Development of an insilico model of eccrine sweat using molecular modelling techniques

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Abstract

Exploring eccrine sweat as an ideal surrogate diagnostic biofluid for physiological and metabolic biomarkers, which are indicators of human health and performance, is an area of significant research interest. These biomarkers correlate well with blood plasma and candidate analytes such as glucose which require periodic monitoring are of particular interest. An insilico model of eccrine sweat can assist in the development these biosensors. In this regard, molecular modelling can be employed to observe the most fundamental interactions. Here, we determine a suitable molecular model for building eccrine sweat. The basic components of sweat are water and sodium chloride, in which glucose and other analytes are present in trace quantities. Given the wide range of water models available in the molecular dynamics space, in this study, we first validate the water models. We use three compounds to represent the base to build bulk sweat fluid and validate the force fields. We compare the self-diffusivity of water, glucose, sodium, and chloride ions as well as bulk viscosity values with the existing literature. This validated model is made available and can serve as an aid for de novo development of biosensors by further addition of other analytes via simulations to expedite their development.

1. Introduction

Eccrine sweat has two distinct advantages over other candidate biofluids owing to its non-invasive, periodic availability and established correlation with blood serum. This has motivated researchers to consider it as a surrogate diagnostic biofluid since the existence of amino acids serine was detected in 1910.\footnote{1} Subsequently, a detailed study of eccrine sweat was conducted by Ray and McSwiney for its composition.\footnote{2} Research in this direction was further fuelled by the findings of glucose and lactic acid in sweat by Silvers in 1928.\footnote{3} Other constituents such as ammonia, glucose, and chloride as candidate biomarkers were isolated and compared with the levels from patients by Ray and Steck.\footnote{3} Similar studies were largely targeted towards differentiating sweat composition amongst healthy subjects and patients which demanded elaborate laboratory experiments in the early twentieth century. Further detailed analysis of the composition of sweat was conducted and established by Robinson and Robinson\footnote{4} which is considered in this paper for model development. Significant interest in other biofluids such as saliva\footnote{5,6} and blood\footnote{7} has motivated the development of insilico models for these fluids using molecular modelling techniques.

However, sweat offers a distinct advantage over other biofluids for non-invasive and periodic monitoring of target analytes such as glucose. Models for blood and saliva though with limited utility in terms of predicting blood viscosity and the components and properties of saliva have demonstrated their benefits via developed insilico models. The detailed physiological mechanisms of determining eccrine sweat have been documented by Baker and Wolfe\footnote{8} in 2020, where they present that sweat composition is not only influenced by extracellular solute concentrations, but also mechanisms of secretion and/or reabsorption, sweat flow rate, by-products of sweat gland metabolism, skin surface contamination, and sebum secretions, among other factors related to methodology.
Such *insilico* models however are not present for sweat to the best of our knowledge and this work attempts to develop, validate and present the utility of an *insilico* model of eccrine sweat. The composition of sweat\(^9,10\) is well studied and the mechanism of natural sweating and iontophoresis\(^11\) is available in the literature. Microfluidic models have been explored for eccrine sweat which is imperative to the development of sensor patches and wearables to ensure high-throughput and continuous measurements for various analytes.\(^12\)

Encouraged by these factors, in terms of availability of sweat composition data as listed in Table 1, advantages of an *insilico* model for the development of biosensors, known mechanism of sweating and successful attempts with other biofluids have led us to develop an *insilico* molecular dynamic model for eccrine sweat.

**Table 1: Composition of eccrine sweat**

| Constituents    | Concentration / Molarity |
|-----------------|--------------------------|
| Cortisol        | 0.022–0.386uM            |
| Glucose         | 10–200uM                 |
| Uric Acid       | 2–10mM                   |
| Na\(^+\)        | 10–100mM                 |
| Cl\(^-\)        | 10–100mM                 |
| K\(^+\)         | 1–18.5mM                 |
| Ca\(^{++}\)     | 0.41–12.4 mM             |
| NH4             | 0.1–1 mM                 |
| Ethanol         | 2.5–22.5 mM              |
| Ascorbic Acid   | 10–50 uM                 |

This model is developed using LAMMPS molecular dynamics tool\(^13\) and presented along with validation results for diffusivity and viscosity. Furthermore, the effect of variation in temperature and concentration of electrolytes is presented as a basis for the development of *de novo* biosensors.

