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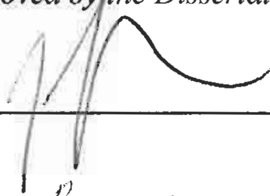

, Chairperson

UNRAVELING THE INTRICACIES OF SPATIAL ORGANIZATION OF THE ERBB RECEPTORS AND DOWNSTREAM SIGNALING PATHWAYS

BY

MICHELLE N. COSTA

B.S., Chemical Engineering, University of New Mexico, 2006

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
Engineering

The University of New Mexico
Albuquerque, New Mexico

August 2009

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Dedication

To the memory of

Thelma I. Salley

And

Joe Costa Jr

Acknowledgments

This work would not be possible without the love and support of my family. I would like to thank my parents Dan and Linda Costa whose love is unconditional and are always by my side through think and thin. I would like to thank my brother Ryan Costa for his love and encouragement. I would like to thank my grandparents Bobby and Thelma Salley who always loved and believed in me. I would like to thank my fiancé Luis Archuleta who helped me in so many ways in graduate school. I would like to thank him for his love and support.

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ABSTRACT OF DISSERTATION

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Albuquerque, New Mexico

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Unraveling the Intricacies of Spatial Organization of the ErbB Receptors and Downstream Signaling Pathways

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B.S Chemical Engineering University of New Mexico-Albuquerque, 2006
Ph.D. Engineering University of New Mexico, 2009

Abstract

Faced with the complexity of diseases such as cancer which has 10^{12} mutations, altering gene expression, and disrupting regulatory networks, there has been a paradigm shift in the biological sciences and what has emerged is a much more quantitative field of biology. Mathematical modeling can aid in biological discovery with the development of predictive models that provide future direction for experimentalist. In this work, I have contributed to the development of novel computational approaches which explore mechanisms of receptor aggregation and predict the effects of downstream signaling. The coupled spatial non-spatial simulation algorithm, CSNSA is a tool that I took part in developing, which implements a spatial kinetic Monte Carlo for capturing receptor interactions on the cell membrane with Gillespie's stochastic simulation algorithm, SSA, for temporal cytosolic interactions. Using this framework we determine that receptor clustering significantly enhances downstream signaling.

In the next study the goal was to understand mechanisms of clustering. Cytoskeletal interactions with mobile proteins are known to hinder diffusion. Using a Monte Carlo approach we simulate these interactions, determining at what cytoskeletal distribution and receptor concentration optimal clustering occurs and when it is inhibited. We investigate oligomerization induced trapping to determine mechanisms of clustering, and our results show that the cytoskeletal interactions lead to receptor clustering. After exploring the mechanisms of clustering we determine how receptor aggregation effects downstream signaling. We further proceed by implementing the adaptively coarse grained Monte Carlo, ACGMC to determine if "receptor-sharing" occurs when receptors are clustered. In our proposed "receptor-sharing" mechanism a cytosolic species binds with a receptor then disassociates and rebinds a neighboring receptor. We tested our hypothesis using a novel computational approach, the ACGMC, an algorithm which enables the spatial temporal evolution of the system in three dimensions by using a coarse graining approach. In this framework we are modeling EGFR reaction-diffusion events on the plasma membrane while capturing the spatial-temporal dynamics of proteins in the cytosol. From this framework we observe "receptor-sharing" which may be an important mechanism in the regulation and overall efficiency of signal transduction. In summary, I have helped to develop predictive computational tools that take systems biology in a new direction.

Table of Contents

Dedication iv

Acknowledgements v

Abstract vii

Table of Figures xv

Table of Tables xvii

Chapter 1. Spatial Stochastic Modeling: A new way of dissecting biology 1

Abstract 3

Introduction 4

- Quantitative Spatial Experimental Approaches in Biology 7
- Fluorescence Recovery After Photobleaching (FRAP) 7
- Single Particle Tracking (SPT) 8
- Forster Resonance Energy Transfer (FRET) 10
- Electron Microscopy (EM) 10
- Transmission Electron Microscopy (TEM) 11
- Scanning Electron Microscopy (SEM) 12
- Discoveries from Quantified Experiments 12
- Paradigm Shift in Membrane Biology 12
- Lipid Rafts 13
- Cytoskeletal Interactions: Picket-Fence Model 15
- Moving Ahead in Membrane Biology 16
- Modeling Approaches 17
- Cornerstones of Modeling Techniques 20

Choosing an Appropriate Method……………………………………………………..24

Spatial-Temporal Stochastic Methods………………………………………………...26

Sorting Out Microdomains: An example using the SKMC……………………….32

A New Direction for Systems Biology……………………………………………..35

Chapter 2. Coupled Stochastic Spatial and Non-Spatial simulations of ErbB1 Signaling Pathways Demonstrate the Importance of Spatial Organization in Signal Transduction 37

Abstract 38

Background 38

Methodology/Principal Findings 38

Conclusions/Significance 38

Introduction 40

Results 43

Establishing Parameters for the Spatial Model 43

Validating the CSNSA hybrid approach 46

Predicting the Impact of Receptor Density vs. Clustering 49

Discussion 51

Methods 53

Coupled Spatial, Non-spatial Simulation Algorithm (CSNSA) 53

Spatial Kinetic Monte Carlo (SKMC) 59

Stochastic Simulation Algorithm (SSA) 61

Interfacial Reactions 61

Sensitivity Analysis 63

Acknowledgements 64

Chapter 3. Picket Fence Densities Determine Enhanced vs. Inhibitive Role in Receptor Aggregation ... 65

Abstract ... 66

Introduction ... 67

Materials and Methods ... 69

Spatial Kinetic Monte Carlo (SKMC) ... 69

Picket Fences ... 74

Quantification of Microdomains ... 78

Results ... 79

Clustering vs. Picket Fence Density ... 83

Clustering vs. Receptor Concentration ... 85

Mechanism of Clustering: Oligomerization Induced Trapping ... 89

Predimerization vs. Dimerization ... 91

Discussion ... 93

Acknowledgements ... 95

Chapter 4. Adaptively Coarse Grained Monte Carlo Method for Capturing the "Receptor–Sharing" Mechanism 96

Abstract 97

Introduction 98

Results 101

Cell Signaling Events are Dependent on Spatial Localization 101

Evidence of a Concentration Gradient 103

The "Receptor-Sharing" Mechanism 105

Quantifying the "Receptor-Sharing" Mechanism 108

Inhibiting the "Receptor-Sharing" Mechanism 112

Discussion 113

Materials and Methods 115

Adaptively Coarse-Grained Monte Carlo (ACGMC)

Adaptively Coarse-Graining & Diffusion Transition Rates 119

Validation of Approach 121

Chapter 5. Future Work ... 139

Introduction ... 141

Computational Improvements ... 141

Computational Predictions ... 146

Understanding the impact of IFNγR clustering on immune response pathways 146

A Monte Carlo Based Approach for Determining Optimal Drug Efficacy in Different Cytoskeletal Distributions ... 149

Microdomains and the Underlying Cytoskeleton Alter the Efficiency of "Receptor-Sharing" ... 151

Conclusion ... 154

Appendix ... 156

Appendix A. The effective kinetic rate constant for diffusion-reaction problems derived by Lauffenburger and Linderman ... 157

Appendix B. Understanding the impact of IFNγR clustering on immune response pathways ... 158

Appendix C. A Monte Carlo Based Approach for Determining Optimal Drug Efficacy in Different Cytoskeletal Distributions ... 160

Appendix D. Microdomains and the Underlying Cytoskeleton Alter the Efficiency of "Receptor-Sharing" ... 194

Appendix E. Abbreviations Used ... 210

References ... 213

Table of Figures

Figure 1 21

Figure 2 24

Figure 3 34

Figure 4 45

Figure 5 47

Figure 6 48

Figure 7 50

Figure 8 57

Figure 9 58

Figure 10 62

Figure 11 75

Figure 12 77

Figure 13 80

Figure 14 82

Figure 15 84

Figure 16 87

Figure 17 88

Figure 18 90

Figure 19 92

Figure 20 102

Figure 21 104

Figure 22 106

Figure 23 107

Figure 24 109

Figure 25 111

Figure 26 118

Table of Tables

Table 1 44

Table 2 56

Table 3 71

Table 4 73

Table 5 123

Chapter1. Spatial Stochastic Modeling: A new way of dissecting biology

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Abstract

The field of membrane biology has undergone a paradigm shift and in the process shaken the foundation of mathematical models built under the well mixed assumption. Advances in technology have led us to a new frontier in the biological sciences with techniques such as SPT, FRET, and EM at our fingertips the possibilities are endless. In order to complement experimental innovation, novel computational platforms must be developed which accurately describe discrete, stochastic, spatial heterogeneity observed in biological systems. The traditional method for modeling signal transduction pathways is using ordinary differential equations (ODEs). ODEs are deterministic, continuum based models that inherently assume spatial homogeneity. However, it is becoming clear that spatial modeling tools will be needed to fully understand the complexities of signaling pathways. In this review we will begin by discussing advancements made in biology through the development of mathematical models and the experiments that gave them their birth. We will go beyond these initial experiments and discuss the new cutting edge experimental techniques which brought about an evolution to the membrane biology community. We will then discuss computational methods; their advantageous and drawbacks. We then propose novel computational platforms which must evolve in order to complement experiments and bring predictability back to systems biology.
Keywords: Mathematical modeling, signal transduction, plasma membrane, ODE, PDE, spatial modeling, Spatial Monte Carlo

Introduction

The physical sciences have always been interwoven with mathematics, through a foundation built equally from theory and experimentation. The life sciences, in contrast, have been a much more observatory science, relying more on description rather than theory and quantification. However, being confronted with complex diseases has altered this approach; cancer, for example, can have as many as 10^{12} mutations (Tomlinson, Novelli et al. 1996; Tomlinson, Sasieni et al. 2002; d'Onofrio and Tomlinson 2007), altering gene expression, and disrupting regulatory networks. This complexity has driven a paradigm shift in biology, complementing the traditional reductionist approach with a systems level approach which builds upon theory. A novel science, quantitative biology or systems biology, has emerged as a result; quantitative biology or systems biology derives principles from fields such as mathematics, physics, chemistry and engineering in order to develop predictive models of biological systems.

The need to develop novel mathematics (Faeder, Blinov et al. 2005; Mayawala, Vlachos et al. 2005; Chatterjee and Vlachos 2006; Mayawala, Vlachos et al. 2006; Borisov, Chistopolsky et al. 2008; Collins, Chatterjee et al. 2008; Hsieh, Yang et al. 2008) and acquire quantified experimental data (Janes, Albeck et al. 2003; Conzelmann, Saez-Rodriguez et al. 2006; Kumar, Zaman et al. 2006; Aksamitiene, Hoek et al. 2007; Wilson, Pfeiffer et al. 2007; Andrews, Lidke et al. 2008) has come full circle with experimentation being done to compliment theoretical models (Janes, Albeck et al. 2005; Birtwistle, Hatakeyama et al. 2007; Hsieh, Yang et al. 2008; Kumar, Afeyan et al. 2008) and models guiding further hypotheseses. Developing a

mathematical model of a cell signaling pathway involves detailed experimentation. For example, cells are stimulated, lysed at various time points, and target proteins are immunoprecipitated. This data provides initial protein concentration as well as dynamic data which are crucial to building a mathematical model of the system. The model in return, plays a predictive role, guiding experimentation, by testing hypothesis which may be infeasible experimentally due to poor cell viability, lack of current technologies, cost, and time.

Over the past decade many mathematical models have been developed, to sort out complex cell signaling networks; an example of this is taken from the mitogen activated protein kinase, MAPK pathway. Intensively studied, the MAPK pathway regulates cellular functions such as proliferation, differentiation, apoptosis, adhesion and migration. The first mathematical model describing this pathway (Huang 1996) was an ordinary differential equation (ODE) model containing 35 reactions. It provided insight into the sensitivity of this system. In 1999, using an ODE approach, Kholodenko et al. published an EGFR signaling model. Although it did not exceed the Huang model in number of reactions, it contained signaling events upstream at the cell membrane where signaling cascades are initiated. In 2002, Schoeberl et al. developed a much more extensive ODE model, containing 125 reactions with 94 species, which spans receptor activation at the cell membrane to ERK phosphorylation and includes receptor degradation and internalization. In 2005, Sasagawa et al. published a much more complex ODE model that linked two receptors to activation of the MAPK pathway. A year later Kiyatkin et al. published a model incorporating additional pathways, such as the GAB1 and Src; it was yet

another model exploding in complexity but built on the well-mixed assumption inherent to ODEs.

What has become clear from the work of these original ODE models is that cell signaling is very complex. Although mathematical models have grown exponentially, ODE have several limitations. Proteins are distinct entities, making signal propagation a discrete process, which is not captured by continuum ODE's. Experimental evidence shows that signaling receptors are not well mixed on the plasma membrane but rather confined to enrichment and depletion zones. Therefore, overall reaction rates for species on the plasma membrane are limited by diffusion which is not taken into account with ODEs. The limitations of ODE models are calling for a new theoretical framework, a spatial-temporal approach which will more accurately describe the biology. In this review we describe a new generation of experimentation and its impact on biology. Then we discuss the evolution of mathematical models, from the ODE to spatial Monte Carlo methods, focusing on what theoretical frameworks must be developed to complement novel experimentation.

Quantitative Spatial Experimental Approaches in Biology

Systems biology relies on the ability to make quantitative measurements. Quantitative measurements of biological systems have been a challenge, and in this section we will summarize the critical experimental techniques for studying the spatial-temporal dynamics of cell membranes: fluorescence recovery after photobleaching (FRAP), single particle tracking (SPT), Forster resonance energy transfer (FRET), and electron microscopy (EM) focusing on how they facilitate systems biology. Then we will talk about the paradigm shift which has occurred in membrane biology as a result of these techniques; highlighting the discoveries of microdomains such as lipid rafts and picket fences.

Fluorescence Recovery After Photobleaching (FRAP)

One of the first methods developed to study the dynamics of proteins in living cells, FRAP has resurfaced due to techniques such as confocal-microscope-based photo-bleaching, and the discovery of GFP (Patterson and Lippincott-Schwartz 2002; Lippincott-Schwartz, Altan-Bonnet et al. 2003). FRAP relies on the fact that extended excitation of a fluorescent protein or molecule leads to photobleaching. Therefore, when a laser is directed to a small region of the cell membrane, photobleaching of this region occurs. The surrounding molecules, not subjugated to these repetitive cycles, will diffuse into the photobleached area. This recovery of fluorescent signal is recorded over time with a low-intensity laser light, making it possible to obtain information about the kinetic parameters, such as diffusion coefficient, mobile fraction, and binding dissociation rate constants(Lippincott-Schwartz, Altan-Bonnet et al. 2003).

FRAP is a powerful technique and has provided estimates of protein diffusion coefficients. However, one of the drawbacks of FRAP is its poor spatial resolution, which makes it difficult to interpret the data. Due to the complexities of the plasma membrane, a variety of mechanisms may determine diffusivity such as obstruction, transient binding, confinement, and hydrodynamic interactions(Saxton and Jacobson 1997). A method to overcome these shortcomings is SPT, which will be reviewed in the following section.

Single Particle Tracking (SPT)

A methodology for deciphering the dynamics of membrane proteins, SPT, enables individual trajectories of molecules and multimolecular complexes to be resolved (Saxton and Jacobson 1997; Kusumi, Ike et al. 2005; Bates, Wiseman et al. 2006). SPT involves labeling proteins with a probe (bead, fluorophore, gold particle, or q-dot), imaging and then tracking the centroid of the imaged probe over time (Bates, Wiseman et al. 2006).

Observables, such as molecular trajectories, translational diffusion in different cell areas, and access to different modes of motion can be determined using SPT(Marguet, Lenne et al. 2006). Given an individual trajectory, it is possible to determine the mode of motion which could be immobile, directed, confined, tethered, normal diffusion, and anomalous diffusion(Saxton and Jacobson 1997). The mode of motion is classified by looking at the time dependence of the mean-square displacement (MSD), (Saxton and Jacobson 1997; Kusumi, Nakada et al. 2005; Bates, Wiseman et al. 2006). The capability to determine the mode of motion makes SPT a very powerful tool, providing insight into the dynamics of signaling receptors.

There are various methods for imaging individual proteins, all of which rely on attaching a moiety to the protein of interest. For example, colloidal gold can be used as a probe due to its strong light scattering ability. Once contrast enhancement and background subtraction are performed, the label is darker than its surroundings (Saxton and Jacobson 1997). However, one of the major concerns with gold particles (size ~30-40 nm diameter) is that may decrease the diffusion rate of the protein (Bates, Wiseman et al. 2006). Multivalency is another issue, which may cause clustering and underestimation of the diffusion coefficient (Kusumi, Nakada et al. 2005). Additionally, researchers have used Fluorescence (both traditional fluors and Q-Dots) SPT. Oraganic fluorophores are another popular probe because they are less susceptible to cross-linking. One of their limitations, however, is that they are susceptible to photobleaching thus limiting their use to very short observation times(Bates, Wiseman et al. 2006). The semiconductor quantum dot has overcome these limitations, making it the preferred probe. With its novel properties such as improved photostability, optical tenability, and multicolor light emission it has taken live cell imaging and in vivo animal models to a new realm of optical resolution (Giepmans, Deerinck et al. 2005; Giepmans, Adams et al. 2006; Smith, Ruan et al. 2006).

Forster Resonance Energy Transfer (FRET)

FRET is an incredibly powerful technology going beyond traditional immunoassays to reveal direct protein-protein interactions. FRET works when a donor in close proximity (<10nm) and with preferred orientation brings about energy transfer which in turn induces emission from the acceptor. FRET donors and acceptors are chosen on the premise that there is an (> 30%) overlap(Sekar and Periasamy 2003) between the emission spectrum of the donor and excitation spectrum of the acceptor. Microscopy techniques capture FRET, when the donor channel signal is quenched and the acceptor channel signal is sensitized. The transfer of energy between an acceptor and a donor can be measured by microscopy and thus spatial organization of two molecules relative to one another can be measured.

Electron Microscopy (EM)

Great advances have been made in biology due to imaging; electron microscopy stands at the cornerstone of these advancements. This technique provides a much greater magnification (10^4) than the traditional light microscopes due to the electron's small de Broglie wavelength. Different types of microscopy have been developed we will be discussing those of most biological importance.

Transmission Electron Microscopy (TEM)

TEM utilizes a high voltage electron beam which is focused on an ultra thin Specimen. As the beam passes through, an image is created which is then magnified and focused(Egerton 2005). An electron gun cases a tungsten filament cathode, the electron source; once a voltage of 40 to 400 keV is applied to the cathode, an electron beam propagates towards the sample. This technique applies a magnification between 1,000X to 1,000,000X, but it is limited by the density of the specimen due to scattering.

Viewing a single atom was beyond the reach of the traditional TEM in the 1970's, when Crewe et al. developed the scanning transmission electron microscope (STEM) capable of viewing bright spots that were arguably individual atoms(Crewe and Wall 1970; Crewe, Wall et al. 1970). STEM builds on the foundation of TEM, by focusing the electron beam on a narrow strip which is scanned over the raster. The data collected can be analyzed with methods such as energy dispersive X-ray (EDX) spectroscopy, electron energy loss spectroscopy (EELS) and annular dark-field imaging (ADF) which allow direct correlation of image. STEM allows, a high contrast image of biological samples without staining due to its use of dark-field microscopy. STEM has been applied to biological problems to resolve and distinguish structure on the molecular level.

Scanning Electron Microscopy (SEM)

SEM is another electron microscopy technique that scans a focused electron beam across the area of the specimen. Scanning produces a mixed array of signal such as cathodoluminescence, back scattered electrons, characteristic x-rays, secondary electrons specimen current, and transmitted electrons which once analyzed give a large depth of field yielding a characteristic three-dimensional appearance.

Discoveries from Quantified Experiments

The technologies presented in the previous section have moved us into the next frontier of biological discoveries. Studying cellular behavior in vivo for example, has lead to novel insights; from the cell membrane with diffusivity, stoichiometry, and protein translation being deciphered, to the cytosol/nucleus with transcription factor binding, to transport through the nuclear pore complex, motor proteins on linear tracks, to reveal new spatial-temporal dynamics (Joo, Balci et al. 2008). In this section we focus on membrane biology, which has been transformed by the previously discussed experimental techniques (Kusumi, Nakada et al. 2005).

Paradigm Shift in Membrane Biology

The original fluid mosaic model portrays protein movement as Brownian motion in a sea of lipids. Although this model is the foundation of the membrane biology literature, it has been plagued by two inconsistencies. The first discrepancy being that the diffusion coefficient for both proteins and lipids is a factor of 5 to 50 times smaller in the plasma membrane than within artificial membranes. The second discrepancy was that oligomers or molecular complexes exhibit a much lower diffusion coefficient (factor of 40) in the plasma membrane in comparison with

artificial membranes. These inadequacies of the original fluid mosaic model were indicative of an alternative model and have led researchers on a 30 year journey to uncover the true nature of the plasma membrane.

Lipid Rafts

The first indication of discrete microdomains within the cell membrane came a year after Singer and Nicholson (1972)(Singer and Nicolson 1972) proposed the fluid mosaic model, when a study by Yu et al. (Yu, Fischman et al. 1973) demonstrated the existence of detergent-resistant sphingolipid-rich domains in erythrocyte's plasma membrane. This was followed up in the 1980's with studies by van Meer et al.(van Meer, Poorthuis et al. 1980; van Meer, Stelzer et al. 1987) in erythrocytes; they showed asymmetry in the distribution of phosoholipids throughout the plasma membrane. In the early 90's Lisanti et al. (Lisanti, Caras et al. 1989; Lisanti, Caras et al. 1991; Lisanti and Rodriguez-Boulan 1991; Hannan, Lisanti et al. 1993) used fluorescence microscopy to link sphingolipids and GPI (glycosylphosphatidylinositol)-anchored proteins. In addition, an isolation method, detergent extraction was developed (Brown and Rose 1992) to separate these sphingolipid-rich microdomains.

First observed in the 70's, lipid microdomains have been given various names such as detergent-resistant membranes (DRMs), and detergent-insoluble glycoplipid-enriched membrane domains (DIGs) (Jacobson and Dietrich 1999), but the name which has stuck with these complex structures is 'lipid rafts'. The idea of lipid rafts has stirred both excitement as well as controversy in the biological community; the evidence of their existence is only suggestive and their biological role is divisive.

Some researchers speculate that lipid rafts could be 'vanishingly small' and may hold no biological significance (Edidin 2001; Kovbasnjuk, Edidin et al. 2001), while others hypothesize that lipid rafts may be hubs of signal transduction (Kabouridis and Jury 2008). While caveats remain in the experimental evidence both in support as well as opposition, data suggest a role for lipid rafts in both health: regulation of signaling pathways (Maffucci, Brancaccio et al. 2003), transport of substrates(Saltiel and Kahn 2001), and uptake of LCFAs (long-chain fatty acids) into adipose tissue(Pohl, Ring et al. 2004; Vial and Evans 2005), as well as disease: cardiovascular disease (Zuo, Ushio-Fukai et al. 2005; Maguy, Hebert et al. 2006) (angiotensin II receptor, activated G-proteins, adrenergic, and, cholinergic collocalization in lipid rafts), carcinogenesis(Nagy, Vereb et al. 2002; Mocanu, Fazekas et al. 2005; Yang, Raymond-Stintz et al. 2007) (delayed catalyses of ceramide synthesis decrease apoptosis), immune response (Oliver, Pfeiffer et al. 2004; Wilson, Steinberg et al. 2004) (alteration in lipid raft composition affect localization of immunogenic receptors), and neurological diseases (Park, Hwang et al. 2003; Abad-Rodriguez, Ledesma et al. 2004)(accumulation of Ab (amyloid b-peptide) in lipid rafts); for an interesting review see (Michel and Bakovic 2007).

Cytoskeletal Interactions: Picket-Fence Model

Fujiwara et al. developed powerful microscopy techniques and tools with the goal of visualizing membrane microdomains or lipid rafts. However, they made an unexpected observation. When a lipid probe, DOPE, was measured at high time resolution, it underwent short-term confined diffusion followed by a long-term “hop diffusion”(Fujiwara, Ritchie et al. 2002). These results shed light on the thirty-year-old enigma; decreased diffusion on the plasma membrane is the result of a highly compartmentalized plasma membrane in which the diffusivity of proteins is greatly hindered.

Clues for compartmentalization due to cytoskeletal interactions were evident before the single-particle tracking era, when FRAP experiments observed an increase in diffusivity for blebbed membranes after partial depolymerization of actin filaments (Tank, Wu et al. 1982; Wu, Tank et al. 1982; Paller 1994). Investigating spectrin-deficient mutant mouse erythrocytes, Sheetz et al. (Sheetz, Schindler et al. 1980)observed increased diffusivity (10-fold) in comparison to the normal cell type. In an effort to explain these findings Sheetz et al.(Sheetz 1983) proposed the membrane skeleton “picket fence” model, which describes the cell membrane as a landscape of boundaries on the cytoplasmic surface (due to interactions with the membrane cytoskeleton) and protrusions (“pickets”) expanding into the extracellular surface.

The picket fence model was expanded by the work of Fujiwara et al.(Fujiwara, Ritchie et al. 2002) and Murase et al.(Murase, Fujiwara et al. 2004), by examining the involvement of the membrane skeleton, extracellular matrices,

extracellular domains of membrane proteins, and cholesterol-rich raft domains on phospholipid diffusion. They noted altered diffusion when the membrane skeleton was disrupted. Their results seemed counterintuitive, namely that a phospholipid on the extracellular leaflet of the plasma membrane would be affected by the membrane skeleton which hinders diffusion on the cytoplasmic leaflet. They reconciled this observation by expanding the picket fence model, suggesting that transmembrane proteins are confined by the membrane skeleton and thus hinder phospholipid diffusion on the extracellular face. These transmembrane proteins were termed "pickets" and adding on to the cytoskeletal membrane model now referenced as the "picket-fence" model.

The "picket-fence" model not only resolved the diffusion coefficient inconsistency of the fluid mosaic model, but it also explained olgiomerization induced trapping, the phenomenon of decreased diffusion in olgiomers observed on the membrane. Many signal transduction pathways are initiated by monomers forming dimers or higher order oligomers. When oligomers are formed the diffusivity decreases due to the additional hindrance endured by a larger molecular complex transversing though the membrane cytoskeleton mesh work. The mechanism of oligomerization induced trapping can enhance the local receptor concentration within a corral and form a "hub" for signal transduction.

Moving Ahead in Membrane Biology

In the midst of a sea of lipids, a landscape of complexity arises, ranging from the coalescences of phospholipids into "lipid rafts" to the hindering interactions caused by the cytoskeleton. This thirty year journey has enlighten the membrane

biology community and provides a new direction for systems biology as a whole. What has been established is that the plasma membrane is a highly compartmentalized surface, which affects the diffusivity of signaling proteins in lipids in the membrane, and hence the initiation and activation of signal transduction pathways. These developments highlight a need for computational algorithms that take into account the biological complexity occurring at the cell membrane.

In this next section we will discuss the following mathematical approaches: temporal deterministic, temporal stochastic, spatial-temporal deterministic and spatial-temporal stochastic and for what systems they are best suited. We will then go into greater detail with the spatial stochastic approach given that it most accurately describes the unique conditions on the plasma membrane. We will then provide an example using the spatial kinetic Monte Carlo to model the initial events of a signaling pathway on the plasma membrane.

Modeling Approaches

Mathematical modeling in an important tool in systems biology. When developing a mathematical model of a biological system it is extremely important that the modeling assumptions are consistent with the system of interest. For example, an inherent assumption in ODE models is that the system is well-mixed, or in other words there are no concentration gradients or spatial heterogeneities in the system. Additionally, ODE models also assume that the species being modeled have large populations acting as a continuum, whereas, small populations require model approaches that handle discrete entities and the inherent stochasticity.

Limits placed on bimolecular reactions span the scale of diffusional to reactional. On the far right are reaction limited conditions inherent for well mixed systems where diffusional effects are negligible. On the far left are diffusion limited conditions with the innate assumption that collision equates with reaction. Such a range of limitations has succumbed to theory born in generality but molded by the assumptions describing the system. Take for example, Smoluchowski seminal work, (Smoluchowski 1917) derived under diffusion limitations; it predicts the evolution of a system of clusters which coalesce forming larger clusters. The Smoluchowski coagulation equation is shown below

$$\frac{d}{dt}n(k,t)=\frac{1}{2}\sum_{j=1}^{k-1}K(j,k-j)n(j,t)n(k-j,t)-n(k,t)\sum_{j=1}^{\infty}K(j,k)n(j,t)$$

where $n(k,t)$ is the concentration of clusters of size k at time t and K is the coagulation kernel. This equation only takes into account coalescence, and speaking in biomolecular reactions terms signifies the far left, collision is reaction. Within the gap of diffusion-limited and reaction-limited conditions falls mathematics which considers both diffusion and reaction. These modeling techniques will be discussed in greater detail in the next section.

Variation of system dynamics could be described either as continuous and predictive, or discrete and random. Mathematics encapsulates variation in dynamics ranging from deterministic approaches with exact solutions, to stochastic approaches with probabilistic solutions. Take for example the stochastic simulation algorithm (SSA), developed by Dan Gillespie in 1977 (Gillespie 1977). The SSA is a formulation of the exact numerical simulation for the underlying master equation. This stochastic temporal method describes a chemical reaction as the “reaction

probability per unit time" (Gillespie 1977) instead of the continuum, deterministic definition of "reaction rate". The unique feature of the SSA is that the reaction transition rates are computed in terms of total number of molecules rather than numbers of molecules per unit volume as is the standard approach with ODEs. Using total number of molecules, reactants are modeled as discrete entities undergoing reaction events.

Each reaction has a propensity such that there exists a constant c_1 which is related to the deterministic chemical rate constant k_1 by $c_1 = \frac{k_1}{V}$. Multiplying c_1 by the number of reactants gives a transition rate for that reaction; summing transition rates yields a total
transition rate. A probability for a event is calculated by taking the transition rate for an individual reaction and dividing it by the total transition rate. Generating a pseudo random number that falls within this calculated probability enables selection of an event and gives the SSA stochasticity.

Cornerstones of Modeling Techniques

Two themes emerge from the previous discussion biomolecular reactions in the presence or absence of diffusional limitations and stochasticity vs deterministicity. Figure 1. shows mathematical techniques that vary on the y-axis from stochastic to deterministic and on the x-axis from methods that take into account diffusion and those that neglect diffusion. This graph defines four approaches temporal deterministic, temporal stochastic, spatial-temporal deterministic, and spatial-temporal stochastic. We have placed mathematical techniques into each category; some techniques span the gray area between two approaches. We will discuss these mathematic platforms beginning with ordinary differential equations, ODEs categorized as temporal deterministic.

One of the most popular techniques in systems biology, ordinary differential equations (ODEs) are used to model the temporal evolution of protein concentrations. ODEs are widely applicable at high population levels in a homogenous system, conditions commonly encountered in the cytosol and extracellular space (Figure 2). The limitations of ODEs come from their intrinsic assumptions: spatial homogeneity, deterministic behavior, and the continuum. An example of the inappropriate use of ODEs is on the plasma membrane, where spatial heterogeneity presides, resulting in a disconnect between biology and algorithm. In addition to the shortcomings in the acquired data, membrane microdomains tend to discretize species populations, hence, leading to a breakdown in the continuum and inaccuracies in the deterministic solution. The loss of information and inaccuracies within the results jeopardizes the algorithm's ability to be predictive.

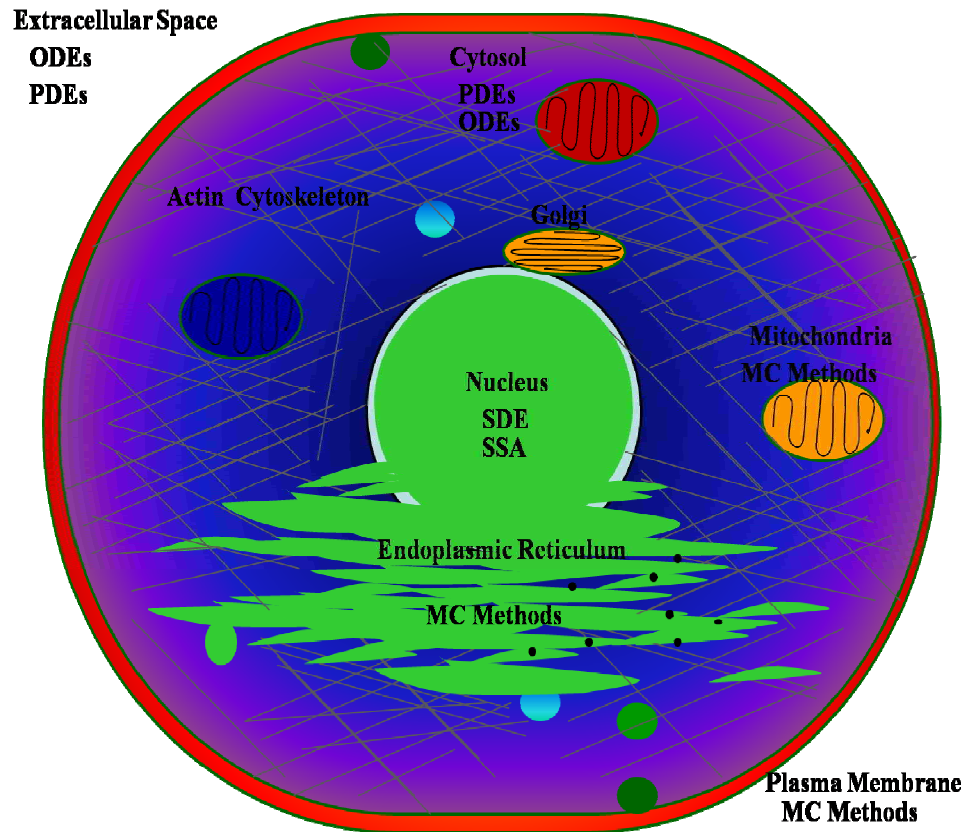

Figure 1. **Modeling Methods Suited for Different Aspects of Cell Biology. This diagram of the cell shows complementary modeling techniques for a given domain of the cell.**

The SSA is a method suitable for homogenoeus system with low species populations that exhibit inherent stochastic noise. It is best suited in the nucleus, which exhibits spatial-homogeneity and small numbers of transcription factors producing innate stochastic responses.

The spatial-temporal toolbox of systems biology represents the other half of modeling approaches (Figure 1). The spatial-temporal deterministic approaches (e.g., partial differential equations, PDEs) are primary used in systems with a single source and sink. The applications of PDE based models range from the diffusional aspects of synaptic transmission (Tai, Bond et al. 2003; Song, Zhang et al. 2004; Zhang, Suen et al. 2005), cytosol nuclear translocation (Haugh and Lauffenburger 1997; Brown and Kholodenko 1999; Kholodenko 2003; Kholodenko 2006), and receptor-ligand dynamics on the plasma membrane (Goldstein and Dembo 1995; Haugh 2002; Monine, Berezhkovskii et al. 2005). The former methods seem to be appropriately applied, utilizing the strengths of the method to gain important spatial-temporal information. The latter application could be questionable due to the characteristics of PDEs, not taking into account a sink-sink overlap. Being that the plasma membrane is a kaleidoscope of microdomains(Sheetz, Schindler et al. 1980; Kusumi, Nakada et al. 2005) this assumption is only valid at low receptor densities; conditions which cause the continuum to fail.

