# SIAM Life Sciences 2001

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## A Mathematical Model of T Cell Activation by Antigen Presenting Cells

# A Mathematical Model of T Cell Activation by Antigen Presenting Cells

T cell activation through T cell receptors (TCRs) remains a major unresolved issue. We present a stochastic two-dimensional model of T cell activation that takes into consideration immunological synapse formation and bystander activation as well as co-modulation of engaged and non-engaged TCRs. This model integrates positive and negative signal amplification and regulation loops that couple cell adhesion, co-stimulation and tyrosine kinase activity modulation to antigen-specific activation of T cells by antigen presenting cells.

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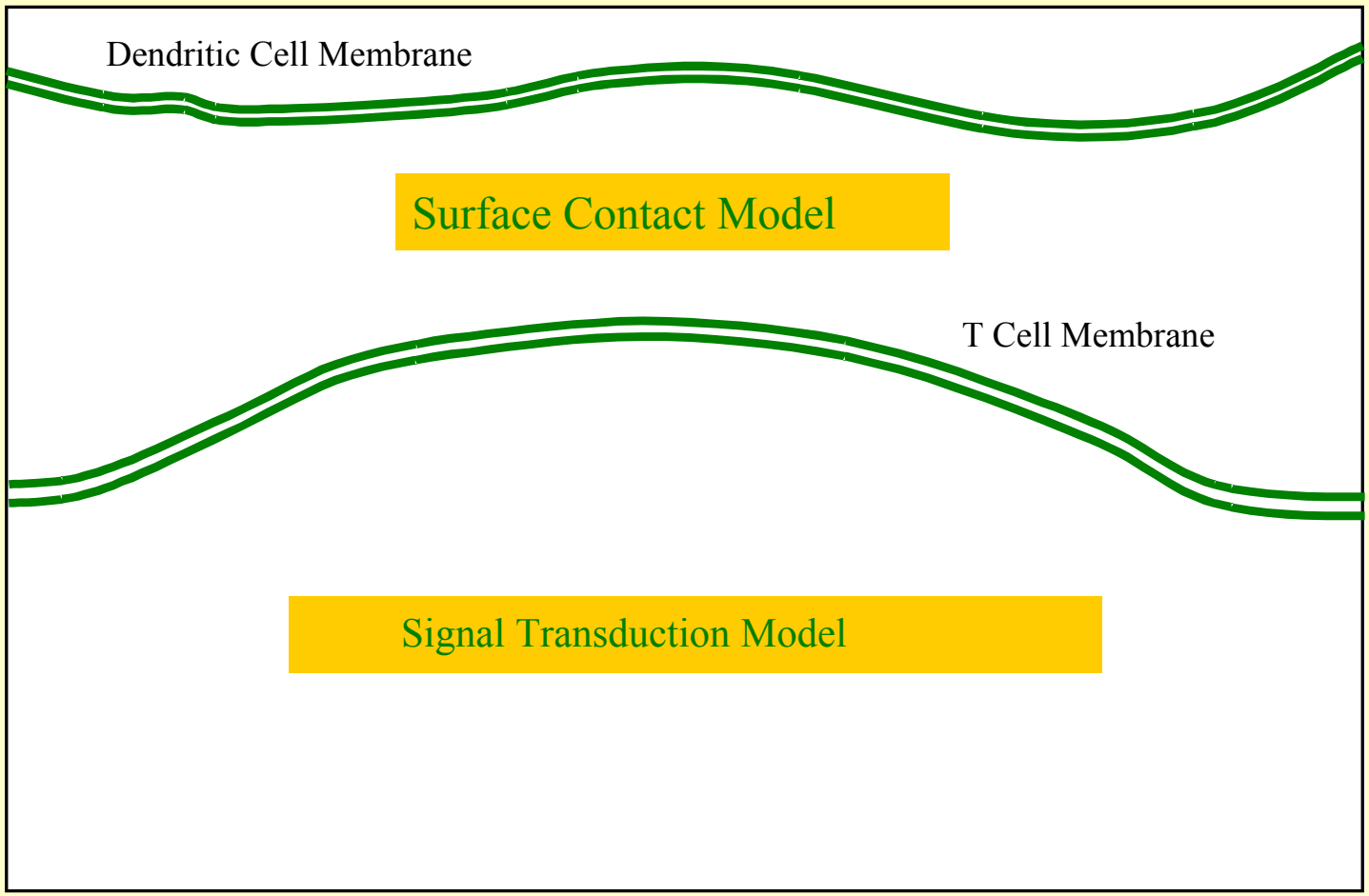
# Potential Limitations of a Deterministic Modeling Framework

- Infinitesimally small molar fractions of reacting species do not satisfy the law of mass action
- Spatial distribution of discrete molecules=> concentration (continuous variable) **only if** system absolutely uniform with infinite volume yet intracellular biochemical reactions often occur in very small compartments with spatial heterogeneity
- System fluctuations can be amplified (stochastic resonance) and can produce measurable effects if the system operates close to unstable equilibria