The purpose of modelling is to identify key experimental parameters such as transport properties to serve as an aid in the pursuit of the development of *de novo* biosensors. These parameters determine the response or output of the sensor and provide a link between the key experimental parameters and the concentration of the analyte and sensor response. Developing this *insilico* model not only aids experimentation but also gives insight into the mechanism and processes involved in the operation of the sensor.
2. Theory And Method

Human eccrine sweat is a biomarker-rich uid with well-established correlations with blood serum. The possibility of detecting these analytes via non-invasive methods using readily available sweat has been abundantly motivated. The advent of nano-biosensing combined with various electrochemistry methods and AI to interpret the results has made it possible to realize such sensors. On-going research on such point-of-care sensors is targeted towards improving their sensitivity and selectivity by testing the various bio-reception combinations of target molecules and target receptors, ensuring reproducibility, and other allied research such as microfluidics and flexible electronics.

The proposed eccrine sweat model will serve as an aid to these multiple laboratory experiments and is offered as a stand-alone application complete with GUI for fellow researchers in this field. The applications for this work will serve as a horizontal means for a broad spectrum of users for monitoring glucose and other analytes at various concentration levels and in the presence of competing / interfering species.

The authors, therefore, present the development of an insilico eccrine sweat model based on fully atomistic molecular dynamic simulation and present the validated model with available experimental and simulation data. This Matlab® based tool complete with GUI as depicted in Fig. 1 allows users to Select constituents, Input conditions (NPT / NVT), and Vary concentrations for the insilico Sweat Model and generate a LAMMPS script.

Furthermore, the general challenges with respect to sensitivity and selectivity can be studied via simulations using the proposed insilico sweat model. Similar studies have been conducted on other body fluids such as composition and properties of saliva\textsuperscript{14} and bulk properties of blood\textsuperscript{15} such as viscosity using molecular dynamics.

Users can subsequently automate this program for varying conditions, and concentrations e.g., the concentration of sodium ions to simulate dehydration and simulate the diurnal circadian cycle. Simulations with candidate substrates and receptors can be conducted to expedite the development of biosensors with larger search space and faster results as compared to experimental analysis. Furthermore, a recent study has quantified urea in sweat for diabetic patients which can be modelled using the proposed model.\textsuperscript{16}

Figure 1: LAMMPS Script Generator

However, there is no readily available insilico sweat model for simulating such studies for detecting primary constituent analytes of sweat such as electrolytes, proteins, and lipids. Our proposed model will facilitate and expedite the selection of suitable substrates, functionalizing as per the target molecule of interest and therefore improve selectivity. Studies with competing or interfering species\textsuperscript{17} too can be carried out by using such an insilico model of sweat. This presents a clear case for developing an eccrine sweat model for simulating insilico experiments.
2.1 Development of an insilico eccrine sweat model

The first step in developing a sweat model involves ensuring the appropriate composition of eccrine sweat. Most of the sweat of our body is produced via eccrine glands as compared to apocrine glands.\textsuperscript{9} The eccrine sweat glands are mainly located on the palms, soles, forehead, and armpits and also cover the rest of the body.\textsuperscript{18} Sweat secreted by these glands is primarily water and the remaining constituents, specifically significant for wearable sensing are listed in Table 2. These concentrations are further translated into the number of molecules according to their molarity. The concentrations of small molecules (< 1000 Da) such as glucose (180.156 g/mol or Da) are present in trace amounts.

