

Two theoretical studies: limits of the poisson-boltzmann theory and study of platelets in a micro-channel Justine Pujos

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Laboratoire Gulliver École Supérieure de Physique et de Chimie Industrielles

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Spécialité : Physique Statistique

présentée par **Justine Pujos**

pour obtenir le grade de DOCTEUR de l'UNIVERSITÉ PARIS 6

Two theoretical studies:

limits of the Poisson-Boltzmann theory and study of platelets in a micro-channel

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Introduction

La simulation trouve ces origines dans le problème des aiguilles posé par Buffon en 1777 et corrigé par Laplace en 1812. En 1899, Gosset utilise les statistiques pour optimiser la production et la qualité de la brasserie Guinness.

Le domaine de la simulation apparaît véritablement avec l'utilisation des premiers ordinateurs pour le développement de l'arme nucléaire en 1943. Il connaît un essor dans les années 50 avec la dé-classification des ordinateurs. De la machine à calculer au premier ordinateur composé uniquement de transistor (Stretch,1960) en passant par l'ordinateur électronique (ENIAC, 1946), de nombreux domaines scientifiques furent explorés à l'aide de simulations. Ces recherches, incluant des simulation de matériaux dans des conditions de pression et de température extrêmes, la résolution d'équations de mécanique des fluides, ou des tentatives de décodage de l'ADN, avaient pour double objectifs de tester la capacité des machines et de résoudre ces problèmes scientifiques.

En 1949, Metropolis et Ulam présentent la méthode de Monte-Carlo qui est implémentée en 1953.

En 1956, Alder et Wainwright programment la première simulation de dynamique moléculaire.

Dans le début des années 60, alors que les premiers calculs en parallèle sont réalisés (SOLOMON), Conway, Johnson et Maxwell étudient la théorie de la simulation numérique. En particulier, ils présentent plusieurs problématiques liées à la simulation. D'une part, la création de simulations est à l'origine de problèmes spécifiques comme l'organisation modulaire d'un programme afin de faciliter sa correction et son entretien, le contrôle des erreurs dues à la discrétisation, ou l'efficacité d'un calcul effectué à chaque pas de temps. D'autre part, l'utilisation de cet outil présente des problématiques autres comme l'influence des conditions initiales ou l'estimation de la précision des résultats.

Les simulations assistées par ordinateurs présentent plusieurs intérêts et se placent entre la théorie où les approximations sont nécessaires pour résoudre analytiquement les équations, et les expériences. En effet, les expériences nu-

mériques permettent de tester des théories en comparant les données fournies par les simulations aux résultats analytiques. Les propriétés calculées numériquement peuvent aussi être comparées aux données expérimentales pour déterminer la valeur des paramètres décrivant le système, comme des forces d'interactions entre particules par exemple.

Une fois validée, une simulation permet de prédire le comportement d'un système, en particulier dans des situations de température et de pression difficilement réalisable expérimentalement ou pour des matériaux pas encore synthétisés.

La simulation numérique permet aussi d'analyser plus rapidement les résultats expérimentaux. L'identification automatique des southern blots facilite le décryptage de brin d'ADN. Des simulations de dynamique moléculaire combinées à des mesures RMN permettent la détermination efficace de structure de molécule.

Enfin, les ordinateurs permettent le stockage de données, leur organisation et partage. Cette utilisation des ressources numériques est particulièrement visible avec le project Génome et la cartographie de l'ADN.

Il est possible de distinguer deux domaines de la biologie numérique :

- le "data-mining" identifie des comportements caractéristiques à partir de la grande quantité de donnée expérimentales;
- les simulations, une fois validées, permettent de prédire le comportement dynamique des systèmes étudiés.

Dans cette thèse, deux domaines sont étudiés.

En premier lieux, je m'intéresse à l'amélioration d'un outil de simulation. Les interactions électrostatiques sont un constituant fondamental des systèmes nano- et micro-métriques naturels ou industriels. Afin de comprendre et décrire ces systèmes, l'électrostatique est décrite par l'équation de Poisson-Boltzmann. La théorie de Poisson-Boltzmann provient de la combinaison de l'équation de Poisson $\nabla \epsilon \nabla \phi = -\rho(\mathbf{r})$ et la description de Boltzmann de la densité d'ions $n_j = n_{j,0} e^{-\beta e z_j \phi}$. Dans ces expressions, ϵ est la constante diélectrique du milieu, ϕ est le potentiel électrostatique, ρ est la densité de charge, n_j est la densité locale de l'ion d'espèce j, $\beta = 1/k_B T$ est l'inverse de la température, e est la charge élémentaire et z_j le nombre de charges élémentaires portées par un ion d'espèce j. Pour relier les deux égalités, il faut détailler la densité de charge : $\rho = e \sum_j z_j n_j + \sigma$ avec σ la densité de charges fixes. L'équation de Poisson-Boltzmann s'écrit donc : $\nabla \epsilon \nabla \phi = -\sum_j z_j e n_{j,0} e^{-\beta e z_j \phi} - \sigma$. Dans le cas d'un électrolyte

symétrique, cette expression devient : $\nabla \epsilon \nabla \phi = 2 n_0 e z \sinh(\beta e z \phi) - \sigma$.

Dans cette thèse, nous considérons l'énergie libre de Poisson-Boltzmann. Elle se compose de l'énergie interne, des interactions électrostatiques et de l'entropie des ions :

$$F = \int d\mathbf{r} \left\{ -\frac{\epsilon}{2} (\nabla \phi)^2 + \rho \, \phi + k_B T \sum_j (n_j \ln (n_j / n_{j0}) - n_j) \right\}$$
$$= \int \left\{ -\frac{\epsilon}{2} (\nabla \phi)^2 - k_B T \sum_j n_{j,0} e^{-\beta e z_j \phi} + \sigma \phi \right\}$$

L'énergie libre de Poisson-Boltzmann est concave. Lorsque d'autre degrés de liberté sont nécessaires à la description du système, l'optimisation de l'énergie libre devient une recherche de point-de-col, opération numérique complexe.

Dans le chapitre 1, la transformation de Legendre est utilisée pour définir une expression équivalente de l'énergie libre qui est complètement convexe et donc plus facilement optimisable numériquement.

Le chapitre 2 traite d'une autre limite de la théorie de Poisson-Boltzmann. En effet, cette théorie est basée sur une approximation de champ moyen et nous utilisons la théorie de champs variationnels pour calculer une correction à l'énergie libre. Cette correction est numériquement estimée et la limite du programme est étudiée.

En second lieu, nous étudions un système micro-fluidique où des plaquettes sanguines, injectées en volume s'accrochent et roulent sur la surface d'un microcanal. Le chapitre 3 porte sur la simulation de ce système et deux modèles sont définis, implémentés et testés.

La transformée de Legendre appliquée à l'électrostatique

La problématique soulevée par la concavité de l'énergie libre électrostatique prend véritablement sens quand le système étudié est décrit par plusieurs degrés de libertés. En effet, l'énergie libre est convexe vis-à-vis de degrés de liberté de conformation mais concave par rapport au potentiel électrostatique. Ainsi il faut, pour optimiser l'énergie libre, trouver non pas son minimum mais son point-de-col. Différentes approches sont possibles et quatre d'entre elles sont implémentées et comparées. Un modèle une-dimension de virus est utilisé pour comparer ces quatre méthodes.

La transformée de Legendre

La transformée de Legendre d'une fonction f(x) est définie par :

$$\begin{cases} \mathcal{L}[f](s) = g(s) = sx - f(x) \\ s = \frac{df}{dx} \end{cases}$$

Une définition équivalente est donnée par $\mathcal{L}[f](s) = g(s) = \max_x (sx - f(x))$. La première définition est particulièrement pratique pour le calcul analytique d'une transformée de Legendre. La deuxième définition permet de comprendre l'intérêt que nous portons à cette transformée. En effet, nous nous intéressons à l'optimisation de l'énergie libre, or la transformée de Legendre fait intervenir explicitement un maximum (une définition utilisant un minimum existe aussi). Une forme symétrique de cet outil mathématique existe aussi : f(x) + g(s) = sx.

La transformée de Legendre possède plusieurs propriétés intéressantes. Elle est une involution : $\mathcal{L}[g](x) = f(x)$. Elle associe à la fonction $x \mapsto -f(x)$ concave, une fonction $s \mapsto g(s)$ convexe équivalente et exprimée en fonction de la dérivée de f.

La transformée de Legendre est utilisée dans de nombreux domaines scientifiques.

En mécanique classique cette transformation permet de passer d'une description lagrangienne $\mathcal{L}(\dot{q})$ à l'hamiltonien $\mathcal{H}(p)$ avec la vitesse \dot{q} et la quantité de mouvement p les variables conjuguées.

En thermodynamique, la transformée de Legendre permet de choisir la variable de description qui correspond le mieux à l'expérience décrite. Par exemple, l'énergie totale *E* est la variable conjuguée de l'inverse de la température β . Ces deux variables décrivent respectivement l'entropie S(E) et l'énergie d'Helmholtz $F(\beta)$. Il faut considérer des quantités adimentionnées pour retrouver la forme symétrique de la transformée de Legendre : $(\beta F(\beta)) + (\frac{S(E)}{k_B}) = \beta E$. Remarquons que, si le système est décrit par l'énergie $F(\beta)$ alors la température est un contrôle et l'énergie totale *E* est la réponse du système. Inversement, si l'entropie S(E) est considérée, l'énergie totale *E* est une contrainte imposée au système et β est la mesure.

En optique, la transformée de Legendre permet de passer d'une description du trajet lumineux par un point à une description angulaire. Ainsi, quatre eikonals (longueur optique d'un rayon entre deux plans) sont définies et décrivent de manière équivalente un système optique. L'outil mathématique permet aussi de déterminer la caustique d'un rayon lumineux de par la connaissance de la surface sur laquelle il est réfléchit ou réfracté. L'inverse est aussi possible et trouve son application dans l'étude du profil d'une surface ou de ses défauts.

La transformée de Legendre peut être appliquée à l'électrostatique d'une manière similaire afin d'obtenir des descriptions équivalentes d'un système. Ainsi, l'énergie libre dépendant du potentiel électrostatique ϕ peut être exprimée en fonction du champ de déplacement électrostatique **D**. Considérons la densité d'énergie libre d'un électrolyte symétrique et monovalent avec des charges fixes notées $\sigma : f(\phi) = -\frac{1}{2}\epsilon(\nabla\phi)^2 - 2c_0\cosh(\beta e\phi) + \sigma\phi$. Le terme $-\nabla\phi$ est remplacé par le champ électrique **E** en utilisant le paramètre de Lagrange **D** :

$$f(\phi, \mathbf{E}, \mathbf{D}) = -\frac{1}{2}\epsilon \mathbf{E}^2 - 2c_0 \cosh(\beta e\phi) + \mathbf{D} \cdot (\mathbf{E} + \nabla\phi) + \sigma\phi$$
$$= \mathbf{D} \cdot \mathbf{E} - \frac{1}{2}\epsilon \mathbf{E}^2 + \phi \cdot (\sigma - \operatorname{div} \mathbf{D}) - 2c_0 \cosh(\beta e\phi)$$

Deux transformées de Legendre sont identifiées dans cette équation. En violet, **E** et **D** sont les variables conjuguées et la transformée s'écrit $\mathcal{L}\left[\frac{\epsilon \mathbf{E}^2}{2}\right](\mathbf{D}) = \frac{\mathbf{D}^2}{2\epsilon}$. En vert il s'agit de la transformée du cosinus hyperbolique de ϕ avec la variable conjuguée σ – div **D**. La transformée de Legendre du cosinus hyperbolique est donnée par :

$$\mathcal{L}[A\cosh(Bx)](s) = A\left[s/(AB)\operatorname{asinh}(s/AB) - \sqrt{(s/AB)^2 + 1}\right]$$
$$= A\,\tilde{g}\,(s/AB)$$

Il est donc possible d'écrire une densité d'énergie libre équivalente à celle d'origine et dépendant du champ de déplacement **D** :

$$f(\mathbf{D}) = \frac{\mathbf{D}^2}{2\epsilon} + 2c_0 \tilde{g} \left(\frac{\sigma - \operatorname{div} \mathbf{D}}{2c_0 \beta e}\right)$$

L'intérêt d'une telle transformation vient de la convexité de l'énergie libre $f(\mathbf{D})$.

Un modèle de virus

La théorie des poly-électrolytes est souvent utilisée en biologie pour décrire l'ADN ou l'ARN. Un poly-électrolyte est un polymère chargé et est décrit par le champ électrostatique ϕ et le champ de configuration du polymère ψ . Il provient

de l'approche développée par Edwards et De Gennes qui considérent la prédominance de l'état fondamental. La densité de monomères s'exprime comme le carré de ce champ : $C_{monomer} = |\psi|^2$. Le poly-électrolyte est défini par son nombre de monomères N, chacun chargé de p charges élémentaires négatives, de taille a et de volume effectif v. Le nombre de monomères étant fixé, l'égalité suivante est imposée : $\int |\psi|^2 = N$. Le modèle du virus utilisé pour cette étude fait appel à cette description de l'ARN.

Le virus est aussi constitué d'une capside représentée par une sphère uniformément chargée σ , de rayon R et perméable aux ions. Le milieu biologique est décrit par un électrolyte symétrique et monovalent. La densité d'énergie de ce système est donnée par :

$$f(\psi,\phi) = k_B T \left\{ \frac{a^2}{6} (\nabla \psi)^2 + \frac{v}{2} \psi^4 \right\} - \frac{\epsilon_0 \epsilon_R}{2} (\nabla \phi)^2 + \left(\sigma - p e \psi^2\right) \phi + 2c_0 \cosh\left(\beta e \phi\right)$$

Cette fonctionnelle se décompose en un terme d'auto-interaction non-électrostatique du poly-électrolyte (première ligne), et de l'énergie électrostatique avec les charges fixes de la capside, les charges portées par l'ARN et le terme ionique. L'énergie libre du système à l'équilibre est donnée par le maximum de f par rapport à ϕ et son minimum vis-à-vis de ψ .

Appliquant la transformée de Legendre à la densité d'énergie libre, on obtient une nouvelle fonctionnelle équivalente :

$$f(\mathbf{D}, \psi) = k_B T \left\{ \frac{a^2}{6} (\nabla \psi)^2 + \frac{v}{2} \psi^4 \right\} + \frac{\mathbf{D}^2}{2\epsilon_0 \epsilon_R} + 2c_0 k_B T \left\{ \xi \operatorname{asinh} \left(\xi \right) - \sqrt{\xi^2 + 1} \right\}$$

avec $\xi(\mathbf{D}, \psi) = \frac{\sigma - pe\psi^2 - \nabla \mathbf{D}}{2ec_0}$. Cette nouvelle expression est certainement moins intuitive que la précédente et l'on ne reconnaît pas de manière évidente la théorie de Poisson-Boltzmann. Cependant, la fonctionnelle est convexe vis-à-vis de chacun des deux champs et il est possible d'utiliser les techniques classiques de recherche de minimum pour trouver l'énergie du virus.

Méthodes numériques

Afin de décrire le système à l'équilibre, il est nécessaire d'optimiser l'énergie libre. Dans le cas du modèle du virus, il s'agit de trouver le point-de-col de $f(\phi, \psi)$. Quatre méthodes numériques sont présentées.

L'optimisation par boucles imbriquées utilise directement l'expression de $f(\phi, \psi)$ et maximise f par rapport à ϕ à chaque estimation de la fonctionnelle lors de sa minimisation vis-à-vis du champ ψ . Ainsi deux boucles d'optimisation sont imbriquées et chaque étape peut être résolue par un algorithme de recherche de minimum classique.

Une méthode classique pour la recherche de point-de-col consiste à utiliser les dérivées de la fonctionnelle. Au point-de-col ces dérivées sont, par définition, égales à zéro. Il est donc possible de construire une nouvelle fonctionnelle constituée de la somme des dérivées au carré :

$$F_{deriv}(\phi,\psi) = \int dr \left[\left(\frac{\partial F}{\partial \psi} \right)^2 + \left(\frac{\partial F}{\partial \phi} \right)^2 \right]$$

La minimisation de cette fonctionnelle a pour résultat $F_{deriv}(\phi_{opt}, \psi_{opt}) = 0$ et donne la position du point-de-col. Avec cette fonctionnelle, une seule boucle d'optimisation est nécessaire. Cependant, un terme en $(\Delta \phi)^2$ est présent dans F_{deriv} et la raideur est donc proportionnelle à q^4 . Une convergence lente est donc attendue.

Il est possible de construire des énergies libres équivalentes à $f(\phi, \psi)$ et entièrement convexes. Une substitution inverse nous permet d'écrire une énergie libre convexe :

$$f_{I}(\phi,\psi) = k_{B}T\left\{\frac{a^{2}}{6}(\nabla\psi)^{2} + \frac{v}{2}\psi^{4}\right\} + \frac{\epsilon_{0}\epsilon_{R}}{2}(\nabla\phi)^{2} + 2c_{0}k_{B}T\left\{-\cosh\left(\beta e\phi\right) + \beta e\phi\,\sinh(\beta e\phi) - \sinh(\xi)\,\sinh(\beta e\phi) + \xi\,\sinh(\xi)\right\}$$

avec $\xi(\phi, \psi) = \frac{\epsilon_0 \epsilon_R \nabla^2 \phi + \rho - pe\psi^2}{2ec_0}$. Cette fonctionnelle peut être directement minimisée mais elle présente une raideur élevée et une convergence lente est prévisible.

La transformée de Legendre permet également d'écrire une énergie libre équivalente et convexe :

$$f_L(\mathbf{D}, \psi) = k_B T \left\{ \frac{a^2}{6} (\nabla \psi)^2 + \frac{v}{2} \psi^4 \right\} + \frac{\mathbf{D}^2}{2\epsilon_0 \epsilon_R} + 2c_0 k_B T \left\{ \xi \operatorname{asinh}\left(\xi\right) - \sqrt{\xi^2 + 1} \right\}$$

avec $\xi(\mathbf{D}, \psi) = \frac{\sigma - pe\psi^2 - \nabla \mathbf{D}}{2ec_0}$. Ces deux fonctionnelles ne nécessitent qu'une seule boucle d'optimisation pour trouver le point d'équilibre.

Résultats

Les programmes sont réalisés dans *Matlab* et la fonction *fminunc* est systématiquement utilisée pour minimiser les fonctionnelles. La fonction *fminunc* implémente un algorithme de Quasi-Newton. Basé sur la méthode de plus forte pente, cet algorithme génère itérativement une matrice inverse permettant de déterminer la position à l'itération suivante. Une autre technique, l'algorithme à région de confiance, est aussi implémenté dans *fminunc*. Cette méthode définit une région dans laquelle l'itération est effectuée en utilisant une approximation quadratique. La position est optimisée à chaque itération ainsi que la taille de la région de confiance ce qui permet de converger même en l'absence de bonnes conditions initiales. La méthode de Quasi-Newton est utilisée pour toutes les optimisations à l'exception de l'étude explicite de l'influence du choix de l'algorithme.

Afin de comparer des simulations équivalentes, il faut que les transformations présentées précédemment soient valables après discrétisation des fonctionnelles. Le modèle utilisé présente une symétrie sphérique ce qui réduit la dimension d'étude à 1 mais complexifie la discrétisation des opérateurs. Nous utilisons l'opérateur de gradient comme l'objet fondamental de la discrétisation et l'identité fondamentale $\int \mathbf{D} \cdot \nabla \phi = -\int \phi \operatorname{div} \mathbf{D} + \oint \phi \mathbf{D} \cdot dS$ pour définir la divergence. Le Laplacien discrétisé est défini à partir de l'égalité $\Delta \phi = \operatorname{div}(\nabla \phi)$.

Les performances de chaque programme sont testées en fonction de la discrétisation à l'aide des considérations suivantes :

- l'énergie libre F doit converger quand le nombre de points utilisés augmente,
- les dérivées des fonctionnelles doivent être nulles (une norme L₁ est utilisée),

 le temps de calcul utilisé par l'ordinateur pour optimiser la fonctionnelle doit être minimal.

L'optimisation du modèle du virus est réalisée pour chacune des quatre méthodes et pour différentes discrétisations. La première observation est que pour une faible densité de points, les quatre méthodes sont en accord : les estimations de l'énergie libre sont identiques et les dérivées sont nulles. Quand le nombre de points augmente, la méthode des boucles imbriquées ne présente pas de convergence de l'énergie libre et ses dérivées en fonction de ψ sont nonnulles. À l'inverse, l'optimisation de la fonctionnelle issue de la transformée de Legendre présente un bon résultat. Son estimation de l'énergie libre converge avec l'augmentation du nombre de points et ses dérivées sont nulles. Les deux autres méthodes ne présentent pas une aussi bonne convergence, ce qui peut se justifier de part leur raideur élevée.

La durée des optimisations est aussi enregistrée. Les méthodes ne présentant qu'une seule boucle d'optimisation ont, de manière attendue, un temps de réalisation beaucoup plus faible que la méthode des boucles imbriquées. Une loi de puissance avec un facteur 2 est observée.

Différentes initialisations sont utilisées afin de tester la stabilités des programmes. Une initialisation avec des champs nuls provoque une erreur lors de l'optimisation. En effet, le champ de description du polyélectrolyte reste nul lorsque plus de 200 points sont utilisés. Ceci correspond vraisemblablement à un minimum local. Une initialisation aléatoire montre la forte stabilité de la méthode de la transformée de Legendre qui est la seule à converger.

L'algorithme de région de confiance est testé avec la méthode de la substitution inversée et celle de la transformée de Legendre. Cet algorithme permet de stabiliser l'optimisation de la fonctionnelle et la méthode de substitution inverse présente alors une convergence de l'énergie libre. Dans le cas de la transformée de Legendre l'utilisation de cet algorithme s'accompagne d'un gain de temps de calcul.

En conclusion, si les quatre méthodes sont fiables pour de faibles discrétisations, les résultat pour une discrétisation dense montre que la méthode de la transformée de Legendre est plus fiable, plus stable ou plus rapide.

La Théorie de Poisson-Boltzmann avec fluctuations

La théorie de Poisson-Boltzmann est issue d'une approximation de champ moyen et des différences sont observées entre la théorie et certaines expériences. En effet, la théorie de Poisson-Boltzmann néglige les corrélations entre les ions. Elle ne décrit donc correctement que les systèmes avec une constante de couplage Ξ faible (ions de faible valence, température élevée). Des théories existent pour décrire des systèmes à forte constante de couplage (système fortement chargés) mais aucune expression théorique ne correspond à des valeurs moyennes de Ξ . La constante de couplage est définie par $\Xi = \frac{q^3 |\sigma| e^4 \beta^2}{8 \pi \epsilon^2}$ et représente la force d'interaction entre un mur chargé et une solution ionique. Afin de modéliser les systèmes qui s'écartent des faibles couplages, la théorie de Poisson-Boltzmann est étendue pour considérer les fluctuations électrostatiques. La théorie des champs est utilisée et les résultats issus d'un principe variationnel sont étudiés.

Principe Variationnel de Gibbs

La théorie de Poisson-Boltzmann exprimée avec une théorie des champs s'écrit comme suit :

$$\begin{aligned} \mathcal{Z}_{\lambda} &= \int \frac{\mathcal{D}\phi}{\mathcal{Z}_{0}} \exp\left\{-H\left[\phi\right]\right\} \\ H\left[\phi\right] &= \frac{1}{8\pi l_{B}q^{2}} \int (\nabla\phi)^{2} + i \int \phi \,\sigma/q \,- \,2\lambda \,\int \,\Omega\cos\left(\phi\right) \end{aligned}$$

Par l'intermédiaire d'un potentiel électrostatique fluctuant, les fluctuations de la densité ionique sont aussi prises en considération.

La procédure variationnelle de Gibbs utilise un hamiltonien variationnel H_0 pour définir l'énergie libre de Gibbs : $\mathcal{F}_{\text{Gibbs}} = \mathcal{F}_0 - \langle H_0 - H \rangle_0 / \Xi$. Cette fonctionnelle est alors minimisée vis-à-vis des paramètres de H_0 . Une forme Gaussienne est utilisée pour l'hamiltonien variationnel et les paramètres variationnels sont le potentiel ϕ_0 et le noyau gaussien v_0 . Cette hypothèse permet de calculer exactement l'énergie libre de Gibbs. Puisqu'il s'agit d'optimiser cette énergie libre en fonction de paramètres variationnels, ses dérivées doivent être nulles : $\frac{\partial \mathcal{F}_{\text{Gibbs}}}{\partial \phi_0} = 0$ et $\frac{\partial \mathcal{F}_{\text{Gibbs}}}{\partial v_0} = 0$. Deux équations variationnelles sont ainsi obtenues.

$$\nabla^2 \phi_0 = -2\,\sigma + \Lambda\,\Omega\,\mathrm{e}^{-v_0(\mathbf{r},\mathbf{r})/2}\,\sinh\left(\phi_0\right)$$
$$4\,\pi\,\Xi\,\delta(\mathbf{r}-\mathbf{r}') = \left[-\nabla^2 + \Lambda\,\Omega\,\mathrm{e}^{-v_0(\mathbf{r},\mathbf{r})/2}\,\cosh\left(\phi_0\right)\right]v_0$$

Solution Numérique

Un procédé itératif est implémenté pour numériquement résoudre ces deux équations différentielles non-linéaires et couplées.

Ainsi la première égalité est utilisée pour déterminer ϕ_0^{n+1} à partir de ϕ_0^n et $v_0^n(\mathbf{r}, \mathbf{r})$. Pour ce faire une méthode itérative faisant intervenir une fonction de relaxation *R* est implémentée. La nouvelle valeur de ϕ_0 est donnée par :

$$\left[\nabla^2 - R\right]\phi_0^{k+1} = -2 \sigma + \Lambda \Omega e^{-v_0^n(\mathbf{r},\mathbf{r})/2} \sinh\left(\phi_0^k\right) - R \phi_0^k$$

La division matricielle de *Matlab* peut être directement utilisée grâce à l'introduction de la fonction de relaxation.

La seconde équation devient une inversion de matrice dans l'espace discrétisé. L'inversion numérique de matrice est un procédé développé pour la résolution d'un grand nombre de problèmes physiques. Ainsi des méthodes générales sont implémentées afin de minimiser le temps et l'espace de calcul nécessaire à l'inversion. De plus, seulement la diagonale de l'inverse est nécessaire dans le cas étudié ici et un algorithme d'inversion sélective peut donc être utilisé.

Si le système possède une symétrie, il est possible d'appliquer la transformée de Fourier à la fonction de corrélation v_0 . Cette fonction dépend alors de la position pour les dimensions ne présentant pas de symétrie et de fréquences pour les autres dimensions. Une telle transformation permet de remplacer l'inversion d'une large matrice 3D par une série d'inversions de matrices plus petites. Un gain de temps et d'espace de calcul est ainsi obtenu.

Limite de la Constante de Couplage

L'objectif du développement de cette méthode est de décrire des systèmes dont la constante de couplage Ξ est supérieure à 0.1. Afin de tester ce programme, un système simple est implémenté et la simulation est effectuée pour une constante de couplage croissante. L'algorithme étant formé d'une boucle d'optimisation, la convergence ou l'absence de convergence est un premier test de validité. Les résultats fournis sous la forme de carte de densités ioniques et

de valeurs de l'énergie libre sont aussi considérés.

Le système de test se compose d'un cylindre chargé positivement pour moitié et négativement pour l'autre moitié. Le cylindre est donc globalement neutre. La constante diélectrique du cylindre est aussi considérée comme différente du milieu. Une solution d'ions symétriques occupe le reste de l'espace et le système est représenté dans un espace en deux-dimensions.

Les premiers tests montrent que la convergence du programme n'est pas obtenue pour des constantes de couplage supérieures à cinq. Les résultats présentent des valeurs d'énergie libre particulièrement élevées et les densités d'ions obtenues ne sont pas physiquement possibles. Une étude plus détaillée montre que pour des constantes de couplage inférieures à 4.6, une convergence est atteinte si l'on considère suffisamment de boucles, ou si les conditions initiales sont proches du résultat attendu. Cette dernière situation est implémentée en utilisant le résultat pour une constante de couplage moindre comme position initiale pour une simulation à plus fort Ξ . Pour $\Xi > 4.7$, une telle initialisation mène à une divergence. Une limite pour la constant de couplage est donc présente. Il s'agit maintenant de comprendre son origine, en particulier de distinguer si la méthode numérique ou la théorie utilisée est en cause.

Une étude de l'évolution de la constant limite Ξ_{lim} en fonction des différents paramètres du système montre que cette limite varie de manière conséquente avec les paramètres physiques comme le rayon du cylindre, sa charge surfacique, ou la fugacité des ions. Cependant la constante de couplage limite varie peu avec des paramètres numériques tel que la discrétisation.

Étude analytique : l'électrolyte seul

Suite à une conversation avec Sahin Buyukdagli, un système composé uniquement de l'électrolyte est considéré afin de cerner l'origine de la limite en constante de couplage. Dans cette situation, le champ électrostatique est nul et la fonction de Green est définie par l'équation : $-\nabla^2 G + \Lambda e^{-\Xi c(\mathbf{r})/2} G = 4 \pi \delta$. Définissant le paramètre κ par $\kappa^2 = e^{-\Xi c(\mathbf{r})/2}$ et résolvant l'équation de la fonction de Green, l'égalité suivante est obtenue :

$$\kappa^2 = e^{a \kappa}$$

avec $a = \Xi \sqrt{\Lambda}/2$. Cette équation a une solution réelle si $a < a_{lim} = \frac{2}{e}$ et ainsi une constante de couplage limite apparaît $\Xi_{lim} = \frac{2 a_{lim}}{\sqrt{\Lambda}} = \frac{4}{e \sqrt{\Lambda}}$.

Cependant, des solutions existent dans le plan complexe et elles s'expriment à l'aide de la fonction de Lambert W(z) définie par $z = W(z) e^{W(z)}$:

$$\kappa^{\pm} = \mp \frac{W(C, \pm a/2)}{\pm a/2}$$

Le nombre entier *C* décrit les différentes branches de la fonction de Lambert. La solution $\kappa^-(C = 0, -a/2)$ est la solution réelle présentée ci-dessus pour $a < a_{lim}$. Chaque branche présente une partie réelle négative pour de large *a*. Cependant, il existe toujours une branche de valeur supérieure dont la solution possède une partie réelle positive.

Utiliser la fonction *Solve* de *Mathematica* permet d'observer l'influence de la condition initiale sur l'unique résultat fourni. Une valeur initiale réelle de $\kappa = 2$ donne uniquement des résultats issus de la branche C = 0 de la fonction de Lambert. Les résultats sont donc réels puis complexes. Une valeur initiale complexe de $\kappa = 5 - 5i$ présente des résultats qui changent de branche quand *a* augmente.

Nos simulations cependant ne peuvent traiter les nombres complexes. De plus, l'équation $\kappa^2 = e^{a \kappa}$ n'est pas linéaire et il est impossible de construite une solution réelle à partir des solutions complexes. Ainsi, il existe une limite théorique au delà de laquelle aucune solution n'est physiquement acceptable.

Une étude de la dépendance de Ξ en fonction de Λ pour le cylindre montre que la constante de couplage limite suit la loi : $\Xi = \frac{a}{\sqrt{\Lambda}} + b$ avec a et b des constantes qui varient avec les paramètres définissant le cylindre. Cette relation est proche de celle trouvée analytiquement pour l'électrolyte seul $\Xi_{lim} = \frac{4}{e\sqrt{\Lambda}}$. Il semble donc que la limite théorique de la constante de couplage existe sous la même forme pour l'électrolyte seul et pour le cylindre.

Conclusion

Ainsi, il est possible de calculer numériquement une correction à l'énergie libre. Les équations sont issues de la théorie des champs variationnels en utilisant un hamiltonien de Gibbs, et une méthode itérative est utilisée pour les résoudre. Ce procédé numérique présente cependant une constante de couplage limite au delà de laquelle l'itération diverge. D'après l'étude analytique de l'électrolyte seul, cette limite provient de la théorie utilisée.

D'autres tests sont nécessaires pour évaluer la qualité de la correction calculée. Il sera alors possible d'utiliser la méthode décrite ici pour simuler des systèmes plus complexes, comme par example un électrolyte dont la répulsion stérique entre les ions est décrite par un champ de Yukawa.

Plaquette roulant sur une surface

Les plaquettes sanguines sont de petites cellules sans noyaux dont la fonction principale est l'hémostase : l'arrêt d'écoulement sanguin hors des vaisseaux. Un autre élément indispensable à l'hémostase est une protéine, le facteur de Von Willebrand, qui permet le roulement et l'agrégation des plaquettes à la parois du vaisseau sanguin.