The remaining niches in the systems biology toolbox, spatial-temporal stochastic methods, are best suited for the plasma membrane, organelle sites, and biochemical cascades. Spatial-stochastic algorithms are not fruitful at high species populations and unnecessary in homogenous solutions. One of the major drawbacks

of these spatial stochastic approaches is the required computational rigor. Spatial stochastic methods, however, provide a powerful computational platform and are ideal for studying the dynamics on the plasma membrane. They will therefore be the focus of our discussion.

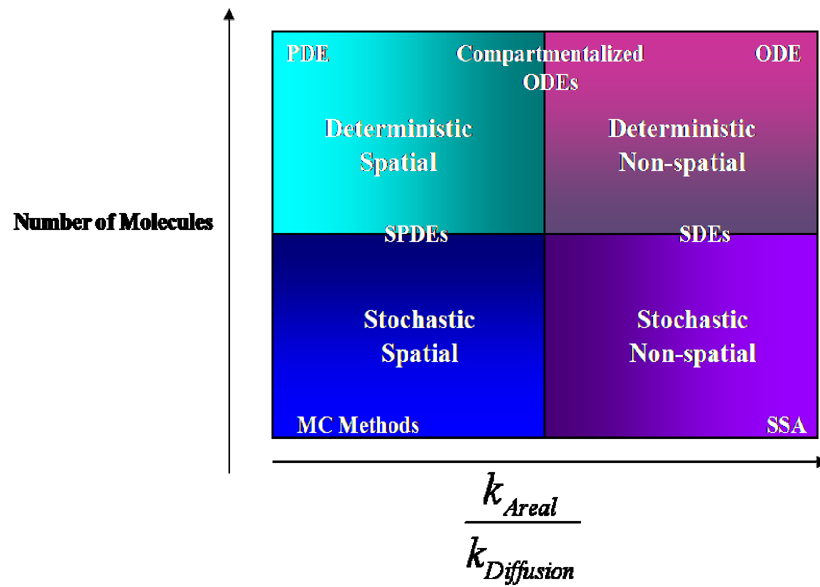

Figure 2. Choosing Appropriate Modeling Technique. We categorized mathematical techniques on the x-axis from spatial-temporal (diffusion limited circumstances) to temporal methods (well mixed solutions) as the ratio of the effective reaction rate per diffusion rate increases. Along the y-axis stochastic solutions to deterministic solutions are shown as a function of number of molecules.

Choosing an Appropriate Method

The art of computational biology comes from understanding the system. Figure 2 shows mathematical models applied to proper biological processes First deciding whether to use a temporal vs. spatial-temporal approach requires calculating the effective kinetic rate constant for diffusion-reaction problems. The following equation was derived by Lauffenburger and Linderman (Lauffenburger and Linderman 1993):

$$k_{PDE} = \frac{2\pi D_{AB} k_{Areal}}{2\pi D_{AB} + k_{Areal} \ln\left(b/s \right)} = \frac{4\pi D_{AB} k_{Areal}}{4\pi D_{AB} + k_{Areal} \ln\left(1/\pi\rho_A s^2 \right)} \quad (1)$$

where $D_{AB} = D_A + D_B$, D_A and D_B are the diffusivities of A and B, ρ_A is the density of molecules of A (number of molecules per unit area), $b = \sqrt{1/\pi\rho_A}$ is one-half of the mean displacement between molecules of A distributed in a certain area, k_{Areal} is the intrinsic reaction rate constant in units of (receptors /area)$^{-1}$ s^{-1}, and s is the encounter radius. The relationship between k_{Areal} and k is given as, $k_{Areal} = ks^2$. Using Eq 1. and combining it with the expression for resistance in a series model

$$k_{PDE} = \left(\frac{1}{k_{Areal}} + \frac{1}{k_{Diffusion}} \right)^{-1} \quad (2),$$

the diffusion-limited reaction rate constant, $k_{Diffusion}$ is determined to be

$$k_{Diffusion} = \frac{4\pi D_{AB}}{\ln\left(1/\pi\rho_A s^2 \right)} \quad (3).$$

Using $k_{Diffusion}, k_{Areal}$ one can determine if in the diffusion limited case $k_{Diffusion} << k_{Areal}$, or in the reaction limited case $k_{Diffusion} >> k_{Areal}$. Using the ratio of $\frac{k_{Areal}}{k_{Diffusion}}$ we obtain a

dimensionless parameter which provides insight into the correct modeling technique (spatial-temporal/temporal). As shown in Figure 1. starting with a small value for $\frac{k_{Areal}}{k_{Diffusion}}$ a spatial temporal model is most desired; however increasing $\frac{k_{Areal}}{k_{Diffusion}}$ validates the temporal approach. Within the gray area between spatial-temporal and temporal models fall techniques such as compartmentalized ODEs that model neighboring organelles as compartments with their own set of initial conditions.

A similar calculation must be preformed when determining whether to use a stochastic or a deterministic approach. This decision must be based on the number of molecules; at high concentrations stochastic variations maybe negligible and better approximated with a continuum model. At low concentrations discrete behavior becomes apparent and undoubtedly leads to intrinsic noisy systems. Figure 1 depicts this concept starting with a stochastic method (SSA/MC) at low molecular numbers and switching to a continuum method (ODE/PDE) at high molecular concentrations.

Spatial-Temporal Stochastic Methods

Since the focus of this review is on mathematical modeling of the plasma membrane we will spend some time now discussing the method most appropriate for the plasma membrane: spatial-temporal stochastic algorithms. These methods are often implemented either off-lattice or on-lattice. The former being difficult to derive and computationally intensive, and the latter providing ease of implementation and computational efficiency. Two types of off-lattice approaches will be discussed the first agent based off-lattice method derives probabilities from a distance factor and the second Metropolis Monte Carlo (MC) method calculates transition rates by free

energy minimization. The agent based off-lattice approach will be briefly described followed by the Metropolis MC which will be summarized in a historical setting leading into the on-lattice spatial kinetic MC.

Agent based off-lattice approaches calculate probabilities for reaction by taking into account the distance between two reactants. Calculating reaction probabilities based on separation distance is by no means trivial. Rigorous theoretical derivations(Sung, Shin et al. 1997; Kim and Shin 1999) have resulted in promising numerical algorithms (Popov, Agmon et al. 2004; Park, Shin et al. 2005; Hsieh, Yang et al. 2008). However many of these derivations rely on assumptions that are contrary to know biological systems of the plasma membrane, such as uniform concentration of reactant B, immobile reactant A, as well as collision which equates with reaction.

The Metropolis MC algorithm was developed in 1953 (Metropolis, Rosenbluth et al. 1953) being the first method to numerically solve the underlying master equation. Describing a physical system with a Hamiltonian, Metropolis et al. constructed the probability for various states of the system weighted in terms of a Markov process by the novelty of a pseudo-random number. A configurational space which includes thermal vibrations and microscopic process, termed as “rare events” was sampled.

At the time this method proved “suitable for fast computing machines” and appropriate for describing equilibrium conditions. However the receptor interactions on the plasma membrane do not occur under equilibrium conditions but rather are dynamic involving billions of diffusion and millions of reaction events. The time scales between thermal vibrations and diffusion (let alone the diffusion which is

necessary for reaction to occur) are large and define the system as “stiff”. This means that most computational time will be spent performing fast vibrations instead of slow diffusion events, or “rare events” that are necessary for the system to evolve. This “stiffness” translates to small time increments making the original off-lattice MC impractical for modeling biological events occurring on the plasma membrane.

With the many drawbacks faced when implementing off-lattice methods, spatial stochastic modeling in biological systems would prove infeasible. However from the popularity of the Metropolis MC, came the desire to apply the MC to study dynamical behavior and thus lead to algorithms such as the dynamic MC (DMC) and spatial kinetic MC (SKMC). Dynamic simulations are now possible using the SKMC because it integrates out the effects of thermal vibrations on the microscopic rates. In these simulations slow events such as reaction and diffusion occur on the spatial coordinates of a lattice and are fired, neglecting the vibrational time. Probabilities for reaction and diffusion can be easily computed by calculating a transition rate for either reaction or diffusion to a neighboring lattice site.

An example of the “null-event” SKMC algorithm is implemented by calculating probabilities for reaction and diffusion events. This is done by normalizing transition rates with a microscopic rate $\Gamma_{\max}$ that makes probabilities less than 1 and gives a null bin at the ith site. The normalized rate $\Gamma_{\max}$ is the maximum sum of all microscopic rates at a site,

$$\Gamma_{\max} = \max_{i=1,\ldots,N_L} \sum_{j=1}^{N_p} \Gamma_j \varepsilon_{ij}$$

in which N_p is the number of processes, N_L is the number of lattice sites, Γ_j is the transition rate for that process, and ε_{ij} is the participation matrix being 1 if the ith site gives rise to the jth process or 0 if it does not. Using the normalization rate $\Gamma_{\max}$ probabilities p^x for successful events (reaction or diffusion) are computed as $p^x = \dfrac{\Gamma^x}{\Gamma_{\max}}$. Since the probabilities do not sum to one for a molecule at the ith site in the jth process there is a probability for a null event or a null bin for each process. The null bin penalizes sites with lower transition probabilities giving rise to more null events while higher transition probabilities result in less null events. Although the idea of null events suggest additional computational cost an excellent review by Chatterjee et al.(Chatterjee and Vlachos 2007) describes null event algorithms and shows how time advancement is independent of the chosen process.

The SKMC is dynamical due to time increments which were not present in the original Metropolis MC. The way in which time is updated varies with the MC method, although consideration should be given to events which occur most frequently in order to have a greater time resolution (Chatterjee and Vlachos 2007). Diffusion for example is a frequent process that can be used to update time

$$\Delta t = \frac{1}{\sum_{\mathrm{i=1}}^{\mathrm{No.of\ sites}} \left(\sigma_{\mathrm{i}} \sum_{j \in B_i} \Gamma^d_{i \to j} \left(1 - \sigma_j \right) \right)}.$$

The term in the denominator describes all available sites a diffusion event can occur with a transition rate $\Gamma^d_{i \to j}$.

Overcoming the Limitations of SKMC Algorithms

Lattice based MCs usually implement periodic boundary conditions, PBCs and are computationally feasible at roughly 10^4-10^6 lattice sites (from 100x100 to 1000x1000 nm^2 with an inner lattice spacing of 1 nm). Large time scales represent another limitation of MC methods. Several novel algorithms have been developed to overcome these limitations: coarse graining techniques and τ-leaping methods. Coarse-graining MC (CGMC) techniques were developed to address the computational limitations occurring in large length scales. Grouping microscopic lattice points into coarse cells, low activity regimes are less computationally expensive, enabling the availability of more resources for high activity regimes or areas of particular interest. Although many of these CGMC techniques have been applied, their implementation of a uniform coarse cell size makes them inefficient for high activity regimes. A multiresolution framework incorporating a dynamic CGMC framework was developed by Chatterjee et al. (Chatterjee, Katsoulakis et al. 2005; Chatterjee and Vlachos 2006; Chatterjee and Vlachos 2007)called an adaptively coarse-grained Monte Carlo (ACGMC). The ACGMC enables large scale simulation with sharp concentration gradients, proving an adequate method for length disparities.

τ-leaping methods were developed in an effort to overcome disparity in time scales and to increase time increments. The first of these methods was introduced by Gillespie and later followed up by others. The τ-leap method computes a coarse-time increment, τ, being larger than the microscopic time and 'fires' all reactions multiple times and updates species populations appropriately within the time increment τ. The number of times reactions are 'fired' is determined randomly from a Poisson distribution. Although errors in the form of negative concentrations

are observed with the unbounded Poisson distribution in which the number of firings is larger than the populations of species, methods using a binomial distribution have proved more accurate for biological systems.

Although MCs are limited computationally they remain the most accurate at capturing biological phenomena, taking into account the inherent stochastic, discrete nature of biological systems as well as important spatial implications; essential aspects for capturing reaction and diffusion events on the plasma membrane. In this next section we will provide an example using an SKMC to gain biological insight into receptor dynamics on the plasma membrane.

Sorting Out Microdomains: An example using the SKMC

In an earlier section we discussed lipid rafts and picket fences on the plasma membrane in this example we illustrate the predicative capabilities of the SKMC at dissecting the effects of these microdomains. We define both a lipid raft and a picket fence on the lattice, and elucidate the effects of these microdomains in receptor aggregation. Lipid rafts range in size from 20 to 350 nm diameter (Jacobson and Dietrich 1999; Edidin 2001; Edidin 2001; Jacobson, Mouritsen et al. 2007) and proteins exhibit a decreased diffusivity on the order of 5 to 50 times on the plasma membrane (Kusumi, Ike et al. 2005; Kusumi, Nakada et al. 2005). We define a lipid raft on the lattice by specifying a region of 400 nm^2 and decreasing receptor diffusion by a factor of 50 in this area, as shown in Figure 3A. Similarly we define a picket fence as shown in Figure 3B. at the perimeter of 400 nm^2 region and allow breaks in the fence to occur every 230 nm at a time of 10 milliseconds.

To determine the effects that the picket fence and lipid raft have on receptor collocalization the Hopkins statistic test was performed as well as the p-value test (indicated as passed by the pink background). Initially 100 receptors were uniformly distributed on the lattice this is evident from the Hopkins test which shows our data following a normal distribution. As time increases to 0.08 seconds and 0.5 seconds we observe a right shift of our data (lipid raft Figure 3A) in the Hopkins test indicative of the clustered state. These results were further confirmed by the passing of the Chi-squared test. Observing the state of the system at similar time points reveals no apparent clustering in the picket fence microdomain. Additional simulations could be performed varying the diffusivity in the lipid raft, the size of the

lipid raft, varying the time between breaks and the number of breaks in the picket fence, and the area enclosed by the picket fence to further elucidate the effects of microdomains on receptor aggregate

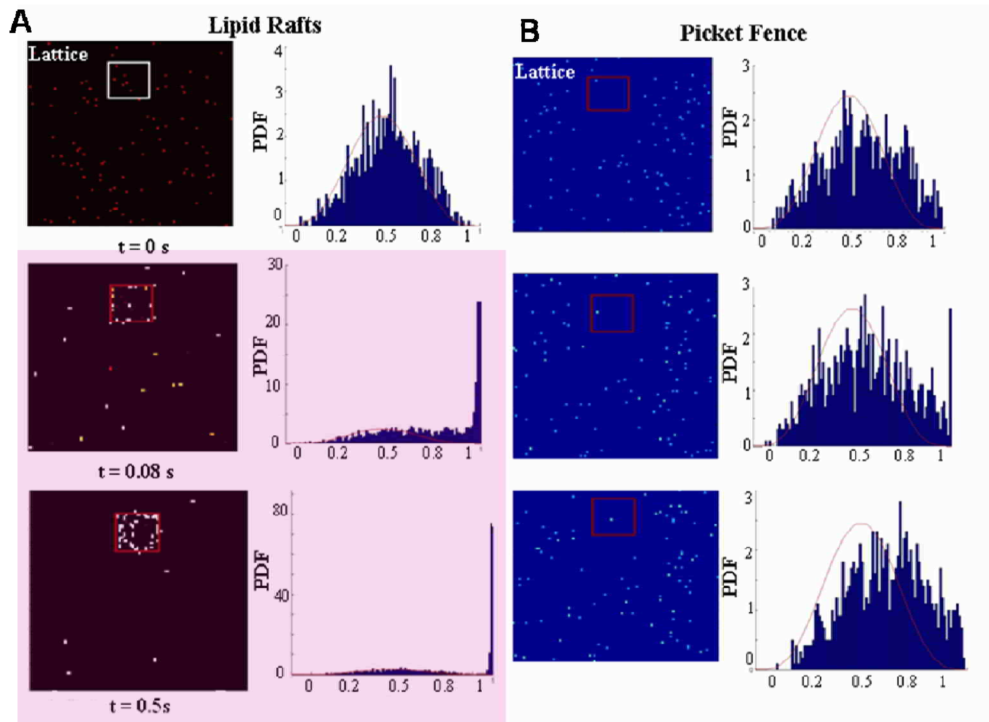

Figure 3. Microdomains vs. Receptor Clustering. Schematic illustrates the lattice (left) and Hopkins test with pink boxes indicating passing of the Chi squared test. Two microdomains were tested lipid raft (left) and picket fence (right). The rows represent different time points (top-to-bottom) time is 0s, 1s, & 2s.

A New Direction for Systems Biology

This example illustrates how mathematical models can be predictive, guide experimentations, and interpret results. Using the SKMC approach we outlined here how one could interpret results from SPT experiments, predict the spatial-temporal evolution of the system based on conditions of the plasma membrane with results that would further guide experimentation.

In this review we have presented modern experimental techniques along with biological discoveries on the plasma membrane which challenge the predictability of mathematical models. The motivation for new computational approaches is driven by two factors: first the prospects of state of the art experimental technologies outdate previous mathematical methods, and two biological discoveries demonstrate an inhomogeneous, stochastic nature whose complexities can no longer be ignored.

Experimental technologies have evolved well beyond the standard western blot, immunprecipation experiments that were originally used to construct mathematical models. At the time, ODEs were complementary to western blot techniques by being able to predict the temporal evolution of a system. However the capacity of SPT and FRET to provide resolution of single protein diffusion and interaction in vivo and in real time can not be complemented with an ODE but rather must be complemented with an equally influential theoretical technique.

In addition to being outdated with experimental technologies the paradigm shift on the plasma membrane exemplifies the true complexity of cell biology which is not captured with ODEs. The plasma membrane is a highly compartmentalized structure,

a stage for discrete receptor diffusion and reaction events' resulting in heterogeneity, which in order to be accurately modeled needs a spatial-temporal stochastic approach. The plasma membrane was our focal point, however as more experimental studies are conducted we may discover intricacies in other biological systems as well providing additional motivation for these algorithms.

Although ODEs are not sufficient on the plasma membrane and do not complement high-tech experimental technologies, they are a tool of systems biology. When used appropriately ODEs are an insightful, predictive method for understanding biology. The challenge to systems biology comes not in the discontinuity of ODE methods but in terms of developing the future mathematical tools to guide and complement experimentation.

Chapter 2. Coupled Stochastic Spatial and Non-Spatial simulations of ErbB1 Signaling Pathways Demonstrate the Importance of Spatial Organization in Signal Transduction

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Abstract

Background: The ErbB family of receptors activates intracellular signaling pathways that control cellular proliferation, growth, differentiation and apoptosis. Given these central roles, it is not surprising that overexpression of the ErbB receptors is often associated with carcinogenesis. Therefore, extensive laboratory studies have been devoted to understanding the signaling events associated with ErbB activation. Systems biology approaches have contributed significantly to current understanding of ErbB signaling networks.

Methodology/Principal Findings. Although computational models have grown in complexity over the years, little work has been done to consider the spatial-temporal dynamics of receptor interactions and to evaluate how spatial organization of membrane receptors influences signaling transduction. Herein, we explore the impact of spatial organization of the epidermal growth factor receptor (ErbB1/EGFR) on the initiation of downstream signaling. We describe the development of an algorithm that couples a spatial stochastic model of membrane receptors with a nonspatial stochastic model of the reactions and interactions in the cytosol. This novel algorithm provides a computationally efficient method to evaluate the effects of spatial heterogeneity on the coupling of receptors to cytosolic signaling partners.

Conclusions/Significance: Mathematical models of signal transduction rarely consider the contributions of spatial organization due to high computational costs. A hybrid stochastic approach simplifies analyses of the spatio-temporal aspects of cell signaling and, as an example, demonstrates that receptor clustering contributes significantly to the efficiency of signal propagation from ligand-engaged growth factor receptors.

Keywords: ErbB Signaling, EGFR, spatial modeling, Spatial Monte Carlo

Introduction

The ErbB family of receptors, under normal physiological conditions, regulates key cellular processes such as growth, proliferation and differentiation (Yarden and Sliwkowski 2001; Linggi and Carpenter 2006; Lajoie, Partridge et al. 2007). Overexpression of these receptors deregulates normal cellular function and is a contributing factor to tumorigenesis (Britten 2004). There are four members of the ErbB family (ErbB1, ErbB2, ErbB3 and ErbB4) and each family member has its own unique ligand specificity (Hynes and Lane 2005), kinase activity (Linggi and Carpenter 2006) and spatial organization on the membrane (Lajoie, Partridge et al. 2007; Yang, Raymond-Stintz et al. 2007). In our current study, we have focused solely on the epidermal growth factor receptor (typically abbreviated ErbB1 or EGFR) and the ErbB1 activation of ERK, which is a mitogen activated protein kinase (Santos, Verveer et al. 2007). Ligand binding to ErbB1 stabilizes a conformation of the extracellular domain that allows receptor dimerization (Blinov, Yang et al. 2006). Dimerized receptors are active tyrosine kinases, capable of transphosphorylation (Blinov, Yang et al. 2006). Phosphorylation of receptor cytoplasmic tails results in recruitment of SH2-containing adaptor and signaling proteins, such as Grb2, Sos, and Shc, that form a signaling scaffold to activate ERK (Blinov, Faeder et al. 2006).

Due to the importance of the ErbB1-activated ERK pathway, several ordinary differential equation (ODE) models have been developed to gain insight into this pathway (Kholodenko, Demin et al. 1999; Schoeberl, Eichler-Jonsson et al. 2002; Hendriks, Opresko et al. 2003; Sasagawa, Ozaki et al. 2005). While ODE models have provided insight into the dynamics of this pathway, these models assume that the cell is a

homogeneous well-mixed system. In other words, the ODE models neglect spatial localization and organization, such as membrane receptor clustering (Yarden and Sliwkowski 2001; Orton, Sturm et al. 2005). Over the past decade, ODE models of ErbB1-induced ERK pathway system have evolved in complexity, becoming both larger and having more experimentally constrained parameters (Kiyatkin, Aksamitiene et al. 2006). The first ErbB1/EGFR model was introduced in 1996 and had 35 reactions (Huang and Ferrell 1996), whereas the most complete models available contain hundreds of reactions (Sasagawa, Ozaki et al. 2005; Kiyatkin, Aksamitiene et al. 2006).

The question remains whether these well-mixed deterministic models are capable of quantitatively describing the temporal dynamics of signaling , since there is significant evidence that cell membrane organization promotes the formation of localized "signaling platforms" (Jiang and Sorkin 2002; Borisov, Markevich et al. 2005; Bluthgen, Bruggeman et al. 2006; Kholodenko and Sauro 2008). Major advances in our understanding of the membrane have led to a revision of the original Fluid Mosaic model (Singer and Nicholson, 1972), to a more ordered structure with distinct membrane microdomains of lipids and proteins (Schroeder, Gallegos et al. 2001; Gallegos, Storey et al. 2006; Lillemeier, Pfeiffer et al. 2006) Advanced microscopy techniques have demonstrated that membrane properties, such as transient confinement zones and corrals, may restrict and govern the spatial-temporal dynamics of lipids and membrane proteins (Fujiwara, Ritchie et al. 2002; Ritchie and Kusumi 2003; Murase, Fujiwara et al. 2004; Koyama-Honda, Ritchie et al. 2005; Orr, Hu et al. 2005; Andrews, Lidke et al. 2008). The challenge is to develop computational approaches that can account for membrane spatial heterogeneity and evaluate the impact on signal propagation.

Spatial modeling has been implemented in many scientific disciplines, including physics, material sciences, chemistry, engineering and biological systems. Modeling approaches vary, including partial differential equations (Mac Gabhann and Popel 2005), agent-based modeling (Hsieh, Yang et al. 2008) and spatial Monte Carlo (MC) methods (Woolf and Linderman 2004; Chatterjee and Vlachos 2005; Chatterjee and Vlachos 2007). Spatial MC platforms are particularly powerful numerical simulation tools for studying the dynamics of membrane components (Woolf and Linderman ; Woolf and Linderman 2003; Brinkerhoff, Woolf et al. 2004; Mayawala, Vlachos et al. 2005). The application of spatial MC methods has been implemented by our group (Mayawala, Vlachos et al. 2005) to study ErbB reaction/diffusion and herein to study the effect of spatial heterogeneity on signal propagation. We report the development of a new computational framework that merges a spatial kinetic Monte Carlo (SKMC) algorithm for modeling reaction and diffusion events on the membrane with a stochastic simulator algorithm (SSA) (Gillespie 1977) for modeling cytosolic reactions. This new algorithm, the Coupled Spatial, Non-spatial Simulation Algorithm (CSNSA), has enabled us to determine the effects that receptor clustering has on the initiation of signaling.

Results

Establishing Parameters for the Spatial Model

One goal of our study was to evaluate whether simulation results from a spatial stochastic model would differ significantly from deterministic solutions that assume all components are well-mixed. As a starting point, we began with the original ODE model developed by Kholodenko and colleagues (Kholodenko, Demin et al. 1999). We noted, however, that the ODE model produced results that deviated from the same group's experimental data (Kholodenko, Demin et al. 1999). We performed a sensitivity analysis using the PottersWheel MatLab toolbox (Maiwald and Timmer 2008) to identify the most important enzymatic reaction parameters in the system. Based upon this analysis, we determined that incorporation of receptor degradation mechanisms results in a better fit to the experimental data (Figure 4A). Additional reactions added during our model development are illustrated in blue within Figure 4B and the entire set of reaction parameters are summarized in Table 1. Our model modifications are consistent with other models that include negative feedback reactions (Schoeberl, Eichler-Jonsson et al. 2002; Hendriks, Opresko et al. 2003; Sasagawa, Ozaki et al. 2005). In addition, it is noteworthy that the new parameters fit using the ODE model were not explicitly dependent on receptor diffusion. Appendix A. describes our analytical approach to demonstrate the validity of this fit, based upon very small error introduced by omission of diffusive properties of degradative machinery.

Table 1

Initial concentrations in nM units are Ru (varied), EGF = 20.42$Vol_{Extracellular}$ ($Vol_{Extracellular}$ is the volume of the cell (diameter of 20 μm) multiplied by the ratio of the volume of incubation medium per cell over the cytoplasmic water volume ~33.3), PLCγ = 105, Grb2 = 85, and Sos = 34. First and second-order rate constants are in units of s^{-1} and $nM^{-1} s^{-1}$ and the Michaelis-Menten constants Km and Vmax are in units of nM and nM s^{-1}. Reactions are categorized as membrane reactions (handled by the SKMC), interfacial reactions (cytosolic species associating or dissociating with receptor) handled by the SKMC, and cytosolic reactions (handled by the SSA).

Reactions	Rate Constants	
Membrane Reactions		
1. EGF + Ru ←→ Rb	Kf = 0.003	Kb = 0.06
2. Rb + Rb ←→ RbRb	Kf = 0.01	Kb = 0.1
3. RbRb ← → R	Kf = 1	Kb = 0.01
4. R → RbRb	Vmax =268	Km = 56.2
5. R-Sh ← → R-pSh	Kf = 6	Kb = 0.06
6. R –PLCγ ← → R –pPLCγ	Kf = 1	Kb = 0.05
Interfacial Reactions		
1. R + Shc ← → R-Sh	Kf = 0.09	Kb = 0.6
2. R-pSh ← → R + pShc	Kf = 0.3	Kb = 9×10^{-4}
3. R-pSh + Grb2 ← → R-pSh-G	Kf = 0.003	Kb = 0.1
4. R-pSh-G ← → R + pSh-G	Kf = 0.3	Kb = 9×10^{-4}
5. R-pSh-G + Sos ← → R-pSh-G-	Kf = 0.01	Kb = 2.14×10^{-2}
6. R-pSh-G-S ← → R + pSh-G-S	Kf = 0.12	Kb = 2.4×10^{-4}
7. R-pSh + G-S ← → R-pSh-G-S	Kf = 0.009	Kb = 4.29×10^{-2}
8. R + Grb ← → R-G	Kf = 0.003	Kb = 0.05
9. R-G + Sos ← → R-G-S	Kf = 0.01	Kb = 0.06
10. R-G-S ← → R + G-S	Kf = 0.03	Kb = 4.5×10^{-3}
11. R + PLCγ ← → R –PLCγ	Kf = 0.06	Kb = 0.2
12. R –pPLCγ ← → R + pPLCγ	Kf = 0.3	Kb = 0.006
13. R-pShGS → R-pShGS + E	Kf = 8	
14. R-GS → R-GS + E	Kf = 48	
15. R + E → Deg + E	Vmax = 4.7	Km = 82
16. R-pShGS + E → Deg + E + pShGS	Vmax = 7560	Km = 78
17. R-GS + E → Deg + E + GS	Vmax = 5520	Km = 7560
Cytosolic Reactions		
1. G-S ← → Grb2 + Sos	Kf = 1.5×10^{-3}	Kb = 10^{-4}
2. pShc → Shc	Vmax = 2.4	Km = 14.2
3. pShc + Grb2 ← → pSh-G	Kf = 0.003	Km = 0.1
4. pSh-G + Sos ← → pSh-G-S	Kf = 0.03	Kb = 0.064
5. pSh-G-S ← → pSh + G-S	Kf = 0.1	Kb = 0.021
6. pPLCg → PLCg	Vmax = 2	Km = 13
7. pPLCg ← → pPLCg-I	Kf = 1	Kb = 0.003

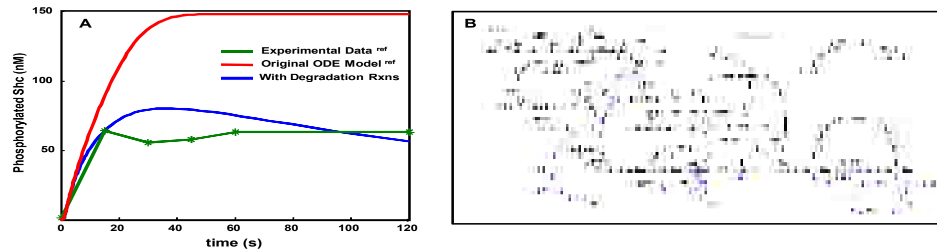

Figure 4. Parameter optimization and summary of reaction network. A) Optimization of modeling parameters based upon sensitivity analysis and ODE solution. Green line: Kinetics of Shc phosphorylation in EGF-stimulated hepatocytes (20 nM EGF) as determined by Kholodenko et al. (Kholodenko, Demin et al. 1999). Red line: results obtained using the ODE model of (Kholodenko, Demin et al. 1999). Blue line: improved fit of ODE solution to experimental data after incorporation of receptor degradation reactions. B) Summary of reaction network in the ODE and CSNSA models. Note that, in the spatial CSNSA model, stars mark membrane reactions handled by the spatial stochastic Monte Carlo algorithm. All remaining reactions are governed by the Gillespie algorithm. Additional reactions that were added to the original ODE model from Kholodenko et al. (Kholodenko, Demin et al. 1999) are shown in blue. Numbering of reactions is arbitrary.

Validating the CSNSA hybrid approach

The novelty of the *CSNSA* approach lies in its computationally efficient framework that considers receptor diffusion and reaction in the 2-dimensional confines of the plasma membrane, while cytosolic reactions occur stochastically under well-mixed conditions. The simulated space is illustrated in Figure 5, with a full description of the CSNSA algorithm in the Methods section below. As an initial test, results were compared with the ODE solution (as described in Figure 4 and compared to the experiment results in (Kholodenko, Demin et al. 1999). The simulation space was populated with a receptor density of 141 receptors per μm^2, each diffusing at 1×10^{-14} m^2s^{-1} (Kusumi, Ike et al. 2005), and a initial random distribution. In both ODE and CSNSA models, reactions were initiated by addition of EGF ligand (20 nM). Results show that, when receptors are randomly distributed, the two approaches give similar results for the rate and extent of ErbB1 phosphorylation (Figure 6A) and for the recruitment of PLCγ (Figure 6B). The CSNSA model predicts a slightly lower peak value and less sustained recruitment of Shc (Figure 6C), when compared to the ODE solution. These results emphasize that the accuracy of the CSNSA hybrid stochastic model is comparable to deterministic solutions in the absence of local concentration gradients or membrane inhomogeneities.

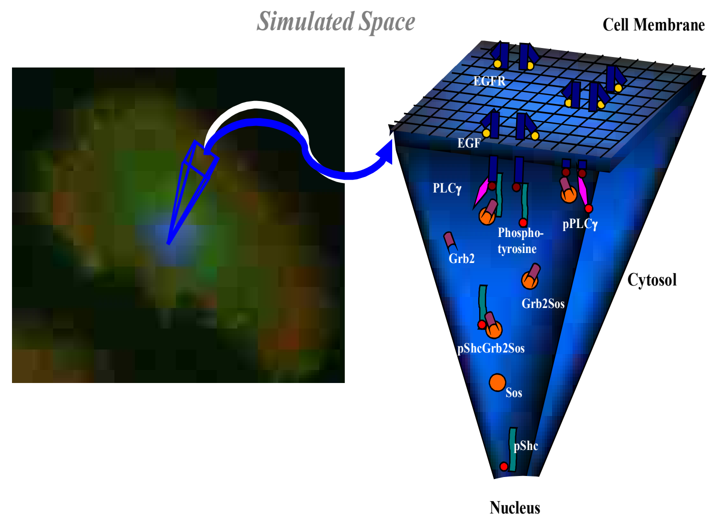

Figure 5. Illustration of the simulated space of the cell, consisting of two distinct domains: the cell membrane and the cytosol. The CSNSA model incorporates a Monte Carlo approach to simulate receptor diffusions and interactions on the cell membrane and couples to a spatial stochastic algorithm (Gillespie) for all cytosol interactions.

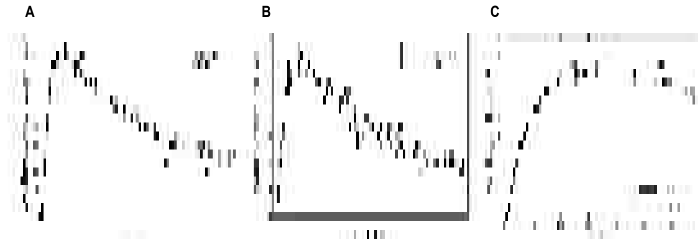

Figure 6. **Comparison of the CSNSA and ODE solutions for receptor phosphorylation, PLCγ and SHC recruitment following EGF stimulation. Simulated kinetics of ErbB1 phosphorylation (A), PLCγ recruitment (B) and Shc phosphorylation after EGF (20 nM) using the ODE model (dashed lines) or the CSNSA model (solid black line). Results (A,B) from both simulation methods compare well with experimental data (solid circles) reported by Kholodenko et al. (Kholodenko, Demin et al. 1999)**

Predicting the Impact of Receptor Density vs. Clustering

We next used the CSNSA to determine the effects of receptor spatial distribution and density on downstream signaling. We defined three different conditions, as shown in the schematic of Figure 7. In the first condition (magenta), the simulation space contained modest density of dispersed receptors (106 receptors per μm^2). In the second condition (dark blue), the simulation space contained a high density of well dispersed receptors (705 receptors per μm^2). The final simulation condition (cyan) began with a dense cluster of receptors, which was initially confined to a central region of 705 receptors per μm^2 and then permitted to diffuse over time to encompass the entire simulation space for a final density of 106 receptors per μm^2. For each regime we examined how initial receptor density and clustering conditions influence coupling to four of ErbB1's signaling partners. The temporal profiles of the cytosolic species Grb2, Sos, and pShc and membrane-bound PLCγ are shown in Figure 7B-E.