Sweat is considered as a dilute water solution with NaCl as the primary solute and other analytes of interest in much smaller ratios\textsuperscript{8}. It is therefore imperative that the water model selected for this work is thoroughly validated to ensure the subsequent complex models developed will retain their accuracy. Thus, the development will have to begin with a complete molecular model of human sweat with the same composition with careful matching of the primary constituents in their appropriate concentrations as listed in Table 2.

Table 2: Molecular model constituents

| Constituents     | Molecules present in 70 x 70 x 70 Å\textsuperscript{3} volume |
|------------------|--------------------------------------------------------------|
| Water molecules  | 11465                                                        |
| Glucose          | 8 64                                                         |
| Na\textsuperscript{+} | 16 160                                                      |
| Cl\textsuperscript{−} | 16 160                                                      |

A sequential approach is considered to develop the proposed sweat model progressing from water-model to water-salt-model to water-salt-biomolecules-model such as water-salt-glucose-models, with validation at each step.

2.1.1 Various candidate Water Models and Force Fields

Since water is the major component of sweat, the suitability of candidate water models effectively determines the usability of the widely used models of water in developing the molecular model of sweat. Thus, to develop a full atomistic sweat model, various candidate water models were validated against the experimental values and established simulation results.
Water models TIP3P and SPC/E have been implemented and their effects assessed on the transport properties such as self-diffusivity. Both these empirical water models used in this simulation are similar and have three interaction sites, but with small differences in their pair potentials composed of Lennard-Jones (LJ) and Coulombic terms resulting in significant differences in the calculated self-diffusion coefficients of water.

The simple point charge extended (SPC/E) model\textsuperscript{19} for water\textsuperscript{19,20} is the more robust but simple of the many interaction models proposed for water. In this paper, a survey of both TIP3P and SPC/E model results for the self-diffusion coefficient, and the viscosity over a range of analytes and 298K and 310K temperatures are presented. This paper is the result of extensive simulations performed by the authors. Experimental values of the diffusivity and viscosity from the literature are compared with the simulated values.

The SPC/E model assumes a water molecule as a rigid molecule with an intramolecular distance of 0.1 nm between oxygen and hydrogen interaction sites (O-H distance) and with an angle of 109.47° between the O-H bonds. The intermolecular site-site interactions are defined in terms of the distances between the sites. Although these sites are commonly interpreted in terms of oxygen and hydrogen atoms, they are merely sites for atom-atom and Coulomb interactions. There are partial charges assigned to the sites to mimic an effective charge distribution of a water molecule in liquid water\textsuperscript{20}. The charge on the oxygen site is -0.8476e and the charge on the hydrogen site is 0.4238e. The SPC/E model assumes an ideal tetrahedral shape (HOH angle of 109.47°) instead of the observed angle of 104.5°.\textsuperscript{19}

The TIP3P model\textsuperscript{19} is similarly specified as a 3-site rigid water molecule with charges and Lennard-Jones parameters assigned to each of the 3 atoms. The charge on the oxygen site is -0.830e and the charge on the hydrogen site is 0.415e. The model assumes an HOH angle of 104.52°. The SHAKE algorithm was used to keep the bonds of water molecules rigid.\textsuperscript{21,22}

### 2.1.2 CHARMM36m Force Field

The force field selected was CHARMM36m\textsuperscript{23} due to its suitability for biomolecules and proven record. The present work utilizes the CHARMM36m\textsuperscript{24} force field equations. CHARMM36m all-atom additive protein force field: validation based on comparison to NMR data\textsuperscript{25}. The implementation of this force field was achieved by CHARMM - GUI\textsuperscript{26}. However, the TIP3P model was manually altered to include the SPC/E parameters for improved results. Development of a molecular dynamics model of eccrine sweat demands both validated composition and validation of transport coefficients such as diffusivity values and bulk properties such as viscosity and density along with the data in the literature both empirical and experimental with the small molecules such as glucose and sodium and chloride ions.

