

Abstract of “Biomechanistic and Bioinformatic Modeling for Diabetes” by Yixiang Deng, Ph.D., Brown University, February 2022.

This dissertation focuses on biomechanistic and bioinformatic modeling of diabetes. Specifically, it is expanded on four fronts:

1) Quantification of fibrinogen-dependent red blood cells adhesion. On this front, I integrate companion microfluidic experiments that provide *in vitro* quantitative information on cell-cell adhesive dynamics, to quantify the rouleau dissociation dynamics using dissipative particle dynamics.

2) Blood cells dynamics in coagulation cascade in normal and diabetic blood. I develop a computational framework that is able to integrate seamlessly four key components of blood clotting, namely transport of coagulation factors, coagulation kinetics, blood cell mechanics and platelet adhesive dynamics, to model the development of thrombi under physiologic conditions and type 2 diabetes.

3) Short-term glucose prediction and long-term hypoglycemia detection. I develop deep learning methods to predict patient-specific blood glucose during various time horizons in the immediate future using patient-specific every 30-min long glucose measurements by the continuous glucose monitoring (CGM) to predict future glucose levels in 5 minutes to 1 hour. For long-term hypoglycemia detection, I utilize multi-view machine learning algorithms to improve accuracy and sensitivity. In both tasks, we are faced with challenges of small dataset and data imbalance, which is commonly seen in real-world data, especially medical data. I will talk about our strategies to tackle the problems.

4) Artificial pancreas design using offline reinforcement learning. I present a novel framework which combines three key components to automating insulin dosage for patients with type 1 diabetes. These important components are a real-world historical medical dataset, a flexible ODEs model defining glucose-insulin dynamics and a offline reinforcement learning algorithm, which is capable of optimizing insulin dosage without interaction with the target environment.

Biomechanistic and Bioinformatic Modeling for Diabetes

by

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This dissertation by Yixiang Deng is accepted in its present form by
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Vita

Yixiang Deng was born to Zengxian Deng and Zhonglan Wen in 1994 in Ganzhou City, Jiangxi Province, China. She completed her Bachelor of Engineering degree in Engineering Mechanics in June 2015 at Shanghai Jiao Tong University in Shanghai, China. She then moved to Providence, Rhode Island, to pursue a Master of Science degree in the School of Engineering at Brown University in August 2015, where she switched to the doctoral track in 2016, obtained a Master of Science degree in Engineering in 2017, and a Master of Science degree in Applied Mathematics in 2019.

Yixiang's interest in engineering is highly motivated by her mother, who is a civil engineer and her father, who was a high school physics teacher. Ever since middle school, she determined to major in engineering for her undergraduate study. At Shanghai Jiao Tong University, she was given the opportunity to lead an undergraduate research project in her junior year under the supervisory of Professor Jubing Chen on measuring the mechanical property of steels with different cross sectional shapes through experiments. She then found stronger interest in computational fluid dynamics during her bachelor's thesis advised by Professor Jiasong Wang on the fluid-structure interaction of a moving cylinder under pulsatile flows using finite difference method.

At Brown University, Yixiang worked under the mentorship of Professor George Em Karniadakis, who is a renown scientist in the field of computational fluid dynamics

and applied mathematics. Besides modeling the biomechanistic phenomena of the diseased blood, she applied bioinformatic knowledge, specifically machine learning algorithms, on real-world medical datasets to assist patient-specific diagnosis and treatments.

In addition, Yixiang has been a head teaching assistant for two introductory courses for engineering: Introduction to Engineering (Fall 2017) and Dynamics and Vibrations (Spring 2018). She has also been actively participating in conference presentations and female researcher networking events. In 2020, she joined the U.S. Association for Computational Mechanics-Female Research Group (USACM-FRG) as a committee member.

Publications

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Chapter 1

Introduction

1.1 Background and Motivations

Diabetes, a metabolic disease characterized by chronically elevated blood glucose levels, affects about 29 million Americans and more than 422 million adults all over the world. It is recognized as the world's fastest growing chronic disease [177], among which type 2 diabetes (T2D) accounts for 90-95% of the vascular diseases cases and its prevalence is increasing due to the rising obesity rates in modern societies. People with T2D demonstrate significantly higher mortality rates mainly due to elevated risks of macrovascular diseases, like ischemic heart disease, stroke and peripheral artery disease [48]. In addition, T2D is associated with many microvascular diseases, like retinopathy, nephropathy and neuropathy [58], which result from the persistent hyperglycemia (usually defined using a threshold of glucose level above 180 mg/dL).