De nombreuses études sur le sang utilisent des canaux micro-fluidiques et testent notamment l'adhésion des plaquettes à une surface recouverte de facteur de Von Willebrand. Ce travail est aussi motivé par l'étude du mécanisme de roulement des cellules sur une surface. En effet le roulement est un comportement qui se retrouve aussi avec les leucocytes ou les cellules cancéreuses.

Dans ce chapitre nous étudions le comportement de plaquettes injectées dans un canal micro-fluidique dont les surfaces sont recouvertes de facteur de Von Willebrand. Des phénomènes d'échange de cellules entre le volume et la surface, et de roulement sur la surface sont observés. Deux modèles sont définis, implémentés et testés. L'objectif est en premier lieu de déterminer si un des deux modèles décrit le système de manière adéquate. En second lieu, la comparaison des modèles avec les données expérimentales permet d'extraire des valeurs décrivant les interactions des plaquettes avec le milieu comme par exemple leur taux d'attachement K_{on} qui ne peut être directement mesuré. Enfin, une fois un modèle validé, il peut être utilisé pour prédire la dynamique du système et optimiser le dispositif expérimental.

Expériences et Observations

Les expériences furent réalisées par l'équipe de Mathilde Reyssat au laboratoire Gulliver, dans l'équipe MMN, de l'ESPCI avec Anne Le Goff, Antoine Blin et Hyacinthe Buisson.

Un canal micro-fluidique droit en PDMS est créé par lithographie. Il est en premier lieu rempli d'une solution contenant du facteur de Von Willebrand et

laissé à incuber pour une nuit. Une couche de facteur de Von Willebrand se crée durant cette période. Cette protéine permet le roulement et l'agrégation de plaquettes au niveau de la paroi de vaisseau sanguin. Cette molécule est un polymère qui est replié sur lui-même à faible taux de cisaillement. Dans cette configuration, les unités du Von Willebrand formant les liens avec les plaquettes sont masquées. Un taux de cisaillement suffisamment grand est donc nécessaire pour que les protéines se déplient et que l'agrégation avec les plaquettes puisse prendre place. Connaissant la taille du canal, un débitmètre permet de maîtriser le taux de cisaillement appliqué à la paroi. Il est choisi à 1800 s⁻¹.

Les plaquettes proviennent de sang complet de donneurs en bonne santé. Leur extraction est réalisée par plusieurs étapes de centrifugation et elles sont immédiatement fixées. Cette étape de fixation au formaldéhyde permet de bloquer les réactions bio-chimiques et de préserver les tissus biologiques. Les interactions entre les plaquettes et le facteur de Von Willebrand sont préservées.

Les observations sont réalisées par vidéo-microscopie. L'acquisition des images se fait grâce à une caméra ultra-rapide focalisée sur la surface du canal. Deux types de mesures sont réalisées. Des vidéos permettent d'observer quatre phénomènes dynamiques : les plaquettes sont advectées dans le volume, elle peuvent adhérer à la surface, rouler sur la surface et se décoller de la surface retournant alors dans le volume. Ces vidéos permettent notamment de mesurer les vitesses de roulement des plaquettes et de tracer leur distribution. Ces vitesses sont de l'ordre de la dizaine de micro-mètre par seconde et peuvent atteindre jusqu'à 30μ m.s⁻¹. La vitesse d'advection est quant à elle de l'ordre du millimètre par seconde au centre du micro-canal.

Des clichés de la surface du canal sont enregistrés et les plaquettes en surface sont comptées. Ces mesures réalisées en plusieurs positions et à différents temps permettent de tracer la cinétique et la dépendance axiale de la concentration de plaquettes en surface. La quantité de plaquettes augmente avec le temps et semble atteindre un plateau pour les positions proches du point d'injection. La dépendance axiale en revanche présente une forte diminution de la concentration de plaquettes lorsque la distance au point d'injection augmente.

Afin de comprendre ces observations, deux modèles sont développés et comparés aux expériences.

Modèle de plaquettes roulantes

Ce modèle se base sur deux observations : la distribution de vitesse de roulement et la forte quantité de plaquettes présentes à l'entrée du canal. Ainsi, une injection à la surface peut être considérée. Elle peut s'expliquer par le flux d'entrée descendant qui pousse les plaquettes vers la surface au point d'injection. Pour ce modèle, l'injection en surface se fait à un débit constant et les plaquettes ont une vitesse fixe, issue d'une distribution gaussienne tronquée. Une plaquette de ce modèle est entièrement décrite par son temps d'injection et sa vitesse. Aucun échange avec le volume n'est ici considéré. De la distribution de vitesse, la concentration de plaquettes en fonction de la position et du temps est calculée. La valeur du débit et la distribution de vitesse du modèle sont ajustées afin que les courbes obtenues soient au plus proche des mesures expérimentales.

Deux expériences sont utilisées pour tester ce modèle. Les courbes obtenues ne correspondent pas complètement et il semble donc que ce modèle soit incomplet. L'une des deux distributions de vitesse obtenues est en accord avec celle mesurée, l'autre fournie des vitesses faibles mais plausibles.

Modèle d'échange de plaquettes

Ce modèle se base sur l'échange de plaquettes entre le volume et la surface. Ces deux espaces sont considérés et un bilan de matière est utilisé pour déterminer les équations décrivant le système. L'échange du volume vers la surface est décrit par un paramètre d'échange K_{on} et l'échange inverse par le paramètre K_{off} . L'advection en volume est décrit par la vitesse v_v et le roulement en surface par la vitesse moyenne v_s . Le volume considéré s'étend sur une hauteur h, distance où les plaquettes interagissent avec le facteur de Von Willebrand. La concentration en surface C_s et celle en volume C_v sont définies par les équations de transport :

$$\begin{cases} \frac{\partial C_v}{\partial t} + v_v \frac{\partial C_v}{\partial x} = -\mathcal{J} \\ \frac{\partial C_s}{\partial t} + v_s \frac{\partial C_s}{\partial x} = h\mathcal{J} \\ \mathcal{J} = K_{on} C_v \left(1 - \frac{C_s}{C_{s,max}}\right) - K_{off} C_s \end{cases}$$

Les conditions initiales sont choisies tel que $C_v(t, x = 0) = C_v^{(in)}$, $C_s(t, x = 0) = 0$ et $C_v(t = 0, x) = C_s(t = 0, x) = 0$. L'injection de plaquettes s'effectue donc

uniquement dans le volume à l'inverse du modèle précédent.

Adimensionner ces équations couplées nous donne un système défini par seulement deux paramètres et la condition d'injection.

$$\begin{cases} v_t + v_x = -J\\ s_t + \epsilon s_x = +J\\ J = v \ (1 - s) - \alpha s \end{cases}$$

Les concentrations de volume et de surface sont respectivement v et s avec les lettres souscrites représentant les dérivées partielles. J est le terme d'échange. Les deux paramètres définissant la dynamique du système sont le rapport des vitesses $\epsilon = \frac{v_s}{v_v}$ et le facteur d'échange $\alpha = \frac{K_{off}}{K_{on}} h$.

Ces équations couplées aux dérivées partielles ne peuvent être résolues analytiquement mais la méthode des caractéristiques nous informe sur la forme générale de la solution. En effet, l'espace des solution peut être découpé en plusieurs parties.

Quand x > t, aucune plaquette n'est présente car le peuplement du canal est limité par la vitesse la plus élevée. Cette vitesse maximale correspond à la vitesse du fluide, et vaut 1 pour le modèle adimensionné.

Quand $x < \epsilon t$, la solution ne dépend pas du temps et est donc la solution stationnaire. La solution stationnaire peut être calculée exactement et est donnée par $s(x) = \frac{A \Delta}{(A-\Delta) e^{-\Delta x} - A} + A$ avec $A = \frac{1}{2} \left(\xi + \sqrt{\xi^2 - 4 \frac{v^{(in)}}{\epsilon}} \right), \Delta = \sqrt{\xi^2 - 4 \frac{v^{(in)}}{\epsilon}}$ et $\xi = \frac{v^{(in)} + \epsilon + \alpha}{\epsilon}$.

Les valeurs expérimentales du paramètre ϵ sont très faibles. Ceci explique pourquoi certaines particularités des courbes analytiques (croisement de courbes, augmentation de la concentration à très faibles positions) ne sont pas observées expérimentalement.

Une intégration temporelle réalisée numériquement nous permet de simuler les résultats d'un tel modèle. Une comparaison entre les prévisions analytiques et les calculs numériques met en évidence l'influence de la discrétisation. En effet, pour des discrétisations trop larges les courbes numériques ne respectent pas exactement les zones de solutions identifiées avec la méthode des caractéristiques. Cependant, ces erreurs numériques sont petites et n'apparaissent qu'à de faibles positions et temps.

Les courbes issues de la simulation sont aussi comparées aux résultats expérimentaux. Trouver un ensemble de paramètres satisfaisant est cependant compliqué. En effet, six paramètres permettent de décrire le système. Trois sont directement liés au modèle et définissent les équations différentielles couplées ; les trois autres paramètres permettent d'adimensionner les valeurs de temps, d'espace et de concentration. Les deux expériences utilisées précédemment servent de test pour cette simulation. La première expérience donne un résultat concluant, mais la deuxième n'est pas parfaitement décrite par ce modèle.

Le modèle décrit dans cette partie peut permettre de déterminer une valeur numérique de ~ $0.1s^{-1}$ pour le paramètre d'échange K_{on} qui ne peut pas être mesuré directement. Remarquons que ce paramètre K_{on} est défini comme un coefficient d'adsorption à l'échelle de la plaquette dans son ensemble, et non au niveau d'un couple ligand-récepteur.

Conclusion

Ainsi nous avons décrit et simulé un système micro-fluidique définit par une injection de plaquettes, leur transport et leur échange entre le volume et la surface. Les protéines de Von Willebrand permettent en effet aux plaquettes d'adhérer et de rouler sur la surface du canal.

Nous avons étudiés deux modèles. Le premier considère une injection de plaquette en surface et une distribution de vitesse. Le deuxième modèle prend en compte une injection en volume et un échange de plaquettes. Le roulement des cellules sur la surface est aussi considéré mais de manière moins détaillée que dans le premier modèle. Les deux simulations fournissent des résultats encourageants. Cependant, il semble qu'aucun des modèles ne décrivent complètement le système étudié.

Un modèle considérant les deux types d'injection, en volume et en surface, permettrait probablement d'obtenir des résultats plus proches des observations. Ceci fournirai un outil pour mieux comprendre le système expérimental et la physique impliquée dans le processus d'hémostase.

Introduction

The origin of simulation is considered to be the needle problem developed by Buffon in 1777 and corrected by Laplace in 1812 [1]. It is used to estimate the value of π from random throws of needles of a given length on a square grid and the number of those crossing one line. Statistical knowledge was also used in 1899 by William Sealy Gosset to not only optimize the production of Arthur Guinness' brewery, but also to improve the quality of the products. This field of research expanded during the second World War with the appearance of the first computers. Moreover it is only during the 50s, with the increasing availability of computers for non-military use that computer simulation truly started [2]. Though we will solely focus on the development and use of simulation in research, it has also taken its place in the industrial domain [3]. Indeed, following in the footsteps of Gosset, Keith Douglas Tocher conceived and implemented the General Simulation Program (GSP) in 1958. This program was the first to combine discrete-event and continuous simulations to model the running and production of plants [1].

The first computers were built during the second World War for two main tasks: code breaking and the development of nuclear weapons. Both fields involve heavy calculations. In 1943, the main theoretical task at Los Alamos (New Mexico, USA) was to determine the dynamical behavior and explosive power of a nuclear detonation [4]. Such research covered a wide spectrum of fields including the physical and chemical properties of the elements at high temperature and pressure, the motion of deformable materials solved by fluid dynamics, and neutron transport. Furthermore, this research was not one that could be undertaken though experiments both due to the destructive capacity of the weapons and the extreme conditions of temperature and pressure the study had to take into account. The scientists of Los Alamos resorted to an electromechanical business machine to simulate an implosion defined by a coupled set of non-linear differential equations. They used one punch card for each point of space and time and the calculation of the next time-step required each card to be run through a dozen machines [4].

In the same period, the university of Pennsylvania developed the first large scale electronic computer employing electron tubes rather than relays or mechanical counters. The Electronic Numerical Integrator And Calculator (ENIAC) computed at electronic speed and was thus much faster than the business machines. In 1946 the ENIAC computed the simulation of a one-dimension thermonuclear burning of deuterium and tritium. This success and the declassification of the subject spurred research in computer and modelization.

It is the same year that the concept of stored program appeared. The idea was to record the program electronically in the same form as data. This would allow for self-modifications to be available in case of contingencies [4].

In March 1952, the Mathematical And Numerical Integrator And Computer (MANIAC) was operational [2] and the team of Los Alamos, led by Metropolis, completed the first large scale hydrodynamic calculation. A broad spectrum of scientific problems were used to test the capacity and versatility of the MA-NIAC, including the first chess-playing program and attempts to decode DNA sequences [4].

In 1953, Metropolis et al. [5] implemented the first simulation of liquid. The system was composed of two-dimensional rigid spheres and two-body forces were considered. The model was computed with the Monte Carlos method presented in 1949 by Metropolis and Ulam [6].

1953 is also the year when John Jackson initiated the research on program languages and Mark Wells et al. started the development of the high-level programming language and operating system ModCap [4].

In 1955, Fermi, Pasta and Ulam published their work [7] on non-linear problems. They studied the dynamical behavior of an an-harmonic one-dimensional crystal.

In 1956, Alder and Wainwright implemented the first molecular dynamic simulation [8, 9]. They studied the dynamic of the assembly of hard spheres and found a two-states system. In 1959, molecular dynamic was applied to a real material as the damage from radiation on a crystalline copper was modeled. And in 1964, Rahman presented the first molecular dynamic simulation of Argon liquid [2].

In 1960, the first all-transistor computer, Stretch, was created by International

Business Machines (IBM). It was also the first computer to use 64-bit words which allowed for greater accuracy [4], and many concepts developed with Stretch (multiprogramming, memory protection, general interrupts, 8-bit bytes) were incorporated in the next generations of computers.

During the period 1960-1961, Geoffrey Gordon, manager of simulation development at IBM, introduced the General Purpose Simulation System (GPSS). This program was based on block diagram interface in order to facilitate the use of this simulation language. Such focus and the marketing policy of IBM established GPSS as a popular simulation tool [1].

In the beginning of the 1960s, the first parallel calculations were explored with the creation of the SOLOMON computer (Simultaneous Operation Linked Ordinal MOdular Network) [10]. A multitude of subjects were explored, including the resolution of partial differential equations, the maintenance of real-time multi-dimensional control and surveillance (satellite tracking) [11] and fluid dynamics analysis using particle-in-cell code [4].

At the same period, the theory of digital simulation was explored by Conway, Johnson and Maxwell [1]. They distinguished issues from building the simulation and problems due to the use of the simulation. In the first category, problems such as the modular design of the program for easy revision, the control of errors from discretization, or the efficiency of time-step mechanisms are considered. The second set of issues covers in particular the influence of the initial conditions, the estimation of the precision, and the comparison of alternative system simulations.

Computer simulation gives exact results for a chosen model of a system. Before the development of this scientific discipline, the only way to predict material properties was to use a theory providing an approximate description. Van der Waals equation for dense gazes, Debye-Hückel theory of electrolytes or Boltzmann equations for the transport properties of dilute gazes are approximate theories that could be solved analytically. However, two hypotheses are systematically used in this process: on the one hand the choice of the theory itself, and on the other hand the estimation of the interactions. Thus, when a model did not match the experiment, each of those hypotheses could be the cause. With computer simulation, we can compare the simulated results with the approximate analytical theory to test the theory. This is called a computer experiment. Calculated properties can also be compared with the experimental data to test the value of the interactions [2].

Introduction

The most common application of computer simulation is the prediction of material properties, in particular for extreme conditions or materials not yet synthesized [4]. As Frenkel and Smit point out in *Understanding Molecular Simulation* [2], "the computer does not care: it does not go up in smoke when you ask it to simulate a system at 10 000 K."

In biology, the computers were used for many purposes. In the genome project for example, computers are effective tools for data storage, management and sharing [12, 4]. They are also fundamental for the assembling of DNA maps. Indeed, those are defined by probabilistic statements and are processed through optimization that can only be performed numerically [12].

Computers are also used for faster analysis of experimental results. Scoring of southern blots are carried out by computers which speeds the identification of DNA strands consequently [13]. Molecular dynamic simulation is also combined with 2D-NMR of a macromolecule to find a structure that has a favorable energy and is compatible with the NMR measurements [2].

Kitona [14] defines two distinct branches of computational biology:

- knowledge discovery, or data-mining, extracts the patterns from huge quantities of experimental data. The prediction of protein structures from their sequences, or the inference of gene-regulatory network from expression profiles are examples of bio-informatics.
- simulation-based analysis typically predicts the dynamic of a system. It is then compared with experimental measurements in order to test the validity of the model. Once validated, the simulation is used to predict or explore situations that are not amenable to experimental inquiries.

Computation systems biology [15] aims at a system-level understanding in opposition to the earlier most-pursued element-wise research (one pathway, one protein, ...). Computational techniques are essential to mine, analyze and connect the enormous and heterogeneous amount of data. The term "data" includes here experimental results as well as elements of biological systems or mathematical models and their derived simulations.

In this thesis we explore two different fields. The first focuses on the improvement of a simulation tool: the computation of Poisson-Boltzmann free energy for electrolytes. With the second part, we study a microfluidic system where platelets are injected in a channel. Its protein-grafted walls can interact with the platelets. The behavior of the cells is observed and recorded, and we compare the simulation results of two models with the experimental data.

Outline

In chapter 1, we study systems described by coupled degrees of freedom. The free energy of such system is concave regarding the electrostatic field and convex regarding the configurational degrees of freedom. We use the Legendre transform to define an equivalent and overall convex free energy. We implement the numerical calculation of this free energy and compare the efficiency of our program with other methods. The testing case used is a one-dimensional simple virus model.

In chapter 2, we present how to compute a correction to the Poisson-Boltzmann free energy. The Poisson-Boltzmann theory being a mean field approximation, it is valid only for small coupling parameters. In this chapter, we expose the field theory description of the Poisson-Boltzmann free energy and show how, using the variational field approach, we can determine a correction to the free energy. Through an iterative numerical scheme we compute this correction and reach a better estimation of the free energy. We then explore how this estimation fairs for medium values of the coupling parameter.

Chapter 3 focuses on the modelization of rolling blood platelets. The system is a micro-fluidic experiment with exchange of platelets between the solution and the grafted surface. We develop two models to describe this system. The first considers only the rolling behavior of the platelets, while the second focuses on the exchange between the surface and the volume. We numerically simulate both models and compare those results with the experimental measurements. The aim is three-fold. First we want to validate the theories used and determine if one model gives a better description than the other. The second goal is to extract from the numerical match the values of the system constants which we are otherwise unable to measure. Last, the simulation, once validated, could be used to predict the platelets' behavior and to optimize the experimental set-up in order to obtain the best output.

Part I.

Beyond Poisson-Boltzmann Theory

Introduction

Electrostatic interactions are a fundamental interaction of nano- and microsized systems encountered in nature and industry. Polyelectrolytes [16], colloids [17], proteins [18], bio-molecules stability and interactions [19] and viruses [20] are only a few examples of these inexhaustible topics. Moreover, almost all organic or inorganic surfaces become effectively charged when they are immersed in water. The correct description and understanding of these systems, therefore, require a reliable treatment of electrostatics. The standard model is the mean-field Poisson-Boltzmann equation.

Poisson-Boltzmann Theory

The Poisson-Boltzmann equation comes from the combination of the Poisson equation describing the relation between the electric potential ϕ and the charge distribution ρ , and the Boltzmann description of the ions density.

The Poisson equation is given by:

$$\nabla \epsilon \nabla \phi = -\rho(\mathbf{r}) \tag{0.1}$$

in S.I. units. ϵ is the dielectric constant of the medium and $\rho(\mathbf{r})$ is the charge density composed of the fixed charges $\sigma(\mathbf{r})$ and of the ionic charges, as expressed in equation (0.2). Equation (0.1) can easily be linked to the differential form of Gauss law: $\nabla \mathbf{D} = \rho$ since the electrostatic displacement field \mathbf{D} is defined by $\mathbf{D} = -\epsilon \nabla \phi$. Thus, equation (0.1) determines the electric potential for a given spatial charge distribution $\rho(\mathbf{r})$.

On the other hand, the charge distribution can be written using the local density distribution n_j of the mobile ions j bearing a charge $z_j e$ and the fixed charges distribution σ :

$$\rho(\mathbf{r}) = e \sum_{j} z_{j} n_{j} + \sigma \tag{0.2}$$

Considering the electro-chemical potential of one ion, we have :

$$\mu_j = e \, z_j \, \phi \, + \, \beta \, \ln(n_j) \tag{0.3}$$
The first term is the electrostatic contribution and the second part is the entropy of the ion in the weak solution limit (low density). The system is considered at thermal equilibrium, thus the electro-chemical potentials are constant through the system. We find the Boltzmann distribution describing the local density distribution of the ions:

$$n_i = n_{i,0} \, e^{-\beta \, e \, z_j \, \phi} \tag{0.4}$$

with $n_{j,0}$ the bulk density of the *j* ions.

To reach the Poisson-Boltzmann equation we need to combine the two equalities given by equation (0.1) and equation (0.4). We obtain:

$$\nabla \epsilon \nabla \phi = -\sum_{j} z_{j} e n_{j,0} e^{-\beta e z_{j} \phi} - \sigma \qquad (0.5)$$

A case often studied is the one of symmetric electrolyte. Two different kinds of ions are considered with their charges opposite. It leads to the simplified Poisson-Boltzmann equation :

$$\nabla \epsilon \nabla \phi = 2 n_0 e z \sinh(\beta e z \phi) - \sigma \tag{0.6}$$

In this thesis, we work with the free energy of electrostatic systems and in particular the Poisson-Boltzmann free energy. We thus consider the internal energy, the electrostatic interactions, and the entropy of the ions in the solution to reach the following expression of the free energy:

$$F = \int d\mathbf{r} \left\{ -\frac{\epsilon}{2} (\nabla \phi)^2 + \rho \phi + k_B T \sum_j (n_j \ln (n_j / n_{j0}) - n_j) \right\}$$
(0.7)

Replacing ρ by the expression given in equation (0.2), we consider the variation of the free energy regarding each n_j , and we find back the Boltzmann equation (0.4). Using this expression of the ions density, we obtain a new expression of the free energy:

$$F = \int \left\{ -\frac{\epsilon}{2} (\nabla \phi)^2 - k_B T \sum_j n_{j,0} e^{-\beta e z_j \phi} + \sigma \phi \right\}$$
(0.8)

From this form of the free energy, we can find the Poisson-Boltzmann equality (0.5) by taking the variation of *F* regarding the electric field ϕ . The symmetric electrolyte case leads to the well-known Poisson-Boltzmann form of the free energy :

$$F = \int \left\{ -\frac{\epsilon}{2} (\nabla \phi)^2 - 2 k_B T n_0 \cosh(\beta e \phi) + \sigma \phi \right\}$$
(0.9)

Limits of the Poisson-Boltzmann Theory

Many factors contribute to deviations from the Poisson-Boltzmann solution, such as short range interactions, solvent effect or Van der Waals forces. One of those is the ion size. Indeed, in Poisson-Boltzmann, the ions are described as point-like charges. The physical repulsion from the space they occupy is not taken into account in the Poisson-Boltzmann theory thus allowing the ions to stack in the presence of strong opposite charges.

Poisson-Boltzmann free energy comes from a mean-field approximation. Indeed, this description of electrostatics does not take into account the fluctuations of the ions and is thus valid only for low charge densities. We explore in **chapter 2** how we can calculate and compute a correction to the Poisson-Boltzmann free energy.

The concavity of the Poisson-Boltzmann free energy leads to numerical limitations. It comes into play when the studied system is described by configurational degrees of freedom combined with the electrostatic degree of freedom. In such case, the free energy optimization is not a simple minimization but a saddle-point search. Yet no general numerical scheme exists to find saddle-points. In **chapter 1**, we present how to find an equivalent free energy whose overall convexity leads to a more efficient numerical optimization.

1. The Legendre Transform applied to Electrostatics

Poisson-Boltzmann theory gives a good description of the electrostatics of ionic solutions, it is thus often used in condensed matter physics and in biology [21]. The Poisson-Boltzmann free energy functional, expressed in term of the electrostatic potential ϕ , is concave and its stationary value is the correct value of the free energy [22].

However, as the level of complexity of the studied systems increases, nonelectrostatic forces and other degrees of freedom enter into the description. The Poisson-Boltzmann model is supplemented with other degrees of freedom. For example, in the study of polyelectrolytes, the monomer probability amplitude needs to be considered [23]. Polyelectrolytes are also used as a model for genetic materials (DNA or RNA) in biology [24]. In the study of blends [25] and fluid mixtures [26, 27, 28], the relative fraction of one of the components is used to describe the systems and is interacting with the electrostatics. The translational and rotational degrees of freedom of a group of atoms would also be coupled to the electrostatic field in the expression of the free energy describing a molecule. In each case, the system is described by differential equations of two or more interacting fields, and the functional is expressed in term of the electrostatic potential and in terms of configurational degrees of freedom.

Diverse numerical methods have been devised to simulate and study these systems, such as molecular dynamics [29], Monte Carlo simulations [29, 30] or the calculation of the free energy [31]. The review-paper of Lu et al [32] details the advances in boundary element methods, interface methods, finite element methods and other. All of these solutions require an important amount of computational time and memory which ultimately limits the size of the studied system or the precision at which such studies can be conducted. Efficiency coupled with accuracy is the goal of the numerous methods developed to solve Poisson-Boltzmann equations. Our approach uses the optimization of the free energy.

In many applications, the free energy is convex with respect to the configurational degrees of freedom and the minimum of energy corresponds to the stable state of equilibrium. It is however, concave with respect to the electrostatic potential. Because we consider complex systems, the electrostatic influences the other parameters and vice versa. This translates into coupled variables and a functional that can not be separated into a concave part (electrostatics) on the one hand and a convex part (other degrees of freedom) on the other hand. This duality concave-convex of the functional renders impossible to simultane-ously optimize over both electrostatic and configurational degrees of freedom in a simulation. Indeed, to study such system, we have to solve a saddle-point problem. Because of the size of the systems studied, a numerical approach is often chosen. But saddle-point problems are not easily solved numerically [33].

Let us consider a function f(x, y) and search for its stationary point (x_s, y_s) . If the function f is concave (or convex) with respect to both variables, there exist numerical solutions to find the stationary point. The Newton-search algorithm or the trust-region search algorithm are both well-known methods and often used to find a minimum (or maximum). However, if we are looking for a saddle-point, such algorithms do not exist. Two different approaches are available. One is to search the optimum value in each direction alternatively and to iterate over both search. This is the iterative algorithm. It is also possible to iteratively search in one direction at each steps of the optimization in the second direction. Another method is to define a new functional $g(\tilde{x}, \tilde{y})$ with an identical stationary point. Such functional should be convex over all fields considered and locally defined, so it can be easily optimised numerically. One simple functional g often considered is

$$g(x,y) = \left(\frac{\partial f}{\partial x}\right)^2 + \left(\frac{\partial f}{\partial y}\right)^2 \tag{1.1}$$

which gives the stationary point (x_s, y_s) when $g = 0 = \min_{(x,y)}(g)$. One can also transform the functional f(x, y) into $g(\tilde{x}, y)$ with an inverse function [34] or with the Legendre transform [35]. These methods will be detailed in section (1.3).

The aim of this chapter is to demonstrate the utility of the Legendre transform in reformulating free energies in electrostatics. The Legendre transform is a powerful tool with multiple applications in physics [36]. This transformation, named after the French mathematician Adrien-Marie Legendre (1752, 1833), allows in classical mechanics the interchange of Lagrangian and Hamiltonian viewpoints. In thermodynamics one regularly transforms ensembles to simplify calculations, choosing the ensemble which most closely idealizes a given experimental set-up. In this chapter, we first present the Legendre transform, its mathematical properties and its uses in different fields of physics. We also show how the Legendre transform is applied to electrostatics.

In the second section, we present systems with coupled degrees of freedom which are found in diverse fields. We detail two cases where we explicitly use the Lengendre transform to define new functionals. One system in particular, the virus model, is used in the next parts as a sample to test our optimization method.

In the third section, we present different methods devised to compute the free energy of systems with interacting degrees of freedom. One method solves the system directly with intertwined iterations, the second uses the derivatives of the free energy, and the last two reformulate the free energy into fully convex computer-friendly forms. Our aim is to compare these methods using the simple model of a virus .

Our numerical results are presented and commented in the last section of this chapter.

1.1. The Legendre Transform

We present the Legendre transform, its definition and properties. Then we review the use of Legendre transforms in different fields of physics : classical mechanics, thermodynamics and optics. Last, we apply this mathematical tool to electrostatics: we show how to render standard functionals convex, at the cost of expressing them in terms of the vector field **D** instead of the potential ϕ .

1.1.1. A mathematical tool

Making sense of the Legendre transform Zia, Redish and McKay Am. J. Phys., Vol. 77, No. 7, July 2009

The Legendre transform of a convex function f(x) is defined by :

$$\begin{cases} \mathcal{L}[f](s) = g(s) = sx - f(x) \\ s = \frac{df}{dx} \end{cases}$$
(1.2)

In the first line of equation (1.2), x is a function of s and is defined by the second line of the definition. x and s are called the conjugate variables.

The Legendre transform can also be written in a more symmetric form :

$$g(s) + f(x) = sx \tag{1.3}$$

We must however be careful with such notation : only one variable is present, and *x* (resp. *s*) must be considered as a function of *s* (resp. *x*) given by $s = \frac{df}{dx}$ (resp. $x = \frac{dg}{ds}$). This symmetric form clearly shows that this transformation is an involution : $\mathcal{L}[g](x) = f(x)$. This is also easily verified with the definition (1.2):

$$\mathcal{L}[g](x) = sx - g(s) = sx - (sx - f(x)) = f(x)$$
(1.4)

The Legendre transform can also be defined with the extremum:

$$\mathcal{L}\left[f\right](s) = g(s) = \max_{x}\left(sx - f(x)\right) \tag{1.5}$$

Equation (1.5) defines the same transformation as equation (1.2). Indeed, if we consider the derivative $\frac{d}{dx}(sx - f(x))$, we obtain the equation that x must verify so that the extremum is reached: $s = \frac{df}{dx}$, and we find the first definition of the Legendre transform. This second definition shows clearly that applying a

Legendre transform is equivalent to considering the extremum of the function : $x \mapsto xs - f(x)$. The notation with a minimum instead of a maximum is equally used.

While the first definition of the Legendre transform (1.2) is used to explicitly calculate the equivalent function, the second definition (1.5) gives a clear understanding of our future reasoning as we aim to optimise free energies.

A graphic representation of the Legendre transform is given in figure (1.1).



Figure 1.1.: Graphic representation of the Legendre transform. Let us consider the function f(x), represented by the blue curve, at a given point x. Its derivative is represented by a straight line of slope $s = \frac{df}{dx}$ in red. This line intersects the ordinate axis, and we call this intersection g. We can see on this figure that the sum of f and g is equal to xs since s is the slope. Thus we find back the symmetric definition of the Legendre transform : f + g = sx. *Picture taken from* [36].

Thus the Legendre transform defines a new function g(s) holding the same information as the original function f(x) does, but expressed in term of the derivative $\frac{df}{dx}$.

One property of the Legendre transform is that, for a function -f(x) concave, the transform $\mathcal{L}[f](s)$ is convex. Since the saddle point problem studied in this chapter comes from the concavity of the electrostatic free energy, such

1. The Legendre Transform applied to Electrostatics

property is central to our use of the Legendre transform. Indeed, we apply this transformation to the electrostatic free energy to create an equivalent convex functional.

A simple example of the use of the Legendre transform is the study of a Hookian spring: $f(x) = kx^2/2$. The transformation of equation (1.2) gives g(s) = sx(s) - f(x(s)) and x(s) is defined by : $s = \frac{df}{dx} = kx(s)$. Replacing x(s) in the expression of g(s) leads to : $g(s) = s^2/(2k)$. We recognise here the expression of the spring potential energy with respect to the position: $f(x) = \frac{kx^2}{2}$ and the energy using the force applied to the spring : $g(s = F) = \frac{F^2}{2k}$. Both expressions fully described the system and we can use either to study the Hookian spring.