# Schematic of Integrated Model



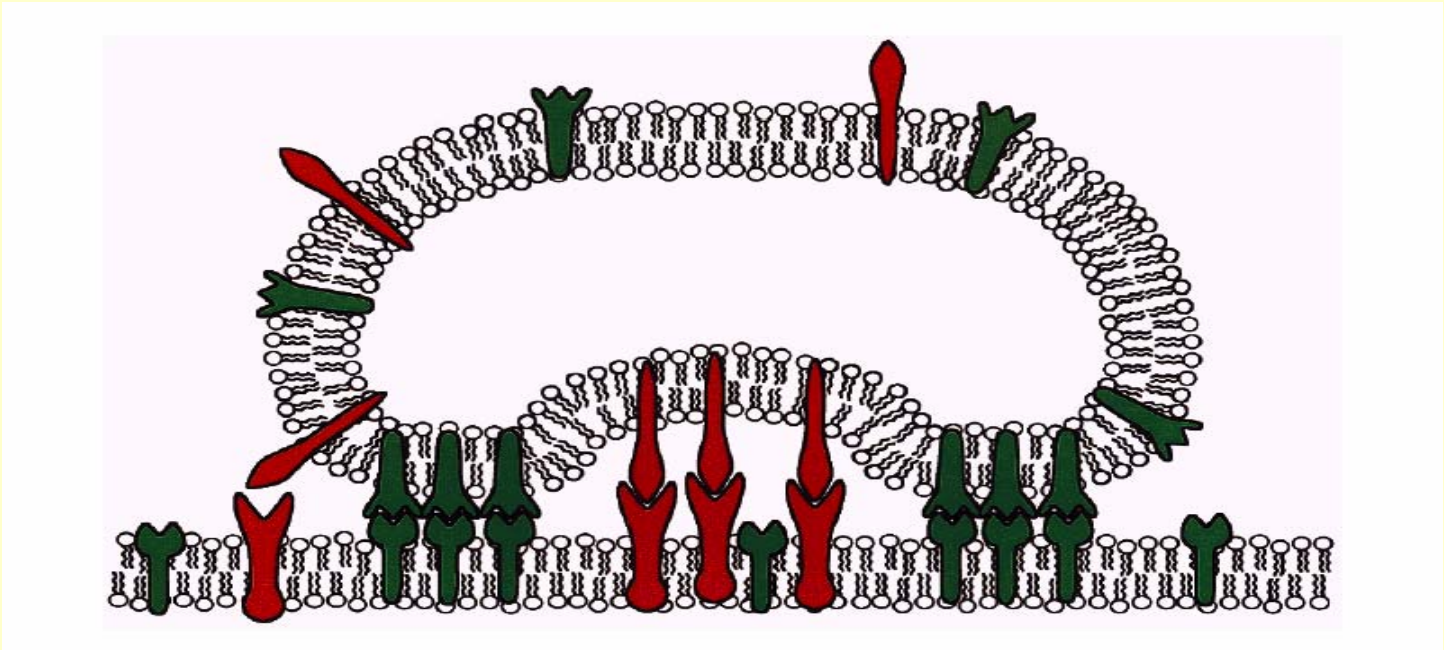
# Surface Contact Modeling Research: Current & Future Directions

- Focus 1

  Reproduce spatial and temporal aspects of synapse formation as outlined in PNAS paper (Qi el als, June 2001) - current simulations with the Surface Contact Model suggest that synapse formation cannot occur without feedback

# Schematic of membrane Undergoing Shape Changes and Interacting with a Planar Membrane

(from S.Y.Qi, J.T. Groves and A.K. Chakraborty, PNAS, June5, 2001, 98, 6548-6553.)



# Synapse Formation According to Qi et als

- Coupling between receptor-ligand bind/dissociation and membrand gap
- Protein mobility
- Membrane shape changes

# Surface Contact Modeling (SCM) Research: Current and Future Directions

- Focus 2

  Continue refining and adding fidelity to the SCM by adding in (a) costimulatory molecule CD28 and phosphatase CD45 (b) van der Merwe's kinetic segregation model of TCR triggering and (c) TCR comodulation of neighboring receptors due to phosphorylation of zeta chains during TCR engagement by a specific pMHC

# Extra-cellular and Trans-membrane Molecular Species

| Species No | Name | Location |
|---|---|---|
| 1 | α:β TCR | T |
| 2 | CD3ε (2) | T |
| 3 | CD3δ (1) | T |
| 4 | CD3γ (1) | T |
| 5 | CD3ζ (2) | T |
| 6 | CD4 | T |
| 7 | MHC-Ag Peptide | D |
| 8 | CD2 | T |
| 9 | CD58 | D |
| 10 | LFA-1 | T |
| 11 | ICAM-1 | D |
| 12 | CD28 | T |
| 13 | CTLA-4 | D |
| 14 | CD80 | D |
| 15 | CD86 | D |
| 16 | CD25 (IL-2Ra) | T |
| 17 | CD122 (IL-2Rb) | T |
| 18 | IL-2 | T, E |
| 19 | CD40L | T |
| 20 | CD40 | D |
| 21 | CD43 | T |
| 22 | CD45 | T |
| 23 | CD69 | T |