All temporal profiles of the CSNSA were compared with their ODE solutions (shown in purple and red). The most notable differences came from the clustered regime (cyan), which had the same receptor concentration of 106 receptors per μm^2 as the non-clustered regime (magenta) but was initially confined to a smaller region. The clustered regime showed a marked increase in the amplitude of signal propagation in comparison to the ODE solution. The data demonstrates that spatial models are needed to accurately predict the consequence of membrane heterogeneity on signal propagation and set the stage for more refined considerations of signaling platforms.

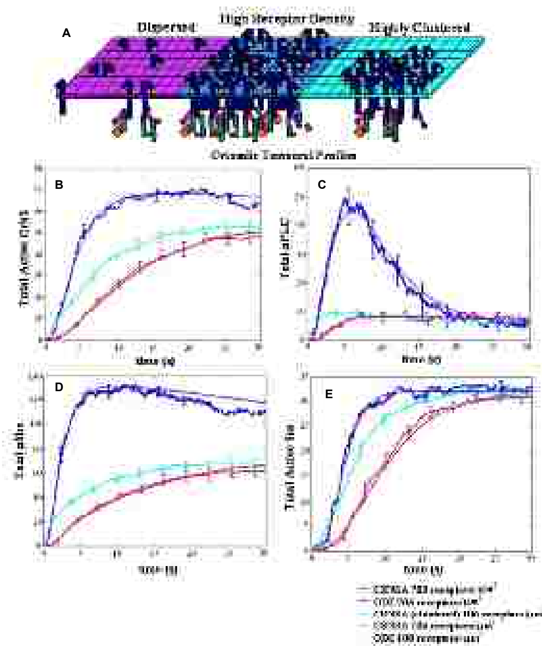

Figure 7. The spatial model predicts that receptor clustering enhances signaling efficiency by creating locally high receptor densities. A) Schematic illustration of three simulation cases: dispersed (left), high-receptor density (middle), and highly clustered (right). See legend for key to colored lines in each plot. Results predict the kinetics of Grb2 activation (B), PLCγ phosphorylation (C), Shc phosphorylation (D) and Sos activation (E). Active Grb2 is equivalent to: RGrb2 + RGrb2Sos + RpShcGrb2 + RpShcGrb2Sos + Grb2Sos + pShcGrb2 + pShcGrb2Sos; Total phosphorylated PLCγ = RpPLCg + pPLCg + pPLCgI; total phosphorylated Shc = RpShc + RpShcGrb2 + RpShcGrb2Sos + pShc + pShcGrb2 + pShcGrb2Sos; total Sos RGrb2Sos + RpShcGrb2Sos + Grb2Sos + pShcGrb2Sos.

Discussion

In this work, we describe a new, efficient computation framework for evaluating the contributions of spatial organization to important cellular processes. Although applied here to study ErbB1 signal initiation at the plasma membrane, the algorithm should be readily adaptable to other receptor systems, organelle sites and biochemical cascades. We show that, when considering well-mixed systems, solutions obtained using the CSNSA hybrid model and the more traditional ODE solutions are comparable. However, given the growing evidence for membrane compartmentalization at both the plasma membrane and internal organelles (Smith, Simon et al. 1995; Yang, Simon et al. 2001; Yang, Raymond-Stintz et al. 2007), we propose that the spatial stochastic model will more accurately predict the outcomes of events that take place between membrane proteins and lipids and their cytosolic binding partners.

As an example, we used CSNSA to demonstrate that receptor clustering creates a more efficient signaling environment. The existence of receptor clusters is well established (Nagy, Vereb et al. 2002; Lillemeier, Pfeiffer et al. 2006; Wilson, Pfeiffer et al. 2007), but the significance of this membrane organization has been approached in only a few recent publications (Mayawala, Vlachos et al. 2006; Hsieh, Yang et al. 2008). Our previous work concluded that ligand-independent ErbB1 dimerization is likely to be dependent on two factors: density and the probability of receptor "fluxing" from a closed (dimerization-incompetent) to an open (dimerization-competent) conformation (Ozcan, Klein et al. 2006; Hsieh, Yang et al. 2008). Because clustering creates locally high receptor concentrations, it enhances the probability for collision between receptors that are transiently in the conformationally "open" state (Hsieh, Yang et al. 2008). Here, we

show that ErbB1 clustering also enhances the signaling output of receptors, based upon the more efficient recruitment of PLCγ, Grb2, Sos and Shc.

The importance of spatial effects is emerging as an important topic in systems biology, with technologies such as single particle tracking and electron microscopy demonstrating unique spatial domains (Fujiwara, Ritchie et al. 2002; Hansen, Prior et al. 2003; Ritchie, Iino et al. 2003; Ritchie, Shan et al. 2005; Suzuki, Ritchie et al. 2005; Birtwistle, Hatakeyama et al. 2007; Andrews, Lidke et al. 2008). In this work, we apply a novel algorithm to show a direct link between spatial heterogeneity and downstream signaling. We propose that future studies of receptor signaling should seek to gain a fundamental understanding of the spatial interactions and spatial organization of the receptors and to apply these concepts to predictions of signaling output. ErbB receptor clustered domains have been observed in many cancers using different microscopy techniques (Nagy, Vereb et al. 2002; Yang, Raymond-Stintz et al. 2007). Understanding this bigger picture of spatial-temporal protein interactions will drive forth knowledge of cell signaling events and offer the potential to lead towards better drug treatment options.

Methods

Coupled Spatial, Non-spatial Simulation Algorithm (CSNSA)

The Coupled Spatial Non-spatial Simulation Algorithm, CSNSA, is a hybrid model that considers the diffusive behavior and organization of receptors and other membrane components within a 2-D framework, bordered by a well-mixed cytosol. A spatial kinetic Monte Carlo algorithm is employed to capture the spatial-temporal dynamics of receptors on the cell membrane (Mayawala, Vlachos et al. 2005); this is a null-event algorithm that allows ease of implementation and variation of the underlying model. For computational simplicity, the cytosol is treated as a well-mixed solution and modeled with the stochastic simulation algorithm of Gillespie (Gillespie 1977). This assumption is reasonable in the cytosol, given that the diffusivity of proteins in the cytosol (1×10^{-10} m^2s^{-1} m^2s^{-1}) (Morimatsu, Takagi et al. 2007)is four orders of magnitude larger than that in the plasma membrane (1×10^{-14} m^2s^{-1} (Kusumi, Ike et al. 2005).

The two algorithms are coupled using the CSNSA, which employs a novel algorithm that selects and executes reactions that allow the molecular species to evolve in space and time. The coupling method takes into account the stochastic nature of biological systems. The first step of the CSNSA is to select a spatial domain (cell membrane or cytosol) and thus the corresponding algorithm for the next event. The selection is made by computing the probabilities of a membrane (SKMC) event or a cytosolic (SSA) event, which are calculated as:

$$P_{SKMC} = \frac{\Gamma_{tot,SKMC}}{\Gamma_{tot}} \quad \text{and}$$

$$P_{SSA} = \frac{\Gamma_{tot,SSA}}{\Gamma_{tot}}$$

where Γ_{tot} is defined as,

$$\Gamma_{tot} = \Gamma_{tot,SKMC} + \Gamma_{tot,SSA}.$$

The total transition rate for the SKMC, $\Gamma_{tot,SKMC}$, is the sum of all transition rates for all SKMC events, or more specifically the transition rate for diffusion ($\Gamma_{tot,\mathrm{Diff}}$) and the sum of the reaction events ($\Gamma_{tot,k}$) for all N_{Rxn} reaction types (Table II),

$\Gamma_{tot,SKMC} = \Gamma_{tot,Diff} + \sum_{k=1}^{N_{Rxn}} \Gamma_{tot,k}$, where $\Gamma_{tot,k}$ is the total transition rate for each reaction type defined over all lattice sites N_L, $\Gamma_{tot,k} = \sum_{i=1}^{N_L} \Gamma_{i,k}$. $\Gamma_{tot,\mathrm{Diff}}$ is defined as the sum of the transition diffusion rate Γ_{Diff} over all lattice sites N_L, $\Gamma_{tot,\mathrm{Diff}} = \sum_{i=1}^{N_L} \Gamma_{i,\mathrm{Diff}}$. Thus, $\Gamma_{tot,SKMC}$ is defined as:

$$\Gamma_{tot,SKMC} = \sum_{i=1}^{N_L} \Gamma_{i,Diff} + \sum_{k=1}^{N_{Rxn}} \sum_{i=1}^{N_L} \Gamma_{i,k}.$$

The SSA only accounts for stochastic variations in species populations and does not consider the spatial organization in the cytosol, and therefore does not contain a diffusion term. The $\Gamma_{tot,SSA}$ is defined as the sum of Γ_k over all reaction types, $\Gamma_{tot,SSA} = \sum_{k=1}^{N_{Rxn}} \Gamma_k$.

The combined MC method operates like a single MC method by considering the superposition of all processes. Time is updated in a "combined" manner from Γ_{tot} with an average time step as, $\Delta t = \frac{1}{\Gamma_{tot}}$. Given that the two algorithms are different (null-

event vs. rejection free), the CSNSA is a kind of a hybrid method. In order to properly match time scales, upon selection of a spatial event, the SKMC model is continuously executed until a successful event is selected, as shown in Figure 10, based on probability theory described in (Chatterjee and Vlachos 2007). The complete algorithm, which is shown in Figure 8, was implemented in Fortran 90. Due to the stochasticity of the algorithm, 10 simulations with different seeds for the random number generator were used for statistics. The *CSNSA* was benchmarked by comparison of an ODE model in a reaction-limited system, where the diffusion was made fast compared to the reaction rates (Figure 7). The typical CPU time for 50 receptors/lattice is ~15 min, for 125 receptors/lattice is ~2880 min, and for 500 receptors/lattice is ~14400 min on an Intel® Xeon™ CPU 3.2 GHz processor with 8.00 GB of Ram.

Table 2. Membrane Microscopic Events and Transition rates

Γ is defined on a square lattice with lattice species M, monomers, D, dimers, and pD, phosphorylated dimmers. Sx are species either within the cytosol SC or in the extracellular space SL. Details are provided in the text.

Microscopic Event	Transition Rate
Diffusion	$\Gamma_{i\to j}^{D}=\frac{1}{4}\Gamma^{D}\sigma_i\left(1-\sigma_j\right)\; j\in B_i$ σ_i is the occupancy(discrete) that is 1, if site i is filled, and 0, if site i is empty (a single index indicating the site is used to simplify notation). $\Gamma^{D}=\frac{D}{a^2}$, where a is the microscopic lattice pixel dimension taken equal to the encounter radius, and D is the diffusivity of a receptor B_i denotes the set of sites to which diffusion from site i can occur which includes all 4 first-nearest neighboring sites
Reactions	
Ligand Association Reaction (S_L + M → M*)	$\Gamma_i^{R}=k\left[S_L\right]\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Ligand Disassociation Reaction (M* → S_L + M)	$\Gamma_i^{R}=k\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Dimerization Reaction (M* + M* → D)	$\Gamma_i^{R}=\frac{k}{2}\sigma_i\sigma_j$ k is the macroscopic reaction rate constant with units as [$(\text{receptors/sites})^{-1}\, s^{-1}$]
Decomposition Reaction (D → M* + M*)	$\Gamma_i^{R}=k\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Phosphorylation/Dephosphorylation Reaction (D ←→ pD)	$\Gamma_i^{R}=k\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Cytosolic Association Reaction	$\Gamma_i^{R}=k\left[S_C\right]\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Cytosolic Disassociation Reaction	$\Gamma_i^{R}=k\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]

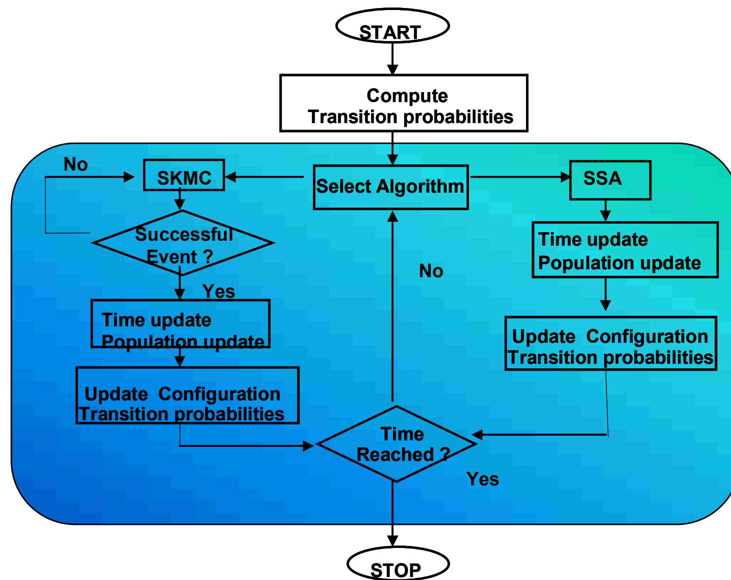

Figure 8. **Schematic of *CSNSA*. Coupled Spatial Nonspatial Simulation Algorithm, *CSNSA*, combines the spatial stochastic algorithm (Gillespie 1977)depicted in the right branch, with the spatial kinetic Monte Carlo algorithm (Mayawala, Vlachos et al. 2005)in the left branch. Upon selection of a branch, a successful event has been executed, species populations are updated, transition rates and probabilities are recomputed, and time advances. The *CSNSA* is described in greater detail within the text.**

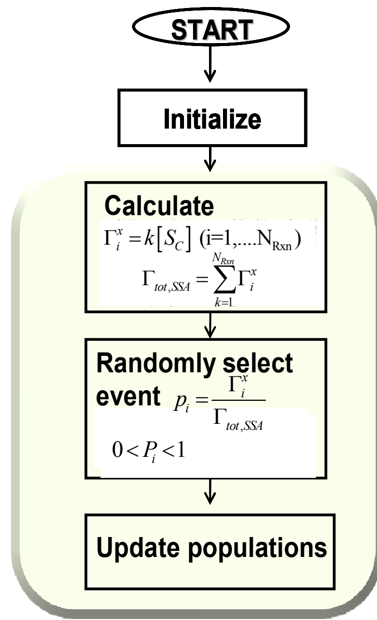

Figure 9. **Schematic of the SSA algorithm, as coupled to the hybrid algorithm. This algorithm is used for all cytosolic interactions. Being a rejection free algorithm, a successful event (reaction) is chosen and executed in each iteration. Our algorithm differs from the original Gillespie algorithm (26) in the time updating.**

Spatial Kinetic Monte Carlo (SKMC)

Once an algorithm is selected and executed, transition probabilities are computed again at each time step. Computing $\Gamma_{tot,SKMC}$ involves computing the Γ values for the SKMC over the entire lattice. This computation is the most CPU intensive step in the simulation algorithm. We, therefore, used an optimized computation method. In order to maximize efficiency, a local region that is affected by the previous reaction event is defined (Mayawala, Vlachos et al. 2005), and the Γ for each lattice site is computed for this region both before and after the event has been executed. This eliminates scanning the entire lattice before and after an event is implemented, and the new $\Gamma_{tot,SKMC}$ is calculated by:

$$\Gamma_{tot,SKMC} = \Gamma^{old}_{tot,SKMC} - \Gamma^{old}_{local} + \Gamma^{new}_{local}$$

where, $\Gamma^{old}_{tot,SKMC}$ is the total transition probability computed initially or at a previous successful MC event, Γ^{old}_{local} is the sum of transition probabilities of all sites affected by an executed event based on the old configuration, and Γ^{new}_{local} is the sum of transition probabilities of all sites affected by an executed event based on the new configuration.

The SKMC algorithm is a modified null-event lattice MC method; for further details see Mayawala et al. (Mayawala, Vlachos et al. 2005). All reactions that are on the lattice or reacting with a species on the lattice are handled by the SKMC. Hereafter and in Figure 5, * denotes membrane reactions and ` denotes interfacial reactions. These reactions include ligand association and dissociation, receptor dimerization and decomposition, receptor phosphorylation and dephosphorylation, and phosphorylated receptor associating with and disassociating from cytosolic species. When an interfacial

reaction occurs, a molecule of the cytosolic species is subtracted from the cytosolic population and the membrane species is converted to a new species at the same location on the lattice.

The spatial domain is a two-dimensional lattice with periodic boundary conditions. The initial condition of the lattice is dependent on user specifications and can either be randomly populated or clustered in pre-defined domains. The algorithm is implemented by selecting an occupied lattice site, choosing a successful (reaction or diffusion) or unsuccessful (null) event based on the probabilities, and if a successful event was chosen, executing the event.

An event is selected by computing the probability distribution for all events, defined as $P_i^X = \frac{\Gamma_i^X}{\Gamma_{\max}}$, for lattice site *i* and event *x*. Table II shows the events executed by this algorithm and the equations for computing Γ^X for each event. Γ_{max} is defined as

$$\Gamma_{\max} = 4\left(\frac{\Gamma^d}{4} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right) + \max\left\{\sum_{\text{all backward reaction events}} \Gamma^r\right\}$$

where the multiple of four accounts for events occurring in each of the four directions on the square lattice.

The spatial algorithm is coupled with the Stochastic Simulation Algorithm (SSA); therefore, unlike the original SKMC algorithm (Mayawala, Vlachos et al. 2005), the *CSNSA* is recursive in that it continuously selects an event until a successful event is chosen and executed as shown in Figure 8; therefore time is not updated if an unsuccessful event is selected.

Stochastic Simulation Algorithm (SSA)

The non-spatial SSA developed by Gillespie (Gillespie 1977) was used to model protein association reactions in the cytosol (Figure 9). The algorithm begins with initializing species populations and time; then propensities for all reactions are computed, and an event is randomly selected and the time is updated. This is a rejection free method; therefore, a reaction event is chosen and time is updated by an increment whose average is $\Delta t = \frac{1}{\Gamma_{tot}}$.

Interfacial Reactions

Interfacial reactions occur when a cytosolic species binds to or detaches from a receptor on the square lattice. In the former case, a molecule from the cytosolic species is subtracted from the cytosol population and a new product is produced at the site that was previously occupied by the reacting receptor. In the latter case, the converse procedure occurs. An example is shown in Table I(Interfacial Reaction #1) in which cytosolic species Shc binds to receptor R, occupying site k producing product R-Shc at site k.

The rate constants for cytosolic reactions are calculated by computing the cytosolic volume to be $V_{cyt} = 1/3\ rL^2$ (units of μm^3), where r is the radius of the cell, and L is the lattice dimension. Next we compute the number of molecules per μm^3, N_{sp}. By multiplying the product of V_{cyt} and N_{sp} with the rate constant (given in terms of molecules^{-1} s^{-1}for bimolecular reactions or s^{-1} for unimolecular reactions), we obtain a transition rate with units of molecules s^{-1}.

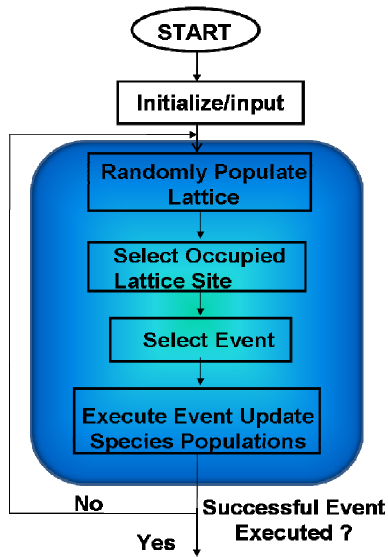

Figure 10. **The spatial kinetic Monte Carlo algorithm, as implemented in the *CSNSA*. This algorithm differs from the original algorithm of Mayawala et al (Mayawala, Vlachos et al. 2006) in the time update, which occurs recursively until a successful event is selected. Time is not updated when a null event occurs. A detailed description is provided in the text.**

Sensitivity Analysis

To elucidate a mechanism that agrees with the experimental results (Kholodenko, Demin et al. 1999) and explains the biological nature of our system, we modified the reaction scheme developed by Kholodenko et al. (Kholodenko, Demin et al. 1999). A sensitivity analysis was performed on the reaction mechanism, using the decoupled direct method and the backward differentiation formula method, as implemented in the NASA Glenn chemical kinetics and sensitivity analysis code LSENS (Radhakrishnan 1991; Radhakrishnan 1999). In addition to the species concentrations, these methods automatically follow the temporal evolution of the first-order sensitivity coefficients $d\underline{C}/d\eta_j$. The vector $\underline{C}$ contains the concentrations of all biochemical species and η_j is a parameter of interest, such as an initial concentration or a rate constant. The parameters of the new system were refined, and fits were performed for the new reactions shown in blue in Figure 4 and for the Michaelis-Menten reactions using PottersWheel, which were determined to be sensitive using the LSENS. The time scale of reactions in this model neglects the long term receptor production rate.

Acknowledgements

The image in Figure 5 was provided by Ulises Martinez.

Chapter 3. Picket Fence Densities Determine Enhanced vs. Inhibitive Role in Receptor Aggregation.

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Abstract

Experimental evidence suggests the cell membrane is a highly order structure of the cell which is compatmentalized by the underlying membrane cytoskeleton, MSK. The interaction between the cell membrane and the cytoskeleton led to the "picket-fence" model which was proposed to understand certain aspects of membrane compartmentalization. The picket fence model assumes that the membrane cytoskeleton sterically hinders and confines the motion of receptors and lipids in the membrane. However, the impact of receptor confinement on receptor clustering and aggregation, as well as downstream signaling remains controversial. Some evidence suggests that the MSK enhances dimerizaton,while other evidence links the MSK to a decrease in dimerization or signal activation. Although both scenarios may be in opposition, each may hold truth. Our hypothesis is that the rate of receptor dimerization is a function of the picket fence density and receptor concentration. Although it has been difficult to measure experimentally the relation between "picket-fence" density and receptor aggregation has been of great interest in recent years. Herein, we take a computational approach which enables us to test our hypothesis. Our results suggests that the peak in receptor clustering depends on the picket fence density as well as receptor concentration.

Keywords: EGFR, spatial modeling, Clustering. MSK, Picket Fences

Introduction

Membrane biology has gone down many new and exciting avenues since the original fluid mosaic model(Singer and Nicolson 1972) was proposed by Singer and Nicholson over 30 years ago (Vereb, Szollosi et al. 2003; Wisniewska, Draus et al. 2003;

Kusumi, Nakada et al. 2005). Great advances in our understanding of the membrane can be primarily attributed to new technology; i.e. high resolution microscopy captures structure on the nanometer scale, (Danuser and Waterman-Storer 2003; Morone, Fujiwara et al. 2006; Morone, Nakada et al. 2008) while protein tracking experiments (Ritchie, Iino et al. 2003; Murase, Fujiwara et al. 2004; Koyama-Honda, Ritchie et al. 2005; Suzuki, Ritchie et al. 2005; Andrews, Lidke et al. 2008) have revealed interesting spatial-temporal dynamics of membrane bound receptors. These new technologies are providing insights and pointing to inadequacies in the original fluid mosaic model.

There are two critical discrepancies between the experimental data and the fluidic mosaic model that demand further investigation (Kusumi, Nakada et al. 2005). First, the diffusion coefficients for both proteins and lipids in the plasma membrane were found to be smaller than those in artificial membranes (Saffman and Delbruck 1975; Cherry, Godfrey et al. 1982; Peters and Cherry 1982). Secondly, a dramatic drop of diffusion rates was observed for protein oligomers or molecular complexes (Nelson, Horvat et al. 1999; Roess, Horvat et al. 2000; Hegener, Prenner et al. 2004). These discrepancies clearly indicate that our understanding of membrane biology is incomplete and have led to a plethora of experimental studies giving a deeper understanding of the plasma membrane and the membrane skeleton (MSK) (Dietrich, Bagatolli et al. 2001; Fujiwara, Ritchie et al. 2002; Wilson, Pfeiffer et al. 2007; Morone, Nakada et al. 2008).

It is has been hypothesized in the literature that the cell membrane is compartmentalized into microdomains, such as protein islands(Wilson, Pfeiffer et al. 2007) and lipid rafts(Nagy, Vereb et al. 2002). The "picket-fence" model is an non-mutually exclusive model that has been proposed as a mechanism for microdomains

formation(Ritchie, Iino et al. 2003; Ritchie and Kusumi 2004). In the picket-fence model the MSK acts as the fence by corralling transmembrane proteins while intergral proteins serve as the "pickets" hindering receptor as well as lipid mobility (Nakada, Ritchie et al. 2003; Murase, Fujiwara et al. 2004). The "picket-fence" model accurately explains changes in diffusion rates; with lipids undergoing short term confined diffusion (with diffusion rates consistent with data on artificial membrane) followed by hop diffusion in between compartments (Ritchie, Shan et al. 2005; Suzuki, Ritchie et al. 2005). Restricted motion by the "picket-fence" also potentially explains differences in receptor diffusion between the artificial and the plasma membrane (Woolf and Linderman 2003; Brinkerhoff, Woolf et al. 2004; Hegener, Prenner et al. 2004).

Herein, we have utilized spatial stochastic simulations to test how picket fence density affects receptor clustering and hence signaling. While many *in silco* methods have been developed to study signaling which includes receptor interactions (i.e. dimerization), spatial information is often and receptors are assumed to be well mixed (Kholodenko, Demin et al. 1999; Sasagawa, Ozaki et al. 2005). Here we utilize the spatial kinetic Monte Carlo, SKMC to investigate the effect of the MSK on receptor clustering.

Materials and Methods

Spatial Kinetic Monte Carlo (SKMC)

Simulations were performed using the SKMC algorithm which is a modified null-event lattice based MC which was developed by our group (Mayawala, Vlachos et al. 2005; Mayawala, Vlachos et al. 2005). The algorithm is implemented by selecting an occupied lattice site, choosing a successful (reaction or diffusion) or unsuccessful (null) event based on probabilities, and if a successful event is chosen, executing the event. Transition rates are computed for both reaction and diffusion; they are presented in Table I. The model which was used as well as the reaction parameters is shown in Table II. The transition rate for diffusion is defined as,

$$\Gamma^{d}_{i\to j} = \frac{1}{4}\Gamma^{d}\sigma_i(1-\sigma_j)\; j \in B_i \quad (1)$$

where $\Gamma^d = \dfrac{4D}{a^2}$ is four times its diffusion coefficient, D, divided by its inner lattice distance, a. B_i signifies the set of sites in which diffusion from site σ_i can occur. Diffusion takes place in four directions, each direction with its occupancy function σ_j which is discrete, equaling 1 if the site is filled, or 0, if the site j is empty. This means that Eq. 1 can be either 0 or $\frac{1}{4}\Gamma^d$ depending on the occupancy of the neighboring site.

The probability distribution for both reaction and diffusion is $P_i^X = \dfrac{\Gamma_i^X}{\Gamma_{\max}}$ defined for lattice site i and event x. $\Gamma_{\max}$ is a normalization constant defined as

$$\Gamma_{\max} = 4\left(\frac{\Gamma^d}{4} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right) + \max\left\{\sum_{\text{all backward reaction events}} \Gamma^r\right\}$$

where the multiple of four accounts for events occurring in four directions on the square lattice; for further details see (Mayawala, Vlachos et al. 2005).

The spatial domain is a two-dimensional lattice with periodic boundary conditions. The initial condition of the lattice is dependent on user specifications and can either be randomly populated or clustered in pre-defined domains. Simulations were preformed 10 times for statistical significance.

Table 3

Γ is defined on a square lattice with lattice species M, monomers, D, dimers, and pD, phosphorylated dimmers. Sx are species either within the cytosol SC or in the extracellular space SL. Details

Microscopic Event	Transition Rate
Diffusion	• $\Gamma^{D}_{i \to j} = \frac{1}{4}\Gamma^{D}\sigma_i\left(1-\sigma_j\right)\; j \in B_i$ • σ_i is the occupancy(discrete) that is 1 if site i is filled, and 0 if site i is empty (a single index indicating the site is used to simplify notation). • $\Gamma^{D} = \frac{D}{a^2}$, where a is the microscopic lattice pixel dimension taken equal to the encounter radius, and D is the diffusivity of a receptor • B_i denotes the set of sites to which diffusion from site i can occur which includes all 4 first-nearest neighboring sites
Reactions	
Ligand Association Reaction (S_L + M → M*)	$\Gamma^{R}_{i} = k\left[S_L\right]\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Ligand Disassociation Reaction (M* → S_L + M)	$\Gamma^{R}_{i} = k\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Dimerization Reaction (M* + M* → D)	$\Gamma^{R}_{i} = \frac{k}{2}\sigma_i\sigma_j$ k is the macroscopic reaction rate constant with units as [(receptors/sites)$^{-1}$ s^{-1}]
Decomposition Reaction (D → M* + M*)	$\Gamma^{R}_{i} = k\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]
Phosphorylation/Dephosphorylation Reaction (D ↔ pD)	$\Gamma^{R}_{i} = k\sigma_i$ k is the macroscopic reaction rate constant with units as [s^{-1}]

Table 4

Initial concentrations in nM units are Ru (varied), EGF = 20.42$Vol_{Extracellular}$ ($Vol_{Extracellular}$ is the volume of the cell (diameter of 20 μm) multiplied by the ratio of the volume of incubation medium per cell over the cytoplasmic water volume ~33.3). Reaction #5 was included in the predimerization simulations

Reactions	Rate Constants	
1. EGF + Ru ←→ Rb	Kf = 0.003	Kb = 0.06
2. Rb + Rb ←→ RbRb	Kf = 0.01	Kb = 0.1
3. RbRb ←→ R	Kf = 1	Kb = 0.01
4. R → RbRb	Vmax =268	Km = 56.2
5. Ru + Ru ←→ RuRu *	Kf = 0.01	Kb = 0.4

*Predimerization

Picket Fences

In order to model cytoskeletal interactions with the cell membrane boundaries, "picket fences" were placed on the lattice; previous work has investigated the use of a lattice to perform these simulations(Niehaus, Vlachos et al. 2008). Three different picket fence densities as shown in Figure 11, 25 corrals/lattice, 100 corrals/lattice, and 400 corrals/lattice were tested. The "picket-fences" occupy lattice sites and therefore prevent reaction and diffusion events in the direction of the boundary. Take for example, a receptor neighbored by a "picket fence" on the jth lattice site, it has an occupancy function, $\sigma_j = 1$ of one, yielding a zero transition probability, $\Gamma^{d}_{i \to j} = 0$ in the direction of the boundary. Similarly, a receptor separated from its partner by a "picket fence" can not dimerize being that the neighboring lattice site is occupied by the boundary.

Single particle tracking reveals short term receptor confinement followed by long term "hop" diffusion. Cytoskeletal rearrangements and actin depolarization are responsible for "hop" diffusion(Murase, Fujiwara et al. 2004; Kusumi, Nakada et al. 2005). In order to simulate "hop" diffusion breaks were randomly inserted into the boundaries an average of time step τ_{PF} of 10 milliseconds per 0.04 μm^2 of picket fences as was observed experimentally (Fujiwara, Ritchie et al. 2002). Placing breaks in the "picket fence" enables receptors to diffuse out of their corrals. After an iteration of the SKMC breaks are closed and τ_{PF} is set to zero.

This is consistent with the rate kinetics of actin dimerization (Adams, Matov et al. 2004; Vallotton, Gupton et al. 2004; Danuser and Waterman-Storer 2006; Deshpande, McMeeking et al. 2006; Andrews, Lidke et al. 2008) which is on the order of the algorithm's time step, Δt.

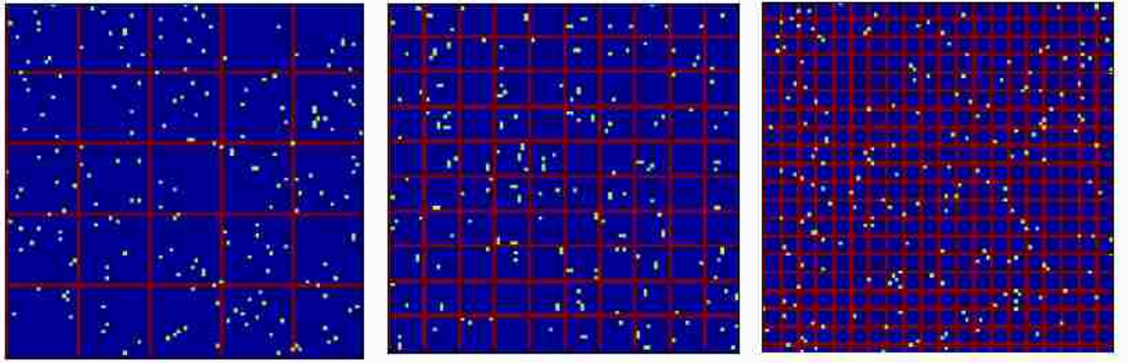


Figure 11. Picket Fence Distribution. The picket fence densities of 25 corrals/μm^2, 100 corrals/μm^2 and 400 corrals/μm^2 were tested.

We wanted to confirm that receptors have an equal probability of escape from each picket fence density. In order to do this we determined the ratio of the number of escapes to the number of collisions. These results are plotted in Figure 12, showing equal escape probability.

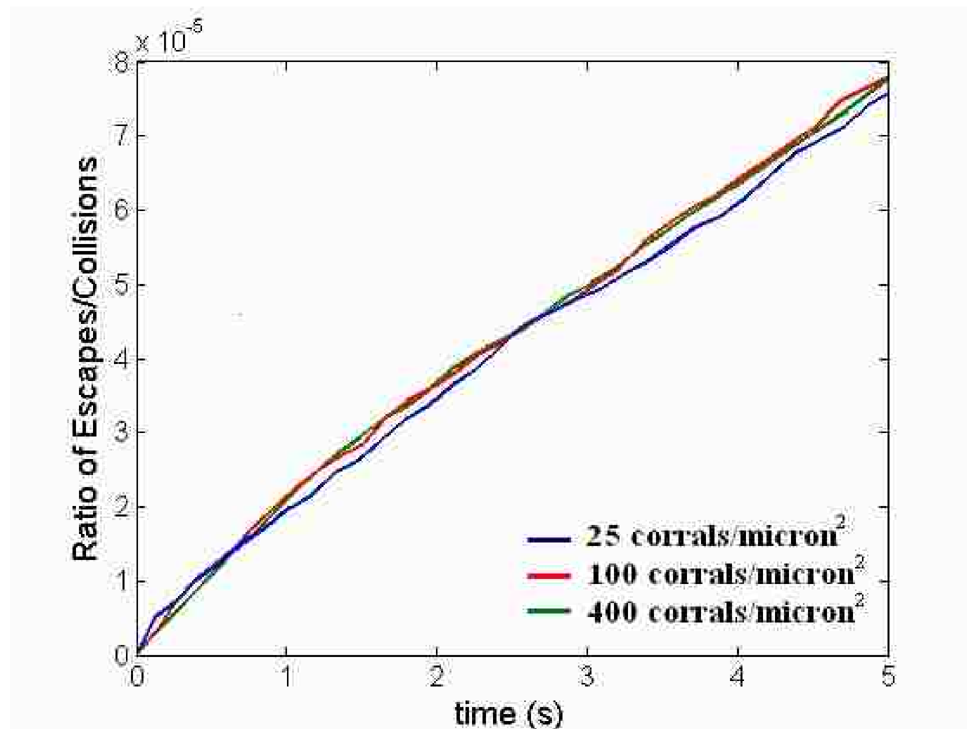


Figure 12 Number of Collisions and Escapes for each Picket Fence Density. The number of collisions (dashed line) and number of escapes (solid line) is shown as a function of time (s) for all picket fence densities 400 corrals/μm^2 (red lines), 100 corrals/μm^2 (green lines), and 25 corrals/μm^2 (blue lines).

