A Monte Carlo Simulation Study of Lipid Bilayer Formation on Hydrophilic Substrates from Vesicle Solutions

Zheming Zheng, Dimitrios Stroumpoulis, Alejandro Parra, Linda Petzold and Matthew Tirrell

Department of Mechanical and Environmental Engineering and Department of Chemical Engineering, University of California, Santa Barbara, California 93106.

A general lattice Monte Carlo model is used for simulating the formation of Supported Lipid Bilayers (SLBs) from vesicle solutions. The model, based on a previously published paper, consists of adsorption, decomposition and lateral diffusion steps, and is derived from fundamental physical interactions and mass transport principles. The Monte Carlo simulation results are fit to experimental data at different vesicle bulk concentrations. A sensitivity analysis reveals that the process strongly depends on the bulk concentration C_0, adsorption rate constant K and all vesicle radii parameters. A measure of "quality of coverage" is proposed. By this measure, the quality of the formed bilayers is found to increase with vesicle bulk concentration.

I. Introduction

Supported lipid bilayers (SLBs) are simple model systems for biological membranes, which are among the most important constituents of living organisms. Interest in SLB formation from vesicle solutions on both hydrophilic and hydrophobic surfaces has been increasing due to their potential application in biosensors, programmed drug delivery, diagnostics etc.[1,2] Vesicle fusion is an effective way to deposit SLBs on both flat and textured surfaces and can be useful in the manufacture of nanodevices, such as analytical devices known colloquially as Lab-on-a-Chip[3].

Gaining insight into the formation of SLB from vesicle solutions is essential to optimizing this process and to predicting its possible applications and limitations. The detailed mechanism is still under investigation, while various experimental techniques, such as surface plasmon resonance (SPR)[4], quartz crystal microbalance-dissipation (QCM-D)[2], surface acoustic wave (SAW) devices[5] and atomic force microscopy (AFM)[6] have been used for this purpose.

The kinetics of vesicle fusion on SiO_2 surfaces has been investigated by our group using three complimentary tools: ellipsometry, a mass transport model and Monte Carlo computer simulation. Ellipsometry and a mass transport model were used in a previous publication[7] to study the mechanism of SLB formation on hydrophilic surfaces. It was concluded that the process is adsorption limited on such surfaces for the range of concentrations studied. Further kinetic ideas were introduced regarding the mechanism of the process. The complexity of the process necessitated the use of an alternative technique to test the mechanistic ideas presented, some of which are difficult to extract experimentally. Computer simulation was applied in an effort to better understand the

elementary steps of vesicle fusion. This method has the potential of providing a priori predictions of the process performance under different conditions or a posteriori validation of an experimental study. Due to the statistical nature of vesicle adsorption, the Monte Carlo method is well-suited for the simulation. The detailed nature of this model allows us to examine the relative contributions of each step of the physical process to the surface coverage. The present paper focuses on the computer simulation of the formation of SLBs on hydrophilic surfaces from vesicle solutions by the Monte Carlo method.

The formation of a SLB on hydrophilic surfaces is believed to proceed through the following mechanism[7,8]: Vesicles first diffuse from the bulk close to the substrate where they get adsorbed, until a critical mass concentration is reached. At that point, rupture of the adsorbed vesicles begins, followed by adsorption of the bilayer fragments onto the surface and lateral diffusion that minimizes hydrophobic edge effects. The adsorption, decomposition and surface diffusion events can be approximated by a stochastic process. The driving force of adsorption and decomposition is a combination of vesicle-surface, vesicle-vesicle and vesicle-lipid membrane interactions, while lipid membrane-lipid membrane interactions are responsible for surface diffusion[8,9,10,11,12].

Zhdanov *et al.*[13] applied the Monte Carlo technique to study the kinetics of vesicle adsorption in the diffusion-limited case, which experimentally arises when hydrophobic surfaces are used[14] or when sufficiently low concentrations of vesicle solutions are fused with hydrophilic surfaces[4]. In that case the rate of vesicle adsorption is limited by the rate of vesicle diffusion in the bulk solution. By considering a mean-field description of the bulk diffusion process and the vesicle-vesicle spatial interactions, the adsorption probability of vesicles was derived. Decomposition of adsorbed vesicles was realized

through different channels (spontaneous, adsorption-induced and lipid-induced decomposition) and a surface diffusion model was presented.

Based on this work a Monte Carlo model for simulating the SLB formation process on SiO_2 substrates is employed here, consisting of adsorption, decomposition and surface diffusion probabilities. The simulation results are fit to previously-obtained experimental data. Sensitivity analysis is conducted to study the relative importance of the parameters involved, in an effort to get a better understanding of the physical process. A measure of "quality of coverage" is introduced, to assess the quality of the formed bilayers.

Section II of this paper focuses on the description of the mass transport model used in the development of the simulation model. In section III the details of the simulation model are given. Section IV presents the simulation results, the sensitivity analysis and the proposed quality of coverage measure.

II. Mass Transport Model

The simulation model incorporates basic mass transport principles of a model previously published by Hubbard *et al*[14]. This model is based on Fick's second law of diffusion:

$$\frac{\partial c(z,t)}{\partial t} = D\frac{\partial^2 c(z,t)}{\partial z^2}, \tag{2.1}$$

where $c(z,t)$ is the concentration of mass at a distance z from the surface and at time t, and D is the mass diffusion coefficient.

The initial condition is given by:

$$c(z,t)\big|_{t=0} = C_0, \tag{2.2}$$

where the concentration, C_0, is a constant.

The diffusive flux on a perfectly adsorbing surface J_{surf} is obtained according to the expression:

$$J_{surf} = D\frac{\partial c(z,t)}{\partial z}\bigg|_{z=0} = Kc(z,t)\big|_{z=0}, \tag{2.3}$$

where the constant K is the adsorption rate constant elsewhere referred to as the reorganization rate constant[14].

Equations (2.1)-(2.3) can be solved analytically to obtain

$$J_{surf} = KC_0 \exp\left(\frac{K^2 t}{D}\right) erfc\left(\frac{K\sqrt{t}}{\sqrt{D}}\right). \tag{2.4}$$

We note that in practice, the solution is not static and the vesicles are not uniformly distributed at t=0. Specifically, at the beginning of the experiment[7] 10 ml of the vesicle solution of interest is injected in a 20 ml ellipsometric cell, initially filled with de-ionized water, in approximately two seconds displacing an equivalent amount of volume. Mixing occurs within a few seconds (much smaller than the time required to reach saturation), while minutes might be required for the solution to become static[7]. The overall influence of transient chaotic convection, though, is being captured by an average value for the diffusion coefficient in Eq. (2.4), as discussed elsewhere[7]. Therefore, we believe Eq. (2.4) is a reasonable approximation of J_{surf}.

III. Simulation Model

In this Lattice Monte Carlo simulation, the surface is discretized into grid sites. Each site can assume only one of the following three states: unoccupied (vacant), occupied by a vesicle, or occupied by a membrane fragment[13], where a membrane fragment is defined as a piece of bilayer with the size of a grid cell. Each vesicle adsorption event, each decomposition event and each diffusion event is assigned a probability. When a vesicle is adsorbed on a grid site, the state of this site is changed from 'unoccupied' to 'occupied by vesicle'. When a vesicle on a site ruptures, the state of this site and the neighboring sites is changed to 'occupied by membrane fragments', assuming the surface area stays constant during the decomposition process. In the following, the details of the Monte Carlo model used in this study are given.

A. Model for adsorption probability

An effort is made to capture some of the physical aspects of the vesicle adsorption process by computing the adsorption probability for each particular site. The driving force of adsorption is the vesicle-surface interaction, which can be limited by additional vesicle-vesicle and vesicle-membrane fragment interactions[8,9,10].

Let the radius of a vesicle in solution be R_0. An effective radius R_1 is defined as the radius of an adsorbed vesicle on the surface. R_1 is greater than R_0 due to vesicle

deformation[13]. It is assumed that adsorbed vesicles can have a limited elastic deformation when they compress each other. The smallest possible radius of an adsorbed vesicle is the vesicle core radius $R_2 (\leq R_1)$.