# Surface Contact Modeling (SCM) Research: Current and Future Directions

## Focus 3

Couple SCM to signal transduction model

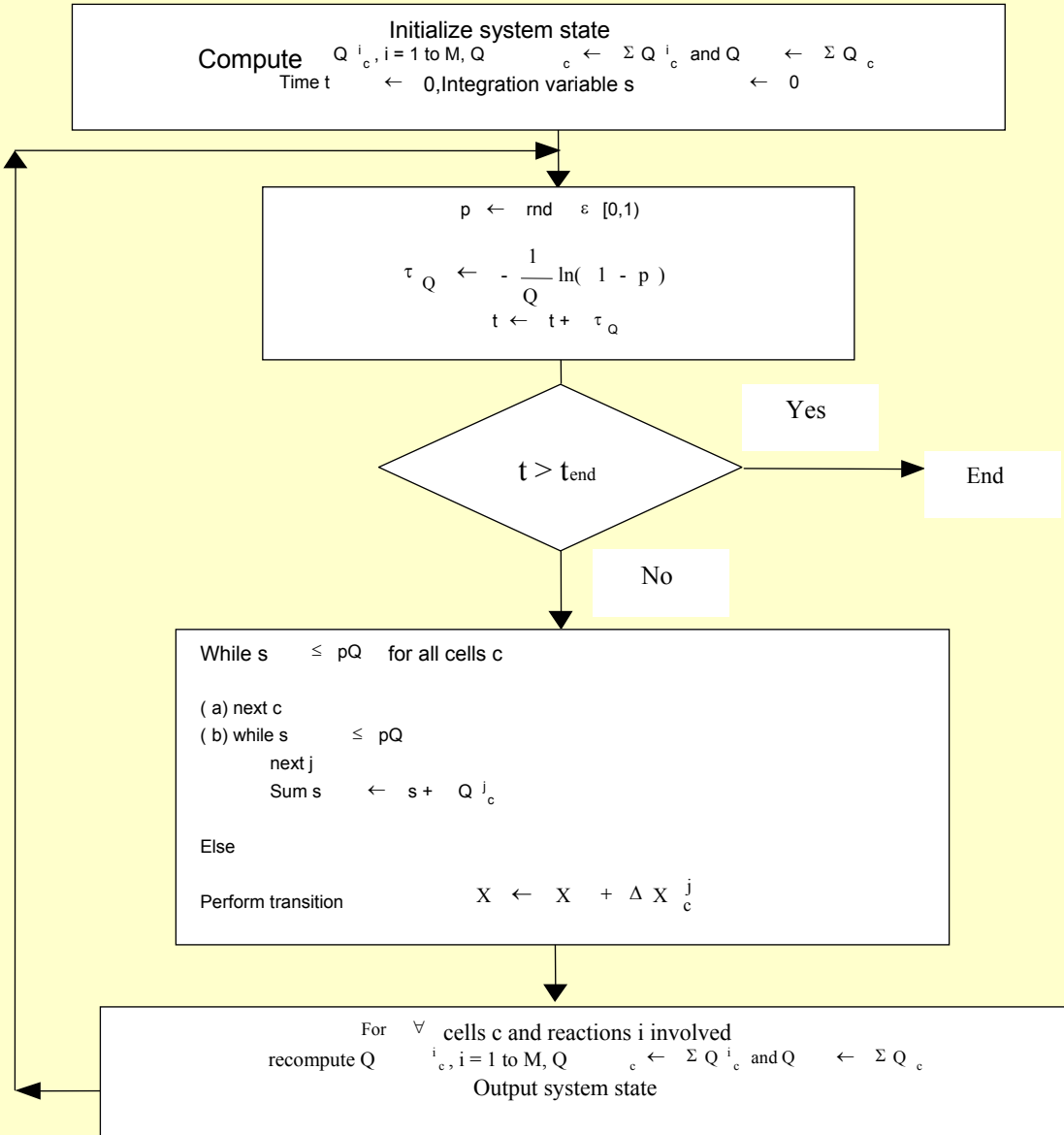
## Focus 4

Prepare version of SCM suitable for signal detection studies by John Keane

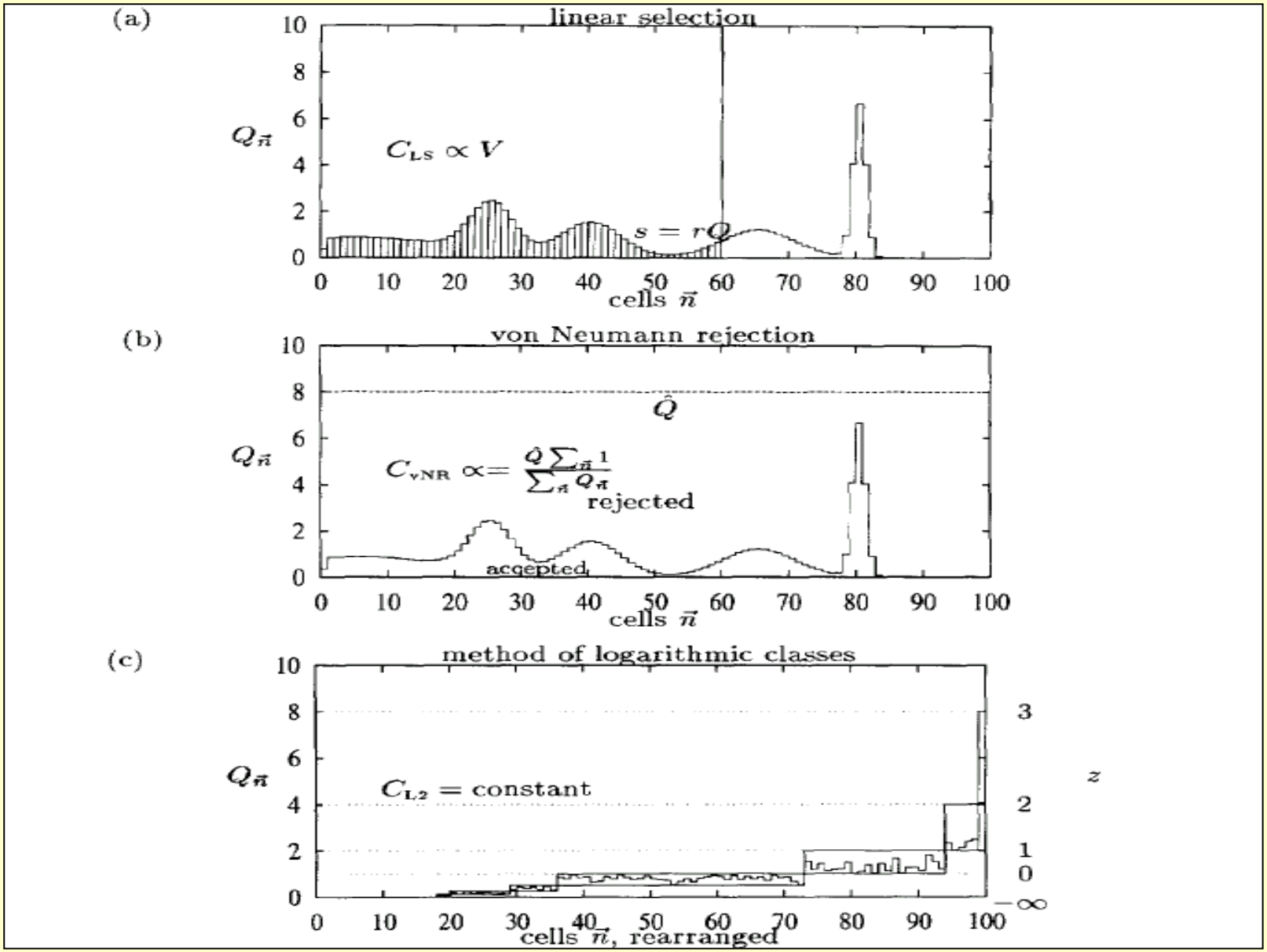
# A Stochastic Algorithm for Reaction Diffusion Systems