To prevent of adverse effects of hyperglycemia, patients with T2D are often prescribed with glucose-lowering drugs, such as insulin injection and metformin. While metformin improves hyperglycemia mainly through the suppression of hepatic gluconeogenesis along with the improvement of insulin signaling [7], direct injection of

insulin through needles or pumps lowers glucose due to insufficient secretion of insulin from patient's pancreas. Although these two drugs have demonstrated their efficacy on reducing the glucose level, patients under these two drug treatments experience some side effects. For example, patients may suffer from undesired low blood glucose below 70 mg/dL, namely hypoglycemia, once the dosage of the medication goes beyond need. Severe hypoglycemia has been linked to focal neurological deficits and transient ischemic attacks, which are reversible with the correction of blood glucose [58].

Hypoglycemia indirectly changes inflammatory cytokine secretion, endothelial function, coagulation, and fibrinolysis in patient's body, all of which may increase the risk of developing cardiovascular diseases [6]. Hypoglycemia also induces abnormalities in platelet function and activation of the fibrinolytic system [58]. Increased epinephrine levels lead to an increase in platelet activation, leukocyte mobilization, and blood coagulability. Recent studies suggest that endothelial function may be compromised during acute hypoglycemia leading to increased vessel wall thickness during hypoglycemia in patients with type 1 diabetes of longer duration than those with a shorter duration of diabetes [58]. Hence, inflammation, blood component, and functional abnormalities and endothelial dysfunction in diabetic patients are closely interdependent and a systematical analysis of these factors needs to be performed to improve our understanding on the pathophysiology of T2D . These abnormalities could potentially be aggravating factors to the subset of patients with preexisting conditions, such as cardiovascular diseases, longer duration of diabetes, and severe autonomic neuropathy. However, most of existing literature focus on short-duration acute observations and the long-term effects of hypoglycemia on inflammation, coagulation, and endothelial dysfunction are not well studied and demand further investigation [58]. The increased risk of cardiovascular (CVD) and cerebrovascular

diseases (CeVD) in T2D is based on some unique properties that demonstrate people with T2D, such as (1) accelerated atherosclerosis with increased plaque vulnerability [81, 29], (2) blood alterations affecting hemorheological properties, blood clot formation, structure and stability [108], (3) involvement of microcirculation in the pathogenesis of CVD and CeVD [156]. For these reasons, T2D is considered today a CVD equivalent because of its importance in this respect. Since patients with T2D are linked with increased risk of developing thrombotic events, understanding the microscale mechanisms of thrombus formation in patients with T2D is of great significance to design efficient anti-clotting medications.

In the current clinical practise, achieving good glycemic control is still the main goal given the benefit of increasing survival rate and improving quality of life [51, 58]. Thus, accurate prediction of blood glucose variations and, in particular, hypoglycemic events is of paramount importance to avoid potential detrimental complications and adjust the therapeutic strategy in a more optimized and personalized treatment strategy for patients with T2D. To this end, well designed predictive models with high sensitivity and accuracy, which are easy to implement, may facilitate glycemic control, decrease the occurrence of hypoglycemic episodes or related complications and increase the quality of life of T2D patients. Of note, due to the complexity of the blood glucose dynamics, the design of pure physiological models that produce an accurate prediction under different circumstances, i.e., hypo/normo/hyperglycemic events, is a challenging task.

The ultimate goal of this thesis is to provide a framework, which bridges the information gap between biomechanics and bioinformatics emphasizing on the diabetes research. To achieve this goal, efforts in two different pathways were accomplished. For one thing, I establish a framework for modeling the complicated cell-cell interaction and cell-fluid interaction in the diabetic blood flow in comparison to those in the

normal blood, see Chapter 2. On the other hand, I need to utilize the power of data-driven algorithms and combine them with the physiological knowledge, to design the digital twin of glucose-insulin systems and eventually create patient-specific models informative to diabetic diagnosis, see Chapter 3.