The effect of vesicle-vesicle spatial constraint on vesicle adsorption is modeled by defining a continuous adsorption probability function P_{ad}^{v} of R^i, the distance between a newly arrived vesicle and an already adsorbed vesicle *i*. If $R^i \leq 2R_2$ (case I), the adsorption attempt fails because the radius of an adsorbed vesicle cannot be smaller than R_2. In this case, the adsorption probability is 0. If $R^i \geq 2R_1$ (case II), there is no physical interaction between the newly arrived vesicle and the adsorbed vesicle *i*, thus the adsorption probability is 1. If $2R_2 \leq R^i \leq 2R_1$ (case III), the adsorption probability is between 0 and 1, and is approximated by the following empirical formula

$$P_{ad}^{v} = \exp\left[-\alpha \sum_i \frac{\left(2R_1 - R^i\right)^2}{\left(R^i - 2R_2\right)^2}\right], \tag{3.1}$$

where α is a constant. Summarizing,

$$P_{ad}^{v} = \begin{cases} 0 & R^i \leq 2R_2 \quad \text{case I} \\ 1 & R^i \geq 2R_1 \quad \text{case II} \\ \exp\left[-\alpha \sum_i \frac{\left(2R_1 - R^i\right)^2}{\left(R^i - 2R_2\right)^2}\right] & 2R_2 \leq R^i \leq 2R_1 \quad \text{case III} \end{cases} \tag{3.2}$$

These three adsorption scenarios are schematically shown in *Figure 1*. Zhdanov *et al.*[13] used the probability reduction factor $P = \exp\left[-\alpha \sum_i \left(2R_1 - R^i\right)^2\right]$, to model the

vesicle-vesicle spatial constraint on adsorption for $2R_2 \le R^i \le 2R_1$, based on the assumption that the adsorption activation energy increases proportionally to the overlap of the vesicle volumes. The advantage of using Eq. (3.2) instead is that P_{ad}^v becomes a continuous function over the entire range of R^i, while $-\log\left(P_{ad}^v\right)$ approximates the repulsive potential energy of hard spheres with an R_2 radius.

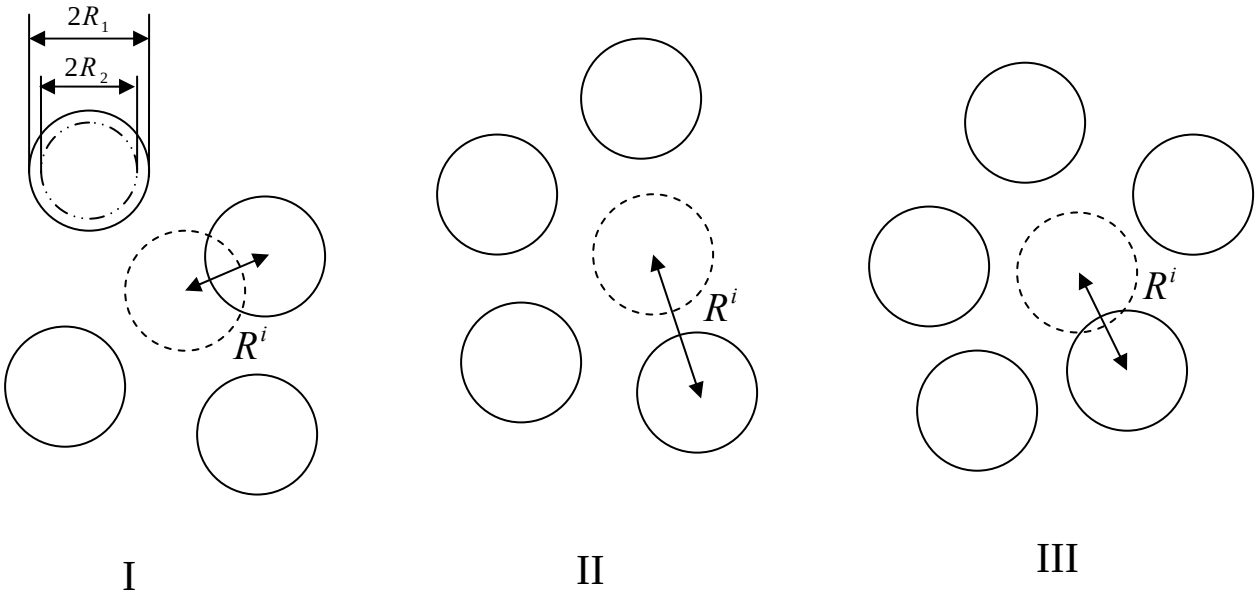


Fig. 1. Vesicle-vesicle spatial constraint scenarios.

A newly arrived vesicle should have enough surface area available to get and stay adsorbed for the given vesicle-surface interaction strength. The larger the surface area for vesicle-surface interaction, the greater the probability of adsorption. However, available surface area can be limited by the amount of membrane fragments adsorbed. The adsorption probability for a site *j* is therefore taken to be

$$P_{ad}(j) = P_{ad}^{v} \times \frac{S_{vacant}}{S_{vacant} + S_{occupied}}, \tag{3.3}$$

where S_{vacant} and $S_{occupied}$ are the vacant and occupied by membrane fragments cells in the neighborhood of site j, respectively.

The adsorption events are also assumed to depend on the flux of vesicles to the surface, which is given by Eq. (2.3). Eq. (3.3) is just the adsorption probability for a vacant site *j* without consideration of the flux limitation. The flux limitation is given by:

$$P_f = \frac{J_{surf}}{J_{\max}}, \tag{3.4}$$

where J_{max} is the maximum flux of mass to the surface, $J_{\max} = (KC_0)_{\max}$ and *t*, in the J_{surf} flux expression, is calculated from the Monte Carlo steps in the simulation algorithm using an appropriate fitting parameter. Thus the final adsorption probability for site *j* can be written as

$$P_{ad}^{*}(j) = P_{ad}(j) \times P_f . \tag{3.5}$$

B. Model for decomposition probability

The adsorbed vesicles decomposition (or rupture) is driven by vesicle-vesicle, vesicle-lipid membrane and vesicle-surface interactions[8,9,10,11], which can be realized though four channels:

(1) Spontaneous single vesicle decomposition.

(2) Decomposition caused by newly adsorbed vesicles.

(3) Fusion to form a larger vesicle, followed by decomposition.

(4) Lipid-induced decomposition.

To realize channels (1) and (4), the following formula[13] is used:

$$P_{dec} = P_{dec}^{0} + n \cdot P_{dec}^{1}, \tag{3.6}$$

where P_{dec}^{0}, P_{dec}^{1} correspond to spontaneous decomposition (channel 1) and lipid-induced decomposition (channel 4) respectively, and n is the number of nearest neighbor sites occupied by membrane fragments.

Channels (2) and (3) are similar in nature and can be combined as the vesicle-vesicle decomposition channel. To realize this channel, i.e., vesicle decomposition induced by a newly arrived vesicle, a critical radius R_c [13] is defined ($R_2 \le R_c \le R_1$). If $\min R_j < 2R_c$, then decomposition of both the nearest neighbor vesicle and the newly arrived vesicle occurs with probability 1. A vesicle decomposition event is simulated by random walks of the membrane fragments released by a vesicle. The parameter *Nl* denotes the number of membrane fragments released by one vesicle decomposition event[13].

C. Surface diffusion model

A fluid membrane fragment can diffuse on the surface and locate positions that minimize the energy associated with its hydrophobic edges. This is the mechanism by which separate membrane fragments bind together through lateral diffusion on the surface, ultimately forming a continuous lipid bilayer. In this simulation, diffusion on the

surface is realized by jumps of membrane fragments between two sites, according to the Metropolis rule[15,16]:

$$P(jump) = \begin{cases} 1 & \Delta E \le 0 \\ \exp\left(-\dfrac{\Delta E}{k_B T}\right) = \exp\left(-\dfrac{(n_{initial} - n_{final})\beta\varepsilon}{k_B T}\right) & \Delta E > 0 \end{cases}, \tag{3.7}$$

where ΔE is the (binding) energy difference between the initial and final states, k_B is the Boltzmann constant, T is the temperature, $n_{initial}$ is the number of membrane fragments directly connected to the initial site, n_{final} is the number of membrane fragments directly connected to the final site, and $\beta\varepsilon$ is the line energy at the bilayer-water interface resulting from a membrane fragment-membrane fragment dissociation event. In this simulation, ε is set equal to $k_B T$ and β is defined as the coefficient of line energy.

D. Outline of the simulation

The simulation begins by setting up all the parameters. Unless the stop condition (90% of the whole surface is covered by membrane fragments) is satisfied, a site is picked up randomly:

(1) If the site is vacant, an adsorption attempt is made according to the probability given by Eq. (3.5).

(2) If the site is occupied by vesicles, a decomposition attempt is made according to Eq. (3.6).

(3) If the site is occupied by membrane fragments, surface diffusion is implemented according to Eq. (3.7).

In all three cases, a uniform random number between 0 and 1 is generated and the attempt is successfully completed if that number is smaller than the probability of the event. After any of these events is carried out, the surface coverage is updated and the loop continues.