The Legendre transform definition can be expended for non-convex and nondifferentiable functions. It is then called the Legendre-Fenchel transform or the convex conjugate. Though this transform is more general, it is not an involution: the transform of the transform gives the convex envelope of the original function rather than the function itself [37].

1.1.2. Uses in different fields

Making sense of the Legendre transform Zia, Redish and McKay Am. J. Phys., Vol. 77, No. 7, July 2009

In classical mechanics, the Legendre transform connects the Lagrangian description $\mathcal{L}(\dot{q})$ with the Hamiltonian $\mathcal{H}(p)$. Both of these formulations bypass the concept of forces applied to a particle and instead focus respectively on the speed \dot{q} and the momentum p. They are conjugate variables and the symmetric form of the Legendre transform gives : $\mathcal{L}(\dot{q}) + \mathcal{H}(p) = \dot{q}p$. If we consider an external potential V(q) in which the system evolves, this potential is unchanged by the transformation and only a sign differs between the well-known expressions of \mathcal{L} and \mathcal{H} :

$$\mathcal{L} = T - V$$

$$\mathcal{H} = T + V$$
(1.6)

The interest of the Legendre transform is shown with the following example: a particle is in a one dimensional convex potential well U(x). This well has a unique minimum x_{min} which corresponds to the particle's stationary position.

If we apply an external force f to this particle, its stationary position is shifted to a new position $x_0(f)$ solution of $\frac{dU}{dx}\Big|_{x_0} = f$. So, to move the particle to a position x, one has to apply the force $f = \frac{dU}{dx}$.

The remaining question follows: is there a counterpart to U(x) that gives x(f) directly? In other words, is there a function V of f which gives x(f) as its derivative? The answer is the Legendre transform of U(x) : V(x) = fx(f) - U(x(f)), which gives : $\frac{dV}{df} = x(f) + f\frac{dx}{df} - \frac{dU}{dx}\frac{dx}{df} = x(f)$.

It is important to remark that the system is fully described by any of the two forms : U(x) or V(f).

In statistical dynamic, the Legendre transform allows us to switch between variables and their conjugates. One of the variables is often easy to think about, while its conjugate is more easily controlled.

For example the total energy *E* of a system is a concept easily grasped, while the associated control parameter is the temperature through β . To see that those two variables are conjugate, we need to consider the Helmholtz energy *F* and the entropy *S*. We know that F = E - TS. Noting $\mathcal{F} = \beta F$ and $\mathcal{S} = S/k_B$ the dimensionless quantities, we obtain : $\beta F = \beta E - \frac{1}{k_B T} TS$, which leads to :

$$\mathcal{F}(\beta) + \mathcal{S}(E) = \beta E \tag{1.7}$$

These two quantities, linked by a Legendre transform, describe equally the system. The temperature being easier to manipulate in an experimental set-up, one will rather consider the Helmholtz free energy. Furthermore, the variation of this energy regarding the temperature is a mark of the system's ability to respond : $\frac{dF}{d\beta}$ = response = *E*. If we look at the transformed version, *E* appears then as a constraint applied to the system (for example, the total energy is constant for an isolated system) and $\beta = \frac{dS}{dE}$ becomes a measure of the system's state. We can summarize these observations as follow :

considering
$$\mathcal{F}(\beta)$$
 $\beta = \text{control}$ $E = \text{response}$
 $\mathcal{S}(E)$ $E = \text{constraint}$ $\beta = \text{measure}$ (1.8)

Thus, the Legendre transform allows us to consider the description that best fits the experiment. This kind of transformation may be applied to other control/response pairs of variables : particle number and chemical potential, magnetization and magnetic field, polarizability and electric field. **In optics,** the Legendre transform allows us to switch between the different eikonals describing an optical system [38]. An eikonal is the optical length of the ray between the input plane and the output plane. There exist four eikonals which differ by how the light in each plane is described : either by a point position (x, y) or by an angle (p, q). The four eikonals and how they relate through the Legendre transform are as follow :

$$point eikonal = S((x, y), (x', y'))$$

$$point-angle eikonal = V((x, y), (p', q')) = -\mathcal{L}_{(x', y') \to (p', q')}[S]$$

$$angle-point eikonal = V'((p, q), (x', y')) = \mathcal{L}_{(x, y) \to (p, q)}[-S]$$

$$angle eikonal = T((p, q), (p', q')) = \mathcal{L}_{(x, y) \to (p, q)}[-V]$$

$$= -\mathcal{L}_{(x', y') \to (p', q')}[V']$$

$$(1.9)$$

The prime notation corresponds to what relates to the output plane. We note that eikonal theory uses a slightly different definition of the Legendre transform than the one given in section (1.1.1) : $\mathcal{L}_{eikonal} [f(x)] = f(x) - xs$. For clarity, I kept in this paragraph the same definition as before, hence the frequent appearance of the minus sign in the above equations.

Those different eikonals are useful to describe different situations. For example, afocal systems require point-eikonal descriptions, while angle-eikonals are useful when the output plan is the image plan [38].

The Legendre transform is also used to determine the caustic of light rays from the profile of the surface which reflects or refracts those rays [39]. The caustic is defined as the curve or surface to which the light rays are tangent. It is, as Starvroudis explains (ref [1] of [40]) : "[...] real and becomes visible by blowing a cloud of smoke in the focus of a lens". As the Legendre transform is an involution, it is also possible to use the caustic form to deduce the surface profile [39]. Such transformation is particularly useful for the study of cracks in materials through the caustics [41]. We find here the same control/response duality as presented in the previous paragraph for the thermodynamics.

1.1.3. Application to electrostatics

Legendre transforms for electrostatic energies J. S. Pujos and A. C. Maggs Proceedings of the CECAM Workshop, 2012

As shown in the previous paragraphs, the Legendre transform is particularly useful to switch between equivalent descriptions of a system. This also applies in electrostatics [35, 42], and we show how the energy functional expressed in

term of the electrostatic potential ϕ , transforms into an equivalent functional depending of the electrostatic displacement **D**. We illustrate this transformation with three systems. First, we study the simple case of fixed charges interacting. Second, we present the case of mobile ions, a system on which we will expend in further studies. Last, we provide a translation between two visions of the theory of dielectrics. Indeed, recent formulations of implicit dielectrics use elaborate field-theory mappings and find a generalized Poisson-Boltzmann equation with a Langevin correction. We show how to map this description onto a free energy expressed in terms of a polarization field with long-ranged dipolar interactions. We believe that these equivalent descriptions can lead to a deeper understanding of the underlying physics.

Interaction between fixed charges is the simplest approach with which we first illustrate the Legendre transform. We consider fixed charges ρ_f in a heterogeneous dielectric medium. The energy functional expressed in terms of the electric potential ϕ is :

$$U(\phi) = \int \left\{ -\frac{\epsilon(\mathbf{r})(\nabla\phi)^2}{2} + \rho_f \phi \right\} d^3 \mathbf{r}$$
(1.10)

with $\epsilon(\mathbf{r})$ the dielectric constant of the medium. To find the state of the system at equilibrium is to find the potential ϕ which optimizes $U(\phi)$. The variational equation with respect to the electrostatic potential leads to the Poisson equation:

div
$$\epsilon(\mathbf{r})$$
grad $\phi = -\rho_f(\mathbf{r})$ (1.11)

We start our transformation of the variational problem by introducing the new variable $\mathbf{E} = -\nabla \phi$, the electric field. To do so we use a vector Lagrange multiplier **D**. The stationary point of equation (1.10) is identical to the one of the following expression [43]:

$$U(\phi, \mathbf{E}, \mathbf{D}) = \int \left\{ -\frac{\epsilon(\mathbf{r})\mathbf{E}^2}{2} + \rho_f \phi + \mathbf{D} \cdot (\mathbf{E} + \nabla \phi) \right\} d^3 \mathbf{r}$$
(1.12)

Re-organizing this equation leads to :

$$U(\phi, \mathbf{E}, \mathbf{D}) = \int \left\{ \mathbf{D} \cdot \mathbf{E} - \frac{\boldsymbol{\epsilon}(\mathbf{r})\mathbf{E}^2}{2} + \rho_f \phi + \mathbf{D} \cdot \nabla \phi \right\} d^3 \mathbf{r}$$
(1.13)

At this point, we recognize the variational equation for **E** which corresponds to

a Legendre transform with dual variable \mathbf{D} (in purple in equation (1.13)):

$$\mathbf{D} \cdot \mathbf{E} - \frac{\epsilon(\mathbf{r})\mathbf{E}^2}{2} = \mathcal{L}\left[\frac{\epsilon(\mathbf{r})}{2}\mathbf{E}^2\right](\mathbf{D}) = \frac{D^2}{2\epsilon(\mathbf{r})}$$
(1.14)

We also integrate by parts the product $\mathbf{D} \cdot \nabla \phi$ to find $-\phi \operatorname{div} \mathbf{D}$, and we assume vanishing boundary terms. Thus the stationary point of equation (1.10) is identical to the stationary point of:

$$U(\mathbf{D},\phi) = \int \left\{ \frac{\mathbf{D}^2}{2\epsilon(\mathbf{r})} + \phi(\rho_f - \operatorname{div} \mathbf{D}) \right\} d^3\mathbf{r}$$
(1.15)

This new functional is convex [44, 45], and variation in ϕ now imposes Gauss law: div $\mathbf{D} - \rho_f = 0$. Thus, the field \mathbf{D} is the electrostatic displacement defined by: $\mathbf{D} = \epsilon \mathbf{E} = -\epsilon \nabla \phi$. We notice that replacing \mathbf{D} in Gauss' law leads back to the Poisson equation (eq. (1.11)), also deduced from the variation of the energy regarding ϕ .

In the following work, we use free energy densities, rather than the integrated energies. Keeping in mind that we are working on equivalent functionals with identical stationary points, equivalent free energies will all be noted f even though they are not strictly equal.

Free mobile ions are now considered. In numerous situations, symmetric monovalent electrolytes are used to describe a ionic medium. We will detail here the application of the Legendre transform to such electrolytes.

The free energy is given by:

$$f(\phi, c_+, c_-) = -\frac{1}{2}\epsilon(\nabla\phi)^2 + (c_+ - c_-)e\phi + k_BT\sum_j (c_j \ln(c_j/c_{j0}) - c_j)$$
(1.16)

with ϕ the electrostatic potential, c_{\pm} the ions concentration and $c_{\pm 0}$ the bulk concentration. ϵ is the dielectric constant of the medium, e the elementary charge and T the temperature with k_B the Boltzmann constant. The first line corresponds to the electrostatic interactions and the second line is the entropy of the ions.

Variation of *f* with respect to c_{\pm} gives:

$$\pm e\phi + k_B T(\ln (c_{\pm}/c_{\pm 0}) + 1 - 1) = 0$$

thus we find the Boltzmann distribution of the ions:

$$c_{\pm} = c_{\pm 0} \exp\left(\mp \beta e \phi\right) \tag{1.17}$$

This leads to the well-known expression of the free energy for monovalent symmetric ions:

$$f(\phi) = -\frac{1}{2}\epsilon(\nabla\phi)^2 - 2c_0\cosh(\beta e\phi)$$
(1.18)

Now we replace $-\nabla \phi$ by **E** and introduce the Lagrange parameter **D**:

$$f(\phi, \mathbf{E}, \mathbf{D}) = -\frac{1}{2}\epsilon \mathbf{E}^2 - 2c_0 \cosh(\beta e\phi) + \mathbf{D} \cdot (\mathbf{E} + \nabla\phi)$$

= $\mathbf{D} \cdot \mathbf{E} - \frac{1}{2}\epsilon \mathbf{E}^2 + \phi \cdot (-\operatorname{div} \mathbf{D}) - 2c_0 \cosh(\beta e\phi)$ (1.19)

We recognize here two different Legendre transforms: one for **E** with the dual variable **D** (in purple), and one for ϕ with the dual variable $-\text{div } \mathbf{D}$ (in green). The first Legendre transform is similar to the Hookian spring example given in section (1.1.1).

$$\mathcal{L}\left[\frac{\epsilon \mathbf{E}^2}{2}\right](\mathbf{D}) = \frac{\mathbf{D}^2}{2\epsilon}$$
(1.20)

We calculate the general Legendre transform of the function $x \mapsto A \cosh(Bx)$. From the definition (1.2), we have:

$$\begin{cases} \mathcal{L} \left[A \cosh(Bx) \right](s) = sx - A \cosh(Bx) \\ s = AB \sinh(Bx) \end{cases}$$
(1.21)

We replace $x = \operatorname{asinh}(s/AB)/B$ in the first line and use the equality $\operatorname{cosh}(\operatorname{asinh}(y)) = \sqrt{y^2 + 1}$. We obtain the Legendre transform of the hyperbolic cosine:

$$\mathcal{L}[A\cosh(Bx)](s) = A\left[s/(AB)\operatorname{asinh}(s/AB) - \sqrt{(s/AB)^2 + 1}\right]$$

$$= A\,\tilde{g}\,(s/AB)$$
(1.22)

Thus we can write an equivalent convex free energy density :

$$f(\mathbf{D}) = \frac{\mathbf{D}^2}{2\epsilon} + 2c_0 \tilde{g} \left(\frac{-\operatorname{div} \mathbf{D}}{2c_0 \beta e}\right)$$
(1.23)

Extending this description to a system with fixed charges and mobile ions, we find the free energy density:

$$f(\mathbf{D}) = \frac{\mathbf{D}^2}{2\epsilon} + 2c_0 \tilde{g} \left(\frac{\rho_f - \operatorname{div} \mathbf{D}}{2c_0 \beta e}\right)$$
(1.24)

In the absence of free ions the function \tilde{g} reduces to the constraint of Gauss' law, and we are back to the first example.

This method can also be applied to a non-symmetric electrolyte. One has to consider the Legendre transform of $e^{\beta q_1 \phi} + e^{-\beta q_2 \phi}$ instead of the function \tilde{g} .

From Poisson-Langevin to Polarization We now consider theories of explicit Langevin dipoles and how these dipoles can be incorporated into a convex free energy. Recent work on improving the description of solvation of proteins [46] has considered an explicit model for the solvent in terms of Langevin dipoles. If we neglect the volume of ions and dipoles, the free energy density for a mixture of symmetric ions and neutral dipoles is :

$$f(\phi) = \rho_f \phi - \frac{\epsilon_0 (\nabla \phi)^2}{2} - 2\lambda_{ion} \cosh\left(\beta q \phi\right) - \lambda_{dip} \frac{\sinh(\beta p_0 |\nabla \phi|)}{\beta p_0 |\nabla \phi|}$$
(1.25)

The parameters λ are related to the chemical activities of the ions and dipoles respectively. All dipoles have the same dipolar moment intensity p_0 and the dipole term comes from the integration over all orientations. We consider here only the vacuum permittivity ϵ_0 since the medium is directly modelled with the dipoles.

As in the previous example and in [35], we use first a Lagrangian multiplier **D** to replace $(\nabla \phi)$ by its electrostatic equivalent $-\mathbf{E}$.

$$f(\phi, \mathbf{E}, \mathbf{D}) = \rho_f \phi - \frac{\epsilon_0 \mathbf{E}^2}{2} - g(\phi) - h(\mathbf{E}) + \mathbf{D} \cdot (\nabla \phi + \mathbf{E})$$
(1.26)

where $g(\phi) = 2\lambda_{ion} \cosh(\beta q \phi)$ is the free energy density due to the free ions and $h(\mathbf{E}) = \lambda_{dip} \frac{\sinh(\beta p_0 |\mathbf{E}|)}{\beta p_0 |\mathbf{E}|}$ the free energy due to the dipoles.

Working in the limit where the linear response is valid, the dipole part of the

free energy can be expanded to the quadratic order and $h(\mathbf{E})$ becomes:

$$h(\mathbf{E}) = \lambda_{dip} + \frac{\lambda_{dip}}{6} \beta^2 p_0^2 \mathbf{E}^2$$

The constant being of no interest since we focus on the optimum, we consider only the quadratic part of $h(\mathbf{E})$. We also integrate by part the product $\mathbf{D} \cdot \nabla \phi$ into $-\phi \cdot \text{div } \mathbf{D}$, and we obtain:

$$f(\phi, \mathbf{E}, \mathbf{D}) = \rho_f \phi - \frac{\epsilon_0 \mathbf{E}^2}{2} - g(\phi) - \frac{\lambda_{dip} \beta^2 p_0^2}{3} \frac{\mathbf{E}^2}{2} + \mathbf{D} \cdot \mathbf{E} - \operatorname{div} \mathbf{D} \cdot \phi$$

$$= \mathbf{D} \cdot \mathbf{E} - \left(\epsilon_0 + \frac{\lambda_{dip} \beta^2 p_0^2}{3}\right) \frac{\mathbf{E}^2}{2} + \phi(\rho_f - \operatorname{div} \mathbf{D}) - g(\phi)$$
(1.27)

At this point, we recognize two Legendre transforms and we reach a new equivalent functional:

$$f(\mathbf{D}) = \frac{1}{\epsilon_0 \left(1 + \lambda_{dip} \beta^2 p_0^2 / 3\epsilon_0\right)} \frac{\mathbf{D}^2}{2} + 2\lambda_{ion} \,\tilde{g}\left(\frac{\rho_f - \operatorname{div} \mathbf{D}}{2\beta q \lambda_{ion}}\right) \tag{1.28}$$

We are here interested by the first term on the right hand side of the equation. It takes the well-known form of $\frac{\mathbf{D}^2}{2\epsilon_0\epsilon_R}$ with $\epsilon_R = 1 + \frac{\lambda_{dip}\beta^2 p_0^2}{3\epsilon_0}$ being a characteristic of the material. We recognize here a classical form of the energy where the dielectrolyte properties are included in the relative dielectric constant of the medium.

We now diverge from our previous treatment and introduce a new variable **P**. We will show later that **P** is the physical polarization. We consider the functional:

$$f(\mathbf{E}, \mathbf{D}, \mathbf{P}) = \phi(\rho_f - \operatorname{div} \mathbf{D}) - \frac{\epsilon_0 \mathbf{E}^2}{2} - g(\phi) + \mathcal{L}[h](\mathbf{P}) + \mathbf{E} \cdot (\mathbf{D} - \mathbf{P})$$
(1.29)

Let us show that this functional is equivalent to the functional given by equation (1.26). We recognize the Legendre transform in \mathbf{P} with the dual variable **E**:

$$\mathbf{EP} - \mathcal{L}[h](\mathbf{P}) = \mathcal{L}[\mathcal{L}[h]](\mathbf{E}) = h(\mathbf{E})$$

The last equality comes from the involution property of the Legendre transform. Thus the two functionals are equivalent.

From equation (1.29), we can apply the Legendre transform on ϕ for the dual

variable (ρ_f – div **D**) and on **E** for the dual variable (**D** – **P**). We find:

$$f(\mathbf{D}, \mathbf{P}) = \frac{(\mathbf{D} - \mathbf{P})^2}{2\epsilon_0} + \mathcal{L}[h](\mathbf{P}) + \mathcal{L}[g](\rho_f - \operatorname{div} \mathbf{D})$$
(1.30)

This is exactly the form postulated in [47]. It is particularly useful to understand the physical limits on response functions [48, 49] and the origin of the negative dielectric constant observed in structured fluids.

Working from equation (1.30), we can demonstrate its equivalence to other formulations of electrostatic interactions expressed in terms of the polarization **P**. To do so, we need to eliminate the variable **D**. This brings us back to other more familiar forms for the electrostatic energy at the cost of re-introducing long-ranged dipole-dipole interactions between the polarization variables.

Using once more the quadratic order of $h(\mathbf{E})$, we have:

$$\mathcal{L}[h](\mathbf{P}) = \frac{\mathbf{P}^2}{2\epsilon_0 \chi} \tag{1.31}$$

where χ is a material parameter. Taking the variations of the functional (1.29) with respect to **P** and **E**, we find that:

$$\mathbf{P} = \epsilon_0 \chi \mathbf{E}, \quad \epsilon_0 \mathbf{E} = \mathbf{D} - \mathbf{P} \tag{1.32}$$

The parameter χ is thus the electric susceptibility of the medium. The polarisation variable is indeed playing the role we expect from standard treatments of Maxwell's equations. The free energy of the fluctuating dipoles in the absence of free ions can then be found from the functional

$$f(\mathbf{D}, \mathbf{P}, \phi) = \frac{(\mathbf{D} - \mathbf{P})^2}{2\epsilon_0} + \frac{\mathbf{P}^2}{2\epsilon_0 \chi(\mathbf{r})} - \phi(\operatorname{div} \mathbf{D} - \rho_f)$$
(1.33)

where the last term is a Lagrange multiplier for the constraint of Gauss' law, which replaces $\mathcal{L}[g]$. The free energy takes here another well-known form where the dielectric properties are directly considered through the polarisation **P** and the electric susceptibility of the material $\chi = \epsilon_R - 1$.

Further re-writing (refer to [42]) leads to a formulation of the free energy

widely used in theoretical study of electron transfer reactions [50] :

$$U = \frac{1}{2} \int \frac{\operatorname{div} \mathbf{P}(\mathbf{r}) \operatorname{div} \mathbf{P}(\mathbf{r}')}{4\pi\epsilon_0 |\mathbf{r} - \mathbf{r}'|} d^3 \mathbf{r} d^3 \mathbf{r}' + \int \left\{ \frac{\epsilon_0 \mathbf{E}_0^2}{2} - \mathbf{E}_0 \cdot \mathbf{P} + \frac{\mathbf{P}^2}{2\epsilon_0 \chi(\mathbf{r})} \right\} d^3 \mathbf{r}$$
(1.34)

We have demonstrated that energy functionals for dielectrics can be translated into equivalent forms by introducing the physical polarization. We conclude that the Legendre transform allows us to switch between equivalent descriptions of the dipoles.

1.1.4. Conclusion

We have shown that the Legendre transform can be used to translate between multiple forms of the energy in mean-field theories. All formulations are equivalent but different forms put the emphasis on different degrees of freedom. For numerical implementation, it is advantageous to work with a formulation which is both convex and local. This is achieved in Poisson-Boltzmann theory by choosing the electrostatic displacement **D** as the fundamental thermodynamic field. This is particularly interesting for systems with more degrees of freedom than the electrostatics. Indeed the stationary point of the free energy shifts from a saddle point to a minimum with the use of the Legendre transform. All physical degrees of freedom can thus be treated in an equivalent manner in numerical solvers. Very similar conclusions have also been found in quantum chemistry [51].

1.2. Electrostatic Interacting Systems

In this section we present three systems described by interacting degrees of freedom. In particular we detail the use the Legendre transform for a phase separation problem (in section 1.2.1), and in the case of the virus model (in section 1.2.3).

1.2.1. Phase separation coupled to electrostatics

We consider the theory of phase separation of immiscible fluids in the presence of electrostatic interactions due to ions. A mixture of two solvents (A and B) near their miscibility limit and in the presence of salt displays interesting properties which have been explored in recent experiments [28]. Density fluctuations couple to the dielectric properties of the medium, which in turn influence the partition of ions in the fluctuating solvent field. The experimental system has turned out to be very rich, and allows one to adjust the effective interaction between colloidal particles using temperature as a control parameter.

A simplified theoretical description of such systems is given in [26, 52] and the free energy density expressed in terms of the densities and potentials is given by:

$$f(\phi, \Psi, c_+, c_-) = f_m(\Psi) - \frac{1}{2}\epsilon(\Psi)(\nabla\phi)^2 + (c_+ - c_-)e\phi - (\Delta u^+ c_+ + \Delta u^- c_-)\Psi + k_BT\sum_j (c_j \ln (c_j/c_{j0}) - c_j)$$
(1.35)

 Ψ describes the composition of the fluid mixture. c_+ and c_- are the concentration of positive and negative monovalent ions, with Δu^+ and Δu^- their relative preferences between a A-liquid environment and a B-liquid environment. As before, ϕ is the electrostatic potential. We see that variations in the fluid composition are coupled with the electrostatic via $\epsilon(\Psi)$.

 $f_m(\Psi)$ includes all the terms that are only dependent on Ψ and is convex:

$$f_m(\Psi) = f_0(\Psi) + \frac{c}{2}(\nabla \Psi)^2 - \mu \Psi$$

with $f_0(\Psi)$ the free energy due to the mixing of the two solvents. It can, for example, be written as a binary mixture free energy density: $f_0(\Psi) \propto \Psi \log(\Psi) + (1 - \Psi) \log(1 - \Psi) + \chi \Psi (1 - \Psi)$, with χ the Flory parameter [27, 53], or as a Landau expansion $f_0(\Psi) \propto \alpha (\Psi - \Psi_c)^2 + \gamma (\Psi - \Psi_c)^4$, with α being temperature dependent, γ positive, and Ψ_c the critical composition [26].

We optimize the functional (1.35) over c_+ and c_- . The free energy density becomes:

$$f(\Psi,\phi) = f_m(\Psi) - \frac{1}{2}\epsilon(\Psi)(\nabla\phi)^2 - k_B T c_{0+} \exp(\beta \Delta u^+ \Psi - \beta e \phi) - k_B T c_{0-} \exp(\beta \Delta u^- \Psi + \beta e \phi)$$
(1.36)

Let us note that using the Legendre transform of the function $c_{\pm} \mapsto \Delta u^{\pm} c_{\pm} - k_B T c_{\pm} \left[\ln \left(\frac{c_{\pm}}{c_{\pm,0}} \right) - 1 \right]$ leads to the same functional (1.36).

With a symmetric electrolyte ($c_{0+} = c_{0-}$) and assuming that the ions have similar interactions with the solvents ($\Delta u^+ = \Delta u^-$), the functional simplifies into :

$$f(\Psi,\phi) = f_m(\Psi) - \frac{1}{2}\epsilon(\Psi)(\nabla\phi)^2 - 2k_B T c_0 \exp(\beta \Delta u \Psi) \cosh(\beta e \phi)$$
(1.37)

We recognize here a generalization of the well known Poisson-Boltzmann functional for a symmetric electrolyte. The description is adapted to analytical solutions yet $f(\Psi, \phi)$ is convex with respect to Ψ but concave for ϕ . To find the equilibrium state numerically, one has to solve a saddle point problem as a simple minimization will not give the correct answer. We now implement the transformation introduced in section (1.1.3) and replace the potential ϕ with the electric displacement **D** :

$$f(\Psi, \mathbf{D}) = f_m(\Psi) + \frac{\mathbf{D}^2}{2\epsilon(\Psi)} + 2k_B T c_0 e^{\beta \Delta u \Psi} \tilde{g}\left(\frac{\operatorname{div}(\mathbf{D}) e^{-\beta \Delta u \Psi}}{2c_0 e}\right)$$
(1.38)

with \tilde{g} the Legendre transform of cosh (equation (1.22)).

We have thus reached our objective: we have built an equivalent description of the system with the stationary conditions conserved and a local and convex functional. One disadvantage is that the number of degrees of freedom is increased due to the use of the vector field **D** instead of the scalar field ϕ . The advantage, however, is that a global minimising principle can be used and the functional can be directly programmed to give the solution of the coupled electrostatic-phase separation problem.

1.2.2. Polyelectrolytes

Polyelectrolytes are charged polymers, thus electrostatics are an important part of their properties. However, the polymer nature can not be neglected and must be considered to study these objects. If the charges interactions are usually described with the electrostatic field ϕ , the polymer configuration is often described with the field ψ [54, 55]. This field comes from the ground state dominance approach and relates to the concentration of monomers though $C_{monomer} = |\psi|^2$. It contributes to the free energy through the integral:

$$I = \int \left\{ \frac{a^2}{6} (\nabla \psi)^2 + \frac{v}{2} |\psi|^4 \right\} \, d\mathbf{r} = \frac{F}{T}$$
(1.39)

The first term in the integral is the entropy contribution. It thus represents the resistance to inhomogeneous distribution. It is the polymer's response to local variation of the concentration and is linked to the connectivity of the chain. It is regulated by the monomer size a. The second term comes from the self-consistent potential. It corresponds to the short range interaction between monomers and is determined by the excluded volume of the polyelectrolyte chain v.

A confined polyelectrolyte was studied by Podgornik [23]. In the fourth part of this article, he describes how this study is an extension of the Poisson-Boltzmann equation. The charge density of the polymeric chain is obtained through the Green's function of the polymer and the free energy is found in one dimension. A similar study was undertaken by Borukhov, Andelman and Orland [56] to explore the attraction between charged colloids in the presence of polyelectrolytes.

In both cases the functional free energies relate to two interacting fields :

$$f(\psi, \phi, c^{+}, c^{-}) = -\frac{\epsilon_{0}\epsilon_{R}}{2} (\nabla \phi)^{2} + \left(ec^{+} - ec^{-} + \rho_{f} - pe\psi^{2}\right)\phi + \sum_{i=\pm} k_{B}T \left\{c^{i}\ln(\frac{c^{i}}{c_{0}^{i}}) - c^{i}\right\} + k_{B}T \left\{\frac{a^{2}}{6} (\nabla \psi)^{2} + \frac{v}{2}\psi^{4}\right\}$$
(1.40)

The first line gives the electrostatic contribution of the free energy with free ions c^{\pm} , fixed charges ρ_f and the polyelectrolyte monomers charged -pe. The second line is the salt entropy. The third line corresponds to the non-electrostatic interactions of a polyelectrolyte, with *a* the monomer size and *v* the excluded

volume. The remaining parameters are: ϵ_0 the vacuum permittivity, ϵ_R the relative permittivity of water, *e* the elementary charge, $\beta = \frac{1}{k_BT}$ the inverse temperature, and c_0 the concentration of monovalent symmetric ions. This functional can be minimized over c^+ and c^- to become:

 $\epsilon_0 \epsilon_{R} = 2 (2)$

$$f(\phi,\psi) = -\frac{10^{-1}K}{2}(\nabla\phi)^2 + \left(\rho_f - pe\psi^2\right)\phi$$

$$-2c_0\cosh(\beta e\phi) + k_BT\left\{\frac{a^2}{6}(\nabla\psi)^2 + \frac{v}{2}\psi^4\right\}$$
(1.41)

The stationary point of this functional gives the free energy of the system. At this point, $\phi(r)$ is the Poisson-Boltzmann electrostatic potential and ψ^2 gives the density of a single polyelectrolyte.

The pseudo-free energy in equation (1.41) is concave with respect to ϕ and convex with respect to ψ . This is problematic for numerical methods as saddle-point searchs are slow to converge.

Extensions of these ideas to different situations were made. For example polyelectrolyte brushes, which are charged polymers densely grafted onto a surface, were studied by Seiki , Suzuki and Orland who investigated the scaling relation of the thickness of the brush [16]. In this case, the Hamiltonian is also expressed in terms of two interacting fields. The mean field approximation leads to a general Poisson-Boltzmann equations and modified diffusion equations that the probability amplitude of the monomer should verify. These equations were numerically solved through iterations.

In [57], the description of polymer brushes is extended with the addition of short range interactions.

1.2.3. The spontaneous virus formation

Polyelectrolyte theory can be used in biology to model structures like DNA or RNA. In [24], Šiber and Podgornik developed a simple model of a ssANR virus. The virus capsid is considered to be a charged sphere of radius *R* with a surface charge σ . The genomic structure is modeled with a charged polymer described by the density of monomers ψ^2 . It is composed of *N* monomers of charge *pe*, of size *a* and of efficient non-electric volume *v*. The virus is immersed in a symmetric monovalent electrolyte of bulk concentration c_0 which models the biological medium.

The pseudo free energy of the virus system is:

$$F = \int f(\psi, \phi, c^+, c^-) + \mu \left(\int \psi^2 - N \right)$$
 (1.42)

where the second term on the right-hand side is the constraint over the number of monomers and μ its Lagrange parameter. The first term is the free energy density:

$$f(\psi,\phi,c^+,c^-) = k_B T \left\{ \frac{a^2}{6} (\nabla \psi)^2 + \frac{v}{2} \psi^4 \right\} - \frac{\epsilon_0 \epsilon_R}{2} (\nabla \phi)^2 + \left(ec^+ - ec^- + \sigma - pe\psi^2 \right) \phi$$
(1.43)
$$+ \sum_{i=\pm} k_B T \left\{ c^i \ln \left(\frac{c^i}{c_0^i} \right) - c^i \right\}$$

This functional is composed of the polyelectrolyte non-electrostatic self-interaction term; the electrostatic energies of polyelectrolyte segments, fixed charges residing on the capsid, and salt ions; as well as the entropies of the salt ions. The free energy corresponds to the minimum with respect to the fields { ψ , c_+ , c_- } and the maximum over the electrostatic field ϕ .