Quantification of Microdomains

In order to quantify microdomains in each simulation, the Fuzzy c-means (FCM) was performed to determine the number of clusters and the size of clusters. The FCM is a data clustering technique wherein each data point belongs to a cluster to some degree which is specified by its membership grade (Bezdek). An initial cluster number was specified in order to determine aggregation due to each corral and was then further reduced using the FCM. If the number of corrals was greater than the number of molecules $x_{corrals} \geq x_{molecules}$ $\mathrm{N}_{\mathrm{Clus}} = \frac{x_{molecules}}{2}$, the cluster number was defined as the number of molecules divided by two; signifying that two or more receptors define a cluster. However, if the number of corrals is less than the number of molecules, $x_{corrals} \leq x_{molecules}$ $\mathrm{N}_{\mathrm{Clus}} = x_{corrals}$, the cluster number was defined as the number of corrals, specifying clustering due to each corral. The FCM algorithm performs an analysis unaware of the “picket fences”, such that different clusters occupy the same corral or a single cluster spans multiple corrals. Assuming that the mechanism of clustering is “picket fences”, we combined or separated clusters dependent on which corral they occupied. For example, clusters occupying the same corral were combined and clusters with receptor members occupying more than one corral were separated or eliminated. Performing this analysis we determined the number of clusters occupying a corral as well as the average cluster size.

Results

Clustering vs. Picket Fence Density

The first question we wanted to address is how does the density of picket fences effect receptor clustering. We tested this by looking at three different densities of picket fences: the first was a low picket fence density of 25 corrals/μm^2 followed by a density of 100 corrals/μm^2 and a hight density of 400 corrals/μm^2. Receptors were randomly placed on the lattice as shown in Figure 13(first row) for all picket fence densities. Random distributions were confirmed with the Hopkins test (Jain, Hamper et al. 1988), showing that the data follows a Gaussian distribution, and the Chi-squared Goodness-of-fit test (Snedecor and Cochran 1989) which validates the null hypothesis. Receptors were allowed to diffuse and at 1s (second row) there is a slight right-shift of the data in the Hopkins test. At 2s receptors cluster, indicated by the dramatic right-shift of the data in the Hopkins test. The Chi-squared values indicated a non-random, or clustered state.

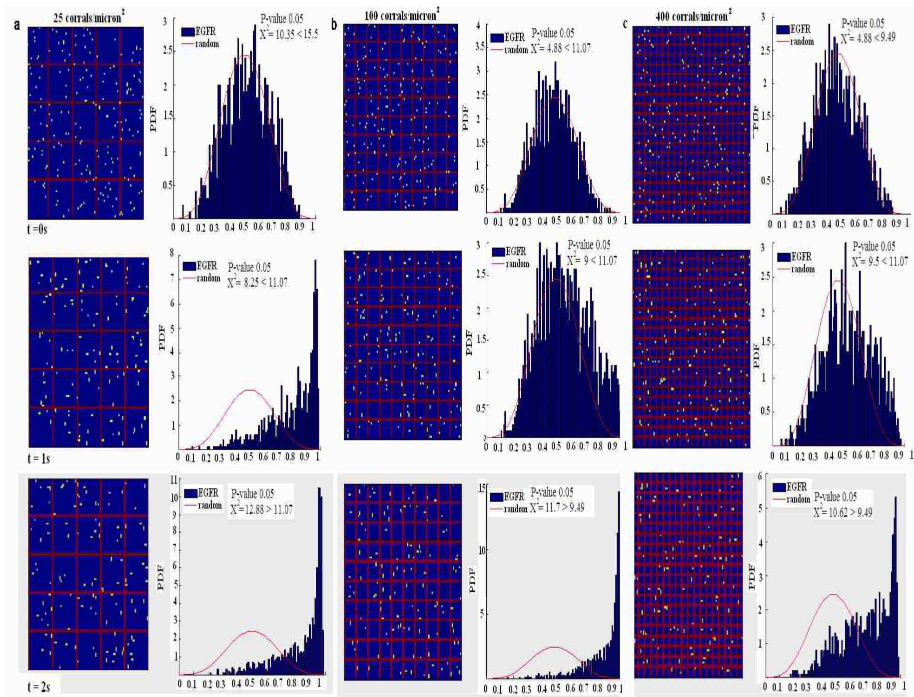


Figure 13. **Picket Fence Density vs. Receptor Clustering**. **Schematic illustrates the lattice (left) and Hopkins test with the chi-square parameters for that lattice. Three different picket fence densities representing the columns (left-to-right) 25 corrals/μm^2, 100 corrals/μm^2, and 400 corrals/μm^2. The rows represent different time points (top-to-bottom) time is 0s, 1s, & 2s.**

Comparing the three picket fence densities at 2s (third row) we see that both the Hopkins as well as the Goodness-of-fit test confirm the greatest amount of clustering at the picket fence density of 100 corrals/μm^2. While the densest picket fence density demonstrated the least amount of clustering as indicated by Hopkins and the Goodness-of-fit test; followed by least dense density.

In order to understand this result, we performed the fuzzy c-means clustering (FCM) algorithm (Bezdek) on the data. The FCM function computes the membership of receptors to a given cluster (Figure 14). The results were then analyzed and clusters were rejected if they border corrals, or contained less than two receptors in a corral. Performing this analysis we were able to determine the number of clusters and the cluster size (receptors per cluster). Ten simulations were performed and results were averaged for statistical significance. The results for each picket fence density are shown in (Figure 13). In this simulation we obtained an average cluster size of 5 receptors per cluster and 19 clusters (each occupying a separate corral) per lattice for the 25 corrals/μm^2 densities. When the corral density was increased to 100 corrals/μm^2 the average cluster size decreased to 3 receptors per cluster and the number of clusters increase to 28 clusters per lattice. The densest distribution of 400 corrals/μm^2 showed a decrease in the number of clusters 17 clusters per lattice as well as cluster size of 2 receptors per cluster.

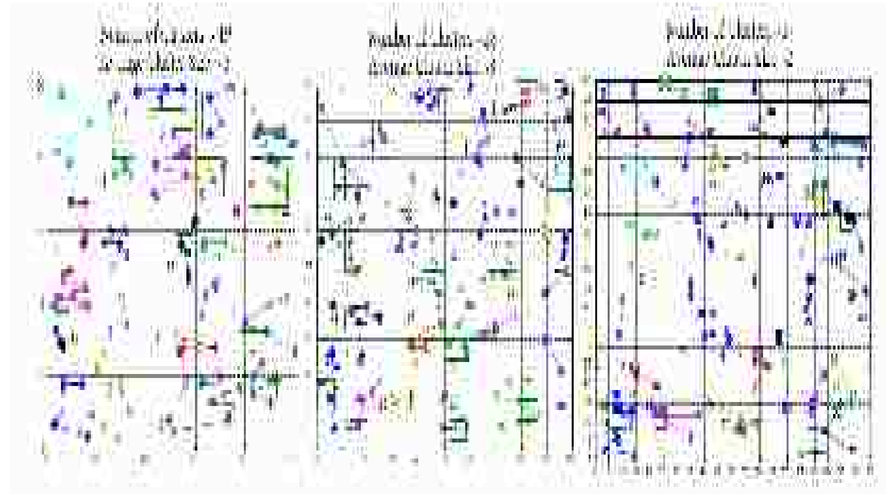


Figure 14. **Cluster Analysis. Each picket fence density at a time of 2s was analyzed using fuzzy c-means clustering. Green boxes indicate the clusters which were due to a picket fence compartment. The diagram illustrates the member of a particular cluster. From this analysis the number of clusters as well as the average size of clusters was determined.**

Clustering vs. Receptor Concentration

Hypothesizing that receptor concentration may affect our results we preformed simulations for receptor concentrations of 30, 50, 200, and 300 (number of receptors per lattice). The results show (Figure 15) that at a low receptor concentration (30-50 receptors per lattice) the greatest amount of clustering occurs at the least dense picket fence density of 25 corrals/μm^2 where 8~13 clusters are observed. At a receptor concentration between 50 to 100 (receptors per lattice) we observe a switch within the data, with the most clustering at the 100 corrals/μm^2 density. Although for higher receptor concentrations the greatest amount of clustering remains at 100 corrals/μm^2, there is an increase in the slope between 25 corrals/μm^2 and 100 corrals/μm^2. Simulations at greater receptor concentrations were not preformed, due to computational limitations, but we predict a switch with the greatest amount of clustering occurring at the densest 400 corrals/μm^2 density in which the cluster size would approximate the number of corrals at this density.

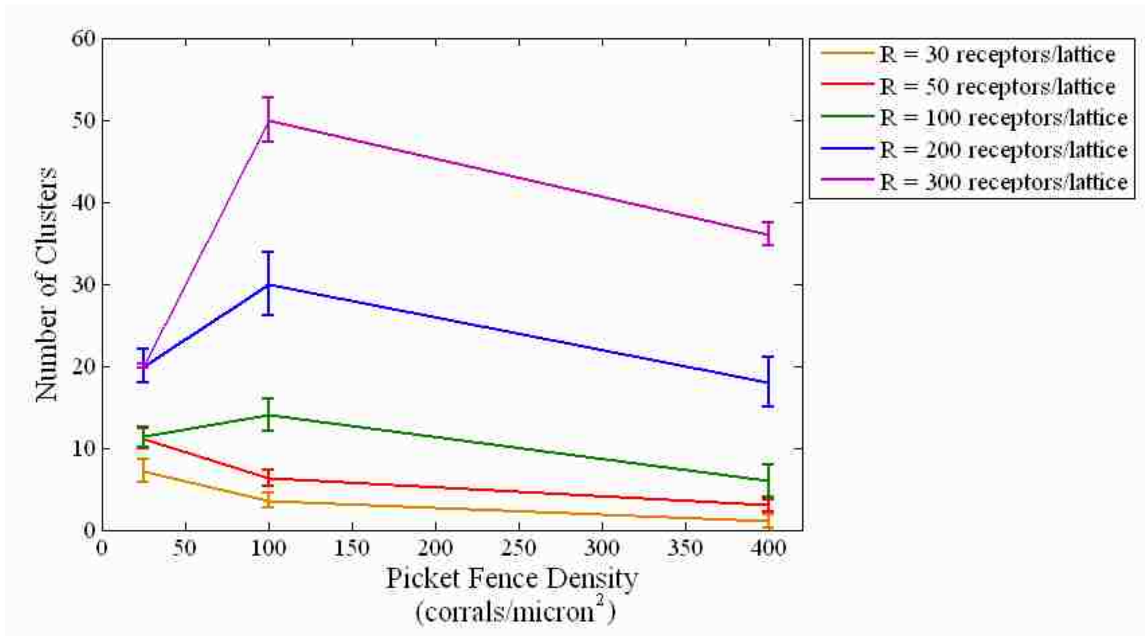


Figure 15. **Number of Clusters and Cluster Size vs. Picket Fence Density. The number of clusters (blue line) and size of clusters (green line) or number of receptors per cluster is plotted as a function of picket fence density.**

Picket Fence Densities Rescale MSD

To test a possible mechanism for clustering, we investigated how dimerization may lead to clustering via oligomerization induced trapping (Ritchie, Iino et al. 2003; Suzuki, Ritchie et al. 2005). We looked at the mean square displacement, MSD, of both monomer and dimer for each of the picket fence densities (rows) as a function of time, Figure 16**Error! Reference source not found.** (left column). In the MSD plots we observed hindered diffusion for all picket fence densities Figure 16. At a density of 400 corrals/μm^2 the monomer escapes at ~0.3s (noted by the shift in MSD) and then is confined until ~1.25 s; the dimer remains confined to a MSD of ~0.002 μm^2 within the 2s simulation. Looking at the single particle tracking trajectories (Figure 16 right most panels) the monomer travels across a much larger area than when it is bound to a partner. The MSD trajectories of the 100 corrals/μm^2 density show both monomer and dimer escaping at ~1.1s; the dimer is more confined moving in MSD area of ~0.013 μm^2 while the monomer's area is ~0.024 μm^2. The single particle trajectories showed less difference between a monomer and dimer in the area traveled when compared with the trajectories of the 400 corrals/μm^2. The MSD plots for the 25 corrals/μm^2 show escapes for monomer and dimer at ~0.5s. The dimer escapes and then seems to be confined from 1.1s till 1.6s and then escapes again, while the monomer "hops" to another corral at 1.1s where it is confined to 0.024 μm^2 area and then escapes again at ~1.5s. The single particle trajectories showed the monomer to have traveled a greater area, but compared with the 400 corrals/μm^2 the differences are small. The results indicated that dimerized receptors

cover less area, which supports oligomerization induced trapping; these results are more pronounced in the densest density of 400 corrals/μm^2.

Next we investigated the MSD trajectories as a function of the number of collisions (Figure 17). Rescaling the time in the MSD plots to number of collisions showed that escapes were only present in the 25 corrals/μm^2 density. Rescaling the 100 and 400 corrals/μm^2 density to 3x10^6 number of collisions, we see an escape for the monomer (400 corrals/μm^2) at ~1.3 x10^6 number of collisions, however, the dimer remains confined. At 100 corrals/μm^2 density both monomer and dimer escape after ~1.55 x10^6 number of collisions. The relation of the different densities shows how time, collisions, and escapes are being scaled. The 25 corrals/μm^2 density shows a larger area traveled and greater number of escapes occurring in a smaller time and number of collision frame. These results illustrates time scaling of receptor signaling events based on the density of the membrane cytoskeleton.

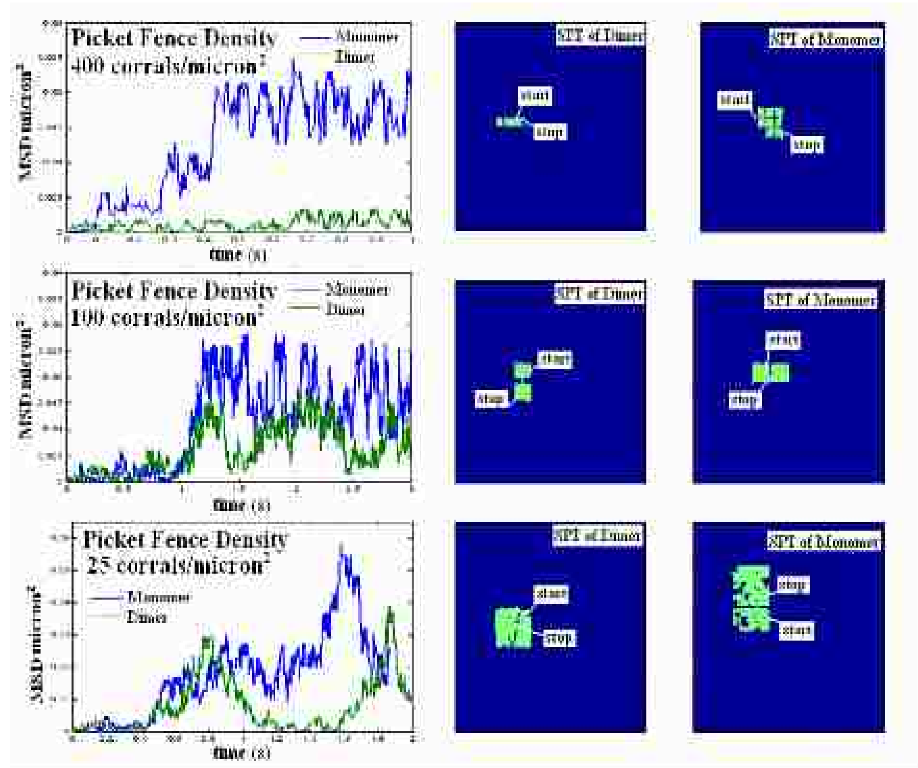


Figure 16. **Mean Squared Displacement as a Function of Time for Monomers and Dimers. The mean squared displacement is plotted as a function of time for both monomer and dimer for each of the picket fence densities. The right image shows single particle tracking on the lattice for both monomer and dimer.**

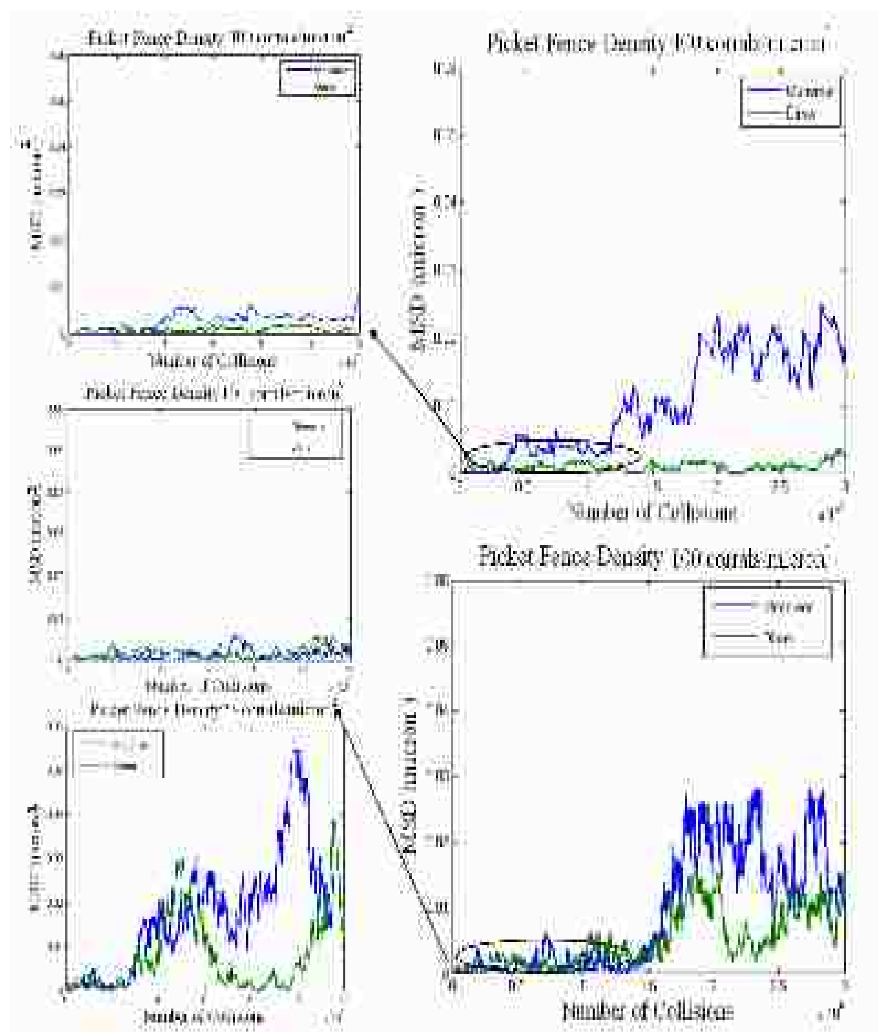


Figure 17. Mean Squared Displacement as a Function of Number of Collisions for Monomers and Dimers. The mean squared displacement is plotted as a function of number of collisions for both monomer and dimer for each of the picket fence densities. The densities of 400 corrals/μm^2, 100 corrals/μm^2, 25 corrals/μm^2 mean square displacements are plotted in lower left column. The right column shows 400 corrals/μm^2, and 100 corrals/μm^2 rescaled.

Oligomerization Induced Trapping

We wanted to determine if clustering is a result of oligomerization induced trapping. To test this we compare all three picket fence densities (25, 100, and 400 corrals/μm^2) in the presence (Figure 18 left column) and absence (Figure 18 right column) of ligand stimulus. Adding ligand stabilizes EGFR in an open confirmation, enabling receptors to form dimers. In these simulations receptors were not allowed to predimerize. When performing the analysis a dimer was counted as a single species, as are monomers. Performing the Hopkins statistic test and the Chi-squared test showed clustering when ligand was added, indicating that clustering occurs as a result of dimerization.

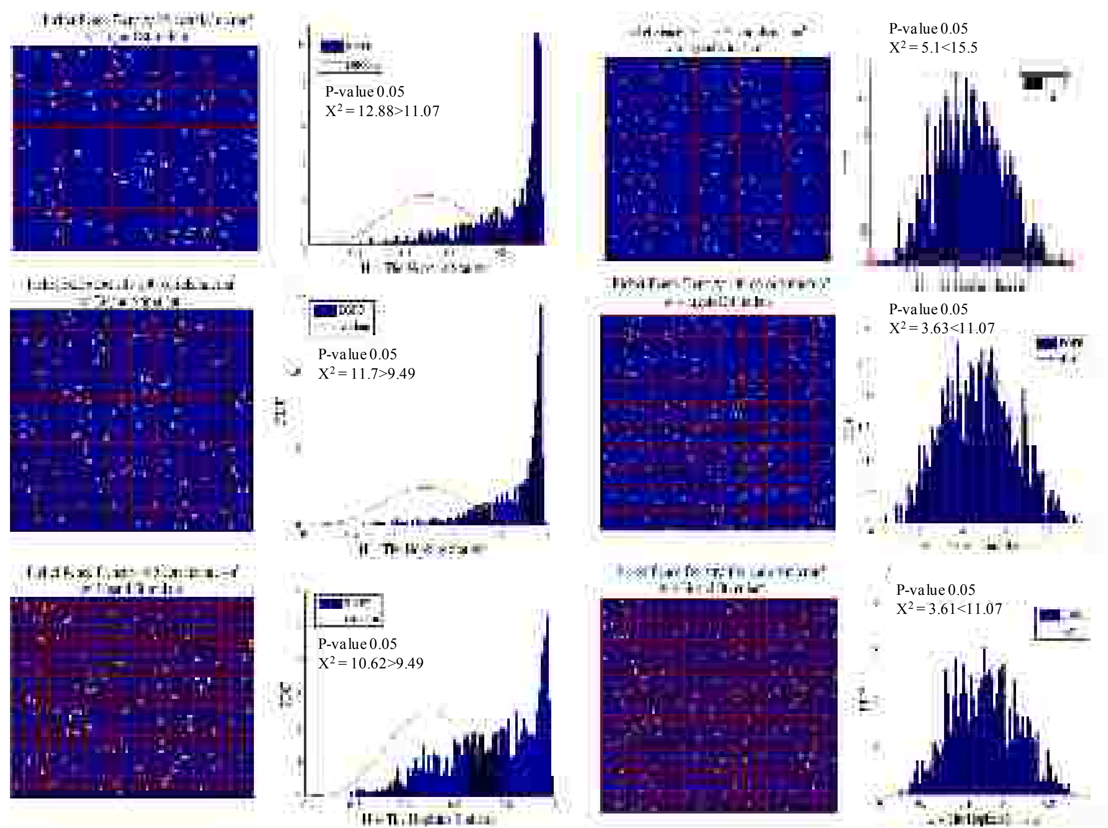
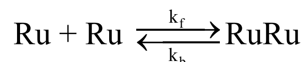


Figure 18. Oligomerization Induced Trapping. Right column shows system in the absence of ligand. Left column shows system with ligand. Rows are for 25, 100, and 400 corrals/μm^2 densities. All lattices are shown at 2s.

Predimerization vs. Dimerization

We wanted to test the effects of clustering for the case of predimerization vs. dimerization. An additional reaction was added to the system to account for dimerization in the absence of ligand,



with kf = 0.01 $(nM\ s)^{-1}$ and kb = 0.4 s^{-1} (Shankaran, Wiley et al. 2006). Simulations were carried out as before with receptors initially distributed randomly and then being allowed to diffuse as time progresses. The 100 fence/μm^2 picket fence density was used for both cases and simulations were carried out to 2s which is when dimerization reaches steady state.

The results are shown in Figure 19, where we see the initial effects of clustering for the predimerization simulation at a time of 1s (Figure 19, right column middle). This was confirmed through the Hopkins statistic which showed a shift in our data, as well as the Chi-squared value which was 10.23, greater than Chi-squared value of 9.49, disproving the null hypothesis. However as time increased to 2s the amount of clustering proved to be statistically similar, leading to the conclusion that pre-dimerization initially increase clustering.

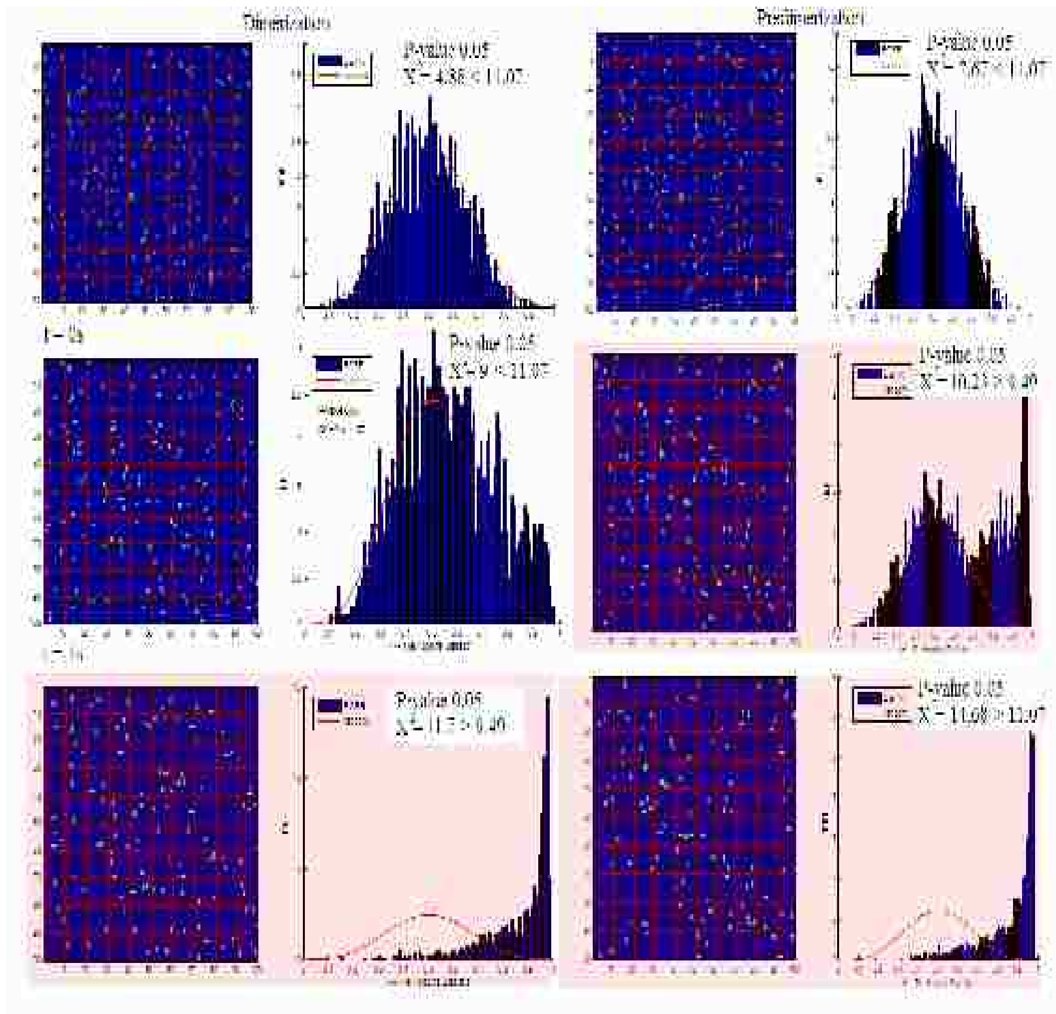


Figure 19. Dimerization vs. Predimerization. The picket fence density of 100 corrals/μm^2 is shown for both dimerization (left column) and predimerization (right column) at times 0s, 1s, and 2s (rows). The Hopkins test as well as the Chi-squared values are shown to the left of each lattice.

Discussion

The role that MSK microdomains, such as picket fences, have on receptor aggregation as well as downstream signaling has been controversial(Allen, Halverson-Tamboli et al. 2007). Some evidence indicates that picket fences may have an inhibitory role in cell signaling (Tank, Wu et al. 1982; Berk and Hochmuth 1992; Ganguly, Pucadyil et al. 2008), while other evidence points to an increase in receptor clustering which enhances downstream signaling (Douglass and Vale 2005; Heneberg, Lebduska et al. 2006; Chichili and Rodgers 2007). Through this work, we have shown that both are valid and dependent on the density of picket fences as well as receptor concentration. At low receptor concentrations (30 to 50 receptors per lattice) increasing picket fence density has an inhibitory effect on clustering; whereas at normal to high receptor concentrations, the greatest amount of clustering was observed at a picket fence density of 100 corrals/μm^2. Increasing from 200 to 300 (receptors per lattice), an increase in number of clusters occurs at the picket fence density of 400 corrals/μm^2. We hypothesize that at greater receptor concentrations there would be a shift in the number of clustering towards increasing picket fence densities.

The ability of the cell to synchronize cytoskeletal interactions in conjunction with signaling events has been shown experimentally (Nakada, Ritchie et al. 2003; Sheetz, Sable et al. 2006). Coordinating microdomain densities to regulate cell signaling could prove to be an important mechanism exploited during oncogenesis. Our data (Figure 13, Figure 16, & Figure 17) shows a time delay in clustering, which could activate some signaling pathways while suppressing other pathways. This time delay is dependent of picket fence density, at 400 corrals/μm^2, we see a shift in the data (Figure 13, left column

center) which indicates a more clustered state. This concept may be of importance to the activation of ERK, which can lead to either differentiation or proliferation dependent on its transient vs. sustained signal (Thrane, Schwarze et al. 2001; Sasagawa, Ozaki et al. 2005). Our results (Figure 19) showed clustering at 1s in the case of predimerization, whereas clustering was not observed until 2s for dimerization. These results support oligomerization induced trapping as a mechanism for clustering. Such a mechanism is further supported by looking at the MSD plots and the SPT simulations for dimers in comparison to their monomer components.

In summary our results show how microdomains on the plasma membrane can both inhibit and enhance clustering. When receptor aggregation is enhanced, oncogenic phenotypes, such as self-sufficiency of growth factors and an amplification of proliferative pathways, contribute to the diseased state. Often times oncogenic events are well coordinated and a mechanism of turning on and off signaling pathways via rearrangement of MSK could facilitate the cancer cell.

Acknowledgements

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Chapter 4. Adaptively Coarse Grained Monte Carlo Method for Capturing the "*Receptor–Sharing*" Mechanism

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Abstract

The concept of the cell being nothing more than a bag of enzymes has come to pass, in its place the understanding that spatial organization dictates the efficiency of signal transduction pathways. It has been understood for sometime that receptor collocalization is an important part of signal transduction. When receptors form aggregates signal is processed in an effective way, reducing the limitations imposed by diffusion. In this work we investigated the extent to which receptor collocaliztion enhances downstream signaling. We observed a significant increase in association rates in comparison to dimerization rates when receptors a clustered. This result leads to our hypothesis that a "receptor-sharing" mechanism exists and contributes to the overall efficiency of signal transduction. The "receptor-sharing" mechanism occurs when cytosolic species binds with a receptor then disassociates and rebinds a neighboring receptor. We tested our hypothesis using a novel computational approach, the ACGMC, an algorithm which enables the spatial temporal evolution of the system in three dimensions by using a coarse graining approach. In this framework we are modeling EGFR reaction-diffusion events on the plasma membrane while capturing the spatial-temporal dynamics of proteins in the cytosol. From this framework we observe "receptor-sharing" which may be an important mechanism in the regulation and overall efficiency of signal transduction.

Keywords: receptor-sharing, adaptively coarse grained Monte Carlo, ErbB Signaling, EGFR, spatial modeling,

Introduction

To respond to the complexities of their external environment and internal queues, living cells have evolved complex signal transduction pathways, which even surpass the complexity of modern processing units (*1-3*). Most signal transduction pathways originate at the plasma membrane with receptor-receptor ligand interactions, followed by receptor-receptor interactions establishing signaling scaffolds and platforms (*4-7*). The rate limiting step in a signal transduction pathway is often receptor-receptor interaction (*8-12*), i.e. dimerization which is diffusion limited and essential to the propagation of signal. The highly controlled process of dimerization is often disrupted in tumor cells which, overexpress receptors (*13, 14*).

The prototypical signal transduction pathway (i.e. the ErbB network) begins with a receptor, (i.e. tyrosine kinase receptor) binding to its ligand when present (*15*). A ligand bound receptor has a greater affinity (eg. conformational orientation) to then form a dimer with neighboring receptors (*8, 16, 17*). Upon dimerization, receptor activation is an autocatalytic process occurring on the time scale of 1 nM s^{-1} (*18*), for example, the C-terminal transphosphorylates very rapidly due to the close proximity of the tyrosine kinase tails. The phosphorylated receptor leads to the recruitment of cytosolic species: adaptor proteins (Grb2, Sos, Shc)(*19-22*), cytosolic membrane tethered species (PLC□, Ras, Rap)(*20, 23-26*), signaling scaffolds (KSR)(*27-29*), scaffold binding proteins (Raf, MEK) (*30-33*)and transcription factors (ERK)(*29, 33-36*). The signaling cascade establishes itself at the plasma membrane, making it the “hub” of signal transduction (*6, 25, 29, 37-39*).

Spatial organization (i.e. receptor clustering) is an important part of signal transduction, which is often neglected in systems biology when modeling with ODEs (*9, 18, 35*). Exemplifying the essentiality of clustering, are INFγ receptors which are expressed at low levels (*40*) ranging from (10^2 to 10^3 receptors per cell) on T-cells and macrophages that have a diameter ~20μm (*41*). The INFγ receptors are experimentally found, using techniques such as electron microscopy and immunoprecipitation, aggregated in caveolar domains; explaining how receptors expressed at low levels propagate signal (*40, 42, 43*). Another example illustrative of the need for receptors to colocalize, comes from the ErbB family of receptors which are observed in electron-microscopy images co-clustering (*13, 44*). It is known the formation of homo and heterodimers in the ErbB family leads to the activation of different signaling cascades(*33, 45*). The formation of ErbB1-ErbB1 homo, ErbB1-ErbB2 hetro dimer leads to PLC□, Grb2, and Shc activation while ErbB1-ErbB3 and ErbB1-ErbB2 initiates binding of multiple PI3K (*45*). Clustering facilitates dimerization and thus the activation of signal transduction pathways (*10, 46-48*).