IV. Results and Discussion

A. Simulation results

(1) Coverage curves

Figure 2 shows how the fraction of occupied sites, the vesicle coverage and the total uptake vary with time. The fraction of occupied sites is the percentage of sites occupied by either vesicles or membrane fragments. A normalization factor, which corresponds to the maximum mass of vesicles that can be adsorbed (assuming no vesicle decomposition), is used to scale the total uptake and the vesicle coverage. The total uptake curve describes the normalized total mass accumulation on the substrate (including vesicles and membrane fragments), and the vesicle coverage curve gives the normalized vesicle mass adsorbed on the substrate. It can be readily seen that the bilayer formation process consists of two stages. In the first stage, vesicles adsorb on the surface up to an appreciable coverage (a critical surface coverage) and the total uptake increases sharply; in the second stage decomposition becomes dominant, hence vesicle coverage starts to decrease and the bilayer is formed. The rate of total uptake begins to decrease,

due to fewer vesicle adsorption events. These observations are in agreement with experimental data[4,8].

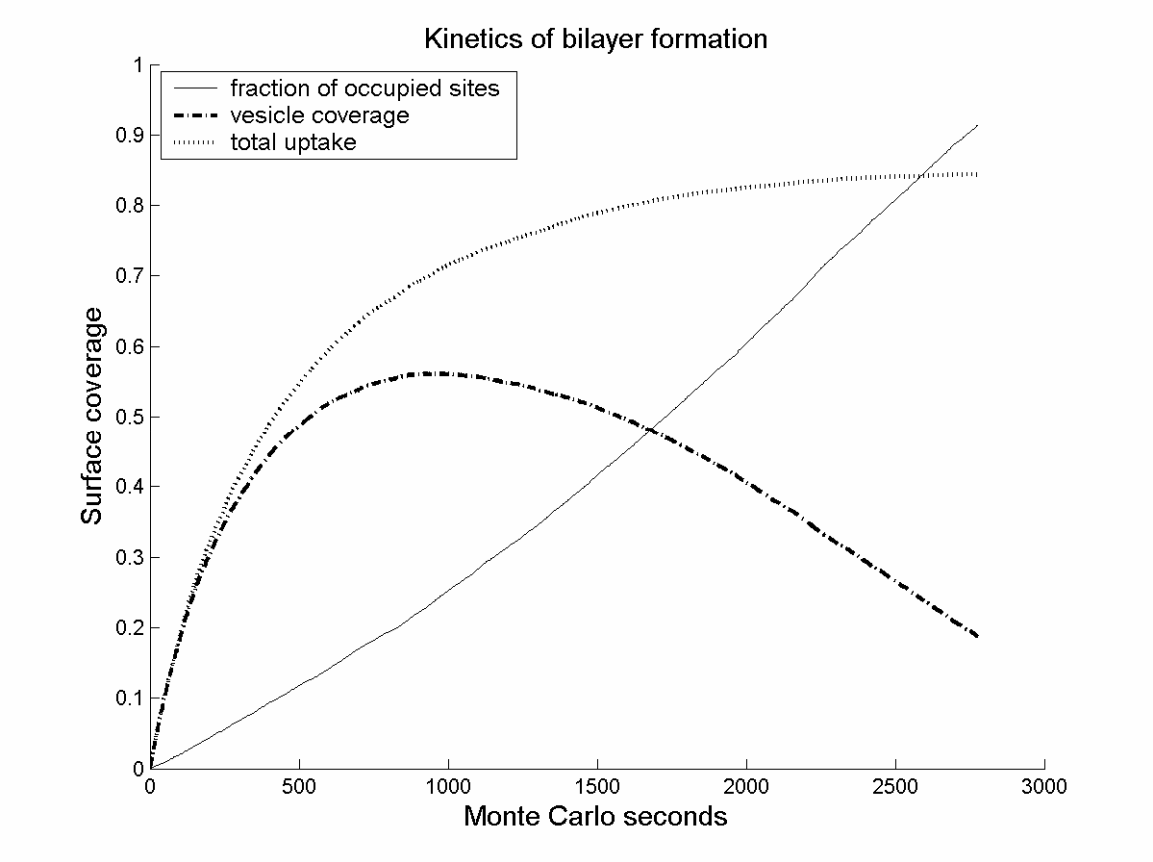


Fig. 2. Fraction of occupied sites (dotted line), normalized vesicle coverage (dashed line) and normalized total uptake (solid line) as a function of Monte Carlo steps (number of steps in the Monte Carlo simulation), at concentration C_0=0.025 mg/ml using a 500×500 grid.

(2) Snapshots of surface

In Figure 3, snapshots of the distribution of vesicles and membrane fragments on the surface are presented, where large circles denote vesicles and small circles denote membrane fragments. This illustrates the bilayer formation process, in which vesicles are adsorbed on the surface, decomposed to release membrane fragments, and fragments "flow" on the surface to form a continuous bilayer. The simulation is interrupted when 90% of the surface is covered by membrane fragments, corresponding to time *T* in Figure 3.

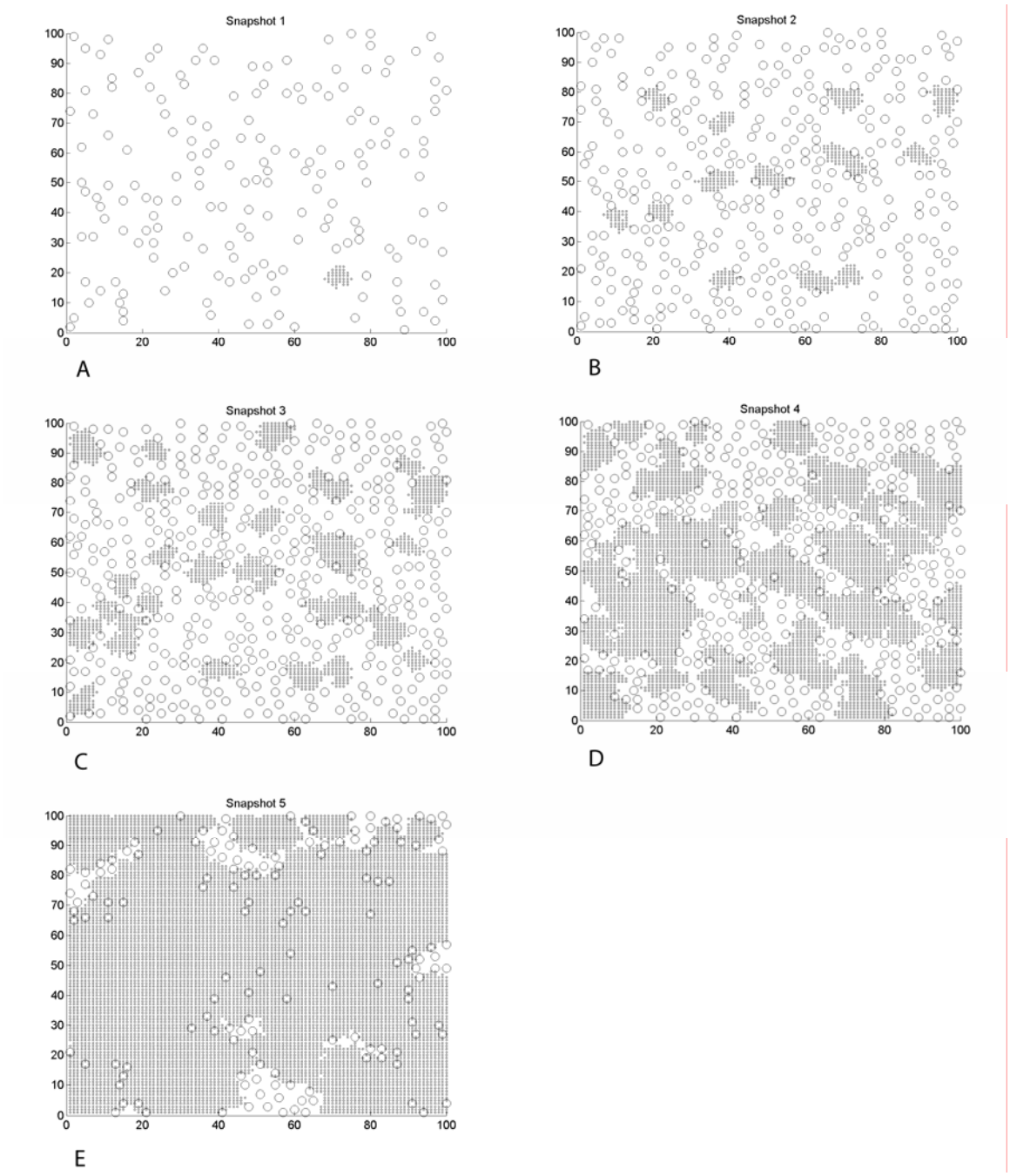


Fig. 3. Snapshots of surface (100×100 grid), at concentration C_0=0.025 mg/ml. A: *t*=*T*/18, B: *t*=3*T*/18, C: *t*=6*T*/18, D: *t*=12*T*/18, E: *t*=18*T*/18. *T* is the time at which 90% of the surface is covered by membrane fragments.