1.2 Biomechanistic Modeling

Compared to normal people, patients with T2D are at higher risk for developing micro- and macrovascular complications induced by chronic inflammations in the blood vessels. Hence, understanding the microscale mechanisms of persistent inflammation in patients with T2D is of great significance to the diagnosis of patients' condition and the design of efficient anti-inflammation medications. Prior studies identified that multiple factors induced by T2D contribute to the prothrombotic status, such as elevated coagulation, impaired fibrinolysis, endothelial dysfunction and platelet hyperreactivity [95, 5, 82]. Recent studies further demonstrated that altered morphology and biomechanics of RBCs and platelets in diabetic blood lead to enhanced platelet margination [32] and abnormal hemorheology [31], both of which potentially aggravate the platelet aggregation and thrombus formation. In particular, T2D RBCs are less deformable than normal RBCs [265, 127, 20, 3, 11], leading to a blood viscosity up to approximately 20% higher than normal samples [169]. However, there is a lack of quantitative studies on how the pathophysiological alterations of the RBCs and platelets contribute to the prothrombotic status in T2D. In addition, numerous experimental and computational studies have been devoted to the understanding of the aggregation dynamics of RBCs under physiologic and pathophysiological conditions, but the adhesion and aggregation dynamics of T2D RBCs are still not well studied. To address this challenge, I quantify the role of the T2D

RBCs adhesion in thrombus development in Chapter 2.1.

In Chapter 2.2, I develop a computational framework that is able to integrate seamlessly four key components of blood clotting, namely transport of coagulation factors, coagulation kinetics, blood cell mechanics and platelet adhesive dynamics, to model the development of thrombi under physiologic conditions and T2D. This framework has the capability to consider not only the well-known factors that contribute to the prothrombotic state in T2D, such as elevated coagulation, impaired fibrinolysis, endothelial dysfunction, but also the effect of the adhesion and aggregation dynamics of T2D RBCs that required further study. An important feature of this proposed framework is that each of its components can be refined by future experimental studies to improve the accuracy and capability of the model predictions. Therefore, this framework can be potentially extended to model more complicated vascular systems and geometries and make predictions based on organ-specific flow conditions and patient-specific blood coagulation factors. As the proposed framework is capable of dissecting complex conditions when multiple factors play a role in triggering thrombosis in blood circulation, it also can be potentially used to identify the key factors in thrombus formation and test the efficacy of anti-thrombosis drugs, thereby accelerating the development of thrombosis medication.

1.3 Bioinformatic Modeling

Recent advances in artificial intelligence, especially the development of deep neural networks provide researchers the opportunity to uncover more sophisticated features beneath the abundant medical data. Current efforts at developing deep learning decision-support algorithms for the diagnosis of diabetes comprise identification of

diabetic retinopathy based on retinal fundus photographs [99], risk prediction on diabetes using electronic medical records [199, 40] and prediction of future blood glucose level using glucose level records from continuous glucose monitors [163, 162]. Despite the promising results obtained using deep neural network, there remain several challenges in the clinical application of deep learning to health care [181]. In particular, researchers need to pay attention to data volume and data quality because health care data are highly heterogeneous, ambiguous, noisy and incomplete. Other factors regarding the design of algorithm part include domain knowledge and interpretability. Although deep learning is well known for its capability of representation for high dimensional data, domain knowledge in diabetes is still indispensable for designing the network architectures and understanding the network output, which further improve the interpretability of deep neural networks.

Maintaining a glucose level within the range of 70 mg/dL and 180 mg/dL in patients with diabetes is a challenging task because numerous factors can directly affect blood glucose (BG) levels, among which the history of BG values, insulin, physical exercises, and dietary intakes are the prominent ones. This complicated multi-factorial interaction has made glycemic stability hard to maintain. Despite extensive knowledge of the damage of hyperglycemia and the passage of 23 years since the Diabetes Control and Complications Trial (DCCT), glycemic control levels in the U.S. remain suboptimal [139]. The reason for glycemic control goals not being achieved varies from individual to individual. However, a general fact is that the tools today do not easily allow for the normalization of glycemia for some patients. With precise prediction of future glucose level, physicians may be able to adjust treatments dynamically by advising on the carbon-hydrate consumption, dosage of glucose-lowering drugs and the amount of physical exercises. Recent work in BG prediction using machine learning is increasing rapidly, including traditional machine

learning methods (e.g., auto-regression with exogenous input (ARX) [250], support vector machines (SVM) [221], Gaussian process (GP) [226], and ensemble methods [187]), as well as deep learning approaches (e.g., feed-forward neural networks (FNNs), recurrent neural networks (RNNs), and convolutional neural networks (CNNs)).