A quantitative understanding of the receptor spatial organization and the downstream signaling proteins is still lacking. We previously showed though a novel algorithm, the *CSNSA*, how receptor clustering enhances downstream signaling. In a study investigating aspects of clustering (*49-51*) synthetic bivalent ligands for FcεRI were constructed from DNA fragments, and it was determined that the effective initiation of FcεRI requires receptor aggregation (*51*). However there has not been a mechanism to describe the effects of receptor aggregation on downstream signaling. Herein, we provide simulation results in support of the hypothesis that a "*receptor-sharing*"

mechanism exists such that a cytosolic species disassociating from its receptor can "*hop on*" or "*share*" a neighboring receptor when receptors are in the clustered state. Although such a mechanism is difficult to test experimentally, we have implemented a novel computational approach, the adaptively coarse-grained Monte Carlo, (ACGMC) (*52-54*) to test our hypothesis. In our mathematical model we are simulating the spatial-temporal interactions of EGFR on the plasma membrane while simultaneously capturing the spatial-temporal dynamics within the cytosol using a coarse-graining technique. To our knowledge this is the first coupled spatial-temporal membrane cytosol MC simulation.

Results

Cell Signaling Events are Dependent on Spatial Localization

Two spatial distributions of receptors were tested, a uniform distribution and a clustered distribution in which receptors cluster in a “lipid raft” with a size of 200 nm. Plotting dimerization vs. time (Figure 20A) we observe an increase in dimerization events for the clustered distribution when compared with the uniform distribution. Dimerization was enhanced when receptors were in the clustered distribution, to further investigate downstream signaling events we plot cytosolic binding events over time. and observe a transient increase in binding events. Figure 20B shows a much more dramatic difference between the clustered and uniformly distributed receptor conditions in terms of the number of binding events when compared with the number of dimerization events (Figure 20AB). This observation was suggestive of a mechanism that would enhance signal in the clustered state.

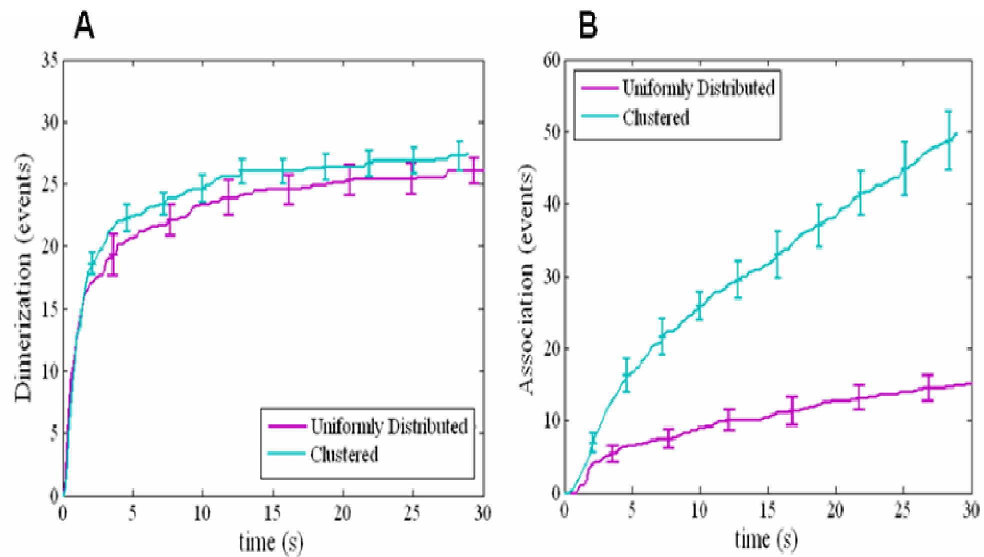


Figure 20. Reaction events for clustered vs. uniformly distributed receptor state. A) EGFR Dimerization (events) as a function of time. B) EGFR Association (events) for receptor binding cytosolic species as a function of time. Teal line: receptors clustered in a lipid raft of 200 nm. Magenta Line: receptors uniformly distributed.

Evidence of a Concentration Gradient

Observing an enhancement of cytosolic association events we hypothesized that a concentration gradient exists under the plasma membrane. To test this we looked at the total concentration of cytosolic species within the cytosol over time, where the total cytosolic species, CS is defined as $CS = Grb2 + Grb2Sos + Shc + pShc + pShcGrb2 + pShcGrb2Sos$. As cytosolic species bind with phosphorylated receptors on the plasma membrane the concentration of these species in the cytosol decreases, as is observed in Figure 21. Comparing receptors which are in a clustered state with those that are uniformly distributed we observe additional concavity (Figure 21) in the cytosolic profile of the clustered state. The solutions deviate significantly between ~3s and ~16s but as time progress the solutions appear to reach a steady state, with small differences in the solutions.

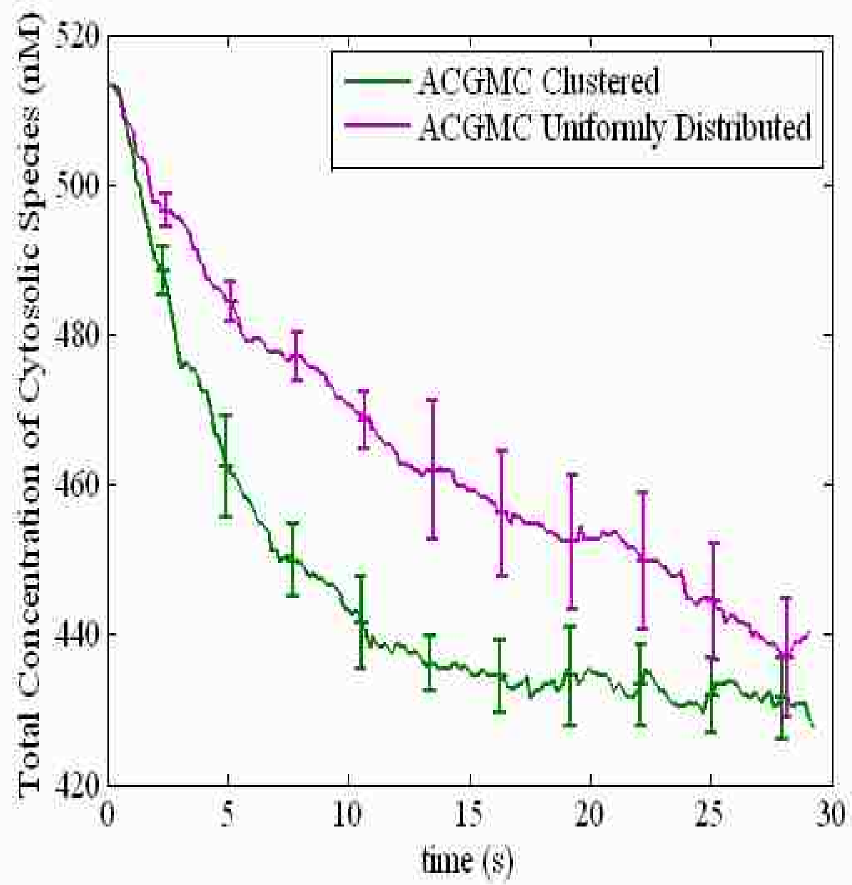


Figure 21. Concentration of cytosolic species over time. The temporal profile of the concentration of cytosolic species in units of nM. <u>Green line:</u> receptors clustered in a lipid raft of 200 nm. <u>Magenta Line</u>: receptors uniformly distributed.

The "Receptor-Sharing" Mechanism

In previous work we showed how receptor aggregation enhances downstream signaling (ref), however our results assume the cytosolic species are well-mixed. We now know that cytosolic species are not well-mixed and their spatial organization also plays a role in cell signaling. We hypothesize that receptor aggregation increases downstream signaling via a "receptor-sharing" mechanism. Figure 22 demonstrates the "receptor-sharing" mechanism; a cytosolic species (CS1) bound with a receptor (R1-CS1) in the clustered state disassociates and "hops" on a neighboring receptor (R2-CS1). In order to observe this mechanism we identified single particle tracking trajectories shown in Figure 23. Cytosolic trajectories are shown in green while cytosolic bound receptor #1 (R1-CS1) trajectories are in red and cytosolic bound receptor #2 (R2-CS1) trajectories are in blue. Figure 23A&B shows a cytosolic species bind to receptor, the receptor-bound species diffuses then disassociating rebinds a neighboring receptor a distance of 20 nm from the original receptor. The "receptor-sharing" event occurred within 80ms, the cytosolic species traveled 10 nm in the z-direction rebinding a receptor 20nm away from the original receptor that it had previously bound. An example of a rebinding event that is clearly not via the receptor sharing mechanism is shown in Figure 23C&D. In this trajectory the cytosolic species binds receptor, diffuses with receptor, disassociates, and enters the cytosol where it diffuses in the z-direction essentially entering a well mixed pool. After 30s the cytosolic species diffuses to the plasma membrane and rebinds receptor, a random event not captured by the "receptor-sharing" mechanism.

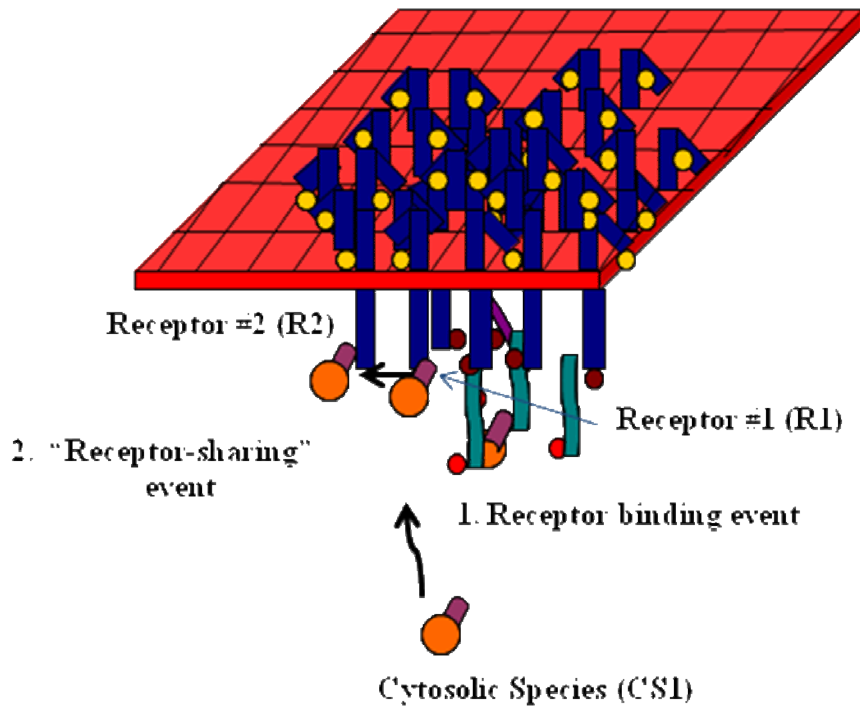


Figure 22. Schematic of "receptor-sharing". The cytosolic species (CS1) binds with receptor #1(R1) then undergoes a "receptor-sharing" event by disassociating with R1 and binding the neighboring receptor #2 (R2).

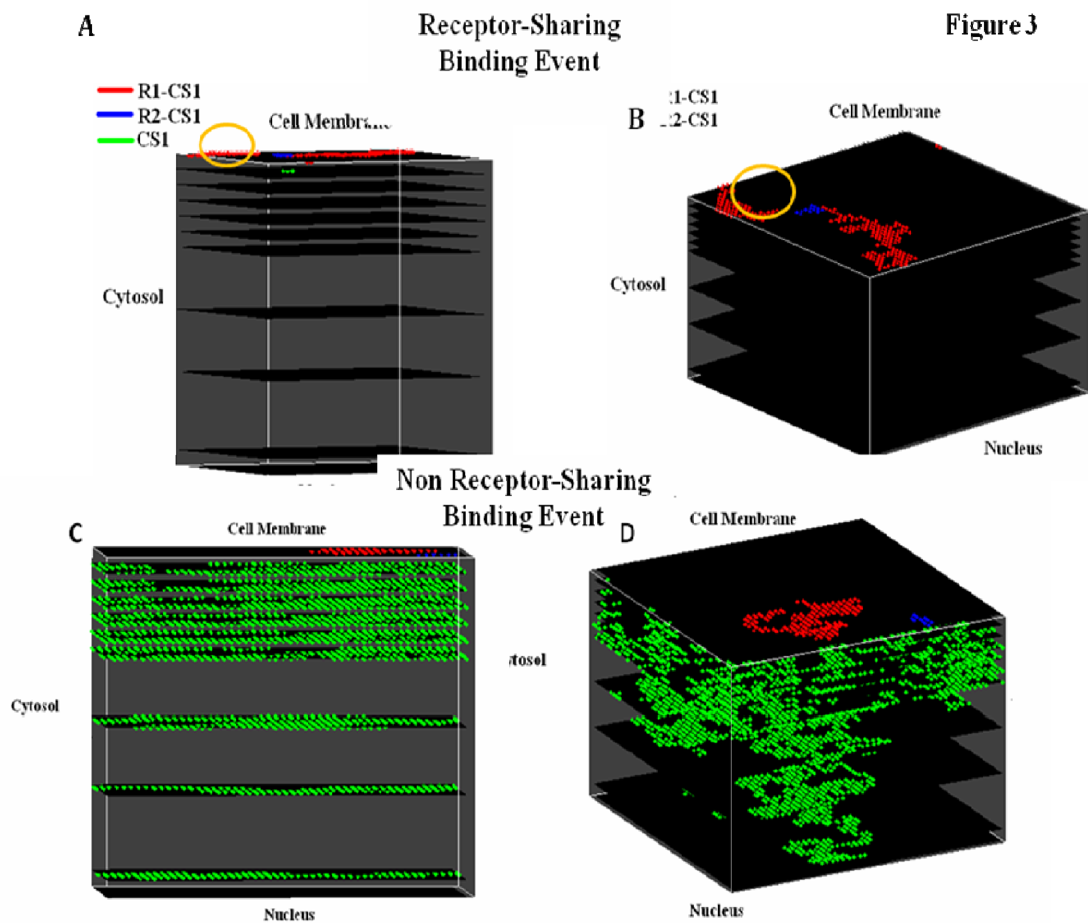


Figure 23. Single particle tracking of receptor-sharing and non receptor-sharing events. Three-dimensional SPT of cytosolic species (CS1), diffusing in the cytosol (green), diffusing on the plasma membrane while bound to receptor 1, R1-CS1 (red) or bound to receptor 2, R2-CS1 (blue). A) "Receptor-sharing" event circled in yellow as viewed in x-z plane B) as viewed in x-y-z plane. C) Non "receptor-sharing" event as viewed in x-z plane D) as viewed in x-y-z plane.

Quantifying the "Receptor-Sharing" Mechanism

In order to quantify the receptor sharing mechanism we calculated the time of receptor sharing, t_{RS} , being defined as

$$t_{RS} = \frac{\langle r \rangle^2}{6D_C}$$

in which $\langle r \rangle^2$ is the mean square displacement in a microdomain of size 0.3 μm (*55*) and D_C is the cytosolic diffusivity coefficient of 1 $\mu m^2/s$ (*56, 57*) . Calculating the time of receptor sharing we are able to quantify a receptor sharing event defined as a receptor binding event occurring within 0.05, seconds $t_{RS} \leq 0.05s$ after it has disassociated from a neighboring receptor.

Turning up cytosolic diffusion in essence eliminates "receptor-sharing". We preformed simulations by increasing cytosolic diffusion two orders of magnitude, 100$\mu m^2/s$. Figure 24 shows plots of the number of binding events as a function of time between binding events for normal cytosolic diffusion and high cytosolic diffusion. We observe a statistical difference in the data at 0.05s, with the number of receptor-sharing events being approximately ~5 for normal cytosolic diffusion and ~1 for high cytosolic diffusion. Performing a two-tailed t-test at 0.05s gives 10.25>6.5 with a 0.005 P-value, indicating the significance between the two distributions.

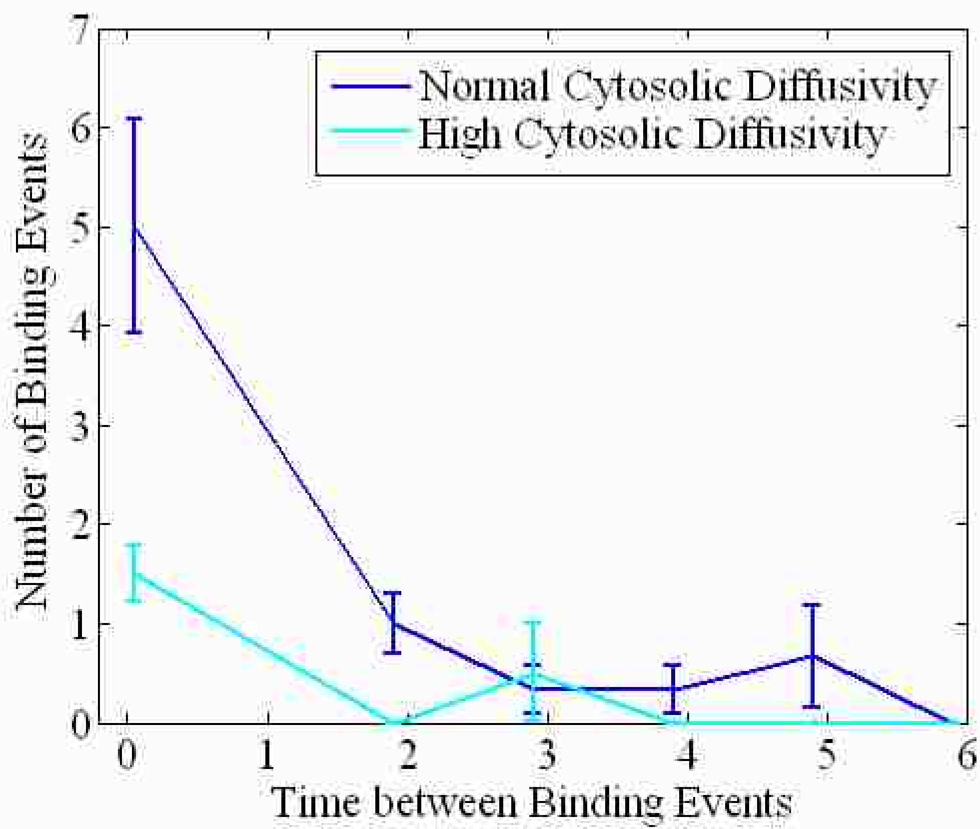


Figure 24. Number of binding events vs. time between binding events. Blue line: Cytosolic species with normal diffusion at 1μm²/s. Cyan line: with high cytosolic at 100μm²/s.

Inhibiting the "Receptor-Sharing" Mechanism

The mechanism of "receptor-sharing" may have important therapeutic applications. We added tyrosine kinase inhibitors, Iressa (Getfitinib) and Tarceva (Erlotinib) to our system. These inhibitors block signal transduction by competitively binding with the receptor's phosphorylation sites on the tyrosine kinase tail (concentration and binding kinetics are provided in the legend of **Figure 25**). We wanted to determine the effectiveness of TKI's at reducing the "receptor-sharing" mechanism. In **Figure 25**, we looked at the number of association events as a function of time for Iressa and Tarceva. The effects of Iressa appear to be more potent at reducing both association events and "receptor-sharing" events.

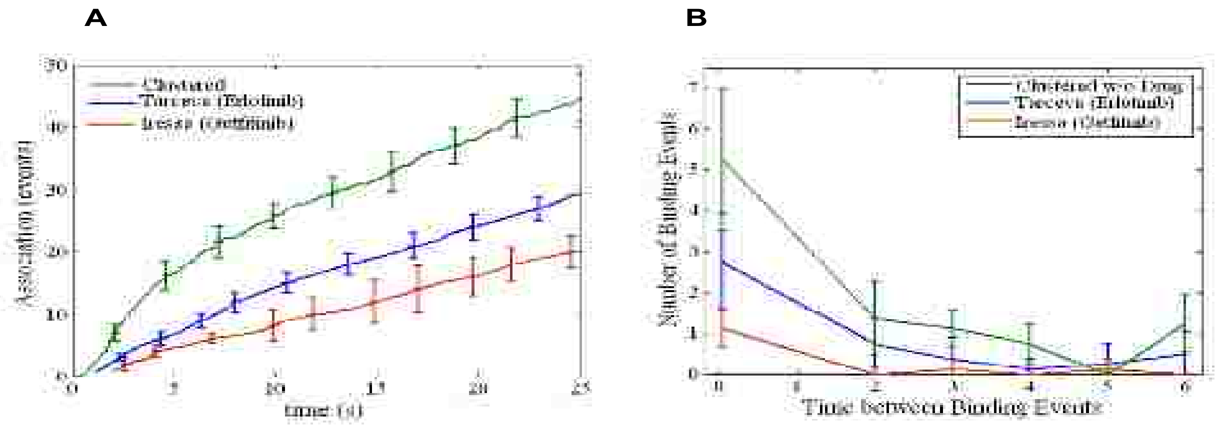


Figure 25. **Inhibition of the "receptor-sharing" mechanism. A) Association (events) vs. time (s) B) Number of binding events vs. time between binding events for <u>green line:</u> EGFR clustered in a lipid raft of 200 nm without drug, <u>red line:</u> treated with Iressa (Getfitinib), and <u>blue line:</u> treated with Tarceva (Erlotinib). An inhibitor concentration of 33 nM was used. Tarceva binding kinetics k_f = 3 nM^{-1} s^{-1} (*74*) and k_b = 1 s^{-1}, Iressa binding kinetics k_f = 0.7 nM^{-1} s^{-1} and k_b = 1 s^{-1} (*75*)**

Discussion

It has been established that receptor aggregation enhances the efficiency of signal transduction(*58-60*). With the underlying mechanism being that a local concentration gradient reduces diffusional limitations, thus increasing the number of dimers. Our results (Figure 20A) confirmed this statement, showing a slight increase in dimerization for receptors in the clustered state. However, when we looked at the number of association events the results were much more dramatic (Figure 20B), showing a significant increase in the number of association events for clustered receptors. These results were suggestive of an additional mechanism.

We hypothesized that a “receptor-sharing” mechanism exists and contributes to the overall efficiency of signal transduction. In our proposed “receptor-sharing” mechanism (Figure 22), a cytosolic species binds to a receptor, and then undergoes a “receptor-sharing” event by disassociating from the previously bound receptor and rebinding a neighboring receptor in close proximity. To confirm that the “receptor-sharing” mechanism exists we performed single particle tracking of cytosolic species. We observed a rebinding event which occurred via the “receptor-sharing” mechanism, disassociating and rebinding within 0.05s. In support of this mechanism, one would expect a concentration gradient to be established under the plasma membrane. This was confirmed by our results Figure 21, which showed additional concavity in the cytosolic concentration profile when receptor aggregation was present.

In order to quantify the “receptor-sharing” mechanism we established a time limit between disassociating and rebinding which would serve as a cut-off for classifying receptor binding events. The time limit was defined as:

$$t_{RS} = \frac{\langle r \rangle^2}{6D_C}$$

in which $\langle r \rangle^2$ is the mean square displacement, D_C is the cytosolic diffusivity coefficient, and 6 represents diffusion in three dimensions. The cytosolic diffusivity coefficient is two orders of magnitude higher in the cytosol than on the plasma membrane (*56, 57*). With measured receptor diffusivity coefficient being of the order 10^{-2} $\mu m^2/s$ (*56*) we used a cytosolic diffusivity coefficient of $1 \mu m^2/s$. We then defined an area, 0.03 μm^2, where "receptor-sharing" occurs. This area was based on the size of receptor aggregates (0.1-0.3μm) (*13, 44*) , microdomains (e.g. lipid rafts 0.02 ̃ 0.5 μm) (*55*), and membrane cytoskeletal corrals (0.03-0.3μm) (*61, 62*). The "receptor-sharing" event is thus quantified as disassociation event-rebinding event occurring within 0.05s.

In this work we tested TKIs to determine their effects on "receptor-sharing". Our results showed a decrease in association events and in "receptor-sharing" events when TKIs were added to the system. Given that "receptor-sharing" involves promiscuous signaling proteins interacting with receptors, and propagating signal more efficiently, this mechanism may be an important consideration for drug developers. Drug therapeutics which decrease "receptor-sharing" may be more effective at inhibiting signal propagation. The efficiency of "receptor-sharing" (unpublished data) is dependent on the binding kinetics, and thus therapeutics could potentially be tailored to reduce this mechanism. The "receptor-sharing" mechanism also hints at the selection of drug targets which may instead include promiscuous adaptor proteins.

It has long been established that signal transduction involves the coordination of proteins in time and space (*47, 63-67*). Experimental studies have shown disruption of

membrane recruitment reduces the amount of signal transduction (*66, 68, 69*). The plasma membrane, the nucleus of signal transduction, connects the extracellular with the intracellular via spatial organization of tethered membrane bound proteins, adaptor proteins, and signaling scaffolds (*15, 70-72*). The "receptor-sharing" mechanism may contribute significantly to this establishment. It may also prove to be a key regulator of signal transduction.

The predictive abilities of mathematical models enable us to test hypotheses which would be unattainable experimentally. In this work using a novel algorithm ACGMC, we tested our hypothesis that a "receptor-sharing" mechanism exists and contributes to the efficiency of signal transduction. Testing such a mechanism experimentally is not feasible using today's technology. With limitations such as cytotoxicity to probes, poor conjugation, endosomal uptake, and resolution limitations, the importance of mathematical approaches becomes evident. This work demonstrates the predictive capacity of mathematical modeling to go beyond the present technology and address important biological questions.

Materials and Methods

Adaptively Coarse-Grained Monte Carlo (ACGMC)

The Adaptively Coarse-Grained Monte Carlo (ACGMC) algorithm extends for three-dimensional spatial modeling building on our previous algorithm, the SKMC, by including nine additional lattices eight of which extend into the cytosol and a lattice at the cytosol nucleus boundary. This framework allows us to study the formation of signaling scaffolds and to observe concentration gradients which result from these scaffolds.

The ACGMC, like the SKMC, begins by selecting a spatial location which could be either the cell membrane (1st lattice) or cytosol (2nd-9th lattices) or the nucleus (10th lattice). The selection is made by computing the probabilities for a spatial event (lattices 1-10).

$$P_{Lat\#1} = \frac{\Gamma_{tot,Lat\#1}}{\Gamma_{tot}},$$

$$P_{Lat\#2} = \frac{\Gamma_{tot,Lat\#2}}{\Gamma_{tot}}, \text{and}$$

$$\ldots P_{Lat\#10} = \frac{\Gamma_{tot,Lat\#10}}{\Gamma_{tot}} \quad (1),$$

where Γ_{tot} is defined as,

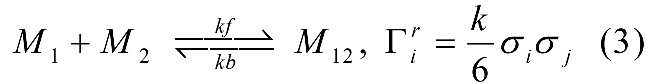
$$\Gamma_{tot} = \sum_{i=1}^{10} \Gamma_{tot,Lat\#i} \quad (2).$$

The probability distribution for the lattices, $\Gamma_{tot,Lat\#i}$, is defined as the sum of all transition rates for all SKMC events; however, the events differ in dimensionality and

type as shown in Table I. For example, on the cell membrane (1st lattice) receptors diffuse in 2D but react with cytolic species (2nd lattice) on the lattice below such that reaction occurs in 2.5D. In the cytosol (3rd-9th lattice) species are able to diffuse and react in 3D. Cytosolic species in the boundary lattice which borders the cell membrane (2nd lattice) are able to react with neighboring receptors on the cell membrane but are not allowed to diffuse onto the membrane. At the boundary nucleus (10th lattice) species diffuse and react in 2.5D.

In the cytosol the following reaction occurs: $M_1 + M_2 \underset{kb}{\overset{kf}{\rightleftharpoons}} M_{12}$, such that the product M_{12} occupies the single site k. This reaction is valid due to the large site separation distance of 10 nm in comparison to the small molecular masses of cytosolic species Shc, Grb2, and Sos 62 kDa 25 kDa, 11 kDa (*20, 22, 73*).

Once a lattice is chosen an event is selected, either reaction or diffusion for the SKMC algorithm as shown in Figure 26. Events are chosen, as in our previous algorithm(*48*), with the exception of dimensionality which changes the way $\Gamma_{\max}$ and Γ_i^X are computed. The transition probabilities for cytosolic reactions in 3D are



$$M_1 + M_2 \underset{kb}{\overset{kf}{\rightleftharpoons}} M_{12},\ \Gamma_i^r = \frac{k}{6}\sigma_i\sigma_j \quad (3)$$

in which reacting species (M_1 and M_2) occupy adjacent sites i and j and k has units of $(\text{molecules/site})^{-1}\text{sec}^{-1}$. Diffusion in 3D is taken into account similarly

$$\Gamma_{i\to j}^d = \frac{1}{6}\Gamma^d\sigma_i(1-\sigma_j)\ j \in B_i \quad (4)$$

where B_i denotes the set of sites to which diffusion from site i can occur.

Table I lists all events, both reaction and diffusion, which make up $\Gamma_{\max}$. $\Gamma_{\max}$ is defined as before but multiplying by a factor of 6 for all 3D event, by a factor of 4 for all 2D events, and a factor of 5 for all 2.5D events such that

$$\Gamma_{\max} = 4\left(\frac{\Gamma^d}{4} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right)_{2D\ \text{Events}} + 5\left(\frac{\Gamma^d}{5} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right)_{2.5D\ \text{Events}}$$
$$6\left(\frac{\Gamma^d}{6} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right)_{3D\ \text{Events}} + \max\left\{\sum_{\text{all backward reaction events}} \Gamma^r\right\} \quad (5)$$

The ACGMC operates like a single MC in which time is updated in a "combined" manner from Γ_{tot} with an average time step as, $\Delta t = \frac{1}{\Gamma_{tot}}$. Execution times vary depending on a chosen algorithm. The complete algorithm, which is shown in Figure 26, was implemented in Fortran 90. Due to the stochasticity of the algorithm, 10 simulations with different seeds for the random number generator were used for statistics.

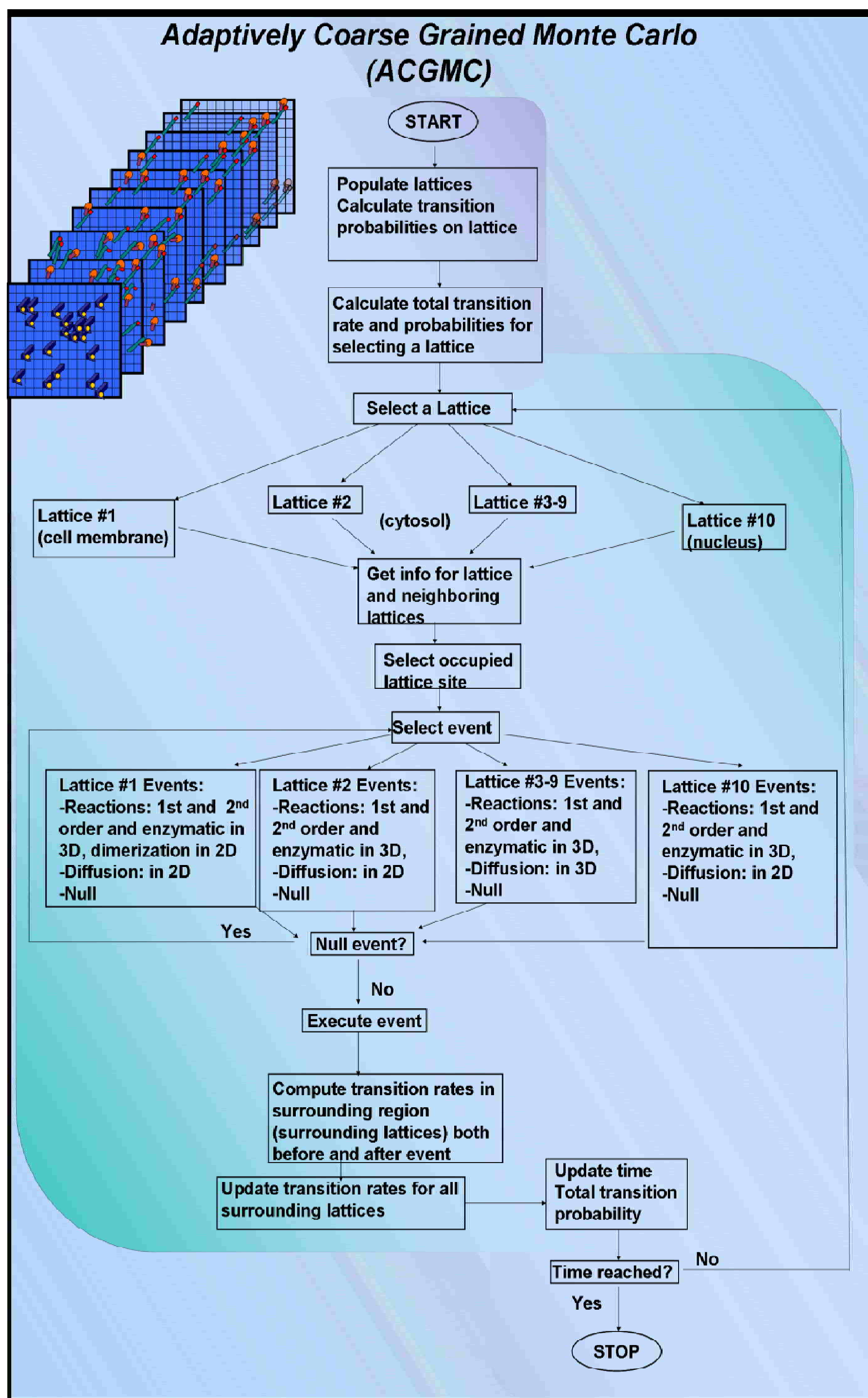


Figure 26. Adaptively Coarse Grained Monte Carlo (ACGMC). Schematic of algorithmic details.

Adaptively Coarse-Graining & Diffusion Transition Rates

In ACGMC, we introduce coarse-graining by grouping microscopic sites into coarse cells, as shown in Figure 27. In our modeling schematic lattices one thru seven have microscopic spacing while lattices eight thru ten are coarse grained in the z-axis. Each coarse lattice L_C has m_x, m_y, and m_z coarse cells along x, y, z, such that the total number of cells is $m = m_x m_y m_z$. Each coarse cell $C_j\left(1 \le j \le m\right)$ has q_j microscopic sites, in which $q_j = q_j^x q_j^y q_j^z$ is the number of microscopic sites in C_j along x, y and z axis. Diffusion between coarse-grained cells was rigorously derived by Chatterjee et al. (*52*),

$$\overline{C}_m(j \to i) = \frac{\Gamma_d}{q_j^z\left(q_j^z + q_i^z\right)}\eta_j(1-\overline{\eta_i}) \quad (6)$$

in which, Γ_D is the diffusion transition rate, η_j, is the coarse-grained occupancy function at C_j is defined as

$$\eta_j = \sum_{p \in C_j} \sigma_p \quad (7).$$

While the occupancy of a coarse cell is in terms of the coarse cell coverage,

$$\overline{\eta}_j = \frac{1}{q_j} \sum_{p \in C_j} \sigma_p \quad (8)$$

which for the microscopic case reduces down to either zero for unoccupied or one for occupied.