- A reaction - cell stochastic algorithm for simulating large complex Markov processes with spatiality
- Reaction diffusion systems - kinetic rate constants and diffusion coefficients may vary with time
- Small numbers of molecules typical of biological systems at the cellular level
- Details on Fricke/Wendt algorithm given in technical document - Exact stochastic algorithms for large reaction diffusion systems, Pettigrew, June 20, 2001, CSI.

# Gillespie Algorithm for RD cells with Linear Selection



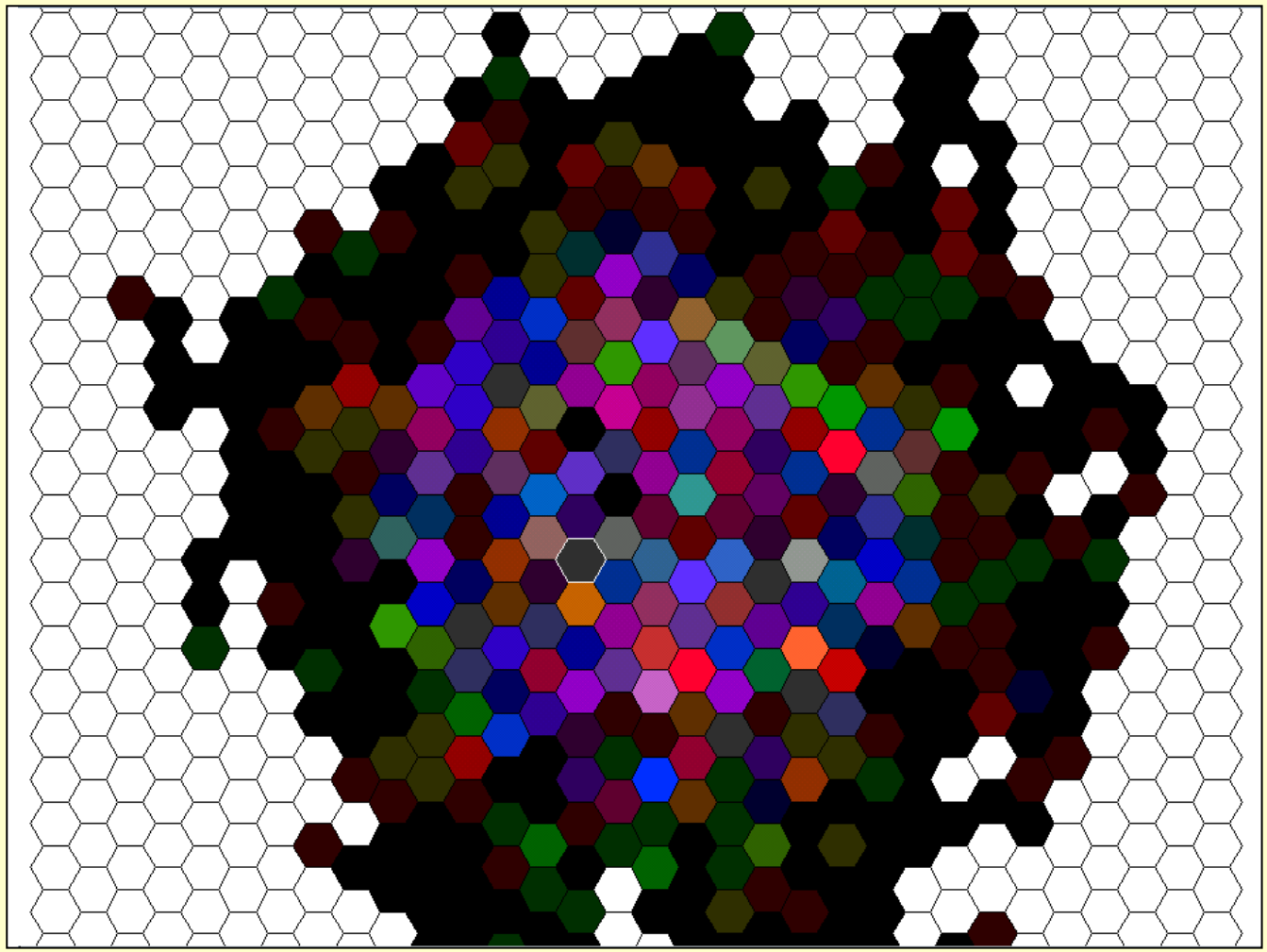
# The F-W Method of Logarithmic Classes is a Type of von Neumann Rejection



# Model Parameters

- $K_d = k_{off}/k_{on} = 10$ molecules/$\mu m^2$ for TCR/MHC-peptide with $k_{off}$=0.06$s^{-1}$(agonist) to 5.1$s^{-1}$(antagonist)
- $K_d = k_{off}/k_{on} = 0.3$ molecules/$\mu m^2$ with $k_{off}$=0.1$s^{-1}$ for LFA-1/ICAM-1
- $D_{ICAM-1}$=0.59$\mu m^2/s$
- $0.01 \leq D_{LFA-1}, D_{TCR} \leq 1.0$ $\mu m^2/s$
- $D_{MHC}$=1.0 $\mu m^2/s$
- $z_{LFA-1/ICAM-1}$= 42nm, $z_{TCR/MHC}$ = 15nm