In Chapter 3.1, I approach BG prediction in purely data-driven manner using past BG glucose history as the model input. Specifically, I propose specially designed neural network architectures for temporal BG data to tackle the challenges like data scarcity and data imbalance observed in clinical data. These two challenges are very commonly observed in medical dataset and especially when faced with the need of patient-specific diagnosis and treatments. Additionally, there is also substantial evidence that a healthy lifestyle, including following a healthy diet, achieving modest weight loss, and performing regular physical activity can maintain healthy blood glucose levels and reduce the risk of complications of type 2 diabetes [41]. To address this need, I develop machine learning algorithms for the long term hypoglycemia risk prediction, through feature extraction on the unstructured medical data. In Chapter 3.2, in complementary to the aforementioned purely data-driven model, I analyze the dynamical interactions between glucose and other dependent factors, like meal intake, insulin level and exercise, through the combination of physiological knowledge and deep learning methods. Specifically, I design a neural network-based agent to automate insulin infusion dosage to maintain the glucose stability.

Chapter 2

Part I: Biomechanistic Modeling

2.1 Fibrinogen-dependent red blood cell aggregation in type 2 diabetes

Manuscript information

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Author contributions: Y.D., D.P.P., X.L., N.P., C.S.M., M.D. and G.E.K. designed research. Y.D. carried out all the computational simulations. D.P.P. performed the microfluidic experiments. N.P. and C.S.M. collected the clinical information and samples, provided the blood samples for the study and performed biochemical measurements. X.L., M.D., C.S.M. and G.E.K. contributed new reagents/analysis tools. Y.D., D.P.P., X.L., M.D. and G.E.K. analyzed data. All authors contributed to writing the paper.

2.1.1 Introduction

Type 2 diabetes mellitus (T2DM) is characterized by relative insulin deficiency caused by pancreatic cell dysfunction and insulin resistance in target organs [33]. Patients with T2DM usually suffer from elevated blood glucose and glycated hemoglobin (hemoglobin A1c, HbA1c) level, which are important predictors of the risk of development for several microvascular complications, e.g., diabetic retinopathy [38, 24] and diabetic peripheral nephropathy [267, 53, 121]. Currently, it is understood that the impaired blood circulation of T2DM patients is a multifactorial event mainly due to endothelial dysfunction [176], platelet hyperreactivity [236, 218, 234] and red blood cell (RBC) hyperaggregability [214, 179]. Under physiological condition, the linear stacking of RBCs forming a chain-like structure, namely rouleau, is a reversible process that occurs in low-speed blood flow [78]. For metabolically healthy but obese patients, obesity is believed to be correlated with increased RBC aggregation [247, 27, 243]. Under pathological condition like T2DM, RBC hyperaggregability leads to enhanced rouleau formation [44] in patient's blood, causing blood hyperviscosity in capillaries [14, 39] and low oxygen levels in tissues [147].

The impaired blood circulation due to the enduring rouleau structures and altered RBC membrane property is undoubtedly a risk for the functionality of organs. Hence, understanding the blood cell dysfunction and quantifying fibrinogen-dependent RBC aggregation dynamics under normal or disturbed metabolism, is of fundamental importance in diabetic research [237]. It is recognized that both the concentration level of plasma fibrinogen and that of dextran are dominant factors in the rouleaux formation. The fibrinogen molecule is considered to be the major plasma protein promoting RBC rouleau formation [141], and the synthetic polymer dextran can also promote