Minimizing over the ions concentration leads back to the polyelectrolyte equation (1.41).

In the case of the formed virus, the polyelectrolyte is contained within the capsid and we set $\psi = 0$ outside of the virus itself.

This model is used to study how the energy formation of the virus varies with the salt concentration or with the size of the RNA. For example, the number of monomers *N* represents the size of the virus' ss-RNA and determines the quantity of genetic information carried by the virus [24].

To use the Legendre transform, the electrostatic displacement field **D** is introduced [35]. It describes the electrostatics of the system instead of the scalar potential ϕ , and the final functional is:

$$f(\mathbf{D}, \psi) = k_B T \left\{ \frac{a^2}{6} (\nabla \psi)^2 + \frac{v}{2} \psi^4 \right\} + \frac{\mathbf{D}^2}{2\epsilon_0 \epsilon_R} + 2c_0 k_B T \left\{ \xi \operatorname{asinh} \left(\xi \right) - \sqrt{\xi^2 + 1} \right\}$$
(1.44)

with $\xi(\mathbf{D}, \psi) = \frac{\sigma - pe\psi^2 - \nabla \mathbf{D}}{2ec_0}$.

The new formulation is perhaps less intuitive than the more familiar Poisson-Boltzmann equation. Yet its convexity with respect to all the fields renders it suitable for simple numerical minimization.

1.2.4. Conclusion

In this part we introduced new variational variables in free energies with the help of Lagrange multipliers, and then performed a Legendre transform to find functionals that are convex with respect to all degrees of freedom. We illustrated this with a mean field formulation of phase separation coupled to electrostatic interactions, and with a simple virus model. In the next parts we will focus on the numerical resolution of systems with interacting degrees of freedom.

1.3. Numerical Methods

The present section focuses on numerical treatments of models with interacting degrees of freedom. As discussed previously, the free energy is concave with respect to the electrostatic field [22] and convex with respect to configurational degrees of freedom. Thus simultaneous optimization of the free energy for both fields is excluded.

Various methods exist which reformulate the free energy so that it is convex with respect to every fields and retains its stationary point. One such method squares the derivatives of the free energy functional (equation (1.1)). The new functional is always positive and vanishes at the stationary point [20, 56]. In other methods the free energy functional is rewritten using inverse functions [34, 35]. If one wants to avoid reformulating the free energy, iterative methods are also available.

In this section, we present four numerical methods that are applied to the virus model presented in the previous section (1.2.3). In the next section (1.4), we implement and compare these four methods.

1.3.1. Nested Loops Optimization

The stationary point of the functional f in equation (1.43) corresponds to the maximum over ϕ and the minimum over ψ . The most straightforward way to find such a point is to search independently for the two extrema: one optimizes iteratively the configuration while solving the electrostatic problem at each calculation of the iterative method. The outside loop of optimization calls upon the inside one until the saddle point is reached (see the algorithm (1) below). We call this method the nested loops optimization as the lack of reformulation of the free energy forces us to use two concatenated loops.

It is interesting to note that this method differs from an iterative scheme where both search loops are on the same level but included in a general loop. Our algorithm, with one search loop inside the other, has a smaller number of loops than the usual iterative method but differentiates heavily between the two fields. The schematic view of these two programs given in figure (1.2) shows these differences.

Algorithm 1 Nested Loops Optimization Program

```
 \begin{array}{l} \mathbf{input} \\ \phi \leftarrow \phi_0 \\ \psi \leftarrow \psi_0 \end{array} \end{array}
```

```
loop over \psi

loop over \phi for \psi_{fixed} \leftarrow \psi

minimize -f(\phi, \psi_{fixed}) over \phi

return \phi_{opt}, f(\phi_{opt}, \psi_{fixed})

\phi \leftarrow \phi_{opt}

end loop
```

 $\phi_{fixed} \leftarrow \phi$ minimize $f(\phi_{fixed}, \psi)$ over ψ return ψ_{opt} , $f(\phi_{opt}, \psi_{opt})$ $\psi \leftarrow \psi_{opt}$ end loop

output ψ_{OPT} , ϕ_{OPT} , $f(\phi_{OPT}, \psi_{OPT})$



Figure 1.2.: Schematic view of two iterative algorithms. On the left-hand side, the nested loops method studied in this thesis optimizes the pseudo freeenergy over one field for each optimization step taken for the other field. On the right hand side, the other iterative method puts both optimization loops on the same level in a third encompassing loop.

The classical iterative method was implemented and tested but no convergence could be reached. One could rectify this problem by taking into account the specifics of the electrostatics and rewriting the optimization loops. Yet, in the present work, we wish to use numerical method that were already optimized for general purposes, rather than writing a specific algorithm for one particular model. We thus focus on the nested loops method.

1.3.2. Using the Derivatives

One common method, presented in the introduction, is based on the derivatives of the free energy with respect to each field. At the saddle point we are searching for, these derivatives are zero.

$$\left(\frac{\partial F}{\partial \phi}\right)_{\phi_{SP},\psi_{SP}} = 0$$
$$\left(\frac{\partial F}{\partial \psi}\right)_{\phi_{SP},\psi_{SP}} = 0$$

We build the new functional:

$$f_{deriv}(\phi,\psi) = \int dr \left[\left(\frac{\partial F}{\partial \psi} \right)^2 + \left(\frac{\partial F}{\partial \phi} \right)^2 \right]$$
(1.45)

which is always positive and vanishes at the stationary point. Thus, the minimum yields the fields at equilibrium.

Algorithm 2 Derivative Method

 $\begin{array}{l} \mathbf{input} \\ \phi \leftarrow \phi_0 \\ \psi \leftarrow \psi_0 \end{array}$

loop minimise $f_{deriv}(\phi, \psi)$ over ψ and ϕ return ψ_{opt} , ϕ_{opt} end loop

output ψ_{OPT} , ϕ_{OPT} , $f(\phi_{OPT}, \psi_{OPT})$

The algorithm based on this functional is composed of a single loop. However, the functional f_{deriv} involves derivatives to the square which gives a problem with greater stiffness. Indeed, using the free energy of the virus given by equation (1.43) leads to the derivative expression:

$$\frac{\partial F}{\partial \phi} = \sigma - p e \psi^2 + \epsilon_0 \epsilon_R \Delta \phi - 2c_0 e \sinh\left(\beta e \phi\right)$$
(1.46)

Thus the term $(\Delta \phi)^2$ appears in f_{deriv} , and this gives a stiffness proportional to q^4 . A slow optimization is expected.

1.3.3. Convexifying the Free Energy

For the next two methods, we build a convexified free energy from equation (1.43). In the first method, an inverse function is used, while in the other, the Legendre transform leads to a convex functional.

An inverse substitution is used in a recent article [34] to reach a new equivalent functional, convex with respect to the electrostatic field ϕ .

The following functional is the starting point of this transformation:

$$f(\psi,\phi,c^{+},c^{-},\mathbf{E}) = k_{B}T\left\{\frac{a^{2}}{6}(\nabla\psi)^{2} + \frac{v}{2}\psi^{4}\right\}$$

+ $\frac{\epsilon_{0}\epsilon_{R}}{2}(\mathbf{E})^{2} + \sum_{i=\pm}k_{B}T\left\{c^{i}\ln\left(\frac{c^{i}}{c_{0}^{i}}\right) - c^{i}\right\}$
- $\phi\left\{\nabla\left(\epsilon_{0}\epsilon_{R}\mathbf{E}\right) - \sigma + pe\psi^{2} - ec^{+} + ec^{-}\right\}$ (1.47)

with **E** the electrostatic field. The variation of $f(\psi, \phi, c^+, c^-, \mathbf{E})$ with respect to **E** gives the equality: $\mathbf{E} = -\nabla \phi$. Replacing the electrostatic field in the expression of the free energy leads back to the original functional (1.43).

To apply the inverse substitution, we need to remember that the derivation of *f* with regards to c^{\pm} gives the ions concentrations in term of the electrostatic potential ϕ . We consider the variation of the free energy regarding ϕ and replace **E** and c^{\pm} in the equality. We obtain a new expression of the electrostatic potential:

$$\phi = \frac{1}{\beta e} \operatorname{asinh}\left(\frac{\epsilon_0 \epsilon_R \nabla^2 \phi + \sigma - p e \psi^2}{2ec_0}\right)$$
(1.48)

We note $\xi(\phi, \psi) = \frac{\epsilon_0 \epsilon_R \nabla^2 \phi + \sigma - pe\psi^2}{2ec_0}$. The electrostatic field, the potential and the concentrations are replaced in the functional (1.47) to reach an equivalent and

convex functional:

$$f_{I}(\phi,\psi) = k_{B}T\left\{\frac{a^{2}}{6}(\nabla\psi)^{2} + \frac{v}{2}\psi^{4}\right\} + \frac{\epsilon_{0}\epsilon_{R}}{2}(\nabla\phi)^{2} + 2c_{0}k_{B}T\left\{-\cosh\left(\beta e\phi\right) + \beta e\phi\,\sinh(\beta e\phi) - \sinh(\xi)\,\sinh(\beta e\phi) + \xi\,\sinh(\xi)\right\}$$
(1.49)
$$- \sinh(\xi)\,\sinh(\beta e\phi) + \xi\,\sinh(\xi)\left\}$$

The global minimum is searched for by means of a single optimization loop. The schematic algorithm is similar to algorithm (2), and we expect the same level of efficiency as for the derivative method of section (1.3.2). Indeed, f_I has the same high stiffness as f_{deriv} from the hyperbolic arcsine: asinh $((\nabla \phi)^2) \sim (\nabla \phi)^4 \rightarrow q^4$

Legendre transform. Like with the inverse substitution, the Legendre transform reformulates the free energy into a convex expression suitable for numerical calculations. The free energy functional was calculated in section (1.2.3) and is given by:

$$f_L(\mathbf{D}, \psi) = k_B T \left\{ \frac{a^2}{6} (\nabla \psi)^2 + \frac{v}{2} \psi^4 \right\} + \frac{\mathbf{D}^2}{2\epsilon_0 \epsilon_R} + 2c_0 k_B T \left\{ \xi \operatorname{asinh} \left(\xi \right) - \sqrt{\xi^2 + 1} \right\}$$
(1.50)

with $\xi(\mathbf{D}, \psi) = \frac{\sigma - pe\psi^2 - \nabla \mathbf{D}}{\frac{2ec_0}{2}}$.

The minimum over both ψ and **D** is found with a single optimization loop. This functional has a lower stiffness than the previous method but uses the vector field **D** which brings a larger number of degrees of freedom.

The aim of the next section is to test these various methods on a single system to achieve clear comparison. The system under consideration is the virus model [24] presented in section (1.2.3).

1.4. Numerical Results

In this section we compare the results of the four methods presented previously. We implement those numerical methods in *Matlab* and we systematically call the function *fminunc* to find the extrema of a functional.

During this study, we keep in mind the main objective of our work: to build a fast and efficient solver for systems with interacting degrees of freedom. We will thus focus first on the validity of the results and then consider the time required to compute the solution.

First we expose the numerical techniques used and some preliminary studies. We then study the validity of the four simulations and their efficiency. We also consider different initializations to further test the stability of the solvers. We end this study with the use of a different minimum-search algorithm which is more efficient but requires the analytical expression of the functional's gradient as an input.

1.4.1. Numerical tools

The *Matlab* **function** *fminunc* **[58]** is used to find to minimum of the different functionals studied.

This function returns the optimized functional, the corresponding fields, as well as feedback on the optimization process. This information allows us to identify the cause of the termination of the search, and to determine if a convergence was reached.

This numerical function *fminunc* implements the minimum search with either the Quasi-Newton method or the Trust-region algorithm. In this study, the first method is systematically called; except in section (1.4.5) where the question of the search algorithm is specifically treated.

The Quasi-Newton algorithm [59] is an iterative method that can deal with two practical problems: solving a system of n-equations with n-unknowns, and the unconstrained minimization of functionals.

Let us call f(x) the functional we wish to minimize. The descent method consists of iteratively searching for the minimum x^* through the update of x_k with $x_{k+1} = x_k + \lambda_k p_k$ such that $f(x_k + 1) < f(x_k)$. p_k is the direction along which we iterate at step k. The method of steepest descent uses the direction p_k such that an iteration along any other direction would give a higher value of the functional:

$$\forall p$$
, $f(x_k + \lambda p_k) < f(x_k + \lambda p)$

This leads to the iteration $x_{k+1} = x_k - \lambda_k \nabla f(x_k)$. However, this method has a slow convergence and Newton's method improve on that point using the inverse of the Hessian:

$$x_{k+1} = x_k - (\nabla^2 f(x_k))^{-1} \nabla f$$
 (1.51)

Descent methods take the general form of $x_{k+1} = x_k - B_k^{-1} \nabla f(x_k)$. Quasi-Newton's methods aim to iteratively generate a series of $\{B_k\}$ such that convergence is reached in a fast manner.

The variation implemented in the *fminunc* function of *Matlab* is the Broyden-Fletche-Goldfarb-Shanno update. It generates iteratively the inverse matrix $B_k^{-1} = H_k$ using the following formula:

$$\bar{H} = \left(I - \frac{sy^T}{\langle y, s \rangle}\right) H \left(I - \frac{ys^T}{\langle y, s \rangle}\right) + \frac{ss^T}{\langle y, s \rangle}$$
(1.52)

with $\overline{H} = H_{k+1}$, $H = H_k$, $s = x_{k+1} - x_k$, $y = f(x_{k+1}) - f(x_k)$ and I the identity matrix. The particularity of such implementation is the hereditary symmetry and positive definiteness that the series of matrix H_k possesses.

The trust region algorithm [60], also called restricted step method, is also implemented in *Matlab*'s function *fminunc*. To use this method, we must give an analytical expression of the functional derivatives as an input. We will compare the Quasi-Newton and the trust-region algorithm in the subsection (1.4.5).

The trust region algorithm first defines a region where the quadratic approximation to the functional is good enough. If the region is too large, it is redefined with a lower diameter until the approximation is acceptable. Then, the next iteration is achieved using the quadratic model and a new point is defined. The trust region is also enlarged if the model is very close to the exact function.

This method allows us to converge despite the lack of good initial guess. Indeed, it avoids over-large steps thanks to the limit imposed by the definition of a trust-region, yet it maintains strong convergence properties.

1.4.2. Preliminary studies

Discretization and Spherical Symmetry. The spherical symmetry reduces the dimensionality of all problems to one, but it must be taken into account when the operators are discretized. As we consider a spherical capsid, we confine our calculations to spherical symmetry. However, the building of equivalent functionals presented earlier uses integrations by parts and the fundamental identity

$$\int \mathbf{D} \cdot \nabla \phi = -\int \phi \operatorname{div} \mathbf{D} + \oint \phi \mathbf{D} \cdot dS$$
(1.53)

In order to compare one identical system solved by different methods, we must ensure that the functionals are equivalent in their discretized forms. Thus the continuum identity (1.53) must be verified in the discretized form.

The potentials ϕ and ψ are defined on the points of the lattice, while $\nabla \phi$, $\nabla \psi$, and **D** are defined on the intermediate links. We use the gradient operator as the fundamental object of discretization and we build the discretized divergence and the Laplacian operators. The left hand side of equation (1.53) gives, in the discretized spherical system:

$$4\pi \sum_{n} r_{n,n+1}^2 \left(\frac{\phi_{n+1} - \phi_n}{\delta}\right) \mathbf{D}_{n,n+1}$$
(1.54)

where δ is the lattice size. Identifying both sides of equation (1.53), a definition of the discretized divergence is obtained:

div _n
$$\mathbf{D} = \frac{\mathbf{D}_{n,n+1} r_{n,n+1}^2 - \mathbf{D}_{n-1,n} r_{n-1,n}^2}{\delta r_n^2}$$
 (1.55)

We can then write the discretized Laplacien operator in spherical symmetry from the identity $\Delta \phi = \text{div} (\nabla \phi)$:

$$(\Delta\phi)_n = \frac{1}{\delta r_n^2} \left[\left(\frac{\phi_{n+1} - \phi_n}{\delta} \right) r_{n,n+1}^2 - \left(\frac{\phi_n - \phi_{n-1}}{\delta} \right) r_{n-1,n}^2 \right]$$
(1.56)

The discretization can thus be applied on any of the functionals previously considered, and the transformations shown in section (1.3) are valid in the discretized form.

As diagnostic tools of the performance of each method, two quantities are considered:

- The free energy F, expressed in $k_B T$ units, is expected to converge when the number of points increases.
- The derivative of the functional with respect to each field should always be zero. Let us note that the derivatives of the functionals are defined at each point of the system. We use the L₁-norm to test the validity of the simu-

lation. We also differentiate between the derivative regarding the electrostatic field $D_{\phi} = \frac{1}{N} \sum_{n=0}^{n=N} \left| \frac{\partial f}{\partial \phi_n} \right|$ or the displacement field $D_{\mathbf{D}} = \frac{1}{N} \sum_{n=0}^{n=N} \left| \frac{\partial f_L}{\partial \mathbf{D}_n} \right|$, and the one with respect to the polyelectrolyte field $D_{\psi} = \frac{1}{M} \sum_{m=0}^{m=M} \left| \frac{\partial f}{\partial \psi_m} \right|$. N is the total number of points used in the model and M is the number of points inside the virus capsid. Indeed, the polyelectrolyte representing the virus genetic material is only present inside the capsid and the field ψ is not defined on the points outside.

These two quantities are plotted as functions of the discretization.

The simple case of an empty virus capsid with *no* polyelectrolyte is first considered. The model reduces to the standard Poisson-Boltzmann model where only the description of the electrostatic through ϕ or **D** remains and all the optimization methods require only one loop. The results for this system are presented in figure (1.3).



Figure 1.3.: (a) Computed free energy of the ionic solution with a fixed charged sphere for different discretizations. (b) Derivatives of the free energy regarding the electrostatic displacement field D for the same system. The four methods studied are: the nested loops method in black squares, the derivative method in green triangles, the inverse substitution method with red X-s, and the Legendre transform method in blue points.

All methods agree for small numbers of lattice points. For dense lattices, the nested loops method and the Legendre method are identical. Furthermore, their derivatives stay zero while the methods based on the inverse substitution and the squared derivatives show difficulties in converging for dense lattices. It is quite surprising to see such differences as we model here a very simple system. We attribute the lack of convergence to the stronger stiffness parameter present in both the derivatives and the inverse substitution methods (coming form the $(\Delta \phi)^2$ and from the $\sinh((\nabla \phi)^2)$ respectively) and absent in the other two methods.

Let us also remark that the free energy converges to its value for 100 points while the two diverging methods can not be relied on when more than 200 points are used (though the difference stay small for the number of points tested). This leaves a small gap of reliable use for these two methods.

The nested loops method is composed, for this simple model, of only one optimization loop since only the electrostatic field is present. The limits of this method and the usefulness of the three other algorithms can only be explored for a system described by two interacting fields.

A pre-study of the nested loops method. By placing the optimum search of one field inside the optimization cycle of another field, the nested loops method differentiates between the two fields (figure (1.2)). To investigate the importance of the positions of the respective fields in the optimization loops (inside loop or outside loop), the two possibilities are computed and compared. Figure (1.4) shows the derivatives of these two cases.



Figure 1.4.: Derivatives of the functional of the virus model for different discretization in both cases of the nested loops method. The black squares represent the case where the optimization over ϕ is performed inside the optimization over ψ ; the magenta diamonds correspond to the opposite situation (ϕ is outside with ψ inside). The left curve shows the derivatives in respect to the electrostatic variable ϕ ; and the figure on the right shows the derivatives over the polymer field ψ . In both cases the inside field is plotted with a continuous line, while the outside field is depicted with dashed lines.

1. The Legendre Transform applied to Electrostatics

We expect that the field solved by the outside loop (dashed lines) is not optimized as well as the field of the inside loops (continuous lines). Indeed the inside loop field is optimized each time the other field is evaluated, thus it is always optimized. Furthermore, the outside optimization loop uses a classical stopping mechanism and does not consider the second field despite its value changing at each iteration. It is possible that the minimization is exited early due to this. Thus the outside loop field is less accurately optimized. This is observed in figure (1.4) as the continuous lines (inside optimization) are at zero while the dashed line (outside optimization) are above.

However, it seems that the optimization of the electrostatics by the inside iteration (black squares) gives better results. In particular, the other method presents convergence difficulties for low numbers of points. There are two possible explanations. First the electrostatic field may be more difficult to estimate and thus its optimization require more care than the polyelectrolyte field. Second, the electrostatic field is defined on a larger number of points than ψ and has thus more values that need to be optimized.

The results presented in the remaining of the article correspond to the case where the electrostatic is fully optimized (inside loop over ϕ) as it produces better results.

1.4.3. Results for the full virus

Using the virus model presented in section (1.2.3), we optimize with the four methods of section (1.3).

The starting point of all optimizations is the value one for the polyelectrolyte field and minus one for the electrostatic field. The system size is 24 nm, where the charge of the capsid is $\sigma = 0.4e$ at R = 12 nm. The bulk concentration of monovalent ions is $c_0 = 10$ mmol.L⁻¹ and the water relative permittivity is $\epsilon_R = 80$. The parameters of the polyelectrolyte are set to a = 0.5 nm, v = 0.05 nm³, and p = 1.

The free energies are depicted in figure (1.5) and figure (1.6) shows the derivatives. Each method is plotted for different lattice density, with their following attributed symbol and color (unless stated otherwise):

- black squares (\Box) for the nested loops method
- green triangles (\triangle) for the derivative method
- red X-s (x) for the results obtained with the inverse substituted functional
- blue dots (•) for the results obtained with the Legendre transformed functional.



Figure 1.5.: Computed free energy of the virus model for different discretizations. The free energy F is expressed in k_BT and the four methods are represented alongside for easier comparison.

The most robust method appears to be the Legendre transform method (blue dots). Indeed, it is the only method that converges when the number of points increases (figure (1.5)) and both derivatives are zero for all tested discretizations (figure (1.6)). On the other hand, the derivative method (green triangles) shows slightly different results even for small number of points and its derivatives are never quite zero. The nested loops method (black squares) present a good estimation of the electrostatics (figure (1.6), left hand side) but as expected, its estimation of the polymer density diverges with an increasingly dense discretizative method (green triangles) and the convexified functional methods (red X-s) were expected to loose accuracy or efficiency with denser discretization.

The computing time of each method is shown in figure (1.7) as a function of discretizations. Since both fields are calculated at each point or link, the number of points used in the simulation gives the number of variables over which we optimized. To be exact, the number of variables is given by: $N_{variable} = \frac{3}{2}N_{point}$. We observe the expected power law relation between the time and the number of variables optimized.

The nested loops method require more computational time than any other method. This can be easily explained by the use of two intertwined loops. Let us also note that, despite the similar solving time presented by the Legendre transform method, the convexified functional and the derivative methods, the


Figure 1.6.: Derivatives of the free energy for the virus model for different discretizations and methods, (a) regarding the electrostatic displacement field, (b) regarding the polymer density field.

last two methods are not as accurate as the first one (as discussed above).

Movement through Phase-Space. To visualize the search process and understand the important time used by the nested loops method, the search path is plotted in the phase-space (figure (1.8)). Each step of the optimization is depicted by a point. The 2D space is defined using principal component analysis (PCA). This mathematical tool gives the direction in a multi-dimension space (in this case the dimension of D, ϕ or ψ) which shows the most variations between the considered elements.

To optimize the free energy, the nested loops method explores each direction alternatively. This is clearly shown in the step-like form of the black curves in figure (1.8). The other functionals however are optimized over both fields at once and the paths taken by these methods in the phase-space are smoother. Thus the exploration of the phase-space clearly explains the larger computational time needed by the nested loops method.

Let us also note that the derivative (green) and inverse substitution (red) methods seem to take a more direct path toward the results. However, they seem to overestimate ψ and show difficulties to converge afterward. Yet such observation is biased by the projection. Indeed, the PCA favors the orientation that shows the most variation but the number of steps undertaken by the search algorithm varies with the method used. Thus the nested loops method presents more points than the other methods and the projection used will show its variations better.



Figure 1.7.: Time used by the search algorithm for different discretization and for the four methods. The grey dotted line represent a fit curve with a power law of 2.

In conclusion, the Legendre transform method appears to be the most reliable of the four tested programs, closely followed by the inverse substitution method.

1.4.4. Initialization

In all the previous tests, the initial situation was 1 for the density field and -1 for the electrostatic field. Other initial conditions are perfectly conceivable and some are tested here. The initial displacement field **D** is systematically calculated from the initial electrostatic field ϕ using : **D** = $-\epsilon \nabla \phi$. We use the same tools as before to study the influence of different initialisations.

Initialization at zero leads to the results presented in figure (1.9). We observe an unexpected step of the free energy between 100 and 200 points, which also corresponds to a sudden lowering of the computing time.

To better understand the meaning of this step, we look at the polyelectrolyte fields resulting from those optimization for L = 100 and for L = 200 points (figure (1.10)).

For 100 points, it appears that the derivative method has not changed from the initial zero situation. However, the initial condition is not physically acceptable as it corresponds to the complete absence of polymer. The two convexifying methods (inverse substitution and Legendre transform) present a polymer



Figure 1.8.: Steps undertaken during the optimization process for (a) 10 points, and (b) 100 points. The x-axis represents the electrostatic variables through the PCA projection on **D**, and the y-axis corresponds to the polymer variables with the PCA projection on ψ . The cyan circles correspond to the starting position, the other circles represents the ending points of each method: in black the nested loops method, in green the derivatives one, in red the inverse substitution method, and in blue the Legendre one.

density which is physically acceptable. In particular, the polymer and the capsid being oppositely charged, we expect an increase of ψ^2 near the capsid (R = 12). This feature is present for both convexifying method.

For 200 points, none of the methods, except the nested loops method, leave the initial position and that explains the step observed.

Let us also remark that the free energy found by the derivatives method with a zero-initialization (figure (1.9), left hand side, green curve) is similar to the free energy of the system without polyelectrolyte (figure (1.3)). This is concordant with the observation of a lack of polymer found by the optimizations (figure (1.10)).



Figure 1.9.: Free energy relative to the number of points and for different methods, on the left. On the right is the corresponding **computation time**.



Figure 1.10.: Polymer density ψ^2 found with the four optimization processes for L = 100 points on the left, and for L = 200 points on the right. The initial zero field is depicted by a black dotted line.

We can conclude that this specific initialization induces an error in the optimization. It is probably due to a local minimum at zero and it shows the complexity of the phase-landscape the algorithms have to explore.

Random uniform distributions are tested as initial conditions. For values taken between 0 and 1 for ψ and 0 and -1 for ϕ , the results are similar to those presented in section (1.4.3). It is not unexpected as the initial position is close to the constants +1 and -1 used previously. We use a larger range of values and initialize ψ between 0 and 10 and ϕ between 0 and -10. The results are presented in figure (1.11).



Figure 1.11.: For a random initialization, the free energy (top left), the computational time (top right), and the polymer density field for L = 100 points (bottom left), and for L = 200 points (bottom right) are plotted for the four methods studied.

The first observation is that the initial position (black dashed line in figure (1.11), bottom) is far from the results of the optimized field. The initial position is even barely visible in figure (1.11) as it is much larger than the results and thus outside of the figure. The second observation is that the Legendre transform method is still valid for this initialization, while the other methods diverge. The last interesting point is that the density field ψ^2 seems to oscillate between the solution and zero for all methods but the Legendre transform one (figure (1.11), bottom right). It suggests that the optimization process is incomplete, even if the search algorithm could not further decrease the function along the search direction. This kind of problem could be solved by rewriting the search algorithm itself, or by adding information for the program to better determine the search direction. This last option is explored in the next paragraph.

1.4.5. The trust-region algorithm

The *fminunc* function of *Matlab* allows the user to give the analytical formula of the functional derivatives. It is used by the minimization tool to perform a better and faster optimization with a trust-region algorithm instead of the quasi-Newton method.

This option is implemented and tested for the Legendre transform method and the inverse substitution method. The nested loops method is not suited for such addition as it is impossible to account for the variation brought by the inner loop in a calculation of the derivative for the outer loop; and the gain from this option for the inside loop would not solve the correctness issue of the result for dense discretizations. The derivative method requires the calculation of a Hessian matrix to give an analytical expression of the derivatives. Indeed, the minimized functional being a gradient, its derivative corresponds to a second derivative of the initial pseudo-free energy. Such calculations would be costing in computer resources and are thus not implemented.



Figure 1.12.: Computed free energy for different discretizations. For the Legendre transform method, the cyan circles depicts results obtained when giving the analytical expression of the gradient (trust-region algorithm), while the blue dots correspond to the results without it (quasi-Newton search). The results from the inverse substitution method are depicted in magenta stars when the trust-region algorithm is used and with red X-s otherwise.

Figure (1.12) presents the free energy for both methods with and without the addition of the derivatives. It clearly shows that such addition is beneficial for the inverse substitution method as the results cease to diverge for dense discretizations (red and magenta curves).

1. The Legendre Transform applied to Electrostatics

The use of the trust-region algorithm also lowers the computational time required by the Legendre-transform method, as shown in figure (1.13). It is not the case for the inverse substitution. Indeed, for a number of points superior to 100 the computational time increases significantly. This is due to the high stiffness of the functional, yet the results obtained present a convergence that is lacking otherwise.

Thus, using the trust-region algorithm renders the optimization more reliable and in most cases more efficient.



Figure 1.13.: Comptational time for different discretisations, with : blue dots : Legendre transform method, quasi-Newton search ; cyan circles : Legendre transform method, trust-region search ; red X-s : inverse substitution method, quasi-Newton search ; magenta stars : inverse substitution method, trust-region search.

1.5. Concluding Remarks

In this chapter, we addressed the numerical optimization of the free energy for systems described by Poisson-Boltzmann theory. The electrostatic contribution to the free energy is concave. Adding configurational degrees of freedom renders the free energy functional simultaneously concave–with respect to the electrostatic potential– and convex–with respect to the other description fields–. To find the equilibrium free energy of the system thus require the implementation of a saddle-point search. This is however a more complex numerical issue than an optimum search. We used the Legendre transform to build an equivalent, overall convex and locally defined functional.

The Legendre transform, applied to a function f(x), builds a new function g(s) which is equivalent to f(x) but expressed in terms of the derivative $s = \frac{df}{dx}$. This mathematical tool is used in many fields of physics to interchange view-points. We applied it to electrostatic studies in order to transform the concave Poisson-Boltzmann free energy functional expressed in term of the electrostatic potential ϕ , into its convex equivalent functional with respect to the electrostatic displacement field **D**. This transformation is particularly useful when we want to numerically model a system described by interacting degrees of freedom.

We used a simple model of a virus to implement and compare the minimization of our new functional with three methods often used to model electrostatic systems. The optimization of the Legendre-transformed functional show a faster convergence and a greater accuracy. The reason is two-fold. First the search path explores all directions at once in the phase-space, rather than an alternating optimization of each description fields. Second, the stiffness of the Legendre-transformed functional is lower than that of the other functionals considered. In conclusion, the numerical application shows that, for a onedimensional system, the Legendre-transformed functional gives the most accurate optimization and the best time performance out of the four tested methods.

Perspectives The Legendre transform can be applied to the free energy of more complex electrostatic systems. Multivalent ions or varying permittivity can be added to our model, and we can consider systems which require a third description field. We could also expand on the study of viruses. For example, the deformation of the virus capsid under external forces is studied [61, 62]. AFM tips are used to deform the shell and bio-molecular simulations, like molecular dynamics applied to a coarse-grained model, are performed to explore the mechanical properties of the capsid. These works aim to shed some

light on the interactions between the proteins constituting the capsid and on the structural changes during the infection process. However, these studies only consider-to our knowledge-the empty capsid and the modelization of the full virus under stress could deepen the understanding brought by these works.

The method presented in this chapter can also be included within other tools. Molecular dynamic simulations [63], for example, are often used in biology to study proteins or DNA. All atoms present in the studied system are considered and the forces applied to each of them are calculated. The movement of the atoms are then deduced from the forces and their positions at the next timestep is computed. Such simulations are costly in memory and computational time. Furthermore, they explore only a small area in the phase-space of the system [29]. In most biological studies, the electrostatic interactions are important and the Poisson-Boltzmann equations need to be solved at each step of the simulation. Using the technique presented in this chapter could lower the time necessary for each calculation and thus allow for a faster simulation.