# SCM Simulation



# A Verification of the Implementation of the Fricke-Wendt Algorithm for Reaction Systems

Consider the following four species system of chemical reactions

$$A + C \underset{k_2}{\overset{k_2}{\rightleftharpoons}} D \quad , k_1 = 10^{-5} \text{ molecule}^{-1}\text{sec}^{-1}, k_{-1} = 1.0 \text{ sec}^{-1}$$

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \quad , k_2 = 10^{-3} \text{ molecule}^{-1}\text{sec}^{-1}, k_{-2} = 0.1 \text{ sec}^{-1}$$

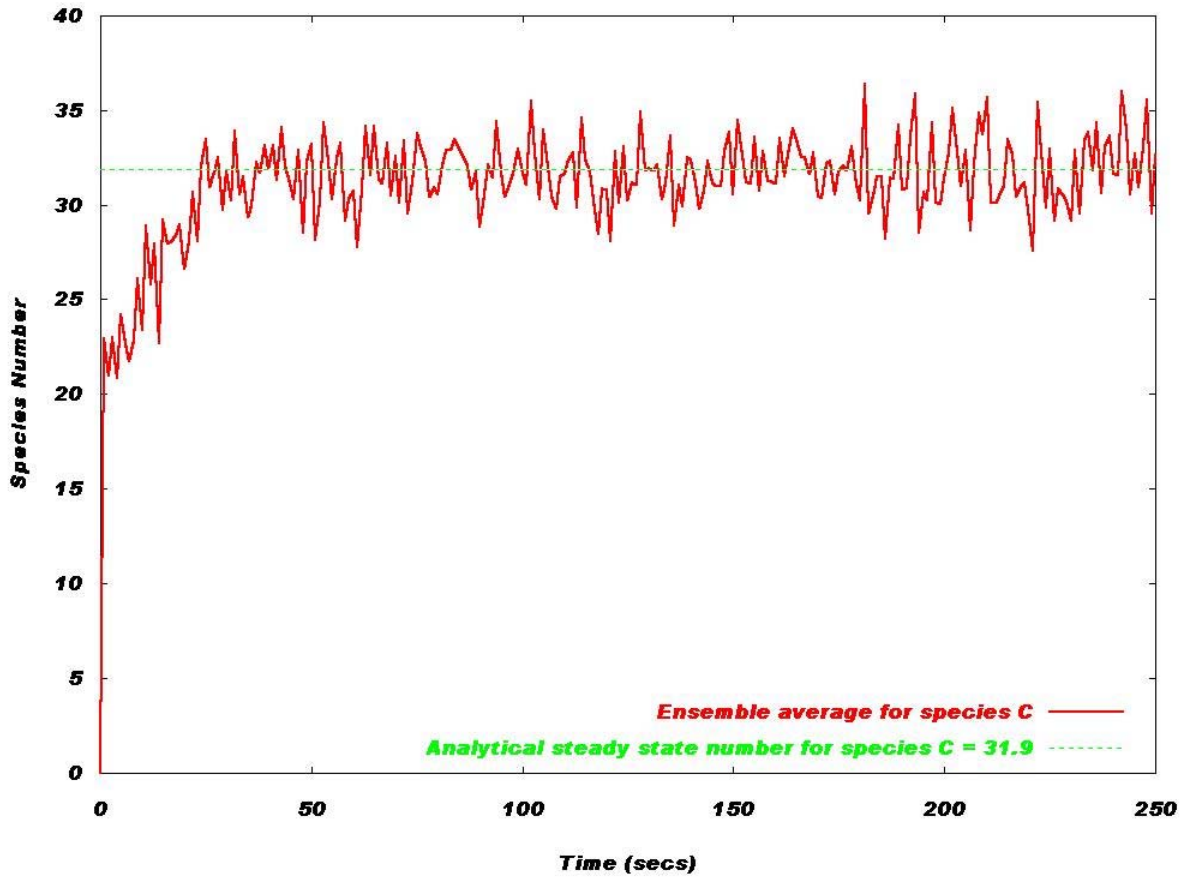
discussed in Resat, Wiley and Dixon, J. Phys. Chem. B, July 2001. It can be shown that if the initial species numbers are