the formation of RBC aggregates [36, 28, 84, 189]. Several studies have been conducted to explore the RBC-RBC aggregation strength using different *in vitro* flow experiments [216, 148]. For example, Chien et al. performed experiments in a flow channel to find that a 50% separation of 2-cell rouleau (doublet) suspended in dextran solution occurs at a critical shear stress of 0.25 ± 0.01 dyn/cm² [36]. Samocha-Bonet et al. visualized the aggregation process of RBCs suspended in autologous plasma or dextran-500 kPa for obese and non-obese patients, respectively, under controllable shear stress in a flow chamber [212]. They showed that plasma of obese patients is a powerful stimulator to RBC aggregation, producing large clusters of aggregates that were resistant to dispersion by flow and concluded that among the plasma components, fibrinogen is a well-characterized RBC aggregation inducer that bridges between RBCs. Several groups have also utilized optical tweezers (OT) to study the RBC aggregation and disaggregation dynamics in plasma and protein solutions [25, 149, 9]. They found that the critical detachment force required to fully separate the RBC doublets ranges from 10 pN to 20 pN [149]. In addition, Avsievich et al. employed OT to investigate the dynamics of rouleau formation in dextran and fibrinogen solutions. They found that these two polymers present distinct aggregation mechanisms in the RBC aggregation dynamics [10]. Atomic force microscopy (AFM) has also been used to investigate the aggregation properties of RBCs. For example, Steffen et al. applied AFM to determine the effect of dextran concentration on the interaction energy of RBC doublets [219]. They measured the interaction forces varied from 14 pN to 23 pN for dextran 70 and from 43 pN to 169 pN for dextran 150. Guedes et al. conducted AFM-based experiments on RBC doublets for patients with essential arterial hypertension (EAH) in plasma solution. They found that the critical force required to fully breakup the RBC doublets from EAH patient's blood is approximately 180 pN, which is about twice as much as those of the healthy RBC

doublets [97, 98].

Along with the experimental studies, recent advances in computational modeling and simulations have also contributed to the understanding of the aggregation dynamics of RBCs under physiological and pathological conditions [248, 249, 84, 264, 263, 78, 79, 251]. For example, Xiao et al. employed dissipative particle dynamics (DPD) to simulate the deformation and aggregation of healthy RBC doublets [248] and their effects on the blood flow dynamics in stenosed microvessels [249]. They found that the blood flow resistance decreases with the increased intercellular interactions when the RBC doublets passed through the stenosis. Flormann et al. carried out numerical simulations and developed theoretical models to characterize the interaction energy of RBC doublets. They found that the RBC doublet deformation increases nonlinearly with the interaction energy [84]. Some researchers also investigated the dynamics of rouleau formation under diseased states. For example, Ye et al. showed that the malaria-infected RBC doublets become harder to be separated with the increase of capillary number [264]. They also showed that both the cell deformation and cell-cell aggregation interaction can affect the trajectory of RBC doublets in microvascular bifurcations [263]. Fedosov et al. employed a multiscale RBC (MS-RBC) model to investigate the effect of cell-cell aggregation interaction on blood viscosity at different shear rate [78]. They identified that the types and sizes of RBC rouleau structures can yield a significant increase of blood viscosity at low shear rates. They also systematically studied the shapes of RBC doublets under different adhesion strength and shear elasticity [112]. They found that the adhesion strength and membrane properties play key roles in determining the doublet phases.

Despite these aforementioned findings, many important aspects of aggregation dynamics of diseased RBCs are still poorly understood. It is known that the RBC deformability and aggregation properties are altered in T2DM blood, but individual