Generally, mass transport can occur by three processes: migration, convection, and diffusion. Migration is the movement of ions in an electric field and does not occur for neutral molecules such as Glucose, nor convection which is the bulk movement caused by external stimulus. Therefore, self-diffusion is the primary cause of the movement of the species and is considered for validation.
2.1.3 LAMMPS Molecular Modelling

All simulations were carried out using 11465 water molecules in a cubic simulation cell furnished with periodic boundary conditions at 298 K. The SHAKE algorithm was used to keep water molecule bonds rigid. We begin by packing the molecules in a 70Å x 70Å x 70Å.

The *in silico* sweat model was developed by using LAMMPS – molecular modelling tool with the above composition by developing the data file using CHARM-GUI. The composition of the various analytes is collected from the RCSB protein database. Initially, the system energy is minimized from its initial configuration using the conjugate gradient. This allows the placement of various atoms and molecules in the control volume avoiding overlap and respecting the minimum distance criterion. Post minimization, the system is equilibrated for 5ns under NPT conditions to achieve the density at 1 atm. Subsequently, the simulations are carried out at NVP for 5ns. Here, N, V, and P denote the number of atoms, volume, and pressure respectively. The choice of timestep for a biological system is based on the vibrational frequency of the individual molecules which is of the order of $10^{15}$ Hz i.e., $T = 1/f = 1$ fs.

Subsequently, these simulations are made to run for another 5ns in the production run at NPT to ensure they produce representative macroscopic values based on the statistical mechanic postulates of ergodicity i.e., the time average = ensemble average. For each composition, and temperature condition, the production phase is run for 5 ns. Atomic coordinates stored during the production phase are utilized to compute time-averaged results of static and dynamic properties such as diffusivity and viscosity at various temperatures.

2.1.4 Computation of transport properties

Water models TIP3P and SPC/E have been implemented and their effects assessed on the transport properties such as diffusivity and bulk properties such as density and viscosity to ascertain their utility.

2.1.5 Viscosity

The dynamic viscosity of the mixture/solution offers an opportunity to validate the bulk properties which are readily available both experimentally and via simulation in the literature. We compute the bulk viscosity based on the Green-Kubo formula which relates the ensemble average of the autocorrelation of the stress/pressure tensor to $\eta$. $\eta$ is a measure of the propensity of a fluid to transmit momentum in a direction perpendicular to the direction of velocity or momentum flow.

$$\eta = \frac{V}{k_B T} \int_0^\infty dt \langle P_x y(0) | P_{x'y}(t) \rangle$$

where, V is a volume of the particle system, T is a temperature, $k_B$ is the Boltzmann constant, $\langle \ldots \rangle$ is averaging over the ensemble, $P_{xy}$ is the off-diagonal element of the stress tensor.

2.1.6 Self-Diffusivity
The diffusivity of a particle indicates the pace at which the particle is transported and computed from the mean square displacement (MSD) of the particles. In Einstein’s theory, the diffusion coefficient can be calculated by using the formula:

$$D = \frac{1}{6t}\langle \sum_{i=1}^{N} r_i(t) - r_i(0) \rangle^2$$

where N is the number of particles, 0 is the reference time, $r_i$ is a radius vector of a particle.\(^{30}\)

We first compute the time average values of MSD for each ion from its trajectory stored (at regular intervals of 100 fs) in a production phase run of 5 ns. The averaged MSD vs t data of all the ions of a type from production run simulations are presented. The diffusivity of given ions and molecules is computed from the ensemble-averaged MSD vs t data and compared with literature values.

3. Results And Discussion

3.1 Validation of Viscosity

Simulations of our models (both TIP3P and SPC/E) at the same temperature 298K conditions are presented along with other literature studies in Table 3 and Table 4 to serve as a first stage validation.\(^{19}\)

Table 3: Various candidate water models

| Dynamic Viscosity of water\(^{19}\) – [mPa.s] |
|-----------------|----------------|----------------|----------------|-----------------|-----------------|
| TIP3P           | TIP4P           | TIP5P           | SPC/E           | TIP4P/2005       | Expt.           |
| 0.321           | 0.494           | 0.699           | 0.729           | 0.855           | 0.896           |