2. Fluctuation Enhanced Poisson-Boltzmann Theory

2.1. Introduction

2.1.1. The limit of the Poisson-Boltzmann theory

Poisson-Boltzmann theory is a mean-field approximation and its limits appear in many experiments. In particular, systems with multivalent ions are not well-described by the Poisson-Boltzmann theory and significant differences are observed between the theory and experimental results [64, 65]. In particular, this limit of validity for the Poisson-Boltzmann theory interferes with the study of biological systems where multivalent ions like Mg^{2+} influence the conformations of molecules [66].

The results presented in the article [64] show a quantitative failure of the Poisson-Boltzmann theory. Indeed, it does not account for the ion-ion correlations which likely lead to the association of Mg^{2+} with DNA. For this reason, researchers in biology are interested in the development of models going beyond the mean-field approximation. This is one of the motivation behind this work.

2.1.2. Weak coupling, strong coupling and in between.

In order to study systems beyond the Poisson-Boltzmann description, a coupling parameter was introduced. It describes the strength of the interactions between a charged wall and the ionic solution.

The weak coupling limit corresponds to weakly charged systems with low valence ions or high temperature. In such systems, the correlations between ions are small and Poisson-Boltzmann theory describes the electrostatic of these systems rather well. The opposite limit is the strong coupling regime for strongly charged systems with high valency ions or low temperature.

Those domains of validity are described by the coupling parameter: $\Xi = \frac{q^3 |\sigma| e^4 \beta^2}{8 \pi e^2}$, where *q* is the ion charge, *e* the elementary charge, σ the wall charge and ϵ the medium dielectric constant. In [67], Monte Carlos simulations are

compared with the results from the Poisson-Boltzmann theory describing the weak-coupling limit, and the strong coupling theory extracted from a field-theory formulation. It shows that, for coupling parameters lower than 0.1, the Poisson-Boltzmann theory is valid, while the strong-coupling theory gives a good description of the system for $\Xi \geq 10^4$. These two different approaches thus complement each other but there is a domain in between where none of the theory fits.

The presence of high valency ions or highly charged surfaces are frequent and many experimental situations fall into this domain of invalidity. Ionic liquids [68] and colloidal particles in binary solvent [28] are examples of such experiments. To reach into this domain, the strong coupling limit can be expanded toward smaller coupling parameters using either the inverse of the coupling constant to build the virial expansion [69, 70], or the square root of this inverse based on a Wigner crystal description [71]. The Poisson-Boltzmann expression can also be systematically expanded in a field-theory framework with the coupling parameter as the small parameter. This is the loop expansion method which is described further in the next section (2.2.1). Another method uses the standard Gibbs variational procedure to build variational equations describing the system (see section (2.3)).

In this chapter, we first detail the one-loop expansion and presents its limit. Then we describe the variational field theory. In part (2.4), we present the numerical solution and, in particular, how the recent advances in applied mathematics allow us to create a solver. We then study the limits of this solver with respect to the coupling parameter and we aim to understand the origin of such a limit.

In both expansions, field theory is used. Thus we first take a closer look at the Poisson-Boltzmann theory expressed within a field theory framework.

2.1.3. How field theory leads to Poisson-Boltzmann equations.

The Poisson-Boltzmann equations can be derived from the combination of the Poisson description of electrostatics and the Boltzmann description of the ions distribution. The Poisson-Boltzmann theory can also be found from a field theory approach as detailed in the paper of Netz and Orland [72]. In this section we describe the main steps of the field theory calculations but we use a slightly different approach from Netz and Orland: we consider only one field to describe the electrostatics rather than differentiate between anions and cations.

The starting point is the partition function of a symmetric electrolyte composed of N_+ ions charged +q and N_- ions charged -q. We also consider fixed charges $\sigma(\mathbf{r}) = q\tilde{\sigma}(\mathbf{r})$. The interactions of those charges are described by the Coulomb pair potential $v(\mathbf{r}) = \frac{1}{\mathbf{r}}$. The partition function is written:

$$\mathcal{Z} = \frac{1}{N_{+}!} \prod_{j=1}^{N_{+}} \left[\int \frac{d\mathbf{r}_{j}^{+}}{\lambda_{t}^{3}} \Omega(\mathbf{r}_{j}^{+}) \right] \frac{1}{N_{-}!} \prod_{j=1}^{N_{-}} \left[\int \frac{d\mathbf{r}_{j}^{-}}{\lambda_{t}^{3}} \Omega(\mathbf{r}_{j}^{-}) \right]$$

$$\exp \left\{ -\frac{l_{B}q^{2}}{2} \int d\mathbf{r} d\mathbf{r}' \,\hat{\rho}(\mathbf{r}) v(\mathbf{r} - \mathbf{r}') \hat{\rho}(\mathbf{r}') + q^{2} l_{B} v(0) \frac{N_{+} + N_{-}}{2} \right\}$$
(2.1)

In this expression, l_B is the Bjerrum length:

$$l_B = \frac{e^2}{4\pi\epsilon k_B T}$$

The Bjerrum length is the distance at which two particles of unit charge interact with thermal energy. *e* is the elementary charge, k_B the Boltzmann constant and *T* the temperature. The functions $\Omega(\mathbf{r}_j^{\pm})$ restrict the ions position to a certain space and can thus account for the existence of hard walls. The term $\hat{\rho}$ is the density operator of charges and is the sum of all the charges present in the system (scaled by the ion charge *q*):

$$\hat{\rho}(\mathbf{r}) = \sum_{j=1}^{N_{+}} \delta\left(\mathbf{r} - \mathbf{r}_{j}^{+}\right) - \sum_{j=1}^{N_{-}} \delta\left(\mathbf{r} - \mathbf{r}_{j}^{-}\right) + \tilde{\sigma}(\mathbf{r})$$
(2.2)

The last term in the exponential of equation (2.1) is the self energy of the ions.

The field theory allows us to replace the density operator $\hat{\rho}(\mathbf{r})$ by the density field $\rho(\mathbf{r})$ though the introduction of the unit operator. Indeed, using the integral representation of the delta function, we have :

$$1 = \int \mathcal{D}\rho \,\delta\left(\rho - \hat{\rho}\right) = \frac{1}{(2\pi)^V} \int \mathcal{D}\rho \,\mathcal{D}\phi \,\exp\left\{i \int d\mathbf{r} \,\phi\left[\rho - \hat{\rho}\right]\right\}$$
(2.3)

with *V* the dimension of the space explored by ϕ .

We introduce this expression in the equation (2.1) and use the definition of $\hat{\rho}(\mathbf{r})$ given by equation (2.2) to reformulate the partition function as an integral over the electrostatic field ϕ and the density field ρ . We isolate the products of

integrals $\prod_{j=1}^{N_{\pm}} \left[\int d\mathbf{r}_{j}^{\pm} \dots \right]$ and simplify them into $\left[\int d\mathbf{r}_{j}^{\pm} \dots \right]^{N_{\pm}}$. This leads to the partition function:

$$\begin{aligned} \mathcal{Z} &= \frac{1}{(2\pi)^{V}} \int \mathcal{D}\rho \, \mathcal{D}\phi \, \exp\left\{-\frac{l_{B}q^{2}}{2} \int \rho v\rho \, + \, i \int \phi\rho \, - \, i \int \phi \, \tilde{\sigma}\right\} \\ &= \frac{1}{N_{+}!} \left[\exp\left\{\frac{q^{2}l_{B}v(0)}{2}\right\} \int \, \frac{d\mathbf{r}}{\lambda_{t}^{3}} \Omega(\mathbf{r}) \exp\left\{-i\phi(\mathbf{r})\right\}\right]^{N_{+}} \\ &= \frac{1}{N_{-}!} \left[\exp\left\{\frac{q^{2}l_{B}v(0)}{2}\right\} \int \, \frac{d\mathbf{r}}{\lambda_{t}^{3}} \, \Omega(\mathbf{r}) \exp\left\{+i\phi(\mathbf{r})\right\}\right]^{N_{-}} \end{aligned}$$

$$(2.4)$$

Moving to the grand-canonical ensemble leads to a simpler partition function as we can use the definition of the exponential function :

$$\exp\left\{x\right\} = \sum_{N=0}^{\infty} \frac{x^N}{N!}$$

We write the grand-canonical partition function:

$$\mathcal{Z}_{\lambda} = \frac{1}{(2\pi)^{V}} \int \mathcal{D}\rho \,\mathcal{D}\phi \,\exp\left\{-H\left[\rho,\phi\right]\right\}$$

$$H\left[\rho,\phi\right] = \frac{l_{B}q^{2}}{2} \int \rho v\rho \,-\,i\int \phi\rho \,+\,i\int \phi\,\tilde{\sigma} \,-\,2\lambda\,\int\,\Omega\cos\left(\phi\right)$$

$$(2.5)$$

where all integrals of *H* are over *d***r** and the parameter λ is the ions fugacity defined by : $\lambda = \frac{\lambda_0}{\lambda_t^3} \exp\left\{\frac{q^2 l_B v(0)}{2}\right\}$. The cosine term comes from the sum of the two exponentials $e^{-i\phi} + e^{+i\phi}$.

The potential description is reached by integrating over the density field $\rho(\mathbf{r})$. This integral is performed exactly as it takes the form of a Gaussian integral :

$$\int \mathcal{D}\rho \, \exp\left\{-\frac{1}{2}\rho A\rho + J\rho\right\} = \frac{(2\pi)^{n/2}}{\det(A)} \exp\left\{\frac{1}{2}\int JA^{-1}J\right\}$$

with *n* the size of the matrix *A*.

Knowing that $v^{-1} = \frac{-1}{4\pi}\Delta$, the Hamiltonian *H* can be expressed in term of the

electrostatic field ϕ alone:

$$\mathcal{Z}_{\lambda} = (2\pi)^{n/2-V} \int \frac{\mathcal{D}\phi}{\mathcal{Z}_{0}} \exp\left\{-H\left[\phi\right]\right\}$$

$$H\left[\phi\right] = \frac{1}{8\pi l_{B}q^{2}} \int (\nabla\phi)^{2} + i \int \phi \,\tilde{\sigma} - 2\lambda \,\int \,\Omega\cos\left(\phi\right)$$
(2.6)

We noted here \mathcal{Z}_0 the determinant of the Gaussian integral (noted det(A) in the definition above). This value is a measure of the free energy of vacuum fluctuations.

In the mean-field approximation, we consider that the smallest value of *H* is dominant in the expression of the partition function : $Z_{\lambda} = \frac{1}{Z_0} \exp(-H_{min})$. This Hamiltonian is reached for the electrostatic field : $\phi = -i \tilde{\phi}_{PB}$ with $\tilde{\phi}_{PB}$ the scaled Poisson-Boltzmann solution. We need to consider $\phi = -i\beta q\phi_{PB}$ to find the well-known free energy :

$$F = \frac{-\epsilon_0 \epsilon_R}{2} (\nabla \phi_{PB})^2 + \sigma \phi_{PB} - 2 k_B T \lambda \Omega \cosh(\beta q \phi_{PB})$$
(2.7)

2.2. Beyond Poisson-Boltzmann Theory : One Loop Expansion

In a field-theory framework, it is possible to systematically expand around the Poisson-Boltzmann solution to take into account ion correlations. This is the loop expansion method. The leading term is the Gaussian term and corresponds to the one loop expansion. Higher orders are also reachable but subsequently lead to longer calculation and computation.

2.2.1. Theory of the one-loop expansion

Beyond Poisson-Boltzmann: Fluctuations and Correlations Roland R. Netz and Henri Orland Eur. Phys. J. E 1, 203-214, 2000

The theory is detailed by Netz and Orland in [73]. This method's purpose is to take into consideration the charges fluctuations and correlations. In the following paragraph we keep close to the notation used in the article.

We start with the partition function for *N* mobile counter-ions charged *q*:

$$Z_N = \frac{1}{N!} \left[\prod_i \int d\mathbf{r}_i \right] \exp\left\{ -q^2 \sum_{j>k} v(\mathbf{r}_j - \mathbf{r}_k) + q \int d\mathbf{r} \,\sigma(\mathbf{r}) \,\sum_j \,v(\mathbf{r} - \mathbf{r}_j) \right\}$$
(2.8)

The first term in the exponential is the Coulomb interaction between the ions and the second term between the ions and the fixed charge distribution $\sigma(\mathbf{r})$. The position \mathbf{r}_i , \mathbf{r}_j and \mathbf{r}_k are the ions positions.

Knowing $v(\mathbf{r})$ is the Coulomb pair potential, introducing the particle density operator and using the Hubbard-Stratanovich transformation, we can express the partition function in the grand-canonical ensemble:

$$Z[\rho,h] = \int \frac{\mathcal{D}\phi}{Z_0} \exp\left\{-l \mathcal{H}[\phi,h] + i l \int d\mathbf{r} \,\phi(\mathbf{r}) \,\rho(\mathbf{r})\right\}$$
(2.9)

with ρ a new source term introduced to calculate directly the electrostatic potential: $\phi = \langle i\phi \rangle = \frac{\partial \ln Z[\rho,h]}{\partial \rho}$. *l* is an arbitrary constant used as the expansion

parameter. The Hamiltonian is given by:

$$\mathcal{H}[\phi,h] = \int d\mathbf{r} \left[\frac{1}{2\tilde{l}_B} (\nabla \phi)^2 + \frac{i \, \sigma \phi}{q} - \lambda \, e^{-i \, \phi + h} \right]$$

The saddle point is defined by: $\frac{\partial \mathcal{H}}{\partial \phi} - i \rho \Big|_{\phi = -i\phi_{PB}} = 0$ and the solution gives the Poisson-Boltzmann field ϕ_{PB} . To expand this solution, we consider the field $\phi = -i \phi_{PB} + \xi$. The Hamiltonian can then be written using the Taylor series:

$$\mathcal{H}[\phi] - i \int d\mathbf{r} \,\phi \,\rho = \mathcal{H}[-i\phi_{PB}] - \int d\mathbf{r} \,\rho \,(\phi_{PB} + i \,\xi) \\ + \sum_{j} \frac{1}{j!} \int \mathcal{H}^{(j)}(\mathbf{r}_{j};\phi_{PB}) \,\xi(\mathbf{r}_{1}) \,\cdots \,\xi(\mathbf{r}_{j})$$
(2.10)

where $\mathcal{H}^{(j)}$ are the vertex function defined by:

$$\mathcal{H}^{(j)}(\mathbf{r}_{j}, \phi_{PB}) = \left. \frac{\partial^{j} \mathcal{H}[\phi]}{\partial \phi(\mathbf{r}_{1}) \cdots \partial \phi(\mathbf{r}_{j})} \right|_{\phi = -i\phi_{PB}}$$

Keeping only the first two vertex functions, we obtain the partition function with the one-loop expansion:

$$\ln(Z[\rho,h]) = l \int d\mathbf{r} \left\{ \frac{1}{2\tilde{l}_B} |\nabla \phi_{PB}|^2 - \frac{\sigma \, \phi_{PB}}{q} + \lambda \, e^{-\phi_{PB}-h} + \rho(\mathbf{r}) \, \psi_P B(\mathbf{r}) \right\} - \frac{1}{2} \ln \, \det\left(\mathcal{H}^{(2)}\left[\phi_{PB}\right]\right)$$
(2.11)

The first line of this equation is the mean-field contribution, while the last term is the correction term from the one-loop method.

An example of the one loop calculation is presented for the system described in [74, 75]. It is composed of a symmetric electrolyte and the water is modeled by dipoles. The partition function is written with the small parameter *l*:

$$Z = e^{-\beta lF} = \int \mathcal{D}\phi \ e^{-lS(\phi)}$$
(2.12)

The action $S(\phi)$ is given by:

$$S(\phi) = \frac{\beta\epsilon_0}{2} \int d\mathbf{r} (\nabla\phi)^2 - 2\lambda_{ion} \int d\mathbf{r} \cos(\beta e\phi) - \lambda_{dip} \int d\mathbf{r} \int e^{i\beta\vec{p}.\nabla\phi} d\mu(\vec{p})$$
(2.13)

where ϕ is the electrostatic potential and \vec{p} is the vector dipole modeling the water molecules. These dipoles have constant and identical intensities $\|\vec{p}\| = p_0$ but their orientations depend on their environment and we must thus integrate over $\mu(\vec{p})$. Using $\vec{u} = \beta p_0 \vec{\nabla} \phi$, we can write the dipole part in a more usual form:

$$\int d\mathbf{r} \int e^{i\beta\vec{p}.\nabla\phi} d\mu(\vec{p}) = \int \sin\theta \, d\theta \, d\varphi e^{iu\cos\theta} = 4\pi \frac{\sin u}{u}$$

We note g(u) the function $u \mapsto \frac{\sin u}{u}$.

We consider the saddle-point expansion: $\phi = \phi_{PB} + \frac{1}{\sqrt{l}}\xi$. We use the Taylor series and rewrite the action around the Poisson-Boltzmann solution:

$$\begin{split} S(\phi) &= S(\phi_{PB} + \frac{1}{\sqrt{l}}\xi) \\ &= S(\phi_{PB}) + \frac{1}{\sqrt{l}} * \frac{\partial S}{\partial \phi} \Big|_{\phi = \phi_{PB}} \\ &+ \frac{1}{l} \left[\frac{\beta \epsilon_0}{2} * \int d\vec{r} \left(\nabla \xi\right)^2 + \lambda_{ion} \int d\vec{r} (\beta e)^2 \xi^2 \cos(\beta e \phi_{PB}) \right. (2.14) \\ &+ \frac{\lambda_{dip} \beta^2}{2} \int d\vec{r} \int d\mu (\vec{p}) e^{i\beta \vec{p}.\vec{\nabla} \phi_{PB}} (\vec{p}.\vec{\nabla}\xi)^2 \Big] \\ &= S(\phi_{PB}) + \frac{1}{\sqrt{l}} * \frac{\partial S}{\partial \phi} \Big|_{\phi = \phi_{PB}} + \frac{1}{l} P(\phi_{PB},\xi) \end{split}$$

The derivative of the action is zero at the saddle point and the partition function becomes:

$$Z = \int \mathcal{D}\phi \ e^{-lS(\phi)} = \int \mathcal{D}\xi \ e^{-lS(\phi_{PB})} \ e^{-P(\phi_{PB},\xi)} = e^{-lS(\phi_{PB})} \mathcal{Q}(\phi_{PB}) \quad (2.15)$$

 $Q(\phi_{PB})$ is defined by:

$$\mathcal{Q}(\phi_{PB}) = \int \mathcal{D}\xi \exp\left[-\frac{\beta\epsilon_0}{2}\int (\nabla\xi)^2 - \lambda_{ion}\int (\beta e)^2\xi^2 \cos(\beta e\phi_{PB}) -\frac{\lambda_{dip}\beta^2}{2}\int\int d\mu(\vec{p})e^{i\beta\vec{p}.\vec{\nabla}\phi_{PB}}(\vec{p}.\vec{\nabla}\xi)^2\right]$$
(2.16)

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Though the saddle point is on the imaginary axis of the complex space, the expansion is considered parallel to the real axis and ξ is thus real.



Figure 2.1.: Path of the integral over the electrostatic field ϕ in the complex plan.

We can express $P(\phi_{PB}, \xi)$ in the form of a matrix multiplication: $P(\phi_{PB}, \xi) = \xi \Gamma \xi$, where Γ is given by:

$$\mathbf{\Gamma} = -\beta\epsilon_0\Delta + 2\lambda_{ion}(\beta e)^2\cosh(\beta e\phi_{PB}) + 4\pi p_0^2\lambda_{dip}\beta^2\sum_{\alpha\gamma}\left(\partial_\alpha\left(K_{\alpha\gamma}\right)\partial_\gamma + K_{\alpha\gamma}\partial_\alpha\partial_\gamma\right)$$

 α and γ represent the axis of the three-dimensions space (x, y, z) and $K_{\alpha, \gamma} = \left[\delta_{\alpha, \gamma} \frac{g'(u)}{u} + \frac{u_{\gamma} u_{\alpha}}{u^2} \left(g''(u) - \frac{g'(u)}{u}\right)\right].$

Thus the one loop correction term becomes:

$$Q(\phi_{PB}) = \int \mathcal{D}\xi \exp\left[-\frac{1}{2}\vec{\xi}\Gamma\vec{\xi}\right]$$

= $\sqrt{\frac{(2\pi)^n}{\det(\Gamma)}}$ (2.17)
= $(2\pi)^{n/2} \exp\left[-\frac{1}{2}\ln\det(\Gamma)\right]$

However, computing this correction gives large values of $Q(\phi_{PB})$.

2.2.2. Limits of the one loop expansion

For $\Xi = 12$, the one loop expansion gives a negative density of counter-ions. This un-physical solution thus present a clear limit of the one-loop expansion method [73].

In [67], Monte Carlo results are compared with Poisson-Boltzmann results. In particular, the one loop expansion is tested. It appears that the correction to the Poisson-Boltzmann result is correct for small coupling parameters such as $\Xi = 0.1$. But in this domain the Poisson-Boltzmann approximation is sufficient and the correction mainly unnecessary. For higher parameters, the correction at the first order is correct but too small. For $\Xi = 1$, the one loop correction is not sufficient and it would be necessary to go to higher degrees of correction. Thus the loop expansion presents a slow convergence.

In [76], Dean and Horgan study a film soap with the loop expansion method. They show how the one-loop expansion leads to a divergence. Indeed, the dielectric discontinuity in the system generates image charges. Those are not taken into account in the mean-field approximation but they cause the divergence of the one-loop correction term. A UV cut-off is thus necessary to calculate the one loop expansion. The two-loops expansion, however, does not present any divergence and UV cut-off is unnecessary. Beyond the two-loop expansion, the collapse of ions onto each other leads to a new divergence and the cut-off should be re-introduced.

In conclusion, the one-loop expansion is not sufficient to describe an electrostatic system beyond the Poisson-Boltzmann approximation and a higher order expansion is necessary. However, other methods are available to go beyond the mean field approximation and the next sections explore the variational field theory approach on this issue.

2.3. Variational Field Theory Approach

Variational charge renormalization in charged systems R.R. Netz and H. Orland Eur. Phys. J. E 11, 301-311, 2003

The variational field theory approach is detailed in the paper from Netz and Orland [72]. In this section, we use the partition function from equation (2.6):

$$\begin{aligned} \mathcal{Z}_{\lambda} &= \int \frac{\mathcal{D}\phi}{\mathcal{Z}_{0}} \exp\left\{-H\left[\phi\right]\right\} \\ H\left[\phi\right] &= \frac{1}{8\pi l_{B}q^{2}} \int (\nabla\phi)^{2} + i \int \phi \,\sigma/q \,- \,2\lambda \,\int \,\Omega\cos\left(\phi\right) \end{aligned}$$

and we apply the standard variational Gibbs procedure. The field theoretic formulation includes the ion density fluctuations through the fluctuating electrostatic potential.

First we rescale the Hamiltonian using the coupling parameter Ξ :

$$\begin{aligned} \mathcal{Z}_{\lambda} &= \int \frac{\mathbf{D}\phi}{\mathcal{Z}_{0}} \exp\left\{-\tilde{H}\left[\phi\right]/\Xi\right\} \\ \tilde{H}\left[\phi\right] &= \Xi H\left[\phi\right] \\ &= \int \frac{d\tilde{\mathbf{r}}}{2\pi} \left\{\frac{1}{4} \left(\nabla\phi(\tilde{\mathbf{r}})\right)^{2} + i \phi(\tilde{\mathbf{r}}) \,\tilde{\sigma}(\tilde{\mathbf{r}}) - \Lambda \frac{\Omega(\tilde{\mathbf{r}})\cos\left(\phi(\tilde{\mathbf{r}})\right)}{2}\right\} \end{aligned}$$
(2.18)

The distances are rescaled with the Gouy-Chapman length $\mu = (2\pi q l_B \sigma_s)^{-1}$ and the rescaled surface charged is given by $\tilde{\sigma}(\tilde{\mathbf{r}}) = \frac{\mu \sigma(\mathbf{r})}{\sigma_s}$. The rescaled fugacity and the coupling parameter are then the only two remaining parameters:

$$\Lambda = 8\pi\lambda\Xi\mu^3$$
$$\Xi = 2\pi q^3 l_B^2 \sigma_s$$

The standard Gibbs variational procedure uses a variational Hamiltonian H_0 to define the Gibbs free energy:

$$\mathcal{F}_{\text{Gibbs}} = \mathcal{F}_0 - \langle H_0 - H \rangle_0 / \Xi$$

This functional is then minimized with respect to the variational parameters of H_0 . This is equivalent to the first-order perturbational variation on the observ-

able [72].

We choose a Gaussian form for the variational Hamiltonian. This is the one hypothesis we make within the variational field theory approach.

$$H_0[\phi] = \frac{1}{2} \int_{\mathbf{r},\mathbf{r}'} [\phi(\mathbf{r}) + i\phi_0(\mathbf{r})] v_0^{-1}(\mathbf{r},\mathbf{r}') [\phi(\mathbf{r}') + i\phi_0(\mathbf{r}')]$$

The mean potential ϕ_0 and Gaussian kernel v_0 are the variational parameters over which we wish to minimize the Gibbs free energy.

Using the expression of the Hamiltonians and the definition of the mean value: $\langle [H_0 - H] \rangle_0 = \int \mathcal{D}\phi [H_0 - H] e^{-H_0}$, we calculate the Gibbs free energy :

$$\mathcal{F}_{\text{Gibbs}} = -\frac{1}{2} \operatorname{Tr} \log v_0 - \frac{1}{2\Xi} - \frac{1}{8\pi\Xi} \int_{\mathbf{r}} (\nabla \phi_0)^2 + \frac{1}{8\pi\Xi} \int_{\mathbf{r},\mathbf{r}'} \nabla_{\mathbf{r}} \nabla_{\mathbf{r}'} v_0(\mathbf{r},\mathbf{r}') \delta(\mathbf{r}-\mathbf{r}')$$
(2.19)
$$+ \frac{1}{2\pi\Xi} \int_{\mathbf{r}} \phi_0 \sigma - \frac{\Lambda}{4\pi\Xi} \int_{\mathbf{r}} \Omega e^{-v_0(\mathbf{r},\mathbf{r})/2} \cosh(\phi_0)$$

The variational equations are obtained when we consider that the derivatives of $\mathcal{F}_{\text{Gibbs}}$ over each variational parameters ϕ_0 and v_0 are zero:

$$\frac{\partial \mathcal{F}_{\text{Gibbs}}}{\partial \phi_0} = \frac{1}{8\pi\Xi} 2\pi \nabla^2 \phi_0 + \frac{1}{2\pi\Xi} \sigma - \frac{\Lambda}{4\pi\Xi} \Omega e^{-v_0(\mathbf{r},\mathbf{r})/2} \sinh(\phi_0) = 0$$

$$\frac{\partial \mathcal{F}_{\text{Gibbs}}}{\partial v_0} = -\frac{1}{2} v_0^{-1} \delta(\mathbf{r} - \mathbf{r}') + \frac{1}{8\pi\Xi} \nabla^2 + \frac{\Lambda}{8\pi\Xi} \Omega e^{-v_0(\mathbf{r},\mathbf{r})/2} \cosh(\phi_0) = 0$$

We re-organize the equalities to reach the two variational equations:

$$\nabla^2 \phi_0 = -2\,\sigma + \Lambda \,\Omega \,\mathrm{e}^{-v_0(\mathbf{r},\mathbf{r})/2} \,\sinh\left(\phi_0\right) \tag{2.20}$$

$$4 \pi \Xi \delta(\mathbf{r} - \mathbf{r}') = \left[-\nabla^2 + \Lambda \Omega e^{-v_0(\mathbf{r}, \mathbf{r})/2} \cosh(\phi_0) \right] v_0 \qquad (2.21)$$

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Equation (2.20) is similar to the Poisson Boltzmann equation but with a correction for the fluctuations added through the Gaussian kernel v_0 . Solving these self-consistent equations leads to the description of the system with fluctuations accounted for.

In the following part, we present the numerical resolution of the variational equations.

2.4. Numerical Solution

Solving Fluctuation-Enhanced Poisson-Boltzmann Equations Zhenli Xu and A.-C. Maggs J. Comput. Phys. 275, 310-322, 2014

The self-consistent equations (2.20, 2.21) are challenging to solve since they are non-linear partial differential equations. This section presents an iterative scheme to numerically find the variational parameters ϕ_0 and v_0 . We also show how systems with high symmetry can be simplified in two- or one-dimension systems.

To reach the same equation than those used in the article [77], we only need to define the Green function

$$G(\mathbf{r},\mathbf{r}')=\Xi v_0(\mathbf{r},\mathbf{r}')$$

and the correlation function $c(\mathbf{r}) = \lim_{\mathbf{r}\to\mathbf{r}'} [G(\mathbf{r},\mathbf{r}') - G_0(\mathbf{r},\mathbf{r}')]$ with $G_0(\mathbf{r},\mathbf{r}') = 1/|\mathbf{r}-\mathbf{r}'|$. For the sake of clarity, we keep the previous notations in the following studies.

2.4.1. The numerical scheme

Discretizing the variational equations is a necessary step before implementing the numerical solver. The electrostatic field $\phi_0(\mathbf{r})$ becomes a vector $[\phi_0(r_i)]_i$ and the Gaussian kernel representing the self-energy of a mobile ion becomes a matrix $[v_0(r_i, r_j)]_{i,i}$.

The operations over both of these variational parameters also take the form of matrices, and the distribution of fixed charge σ becomes a vector. The charges in the continuous space are distributed over the nearest lattice sites using a linear weighting function [78]:

$$\sigma_i = \sum_{\mathbf{r}} \left(1 - \frac{|x_i - x|}{h} \right) \left(1 - \frac{|y_i - y|}{h} \right) \left(1 - \frac{|z_i - z|}{h} \right) \sigma(\mathbf{r})$$
(2.22)

with (x_i, y_i, z_i) the coordinate of the lattice point *i* and *h* the lattice size taken identical in every direction. $\mathbf{r}(x, y, z)$ is a general position taken around the point *i*. The second order derivative of the field $\nabla^2 \phi_0$ becomes, with the discretization, a simple multiplication of the derivation matrix with the vector ϕ_0 . The matrix is defined thanks to a seven-point finite difference discretization [78] and is symmetric. In one dimension, the matrix is given by the three-point finite difference:

$$\left[\nabla^{2}\right] = \frac{1}{h^{2}} \begin{bmatrix} -2 & 1 & & \\ 1 & \ddots & \ddots & \\ & \ddots & \ddots & 1 \\ & & 1 & -2 \end{bmatrix}$$
(2.23)

A self-consistent iterative scheme is used for the resolution of the equations. Each equation is solved in turn: equation (2.20) allows us to determine a new field ϕ_0^{n+1} in terms of ϕ_0^n and $v_0^n(\mathbf{r}, \mathbf{r})$, with *n* representing the step of the iteration. In a similar fashion, equation (2.21) leads to v_0^{n+1} from knowing ϕ_0^{n+1} and $v_0^n(\mathbf{r}, \mathbf{r})$. The first step of the iteration thus solves the modified Poisson-Boltzmann equation while the second steps consist of a matrix inversion to determined the Green function. The method converges when the results of two successive iterations are nearly identical. This is tested through a comparison with a small parameter ϵ which sets the precision of the solver.

The modified Poisson-Boltzmann equation is solved with an iterative method [79] using the relaxation function:

$$R(\mathbf{r}) = \Lambda \Omega e^{-v_0(\mathbf{r},\mathbf{r})/2} \sinh(\phi_0) / (|\phi_0(\mathbf{r})| + \epsilon)$$
(2.24)

with ϵ the small parameter used in the global numerical scheme to define the convergence. This relaxation function is introduced in equation (2.20) as follows:

$$\left[\nabla^2 - R\right]\phi_0^{k+1} = -2 \sigma + \Lambda \Omega e^{-v_0^n(\mathbf{r},\mathbf{r})/2} \sinh\left(\phi_0^k\right) - R \phi_0^k \qquad (2.25)$$

This new equation leads back to equation (2.20) when the numerical method converges ($\phi^{k+1} = \phi^k$) and this addition allows us to use existing direct solver to find the new electrostatic field ϕ_0^n . The matrix division in *Matlab* is used for this particular implementation, since the addition of the relaxation function guarantees the absence of division by zero.

The inversion of a matrix is the second step in the iteration. Indeed the equation (2.21) can be rewritten in matrix form as :

$$\mathbf{A} \mathbf{V} = \mathbf{I} \tag{2.26}$$

with **I** the identity matrix, **V** the matrix $[v_0(r_i, r_j)]_{i,i'}$ and **A** defined by :

$$\mathbf{A} = \left[-\nabla^2 + \Lambda \Omega \, \mathrm{e}^{-v_0(\mathbf{r},\mathbf{r})/2} \, \cosh\left(\phi_0\right) \right] / 4 \, \pi \, \Xi \tag{2.27}$$

Finding **V** is thus a matter of inverting the matrix **A**. However the inversion of full matrices is costly in computer resources.