patients with T2DM have a highly variable clinical phenotype. For this reason, there is a compelling need to develop a predictive *patient-specific* RBC model to quantify the aggregation and disaggregation dynamics of RBCs in T2DM. Such a model would provide a more reliable method and an overall modeling framework to extract aggregation properties of T2DM RBCs from a variety of independent experimental methods. In this work, we aim to first establish patient-specific RBC models that invoke key parameters derived from microfluidic experiments, and subsequently to investigate the fibrinogen-dependent aggregation dynamics of T2DM RBCs through patient-specific computational simulations. To build such multiscale patient-specific models we develop a workflow that incorporates useful experimental data and utilizes simulations as a surrogate tool for quantitative investigations of cell mechanical and rheological properties whereas some critical parameters cannot be provided directly by microfluidics, AFM or OT experiments (i.e., these physical parameters can only be inferred through a simulation model closely following the experimental set up). The motivation for the present work is to demonstrate that by incorporating the data from experiments and simulations, our predictive computational model could be employed to quantify patient-specific and fibrinogen-dependent RBC aggregation dynamics. Specifically, we quantify the fibrinogen-dependent aggregation of RBCs from six patients with disparate severity of metabolic syndrome and T2DM (i.e., three patients with T2DM and the other three patients without T2DM, marked by distinct plasma fibrinogen concentrations, see Table 2.1), through patient-specific predictive computational simulations that invoke key parameters derived from *in vitro* microfluidic experiments. We note that these six patients are obese, indicated by their body mass indices (BMIs) and metabolic parameters in Table A.1. In the microfluidic experiments, we employed a microfluidic device consisting of an ordered array

of microgates that mimic the structure and characteristics of microvascular capillaries [63, 164, 194]. In the numerical simulations, we combined previously validated MS-RBC model for RBCs in T2DM patients [31, 32] and in obese patients with cell-cell aggregation model to capture the functional dependence of doublet breakup force on fibrinogen concentration in Refs. [97, 149].

Motivated by the phenomenon that patients exhibit heterogeneous distribution of rouleau length¹, see Fig. 2.1, we hypothesize that every patient's blood sample may have different levels of RBC aggregation strength, whose distribution can be inferred from the rouleau length distribution observed under controlled flow condition. based on this hypothesis, we first quantify the cell-cell adhesion strength through matching the experimental measured detachment forces required to separate RBC doublets under different fibrinogen concentration [97, 149]. Then, informed by our companion *in vitro* microfluidic experiments, we perform numerical simulations to study the traversal of patient-specific RBC doublets through microgates. We compare the simulated RBC doublet dissociation rate (the number of RBC doublets broken apart over the total number of RBC doublets observed in the region of interest (ROI)) with those obtained in microfluidic experiments. Next, using the calibrated parameters we present some additional simulations to probe the cell-cell detachment dynamics of the RBC rouleaux with chain-like structures under different inclination angle to the overall flow direction.

¹Rouleau length denotes the number of RBCs in the rouleau.

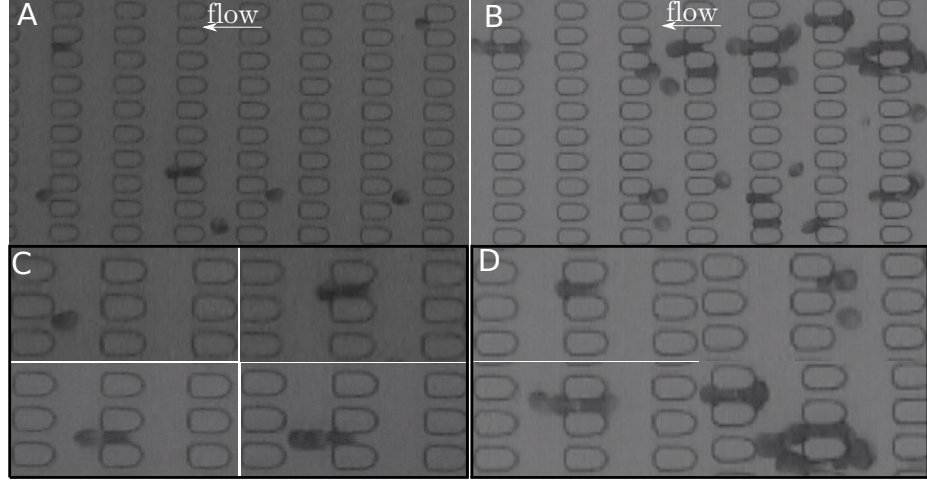


Figure 2.1: **Rouleau structures inside the microfluidic device** for (A) patient II (no T2DM) and (B) patient V (poorly-controlled T2DM). Zoomed-in rouleau structures of different lengths (C) for patient II, which are a singlet (upper left), a doublet (upper right and lower left) and a triplet (lower right), and (D) for patient V, which are a singlet (upper left), a doublet with a singlet (upper right) and several multiplets (lower left and lower right). See Movie S1 for patient II and Movie S2 for patient V in Ref. [57], see Table 2.1 for patients' medical information.