(3) Coverage quality

We propose the concept of "quality of coverage" to gauge the success of the SLB formation process, together with coverage. The quality of coverage is introduced to quantify the uniformity of SLBs that, along with the completeness of coverage, constitute two critical parameters in realistic applications of interfacial membranes. The percentage of coverage, used in common practice, is incomplete, since it includes no measure of uniformity. For example, a surface could be 90% covered, but if the uncovered portion consists mostly of a large defect then the coverage would be highly non-uniform and of low quality.

We define the quality of coverage Q by:

$$Q = 1 - \frac{1}{M-1}\sum_{i=2}^{M} C_i \sum_j \left(N_j - i^2\theta\right)^2 , \tag{4.1}$$

where i is the scale index, j is the square box index of scale i (meaning the jth square box with length i on the surface), M is the largest scale, N_j is the number of sites occupied by membrane fragments inside the box j, θ is the fraction of sites occupied by membrane fragments over the entire grid and C_i is the normalization factor, given by:

$$C_i = \begin{cases} \dfrac{1}{\sum_j (i^2\theta)^2}, & \theta \geq 0.5 \\ \dfrac{1}{\sum_j [i^2(1-\theta)]^2}, & \theta < 0.5 \end{cases} . \tag{4.2}$$

This measure, which was inspired by a concept proposed for the quantification of mixing in fluids[17], is an average over all possible different boxes of all scales, the scale being the

resolution of the measure. A non-uniform quality of coverage would be sensitive to resolution. In our measure this is compensated by averaging over all scales. As defined by Eq. (4.1) $Q \in [0,1]$, where the larger the value the better the coverage quality.

Figure 4 illustrates that the mean Q (out of 20 runs) as well as its standard deviation appear to be converging, as the grid is refined.

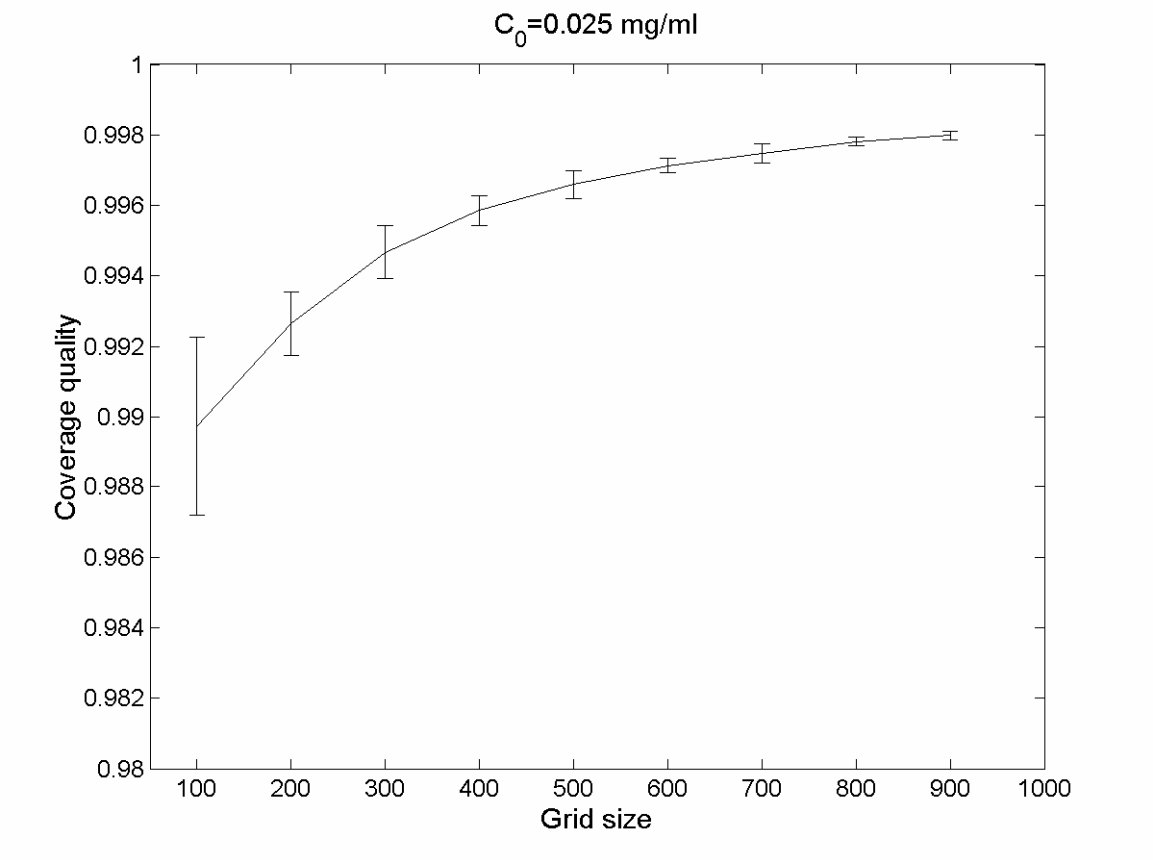


Fig. 4. Coverage quality versus grid size, at concentration C_0=0.025 mg/ml.

The coverage quality at four different vesicle bulk concentrations is presented in Figure 5. The figure shows that the higher the vesicle concentration, the better the coverage quality, for the range of concentrations studied.

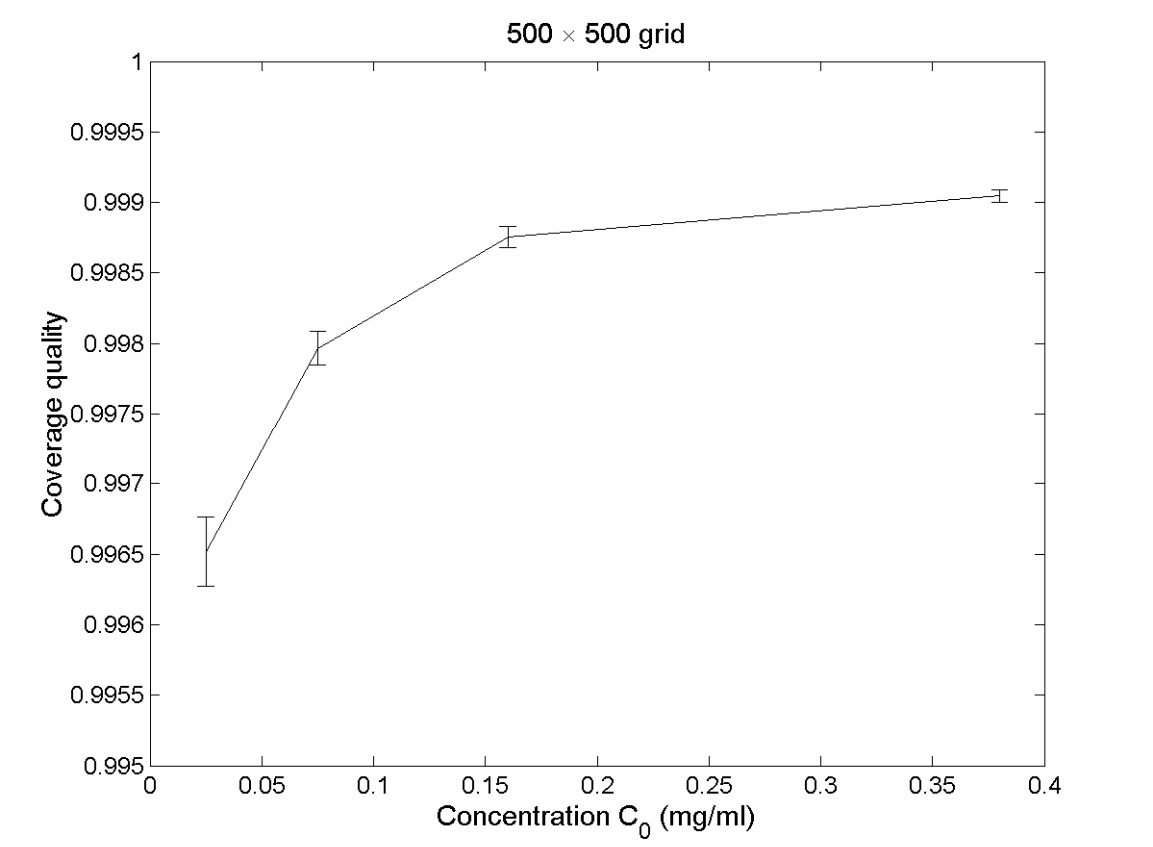


Fig. 5. Coverage quality at different concentrations using a 500×500 grid.