Inverting matrices is a well-researched numerical problem as it appears in a number of calculations and simulations. The usual method uses the Cholesky factorization of a matrix A into triangular matrices : $A = LL^T$. However, if A is a sparse matrix, the classical process fills the matrix and the sparsity is lost. This leads to steps in the factorization that requires more arithmetic operations and storage. To avoid such loss of sparsity, one can reorder the matrix into PAP^T such that the sparsity is fully exploited. This is equivalent to numbering nodes in a certain order to minimize the complexity of the inversion.

Different methods exist and their complexity and numerical storage for a 2D system are given in table (2.1). The standard band scheme factorization of a N-by-N matrix with the nested dissection [80, 81, 82] is based on a rearrangement of the nodes. The one-way dissection ordering [81, 83] is a compromise between the standard factorization and the nested dissection.

	std factorization	nested d	issection	one-way method
complexity	$\mathcal{O}(N^2)$	$\mathcal{O}(N^{3/2})$	$\mathcal{O}(N^{\frac{3}{d}(d-1)})$	$\mathcal{O}(N^{7/4})$
storage	$\mathcal{O}(N^{3/2})$	$\mathcal{O}(N \log N)$	$\mathcal{O}(N^{\frac{2}{d}(d-1)})$	$\mathcal{O}(N^{5/4})$

Table 2.1.: Complexity and numerical storage used for the factorization of a N-by-N matrix representing a 2D system, by three methods. The first one is the standard band-scheme factorization. The other two methods use the sparsity of the matrix to lower the algorithm complexity. In gray the expression for any dimension d.

Moreover, we need only the diagonal of the inverse green function to solve the variational equations. This is a particular case of a selected inversion where only parts of the inverse matrix are computed. It is exploited to lower the complexity of the algorithm [84, 85] and we use here the algorithm developed by Lin Lin et. al. and described in [85].

Increasing the efficiency of the inversion step allows us to model larger systems.

2.4.2. The Fourier transform

We can apply the Fourier transform to the correlation function. If the system presents a symmetry, the Fourier transform along the axis of symmetry can be calculated exactly and the correlation function is thus expressed in term of two dimensions and one frequency. There is two consequences to that transformation. First, we need to integrate over the frequencies. Second, the functions we consider are two-dimensional correlation functions. In the discretized form, the inversion of a large matrix becomes a sum of smaller inverted matrices.

This results into a large gain of computer resources. Indeed, if we study a three-dimensional system of size n, then the matrix describing the system is of dimension $N = n^3$. Let us consider a numerical operation of complexity $O(N^x)$. Then, for the 3-D system, we have a computing complexity of $O(n^{3x})$. If the system has a symmetry, we can use the Fourier transform to work with matrices of dimension $N = n^2$. We can choose to use n frequencies for example. Then the overall complexity of the numerical scheme becomes $O(n n^{2x})$ as we need to apply the operation to each of the n matrices. This is a gain in computer resources if x is larger than one (2x + 1 < 3x), which is the case for matrix inversion.

If we consider a system with two axis of symmetry, the sum must be performed over two sets of frequencies but the matrices inverted are of dimension N = n. The complexity thus become $O(n^2 n^x)$.

2.5. Limit Coupling Parameter

This numerical method was developed to account for the charge fluctuations in the description of electrostatic systems. We aim to model systems beyond the weak-coupling limit using this approach. The coupling parameter Ξ represents the overall strength of the ionic interactions and we test the program for increasing coupling constants to explore the solver's capacity.

The program is composed of one large loop to iteratively determine the variational parameters ϕ_0 and v_0 . The convergence (or the lack of convergence) of this search-loop is the first test of validity we use. The results of the program, in the form of negative ions density maps and the values of the free energy, are also considered. A limit of the coupling parameter appears from those observations. We conclude with the analytical study of this limit for a bulk situation.

2.5.1. Observations

The system used for this test is composed of a permeable cylinder charged positively on one side and negatively on the other side. Its total charge is zero. The electrolyte considered is symmetric, and the system is represented in two dimensions.

The surface charge is $\sigma = 1$, the ratio of dielectric constant between the cylinder and the medium is taken at $\epsilon_{ratio} = 0.1$, the radius of the cylinder is of 3 and the length of the box onto which the simulation is run is 32. All these dimensions are scaled as shown in section (2.3). The rescaled fugacity $\Lambda = 8\pi\lambda\mu^3\Xi$ is set at 0.2.

The first test is to check that a convergence is reached for increasing Ξ . Using a maximum of 50 loops, it appears that the method converges for $\Xi \leq 4$. Increasing the maximum number of loops to 200 does not lead to convergence for $\Xi \geq 5$. This lack of convergence is also observed for much larger coupling parameters such as $\Xi = 50$ or $\Xi = 100$ and we extrapolate that this result holds for every $\Xi \geq 5$. It is important to point out that this lack of convergence is not a divergence as the program simply reaches the maximum number of loops. At this point, it is impossible to tell if this is only a very slow convergence or a divergence.

We look at the results from the program in order to better understand this observation. In figure (2.2) we draw the negative ions density for different coupling parameters. We observe an important difference between the ions density

for $\Xi \leq 4$ and those for $\Xi \geq 5$. This difference appears plainly in figure (2.3) where the resulting free energy is plotted in regards to Ξ . Indeed, for $\Xi \geq 5$ the free energies are much larger than those for $\Xi \leq 4$.



Figure 2.2.: Negative ions density around a cylinder charged negatively on the one half and positively on the other half, for different coupling parameters: $\Xi = 0.1$, $\Xi = 4$, $\Xi = 5$ and $\Xi = 10$. Let us note that the color scale is largely different between the top curves ($\Xi \le 4$) and the bottom curves ($\Xi \ge 5$).



Figure 2.3.: Free energy for different coupling parameters Ξ , using a maximum of 50 loops in blue stars and 200 loops in green circles. The figure on the left hand side presents the result in a semi-log scale. The negative results are not shown (small Ξ) but the step between $\Xi = 4$ and $\Xi = 5$ appears clearly. The right hand side figure shows the free energy values for coupling parameters smaller than 4 (linear scale).

This step in the free energy can be due to :

- either the physics of the system. It could be, for example, a Manning condensation [86]. However, this system is composed of a cylinder with half it surface positively charged and the other half bearing negative charges. Furthermore, the coupling parameter limit also exists for one-dimension systems. We can thus conclude that the above observations do not come from a Manning condensation.
- or to the program not reaching a good result, which is in agreement with the lack of convergence for those coupling parameters.

We introduce a new initialization to clarify this last point. So far, every searching loop started with zero values. We expect that starting with a different situation will change the search path taken by the algorithm, and may enlighten us on the problem exposed above. In an approach similar to an adiabatic method, we use the solution found for low Ξ as the initialization for higher Ξ . We expect a faster convergence with this initialization.

We study the program's convergence for coupling parameters taken between 4 and 5. The results are shown in table (2.2). We observe first that, for a range of coupling parameters between 4.3 and 4.6, 50 loops does not lead to convergence but it is achieved for 200 loops. It also appears that, even if the convergence is

	$max \ loops = 50$		max loops = 200	
Ξ	Init = 0	Init = $\mathcal{R}(\Xi = 4)$	Init = 0	Init = $\mathcal{R}(\Xi = 4)$
4.0	converge		converge	
4.1	converge	converge	converge	converge
4.2	converge	converge	converge	converge
4.3	No convergence	converge	converge	converge
4.4	No convergence	No convergence	converge	converge
4.5	No convergence	No convergence	converge	converge
4.6	No convergence	No convergence	converge	converge
4.7	No convergence	No convergence	No convergence	No convergence
4.8	No convergence	diverge	No convergence	diverge
4.9	No convergence	diverge	No convergence	diverge
5.0	No convergence	diverge	No convergence	diverge

not reached, the free energy is of the same order of magnitude than that of lower Ξ (figure (2.4)).

Table 2.2.: Study of the convergence for coupling parameters between 4 and 5 using 50 loops (right hand side) and 200 loops (left hand side) and two types of initializations: one uses a zero starting point ("Init=0", left hand columns) while the other uses the result from $\Xi = 4$ ("Init= $\mathcal{R}(\Xi = 4)$ ", right hand columns).

The color code is: in green the program converges and the free energy has a "low" value; in magenta when there is no convergence but the free energy has a "low" value; in red the solver does not converge and the free energy is very large; and in blue the cases where there is a divergence since *Not-a-Number* values are found during the numerical resolution of the equations.

Second, using the results obtained for a lower coupling parameter ($\Xi = 4$) lead either to a fast convergence for small coupling parameters ($\Xi \leq 4.6$), or to the apparition of extreme values: part of the kernel increases up to infinite values which then give *Not-a-Number* values in the next iteration of the program (table (2.2), blue results). We conclude that, for a coupling parameter larger than 4.7, the program diverges.



Figure 2.4.: Free energy for different coupling parameters Ξ between 4 and 5, using a maximum of 50 loops in blue and 200 loops in green.

We study if this Ξ limit is linked to the system considered. We reiterate the previous study to find the limit coupling parameters for different situations.

Increasing the number of points used for the discretization leads to a slight increase of the limit coupling parameter (table (2.3)). However, the fixed charges are distributed on the closest points. Thus the repartition of the charges changes slightly with the discretization and it can be the origin of this small variation.

number of points	limit coupling parameter
32	4.7
36	4.7
128	4.8
256	4.9

Table 2.3.: Limit coupling parameter for different discretization

Changing the parameters defining the system leads to significant variations of the limit coupling parameter. Indeed, increasing the radius *R* of the cylinder, its surface charge σ , or the rescaled ions fugacity Λ leads to a decrease of the limit coupling parameter Ξ_{lim} as shown in figure (2.5) and table (2.4).



Figure 2.5.: Limit coupling parameter for different surface charge σ on the left hand side. On the right hand side, the limit coupling parameter for different ion fugacity Λ .

radius of the cylinder	limit coupling parameter
1	13.2
3	4.7
5	3.9
7	3.8
10	3.6

 Table 2.4.: Limit coupling parameter for different radius R

Thus it appears that the physical parameters of the studied system influence greatly the limit at which we can model the system.

There are two possible origins for the Ξ limit :

On the one hand, it could be a numerical limit linked to the iterative scheme used to solve the equations. On the other hand, the limit can steam from the theoretical model used. The next paragraph explores this possibility with the very simple model of a bulk situation.

2.5.2. Analytical study: the bulk system

We consider a bulk situation to study the Ξ limit. This theoretical analysis was performed following an interesting conversation with Sahin Buyukdagli.

In the bulk situation, the electrostatic field ϕ is zero and the green function follows:

$$-\nabla^2 G + \Lambda e^{-\Xi c(\mathbf{r})/2} G = 4 \pi \delta$$
(2.28)

The correlation function $c(\mathbf{r})$ is given by :

$$c = \lim_{\mathbf{r}\to\mathbf{r}'} \left(G(\mathbf{r},\mathbf{r}') - \frac{1}{|\mathbf{r}-\mathbf{r}'|} \right)$$
(2.29)

Defining $\kappa^2 = \Lambda e^{-\Xi c(\mathbf{r})/2}$ and replacing it in equation (2.28), we can solve the green function:

$$G(\mathbf{r},\mathbf{r}') = \frac{e^{-\kappa |\mathbf{r}-\mathbf{r}'|}}{|\mathbf{r}-\mathbf{r}'|}$$
(2.30)

From that expression, we write the correlation function :

$$c = \lim_{\mathbf{r} \to \mathbf{r}'} \left[\frac{e^{-\kappa |\mathbf{r} - \mathbf{r}'|} - 1}{|\mathbf{r} - \mathbf{r}'|} \right]$$

=
$$\lim_{R \to 0} \left[\frac{e^{-\kappa R} - e^{-\kappa 0}}{R - 0} \right]$$

=
$$\frac{d e^{-\kappa R}}{dR} \Big|_{R=0}$$

=
$$-\kappa$$
 (2.31)

And replacing *c* in the equation defining κ , we obtain :

$$\kappa^2 = \Lambda \, e^{\Xi \, \kappa \, /2} \tag{2.32}$$

We consider the rescaled form of the above equation :

$$\tilde{\kappa}^2 = e^{a\,\tilde{\kappa}} \tag{2.33}$$

with $\tilde{\kappa} = \frac{\kappa}{\sqrt{\Lambda}}$ and $a = \frac{\Xi}{2}\sqrt{\Lambda}$. In this form, the limit is only dependent of one parameter *a*. For simplicity of notation, we note κ the value $\tilde{\kappa}$ in the following study.

We can solve this equation visually by plotting the two curves : $\kappa \to \kappa^2$ and $\kappa \to e^{a \kappa}$ and finding their intersection for different coupling parameters (figure (2.6)).

Figure (2.6) clearly shows that for large a equation (2.33) has no real solution (the dashed aquamarine curve does not intersect the blue line). We can find



Figure 2.6.: Visual resolution of the equation $\kappa^2 = e^{a\kappa}$. The curve $\kappa \to \kappa^2$ is plotted in blue. The dotted lines represent $\kappa \to e^{a\kappa}$ for different values of *a* :

- the green curve corresponds to a = 0.1 and it intersects the blue curve at $\kappa \sim 1$
- the aquamarine curve corresponds to a = 1 and does not intersect the blue curve. Thus the equation (2.33) has no solution for a = 1.
- the red curve corresponds to $a = a_{lim} = \frac{2}{e}$ which is the limit at which a solution exists.

the limit parameter with considering that, for a_{lim} , the two curves intersect and share the same tangent (red and blue curve of figure (2.6)). Thus we want to solve the equations:

$$\begin{cases} \exp(a\kappa) = \kappa^2 \\ a \, \exp(a\kappa) = 2 \,\kappa \end{cases}$$
(2.34)

This leads to the solution : $a_{lim} = \frac{2}{e}$ and $\kappa = \frac{2}{a}$. Thus there is no solution for $a > \frac{2}{e}$. This is an effective limit for the coupling parameter when we consider the bulk.

However, only real solutions can be found with this visual analysis and we explore the problem in the complex plan in the next paragraph.

Solving this equation in the complex plan leads to two sets of solutions expressed with the Lambert W-function. The Lambert W-function is defined by:

$$z = W(z) e^{W(z)} (2.35)$$

We can rewrite equation (2.33) so the above definition clearly appears:

$$\kappa^{2} = e^{a \kappa} \Leftrightarrow 1 = \kappa^{2} e^{-a \kappa}$$

$$\Leftrightarrow 1 = \pm \kappa e^{-a \kappa/2}$$

$$\Leftrightarrow \mp \frac{a}{2} = \left(-\frac{a}{2}\kappa\right) e^{\left(-\frac{a}{2}\kappa\right)}$$

$$\Leftrightarrow \left(-\frac{a}{2}\kappa\right) = W(\mp \frac{a}{2})$$
(2.36)

Thus there are two sets of solutions :

$$\kappa^{+} = - \frac{W(C, a/2)}{a/2}$$

$$\kappa^{-} = + \frac{W(C, -a/2)}{-a/2}$$
(2.37)

with *C* an integer corresponding to the branch of the W-function. Indeed, the Lambert W-function is defined in the complex plan and the periodicity of the complex exponential explains the presence of branches [87].

We define $z^{\pm} = \pm \frac{a}{2}$ which is a real number, and the solutions become : $\kappa^{\pm} = \mp \frac{W(C, z^{\pm})}{z^{\pm}} = \mp e^{-W(C, z^{\pm})}$. We plot the different branches of the solution in figure (2.7).

We first observe that the zero-branch of the minus solution $\kappa^-(C = 0, z^-)$ is the real solution previously studied. Since the W(z) function exists in the real plan only for $z \ge -\frac{1}{e}$ [87], we find the same limit $a \le \frac{2}{e}$. The other solutions have an imaginary part.

Second, we observe that each branch has a real part positive for small *a* and negative for larger *a*. This limit increases as *C* increases. Indeed, if we separate the Lambert W-function in its real and imaginary parts : $W(C, z) = W_r(C, z) + iW_i(C, z)$, then we can calculate the point where the real part of the solution changes sign : $Re(\kappa) = \frac{W_r}{z} = 0$, since *z* is real. We separate the real and imaginary part of the equality $\frac{W(C,z)}{z} = e^{-W(C,z)}$.

$$\frac{W_r}{z} = e^{-W_r} \cos(W_i)$$

$$\frac{W_i}{z} = -e^{-W_r} \sin(W_i)$$
(2.38)

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Figure 2.7.: Complex solution $\kappa(a)$ of the equation $\kappa = e^{a\kappa}$. The set of plus-solution is depicted in the top curves and the minus-solutions are plotted in the bottom curves. The real parts of κ are on the left hand side, with the imaginary parts on the right hand side. The 0-branches are in blue, the 1-branches in purple and so on.

Thus $Re(\kappa^{\pm}) = 0$ gives $W_r = 0 = e^{-W_r} \cos(W_i)$. We deduce an expression of the imaginary part of the Lambert W-function $W_i(C, z) = \frac{\pi}{2} + C\pi$. We then replace W_r and W_i in the second line of equation (2.38):

$$\frac{W_i}{z} = \frac{1}{z} \left(\frac{\pi}{2} + C\pi \right) = -e^{-0} \sin\left(\frac{\pi}{2} + C\pi \right) = \pm 1$$

We extract from this equation an expression of the position *z* at which the real part of κ is zero:

$$z = \pm \frac{\pi}{2} + C\pi \tag{2.39}$$

Considering the plus solution κ^+ for example, z must be positive and $z_{lim} = +\frac{a_{lim}}{2} = \frac{\pi}{2} + C\pi$. The positive integer C corresponds to the branch of the W-function and we conclude that each branch of higher C has a larger z_{lim} . Thus it should be possible to find a complex solution for any value of the parameter a.
2. Fluctuation Enhanced Poisson-Boltzmann Theory

Can we find the complex solutions ?

We use the *Solve* function of *Mathematica* to find a solution κ for different parameter *a*. The solutions are presented on figure (2.8) for two different initializations: in red stars the solutions for the initial value $\kappa = 2$ and in black circles the solutions for a complex initial value $\kappa = 5 - i5$.

The real initialization leads to real results on the 0-branch of the minus solution and complex κ -s are soon found. Using the complex initialization forces the solver to explore other branches of the Lambert W-function, and the solutions obtained are complex.



Figure 2.8.: Complex solution $\kappa(a)$ of the equation $\kappa = e^{a\kappa}$. The plus-solutions are plotted with continuous lines, the minus-solutions with dashed lines. The real part of κ are on the left hand side, with the imaginary part on the right hand side. The solutions found by *Mathematica* for an real initial condition $\kappa = 2$ are plotted with red starts, the solutions found with a complex initial situation $\kappa = 5 - i5$ are in black circles. The 0-branches are in blue, the 1-branches in purple and so on.

However, the program we use can not solve complex equations. Indeed, the numerical scheme used to inverse the matrix does not manage complex numbers.

Furthermore, equation (2.33) is not linear. We can not combine two complex solutions to build a real and physical one. Indeed, if we consider κ_1 and κ_2 solutions of $\kappa^2 = e^{a\kappa}$, then we have

$$(\kappa_1 + \kappa_2)^2 = e^{a\kappa_1} + e^{a\kappa_2} + 2e^{a\sqrt{\kappa_1\kappa_2}}$$

and

$$(\kappa_1 \ \kappa_2)^2 = e^{a\kappa_1} \ e^{a\kappa_2} = e^{a(\kappa_1 + \kappa_2)}$$

We can conclude that no real solution exists for $a > \frac{2}{e}$ and we thus found a

theoretical limit for the coupling parameter in the bulk situation: $\Xi_{lim} = \frac{4}{e\sqrt{\Lambda}}$.

The dependence of $\Xi \propto \frac{1}{\sqrt{\Lambda}}$. To ascertain if the limit found for the bulk system is valid for the cylinder system, we plot the values of the limit coupling parameter Ξ_{lim} for different ion fugacities Λ .

We consider two situations plotted on figure (2.9).

- For a cylinder of radius R = 3, of surface charge σ = 1 and with the dielectric constant ratio ε_{ratio} = 0.1, we find: Ξ_{lim} = 1.2/√Λ + 2. If we neglect the offset +2, this fit leads to a_{lim} = 0.6. This value is quite close to the one given by the theory for the bulk: a^{bulk}_{lim} = 2/e = 0.74.
 For a cylinder or radius R = 1, of surface charge σ = 1 and of dielectric
- For a cylinder or radius R = 1, of surface charge $\sigma = 1$ and of dielectric constant ratio $\epsilon_{ratio} = 1$, we find: $\Xi_{lim} = \frac{3.6}{\sqrt{\Lambda}} + 1$. The offset is lower than for the precedent situation, but the value of the parameter $a_{lim} = 1.8$ is further from the bulk limit.



Figure 2.9.: Limit coupling parameters for different fugacities (blue stars) and their fits (dotted red line). On the left hand side, the measures for a cylinder defined by: R = 3, $\sigma = 1$ and $\epsilon_{ratio} = 0.1$. The fit is given by: $\Xi_{lim} = \frac{1.2}{\sqrt{\Lambda}} + 2$. On the right hand side, the results for a cylinder defined by: R = 1, $\sigma = 1$ and $\epsilon_{ratio} = 1$. The fit is given by: $\Xi_{lim} = \frac{3.6}{\sqrt{\Lambda}} + 1$. In both cases the limit coupling parameter is measure with a precision of ± 0.1 .

Thus we find the correct form for the limit coupling parameter with respect to the fugacity, but we can not relate the constants to the bulk model.

2.5.3. Concluding remarks

The solver allows us to model electrostatic systems for higher coupling parameters than Poisson-Boltzmann theory. However, a limit still exists. From the analytical study of the bulk situation and observations of the dependence of this limit, we conclude that the limit coupling parameter varies with the system modeled and comes from the theory used.

2.6. Perspective: Two fields

In this section, we show how our solver can be adapted to more complex situations. We first model ion core repulsion with the addition of a Yukawa field. Then we present a system of colloidal particles suspended in binary solvent. One needs two fields to model these systems and to take into account their fluctuations in order to understand the experimental results.

2.6.1. Yukawa potential

The steric repulsion between ions is not taken into account by the Poisson-Boltzmann description. This leads for example to an un-physical density of counter-ions close to a highly charged surface.

Different approaches exist. One can add a Stern layer [88] which is a narrow space where ions are excluded; it is also possible to consider a lattice formulation where the space, divided into ion-sized cells, is filled with either ions or solvent molecules [89, 90]. In this method, the entropic contribution of the free space is considered.

The method we explore here uses a second field to describe the ion-ion steric repulsion: the Yukawa field [91].

The calculation with the Yukawa field follows the same steps than presented in the section (2.3) with the added term in $\hat{\rho}_S w \hat{\rho}_S$ where $w(\mathbf{r} - \mathbf{r}')$ is the Yukawa interaction potential and $\hat{\rho}_S$ is the ion density operator [91]. $\hat{\rho}$ and v are the charge density operator and Coulomb pair potential. The partition function is given by the following equation where we write in green the part due to the added Yukawa interactions:

$$\mathcal{Z} = \frac{1}{N_{+}!} \prod_{j=1}^{N_{+}} \left[\int \frac{d\mathbf{r}_{j}^{+}}{\lambda_{t}^{3}} \Omega(\mathbf{r}_{j}^{+}) \right] \frac{1}{N_{-}!} \prod_{j=1}^{N_{-}} \left[\int \frac{d\mathbf{r}_{j}^{-}}{\lambda_{t}^{3}} \Omega(\mathbf{r}_{j}^{-}) \right]$$
$$\exp \left\{ -\frac{l_{B}q^{2}}{2} \int d\mathbf{r} d\mathbf{r}' \, \hat{\rho}(\mathbf{r}) v(\mathbf{r} - \mathbf{r}') \hat{\rho}(\mathbf{r}') + q^{2} l_{B} v(0) \frac{N_{+} + N_{-}}{2} - \frac{C l_{B}}{2} \int d\mathbf{r} d\mathbf{r}' \, \hat{\rho}_{S}(\mathbf{r}) w(\mathbf{r} - \mathbf{r}') \hat{\rho}_{S}(\mathbf{r}') \right\}$$
(2.40)

The constant *C* represents the strength of the Yukawa interaction and is dimensionless.

The density operators are defined by:

$$\hat{\rho}(\mathbf{r}) = \sum_{j=1}^{N_{+}} \delta\left(\mathbf{r} - \mathbf{r}_{j}^{+}\right) - \sum_{j=1}^{N_{-}} \delta\left(\mathbf{r} - \mathbf{r}_{j}^{-}\right) + \sigma(\mathbf{r})/q$$

$$\hat{\rho}_{S}(\mathbf{r}) = \sum_{j=1}^{N_{+}} \delta\left(\mathbf{r} - \mathbf{r}_{j}^{+}\right) + \sum_{j=1}^{N_{-}} \delta\left(\mathbf{r} - \mathbf{r}_{j}^{-}\right)$$
(2.41)

The pair potentials and their respective inverse are given by:

$$v(\mathbf{r}) = \frac{1}{\mathbf{r}} \qquad v^{-1} = \frac{-1}{4\pi}\Delta$$

$$w(\mathbf{r}) = \frac{e^{-\kappa \mathbf{r}}}{\mathbf{r}} \qquad w^{-1} = \frac{-1}{4\pi} \left(\Delta - \kappa^2\right) \qquad (2.42)$$

The parameter κ is the inverse screening length of the Yukawa potential. A strong (*C* large), short range (κ large) interaction must be chosen to model the core repulsions between ions.

The calculation steps are identical to those previously presented in section (2.3) and are also detailed in [92]. In this article, charged Yukawa liquids are modeled near neutral planar interfaces with dielectric discontinuity. In this work, instead of searching for the variational electrostatic potential v_0 and the variational Yukawa potential w_0 , their form are chosen with two unknown variational parameters. These two parameters and the two variational potentials ϕ_0 and ψ_0 are found through an iterative scheme. This article [92] shows that the variational theory gives a better agreement with simulation results than the mean field approximation.

2.6.2. Colloidal particles suspended in binary solvent

In [28], Bonn et al. present the study of a complex electrostatic system. It is composed of two solvents, ions and colloids. The different states of the system are reached though varying temperatures. Furthermore, the addition of ions leads to a variation of the critical temperature at which the aggregation of the colloids occurs. The system is described by two fields: the electrostatic field for the ions and charged colloids on the one hand, and the relative fraction of one of the solvent to describe the mixture on the other hand (refer to subsection (1.2.1) for a more detailed description).

For this system, the coupling parameter is of the order of $\Xi \sim 4$, and the Poisson-Boltzmann description is not sufficient. Indeed, it seems that the fluc-

tuations of the ionic interactions and of the solvent mixture are at the core of the observed phenomenon. To study this system, we need to write the variational equations and take into account the fluctuations of the electrostatics and of the fluid mixture.

2.7. Concluding Remarks

In this chapter we worked on the addition of electrostatic fluctuations to the Poisson-Boltzmann model. Our aim is to better describe systems with coupling constants small but larger than 1. Indeed the Poisson-Boltzmann model is valid only for small $\Xi < 1$, while the strong-coupling theory covers only the large coupling parameter ($\Xi > 10^{+4}$).

We first studied the one loop expansion which is not a sufficient correction [67].

We then used the variational field theory approach to define self consistent equations. To solve those, an iterative numerical scheme was devised and implemented. We tested this tool on a simple 2-dimensions system composed of a permeable charged cylinder. A limit appears for high coupling parameters ($\Xi > 4.7$) and varies when the system is changed (charge of the cylinder, relative dielectric constant,...).

From our analytical study of the bulk situation, it seems that this limit originates from the theory we use.

The next step in this study would be to compare the results from our solver with other modelization tools like molecular dynamic. This would allow us to judge of the pertinence of the correction we calculate with the variational approach.

Part II.

Rolling Platelets on a Surface

3. Rolling Platelets on a Surface

Platelets are small anucleate cells. A component of blood, their main function is hemostasis: to stop the loss of blood at wounded sites. The process of hemostasis following an injury can be decomposed into three main steps: vaso-constriction where the damaged blood vessel constricts to reduce the blood flow in the vessel and thus limits the blood loss; primary hemostasis [93] during which platelets and vessel walls interact via von Willebrand factors (vWF) and form a protein binding matrix (figure (3.1)); and the coagulation cascade where the platelets agglomerate and form a thrombotic plug.



Figure 3.1.: vWF-dependent platelet adhesion at high shear [94]. The shear induced changes in the binding interaction between vWF and GPIb*α* show how platelet adhesion is enhanced under the influence of shear force and how thrombus formation can be initiated at the vessel wall in flowing blood.

Platelets are fragments of megakaryocytes and are produced *in vivo* through the migration of the megakaryocytes from the bone marrows to the blood vessels [95, 96]. This process produce 10¹¹ platelets per day in a healthy human adult.

A challenge largely studied is to produce platelets *in vitro*. Indeed, platelets are used in a large variety of medical interventions such as leukemia treatment, during chemotherapy or for heavy surgery. So far platelets come from donation with more than 130 thousands of platelets donations in 2012 in France [97]. However, the extraction procedure involves separation of the platelets from the blood which is then re-injected to the donor. This process is tiring and time-consuming. Furthermore, platelets collected by this method have a low life span of five days [97]. Platelets are in constant demand from medical facilities and in vitro production would be a solution to this issue.

Transport of cells in blood is mainly realized through advection in the bulk pumped by the heart. White blood cells and platelets, however, target sites near the vessels walls. Between bulk advection and eventual adhesion, complex rolling behavior is one of the main pathway for these cells to reach their targeted sites. Such behavior is exhibited by several types of blood cells *in vivo*, such as leukocytes [98] or platelets. It has also been observed in cancer cells, and shown to be a preliminary step to tumor cell transport in and out of the blood flow [99]. This passage of circulating cancer cells across the endothelium is called diapedesis and is a precursor to metastasis.

In order to faithfully mimic their transport in micro-vessels, we need to take into account the specific interactions of rolling cells with walls.

Von Willebrand Factor. Platelets interact with vessel walls through the creation and break of bounds with von Willebrand factor (vWF). This large multimeric protein is expressed by endothelial cells close to sites of vessel injury [100]. vWF is a polymer with large repeating units. At low shear rate, it is coiled, while at high shear rates the vWF molecule unfolds as presented in figure (3.2) [101]. This unfolded state exposes the A1 domain of the von Willebrand factor where the binding sites for the platelet protein GPIb are located [102]. This binding is specific, reversible, and shear dependent.

Von Willebrand factor has actually two ways to interact with platelets. It is capable of establishing transient bonds with GPIb, but it is also mediating firm adhesion through interaction with activated integrin $\alpha IIb\beta 3$ [98, 103].

Many microchips are designed to handle blood samples for analysis or fundamental purpose [104]. One of the main objective in devising lab-on-chip is the gain of precise control and the reduction of the sampled volume needed for analysis. A gain of time and cost is also expected from such development. Microchips were devised for platelet injections in order to test the efficiency of anti-thombotic treatments [105]. The microfluidic device described in this article recreates an *open* system where the responsiveness of platelets to a set of inhibitors is tested. The parallel channels allow one to test different concentrations of inhibitors and generate a dose-response curve.

We study here the flow of fixed platelets in a microfluidic chamber coated with vWF. The local surface concentration C_s of platelets adhering to the wall is measured and found to be a decreasing function of the distance x between the channel entrance and the observation position. This phenomenon, called



Figure 3.2.: The conformation of von Willebrand factor under different shear stresses [101].

Schematic model using actual AFM images of vWF illustrating shearinduced conformational changes in vWF under aqueous conditions. The three images of vWF are on the same scale so they are directly comparable. Under negligible shear (left side), vWF has a globular conformation on the hydrophobic surface, comparable in maximal dimension with the native solution conformation. Shear forces (center) (7.4 to 19 nN) applied by the AFM probe tip, cause protein unfolding, and the vWF has a short extended chain conformation in which individual globular domains are visualized. After exposure to a shear stress field of 35 ± 3.5 dyn.cm⁻², vWF is observed in extended conformation (right side), with molecular length ranging from 146 to 774 nm.

axial dependency, has been observed in experiments involving whole blood in a flow chamber [106]. Several theoretical [107] and numerical [108] studies focus on platelet diffusivity in the transverse direction. Indeed, the presence of large flexible red blood cells induces a near-wall excess of platelets. However, no predictions-to the best of our knowledge-have been made regarding the axial dependency of platelet concentration, whether in volume or at the surface.