2.1.2 Methods

Experimental data

Subject recruitment, blood sample preparation and biochemical measurements. All studies involving human blood were approved by the institutional review board (IRB) of the Beth Israel Deaconess Medical Center (BIDMC) and the Massachusetts Institute of Technology (MIT). Blood samples from six obese patients were collected for this study at BIDMC. Patients were selected with different chronic glucose conditions, i.e., three without T2DM and $\text{HbA1c} < 6\%$ (Subject I, II and III) and three diagnosed with T2DM and $\text{HbA1c} \geq 6\%$ (Subject IV, V and VI). Plasma fibrinogen concentration level for each patient was measured with the Enzyme-linked Immunosorbent Assay (Abcam, Burlingame, CA, USA). In general, patients with T2DM have high levels of plasma fibrinogen compared with those without T2DM,

which is consistent with the observations in [167]. A detailed lab report is shown in Table 2.1 and see Table A.1 in Appendix A.1 for patients' metabolism measurements including medications.

All blood samples were collected into separate 4 mL K2-ethylenediaminetetraacetic acid (EDTA) spray-coated anticoagulant vacutainers (7.2 mg/4 mL). De-identified samples were transferred to MIT within three hours of blood draw, and were processed immediately. Following whole blood density gradient centrifugation at 820 Relative Centrifugal Force (RCF or $\times g$, where g stands for gravitational force) for 5 min, the blood plasma was removed and kept in a separate tube; also, the buffy coat was removed and discarded. To remove the anticoagulant, packed RBCs (pRBCs) were washed twice for 5 minutes under centrifugation. The RBCs were then re-suspended in autologous plasma giving a hematocrit at 2-3%. Low retention pipette tips were used throughout blood processing.

Patient ID	I	II	III	IV	V	VI
Info.	Obese	Obese	Obese, HBP, HLD	Obese, T2DM	Obese, T2DM, HBP	Obese, T2DM, HBP, HLD
Hb1Ac, g/dL	5.8	5.3	5.5	6.2	8.6	6.9
Fibrinogen, mg/mL	4.656	2.641	3.114	3.373	5.122	3.985
Hb, g/dL	15.2	17.8	14.1	11.9	14.5	12.7
HCT, %	44.6	50.3	39.8	39.3	43.5	39.1
RBC, $\times 10^6$ count/ μ l	4.97	5.52	4.38	5.72	4.96	4.51
WBC, $\times 10^3$ count/ μ l	8.8	5.4	4.9	6.7	6.1	4.7
MCV, fL	90	91	91	69	88	87
MCH, pg	30.6	32.3	20.8	29.2	29.2	28.2
MCHC, g/dL	34.1	35.4	35.4	30.3	33.3	32.5
RDW, %	13.5	13.0	13.4	17.0	13.5	14.2

Table 2.1: Complete Blood Count (CBC) Analysis and the ELISA Test Results. HbA1c, glycated hemoglobin; Hb, total hemoglobin; HCT, hematocrit; RBC, red blood cell count; WBC, white blood cell count; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; HBP, hypertension and HLD, hyperlipidemia.

Microfluidic experiments. To study the rouleau dynamics under flow, we

conducted experiments within microfluidic devices, see Fig. 2.2(A). In brief, the devices comprise a free-standing gas-permeable polydimethylsiloxane (PDMS) membrane ($H_{\text{PDMS}} = 150 \mu\text{m}$) within a dual-layer microchannel construction. The dual-layer device consists of a “flow microchannel” in which there is flow of RBC suspension and a “gas microchannel” in a cross configuration. In this work, we only utilized the flow microchannel, which is 3 mm in length and 1.326 mm in width, and is connected to in-line pressure and flow sensors. The flow microchannel consists of periodic obstacles with 15- μm -long, 4- μm -wide and 5- μm -high microgates (marked in Fig. 2.2(A)), mimicking the mechanical challenges RBCs encounter when passing through the smallest capillaries or spleen slits in the human body [63, 194]. Before being filled with the RBC/plasma suspension, the microfluidic device was degassed for a minimum of 10 min to prevent trapping of air bubbles.

