications are available at **http://www.aston.ac.uk/eas/staff/a-z/amit-k-chattopadhyay/**.

THANKS

- To my principal collaborator in this project - Daniel Bush
- To the audience!