$$A(t = 0) = 10000$$
$$B(t = 0) = 2500$$
$$C(t = 0) = 0$$
$$D(t = 0) = 0$$

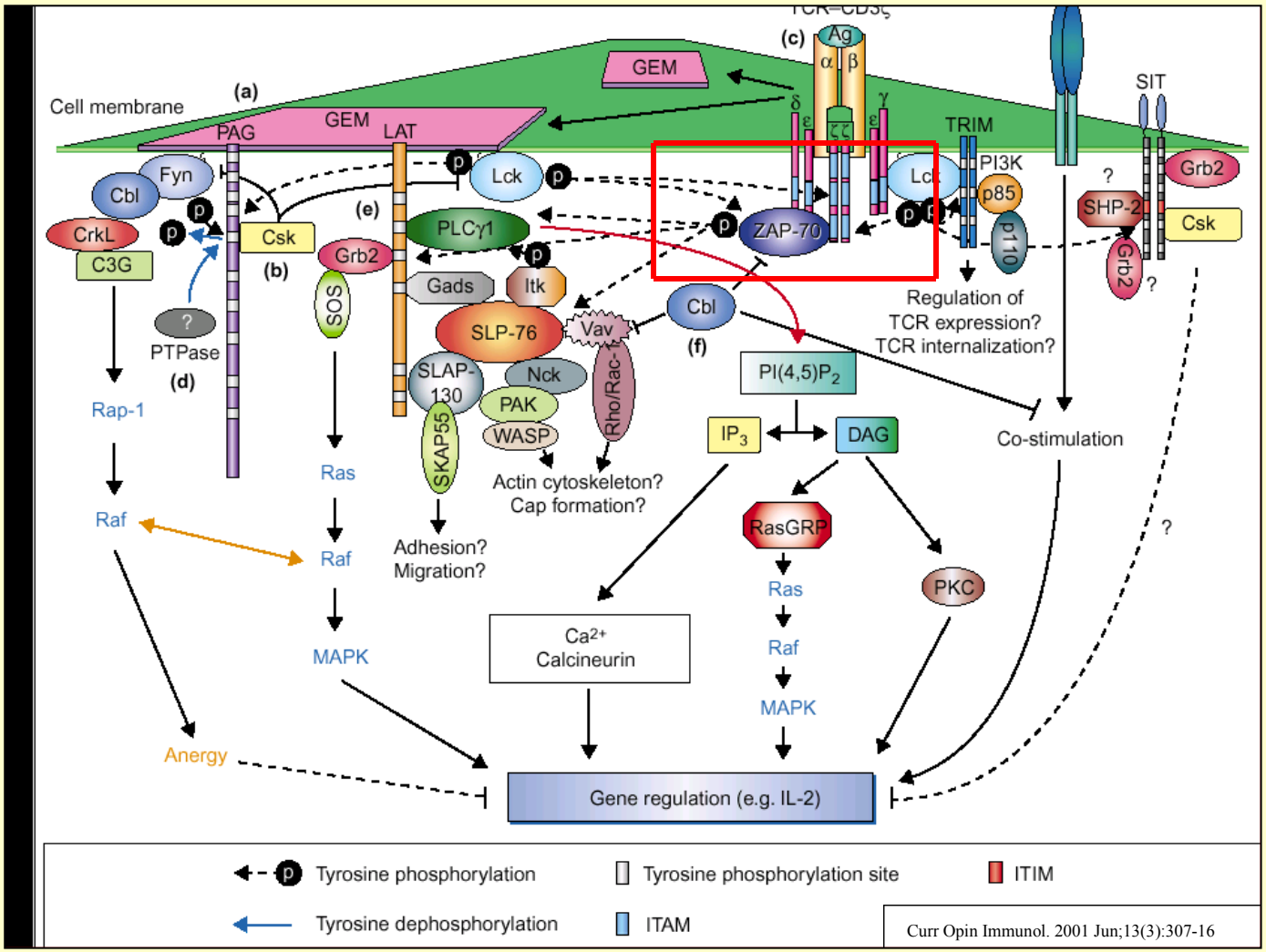
then the steady state species numbers can be determined analytically to be

$$A(t \to \infty) = 6082.3$$
$$B(t \to \infty) = 525.5$$
$$C(t \to \infty) = 31.9$$
$$D(t \to \infty) = 1942.9$$

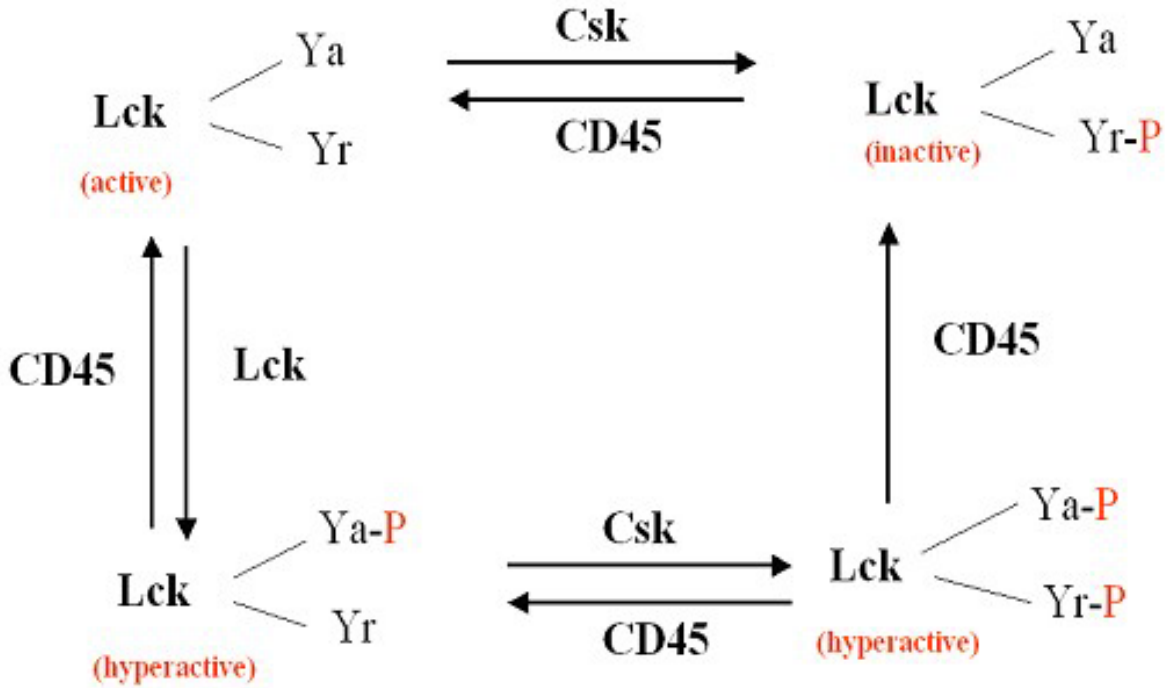
# Fluctuations in Species C about Analytical Steady State Number



# Signal Transduction Pathways Involved in T Cell Activation



# Regulation of Lck Activity by Reversible Autophosphorylation and Csk Phosphorylation




Feedback to the Surface Contact Model will occur through CD45 and through CD4 which binds and transports Lck to the vicinity of the TCR zeta chains.