(4) Comparison of simulation results with experimental data

In Figure 6 the simulation results for surface coverage are compared to the experimental data[7] at four different vesicle bulk concentrations. It can be concluded that the simulation results agree reasonably well with the experimental data.

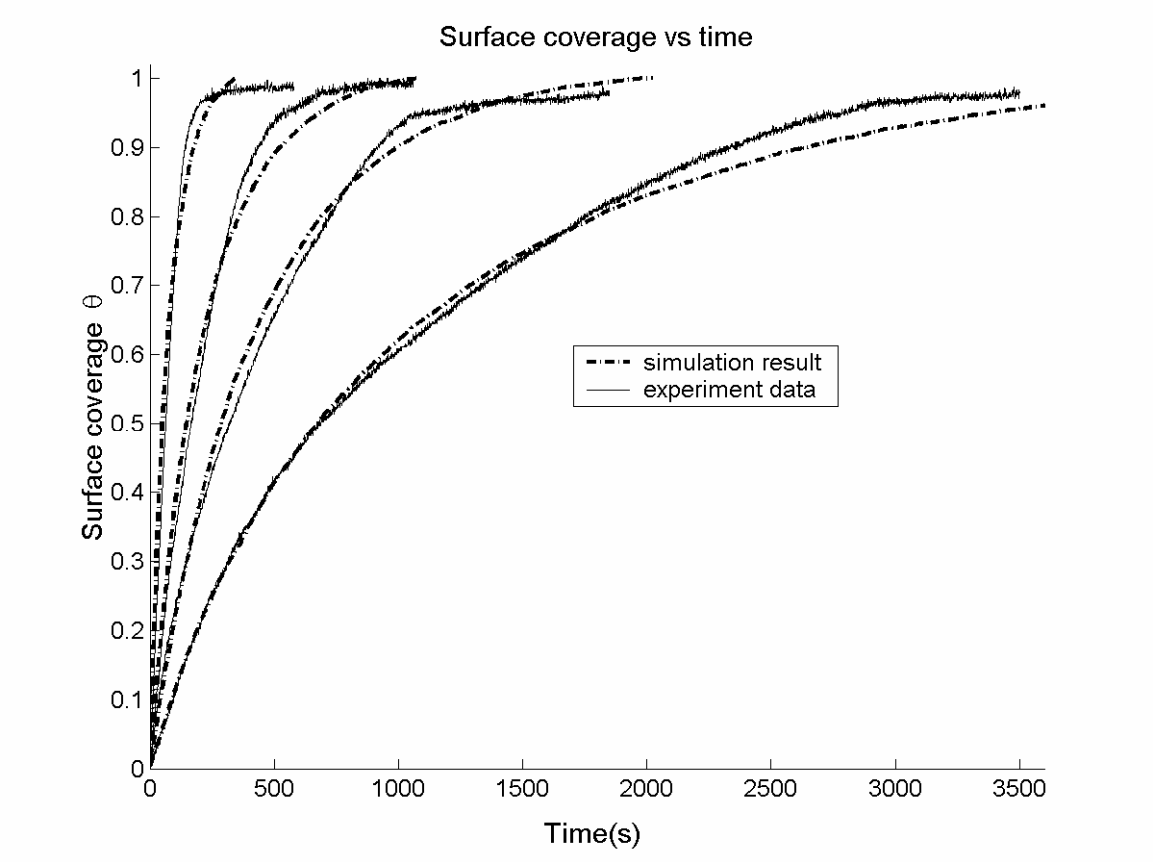


Fig. 6. Comparison of the simulation results to the experimental data. The four curves are for bulk concentrations of C_0=0.025, 0.075, 0.16, 0.38 mg/ml respectively.

B. Parameter sensitivity analysis

Analyzing the sensitivity of the simulation experiment to the various parameters involved can be a useful method for determining their physical significance. In this paper, sensitivities are calculated by a finite difference method. We define the variable S as the L_2 error between the simulation result Γ_s and the experimental data Γ_e:

$$S = \left(\int_0^T (\Gamma_s - \Gamma_e)^2 \, dt\right)^{\frac{1}{2}}. \tag{4.3}$$

The sensitivity of the SLB formation process to a parameter P is given by $\frac{dS}{dP}$. This is approximated by finite differencing as:

$$\frac{dS}{dP} \approx \frac{S(P + \Delta P) - S(P)}{\Delta P}, \tag{4.4}$$

where the perturbation ΔP is the smallest possible that makes $\left|S\left(P + \Delta P\right) - S\left(P\right)\right|$ much larger than random noise, where the latter is estimated by the standard deviation of an S sampling. ΔP is then determined by trial and error through comparison of $\left|S\left(P + \Delta P\right) - S\left(P\right)\right|$ with the estimated random noise of S. The sensitivities $\frac{dS}{dP}$ and the scaled, dimensionless, sensitivities $\frac{dS}{dP} \cdot \frac{P}{S}$ with respect to the parameters used in this simulation are given in Table 1.

TABLE 1. Parameter sensitivities

Parameter symbol	Parameter meaning	Value of parameter in the program	Sensitivities	
			$\frac{dS}{dP}$	$\frac{dS}{dP}\cdot\frac{P}{S}$
C_0	Bulk concentration in the solution	0.025 (mg/ml)	1235	5.807
K	Adsorption rate constant	1.6 (10^{-7} m/s)	17.03	5.443
D	Diffusion coefficient	8.7 (10^{-10} m^2/s)	0.1671	0.2733
Nl	No. of fragments released by one vesicle decomposition	19	1.626	5.809
P_{dec}^0	Spontaneous decomposition probability	0.005	43.37	0.04077
P_{dec}^1	Lipid-induced decomposition probability	0.49	4.545	0.4188
R_1	Vesicle effective radius	2.0	10.58	3.980
R_2	Vesicle core radius	1.4	329.9	86.83
R_c	Vesicle critical radius	1.5	159.2	44.90
α	Exponential coefficient of adsorption probability	4.0e-4	$8.96\cdot10^3$	0.6736
β	Coefficient of line energy	3.53	<0.3	<0.2

The adsorption rate constant (K) and the diffusion coefficient (D) values were determined by fitting the mass transport model described in section II to the experimental data[7] at vesicle bulk concentration C_0=0.025 mg/ml. The diffusion coefficient for 100 nm

diameter vesicles as predicted by the Stokes-Einstein equation is $5x10^{-12}$ m^2/s. The discrepancy with the value determined by the mass transport model is discussed elsewhere[7]. The vesicle effective radius (R_1) was set to the dimensionless value 2 (2 times the lattice spacing), while the vesicle core radius (R_2), the vesicle critical radius (R_c), the exponential coefficient of the adsorption probability (α), the line energy coefficient (β) and the number of membrane fragments released per vesicle decomposition (Nl) were the fitting parameters. It is assumed that the lipid-induced decomposition channel is more important than the spontaneous decomposition channel, as reflected by the relative magnitude of those two parameters[13].

As shown in Table 1, the scaled sensitivities indicate that the bilayer formation process is an order of magnitude more sensitive to the concentration (C_0) and to the adsorption rate constant (K), than it is to the diffusion coefficient (D). This agrees with the experimentally observed adsorption limited kinetics[7]. Since the sensitivity with respect to the parameter P_{dec}^1 (lipid-induced decomposition) is an order of magnitude greater than the sensitivity to the parameter P_{dec}^0 (spontaneous decomposition), it can be concluded that the lipid-induced decomposition channel is indeed more significant than the spontaneous decomposition channel. This is not surprising since one would expect that the spontaneous decomposition channel would be more important when hydrophobic surfaces are considered. In such a case vesicles would be prone to rupture immediately after adsorption, possibly due to complete dehydration of their contact area.