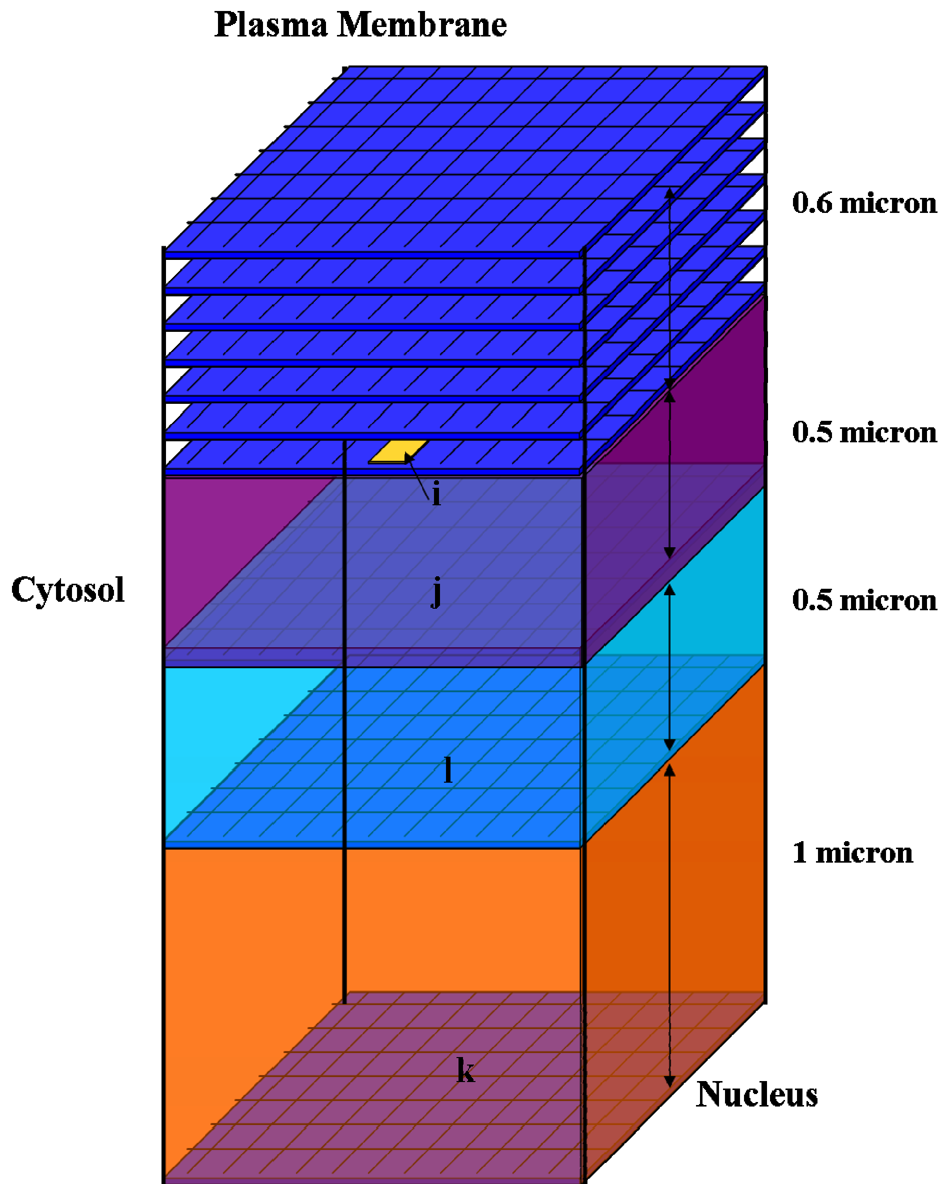


Figure 27. Modeling Schematic. 1st lattice is the plasma membrane, lattices 2-10 are within the cytosol, lattice 10 is the cytosol-nucleus boundary. Lattices 1-7 have microscopic spacing of 10 nm, while lattices 8-10 are coarse grained with spacing of 0.5�m, and 1 �m.

Validation of Approach

In order to validate our approach we initially placed all molecules within lattices one thru nine and allowed them to diffuse a distance of 1□m into lattice ten over time. Turning off reaction we have reflective boundary conditions at the cytosol membrane boundary (lattice two) and at the cytosol nucleus boundary (lattice 10) and periodic boundary conditions in the plane parallel to the plasma membrane. Using a diffusivity coefficient of $10\mu m^2\ s^{-1}$ and a distance 1μm and implementing reflective boundary conditions we compared the ACGMC with the PDE solution. Starting with a cytosolic species concentration 105 nM we observe similar predications between the ACGMC and PDE profiles (Figure 28).

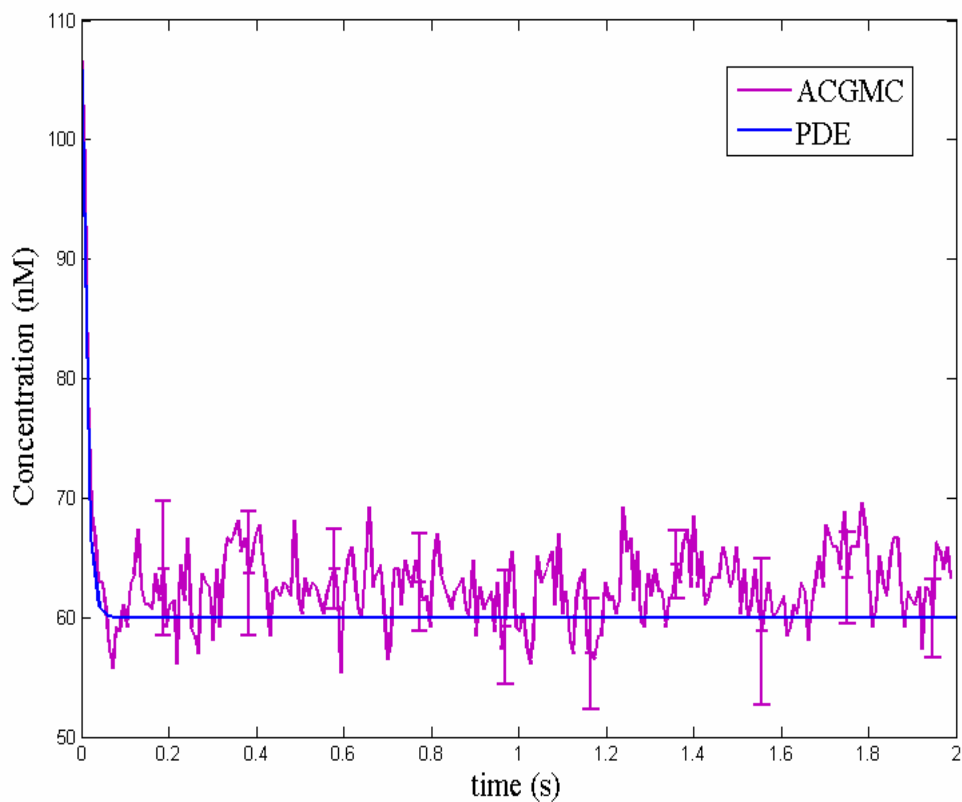


Figure 28. Validation of ACGMC. Concentration profile of cytosolic species (nM) at diffusivity of 10μm^2/s and a distance of 1μm. <u>magenta line:</u> ACGMC <u>blue line:</u> PDE.

Table 5. Membrane & Cytocolic Microscopic Events and Transition

Microscopic event	Transition Rate	Lattices
Diffusion	$\Gamma_{i\to j}^{D}=\frac{1}{L_d}\Gamma^{d}\sigma_i\left(1-\sigma_j\right)\ j\in B_i$ - σ_i is the occupancy (discrete) that is 1, if site i is filled, and 0, if site i is empty (a single index indicating the site is used to simplify notation). - $\Gamma^{d}=D/a^2$, where a is the microscopic lattice pixel dimension taken equal to the encounter radius, and is the diffusivity of a receptor - L_d is the dimensions in which a particle can move in - B_i denotes the set of sites to which diffusion from site i can occur and is dependent on selected lattice for nearest neighboring sites	$L_d=4$ for Lattice #1 (cell membrane) $L_d=5$ for Lattice #2 & #10 (boundary lattices) $L_d=6$ for Lattices #3-#9 (cytosolic lattices)
Ligand Association Reaction $\left(S_L+M\xrightarrow{k}M^*\right)$	$\Gamma_i^R=k\left[S_L\right]\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #1 (cell membrane)
Ligand Dissociation Reaction $\left(M^*\xrightarrow{k}S_L+M\right)$	$\Gamma_i^R=k\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #1 (cell membrane)
Dimerization Reaction $\left(M^*+M^*\xrightarrow{k}D\right)$	$\Gamma_i^R=k/2\,\sigma_j\sigma_i$ - k is the macroscopic reaction rate constant with units as [(receptors/site)$^{-1}$s^{-1}].	Lattice #1 (cell membrane)
Decomposition Reaction $\left(D\xrightarrow{k}M^*+M^*\right)$	$\Gamma_i^R=k\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #1 (cell membrane)
Phosphorylation/Dephosphorylation Reaction $\left(D\underset{k}{\overset{k}{\rightleftarrows}}pD\right)$	$\Gamma_i^R=k\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #1 (cell membrane)
Cytosolic Association Reaction $\left(M_1+M_2\xrightarrow{k}M_{12}\right)$	$\Gamma_i^R=k\sigma_j\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #1 (cell membrane-cytosolic)
Cytosolic Disassociation Reaction $\left(M_{12}\xrightarrow{k}M_1+M_2\right)$	$\Gamma_i^R=k\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #1 (cell membrane-cytosolic)
Cytosolic 1st Order Reaction $\left(M_C\xrightarrow{k}M_C^*\right)$	$\Gamma_i^R=k\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #2-#10 (cytosolic-cytosolic)
Cytosolic Dimerization Reaction $\left(M_1+M_2\xrightarrow{k}M_{12}\right)$	$\Gamma_i^R=k\sigma_j\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #2-#10 (cytosolic-cytosolic)
Cytosolic Decomposition Reaction $\left(M_{12}\xrightarrow{k}M_1+M_2\right)$	$\Gamma_i^R=k\sigma_i$ - k is the macroscopic reaction rate constant with units as [s^{-1}]	Lattice #2-#10 (cytosolic-cytosolic)
Cytosolic Flux Event	$\Gamma_{i,Lat}^{J}=D(C_{Lat}-C_{SSA})r_{SSA}(1-\sigma_j)\ j\in B_i$ - C_{Lat} is the concentration of a given species within the spatial domain with units of [molecules/μm^3] - C_{SSA} is the concentration of a given species within the well-mixed domain with units of [molecules/μm^3] - r_{SSA} is the radius of the cell minus the cytosolic spatial domain - σ_j is the occupancy (discrete) that is 1, if site i is filled, and 0, if site i is empty (for lattice #10). - D diffusivity coefficient - B_i denotes the set of sites to which species can be populated on Lattice #10	Lattice #10-SSA (cytosolic lattice-cytosolic well mixed)

Chapter 5. Future Work

Introduction

The Human Genome Project was one of the first modern biological endeavors which altered the way in which biology was practiced. Producing vast amounts of data the necessity became analysis and the need to develop computational tools. Data analysis of the human genome revealed higher order complexity and connectivity providing a new systematic prospective to biology. Unlike the reductionistic approach in which components are studied in isolation, the systematic approach investigates the role of a component within the system in order to understand the dynamics and stability of that system. Mathematical modeling has become essential to the systematic approach, with the ability to make predictions of the evolving system in time and space.

In this work I have showed mathematical models complementing experimentation with the ability to make novel predictions which may be unattainable experimentally. I envision this work proceeding in two directions: the first to make algorithmic improvements and increase computational efficiency, and the second to make future biological predictions of cell signaling processes. I will discuss each of these directions along with current work.

Computational Improvements

The algorithms which were developed implement a hybrid null-event spatial kinetic Monte Carlo, SKMC method. The algorithm calculates probabilities for every event, by calculating the maximum transition rate, $\Gamma_{\max}$ which is defined as

$$\Gamma_{\max} = 4\left(\frac{\Gamma^d}{4} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right) + \max\left\{\sum_{\text{all backward reaction events}} \Gamma^r\right\}$$

where four takes into diffusion in two-dimensions on the plasma membrane. The probability for a given event is then defined as $P_i^X = \frac{\Gamma_i^X}{\Gamma_{\max}}$ the transition rate Γ_i^X for the given event divided by the the maximum transition rate. The algorithm will then select an occupied lattice site and update diffusion and reaction probabilities based on the state of the system. The maximum transition rate is greater than reaction and diffusion transition rates which gives rise to a null event probability P_i^{null} . Using this method events with low probabilities are penalized with additional null events. Incorporating null events means loss of computational time in selecting an occupied lattice site, determinging probabilites based on neighboring species, and selecting an event.

Although the null-event algorithm has been used throughout this work computational efficiency could be improved by making this a rejection free algorithm. The stochastic simulation algorithm, SSA is an example of a rejection free method in which probabilities are determined by computing a total transition rate, $\Gamma_{total} = \sum_{X=1}^{N_j} \sum_{i=1}^{N_L} \Gamma_i^X$ for all lattice sites, N_L and all events, N_J . Probabilities are then defined as $P_i^X = \frac{\Gamma_i^X}{\Gamma_{total}}$. In order to eliminate the null bin, the total transition rate would be dependent on the state of the system.

Parralliziation would be the next step to improving the overall algorithm efficiecy. The *CSNSA* code could be parrallized in such a way that the lattice would be broken up into quadrants. Information would be passed between the quadrants using MPI. The most logical way to parrallize the *ACGMC* algorithm would be to break up the lattices and submit them to different processors. The current *ACGMC* algorithm operates in a similar

fashion by sending information about the current lattices as well as the surrounding lattices to the MC subroutine. Modifications would be made by implementing MPI to pass information between lattices. Parraliziation I would expect to result in the greatest computational speedup.

Computational Predictions

Understanding the impact of IFNγR clustering on immune response pathways

Introduction

Within a sea of lipids, a highly compartmentalized landscape exists, limiting the diffusion of signaling receptors and altering the spatial-temporal activation of signaling pathways. In this work we have unraveled the intricacies of spatial organization of the ErbB receptors and downstream signaling pathways, showing that clustering enhances signal transduction via "receptor-sharing" mechanism andthat the MSK is a mechanism of receptor clustering. However, in order to come full circle, an understanding of how signal transduction regulates protein expression levels that as a result, restructures the plasma membrane, needs to be further elucidated.

Background

Caveolin-1, a 22-24 kDa integral protein, is the backbone to caveolar microdomains, and its expression level determines the number, size, and flexibility of caveolar domains. Caveolin-1 is regulated by many signal transduction pathways; PKCε and androgen receptor signaling pathways lead to its upregulation whereas MAPK-Ras, c-Myc, INFγR leads to its down regulation. A431cells with decreased caveolin-1 expression have diverse membrane morphologies that alter the spatial organization of signaling receptors.

Electron microscopy images show interferon-γ receptor, INF□R, collocalized within caveola microdomains. INFγR, being responsible for the activation of macrophages during the early steps of innate immunity, induces direct antimicrobial mechanisms and up-regulates antigen processing and presentation pathways. Interferon-γ activates these immune responses via the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway. The initial signaling events of IFNγR are often the rate-limiting step and dependent on the spatial distribution of the IFNγR.

Experimental evidence shows that the relationship between IFNγ and caveolar domains goes beyond spatial organization on the plasma membrane, gene networks of caveolin-1, and IFNγseem to be entwined. Stimulating macrophages with IFNγ had an inhibitory effect on caveolin-1, the marker protein of caveola. In addition, when transfecting cell lines HT20 and DLD1with caveolin-1 cDNA, there is downregulation in iNos, a metabolic product of INFγ immune response.

Motivation

A complex regulatory network exists between caveolin-1, INFγand iNos. This is a model system to explore two relationships: colocalization of IFNγR on downstream signaling pathways, and protein expression levels on the structure of caveolar microdomains. In order to elucidate these relationships, a novel computational approach must be developed which would combine a spatial stochastic algorithm (CSNSA) with a deterministic circuit-based platform (BioXyce). This would enable spatial-temporal receptor dynamics to be coupled with regulatory and metabolic networks.

Approach

The computational challenges of this work are coupling deterministic and stochastic approaches which require the appropriate closure. A stochastic closure similar to that used in Katsoulakis et al. would be implemented. The hybrid algorithm would use the CSNSA to capture receptor diffusion reaction events on the plasma membrane, and the BioXyce circuit simulator would be implemented in the cytosol, nucleus, and mitochondria to simulate regulatory, metabolic, and signal transduction processes.

The coupled system would operate like a single MC with a stochastic variable time step Δt_s. Probabilities would be computed for the MC, based on transition rates for reaction diffusion events (MC). The MC algorithm would be iterated until a successful event is executed and time is updated $\Delta t_s = \frac{1}{\Gamma_{tot}}$ in which Γ_{tot} is the total of the transition rates. The MC would pause and the ODE would be executed for the time step, Δt_s. The procedure would be iterated until the final time is reached. Simulations would compare the hybrid algorithm with the CSNSA to verify appropriate levels of noise and temporal profiles of species.

Simulations

To elucidate the relationship between caveolin-1 and INFγR, we will perform simulations at different concentrations of caveolin-1 and test the downstream signal propagation. We will then look at the upregulation and downregulation of gene networks based on different levels of signal. Gene networks will determine the protein expression levels of caveolin-1 and thus alter the size, density, and number of caveolar microdomains. Simulations will be preformed, looking at different combinations of regulatory networks and observing the diffusivity of INFγR through the caveolar microdomains. This work will be presented at the Q-bio conference, Santa Fe, for further details refer to Appendix B. It will be written up in a manuscript.

A Monte Carlo Based Approach for Determining Optimal Drug Efficacy in Different Cytoskeletal Distributions

Introduction

In the previous work we investigated various cytoskeletal densities in order to determine the effects on receptor clustering. Our results showed different receptor dynamics being dependent on cytoskeletal density. Experimental techniques show the MSK to vary in general morphology and distribution in different cell types. Based upon these fundamental differences in the cytoskeletal distributions, drug therapies can be tailored to specific tissue types. Although drugs have been designed for maximum potency in the past, emerging evidence suggests that the drug's disassociation rate may be altered to maximize signal as well as reduce densensitization. We hypothesized that optimal drug parameters are dependent on MSK density. Using a computational approach, we have tested different dissociation constants in various MSK densities, with the goal of finding an optimal drug design criteria that is specific for different cell types.

Background

Recent work using single particle tracking has revealed that the density of the MSK varies with cell type. Measurements of time proteins spent in confinement yield compartment sizes ranging from 32 nm for CHO-B1 cells to 230 nm for normal rat kidney fibroblast (NRK) cells. Similarly, three-dimensional reconstructed images of the plasma membrane in NRK cells and FRSK cells revealed differences in MSK density. The variation in MSK density appears to be of physiological significance, as observed in hippocampal neurons. These specialized cells contain a diffusional barrier highly concentrated with the MSK and transmembrane proteins located between the

somatodendritic and axonal domains, limiting the diffusion of even phospholipids. Such diffusive barriers have been observed in tight junctions, the neck of the bud in budding yeast, and between compartments in sperm. Although few studies have investigated the variation in MSK density and its role in cellular function, one could hypothesize that the diversity of MSK densities facilitates cell type specific physiology.

Motivation

With such variation in the MSK, we propose the concept of tailoring therapeutics with cell specificity in mind, an idea which to our knowledge has not been suggested before. Our hypothesis is that the membrane cytoskeletal distributions have diverse drug-binding parameters, k_{off} which correspond to optimal inhibition. The motivation for our hypothesis comes from previous work done by Woolf et al., performing Monte Carlo (MC) simulations a minimum rate of G-protein-coupled receptor (GPCR) phosphorylation was observed at an intermediate koff value. Their results were explained in terms of the spatial-temporal dynamics of receptors at different k_{off} parameters.

Approach & Results

In this work we have implemented a lattice-based spatial kinetic Monte Carlo (SKMC) algorithm which incorporates "picket-fence" boundaries enabling us to test different membrane cytoskeletal densities. Adding a drug to our system that inhibits epidermal growth factor receptor (ErbB or EGFR) homo and hetero dimerization, we are able to determine the optimal binding parameter k_{off} at a given cytoskeletal density. Our results show optimal inhibition at koff values of 100 s^{-1}, 8500 s^{-1} in the case without picket fences and at 100 s^{-1}, and 6000 s^{-1}at a picket fence distribution of 25 corrals/μm^2.

Future work

Future work will explain our results by computing the mean square displacement, MSD for all receptors bound to drug for a given k_{off} value. The results will show the MSD traveled by receptors bound to drug for a specific koff parameter, enabling us to compare

and contrast MSD as a function of time for different k_{off} parameters. This work is being prepared in a manuscript (see Appendix C.).

Microdomains and the Underlying Cytoskeleton Alter the Efficiency of "Receptor-Sharing"

Introduction

In our previous work we quantified the "receptor-sharing" mechanism;however, understanding the "receptor-sharing" mechanism in terms of microdomains and that the underlying cytoskeleton is of biological importance. In this work we implemented the ACGMC algorithm with microdomains and at different picket fence densities.

Background

Signal transduction, the cell's communication network, comes to a crossroads on the highly compartmentalized plasma membrane. Often oversimplified in mathematical models, the plasma membrane is a facet of heterogeneity that alters receptor organization from transient confinement zones or signal transduction "hot spots" to depletion zones. The spatial heterogeneity of receptors comes as a result of sphingolipid-rich microdomains 'lipid rafts', caveolar formation, clathrin cages, and the hindering interactions with the membrane cytoskeleton. Diffusional limitations are the result, herein altering the initiation and activation of signal transduction pathways. Localized concentration gradients become a consequence of the membrane architecture and enhance the efficiency of signal propagation.

Motivation

Signal transduction and plasma membrane microdomains have typically been studied in isolation. Although growing evidence shows their intimate nature, with coalescing lipids and transient meshes altering signal transduction which come full circle, activating transcription factors that regulate protein expression levels on the cell membrane. The motivation for this work is to understand signal transduction in the contest of membrane microdomains. Using the adaptively coarse-grained Monte Carlo (ACGMC), we observe signal transduction in terms of our previously proposed "receptor-sharing" mechanism under various microdomain conditions.

Future Work

We preformed simulations which compare receptor sharing in different plasma membrane conditions such as lipid rafts, and with the underlying membrane cytoskeleton. Simulations have been run to test receptor sharing within lipid rafts at different parameters such as lipid raft size and receptor diffusivity through a lipid raft. Similarly, we have tested receptor sharing at three different MSK densities at varying receptor concentrations. Future work will include running additional simulations at biologically relevant diffusivities in lipid raft domains. The data will be further interrupted by quantification of the "receptor-sharing" mechanism and be presented in the most appropriate figures. This work will be written up in a manuscript; preliminary results are presented in Appendix D.

Monte Carlo Simulations Reveal Formation and Activation of the MAPK Pathway

Introduction

In our previous work we have looked at several mechanisms that are applicable for other signal transduction networks. In this work we investigate the mitogen-activated protein kinase, MAPK pathway to determine mechanisms of efficiency and adaptability. We utilize the adaptively coarse- grained Monte Carl (ACGMC) algorithm to observe the spatial temporal dynamics of scaffold formation.

Background

Signal transduction pathways process internal queues, relaying information that brings about a physiological response. Within this finely tuned system are mechanisms for efficiency and adaptability; to illustrate this are signaling scaffolds. The function of signaling scaffolds is similar to a circuit board in that both upstream and downstream signaling proteins can be spatially arranged and compartmentalized signaling nodes. Scaffolds are often necessary to catalyze enzymatic reactions, phosphorylate or dephosphorylate kinases, and to facilitate both positive and negative feedback loops.

Among the most extensively studied signaling scaffold systems is the mitogen-activated protein kinase, MAPK pathway which in mammalian cells regulates many key cellular processes such as proliferation, survival, motility, and differentiation. The initial signaling events in the MAPK pathway involve receptor ligation, dimerization, and phosphorylation which initiate the recruitment of adaptor signaling proteins such as Grb2 (growth factor receptor-binding protein 2), Shc (Src homology 2 and collagen domain protein), and SOS (son of the sevenless). The interactions of these adaptor proteins mimic the functionality of signaling scaffolds. Grb2 through its SH2 domain binds phosphorylated tyrosine residues of either EGFR or Shc and also has the capability of binding the guanine nucleotide exchange factor (GEF) SOS through its N-terminal SH3 domain. SOS exchanging a guanine transforms membrane bound (Ras–GDP) to its active form (Ras-GTP), thus inducing the MAPK pathway.

The aggregation of EGFR trickles down to the signaling cascade, effecting the spatial distribution of signaling scaffolds. A receptor bound scaffold in close proximity with another receptor can disassociate and then reattach to the proximal receptor,

enabling "receptor sharing" to occur between proteins in the signaling cascade. The effect of spatial distribution on signaling scaffolds has not been well elucidated. In this study we aim to uncover the downstream effects of receptor aggregation on the formation of signaling scaffolds.

Future Work

Implementing the Sasagawa et al. model of the MAPK pathway in the ACGMC, we will ask what cytosolic species are better at "receptor-sharing." We will test binding rate affinities to observe optimal "receptor-sharing." We will look at phosphotases and their receptor-sharing abilities and how they can dramatically alter signal transduction. We will cluster receptors to see if this leads to a colocalization of the Ras membrane-tethered protein. We will observe the formation of signaling scaffolds to observe its spatial temporal dynamics.

Conclusions

In the post Human Genome era, a new vision of personalized medicine is emerging which will be obtained through decades of multidisciplinary research that undoubtly will build its foundation from predictions of mathematical models. Personalized medicine could entail going to a doctor having your human genome sequenced, analyzed, and a mathematical model generated which would describe cell signaling processes, gene and metabolic networks. The mathematical model would be personalized built from a patient's genome and updated overtime. The personalized model could determine optimal drug treatment, and therefore provide patient specific care.

Although such a vision is beyond the horizon it will be achieved by multidisciplinary approaches relying on both experimentation and theory. It will incorporate the understanding of spatial-temporal dynamics of signaling proteins and its connection will the compartmentalized plasma membrane. This work will serve as a minute stepping stone in the direction of personalized medicine.

Appendix

Appendix A. The effective kinetic rate constant for diffusion-reaction problems derived by Lauffenburger and Linderman is

$$k_{PDE} = \frac{2\pi D_{AB} k_{Areal}}{2\pi D_{AB} + k_{Areal} \ln\left(b/s\right)} = \frac{4\pi D_{AB} k_{Areal}}{4\pi D_{AB} + k_{Areal} \ln\left(1/\pi\rho_A s^2\right)} \quad (1)$$

where $D_{AB} = D_A + D_B$, D_A and D_B are the diffusivities of A and B, ρ_A is the density of molecules of A (number of molecules per unit area), $b = \sqrt{1/\pi\rho_A}$ is one-half of the mean displacement between molecules of A distributed in a certain area, k_{Areal} is the intrinsic reaction rate constant in units of (receptors /area)$^{-1}$ s^{-1}, and s is the encounter radius. The relationship between k_{Areal} and k is given as, $k_{Areal} = ks^2$.

Using Eq 1. and combining it with the expression for resistance in a series model

$$k_{PDE} = \left(\frac{1}{k_{Areal}} + \frac{1}{k_{Diffusion}}\right)^{-1} \quad (2),$$

the diffusion-limited reaction rate constant, $k_{Diffusion}$ is determined to be

$$k_{Diffusion} = \frac{4\pi D_{AB}}{\ln\left(1/\pi\rho_A s^2\right)} \quad (3).$$

for diffusion limited cases, $k_{Diffusion} << k_{Areal}$, $k_{PDE} \approx k_{Areal}$ as was the case for the fitted parameters in this work. In diffusion limited cases, k_{PDE} is the fitted parameter and can be related back to the ODE parameter using Eq. 1. Using this approach, small differences were found in enzymatic reactions leading to the conclusion that omission of diffusion-limited contributions contributed negligible effects on the model.

Appendix B. Understanding the impact of IFNγR clustering on immune response pathways

Michelle N. Costa[1], Elebeoba E. May[2]

***Short Abstract* — Interferon-γ plays an important role in macrophage activation during the early steps of innate immunity. Propagation of immune response via INFγ is dependent on the spatial localization of the INFγR. EM images have found INFγR to be colocalized in caveolar membrane domains; whether this enhances or restricts signal remains to be elucidated, However, in an interesting twist, experimental evidence points to INFγas a negative regulator of caveolin-1. In order to understand the spatial-temporal dynamics of INFγR membrane localization and further investigate the impact of IFNγR activation on gene and metabolic pathways that regulate caveolin-1 production we developed a simulation-based model using a coupled CSNSA-BioXyce platform that combines a spatial Monte Carlo method (CSNSA) with a circuit-based intracellular network simulator (BioXyce). In this work we explore the impact of receptor spatial organization on immune effector mechanisms and to complete the circle, the impact of IFNγ mediated effectors on spatial organization.**

***Keywords* — Spatial organization, gene networks, INFγR, caveolin-1, spatial modeling**

Purpose

Interferon-γ induces direct antimicrobial mechanisms and up-regulates antigen processing and presentation pathways (9). Interferon-γ activates these immune responses via the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway. The initial signaling events of IFNγ receptor (IFNγR) are often the rate limiting step and dependent on the spatial distribution of the IFNγ receptors (3).

Electron microscopy using immunogold labeled particles has revealed aggregation of IFNγR in membrane domains (1). With low numbers of receptors (10^2 to 10^3 receptors per cell (1)) spanning large distances (20um T cell and macrophage (3)) aggregation and colocalization are necessary mechanisms in the signal transduction pathway. Although the cell membrane is a vastly complex structure filled with heterogeneous microdomains IFNγR has been observed to colocalize in caveolar membrane domains (1, 2, 4, 5).

Experimental evidence shows the link between IFNγ and caveolar domains goes beyond spatial organization on the plasma membrane, gene networks of caveolin-1 and IFNγseem to be entwined. Stimulating macrophages with IFNγ had an inhibitory effect on caveolin-1, the marker protein of caveola (7). In addition when transfecting cell lines HT20 and DLD1with caveolin-1 cDNA there is downregulation in iNos(6), a metabolic product of INFγimmune response. A complex regulatory network exists between caveolin-1, INFγand iNos.

This distinct network has yet to be fully elucidated. Starting with a model of the INFγimmune response (8) we have added gene networks of caveolin-1 as well as gene and metabolic networks of iNOS. In this study our aim is to understand the effects that spatial clustering has on IFNγR downstream signaling using the coupled spatial non-spatial simulation algorithm (CSNSA) to simulate the IFNγ/IFNγR mediated activation of the JAK-STAT signal transduction cascade. We then investigate the relationship between iNOS and caveolin-1 using a modeling framework which combines the CSNSA with BioXyce, where BioXyce is used to simulate the STAT mediated intracellular reactions that lead to the production of IFNγ activated genes and the metabolic reactions that lead to the production of immune effector molecules. We discuss the challenges and benefits of the coupled platform in providing a multiscale understanding of host immune response mechanisms.

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Appendix C. A Monte Carlo Based Approach for Determining Optimal Drug Efficacy in Different Cytoskeletal Distributions

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Abstract

The membrane skeleton (MSK) is the portion of the cytoskeleton that is closely associated with the cytoplasmic surface of the plasma membrane, varying in general morphology and distribution in different cell types. The MSK is composed of actin filaments and various integral proteins, which provides the cell with structure. It has been hypothesized that MSK rearrangements are associated with an upregulation in proliferative pathways, which is a hallmark of cancer. Based upon these fundamental differences in the cytoskeletal distributions, drug therapies can be tailored to specific tissue types. Although drugs have been designed for maximum potency in the past, emerging evidence suggests that the drug's disassociation rate may be altered to maximize signal as well as reduce desensitization. We hypothesized that optimal drug parameters are dependent on MSK distribution. Using a computational approach, we have tested different dissociation constants in various MSK distributions, with the goal of finding an optimal drug design criteria that is specific for different cell types. Our results suggest that therapeutic techniques should be tailored with tissue specificity in mind.

Keywords: cytoskeleton, picket-fence, drug efficacy, Spatial Monte Carlo

Introduction

The cytoskeleton is the sole structure spanning from the plasma membrane to the nucleus, coordinating all cellular processes in between (Janmey 1998; Janmey, Kas et al. 1998; Kusumi, Nakada et al. 2005). The membrane cytoskeleton (MSK), an interfacial structure of the bulk cytoskeleton located at the plasma membrane, plays an essential role in membrane function as well as cytoskeletal regulation (Fujiwara, Ritchie et al. 2002). Controlling processes such as endocytosis and exocytosis, the MSK provides the plasma membrane with structure yet adaptability (Dai and Sheetz 1999; Gaidarov and Keen 1999; Gaidarov, Santini et al. 1999; Valentijn, Valentijn et al. 2000; Gauthier, Rossier et al. 2009). Experimental evidence has shown that the MSK regulates site specific localization of transmembrane proteins (Bennett 1990; Saxton and Jacobson 1997; Bennett and Baines 2001; Pan, Kao et al. 2006), membrane tension (Togo, Alderton et al. 2000; Doherty and McMahon 2008; Lundmark, Doherty et al. 2008), global cell shape/volume (Linshaw, Fogel et al. 1992; Pedersen, Hoffmann et al. 2001; Sheetz, Sable et al. 2006), and membrane deformation at the leading edge(Svitkina and Borisy 1999; Svitkina and Borisy 1999). Arguably, the most important function of the MSK is the regulation of protein and lipid mobility on the plasma membrane (Fujiwara, Ritchie et al. 2002; Ike, Kosugi et al. 2003; Forgacs, Yook et al. 2004; Kusumi, Nakada et al. 2005). This particular function, an enigma that plagued the fluid mosaic model, is of great consequence for signal transduction.

Fujiwara et al. performed single particle tracking on the 1,2-dioleoyl*sn*-glycero-3-phosphoethanolamine (DOPE), a non-raft lipid, and observed interesting diffusive behavior when the DOPE lipid underwent short-term confinement, followed by long term

“hop” diffusion (Fujiwara, Ritchie et al. 2002). Hypothesizing an explanation to this curious diffusive behavior, cells were treated with latrunculin-A, an actin binding toxin which partially depolarizes filamentous actin, and showed an increase (factor of ~1.5) in diffusive compartment sizes. This evidence was indicative of the diffusional restrictions imposed by the MSK and supported the “picket-fence” model, also known as the anchored-protein picket model. The “picket-fence” model (Edidin, Kuo et al. 1991; Kusumi, Nakada et al. 2005) describes the plasma membrane as a landscape of boundaries: the fences are composed of the mesh-work of the MSK, while the pickets are integral proteins that are themselves tethered or confined by the MSK, inhibiting diffusion on the extracellular face.

Recent work using single particle tracking has revealed that the density of the MSK varies with cell type (Murase, Fujiwara et al. 2004). Measurements of time intervals that proteins have spent in confinement yield compartment sizes ranging from 32 nm for CHO-B1 cells to 230 nm for normal rat kidney fibroblast (NRK) cells (Murase, Fujiwara et al. 2004). Similarly, three-dimensional reconstructed images of the plasma membrane in NRK cells and FRSK cells revealed differences in MSK distribution (Morone, Fujiwara et al. 2006). The variation in MSK density appears to be of physiological significance, observed in hippocampal neurons. These specialized cells contain a diffusional barrier highly concentrated with the MSK and transmembrane proteins located between the somatodendritic and axonal domains, limiting the diffusion of even phospholipids (Nakada, Ritchie et al. 2003). Such diffusive barriers have been observed in tight junctions(Dragsten, Blumenthal et al. 1981; Dragsten, Handler et al. 1982; van Meer, Gumbiner et al. 1986; van Meer and Simons 1986), the neck of the bud in budding

yeast (Takizawa, Sil et al. 1997; Takizawa, DeRisi et al. 2000), and between compartments in sperm (Ladha, James et al. 1997). Although few studies have investigated the variation in MSK distribution and its role in cellular function, one could hypothesize that the diversity of MSK densities facilitates cell type specific physiology (Murase, Fujiwara et al. 2004; Morone, Fujiwara et al. 2006).