# Table of Lck States

| $Y_r$ | $Y_s$ | SH2 | SH3 | State description |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | active |
| 0 | 1 | 0 | 0 | hyperactive |
| 1 | 0 | 0 | 0 | inactive |
| 1 | 1 | 0 | 0 | hyperactive |
| ? | 0 | 1 | ? | active |
| ? | 1 | 1 | ? | hyperactive |
| ? | 0 | ? | 1 | active |
| ? | 1 | ? | 1 | hyperactive |

- **1** means that the state is **on**;
- **0** means that the state is **off**
- **?** means that the state is not important

# Signal Amplification

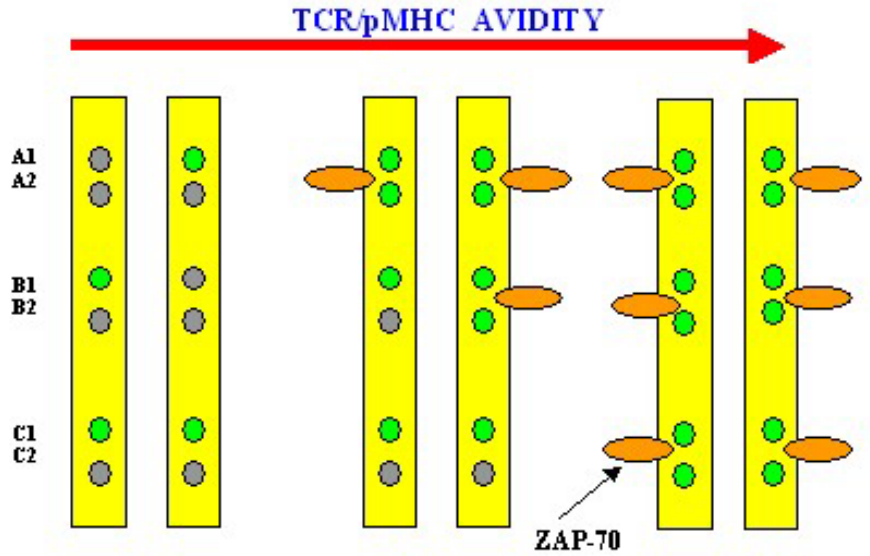
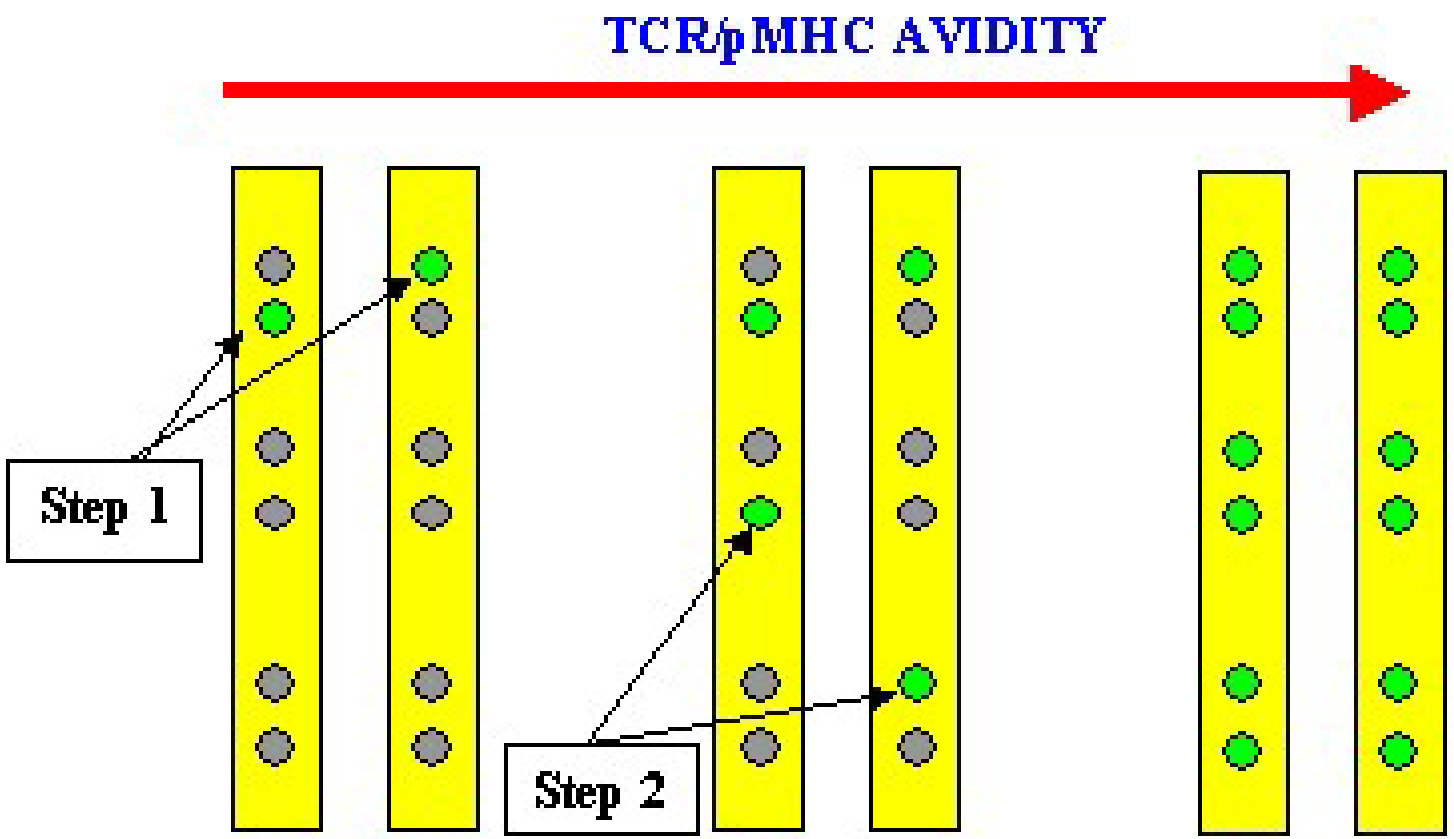