The process appears to be sensitive to all radii parameters R_1 (vesicle effective radius), R_2 (vesicle core radius) and R_c (vesicle critical radius) and especially R_2 and R_c. The sensitivity to both R_1 and R_2 is not surprising since they determine whether or not an

adsorption event is going to be successful. The larger sensitivity to the R_2 parameter, as compared to R_1, is probably associated with the hard sphere potential approximation used in the derivation of the adsorption probability. On the other hand, the sensitivity to R_c suggests that the vesicle-vesicle decomposition pathway is very important in the SLB formation process. By increasing the vesicle effective radius R_1 or the vesicle core radius R_2, the bilayer formation is decelerated because of a decrease in the adsorption probability. Finally, a larger vesicle core radius R_c means a less stringent criterion for the vesicle-vesicle decomposition channel. Hence rupture becomes more favorable, resulting in a faster process.

The SLB formation process is also sensitive to the parameter *Nl*, the number of membrane fragments released per vesicle decomposition. This parameter is a function of the real vesicle size. Large *Nl* values correspond to a faster rate of surface coverage by membrane fragments. Finally, the low sensitivity to the parameter β, the coefficient of line energy, suggests that the rate of the process, as described by this MC model, is not limited by surface diffusion.

V. Conclusion

In this work the Monte Carlo method was used for simulating the SLB formation process, based on a model developed by Zhdanov et al[13]. This model associates adsorption, decomposition and surface diffusion processes with probability functions formulated using fundamental physical interactions as well as mass transport principles.

Sensitivity analysis was used to determine the relative significance of the parameters used in the model. It was concluded that the bilayer formation process is sensitive to the bulk concentration C_0 and to the adsorption rate constant K and to a lesser degree to the diffusion coefficient D. These conclusions are consistent with the results of a previously conducted kinetic study[7]. The analysis also revealed that the lipid-induced decomposition channel is more significant than the spontaneous decomposition channel and that the process is sensitive to the vesicle radii parameters and to the parameter Nl, the number of fragments released per vesicle decomposition.

The concept of "coverage quality" was proposed to measure the quality of the formed SLB. The importance of this index lies in that it provides a measure for comparison and a basis for future optimization of SLB formation processes. It was determined that coverage quality increases with increasing vesicle bulk concentration, over the range of concentrations studied.

The model presented is capable of simulating how parameters such as concentration, bulk and surface mass diffusion, adsorption rate constant and different adsorption and rupture scenarios affect the fusion process on both hydrophilic and hydrophobic substrates. The effects of temperature and real vesicle radius on the process are still not accurately represented by this model, since for example their impact on adsorption and rupture is not captured. Current efforts on improving the model are focused on extending to arbitrary geometries and on coupling fusion with flow, which better reflects the deposition conditions in microdevices.

ACKNOWLEDGEMENTS:

This work was supported in part by the National Science Foundation under NSF awards NSF/MRSEC DMR00-80034, NSF/NIRT CTS-0103516, NSF/ITR ACI-0086061, NSF/CCF-0428912 and NSF/CTS-0205584 and the Army Research Office through the Institute for Collaborative Biotechnologies.

References

[1] E. Sackmann, Science **271** (5245), 43 (1996).

[2] C. A. Keller and B. Kasemo, Biophysical Journal **75** (3), 1397 (1998).

[3] J. Texter and M. Tirrell, AIChE Journal **47** (8), 1706 (2001).

[4] C. A. Keller, K. Glasmastar, V. P. Zhdanov, and B. Kasemo, Physical Review Letters **84** (23), 5443 (2000).

[5] E. Gizeli, C. R. Lowe, M. Liley, and H. Vogel, Sensors and Actuators B-Chemical **34** (1-3), 295 (1996).

[6] I. Reviakine and A. Brisson, Langmuir **16** (4), 1806 (2000).

[7] D. Stroumpoulis, A. Parra, and M. Tirrell, Submitted to AIChE Journal (2005).

[8] E. Reimhult, F. Hook, and B. Kasemo, Langmuir **19** (5), 1681 (2003).

[9] E. Reimhult, F. Hook, and B. Kasemo, Physical Review E **66** (5) (2002).

[10] U. Seifert, Advances in Physics **46** (1), 13 (1997).

[11] V. P. Zhdanov and B. Kasemo, Langmuir **17** (12), 3518 (2001).

[12] E. Reimhult, F. Hook, and B. Kasemo, Journal of Chemical Physics **117** (16), 7401 (2002).

[13] V. P. Zhdanov, C. A. Keller, K. Glasmastar, and B. Kasemo, Journal of Chemical Physics **112** (2), 900 (2000).

[14] J. B. Hubbard, V. Silin, and A. L. Plant, Biophysical Chemistry **75** (3), 163 (1998).

[15] V. P. Zhdanov, Surface Science **392** (1-3), 185 (1997).

[16] V. P. Zhdanov and B. Kasemo, Journal of Chemical Physics **109** (15), 6497 (1998).

[17] G. Mathew, I. Mezic, and L. Petzold, Submitted to Physica D: Nonlinear Phenomena (2005).

TABLE 1. Parameter sensitivities

Parameter symbol	Parameter meaning	Value of parameter in the program	Sensitivities	
			$\frac{dS}{dP}$	$\frac{dS}{dP}\cdot\frac{P}{S}$
C_0	Bulk concentration in the solution	0.025 (mg/ml)	1235.4	5.807
K	Adsorption rate constant	1.6 (10^{-7} m/s)	17.027	5.443
D	Diffusion coefficient	8.7 (10^{-10} m^2/s)	0.1671	0.2733
Nl	No. of fragments released by one vesicle decomposition	19	1.6259	5.8085
P_{dec}^0	Spontaneous decomposition probability	0.005	43.369	0.04077
P_{dec}^1	Lipid-induced decomposition probability	0.49	4.5453	0.4188
R_1	Vesicle effective radius	2.0	10.5832	3.9797
R_2	Vesicle core radius	1.4	329.8581	86.8287
R_c	Vesicle critical radius	1.5	159.2001	44.8996
α	Exponential coefficient of adsorption probability	4.0e-4	$8.96\cdot10^3$	0.6736
β	Coefficient of line energy	3.53	<0.3	<0.2

Fig. 1. Vesicle-vesicle spatial constraint scenarios.

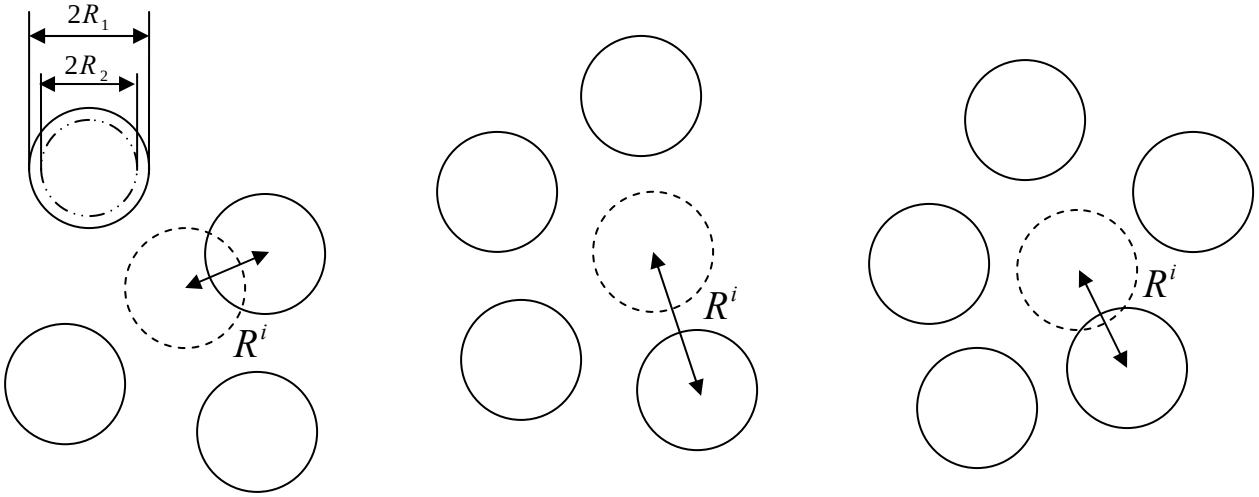
Fig. 2. Fraction of occupied sites (dotted line), normalized vesicle coverage (dashed line) and normalized total uptake (solid line) as a function of Monte Carlo steps (number of steps in the Monte Carlo simulation), at concentration C_0=0.025 mg/ml using a 500×500 grid.

Fig. 3. Snapshots of surface (100×100 grid), at concentration C_0=0.025 mg/ml. A: $t=T/18$, B: $t=3T/18$, C: $t=6T/18$, D: $t=12T/18$, E: $t=18T/18$. T is the time at which 90% of the surface is covered by membrane fragments.