Variation in the MSK is not only a striking feature observed between cell types, but it is also seen in disease. Morphological changes occur in the MSK during cancer, specifically during metastasis in which cell-cell interactions are often disrupted (Chopra, Fligiel et al. 1990). Studies investigating metastatic characteristics exhibit a decreased interaction of tumor cells with platelets, a trait that is inherently dependent on the lateral mobility of specific receptors (Chopra, Hatfield et al. 1988; Chopra, Timar et al. 1992; Olorundare, Simmons et al. 1992). Antitumerigenic effects were observed when actin-binding proteins were overexpessed, leading to a stabilization of focal adhesion (Nebl, Oh et al. 2000). In addition, oncogenes that alter the actin binding protein expression have been identified (Vandekerckhove, Bauw et al. 1990; Janmey 1998). Another MSK function exploited in cancer, which has not been extensively studied, is the ability to enhance proliferative signal transduction pathways (e.g. clustering) and inhibit regulatory apoptotic pathways (Forgacs, Yook et al. 2004; Doherty and McMahon 2008).

With such variation in the MSK, we propose the concept of tailoring therapeutics with cell specificity in mind, an idea which to our knowledge has not been suggested before. Our hypothesis is that the membrane cytoskeletal distributions have diverse drug binding parameters, k_{off} which correspond to optimal drug inhibition. The motivation for our hypothesis comes from previous work (Woolf and Linderman 2003) done by Woolf et al.

in which performing Monte Carlo (MC) simulations, a minimum rate of G-protein-coupled receptor (GPCR) phosphorylation at an intermediate koff value. Their results were explained in terms of the spatial-temporal dynamics of receptors at different k_{off} parameters.

In this work we have implemented a lattice based spatial kinetic Monte Carlo (SKMC) algorithm which incorporates "picket-fence" boundaries enabling us to test different membrane cytoskeletal distributions. Adding a drug to our system that inhibits epidermal growth factor receptor (ErbB or EGFR) homo and hetero dimerization, we are able to determine the optimal binding parameter k_{off} at a given cytoskeletal distribution. Our results show optimal inhibition at koff values of 100 s^{-1}, 8500 s^{-1} in the case without picket fences and at 100 s^{-1}, and 6000 s^{-1}at a picket fence distribution of 25 corrals/□m^2.

Materials and Methods

Spatial Kinetic Monte Carlo (SKMC)

Simulations were performed using a spatial kinetic Monte Carlo (SKMC) algorithm which is a modified null-event lattice based MC, developed by our group (Mayawala, Vlachos et al. 2005; Mayawala, Vlachos et al. 2005). The spatial domain is a two-dimensional square lattice which is implemented with periodic boundary conditions. The algorithm begins by populating receptors onto the lattice. It then computes transition rates for reaction and diffusion rates as shown in Table II. Probabilities are determined based on the normalization transition rate $\Gamma_{\max}$ for further details see (put Ref). The algorithm proceeds iteratively by selecting an occupied lattice site, choosing a successful (reaction or diffusion) or unsuccessful (null) event based on the probabilities. If a successful event was chosen, the event is executed and species populations as well as

time are updated, if the selected event is a "null-event" the algorithm proceeds until a successful event is chosen. A schematic of our algorithm is shown in Fig 2.

Picket Fences

Spatial boundaries were placed on the lattice to simulate the cytoskeletal distributions interacting with the plasma membrane. Using the term "picket-fences" to describe the cytoskeletal interactions, we quantified the density of boundaries in units of corrals/area, establishing three distributions of 25 corrals/μm^2, 100 corrals/μm^2, and 400 corrals/μm^2 as shown in Fig 1. The "picket-fences" reduce the diffusional transition rates of the receptors, as shown from the definition of this rate:

$$\Gamma^d_{i \to j} = \frac{1}{4}\Gamma^d \sigma_i (1-\sigma_j)\; j \in B_i$$

where $\Gamma^d = \frac{4D}{a^2}$ is four times its diffusion coefficient, D, divide by its inner lattice distance, a squared. B_i signifies the set of sites in which diffusion from site σ_i can occur. Diffusion takes place in four directions, each direction with its occupancy function σ_j which is discrete. σ_j equals one if the site is filled, or zero if the site j is empty. This means that Eq. 1 can be either 0 or $\frac{1}{4}\Gamma^d$, depending on the occupancy of the neighboring site. Effective confinement of the receptor occurs when a receptor is neighbored by a "picket-fence". In this instance, the σ_j term will be equal to one, yielding a diffusion transition rate of zero in that direction.

The membrane cytoskeleton is a very dynamical structure, undergoing rearrangements which enable receptors to escape the confinement of a corral. Single particle tracking shows that receptors hop to a new compartment every 10ms per 230-nm-diameter of

membrane cytoskeletal obstruction (Fujiwara, Ritchie et al. 2002). We simulate the picket-fence dynamics by placing breaks at a time step, Δt_{PF} of 10 ms per 0.04 □m^2 of picket fences, therefore allowing receptors to diffuse through compartments. After an iteration of the SKMC, breaks are closed and Δt_{PF} is set to zero. This is consistent with the rate kinetics of actin dimerization (Adams, Matov et al. 2004; Vallotton, Gupton et al. 2004; Danuser and Waterman-Storer 2006; Deshpande, McMeeking et al. 2006; Andrews, Lidke et al. 2008) which is on the order of the algorithm's time step of 10 µs.

Drug Binding Kinetics & Parameters

A drug was added to the SKMC model to determine the most effective binding parameter within each picket fence density. This drug was modeled as a monoclonal antibody, inhibiting the formation of homo or heterodimers of the EGFR receptor, also known as ErbB1. A schematic of the primary and secondary inhibition due to the monoclonal antibody are presented in fig. 3. Three receptors belonging to the ErbB family are illustrated in the schematic in fig. 3, however our focus will be on ErbB1 represented as R1u, (receptor 1 unbound) and R1b (receptor 1 bound to ligand). The monoclonal antibody prevents EGF from binding to R1u, ultimately decreasing the probability of dimerization. Arrows highlighted as red indicate direct inhibition and arrows highlighted as blue indicate indirect inhibition.

In every simulation, the drug concentration was varied to maintain an average value of receptor bound drug occupancy of 2.5%, independent of the drug's binding constants (41). The concentration of the drug was determined according to the relationship

$$D = \frac{kon}{koff} \frac{f}{(1-f)}$$

where f is the fraction of receptors bound to ligand at equilibrium (f = 0.025). Defining drug occupancy in this way allows the instantaneous drug occupancy to change over the course of the simulation, while maintaining average receptor occupancy constant. This allows us to determine the spatial implications of a particular drug binding parameter. Each MSK distribution contained the k_{off} values and drug concentrations indicated in Table III. For statistical purposes, ten simulations were performed for each of the ten k_{off} values.

Results

Determining Optimal Drug Parameters

To determine if membrane cytoskeletal distributions have diverse binding parameters, we tested different k_{off} parameters in each MSK density (Fig. 2). The simulations were performed without picket fences, and with picket fence densities of 25 corrals/μm^2, 100 corrals/μm^2, and 400 corrals/μm^2. At a time of two seconds, the total rate of dimerization of EGFR as a function of k_{off} value (Fig. 4) was observed. The most dramatic differences in the rate of dimerization were observed without picket fences (blue line) and at a picket fence distribution of 25 corrals/μm^2 (pink line). Without picket fences, the optimal drug inhibition values (minimum points, blue line Fig 4) were observed at 100 s^{-1} and 8500 s^{-1}, while the least effective koff parameters were 6000 s^{-1} and 10000s^{-1} (maximum points, blue line Fig 4). However, the optimal drug binding parameters, k_{off}, occurred at 100 s^{-1} and 6000 s^{-1} (minimum points, pink line Fig_4) for

the 25 corrals/μm^2 distribution, and the least effective parameter was 4000 s^{-1} and 10000 s^{-1}.

Temporal profiles of optimal and least effective k_{off} Parameters

Next we wanted to determine the effectiveness of both the optimized parameters (minimums) and the least inhibitive parameters (maximums) over time. Fig. 5a shows the temporal profiles of the rate of EGFR dimerization for simulations preformed at the selected k_{off} value, without fences. The k_{off} parameters demonstrated in Fig. 5a are the two least effective k_{off} values of 6000 s^{-1}, 10000 s^{-1} and the optimal k_{off} parameters of 100 s^{-1}, and 8500 s^{-1}. Differences are seen in the rate of EGFR dimerization between optimal and least effective parameters, however differences between the optimal values of 100 s^{-1}, and 8500 s^{-1} was marginal. Differences between least effective parameters of 6000 s^{-1}, 10000 s^{-1} were marginal. Similar results were observed in the temporal profiles of simulations with optimized and non-optimized parameters seen in the 25 corrals/μm^2 distribution. However, the most effective parameters for the 25 corrals/μm^2 distribution were 6000 s^{-1}, 100 s^{-1} and the least effective k_{off} values were 4000 s^{-1}, 10000 s^{-1}.

Different Predictions between SKMC vs ODE with Drug

We graphed the dimerization profiles using an ODE code without drug (blue line Fig.6A) and with optimal drug (red dots). Results from the SKMC (green line) without drug and SKMC with optimized drug (magenta line) are represented in Fig.6A. Differences in the rate of dimerization between the ODE without drug and ODE with optimized drug were unable to be determined, however, the results from the SKMC showed a decrease in dimerization rate with optimized drug when compared to the same

picket fence density without drug. In Fig.6B, the picket fence density of 100 corrals/μm^2 yielded a similar result. A clear distinction can be seen between the SKMC with optimal drug (green line Fig 6B) when compared to the instance where there is not drug present (magenta line). In addition, looking at the SKMC model without drug (green line), Fig.6B also reveals a decrease in dimerization rate which is not depicted in the standard ODE model. The difference in dimerization rate can be attributed to the spatial parameters of the SKMC, which is not integrated into the ODE model. The ODE also neglects the heterogeneity of receptors on the membrane, suggesting that the SKMC is a more accurate model for simulating this biological system.

Spatially tracking ErbB1 receptors

Using the SKMC, we wanted to investigate the movement of a ErbB1 receptor in order to determine how different MSK distributions inhibit diffusion rates. In order to do so, we tracked each position on the lattice where the receptor traveled. From this data we determined a MSD plot for each MSK distribution, illustrated in Fig.8. The MSD plot in Fig. 8A shows a movement of the receptor within a domain with out picket fences (Fig. 8Ablue line). The displacement of the receptor was dramatically greater than the other three picket fence densities, since the movement of the receptor was not confined by the MSK. Figure 8B shows the MSD plot of the picket fence density of 25 corrals/μm^2, which had a displacement that was greater than the picket fence densities of 100 corrals/μm^2 and 400 corrals/μm^2, but still significantly less than the domain with out picket fences (Fig. 8B green line). Due to the confinement of the receptor within a dense MSK distribution, the movement of the receptor simulated in the MSK distributions of 100 corrals/μm^2 (Fig. 8C red line) and 400 corrals/μm^2 (Fig. 8D purple line) was limited.

Next we wanted to determine the relationship between the lifetime of the drug bound receptor and the corresponding k_{off} value. By tracking the location of all 40 ErbB1 receptors bound to drug, we were able to determine the life time of the drug as a function of time (Fig.7). As shown in Fig. 8, the relationship between the lifetime of a drug bound receptor and the k_{off} value is exponentially negative. This result indicates that the k_{off} value greatly influences the life time of drug, ultimately influencing the effective area of the drug.

Discussions

Experiments using single particle tracking have shown that different cell types express variations in corral sizes. CHO-B1 cells have corral sizes ranging from 3-4 nm, whereas NSK cells have corral sizes of 320 nm. Based upon the differences in MSK distributions, one would observe variations in the lateral diffusion of membrane bound receptors. Since receptor interactions depend on lateral diffusion, cell types expressing different MSK distributions will have distinct receptor dynamics. These results suggest that drug therapies should be tailored for cytoskeleton distributions.

After simulating various k_{off} values of a drug in different cytoskeleton distributions, the k_{off} parameters that were most effective depended upon the picket fence density. As shown in Fig. 4, the optimal and least effective k_{off} values occurring within the picket fence density of 25 corrals/μm^2 (pink line) dramatically shifted from the k_{off} parameters that are present in the domain without picket fences. This result implies that the mechanism of the drug may vary depending on the type of cytoskeleton distribution. Different distributions of the picket fences alter the diffusivity of a drug bound receptor,

ultimately affecting the rate of dimerization. Within the picket fence density of 25 corrals/μm^2, the diffusion rates of a drug bound receptors are hindered by the MSK meshwork, reducing the dimerization rate and shifting the optimal and least optimal k_{off} values. Since different cell types express a variation in MSK densities, it is important to acknowledge the difference in diffusion rates that occur in different cell types.

However, the domains containing 100 corrals/μm^2 and 400 corrals/μm^2 displayed little variation in the rate of dimerization at different k_{off} values. As seen in Fig. 8C and Fig. 8D, the diffusivity of drug bound receptor may be inhibited at these dense picket fence distributions, causing the variations in the k_{off} parameter to have little effect. Previous work has suggested that the receptor concentrations alter the effects of dimerization within a confined corral. We speculate that more variation between k_{off} values would be observed at higher receptor concentration in these picket fence densities.

In addition to addressing tissue specific parameters, drug resistance and desensitization are also important factors that influence the development of a useful drug. Receptor desensitization can be defined as either a loss or reduction in receptor responsiveness after agonist exposure. In the past, drug development has searched for drugs that are potent and have a high affinity for their receptor, viewing desensitization simply as a side effect. However, investigating receptor activation and desensitization as events that can be altered independently can provide better insight into developing new drugs with less side affects and greater applications (Woolf and Linderman 2003).

Experiments performed by Lewis et. al applied a range of full and partial agonists to C-6 glioma cells in order to investigate the role of drug efficacy in agonist-induced desensitization. They observed desensitization in C-6 glioma cells that contained A77636, a compound shown to have a low k_{off} value. Compounds that contain a low k_{off} value result in a long residence time on the receptor, which holds the receptor in an active conformation (Lewis et. al 1998). In the case of a G-protein-coupled receptor (GPCR), holding the receptor in the active state allows phosphorylation to occur, which is known to be the first step in desensitization.

Our results direct the focus of finding a new k_{off} parameter that would reduce the effect of desensitization. Temporal profiles of the simulations without picket fences and the simulations with a picket fence density of 25 corrals/μm2 (Fig. 5a and Fig. 5b) demonstrate similar inhibitive behavior between a high k_{off} value and a low k_{off} value. Our data indicates that a compound containing a high k_{off} value may be just as effective as a compound with a low k_{off} value, but reduces the effects of desensitization. The shift in our data between the two picket fence densities also suggests that the efficiency of high k_{off} value may also depend on cell-specific parameters.

Performing simulations using a SKMC model has allowed us to determine the spatial and heterogeneity effects of a biological system that are not addressed in ODE models. As shown in Fig.6, a discrepancy occurred between a comparison between the SKMC and ODE simulations. After adding the optimal drug to the ODE model, the ODE failed to determine a difference in dimerization rate. Although, as shown in the SKMC

model in Fig. 6, there seems to de a discrete difference in dimerization rate that are effected by spatial factors that the SKMC is able to detect.

The work performed in this study would be difficult to test experimentally, due to the viability of cells, cost of supplies and the many variables that would be difficult to control. However, computational biology is a useful tool that can provide predictive results that can be used to guide experimental work. In this work, taking a computational approach has allowed us to explore the complex interactions between membrane receptors and the space around them. We have determined that different MSK distributions contain different k_{off} parameters, as well as identify similar efficiencies between high and low k_{off} values, suggesting new ways of addressing drug desensitization. Our findings suggest that determining specific parameters that are optimal for different cell types and tailoring drugs to meet that criterion may be the latest direction of effective drug design.

Future Work

Our results (Fig. 4) show marginal effects between k_{off} values at distributions of 100 corrals/μm^2 and 400 corrals/mm2. As shown in preliminary work, increased dimerization in each picket fence density depends on the receptor concentration. A low receptor concentration within a highly dense MSK distribution decreases the rate of dimerization. Alternatively, a high receptor concentration within a highly dense MSK distribution increases dimerization due to the clustering of receptors within a corral. We hypothesize that limited differences in k_{off} values is due to the effects of hindered diffusion; preventing EGFR receptors from interacting with homo and hetero partners. To

test this hypothesis, we will perform the same simulation at a higher receptor concentration of 80 receptors/lattice for both picket fence densities

To understand why some k_{off} parameters demonstrated greater inhibition than others, we will investigate the area covered by a receptor as a function of time. In order to do so, the position on the lattice where ErbB1 receptors are bound to drug will be tracked. In each MSK distribution, we will then determine the MSD for each drug bound receptor. Comparing the MSD of the most effective drug parameters with the least effective drug parameters may explain the mechanism for optimal inhibition. As determined from Fig. 7, the k_{off} value has an impact on the life time of the drug bound receptor, affecting the area traveled by the receptor. We hypothesize that the k_{off} parameters that show the greatest inhibition will transverse a greater portion of the plasma membrane.

Figure Legends

Figure 29 Three picket fence densities

A) 25 corrals/μm^2 B) 100 corrals/μm^2, and C) 400 corrals/μm^2

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Demonstrates a sequence of events that can occur within SKMC algorithm

Figure 30 Schematic of Drug Inhibition

Illustrates inhibition mechanism used by a monoclonal antibody. Primary inhibition is highlighted in pink, while secondary inhibition is indicated by blue.

Figure 31 Rate of EGFR Dimerization as a function of k_{off} for each MSK density

MSK distribution without picket fences (blue line) contain optimal k_{off} parameters of 100 s^{-1}, and 8500 s^{-1} and the least optimal k_{off} values of 6000 $s^{-1}$and 10000 s^{-1}. Optimal drug binding parameters, k_{off}, occurred at 100 s^{-1} and 6000 s^{-1} (minimum points, pink line) for the 25 corrals/μm^2 distribution, and the least effective parameters were 4000 s^{-1} and 10000 s^{-1}. Total rate of dimerization was defined by the total amount of dimerization events that occurred at two seconds.

Figure 5 Temporal profile of maximum and minimum k_{off} values in MSK distribution with out picket fences and with a picket fence density of 25 corrals/μm^2

Without picket fences the k_{off} vales of 6000 s^{-1} (orange line), and 10000 s^{-1} (pink line) represent the least optimal k_{off} parameters. k_{off} parameters of 100 s^{-1} (blue line), and 8500 s^{-1} (green line) represent optimal k_{off} parameters. B) With a picket fence density of 25 corrals/μm^2, the most effective parameters for the 25 corrals/μm^2 distribution were 6000 s^{-1}, 100 s^{-1} and the least effective k_{off} values were 4000 s^{-1}, 10000 s^{-1}.

Figure 6 Comparison between SKMC and ODE simulations

Figure 6A shows the dimerization profile within the 25 corrals/μm^2 picket fence density. The SKMC illustrates a clear difference between the system without drug(teal line) and with optimized drug(purple line), whereas in the ODE simulation, there is no difference(red doted line). Similar results are presented in Fig. 6B where the SKMC was

simulated in the 100 corrals/μm^2 picket fence density. However, in the case without drug, (Fig. 6B teal line) the increased picket fence density revealed a decrease in the rate of dimerization when compared to the picket fence density of 25 corrals/μm^2 without drug (Fig 6A teal line).

Figure 7 Average time vs. koff value

The average life time of a drug bound receptor as a function of time is demonstrated in this figure.

Figure 8 MSD plots

Fig. 8A shows a MSD plot containing all four picket fence densities. The displacement of the receptor in the domain without picket fences is dramatically greater than all other domains. Fig. 8B demonstrates a scaled down view of the picket fence densities of 25 corrals/μm^2, 100 corrals/μm^2 and 400corrals/μm^2**.** Fig. 8C shows the MSD plot of 100 corrals/μm^2 and 400corrals/μm^2, which are scaled down further. Fig.8D shows the MSD plot for the picket fence density of 400corrals/μm^2 exclusively.

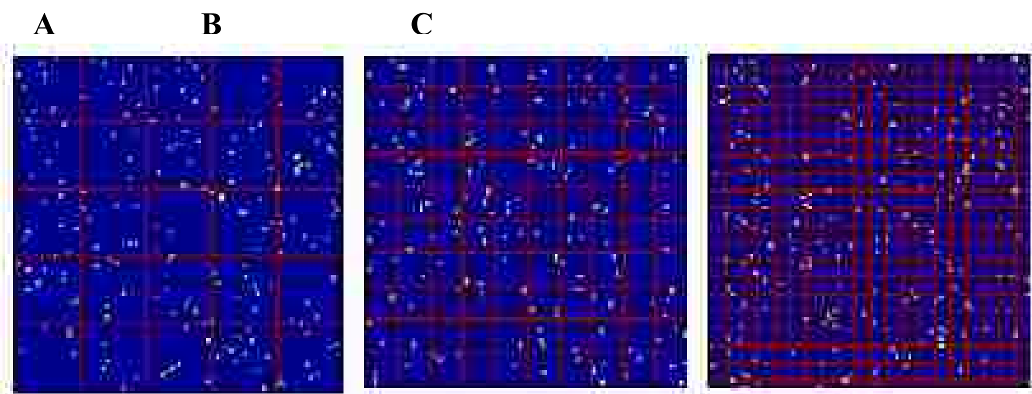


Figure 1

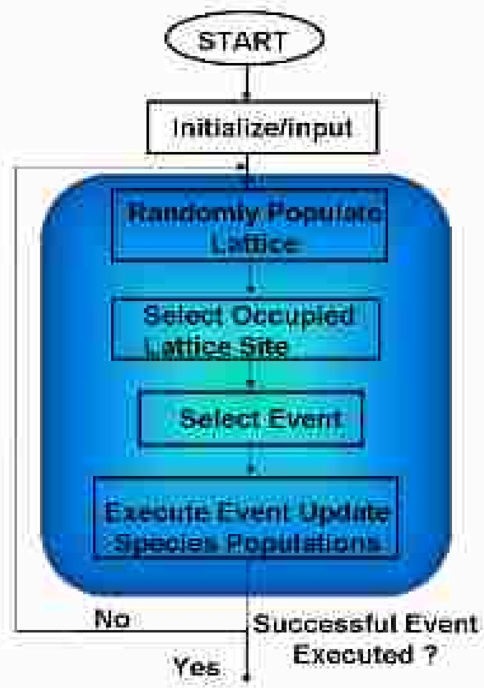


Figure 2

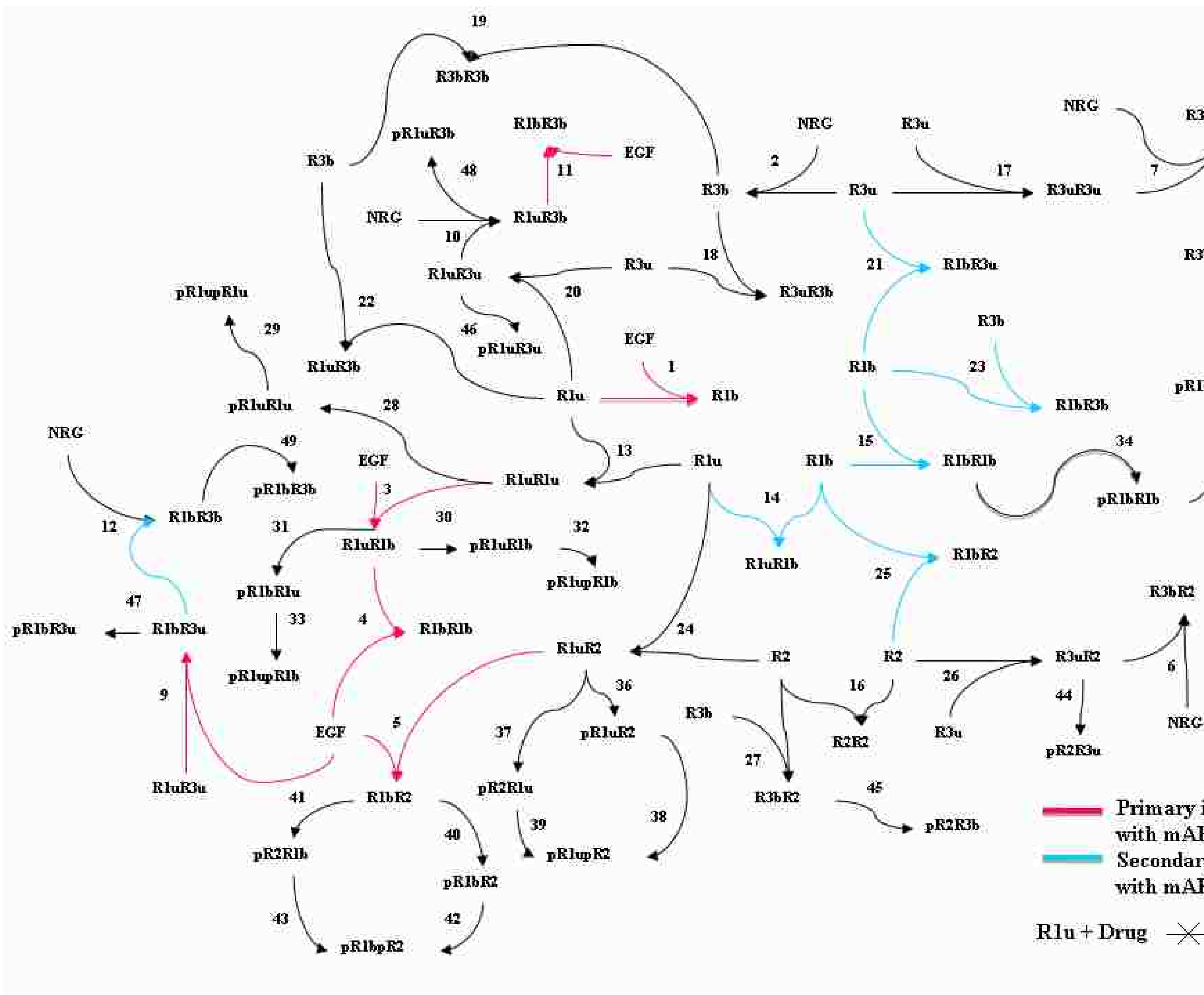


Figure 3

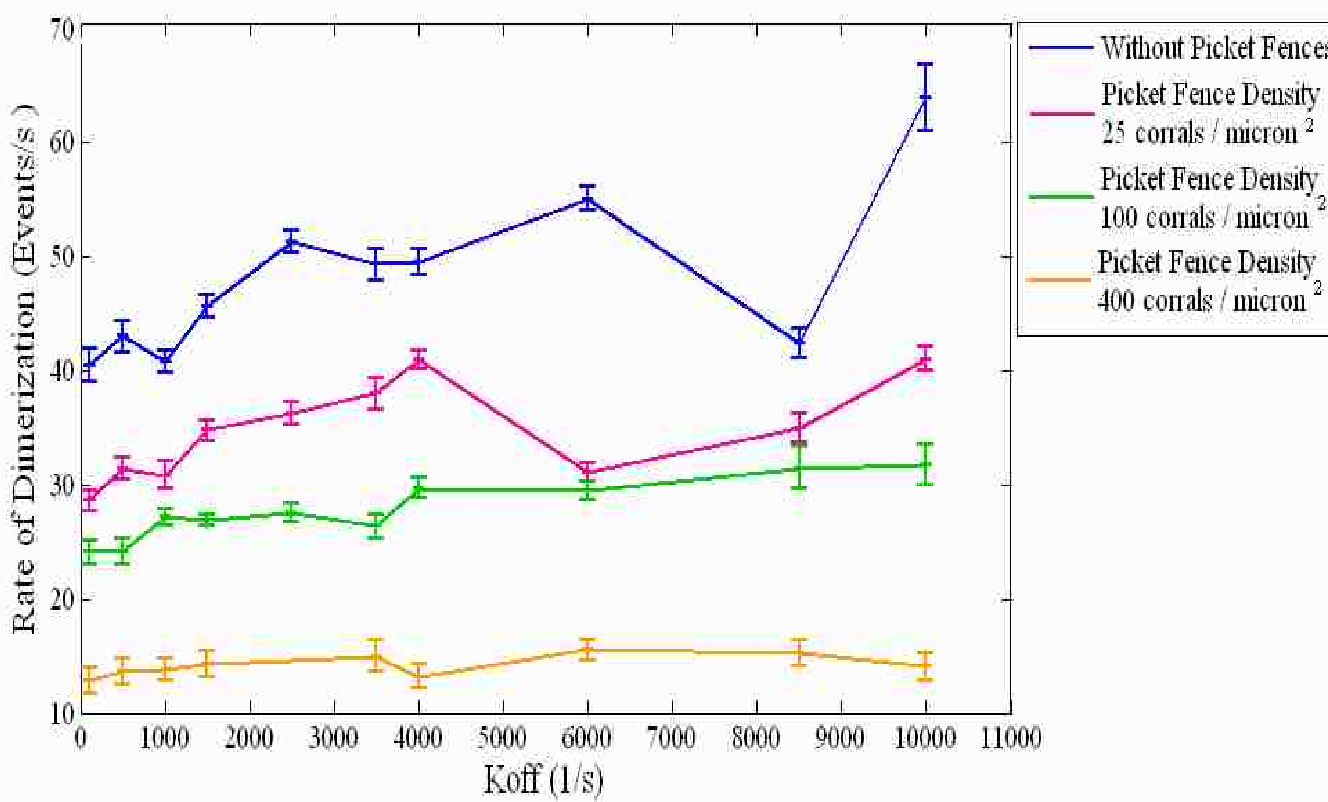
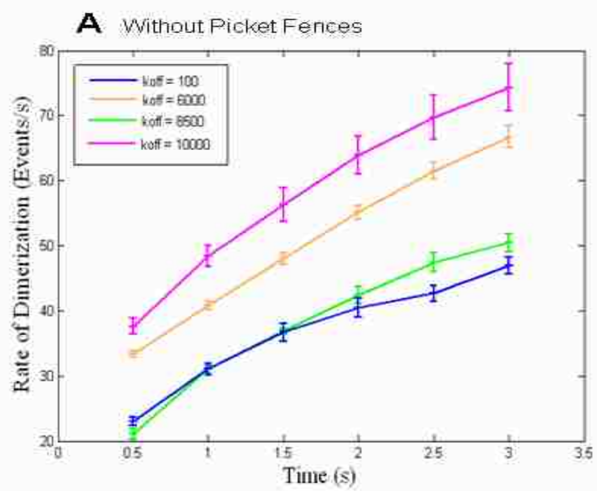


Figure 4



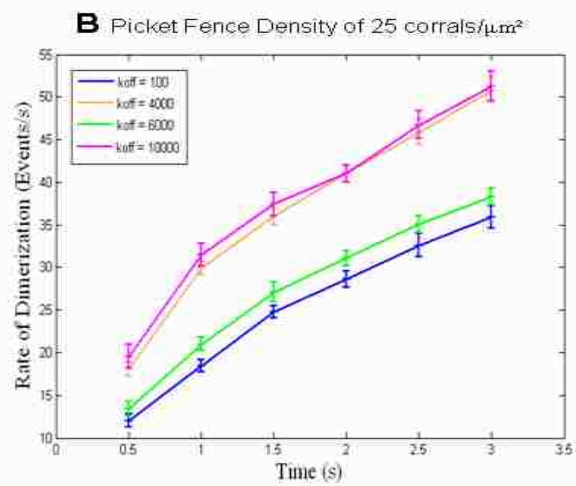


Figure 5

A Picket Fence Density of 25 corrals/μm^2 **B** Picket Fence Density of 100 corrals/μm^2