Table 4: Dynamic Viscosity for different water models

| Dynamic Viscosity at 298K [mPa s] | TIP3P Model [mPa s] | SPC/E Model [mPa s] |
|----------------------------------|---------------------|---------------------|
| Literature Values\(^{19}\)       | 0.321               | 0.729               |
| \textit{Insilico} Sweat Model    | 0.325               | 0.710               |

Both these simulations are carried out for a total production run of approx. 5ns with each timestep of 1fs with the implementation of appropriate water models namely, TIP3P and SPC/E. Since these simulations are carried out with a sufficiently large number of water molecules i.e., 11465 and for 5x10^6 steps i.e., 3ns, the results are depicted as mean values and in close agreement with the literature. The experimental values for dynamic viscosity of water are 0.89 mPa.s,\(^{22,31}\) the SPC/E model appears to be better suited
than the TIP3P model. The same is supported in the literature and scaling is suggested for using the TIP3P model.\textsuperscript{19}

### 3.2 Validation of Water Self-Diffusivity

The presented water model is developed using both TIP3P and SPC/E with parameters reported in the literature and compared with the values of self-diffusivity of water from these simulations to establish the transport properties. The values of diffusivity computed via our models namely, TIP3P and SPC/E are compared with these simulation results. The results for SPC/E water model are found to be in close agreement with experimental values found in literature.

The self-diffusion coefficient of pure water has been measured to be $2.3 \times 10^{-9} \text{ m}^2 /\text{s}$ at 298 K using the diaphragm-cell technique or the pulsed-gradient spin-echo (PGSE) NMR method.\textsuperscript{32} This validation of the water model, proven with experimental results ensures subsequent confidence in the results. Additionally, comparison with the Stokes-Einstein Eq. \textsuperscript{3}\textsuperscript{3} which has been studied for more than 100 yrs. and is the equation first derived by Einstein in his PhD thesis. This equation computes the diffusion coefficient of a “Stokes” particle at a uniform temperature assuming spherical geometry of the molecules and no micro-viscosity effects. The proposed \textit{insilico} model results are verified with the Einstein-Stokes equation, SEGWE a data-based model developed by researchers at Manchester University NMR Methodology Group\textsuperscript{25} as well as other recent available literature. The SEGWE tool developed by NMR offers improvisations and better prediction abilities using a combined analytical and data-driven approach complete with GUI.\textsuperscript{25}

Both water models TIP3P and SPC/E have been implemented and their effects assessed on the transport properties such as diffusivity and bulk properties such as density and viscosity to ascertain their utility as listed in Table 5. Since, SPC/E model values are found to be in close agreement with both experimental and simulation results from literature, this model is implemented in our work.

#### Table 5: Mean water self-diffusivity

| Water Self diffusivity at 298K – [10−9 m2 /s] |   |
|---------------------------------------------|---|
| Literature Values\textsuperscript{34}  | 2.3 |
| Insilico Sweat Model (TIP3P) | 5.64 |
| Insilico Sweat Model (SPC/E) | 2.52 |
| SEGWE\textsuperscript{25} | 2.128 |

#### 3.2.1 Validation with Glucose Diffusivity
Since glucose diffusivity values are readily available in literature both as simulations as well as experimental, it is selected as the candidate analyte. The values of glucose diffusivity are computed via molecular dynamics simulations and compared with the ones in the literature.\textsuperscript{35,36} All the experiments and simulations were conducted at 25°C and the values thus experimentally arrived at were compared with the Stokes-Einstein relation. The experimental studies presented were performed using a Spinco Model H diffusion apparatus as a Rayleigh interferometer\textsuperscript{37}. Solvent—distilled and deionized water and sugar included as per molarity of 0.1M. The values of diffusivity of glucose in water were reported as 6\times10^{-10} \text{ m}^2/\text{s}.\textsuperscript{38}