Fig. 4. Coverage quality versus grid size, at concentration C_0=0.025 mg/ml.

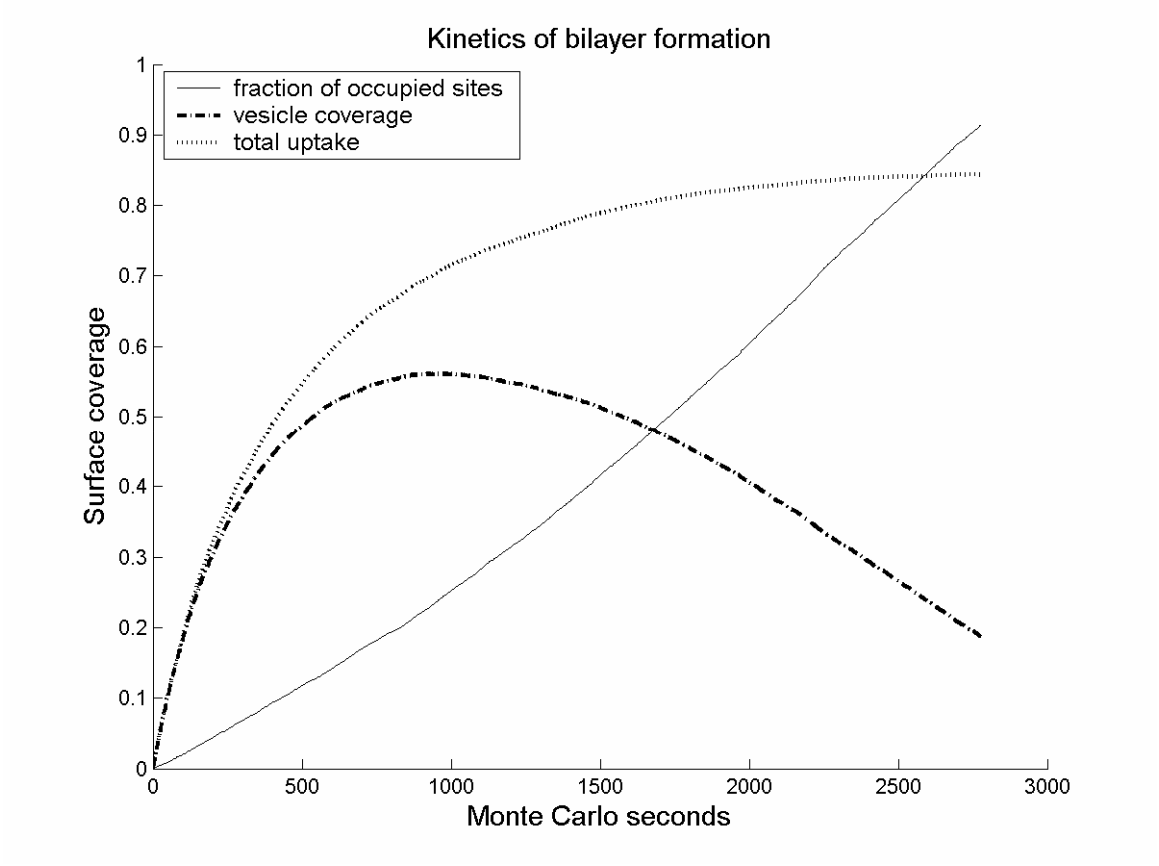
Fig. 5. Coverage quality at different concentrations with a 500×500 grid.

Fig. 6. Comparison of the simulation results to the experimental data. The four curves are for bulk concentrations of C_0=0.025, 0.075, 0.16, 0.38 mg/ml respectively.