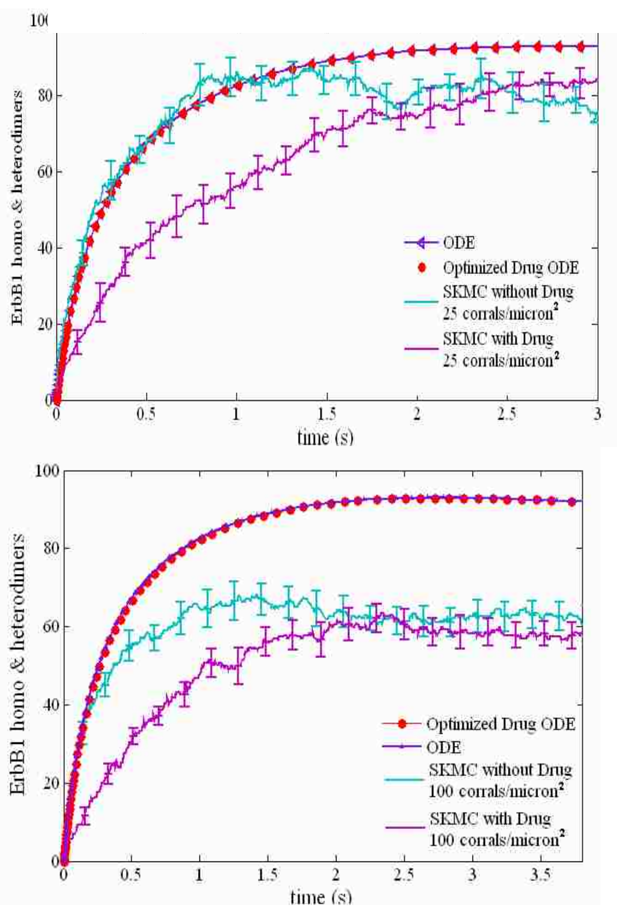


Figure 6

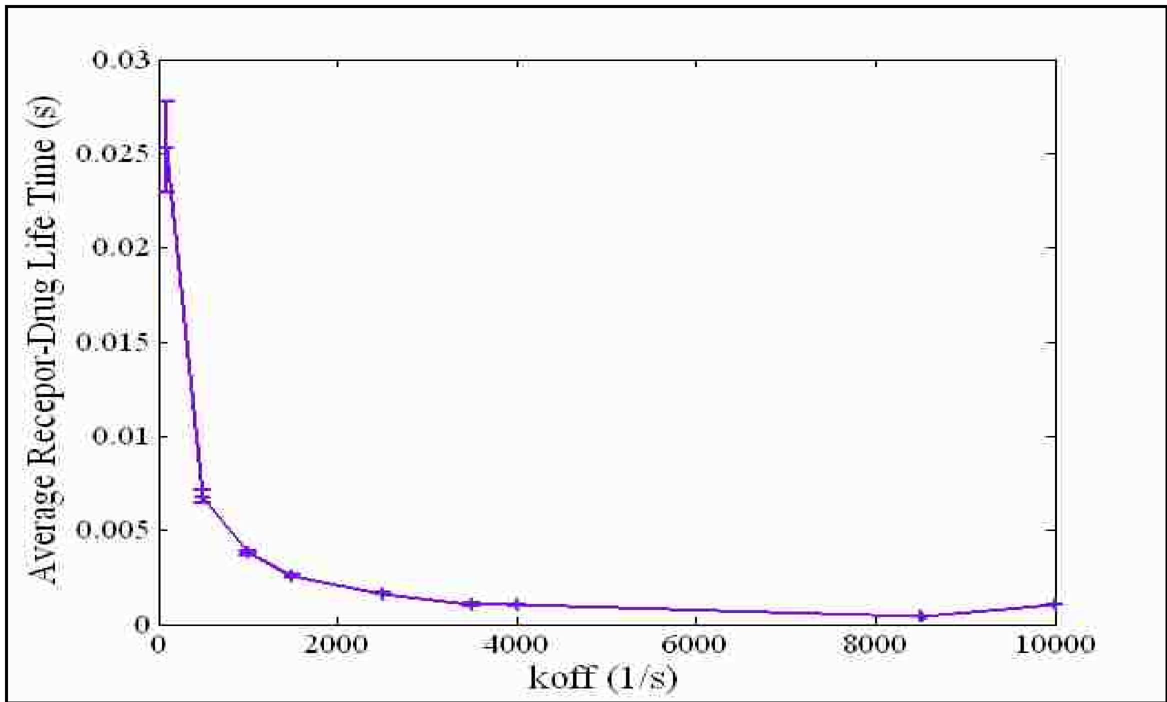


Figure 7

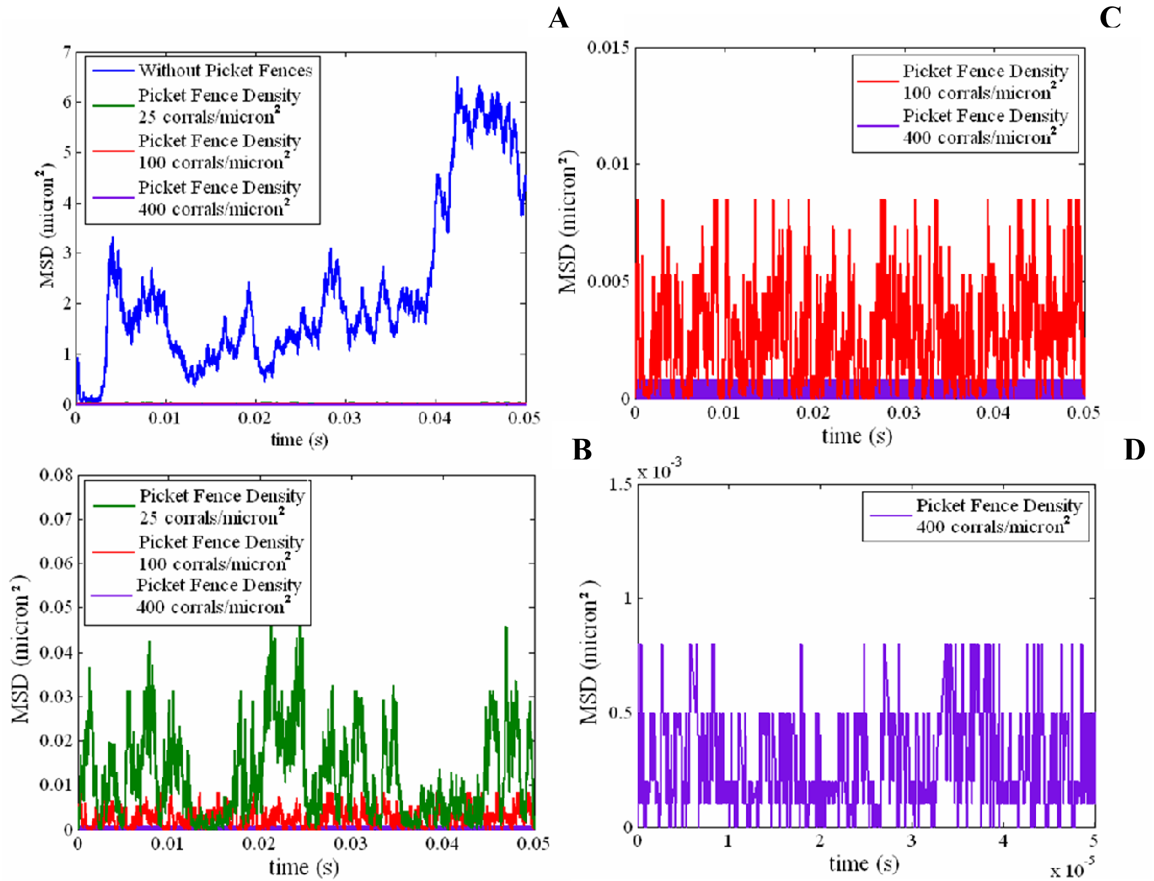


Figure 8

Table I. ErbB Reactions and Reaction Rates

Reactions	Rate Constants (1/s)	
1. R1u + EGF ←→ R1b	Kf = 0.003	Kb = 0.004
2. R3u + NRG ←→ R3b	Kf = 0.003	Kb = 0.004
3. R1uR1u + EGF ←→ R1bR1u	Kf = 0.003	Kb = 0.004
4. R1bR1u + EGF ← → R1bR1b	Kf = 0.003	Kb = 0.004
5. R1uR2 + EGF → R1bR2	Kf = 0.003	Kb = 0.004
6. R3uR2 + NRG← → R3bR2	Kf = 0.003	Kb = 0.00004
7. R3uR3u + NRG ← → R3bR3u	Kf = 0.003	Kb = 0.004

8. R3bR3u + NRG ← → R3bR3b Kf = 0.003 Kb = 0.004

9. R1uR3u + EGF ← → R1bR3u Kf = 0.0015 Kb = 0.006

10. R1uR3u + NRG ← → R1uR3b Kf = 0.003 Kb = 0.004

11. R1uR3b + EGF ← → R1bR3b Kf = 0.0015 Kb = 0.006

12. R1bR3u + NRG ← → R1bR3b Kf = 0.003 Kb = 0.004

13. R1u + R1u ← → R1uR1u Kf = 0.01 Kb = 0.04

14. R1b + R1u ← → R1uR1b Kf = 0.01 Kb = 0.2

15. R1b + R1b ← → R1bR1b Kf = 0.01 Kb = 0.04

16. R2 + R2 ← → R2R2 Kf = 0.01 Kb = 1

17. R3u + 3Ru ← → R3uR3u Kf = 0.01 Kb = 0.4

18. R3b + R3u ← → R3bR3u Kf = 0.01 Kb = 0.2

19. R3b + R3ḅ← → R3bR3ḅ Kf = 0.01 Kb = 0.04

20. R1u + R3u ← → R1uR3ụ Kf = 0.01 Kb = 0.04

21. R1b + R3u ← → R1bR3u Kf = 0.01 Kb = 0.02

22. R1u + R3b← →R1uR3b Kf = 0.01 Kb = 0.02

23. R1b + R3b ← → R1bR3b Kf = 0.01 Kb = 0.04

24. R1u + R2← → R1uR2 Kf = 0.01 Kb = 0.8

25. R1b+ R2 ← → R1bR2 Kf = 0.01 Kb = 0.4

26. R3u + R2 ← → R3uR2 Kf = 0.01 Kb = 0.8

27. R3b + R2 ← → R3bR2 Kf = 0.01 Kb = 0.4

28. R1uR1u ← → p R1uR1u Kf = 0.01 Kb = 0.16

29. R1uR1u ← → pR1uR1u Kf = 0.03 Kb = 0.08

30. R1uR1b ← → pR1uR1b Kf = 0.02 Kb = 0.08

31. R1bR1b ← → pR1bR1b Kf = 0.04 Kb = 0.02

32. pR1bR1b ← → pR1bpR1b Kf = 0.12 Kb = 0.01

33. R1uR2 ← → pR1uR2 Kf = 0.008 Kb = 0.16

34. pR1uR2 ← → pR1upR2 Kf = 0.024 Kb = 0.08

35. R1bR2 ← → pR1bR2 Kf = 0.024 Kb = 0.08

36. pR1bR2 ← → pR1bpR2 Kf = 0.016 Kb = 0.08

37. pR2R1b ←→ pR2pR1b Kf = 0.048 Kb = 0.04

38. R3uR2 ←→ pR2R3u Kf = 0.008 Kb = 0.16

39. R3bR2 ←→ pR2R3b Kf = 0.016 Kb = 0.08

40. R1uR3b ← → pR1uR3u Kf = 0.008 Kb = 0.16

41. R1bR3u ← → pR1bR3u Kf = 0.016 Kb = 0.08

42. R3bR1u ← → pR1uR3b Kf = 0.016 Kb = 0.08

43. R1bR3b ← → pR1bR3b Kf = 0.032 Kb = 0.02

44. R1u + D → R1b Kf = 2.6*10^3 koff = 100

koff = 500

koff = 1000

koff = 1500

koff = 2500

koff = 3500

koff = 4000

koff = 6000

koff = 8500

koff = 10000

Table II. Membrane Microscopic Events and Transition rates

Microscopic Event	**Transition Rate**
Diffusion	$\Gamma^{D}_{i\to j} = \frac{1}{4}\Gamma^{D}\sigma_i\left(1-\sigma_j\right) j \in B_i$ σ_i is the occupancy(discrete) that is 1, if site i is filled, and 0, if site i is empty (a single index indicating the site is used to simplify notation). $\Gamma^{D} = \frac{D}{a^2}$, where a is the microscopic lattice pixel dimension taken equal to the encounter radius, and D is the diffusivity of a receptor B_i denotes the set of sites to which diffusion from site i can occur which includes all 4 first-nearest neighboring sites
Reactions	
Ligand Association Reaction (S_L + M → M*)	$\Gamma^{R}_{i} = k\left[S_L\right]\sigma_i$ k is the macroscopic reaction rate constant

with units as [s^{-1}]

Ligand Disassociation Reaction

($M^* \rightarrow S_L + M$)

$$\Gamma_i^R = k\sigma_i$$

k is the macroscopic reaction rate constant

with units as [s^{-1}]

Dimerization Reaction

($M^* + M^* \rightarrow D$)

$$\Gamma_i^R = \frac{k}{2}\sigma_i\sigma_j$$

k is the macroscopic reaction rate constant

with units as [(receptors/sites)$^{-1}$ s^{-1}]

Decomposition Reaction

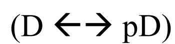
($D \rightarrow M^* + M^*$)

$$\Gamma_i^R = k\sigma_i$$

k is the macroscopic reaction rate constant

with units as [s^{-1}]

Phosphorylation/Dephosphorylation Reaction


($D \leftrightarrow pD$)

$$\Gamma_i^R = k\sigma_i$$

k is the macroscopic reaction rate constant

with units as [s^{-1}]

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Appendix D. Microdomains and the Underlying Cytoskeleton Alter the Efficiency of "Receptor-Sharing"

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Abstract

Experimental evidence suggests

Keywords: EGFR, spatial modeling, Clustering. MSK, Picket Fences

Introduction

Signal transduction, the cell's communication network, comes to a crossroads on the highly compartmentalized plasma membrane. Often oversimplified in mathematical models (*1-3*), the plasma membrane is a facet of heterogeneity that alters receptor organization from transient confinement zones (*4, 5*) or signal transduction "hot spots" to depletion zones. The spatial heterogeneity of receptors comes as a result of sphingolipid-rich microdomains 'lipid rafts'(*6-8*), caveolar formation (*9, 10*), clathrin cages (*11-13*), and the hindering interactions with the membrane cytoskeleton (*14-16*). Diffusional limitations are the result herein altering the initiation, and activation of signal transduction pathways (*17*). Localized concentration gradients become a consequence of the membrane architecture and enhance the efficiency of signal propagation (*15, 18*).

The notion that the plasma membrane is a highly compartmentalized surface with intrinsic microdomains, came a few years after the fluid mosaic model was proposed by Singer and Nicholson in 1972 (*19*). Two major hypotheses, the lipid raft (*20-22*) and the membrane skeleton "*picket fence*" model (*23, 24*) were proposed to describe the structure of the plasma membrane. The lipid raft hypothesis was postulated to explain the aggregation of glycosphinoglipids in the Golgi apparatus before being sorted to the apical surface of polarized epithelial cells(*20*). Using cold non-ionic extraction techniques on specialized lipid fractions taken from Golgi membranes, Simons et al. found that the lipid domains were detergent-resistant(*21*). These domains became known as lipid rafts.

The composition of lipid rafts consists of a highly saturated assembly of cholesterol and sphingolipids which form a lipid order structure ranging from 10-300 nm in size (*25, 26*). Perhaps one of the more interesting phenomenas of lipid rafts is their ability to include or

exclude proteins. The amino acid structure often dictates favorability with hydrophobic modifications increasing affinity for lipid raft domains(*18*). Signaling complexes formed within the lipid raft microenviroments are therefore, protected by a buffer zone which excludes non-raft enzymes such as membrane phosphatases.

Diffusion within lipid rafts decreases by a factor of three to five as observed on artificial membranes (*27-29*) and by a factor of two in SPT experiments(*5*). Crowding effects are thought to be responsible for the decreased diffusivity, which is a mechanism of clustering and a precursor to signaling scaffold formation (*10, 30*). Experimental techniques have shown lipid rafts intimately involved in signal transduction pathways (*18, 31-33*). Take for example the inhibition of H-Ras mediated Raf activation, occurring when cells are treated with methyl-β-cyclodextrin, an agent that depletes cholesterol (*34*). The evidence is suggestive that H-Ras signals only in the presence of lipid rafts (*35, 36*).

Another insightful theory, describing the structure of the plasma membrane, the membrane skeleton "*picket fence*" model was proposed in an attempt to explain anomalous diffusion (*23, 24*). Using FRAP techniques to measure diffusion rates in spectrin-deficient mutant mouse erythrocytes, Sheetz et al found that the transmembrane protein band 3 diffuses 10 times faster than in wild type erythrocytes (*24*). Knowing that the spectrin meshwork, makes up the membrane skeleton, a model describing the hinderance on protein diffusion, the picket fence model was hypothesized (*23*). The model describes the plasma membrane as a meshwork of "fences", interactions from the underlying membrane cytoskeleton (MSK), and "pickets" or protruding transmembrane proteins inhibited by the MSK on the cytoplasmic face. This model was further supported by single particle tracking of the DOPE lipid which underwent short term confinement followed by long term "hop" diffusion (*14, 37-39*).

The MSK is known to vary in structure and density between cell types, with corral sizes ranging from 30 to 230 nm (*40, 41*). Along with cell specific variation, morphological changes occur in the MSK during disease (*42, 43*). The density of the MSK has the capacity to inhibit as well as enhance signal transduction pathways (*44*). Receptor signaling events: oligomerization, crosslinking, and scaffold formation occurring within the constraints of the MSK lead to concentration gradients which facilitate downstream signaling (*45, 46*). At the same time the MSK can be restrictive hindering diffusion and isolating receptors. Take for example; hippocampal neurons with a diffusional barrier highly concentrated in MSK, phospholipid movement is restricted (*37*).

Signal transduction and plasma membrane microdomains have typically been studied in isolation. Although growing evidence shows their intimate nature, with coalescing lipids and transient meshes altering signal transduction (*47, 48*) which comes full circle activating transcription factors that regulate protein expression levels on the cell membrane (*34*). The motivation for this work is to understand signal transduction in the contest of membrane microdomains. Using the adaptively coarse-grained Monte Carlo (ACGMC) we observe signal transduction in terms of our previously proposed “receptor-sharing” mechanism under various microdomain conditions.

Results/Future Work

Effects of Microdomains and MSK on Association Events

To determine the effects of microdomains and the underlying MSK on association events and receptor sharing events, simulations were performed for a lipid raft of size 200nm with diffusivity decreased by 100, for picket fences with densities of 16 corrals/μm^2, 100 corrals/μm^2, 400 corrals/μm^2, and a control (without lipid rafts or an MSK density). Fig 1. shows our results we observe a significant increase between the control and simulations performed with either picket fences or lipid rafts. The most significant increase occurred between the lipid raft and the control. Further investigating these results it was determined that decreasing the diffusivity by a factor 100 is not representative of diffusivity of a receptor through a lipid raft which decreases by a factor of 5. Fig 2. shows the distributions of receptor binding events, from these results we observe an increase in "receptor-sharing" for the lipid raft condition. The picket fence densities seem to inhibit "receptor-sharing". Simulations with an experimentally determined diffusivity in the lipid raft will be run. This will reduce the number of association events and thus "receptor-sharing", however I hypothesis that the number of "receptor-sharing" events will increase from the control.

Simulations will also be preformed to further elucidate the results shown in Fig 1&2. Performing simulations in which the diffusivity and the size will be varied in lipid rafts will allow us to determine the effects of lipid rafts. Similarly we will perform simulations at different receptor concentrations to determine which picket fence density will increase "receptor-sharing".

Materials and Methods

Adaptively Coarse-Grained Monte Carlo (ACGMC)

The Adaptively Coarse-Grained Monte Carlo (ACGMC) algorithm extends for three-dimensional spatial modeling building on our previous algorithm, the SKMC, by including nine additional lattices eight of which extend into the cytosol and the ninth on the nucleus. This framework allows us to study the formation of signaling scaffolds and to observe concentration gradients which result from these scaffolds.

The ACGMC, like the SKMC, begins by selecting a spatial location which could be either the cell membrane (1st lattice) or cytosol (2nd-9th lattices) or the nucleus (10th lattice). The selection is made by computing the probabilities for a spatial event (lattices 1-10).

$$P_{Lat\#1} = \frac{\Gamma_{tot,Lat\#1}}{\Gamma_{tot}},$$

$$P_{Lat\#2} = \frac{\Gamma_{tot,Lat\#2}}{\Gamma_{tot}} \text{ ,and}$$

$$\ldots P_{Lat\#10} = \frac{\Gamma_{tot,Lat\#10}}{\Gamma_{tot}} \quad (1),$$

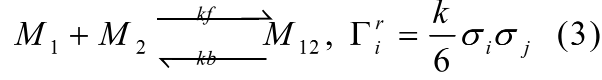
where Γ_{tot} is defined as,

$$\Gamma_{tot} = \sum_{i=1}^{10} \Gamma_{tot,Lat\#i} \; (2).$$

The probability distribution for the lattices, $\Gamma_{tot,Lat\#i}$, is defined as the sum of all transition rates for all SKMC events; however, the events differ in dimensionality and type as shown in Table ?. For example, on the cell membrane (1st lattice) receptors diffuse in 2D but react with cytolic species (2nd lattice) on the lattice below such that reaction occurs in 2.5D. In the cytosol (3rd-9th lattice) species are able to diffuse and react in 3D. Cytosolic species in the boundary lattice which borders the cell membrane (2nd lattice) are able to react with neighboring receptors on the cell membrane but are not allowed to diffuse onto the membrane. At the boundary nucleus (10th lattice) species diffuse and react in 2.5D. In the cytosol the following reaction occurs: $M_1 + M_2 \underset{kb}{\overset{kf}{\rightleftharpoons}} M_{12}$, such that the product M_{12} occupies the single site k. This reaction is valid due to the large site separation distance of 10 nm in comparison to the small molecular masses of cytosolic species Shc, Grb2, and Sos 62 kDa 25 kDa, 11 kDa (*49-51*).

Once a lattice is chosen an event is selected, either reaction or diffusion for the SKMC algorithm as shown in Fig 3. Events are chosen, as in our previous algorithm(*52*), with

the exception of dimensionality which changes the way $\Gamma_{\max}$ and Γ_i^X are computed. The transition probabilities for cytosolic reactions in 3D are



$$M_1 + M_2 \underset{kb}{\overset{kf}{\rightleftharpoons}} M_{12}, \quad \Gamma_i^r = \frac{k}{6}\sigma_i \sigma_j \quad (3)$$

in which reacting species (M_1 and M_2) occupy adjacent sites i and j and k has units of $(\text{molecules/site})^{-1}\text{sec}^{-1}$. Diffusion in 3D is taken into account similarly

$$\Gamma_{i \to j}^d = \frac{1}{6}\Gamma^d \sigma_i (1 - \sigma_j)\; j \in B_i \quad (4)$$

where B_i denotes the set of sites to which diffusion from site i can occur. Table I lists all events, both reaction and diffusion, which make up $\Gamma_{\max}$. $\Gamma_{\max}$ is defined as before but multiplying by a factor of 6 for all 3D event, by a factor of 4 for all 2D events, and a factor of 5 for all 2.5D events such that

$$\Gamma_{\max} = 4\left(\frac{\Gamma^d}{4} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right)_{2D\text{ Events}} + 5\left(\frac{\Gamma^d}{5} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right)_{2.5D\text{ Events}}$$
$$6\left(\frac{\Gamma^d}{6} + \max\left\{\sum_{\text{all forward reaction events}} \Gamma^r\right\}\right)_{3D\text{ Events}} + \max\left\{\sum_{\text{all backward reaction events}} \Gamma^r\right\} \quad (5)$$

The ACGMC operates like a single MC in which time is updated in a “combined” manner from Γ_{tot} with an average time step as, $\Delta t = \frac{1}{\Gamma_{tot}}$. Execution times vary depending on a chosen algorithm. The complete algorithm, which is shown in Fig. 3, was implemented in Fortran 90. Due to the stochasticity of the algorithm, 10 simulations with different seeds for the random number generator were used for statistics.

Adaptively Coarse-Graining & Diffusion Transition Rates

In ACGMC, we introduce coarse-graining by grouping microscopic sites into coarse cells, as shown in Fig 4 in which coarse lattice L_C has m_x, m_y, and m_z coarse cells along x, y, z, such that the total number of cells is $m = m_x m_y m_z$. Each coarse cell $C_j \left(1 \le j \le m\right)$ has q_j microscopic sites, in which $q_j = q_j^x q_j^y q_j^z$ is the number of microscopic sites in C_j along x, y and z axis. Diffusion between coarse-grained cells was rigorously derived by (Chatterjee),

$$\overline{C}_m(j \to i) = \frac{\Gamma_d}{q_j^z\left(q_j^z + q_i^z\right)}\eta_j(1-\overline{\eta}_i) \quad (6)$$

in which, Γ_D is the diffusion transition rate, η_j, is the coarse-grained occupancy function at C_j is defined as

$$\eta_j = \sum_{p \in C_j} \sigma_p \quad (7)$$

While the occupancy of a coarse cell is in terms of the coarse cell coverage,

$$\overline{\eta}_j = \frac{1}{q_j}\sum_{p \in C_j} \sigma_p \quad (8)$$

which for the microscopic case reduces down to either zero for unoccupied or one for occupied.

Validation of Approach

In order to validate our approach we initially placed all molecules within lattices one thru nine and allowed them to diffuse a distance of 1µm into lattice ten over time (Fig 5).

Turning off reaction we have reflective boundary conditions at the cytosol membrane boundary (lattice two) and at the cytosol nucleus boundary (lattice 10) and periodic boundary conditions in the plane parallel to the plasma membrane. Using a diffusivity coefficient of 10μm^2 s^{-1} and a distance 1μm and implementing reflective boundary conditions we compared the ACGMC with the PDE solution. Starting with a cytosolic species concentration 105 nM we observe similar predications between the ACGMC and PDE profiles.

Lipid Rafts & Picket Fences.

Lipid rafts are modeled as a square on the lattice with a predefined size. The diffusivity of a receptor through a lipid raft is decreased by an experimentally determined factor. In order to model cytoskeletal interactions with the cell membrane boundaries, "picket fences" were placed on the lattices. The "picket-fences" occupy lattice sites and therefore prevent reaction and diffusion events in the direction of the boundary. Take for example, a receptor neighbored by a "picket fence" on the jth lattice site, it has an occupancy function, $\sigma_j = 1$ of one, yielding a zero transition probability, $\Gamma^d_{i \to j} = 0$ in the direction of the boundary. Similarly, a receptor separated from its partner by a "picket fence" can not dimerize being that the neighboring lattice site is occupied by the boundary.

Single particle tracking reveals short term receptor confinement followed by long term "hop" diffusion. Cytoskeletal rearrangements and actin depolarization are responsible for "hop" diffusion(*15, 40*). In order to simulate "hop" diffusion breaks were randomly inserted into the boundaries an average of time step τ_{PF} of 10 milliseconds per 0.04 μm^2 of picket fences as was observed experimentally (*14*). Placing breaks in the "picket fence" enables receptors to diffuse out of their corrals. After an iteration of the SKMC

breaks are closed and τ_{PF} is set to zero. This is consistent with the rate kinetics of actin dimerization (*16, 53-56*) which is on the order of the algorithm's time step, Δt.

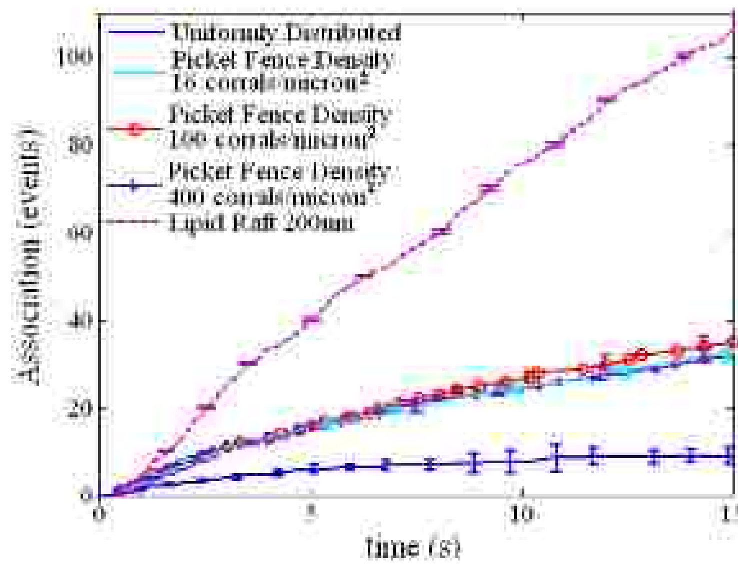


Figure 1.

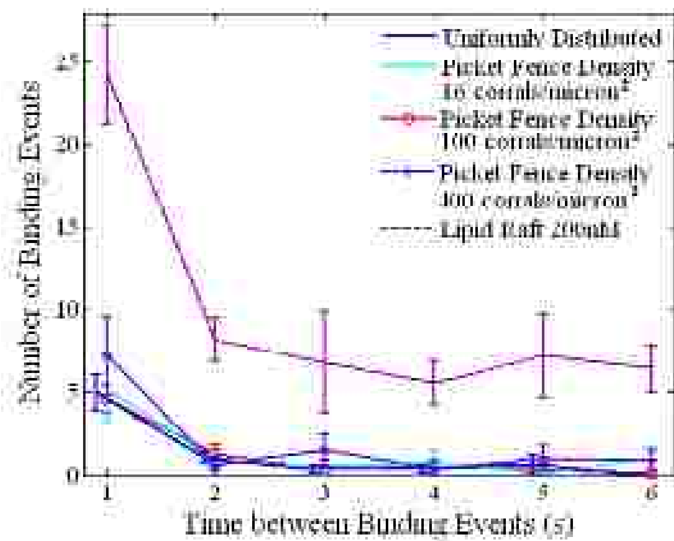


Figure 2.

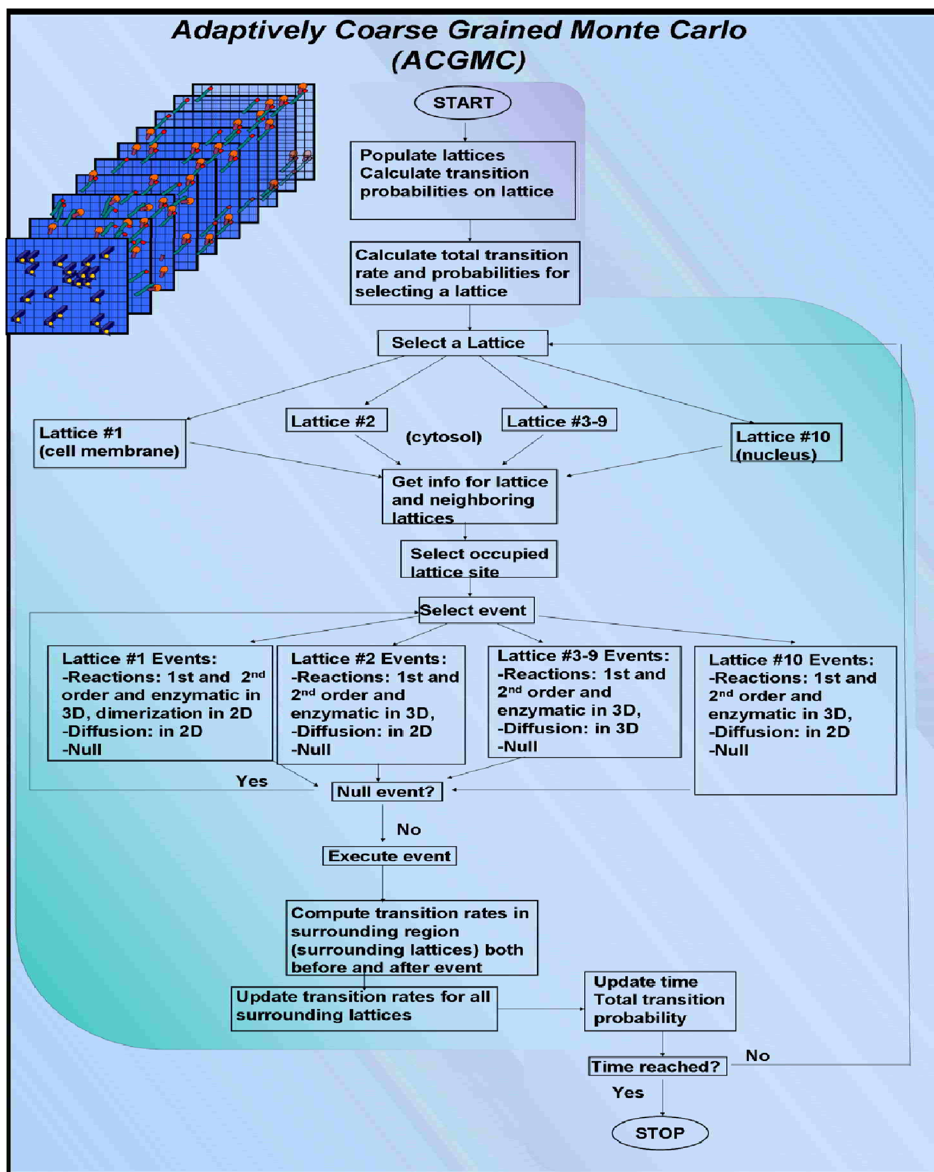


Figure 3.

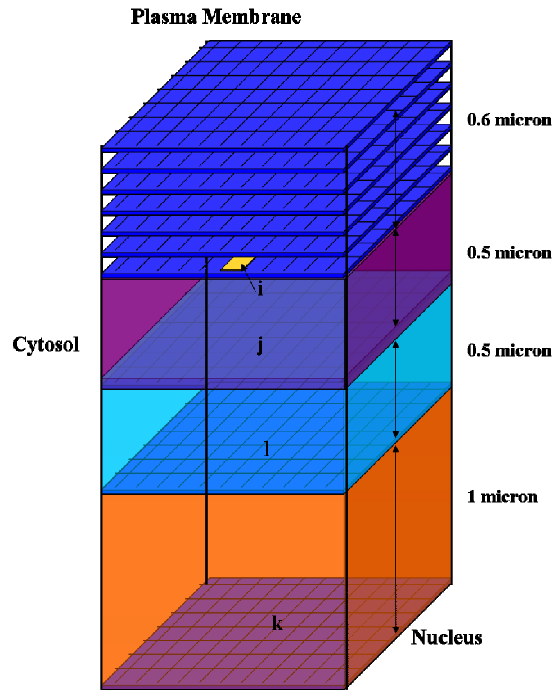


Figure 4.

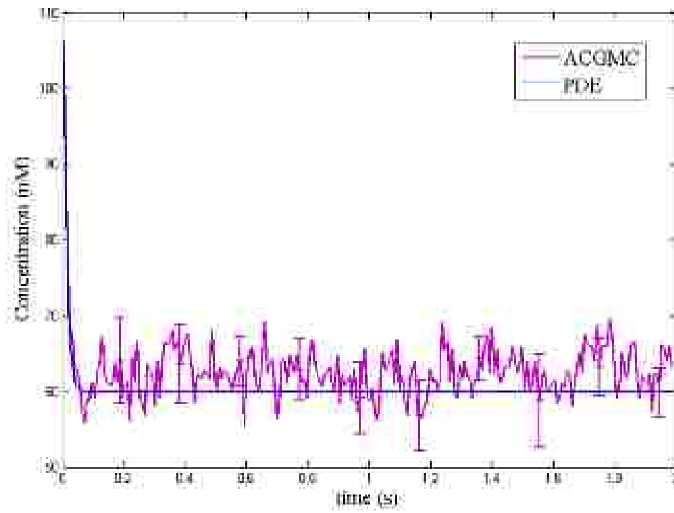


Figure 5.

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Appendix E. Abbreviations Used

ErbB1 Epidermal growth factor receptor

ErbB2 Human epidermal growth factor receptor 2

ErbB3 V-erb-b2 erythroblastic leukemia viral oncogene homolog 3

ErbB4 V-erb-a erythroblastic leukemia viral oncogene homolog 4

EGFR Epidermal growth factor receptor

ERK Extracellular regulated kinase

SH2 Src homology 2

Grb2 Growth factor receptor-bound protein 2

SOS on of the sevenless

Shc Transforming protein 1 and collagen domain protein

ODE Ordinary differential equation

MC Monte Carlo

SKMC Spatial kinetic Monte Carlo

SSA Stochastic simulator algorithm

CSNSA Coupled spatial non-spatial simulation algorithm

PLCγl Phospholipase Cγ1

CPU Central processing unit

LSENS Lewis General Chemical Kinetics and Sensitivity Analysis Code

MSK Membrane skeleton

FCM Fuzzy c-means

MSD Mean squared displacement

SPT Single particle tracking

FRET Fluorescence resonance energy transfer

EM Electron microscopy

MAPK Mitogen-activated protein kinase

GAB1 GRB2-associated binding protein 1

Src Tyrosine kinase

FRAP Fluorescence recovery after photobleaching

FRET Forster resonance energy transfer

TEM Transmission electron microscope

STEM Scanning transmission electron microscope

EDX Energy dispersive X-ray

EELS Electron energy loss spectroscopy

ADF Annular dark-field imaging

SEM Scanning electron microscope

GPI Glycosylphosphatidylinositol

DRM Detergent-resistant membrane

DIG Detergent-insoluble glycoplipid

LCFAs Long-chain fatty acids

DOPE 1,2-dioleoyl*sn*-glycero-3-phosphoethanolamine

SDE Stochastic differential equations

SPDE stochastic partial differential equations

DMC Dynamic Monte Carlo

PBCs Periodic boundary conditions

CGMC Coarse-graining Monte Carlo

ACGMC Adaptively coarse-grained Monte Carlo

PDE Partial differential equations

GFP green fluorescent protein

PKCε Protein kinase c

INFγR Interferon-γ receptor

JAK Janus kinase

STAT Signal transducer and activator of transcription pathway

BioXyce Deterministic circuit-based platform

NRK Normal rat kidney fibroblast

GPCR G-protein-coupled receptor

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