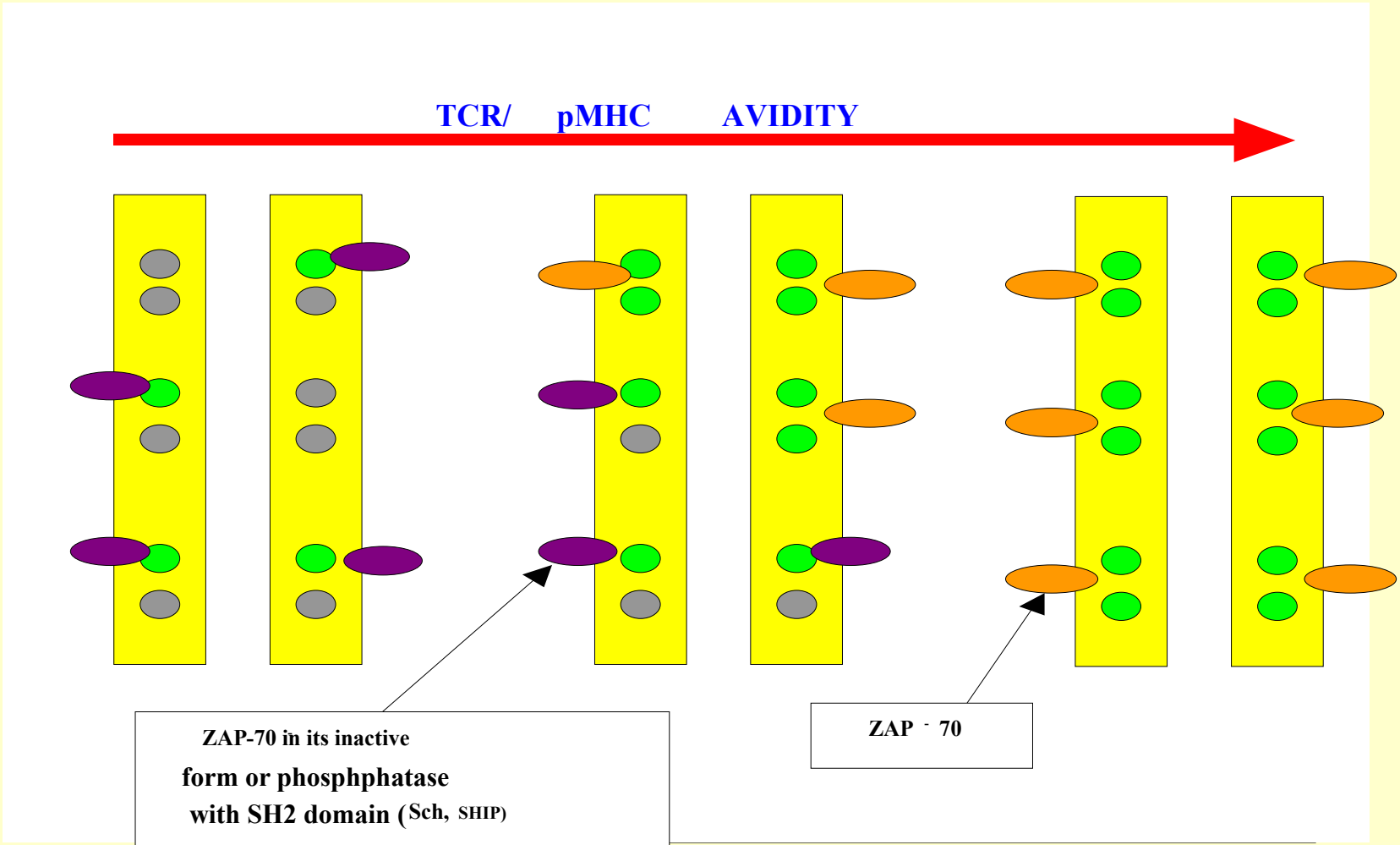

Table of ζ-chain States →

| A1 | A2 | B1 | B2 | C1 | C2 |
|---|---|---|---|---|---|
| 0 | ? | ? | ? | ? | ? |
| ? | 0 | ? | ? | ? | ? |
| ? | ? | 0 | ? | ? | ? |
| ? | ? | ? | 0 | ? | ? |
| ? | ? | ? | ? | 0 | ? |
| ? | ? | ? | ? | ? | 0 |

# Signal Discrimination



# Signal Inhibition



# StochSim

- Developed by Carl J. Morton-Firth (1998) for Phd under Dennis Bray, Dept of Zoology, Cambridge
- Used in simulation studies of the intracellular signaling pathways responsible for bacterial chemotaxis (Predicting Temporal Fluctuations in an Intracellular Signaling Pathway, C. J. Morton-Firth and D. Bray, J. theor. Biol., (1998), 192, 117-128)
- New versions of StochSim (N. Le Novere and T. Shimizu)

# Gillespie versus StochSim

- For biochemical networks with relatively few independent pathways Gillespie is faster and it is exact
- Biochemical signal transduction networks exhibiting a combinatorial explosion in the number of independent pathways tend to favor StochSim
- Gillespie maintains total numbers of molecules of each chemical species but does not track of individual molecules
- StochSim is an inexact algorithm generally requiring small time steps to maintain accuracy but the time step may be chosen fixed

# Summary of New Activities

- 3rd year work-study student is implementing a StochSim module
- New collaborations between CSI and PNNL - Resat to use Fricke Wendt alg (with speedup modification) to model EFG receptor signal transduction with diffusion
- Joint PNNL/CSI/Bioengineering NSF proposal on Petri nets and related flux based methodologies for investigating steady state signal transduction / metabolic pathways