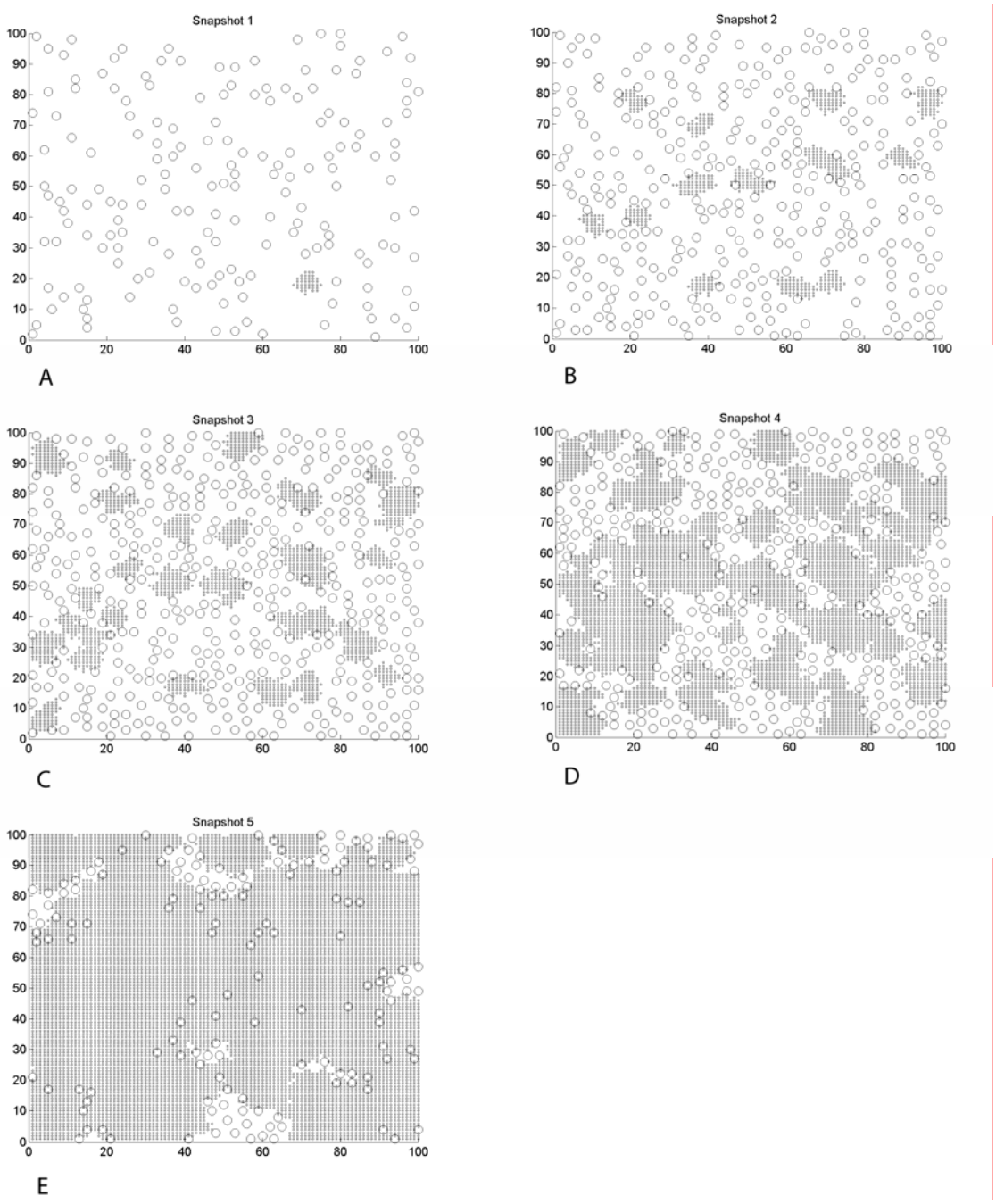


I II III

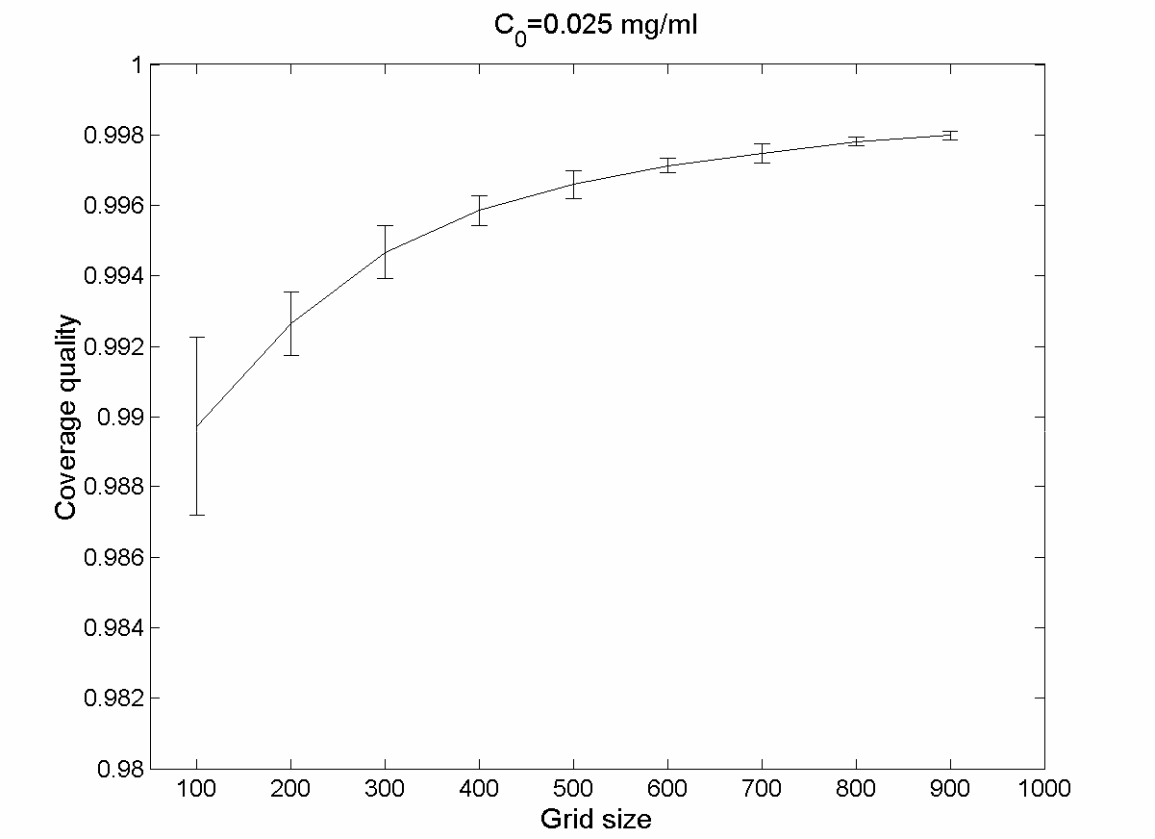
Z. Zheng et al., Fig. 1



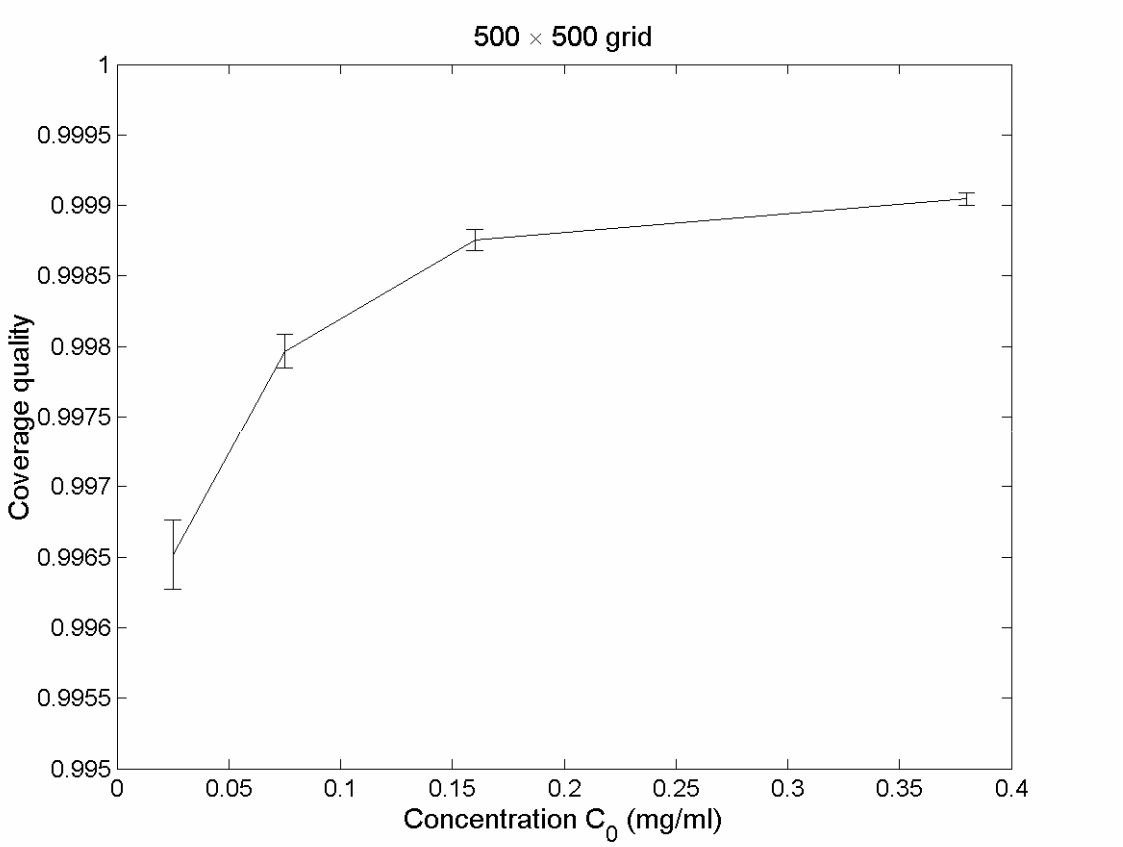
Z. Zheng et al., Fig. 2



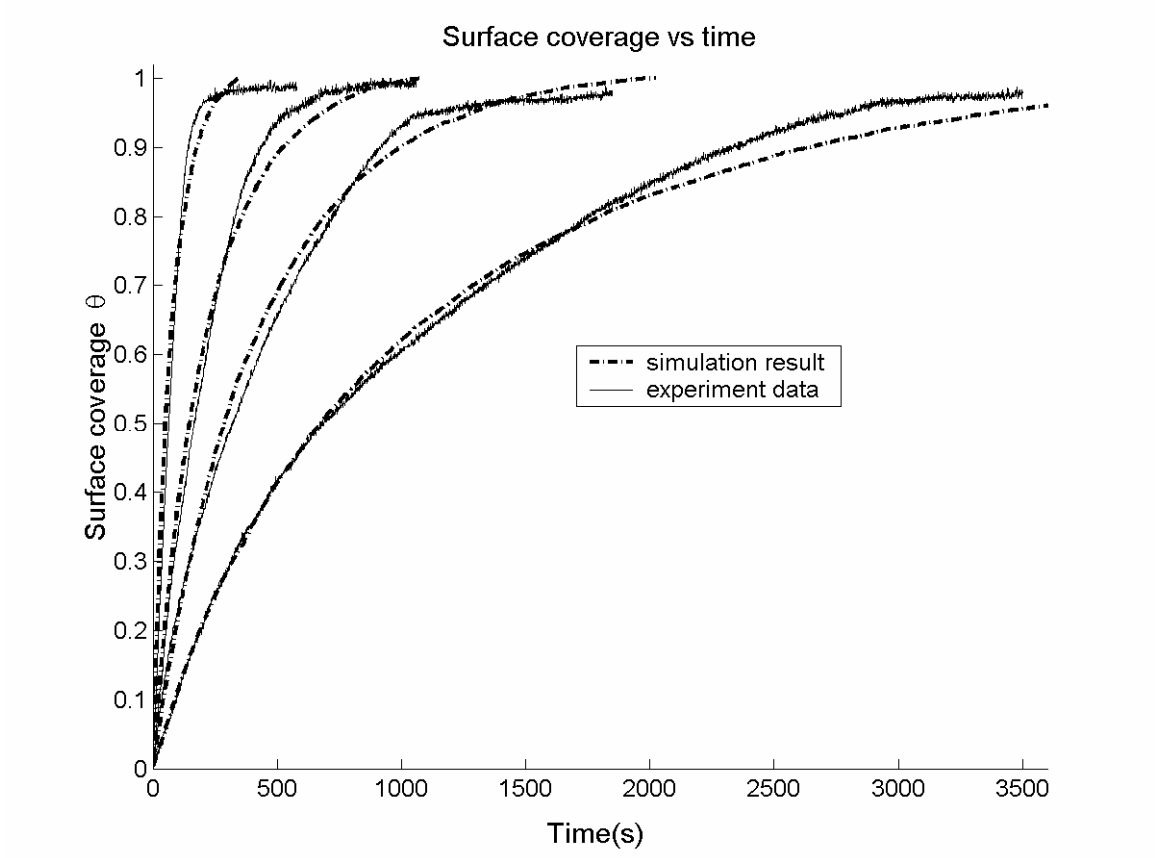
Z. Zheng et al., Fig. 3



Z. Zheng et al., Fig. 4



Z. Zheng et al., Fig. 5



Z. Zheng et al., Fig. 6