In this chapter, we present the experiment devised and realized by the team led by Mathilde Reyssat at MMN, ESPCI. They gathered experimental data on the rolling behavior of fixed platelets in a microfluidic channel. We develop here two models that describe the transport of rolling cells in a channel. The rolling mechanism, as well as the binding and escape of biological materials on grafted surface were studied at the ligand-receptor level quite extensively [109, 98, 103]. Our models focus on a population of cells rather than the individual interactions. The first model considers only the rolling mechanism and attributes a speed to each particle injected at the surface of the channel. The second model considers two populations of platelets: those bound to the surface through their interaction with the vWF, and those in the fluid. Exchanges between both populations, and platelet axial displacement through rolling and advection are considered. Among the fitting parameters of this model is the attachment rate K_{on} of a platelet on a vWF-coated wall. There is no known experimental method to measure such an attachment rate at the cell level.

3.1. Experiment

The experiments were carried out in the MMN laboratory (Microfluidics, MEMs, Nanostructures) at the ESPCI by the team of Mathilde Reyssat: Anne Le Goff, Antoine Blin and Hyacinthe Buisson who also contributed to the development of the models. The platelets were obtained by the INSERM team led by Dominique Baruch, and in particular with the help of Aurélie Magniez who prepared the platelets.

3.1.1. The microfluidic set-up

PDMS microchannels were fabricated using standard soft lithography techniques [110]. Straight channels were used with rectangular cross-section, of fixed width $W = 400 \ \mu m$ and length $L = 4 \ cm$ and variable height $H \in$ [14,62] μm . After plasma treatment, channels are sealed on a glass slide and filled with a solution containing von Willebrand factor (20 $\mu g.mL^{-1}$ in PBS) and incubated overnight at 4°C. This creates a coating of vWF which acts as a binding mesh and rolling medium for the platelets.

Platelets are injected into the channel with a concentration $C_v^{(in)}$ of 140 10³ mm⁻³. Connection between the flask containing the cells and the channel is achieved with PEEK tubing (polyether ether ketone, internal diameter 228 μ m), avoiding cell adhesion in the tubing. The homogeneity of the suspension in the entrance reservoir is maintained by gentle agitation. A commercial computer-driven pressure control system (Fluigent MFCS-4C) is used and a compatible flowmeter (Flowell) is employed to establish a calibration curve $Q = f(\Delta P)$. The flow rate is chosen for each of the parallel channels so the desired shear rate is achieved. In the following experiments, the wall shear rate is fixed to $\dot{\gamma} = 1800 \text{ s}^{-1}$. Let us recall that the shear rate $\dot{\gamma}$ is directly related to the shear stress by $\sigma = \eta \dot{\gamma}$ where η is the fluid viscosity. In this experiment, the shear stress is thus $\sigma = 1.8 \text{ Pa} = 18 \text{ dyn/cm}^2$.

3.1.2. The platelets

Platelets are isolated from fresh blood samples from healthy donors by several steps of centrifugation, and immediately fixed. Fixation is an operation by which chemicals such as formaldehyde block biochemical reactions and preserve tissues. Fixed platelets exhibit the same surface proteins as fresh platelets, thus they interact with von Willebrand factor though they can not be activated.



Figure 3.3.: Schematic representation of the experimental set up. The solution of platelets (in green) is injected into a simple straight microchannel coated with von Willebrand factor proteins (in red). The shear rate is imposed through the pressure control. Videos and instant pictures are taken through an inverted microscope.

3.1.3. Videomicroscopy

Observations are made with a Leica inverted microscope, using 40x magnification dry lens in phase contrast mode. Images are obtained with a highspeed camera (Photron Fastcam SA3). Recording parameters are the following: to measure the rolling velocity of adherent cells, acquisition frequency is 0.5 fps with a 20 ms shutter; for freely flowing cells, acquisition frequency is 2000 fps with a 0.1 ms shutter. During the kinetics measurements, only snapshots are acquired. The motorized stage allows us to navigate between several prerecorded positions in the channel and to sample its whole length in less than 2 minutes.

The focus of the microscope being on the surface, only the platelets bounded to von Willebrand factors appear clearly in the picture (figure (3.4)). Platelets in the flow move faster than the acquisition frequency can capture and can not be seen on the pictures. Images were analyzed with ImageJ software, using a routine to automatically count the number of adherent cells in a microscope field. Both the axial dependence and the kinetics of the surface concentration of platelets are extracted from these analysis.



Figure 3.4.: Instant picture of the surface of the channel at different positions. Platelets on the surface, bound with vWF are observed while platelets advected in the volume do not appear.

3.2. Observations

From video recordings, we observe dynamical events such as adhesion of platelets to the grafted surface, desorption or axial movement. The advection of volume platelets appears only as white streak on films, while the rolling on the surface can be studied in more details.

From the pictures taken at different times and positions, we count the platelets and draw curves of surface concentration.

3.2.1. Rolling velocity

We measure the rolling speeds of absorbed platelets and the distributions are plotted in figure (3.5).



Figure 3.5.: Distribution of rolling velocity *V*_{*R*} of fixed platelets on a vWF-coated wall surface at different wall shear rates.

Rolling velocity depends on the shear rate, as observed experimentally [111]. An analytical study of the peeling mechanism involved in the rolling has been proposed in [109]. We check in figure (3.6) that our measurements of the rolling velocity of fixed platelets, plotted against wall shear stress σ , are compatible with those of reference [112]. In this article, it was also shown that fixed and washed platelets exhibit the same rolling velocity in the range of shear rate that we explore.

3.2.2. Adsorption kinetics and axial dependency

The number of platelets adsorbed at the channel wall is plotted as a function of time. Typical adsorption kinetics curves are displayed in the left hand side curve of figure (3.7).



Figure 3.6.: Rolling velocity V_R of fixed platelets on a vWF-coated wall surface, as a function of wall shear stress σ . We superimpose our results (•) and those extracted from [112] (\blacksquare).

At the channel entrance, surface concentration increases very fast and saturates after about 2 hours. When the position increases, the number of platelets bound decreases strongly. This can be observed on the right-hand curves of figure (3.7) where the axial dependence of the surface concentration is plotted at different times.



Figure 3.7.: Surface concentration of platelets (in mm⁻²). On the left hand side, the kinetic adsorption of platelets on the vWF-coated surface, for different positions in the micro-channel. On the right hand side, the axial dependency of the surface concentration at different times.

3. Rolling Platelets on a Surface

We observe a large concentration at the injection point. There are two possible phenomena which could explain this large values. On the one hand, an exchange of platelets between the volume and the surface can be present everywhere in the channel, and the adsorption at the initial position could deplete the volume. On the other hand, the injection point is a position with a downward, turbulent flow which may push the platelets toward the wall thus favoring a strong binding. Of course both hypothesis can be considered at once. We base the first model on the latter hypothesis, while the second model relies on the former one.

To understand the experimental measurements, we model ensemble of cells and do not detail the attachment, detachment and rolling mechanisms at the individual cell level.

We use two sets of experimental data to confront the models with the experiments: Exp. 1 was realized in October 2012 and Exp. 2 in February 2014. The platelets used come from different batches but the set-ups are otherwise identical. Yet they yielded different results with, for example, a larger surface concentration with the second experiments (see table (3.1)).

3.3. Model of Rolling Platelets

We base this model on the observation that platelets at the channel's entrance are numerous. We make the following hypothesis:

- platelets are injected on the surface at the entrance point x = 0 only,
- the injection is achieved at a constant rate D expressed in s^{-1} (1D model),
- there is no detachment phenomenon,
- platelets roll on the surface with a constant speed,
- the rolling velocity follows a Gaussian distribution.

In this model, a platelet is characterized by its speed and time of injection. The whole system is described by the speed distribution with the mean value \bar{v} and the standard deviation σ and by the injection rate *D*. We can write the probability density for a particle to have a speed *v*:

$$P(v) = \frac{1}{\sqrt{2\pi\sigma}} e^{-(v-\bar{v})^2/2\sigma^2}$$
(3.1)

We consider a minimum and maximum speed and we choose zero as the lower bound and the new parameter v_M as the higher limit.

$$P(v) = \begin{cases} \frac{1}{P_0} e^{-(v-\bar{v})^2/2\sigma^2} & \text{for } 0 \le v \le v_M \\ 0 & \text{otherwise} \end{cases}$$
(3.2)

with P_0 the integral of the exponential between 0 and v_M . Figure (3.8) shows the velocity distribution.



Figure 3.8.: The rolling velocity distribution is a cut Gaussian (continuous blue line). The dashed line is the full Gaussian distribution. The parameters used are: $\bar{v} = 2$, $\sigma = 5$ and $v_M = 13$.

3. Rolling Platelets on a Surface

We introduce the following quantities: C(x, t) is the density of platelets at position x and time t; dn(x, t) is the number of cells between the positions x and x + dx at time t; dm = m(x, t, v) dv is the number of cells with velocity v between the positions x and x + dx at time t; dN = N(t, v) dv is the total number of particles in the channel with a speed taken between v and v + dv at time t. From these definitions, we can write the equalities:

$$C(x,t) = \frac{dn(x,t)}{dx}$$

$$dn(x,t) = \int_{v=0}^{v=v_M} m(x,t,v) dv$$

$$dN(t,v) = D t P(v) dv$$
(3.3)

As particles do not change speed, we can link m(x, t, v) and N(t, v). Indeed, the distribution of cells rolling at a given speed is homogenous along the channel for $x \le vt$ and null otherwise. Thus we have:

$$m(x,t,v) = \begin{cases} \frac{dx}{v t} N(t,v) & \text{for } x \le vt\\ 0 & \text{for } x > vt \end{cases}$$
(3.4)

We can write the expression of the platelets density:

$$C(x,t) = \frac{dn(x,t)}{dx} = \frac{1}{dx} \int_{v=0}^{v=v_M} m(x,t,v) dv$$

=
$$\begin{cases} D \int_{x/t}^{v_M} \frac{P(v)}{v} dv & \text{if } x/t \le v_M \\ 0 & \text{if } x/t > v_M \end{cases}$$
(3.5)

We now fit this model to the experimental measurements with the least-square, non-linear, curve fitting routine *lsqcurvefit* from *Matlab* and find the parameters \bar{v} , σ , v_M and D. Using the distributions of velocity presented in figure (3.5), we use $\bar{v} = 10 \ \mu \text{m.s}^{-1}$, $\sigma = 5 \ \mu \text{m.s}^{-1}$ and $v_M = 40 \ \mu \text{m.s}^{-1}$ as starting point of the curve-fitting search. Table (3.1) presents two fitted results. For Exp. 1 (left hand curves), the measurements at the first position are not well fitted but the curves match well for larger *x*. However, for Exp. 2 (right hand curves) the shape of the experimental curves is not completely captured by the model. Yet its distribution of velocity seems closer to the one presented in figure (3.5) than the one from Exp. 1 where only very small speed are considered. Let us note that the maximum velocity is very large. We can conclude from this observation that

the higher limit is not a relevant parameter in this case.

We conclude that this model lacks some important features of the system, yet it is no completely irrelevant. In the next section, we develop a model focused on the exchange of platelets between the volume and the surface.



Table 3.1.: Fitting experimental data with the rolling model. On the left hand side the figures for Exp. 1 and on the right hand side for Exp. 2. In each curves the points are the experimental data and the lines the fit curves. The top curves are the concentration with respect to time for different positions, the second lines correspond to the surface concentration with respect to position for different times, the bottom figures are the rolling velocity distributions used in the model. The parameters found are the following: Exp. 1: $\bar{v} = 0.5\mu \text{m.s}^{-1}$, $\sigma = 0.5\mu \text{m.s}^{-1}$, $v_M = 50 \text{mm.s}^{-1}$ and $D = 3.4\text{s}^{-1}$; Exp. 2: $\bar{v} = 2 \ 10^{-3} \mu \text{m.s}^{-1}$, $\sigma = 4\mu \text{m.s}^{-1}$, $v_M = 0.1 \text{mm.s}^{-1}$ and $D = 31\text{s}^{-1}$.

3.4. Model with Exchange of Platelets

This model, developed with the help of Olivier Dauchot, is based on the observed exchange of cells between the volume and the surface. The injection of platelets is solely in the volume.

3.4.1. The model

We observe in the videos four phenomena that we take into account in our model: the movement of the platelets in the volume, the binding of the platelets on the surface, their rolling and their detachment.

The system is divided into two parts: the volume where the platelets are advected with the speed of the fluid noted v_v , and the surface on which the platelets are bound by the vWF molecules and roll at the speed v_s . This rolling velocity is the mean rolling speed since we consider only one velocity identical for all platelets. A more complex model would consider a distribution of rolling velocities. However, this allows us to compare the previous model with this one and to determine if one phenomena is predominant in the axial and temporal dependence: exchange phenomena or rolling speed distribution.

The two environments exchange platelets: the binding of platelets to the surface is described by a coefficient K_{on} and is proportional to the presence of objects in the volume. It is also limited by the quantity of platelets already bound to the surface. Indeed, either by the number of binding sites, or by the surface occupied by the platelets, the surface concentration is limited. As the vWF covers the surface densely, the second limit is considered. We choose a linear expression to model this close packing limit.

The platelets can also detach from the surface and there is a flow of particles from the surface to the volume that is directly proportional to the number of bound particles and described by the parameter K_{off} . We note n_v (resp. n_s) and C_v (resp. C_s) the volume (resp. surface) number of platelets and its associated concentration.

A schematic description of these phenomenons is given in figure (3.9).



Figure 3.9.: Flow and exchanges of platelets in the system.

From this description we calculate the number of platelets in the volume and on the surface at the next time step :

$$\begin{cases} n_v(x,t+dt) = n_v(x,t) + n_{v,in} - n_{v,out} \\ = n_v(x,t) + \{C_v(x,t) v_v dt dy h + k_{off} dt n_s\} \\ - \{C_v(x+dx,t) v_v dt dy h + K_{on} dt n_v (1-n_s/n_{s,max})\} \\ n_s(x,t+dt) = n_s(x,t) + n_{s,in} - n_{s,out} \\ = n_s(x,t) + \{C_s(x,t) v_s dt dy + K_{on} dt n_v (1-n_s/n_{s,max})\} \\ - \{C_s(x+dx,t) v_s dt dy h + k_{off} dt n_s\} \end{cases}$$
(3.6)

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We note $K_{off} = k_{off}/h$, the exchange parameter similar to the one used in publications studying vWF [111, 113]. We use this notation but we must be careful to not rush any later comparisons with values found by other teams. Indeed, some studies consider one-link tether bonds between the vWF and the cell, rather than the uncontrolled number of links we expect in this system.

We replace in equation (3.6) the number of platelets by the concentrations.

$$\begin{cases} (C_{v}(x,t+dt) - C_{v}(x,t)) \, dx \, dy \, h \\ &= -(C_{v}(x+dx,t) - C_{v}(x,t)) \, v_{v} \, dt \, dy \, h \\ &+ K_{off} \, h \, dt \, C_{s} \, dx \, dy - K_{on} \, dt \, C_{v} \, dx \, dy \, h \, (1 - C_{s}/C_{s,max}) \\ (C_{s}(x,t+dt) - C_{s}(x,t)) \, dx \, dy \\ &= -(C_{s}(x+dx,t) - C_{s}(x,t)) \, v_{s} \, dt \, dy \\ &+ K_{on} \, dt \, C_{v} \, dx \, dy \, h \, (1 - C_{s}/C_{s,max}) - K_{off} \, h \, dt \, C_{s} \, dx \, dy \\ \end{cases}$$
(3.7)

We introduce the partial derivatives of the concentration with respect to time and space, and we reach the set of equations:

$$\begin{cases} \frac{\partial C_v}{\partial t} + v_v \frac{\partial C_v}{\partial x} = -\mathcal{J} \\ \frac{\partial C_s}{\partial t} + v_s \frac{\partial C_s}{\partial x} = h\mathcal{J} \\ \mathcal{J} = K_{on} C_v \left(1 - \frac{C_s}{C_{s,max}}\right) - K_{off} C_s \end{cases}$$
(3.8)

 C_v and C_s are respectively the volume and surface concentration, v_v and v_s the speed of the particles in each phase, K_{on} and K_{off} the exchange parameters between the volume and the surface, $C_{s,max}$ the maximal concentration on the surface at the packing limit and *h* the height in which the exchange takes place.

We render these coupled equations dimensionless. First we consider a modified surface concentration:

$$C_s \longrightarrow \tilde{C}_s = \frac{C_s}{h}$$
 (3.9)

This corresponds to the study of a volume-volume exchange instead of the volume-surface model. We now consider two equivalent environments, one with a slow velocity (former surface), the other with a fast speed (previously

the volume).

$$\begin{cases}
\frac{\partial C_v}{\partial t} + v_v \frac{\partial C_v}{\partial x} = -\mathcal{J} \\
\frac{\partial \tilde{\mathcal{C}}_s}{\partial t} + v_s \frac{\partial \tilde{\mathcal{C}}_s}{\partial x} = \mathcal{J} \\
\mathcal{J} = K_{on} C_v \left(1 - \frac{\tilde{\mathcal{C}}_s}{\tilde{\mathcal{C}}_{s,max}}\right) - K_{off} h \tilde{\mathcal{C}}_s
\end{cases}$$
(3.10)

Second, we choose $\tilde{C}_{s,max}$ as a reference concentration and consider the transformations:

$$\tilde{C}_{s} \longrightarrow \bar{C}_{s} = \frac{C_{s}}{C_{s,max}}$$

$$C_{v} \longrightarrow \bar{C}_{v} = \frac{C_{v}}{C_{s,max}}$$

$$\mathcal{J} \longrightarrow \bar{\mathcal{J}} = \frac{\mathcal{J}}{C_{s,max}}$$
(3.11)

This leads to :

$$\begin{cases}
\frac{\partial \bar{C}_v}{\partial t} + v_v \frac{\partial \bar{C}_v}{\partial x} = -\bar{\mathcal{J}} \\
\frac{\partial \bar{C}_s}{\partial t} + v_s \frac{\partial \bar{C}_s}{\partial x} = \bar{\mathcal{J}} \\
\bar{\mathcal{J}} = K_{on} \bar{C}_v (1 - \bar{C}_s) - K_{off} h \bar{C}_s
\end{cases}$$
(3.12)

We remark that while \bar{C}_s is comprised between 0 and 1, \bar{C}_v has not such higher limit. Indeed it is possible to inject a concentration of particles higher than $C_{s,max}$, that would correspond to putting more platelets in the system than what the surface can absorb. The optimal system would present a complete transfer of the platelets from the volume to the surface with the input at x = 0 $(\bar{C}_v = 1, \bar{C}_s = 0)$ and the output $(\bar{C}_v = 0, \bar{C}_s = 1)$.

We now define a characteristic time $\tau = \frac{1}{K_{on}}$ and a characteristic length $\lambda = \frac{v_v}{K_{on}}$. Thus we consider the following transformations :

$$\begin{aligned} x &\longrightarrow \tilde{x} = \frac{x}{\lambda} = \frac{K_{on}}{v_v} x \\ t &\longrightarrow \tilde{t} = \frac{t}{\tau} = K_{on} t \end{aligned}$$
(3.13)

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which leads to the following set of equations :

$$\begin{cases} K_{on} \frac{\partial \bar{\mathcal{C}}_{v}}{\partial \tilde{t}} + \frac{v_{v} K_{on}}{v_{v}} \frac{\partial \bar{\mathcal{C}}_{v}}{\partial \tilde{x}} = -\bar{\mathcal{J}} \\ K_{on} \frac{\partial \bar{\mathcal{C}}_{s}}{\partial \tilde{t}} + \frac{v_{s} K_{on}}{v_{v}} \frac{\partial \bar{\mathcal{C}}_{s}}{\partial \tilde{x}} = \bar{\mathcal{J}} \\ \bar{\mathcal{J}} = K_{on} \left\{ \bar{\mathcal{C}}_{v} \left(1 - \bar{\mathcal{C}}_{s} \right) - h \frac{K_{off}}{K_{on}} \bar{\mathcal{C}}_{s} \right\} \end{cases}$$
(3.14)

Additionally, we call $\tilde{\mathcal{J}} = \frac{1}{K_{on}} \bar{\mathcal{J}}$ and thus obtain:

$$\begin{cases} \frac{\partial \bar{C}_v}{\partial \tilde{t}} + \frac{\partial \bar{C}_v}{\partial \tilde{x}} = -\tilde{\mathcal{J}} \\ \frac{\partial \bar{C}_s}{\partial \tilde{t}} + \epsilon \frac{\partial \bar{C}_s}{\partial \tilde{x}} = \tilde{\mathcal{J}} \\ \tilde{\mathcal{J}} = \bar{C}_v (1 - \bar{C}_s) - \alpha \bar{C}_s \end{cases}$$

$$(3.15)$$

The newly defined $\tilde{\mathcal{J}}$ is dimensionless and the system is described by two dimensionless parameters:

$$\epsilon = \frac{v_s}{v_v}$$

$$\alpha = h \frac{K_{off}}{K_{on}}$$
(3.16)

The parameter ϵ represents the velocity of the platelets on the surface, while they move at a speed of 1 in the volume. It is, for the system we study, always lower than 1 as the platelets roll at a much slower speed than they are advected. The parameter α represents the exchange between volume and surface. It is also expected to be smaller than one since the filling of the surface should be more important than its emptying.

In the next parts we use the following notation:

$$v = \bar{C}_{v} = \frac{C_{v} h}{C_{s,max}} \qquad \qquad \epsilon = \frac{v_{s}}{v_{v}} \\ s = \bar{C}_{s} = \frac{C_{s}}{C_{s,max}} \qquad \qquad \epsilon = \frac{w_{s}}{v_{v}} \\ J = \tilde{J} = \frac{J h}{C_{s,max}K_{on}} \qquad \qquad \alpha = \frac{K_{off}}{K_{on}} h$$

$$(3.17)$$

We use the subscript *t* and *x* to represent the partial derivative over time and

space; for example: $v_t = \frac{\partial v}{\partial t}$. The resulting equations are given by:

$$\begin{cases} v_t + v_x = -J \\ s_t + \epsilon s_x = +J \\ J = v \ (1-s) - \alpha s \end{cases}$$
(3.18)

Let us point out that the physics of the system is described by only two parameters. The parameter α describes the exchange of platelets between the two environments, and the parameter ϵ corresponds to the relative speed of the platelets on the surface, compared to the advection velocity in the volume.

A simple sum of the first two lines gives :

$$(v+s)_t + (v+\epsilon s)_x = 0 \tag{3.19}$$

This corresponds to the local conservation of the total number of platelets.

We consider the following initial and boundary conditions:

- s(t = 0, x) = 0 as the surface is initially empty of platelets.
- -s(t, x = 0) = 0 as no platelets are injected in the system directly at the surface.
- -v(t = 0, x > 0) = 0 since the channel is empty at the beginning of the experiment.
- $v(t, x = 0) = v^{(in)}$ corresponds to the injection of platelets in the volume at every time.

Let us remark that the concentrations are defined only for positive times and positions. Indeed, the position x = 0 corresponds to the entrance of the channel and injection point, and the time t = 0 is the beginning of the experiment with the beginning of platelets' injection.

We now aim to find an analytical solution for this model. We first explore simple solutions (the constant solution and the stationary case), then we use the characteristic method to understand the general shape of the full solution. Last we numerically solve these equations and compare the results first to our analytical expectations and second to experimental data.

3.4.2. Constant solution

One simple solution exists where both concentrations are constant. This would correspond to large time situation and a far position along the channel.

For this very simple case, we only need to solve :

$$J = v (1 - s) - \alpha s = 0 \tag{3.20}$$

We express the surface concentration in term of the volume concentration.

$$s(v) = \frac{v}{\alpha + v} = \frac{1}{1 + \frac{\alpha}{v}}$$
(3.21)

We have s(v) < 1 since α is positive. We look at the condition for the surface concentration to be equal to one which corresponds to the complete filling of the surface.

$$s(v) \to 1 \Leftrightarrow \begin{cases} \alpha = 0 \\ \text{or} \\ v \to \infty \end{cases} \begin{cases} K_{off} = 0 & \text{or} \\ K_{on} \to \infty & \text{or} \\ v \to \infty \end{cases}$$
(3.22)

In conclusion, we have the constant solution :

$$s^{(\infty)} = \frac{v^{(in)}}{\alpha + v^{(in)}}$$

$$v^{(\infty)} = v^{(in)}$$
(3.23)

 $v^{(in)}$ is the quantity of platelets injected in the system since we have no platelet injection on the surface.

3.4.3. Stationary solution

The equations, if we consider no temporal dependency, become:

$$\begin{cases} v_x = -J\\ \epsilon s_x = +J\\ J = v \ (1-s) \ -\alpha s \end{cases}$$
(3.24)

Summing the first two lines allows us to express *v* in term of *s* and a constant.

$$(v + \epsilon s)_x = 0 \quad \Rightarrow \quad v = C - \epsilon s$$
 (3.25)

The constant can be expressed using the values of the concentration at the initial position: $C = v(x = 0) + \epsilon s(x = 0) = v^{(in)}$. We replace v by its new expression in the second and third lines of equation (3.24). We obtain the equivalent system of equations:

$$\begin{cases} v = v^{(in)} - \epsilon s \\ \epsilon s_x = (v^{(in)} - \epsilon s) (1 - s) - \alpha s \end{cases}$$
(3.26)

We find the surface concentration when we solve the following equation:

$$s_x = s^2 - \frac{v^{(in)} + \epsilon + \alpha}{\epsilon} s + \frac{v^{(in)}}{\epsilon}$$
(3.27)

We transform this equation into an homogeneous non-linear equation with a translation of the solution: $s(x) = \tilde{s}(x) + A$. *A* is a constant that will be chosen so no constant term remains in the equation defining $\tilde{s}(x)$. We note

$$\xi = \frac{v^{(in)} + \epsilon + \alpha}{\epsilon} \tag{3.28}$$

and we replace the new expression of s(x) in the equation (3.27) to obtain:

$$\tilde{s}_x = \tilde{s}' = \tilde{s}^2 - (\xi - 2A)\tilde{s} + \left(A^2 - \xi A + \frac{v^{(in)}}{\epsilon}\right)$$
(3.29)

The constant *A* is defined by $A^2 - \xi A + \frac{v^{(in)}}{\epsilon} = 0$ and can thus take two values:

$$A_{\pm} = \frac{1}{2} \left(\xi \pm \sqrt{\xi^2 - 4 \frac{v^{(in)}}{\epsilon}} \right)$$
(3.30)

The part in the square root is positive as we can write it as a sum of positive terms using the definition of ξ (equation (3.28)):

$$\xi^2 - 4v^{(in)}/\epsilon = \frac{1}{\epsilon^2} \left[\left(v^{(in)} - \epsilon \right)^2 + \alpha^2 + 2\alpha (v^{(in)} + \epsilon) \right]$$

This means we have two solutions:

$$s_{+} = \tilde{s}_{+} + A_{+} \qquad \tilde{s}'_{+} = \tilde{s}^{2}_{+} + (2A_{+} - \xi)\tilde{s}_{+}$$

$$s_{-} = \tilde{s}_{-} + A_{-} \qquad \tilde{s}'_{-} = \tilde{s}^{2}_{-} + (2A_{-} - \xi)\tilde{s}_{-} \qquad (3.31)$$

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We note $\Delta_{\pm} = 2A_{\pm} - \xi = \pm \sqrt{\xi^2 - 4 \frac{v^{(in)}}{\epsilon}} = \pm \Delta.$

To solve those equations, we define a pair of new functions $u_{\pm} = \frac{1}{s_{\pm}}$ which are the solutions of:

$$u_{\pm}' \pm \Delta u_{\pm} + 1 = 0$$

Thus we obtain the two intermediate solutions:

$$u_{\pm} = \mp \frac{1}{\Delta} + B_{\pm} e^{\mp \Delta x} \tag{3.32}$$

with *B* a constant which will be different for each solution plus or minus.

We plot the intermediate solutions \tilde{s}_{\pm} in figure (3.10). Let us note that \tilde{s}_{\pm} being given by $\frac{1}{u_{\pm}}$ is not defined when u_{\pm} is null (red dashed lines in figure (3.10)).

$$u_{\pm} = 0 \quad \Rightarrow \quad x_{\pm} = \frac{\pm 1}{\Delta} \ln(\pm \Delta B_{+})$$
 (3.33)

If the constant B_+ (respectively B_-) is negative (resp. positive), then the position x_+ (resp. x_-) is undefined and the function \tilde{s}_+ (resp. \tilde{s}_-) does not diverge.

We now write the final solution:

$$s_{\pm} = \tilde{s}_{\pm} + A_{\pm}$$

= $\frac{1}{B_{\pm}e^{\pm\Delta x} \pm 1/\Delta} + A_{\pm}$ (3.34)

The constants B_{\pm} are determined with the vanishing boundary condition s(x = 0) = 0.

$$B_{\pm} = \pm \frac{1}{\Delta} - \frac{1}{A_{\pm}} = \pm \frac{1}{\Delta} - \frac{2}{\xi \pm \Delta}$$
 (3.35)

The solutions become:

$$s_{\pm} = \frac{A_{\pm} \Delta}{\mp A_{\pm} + (\pm A_{\pm} - \Delta) e^{\mp \Delta x}} + A_{\pm}$$

=
$$\frac{\Delta (\xi \pm \Delta)}{\mp (\xi \pm \Delta) \pm (\xi \mp \Delta) e^{\mp \Delta x}} + \frac{1}{2} (\xi \pm \Delta)$$
(3.36)

The two solutions $s_+(x)$ and $s_-(x)$ are the same function. To prove this equality, we use the first line of equation (3.36), and the fact that $A_- = A_+ - \Delta$. We consider the minus solution:

$$s_{-} = \frac{A_{-} \Delta}{A_{-} + (-A_{-} - \Delta) e^{+\Delta x}} + A_{-}$$
(3.37)



Figure 3.10.: The intermediary result $\tilde{s}(x)$. On the left hand side, the "plus" solution $\tilde{s}_{+}(x) = \frac{1}{Be^{-\Delta x} - 1/\Delta}$; on the right hand side the minus solution $\tilde{s}_{-}(x) = \frac{1}{Be^{\Delta x} + 1/\Delta}$. The curves are plotted for $\Delta = 1$ and for B = 5 for the top curves and B = -5 for the bottom curves. The red dashed vertical lines represent the positions x_{\pm} where the functions \tilde{s}_{\pm} diverge. Such positions exist only in two of the four possible cases.

We replace the constant A_{-} and multiply the fraction by $e^{-\Delta x}$ to obtain:

$$s_{-} = \frac{(A_{+} - \Delta)e^{-\Delta x} \Delta}{(A_{+} - \Delta)e^{-\Delta x} + (-A_{+} + \Delta - \Delta)} + A_{+} - \Delta$$

= $\frac{(A_{+} - \Delta)e^{-\Delta x} \Delta + (A_{+} - \Delta)((A_{+} - \Delta)e^{-\Delta x} - -A_{+} -)}{(A_{+} - \Delta)e^{-\Delta x} - A_{+}}$ (3.38)

We recognize here the same denominator as in s_+ . We re-organize the numerator of s_- into:

$$(A_{+} - \Delta)e^{-\Delta x} \Delta + (A_{+} - \Delta)\left((A_{+} - \Delta)e^{-\Delta x} - A_{+}\right) = (A_{+} - \Delta)e^{-\Delta x} (\Delta + (A_{+} - \Delta)) + (A_{+} - \Delta)(-A_{+}) = A_{+} ((A_{+} - \Delta)e^{-\Delta x} - A_{+}) + A_{+}\Delta$$
(3.39)

Thus, we obtain:

$$s_{-} = \frac{A_{+}\Delta}{(A_{+} - \Delta)e^{-\Delta x} - A_{+}} + A_{+}$$

= s_{+} (3.40)

We consider only the "plus" solution in further study as the two are strictly identical. We have thus found the stationary surface concentration s(x):

$$s(x) = \frac{A \Delta}{(A - \Delta) e^{-\Delta x} - A} + A$$
(3.41)

Let us remark that the constant $B = \frac{1}{\Delta} - \frac{2}{\xi + \Delta}$ is positive since $\Delta = \sqrt{\xi^2 - 4\frac{v^{(in)}}{\epsilon}}$ is smaller than ξ . That leads to the existence of a position $x = \frac{1}{\Delta} \ln(\Delta B)$ where the solution diverges. However, this position is negative as $\Delta B = 1 - \frac{2\Delta}{\xi + \Delta} < 1$. Since we are interested in the surface concentration for positive positions, with the origin of the axis taken at the beginning of the channel, we do not see the divergence.