The slight variation from the Stokes-Einstein relationship\textsuperscript{33} is attributed to the non-spherical nature of the glucose molecule and the effects of microviscosity around the molecules. Since glucose is nearly spherical, these effects can be attributed to microviscosity\textsuperscript{39}.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Glucose diffusivity at 298K – 10^{-9} \text{ m}^2/\text{s} & 310K – 10^{-9} \text{ m}^2/\text{s} \\
\hline
Literature Values\textsuperscript{36} & 0.63 & 0.95 \\
\textit{Insilico} Sweat Model & 0.65 & 1.1 \\
SEGWE\textsuperscript{25} & 0.681 & 0.930 \\
\hline
\end{tabular}
\caption{Mean glucose diffusivity}
\end{table}

As can be seen from the Table 6, the SPC/E model is in close agreement with the modelling results and experimental data. The model is thus developed with water as the solvent with a proportionate number of glucose molecules. The individual biomolecules are selected from protein data bank\textsuperscript{27} and added to the water molecules from the earlier SPC/E model.

3.3 Validation with Sodium and Chloride Diffusivity

Na\textsuperscript{+} or Cl\textsuperscript{−} can be directly measured using ion-selective electrodes\textsuperscript{6,7} or electrical conductivity of the sweat can be measured, since Na\textsuperscript{+} and Cl\textsuperscript{−} are the dominantly abundant ions in sweat. These Diffusion coefficients are readily available in the literature and can be compared with the simulated results to ensure the developed \textit{insilico} model is valid.\textsuperscript{40}

These values are temperature-dependent, and a valid model will have significant utility provided all the diffusion coefficient values are in close agreement with the literature. The simulation results are in close agreement with the SEGWE values as well as the ones found in the literature.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
& & \\
\hline
\end{tabular}
\caption{Mean Sodium and Chloride Diffusivity}
\end{table}
3.4 Validation at elevated temperatures and varying concentrations

Subsequently, the *in-silico* sweat model is rigorously validated at elevated temperatures and varying salt concentrations to simulate disease/fever conditions and dehydration in subjects is presented in Table 8.

Table 8: Mean diffusivity of species at 310K

| Comparison of values at 310K – Literature and *in silico* model |
|---------------------------------------------------------------|
|                                | Literature / SEGWE  | *in silico* Sweat Model |
| Water Viscosity [mPa s]        | 0.6                | 0.6942                  |
| Glucose Diff. [10^{-9} m^2 /s] | 0.93               | 1.1                     |
| Sodium [10^{-9} m^2 /s]        | 2.54               | 1.5                     |
| Chloride [10^{-9} m^2 /s]      | 2.032              | 1.65                    |
| Water [10^{-9} m^2 /s]         | 2.906              | 3.4                     |

The salt concentration is varied from 10-100mM as per the range of conditions expected in normal to dehydrated subjects and their variation in diffusivity presented in Table 9.

Table 9: Mean diffusivity at various concentrations
4. Summary

The *insilico* sweat model is presented as a validated tool to assist in the development of various biosensors such as the ones to detect glucose and other target analytes. This LAMMPS-based tool is made available for fellow researchers to simulate different conditions such as temperature and concentration of salt. The slight variation in the values for diffusivity of glucose in water with various salt concentrations can be attributed to the micro-viscosity changes in the fluid. Additionally, the Stokes-Einstein equation assumes glucose to be a spherical molecule and neglects the micro-viscosity variations. The number of molecules of glucose is significantly less as compared to the salt ions and therefore the computed diffusivity may not have the averaging advantage. The available viscosity and diffusivity literature values via empirical equations and experiments for varying values of salt concentrations and temperatures nevertheless agree with the proposed *insilico* model and therefore can be considered as a prospective tool for further research in this direction.

Declarations

Data availability statement

The data and *insilico* sweat model tool developed that support this study are available upon reasonable request from the authors.

Ethics Statement

The entire data presented in this publication is simulated data and no human/animal tests were conducted.

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41. Diffusion coefficients of various substances in Water.

**Figures**

![CortisolInput](image)

**Figure 1**
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