In the expression of the surface concentration given in equation (3.41), the two parameters describing the physics of the system are *A* and Δ . Considering the third parameter $v^{(in)}$ from the boundary condition $v(x = 0) = v^{(in)}$, we can easily switch between sets of parameters.

$$\begin{cases} \alpha \\ \epsilon \\ v^{(in)} \end{cases} \Leftrightarrow \begin{cases} \xi = \frac{\alpha + \epsilon + v^{(in)}}{\epsilon} \\ \epsilon \\ v^{(in)} \end{cases} \Leftrightarrow \begin{cases} A = \frac{1}{2} \left(\xi + \sqrt{\xi^2 - 4 \frac{v^{(in)}}{\epsilon}} \right) \\ \Delta = \sqrt{\xi^2 - 4 \frac{v^{(in)}}{\epsilon}} \\ v^{(in)} \end{cases}$$
(3.42)

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$$\begin{cases} A \\ \Delta \\ v^{(in)} \end{cases} \Leftrightarrow \begin{cases} \xi = 2A - \Delta \\ \epsilon = \frac{v^{(in)}}{A(A - \Delta)} \Leftrightarrow \begin{cases} \alpha = \epsilon \xi - \epsilon - v^{(in)} \\ \epsilon \\ v^{(in)} \end{cases}$$
(3.43)

We study the form of the solution s(x) for different parameters.



Figure 3.11.: Stationary surface concentration (a) for different parameters $v^{(in)}$ with $\epsilon = 0.01$ and $\alpha = 0.1$; (b) for different parameters ϵ with $\alpha = 0.1$ and $v^{(in)} = 0.7$; (c) for different parameters α with $\epsilon = 0.01$ and $v^{(in)} = 0.7$.

First we observe that the surface concentration tends toward a constant for large positions. This constant can be calculated:

$$s(x) \xrightarrow[x \to \infty]{} A - \Delta = \frac{1}{2} \left(\xi - \sqrt{\xi^2 - 4 \frac{v^{(in)}}{\epsilon}} \right)$$
 (3.44)

We observe on figure (3.11) that this value $s(x \to \infty)$ increases with the volume concentration injected in the system $v^{(in)}$. It also decreases when we increase

the parameter α . This can be easily understood as α represents the capacity of the platelets to leave the surface.

A characteristic length scale appears from the exponential in the expression of the surface concentration (3.41): $1/\Delta$. We can also find this length scale if we calculate the derivative of the concentration at the initial position:

$$\left. \frac{ds}{dx} \right|_{x=0} = \frac{v^{(in)}}{\epsilon} \Delta \tag{3.45}$$

In this equation, $\frac{v^{(in)}}{\epsilon}$ corresponds to the characteristic surface concentration and Δ to the inverse of the characteristic length. From the curves of figure (3.11), we see that this initial slope is greatly influenced by the injection concentration $v^{(in)}$ and by the movement parameter ϵ .

3.4.4. Analytical study of the full model: the characteristic method

We use the characteristic method to try and solve the coupled equations describing the system of platelets. We first give a small reminder of the use of the characteristic method, then we apply it to the coupled equations.

The characteristic method is used to solve the general equation :

$$a(x,t,u) \frac{\partial u}{\partial x} + b(x,t,u) \frac{\partial u}{\partial t} = c(x,t,u)$$
(3.46)

where a(x, t, u), $b(x, t, u) \neq 0$ and c(x, t, u) are known, and we are looking for u(x, t) such that the boundary condition $u = u_0(x, t)$ on the curve f(x, t) = 0 is observed.

We can visualize the solution u(x, t) as a surface in a three-dimensional space as shown in figure (3.12).

If the point M(x, t, u(x, t)) belongs to the surface solution, the tangent plan to the surface *u* is given by two vectors: $(1;0;\frac{\partial u}{\partial x})$ and $(0;1;\frac{\partial u}{\partial t})$. Thus, if the vector (a, b, c) belongs to the tangent plan, then the equations are solved. In other words, we are looking for the surface which is tangent everywhere to the known vector (a(x, t, u), b(x, t, u), c(x, t, u)) and which is set on u_0 .

We define a curve x(t) and we consider the solution u(x(t), t) = U(t). From equation (3.46) that we wish to solve and the derivative of U(t), we have to



Figure 3.12.: Visualisation of the characteristic method with u(x, t) the surface solution of the general equation $a\frac{\partial u}{\partial x} + b\frac{\partial u}{\partial t} = c$. On the curve defined by f(x,t) = 0, the boundary condition gives $u(x,t) = u_0(x,t)$ (in green). We are looking for the characteristic curves $x_c(t)$ on which the solution is given by with $U_c(t) = u(x_c(t), t)$ (in purple).

solve the set of equations:

$$\begin{cases} a\frac{\partial u}{\partial x} + b\frac{\partial u}{\partial t} = c\\ \frac{dU}{dt} = \frac{\partial u}{\partial t} + x'\frac{\partial u}{\partial x} \end{cases}$$
(3.47)

with $x' = \frac{dx}{dt}$. Multiplying the second line by *b* and adding it to the first line, we obtain:

$$(a-b x') \frac{\partial u}{\partial x} = c - b \frac{dU}{dt}$$

Let us consider the case where a - bx' = 0. Then, either $c \neq b\frac{dU}{dt}$ and there is no solution; or $c = b\frac{dU}{dt}$ and the equation is unsolvable. In this last situation we actually define the characteristic curves with $\frac{dx}{dt} = \frac{a}{b}$ unto which the differential equation $\frac{dU}{dt} = \frac{c}{b}$ gives the solution on the curve.

In short, the characteristic method splits the problem into two parts:

- finding the characteristic curves
- solving the non-partial differential equation on the characteristic curves.

The rolling platelets system is described by the coupled partial equations:

$$\begin{cases} \frac{\partial v}{\partial x} + \frac{\partial v}{\partial t} = -v(1-s) + \alpha s\\ \epsilon \frac{\partial s}{\partial x} + \frac{\partial s}{\partial t} = +v(1-s) - \alpha s \end{cases}$$
(3.48)

Introducing the vector : $u = \begin{pmatrix} v \\ s \end{pmatrix}$, the coupled equations can be written as one equation:

$$A\frac{\partial u}{\partial x} + 1 \frac{\partial u}{\partial t} = C \tag{3.49}$$

with $A = \begin{bmatrix} 1 & 0 \\ 0 & \epsilon \end{bmatrix}$, $C = \begin{bmatrix} -J \\ +J \end{bmatrix}$ and $J = v(1-s) - \alpha s$. Using the characteristic method leads to the equality:

$$(A - 1x') \frac{\partial u}{\partial x} = C - 1\frac{dU}{dt}$$

The characteristic curves and their associated differential equations are given by:

$$\begin{vmatrix} 1 - x' & -J - \frac{dv}{dt} \\ 0 & +J - \frac{ds}{dt} \end{vmatrix} = 0 = (1 - x')(J - \frac{ds}{dt})$$

$$\begin{vmatrix} -J - \frac{dv}{dt} & 0 \\ +J - \frac{ds}{dt} & \epsilon - x' \end{vmatrix} = 0 = (\epsilon - x')(J + \frac{dv}{dt})$$
(3.50)

Both values must be null which leads to two sets of characteristic curves:

- on the domain \mathcal{K}_1 , defined by $\frac{dx}{dt} = 1$ (straight lines of slope 1), the differential equation is: $\frac{dv}{dt} = -J = -v(1-s) + \alpha s$
- on the domain \mathcal{K}_{ϵ} , defined by $\frac{dx}{dt} = \epsilon$ (straight lines of slope ϵ), the differential equation is: $\frac{ds}{dt} = J = v(1-s) \alpha s$

Here we have to tread carefully since each differential equation has to be solved on its attributed characteristic curve as presented in figure (3.13).

Let us remark that, to solve the system at one point (x, t), we need to know



Figure 3.13.: Visualization of the characteristic method. Two sets of characteristic curves are defined: the domain \mathcal{K}_1 in blue, and the domain \mathcal{K}_{ϵ} in red. The initial and boundary conditions are added in green.

the system on two points, one for each domain. In particular, we can consider two points either horizontally aligned or vertically aligned. Those will then be defined at the same time $t - \delta t$, or at the same position $x - \delta x$. The last case is used in a later analysis and is depicted in figure (3.15).

We consider the situation where x > t. This corresponds, in the (t, x) plan, to the upper left part (in yellow in figure (3.14)). For initial time and at every position strictly positive, both the surface and volume concentrations are null:

$$\begin{cases} v_0(t=0, x > 0) = 0\\ s_0(t=0, x > 0) = 0 \end{cases}$$

For each point in the half-space x > t, the origin is 0 and thus the concentrations remain null:

$$\begin{cases} \text{on } \mathcal{K}_1 : \frac{\partial v}{\partial t} = 0 \quad \Rightarrow v(x > t) = v(t = 0, x > 0) = 0\\ \text{on } \mathcal{K}_{\epsilon} : \frac{\partial s}{\partial t} = 0 \quad \Rightarrow s(x > t) = s(t = 0, x > 0) = 0 \end{cases}$$

This is easily explained by reminding ourselves that "1" is the rescaled speed of the fastest platelets (those in the volume). Thus, the platelets reach a certain position at a certain time defined by x = 1 * t and none are present before.

On the line $\mathbf{x} = t$ (orange line in figure (3.14)), we consider first the characteristic curses \mathcal{K}_{ϵ} where $\frac{\partial s}{\partial t} = +J = 0$ since it is defined in the x > t half-space. Thus we can solve the surface concentration: s(x = t) = 0.

We consider then the characteristic curve \mathcal{K}_1 onto which we solve $\frac{\partial v}{\partial t} = -J$ On this curve we showed previously that s = 0 and thus, we have J = v. We solve the equation and find the expression of the volume concentration $v(x = t) = v^{(in)} e^{-t}$, with $v^{(in)}$ the initial volume concentration injected at the channel entrance x = 0 at all time.



Figure 3.14.: Visualization of the characteristic methods and the two sub-spaces x > t and $x < \epsilon t$. In yellow the half-space x > t where the concentrations are null. In blue the sub-space $x < \epsilon t$ where the solution is the stationary solution. The green lines correspond to the initial and boundary conditions, the blue lines represents the \mathcal{K}_1 domain and the red lines the \mathcal{K}_{ϵ} domain.

We now consider the situation where $x < \epsilon t$, the lower most section in the (t, x) space (blue domain in figure (3.14)). We will show that in this section, the concentrations are not time-dependent. We note M_i the points in the $(t, x < \epsilon t)$ space, with i = 0 for points on the t-axis, i = 1 for points on the line parallel to the t-axis and at $x = \delta x$ and M_i the points of the line $x = i \delta x$. We note $v(M_i)$, $s(M_i)$ and $J(M_i)$ the volume concentration, surface concentration and exchange

quantity at the point $M_i(t > x/\epsilon, x = i \delta x)$. From the initial conditions, we have:

$$\forall M_0(t, x = 0) , \begin{cases} v(M_0) = v^{(in)} \\ s(M_0) = 0 \\ J(M_0) = v^{(in)}(1 - 0) - \alpha 0 = v^{(in)} \end{cases}$$
(3.51)

We consider the point M_1 ($t > x/\epsilon, x = \delta x$). To determine the concentrations at M_1 , we need to consider the situation at $M_0(t - \delta x/\epsilon, x = 0)$ for the surface concentration and at $M'_0(t - \delta x, x = 0)$ for the volume concentration (refer to figure (3.15)). We note $\delta t = \delta x$. On the domain \mathcal{K}_1 , defined by the line ($M'_0 M_1$), we have $\frac{dv}{dt} = -J$ and, in this particular situation, we can write : $\frac{v(M_1) - v(M'_0)}{\delta t} = -J(M'_0)$ thus: $v(M_1) = v(M'_0) - J(M'_0) \delta t$.

In a similar way, on the line $(M_0 M_1)$, we solve $\frac{ds}{dt} = J$ and obtain: $s(M_1) = s(M_0) + J(M_0) \, \delta t / \epsilon$.



Figure 3.15.: Solution on the subspace $x < \epsilon t$. The boundary conditions give on the green line $v(x = 0, t) = v^{(in)}$ and s(x = 0, t) = 0. The solution at the point $M_1(\delta x, t)$ is determined from the point $M_0(0, t - \delta x/\epsilon)$ and $M'_0(0, t - \delta x)$. The concentrations at \tilde{M}_1 also come from the boundary conditions and are identical to those on M_1 .

Considering a point \tilde{M}_1 on the same line $x = \delta x$ than M_1 , we can write:

$$\begin{aligned} v(\tilde{M}_1) &= v(\tilde{M}_0') - J(\tilde{M}_0') \,\delta t \\ s(\tilde{M}_1) &= s(\tilde{M}_0) + J(\tilde{M}_0) \,\delta t/\epsilon \end{aligned} (3.52)$$

Since all solutions on the t-axis are identical, we have also identical solution for M_1 and \tilde{M}_1 and thus for all points on the line $x = \delta x$ for $t > x/\epsilon$.

Considering a point $M_2(t > x/\epsilon, x = 2\delta x)$, we can write the concentrations from M_1 and \tilde{M}_1 and in the same manner as above, all points M_2 give identical results.

Thus, we have shown that for $t > x/\epsilon$, the results on lines parallel to the t-axis are equal. This means that the concentrations in this subspace are not time-dependent and the solution is the stationary solution.

We can deduce the form of the solution from our knowledge of the two domains presented in figure (3.14). Indeed, we know the stationary solution from the subsection (3.4.3) and, despite our lack of analytical expression for s(x, t) in the middle zone, we can plot the general form of the surface concentration as shown in figure (3.16). In these curves, ϵ was taken as $\frac{1}{3}$.

We observe a cross over between the curves at different position (figure (3.16), bottom, left hand curve) and an increase of cell concentration with the position before the expected decrease (figure (3.16), bottom, right hand curve). The observation of these two features are directly linked to the value of ϵ . If ϵ is decreased, the increase of cell concentration for small x will be very short and could only be seen at very large time. Likewise, the crossover in the time dependency curve is due to the concentration reaching its stationary value. But with a small ϵ , such occurrence happens at very large time and we only observe the beginning of the concentration increase (figure (3.16), bottom left, position x_3 in grey). As $\epsilon = \frac{v_s}{v_n}$, we expect a very small value for this parameter: $\epsilon \sim 10^{-2} - 10^{-3}$ which would explain the lack of observation of these features in experimental curves. For example, we consider the time dependency of the concentration at the position $x_{exp} = 5mm$. The stationary solution is reached at $t_{exp} = \frac{x_{exp}}{v_s}$ (we use the time and position renormalization and the equality $x_{renorm} = \epsilon t_{renorm}$). Using the mean value of the rolling velocity distribution found with the first model in section (3.3), we obtain, for Exp. 1: t_{exp} =2h46min40s which, though long, is still a reasonable experimental time. However, for Exp.2, we find an experimental time a bit short of a month. In this case, the crossover of concentration and increase of concentration in positiondependent curves are impossible to observe experimentally.



Figure 3.16.: General form of the surface concentration profile (bottom) depending on time (left) or on position (right), deduced from the characteristic method (top figures). In this representation, ϵ is taken as 1/3, $x_1 < x_2 < x_3$ and $t_1 < t_2$. The stationary solution is depicted in red in the $C_s(x)$ curve (bottom right) and was calculated in the subsection (3.4.3).

As analytical analysis can not give an exact solution of these coupled equations, we solve them numerically. In the next subsections, we describe the method used and we compare its results with our expectation from this analytical part. Then we fit experimental data to test the validity of the model.

3.4.5. Numerical method

We use the matrix form of the equations as described for the characteristic method in equation (3.49). As we consider the time evolution of the surface concentration at every point of the channel, we can write the derivation with respect to space in a matrix form. The equation takes the following form:

$$\frac{\partial u}{\partial t} = C - A u \tag{3.53}$$

In this equation, *u* is the vector comprised of the volume then surface concentrations at every points, *C* and *A* are matrices and $J = v(1 - s) - \alpha s$.

$$u = \begin{bmatrix} v(x=0) \\ \vdots \\ v(x=x_{max}) \\ s(x=0) \\ \vdots \\ s(x=x_{max}) \end{bmatrix} \quad A = \frac{1}{\delta x} \begin{bmatrix} 1 & & & \\ -1 & \ddots & 0 \\ & -1 & 1 & & \\ & & \epsilon \\ 0 & & -\epsilon & \ddots \\ & & & -\epsilon & \epsilon \end{bmatrix} \quad C = \begin{bmatrix} -J \\ +J \end{bmatrix}$$

$$(3.54)$$

We use the *Matlab* function *ode15s* which calculates the values of a function f(x,t) at different times. The function is defined by the equation $\frac{\partial f}{\partial t} = F(t, x, f)$ and the initial condition $f(x, t = 0) = f_0(x)$. This allows us to quickly generate the numerical solution of our model. The goal is now to compare the numerically generated curves with the experimental points in order to extract physical parameters.

We consider the influence of the parameters on the form taken by the **curves** as shown in figure (3.17). The first observation is that for α (top curves) and ϵ (middle curves) taken between 0 and 10^{-2} , the C_s curves are similar. On the other hand, changing $v^{(in)}$ (bottom curves) strongly influences the shapes of $C_s(x, t)$. We expect α and ϵ to be of the order of 10^{-1} or smaller. When we fit the experimental data, we use the fact that these two parameters influence the general form of the curves less than $v^{(in)}$ and we consider them as secondary fit parameters. Thus, in subsection (3.4.7), we first search for the value of $v^{(in)}$ with $\alpha = 0$ (no unbinding) and $\epsilon = 0$ (no rolling) then we vary those two parameters.



Figure 3.17.: Influence of the parameters α (top), ϵ (middle) and $v^{(in)}$ (bottom). The curves use normalized values of C_s depending on t at position x = 2 (left), and C_s depending on x at time t = 5 (right). The top curves use $\epsilon = 10^{-2}$ and $v^{(in)} = 0.5$, the middle curves $\alpha = 10^{-2}$ and $v^{(in)} = 0.5$, and the bottom curves are plotted for $\epsilon = 10^{-2}$ and $\alpha = 10^{-2}$.

3.4.6. Analytical and numerical solutions

We compare the solution given by our program with the results expected from the analytical analysis performed previously in section (3.4.4).



Figure 3.18.: Comparison between numerical simulations and analytical results. The top curves represent the (t,x) space used for the characteristic method, on the bottom curves are reported the times (resp. positions) when the solution changes regime for the given positions (resp. times). ϵ is taken at 0.1.

The results are shown in figure (3.18). We observe a good fit between the expected results and those generate numerically. However, if we look at the details of the fit, in particular at the time when the solution changes regime (from null solution to transition, and from transition to stationary solution), we observe a difference between the two results as can be seen with the continuous lines in the bottom curve of figure (3.19). In this figure, we show the influence of the spacial discretization. Indeed, if we use a denser mesh for the numerical simulation, the results is closer to the analytical prediction (continuous line, dashed line, dotted line). Thus this difference is a numerical artifact.



Figure 3.19.: Comparison between numerical simulations and analytical results. The top curves represents the (t,x) space used for the characteristic method, on the bottom curves are reported the times when the solution changes regime for each positions: in green $x = 3.2 \ \mu$ m, in magenta $x = 83.2 \ \mu$ m and in blue $x = 163.2 \ \mu$ m. On the bottom curve three discretization are plotted: with continuous lines $dx = 1.6 \ \mu$ m, in dashed lines $dx = 0.6 \ \mu$ m and in dotted lines $dx = 0.4 \ \mu$ m. The horizontal black dashed line corresponds to the stationary solution at $x = 3.2 \ \mu$ m; we use $\epsilon = 0.1$

3.4.7. Experiments and numerical comparison

Fitting experiments with this model pursues two aims. First we want to validate this model and extract physical parameters from the surface concentration measurements. Second, we can compare the quality of the two models to further our understanding of the system. Indeed, if the first model considers only the rolling velocity distribution to explain the axial and time dependence, this model is based on the exchange between the volume and the surface. We will here focus on the task of finding parameters and fitting the experimental data. The quality of the fit is estimated though the evaluation of the Euclidean norm of the distance between the fit and the experimental measurements. **Six fitting parameters** are needed to perform the comparison between the model and the experiments. Three parameters are necessary to rescale the experimental data, with one for the time, one for the position and one for the surface concentration. We chose to use \mathcal{K}_{on} , v_v and $C_{s,max}$ to rescale the time, space and concentration values : $t \to t\mathcal{K}_{on}$, $x \to x\mathcal{K}_{on}/v_v$, $C_s \to C_s/C_{s,max}$. The three other parameters are those used by the model α , ϵ and $v^{(in)}$.

From these parameters and knowing the injection concentration $C_v^{(in)}$, we can find all the physical parameters initially used to describe the system:

$$\begin{cases} C_{s,max}, \mathcal{K}_{on}, v_{v}, C_{v}^{(in)} \\ \epsilon \\ \alpha \\ v^{(in)} \end{cases} \implies \begin{cases} C_{s,max}, \mathcal{K}_{on}, v_{v}, C_{v}^{(in)} \\ v_{s} = \epsilon v_{v} \\ \mathcal{K}_{off} = \alpha \mathcal{K}_{on} C_{v}^{(in)} / v^{(in)} C_{s,max} \\ h = v^{(in)} C_{s,max} / C_{v}^{(in)} \end{cases}$$

$$(3.55)$$

Let us consider each of the six parameters in more detail:

- $C_{s,max}$ is the maximal surface concentration the system can reach. It corresponds either to a close packing of the surface, or to the use of all links with the vWF. As we use densely grafted surface, we expect the first case to be the limit. We can thus estimate the range of $C_{s,max}$. Platelets vary in size from 2 to 4 μ m. Considering a circular shape, we estimate that $C_{s,max}$ is comprised between 50 000 and 250 000 mm⁻².
- \mathcal{K}_{on} represents the capacity of the platelets to be absorbed on the surface.
- v_v is the speed of the advected platelets. Through a careful choice of the pressure applied to the microfluidic channel, we control the shear rate $\dot{\gamma} = 1800 \text{ s}^{-1}$ and thus the speed of the fluid varies with the height from the channel surface. In our model, the volume part of the system is at a small height *h* from the wall and we approximate the Poisseuille flux by a straight line. Thus $v_v = \dot{\gamma}h$. The height *h* could be either the size of the link between the vWF and the platelets, or the platelet size. Indeed it corresponds to the distance at which the platelets and the grafted von Willebrand factors interact and bind. If we consider the size of the link the volume velocity becomes much smaller with $v_v \sim 20 \ \mu \text{m.s}^{-1}$.
- α is the relative exchange rate and is smaller than 1 since the surface tends to be covered in platelets.
- ϵ is the relative speed and was estimated in the previous paragraph as: $\epsilon \sim 10^{-2} - 10^{-3}$ (indeed, we can estimate $v_s \sim 1 \mu \text{m.s}^{-1}$).

 $-v^{(in)}$ is the volume concentration injected at the entrance of the channel. This parameter is positive but has no theoretical limit.

Fitting the experiments can not be done automatically with a *Matlab* function. Indeed, the six parameters over which we optimize influence the results in a very non-linear way. They are not parameters of a system of equations but of a model and thus the *Matlab* fitting schemes can not find the best set. We build a semi-automatic search engine to fit the experiments using the Euclidian norm *R* to estimate the quality of a fit and compare the different sets of parameters tested.



Figure 3.20.: Fit with the exchange model. The top curves correspond to the Exp. 1, the bottom ones to Exp. 2. The points are the experimental data while the continuous line of identical colors corresponds to the results from the model. On the left hand side are the time-dependence curves, on the right hand side, the axial-dependence ones. The parameters used to fit Exp. 1 (top) are: $C_{s,max} = 18000 \text{ mm}^{-2}$, $\mathcal{K}_{on} = 0.064 \text{ s}^{-1}$, $v_v = 0.1 \text{ mm.s}^{-1}$, $\epsilon = 2.6 \times 10^{-5}$, $\alpha = 0.74 \times 10^{-3}$, and $v^{(in)} = 0.002$. The Euclidean norm between the model and the experiment is given by $R = 4.5 \times 10^{3}$. The parameters used to fit Exp. 2 (bottom) are: $C_{s,max} = 53000 \text{ mm}^{-2}$, $\mathcal{K}_{on} = 0.12 \text{ s}^{-1}$, $v_v = 0.11 \text{ mm.s}^{-1}$, $\epsilon = 0.72 \times 10^{-3}$, $\alpha = 6.6 \times 10^{-3}$, and $v^{(in)} = 0.0036$. The Euclidean norm is given by $R = 17.9 \times 10^{3}$

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The fit for Exp. 1 is presented in figure (3.20, top) and the one for Exp. 2 in figure (3.20, bottom). While Exp. 1 seems to be well fitted by the model, the exchange model does not fit the second experiment so well. This can be due to either to the lack of an essential feature in the model, or to the difficulty of finding the appropriate set of parameters. Indeed, the phase space through which we search for the six parameters is a complex one. To illustrate that, we plot *R* as a function of $C_{s,max}$ and v_v for three combinations of \mathcal{K}_{on} and $v^{(in)}$ with $\alpha = \epsilon = 0$. Figure (3.21) shows that each surface has a minimum of *R* at a different position ($C_{s,max}, v_v$) than the other two.



Figure 3.21.: Phase space explored when fitting Exp. 2 with the exchange model. The parameters α and ϵ are set to 0. The surface of the Euclidean norm R are plotted for different $C_{s,max}$ and v_v in logarithmic scales and for three sets of $(\mathcal{K}_{on}, v^{(in)})$: in blue $\mathcal{K}_{on} = 0.1$ and $v^{(in)} = 0.01$, in red $\mathcal{K}_{on} = 0.1$ and $v^{(in)} = 0.002$, and in green $\mathcal{K}_{on} = 0.01$ and $v^{(in)} = 0.02$.

3.5. Concluding Remarks

In this chapter, we presented a microfluidic experiment where platelets are injected in a channel with von Willebrand factor grafted on the surface. Advection in the volume, attachment to the surface, rolling and detachment were observed, and the surface concentration of platelets were measured as a function of time and distance.

We studied two models to try and understand the experimental observations. The first model focuses on the rolling velocity distribution of the platelets and considers a surface-source at the entrance of the channel. The second one focuses on the exchange between the volume and the surface. In this model, the injection of platelets takes place in the volume at the entrance of the channel. Both models were used to fit two experiments.

In the case of the first experiment, the Euclidean norms are respectively $R = 4.8 \, 10^3$ for the rolling model and $R = 4.5 \, 10^3$ for the exchange model. In the case of Exp. 2, they are given by $R = 16.9 \, 10^3$ and $R = 17.8 \, 10^3$. According to those norms alone, the first experiment is better described by the exchange model while the second experiment is better fitted by the rolling model. However, we think that the models need to be merged to reach a more complete description of the experiments, in particular for Exp. 2. Indeed, it is likely that the downward flux at the injection position pushes the platelets to the surface, and a larger number of cells would bind to the vWF than the simple exchange can account for. Thus our future studies should consider both the volume and the surface sources at the entrance of the channel

Concluding remarks

In this thesis we explored two approaches to simulation. On the one hand, we worked on the Poisson-Boltzmann theory and our goal was to build solvers to speed up the simulations or to include electrostatic fluctuations in the model. On the other hand, we used simulations to better understand experimental results. We aimed to distinguish the physical phenomena involved and to estimate their relative importance.

We first studied a numerical limit of the Poisson-Boltzmann theory. The electrostatic free energy is concave with respect to the electrostatic field. To find the free energy value at equilibrium, it must be maximized. This becomes a saddle point search when configurational degrees of freedom are involved since they add a convex part to the free energy. We showed how the Legendre transform is used to define an equivalent, overall convex free energy. We then used a simple one-dimension model of a virus to compare different numerical methods to compute the free energy. The first method is composed of two nested optimization loops, the second one defines a functional with the derivatives of the free energy, the third uses an inverse substitution to define an equivalent and convex free energy, and the fourth minimizes the Legendre-transformed free energy. We studied the validity of the results given by these four methods and their efficiency. We found that the Legendre transform method gives the most accurate optimization and the best time performance. The tool developed in this part could be used to model more complex systems or to be included within a molecular dynamic calculator.

In a second study, we showed how to add the electrostatic fluctuations to the Poisson-Boltzmann mean-field theory. We used a variational field theory method and we presented the numerical scheme allowing us to estimate the correction to the free energy. We then explored the limit of this correction to the mean field theory. We found that a limit coupling constant exists beyond which the program diverges. We studied the bulk case to better understand the origin of this limit. We found that the solution, in this simple case, is expressed with the Lambert W-function and exists only for small coupling constants. We stud-

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ied the dependance of the limit coupling constant with respect to the rescaled fugacity, and observed that it is similar for the cylinder case than for the bulk theoretical study. We concluded that the limit observed originates from the theory used. Further research would explore in more details the correction calculated and compare our results with those produced by other modelization tools , such as molecular dynamics. This step would validate, or invalidate our method which could then be used to model more complex systems, or be discarded or reworked at the theory level.

Our third study focused on understanding experimental results. Platelets were injected into a micro-channel with protein-coated walls. The proteins can create and break bounds with the platelets, and thus form a binding mesh and rolling medium. From our observations, we identified four phenomena: the binding and unbinding of platelets from the surface, the advection in the volume and the rolling on the surface. We defined two models, the first one considers only the rolling of the platelets on the surface while the second one focuses on the exchange of platelets between the volume and the surface. We compared the results of the simulations with the experimental measurements. We found that both models can match the experiments partially but not thoroughly. We concluded that both the rolling behavior and the exchange mechanism should be considered at once to describe the system fully. To validate such a model would then allow us to better characterize the experiments and to gain a deeper understanding of the physical phenomena involved.

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Résumé

La théorie de Poisson-Boltzmann décrit l'électrostatique de solutions ioniques. Le calcul de l'énergie libre électrostatique présente cependant plusieurs limites.

L'énergie libre de Poisson-Boltzmann est concave. Quand le modèle est complété par d'autres degrés de libertés, l'estimation de l'énergie libre devient une recherche de point-de-col, opération numérique complexe. À l'aide de la transformée de Legendre, nous écrivons une fonctionnelle équivalente, convexe et définie localement. Un algorithme classique de minimisation est utilisé, et, comparé à d'autres procédés numériques, il présente une meilleure convergence.

La théorie de Poisson-Boltzmann est une approximation de champ moyen. À l'aide de la théorie de champ variationnel, nous ajoutons les fluctuations et les corrélations du champ électrostatique. Les équations sont résolues numériquement. Nous montrons que la constante de couplage possède une limite théorique, au delà de laquelle les équations n'ont pas de solution.

Les plaquettes sanguines ont un rôle essentiel dans l'hémostase. Nous étudions le flux de plaquettes dans un micro-canal greffé de protéines liantes. Nous développons deux modèles. L'un considère le roulement des plaquettes, l'autre est centré sur l'échange de cellules entre le volume et la surface. Ces modèles sont en accord avec les résultats expérimentaux mais pas en complète adéquation. Nous en concluons que le comportement de roulement et le mécanisme d'échange devraient être considérés simultanément pour décrire ce système.

Mots-clés : au-delà de Poisson-Boltzmann, énergie libre, transformée de Legendre, champ moyen, théorie de champ variationnel, paramètre de couplage, plaquettes, roulement, échange.

Abstract

Poisson-Boltzmann theory gives a good description of the electrostatics of ionic solutions. The estimation of the electrostatic free energy presents limits of different kinds.

The Poisson-Boltzmann free energy is concave. When it is supplemented with other degrees of freedom, finding the free energy translates into a saddle-point search. Using the Legendre transform, we write an equivalent, convex and locally defined functional. A classical minimum search is used and, compared to other numerical schemes, it gives a better convergence.

The Poisson-Boltzmann theory is a mean-field approximation. Using the variational field theory, we include the fluctuations and correlations of the electrostatics. The equations are solved numerically. We show that a theoretical limit exists for the coupling constant, beyond which the equations have no solution.

Platelets are essential to the stop of blood loss. The flow of platelets in a microfluidic chamber coated with binding proteins is studied. We develop two models. One focuses on the rolling speed, the other on the exchange between the volume and the grafted surface. Both models can match the experiments partially but not thoroughly. We conclude that both behaviors should probably be considered at once to describe the system fully.

Key words: beyond Poisson-Boltzmann, free energy, Legendre transform, mean field, variational field theory, coupling parameter, platelets, rolling behavior, exchange of cells.