Microfluidic device imaging was performed using Zeiss Axiovert 200 (Zeiss, Oberkochen, Germany) and Olympus IX71 inverted microscopes (Olympus, Tokyo, Japan). The Hitachi KP-D20A (Hitachi, Tokyo, Japan) charge-coupled device and the Olympus DP72 cameras (Olympus, Tokyo, Japan) were used for image acquisition. All testing was performed at 37 °C using the ibidi Heating System (ibidi USA, Fitchburg, WI) as a heating incubator.

Simulation models and methods

RBC models. In order to investigate the mechanical, rheological and dynamic properties of RBCs at different length scales, we have developed a unified multiscale modeling framework based on dissipative particle dynamics (DPD) [200, 77, 197]. Specifically, the membrane of RBC was modeled by a two-dimensional triangulated network with N_v vertices connected by N_s edges and N_t triangles. With the help of the MS-RBC models, we have conducted a variety of simulations to probe a broad

range of mechanical and rheological problems associated with RBCs under normal and pathological conditions including T2DM [78, 75, 152, 164, 161, 56]. Following our prior simulations on T2DM RBCs [31, 32], we performed simulations with two types of MS-RBC models: one characterized the morphological and mechanical properties of normal RBC (N-RBC) and the other mimicked those of T2DM RBCs (D-RBCs) (Fig. 2.2(B)). Both the N-RBC and D-RBC maintained similar cell surface area $A_0^N = A_0^D = 132.9 \mu\text{m}^2$ but had different morphological characteristics; the N-RBC in a static condition was characterized by a biconcave shape with cell volume $V_0^N = 92.5 \mu\text{m}^3$, whereas the D-RBC was characterized by a more oblate shape with cell volume $V_0^D = 127.4 \mu\text{m}^3$. Specifically, the N-RBC was modeled with shear modulus $\mu_0^N = 4.73 \mu\text{N/m}$ and bending rigidity $k_0^N = 2.4 \times 10^{-19} \text{ J}$, while the D-RBC with shear modulus $\mu_0^D = 2\mu_0^N$, considering the decreased RBC deformability in diabetics [233, 214] and bending rigidity $k_0^D = k_0^N$. Detailed formulas for pairwise interaction potentials to maintain the morphology and mechanical property of RBCs can be found in the Appendix A.1. In this study, we extended these two MS-RBC models and investigated the (dis)aggregation dynamics of T2DM RBCs. In most simulations, we have used $N_v = 500$, a coarse-grained RBC model which has been employed to conduct efficient simulations of RBCs in microcirculation. For comparison, we also considered a much finer MS-RBC model with $N_v = 2000$. An example of simulation snapshot in this study is shown in Fig. 2.2(C).

Cell-cell interaction models. The aggregation interaction between RBCs plays a major role in determining the size and shape of the RBC aggregates. As suggested by Fedosov et al. [78], we employed the Morse potential to model fibrinogen-dependent intercellular aggregation interactions. The Morse potential reads

$$U_M(r) = D_0[e^{2\beta(r_0-r)} - 2e^{\beta(r_0-r)}], \quad (2.1)$$

where D_0 denotes the depth of the potential well, e is the base of the natural logarithm, r denotes the distance between two vertices, r_0 represents zero force distance and β represents a distance scaling constant. Specifically, the Morse potential is imposed on a specific type of vertices, called “interactive vertices” represented by the blue vertices in Fig. 2.2(D). In addition, we imposed the repulsive term of the Lennard-Jones potential on the membrane vertices to prevent the RBC membranes from overlapping. The corresponding potential is given by

$$U_{LJ}(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6\right], \quad (r \leq r_{LJ}) \quad (2.2)$$

where r_{LJ} is the cutoff distance, and ϵ and σ are scaling constants for energy and distance, respectively. Detailed model parameters can be found in the Appendix A.1.

Fibrinogen concentration dependent RBC models. To construct RBC models that reflect the different levels of cell-cell adhesion strength, we adopted the hypothesis that rouleau formation is mainly due to “cross-bridging” effect created by the binding of each end of a fibrinogen molecule to two different RBCs [13]. In the “cross-bridging” hypothesis, the pair-wise connection (the bridges) strength between “interactive vertices” is considered to be a fixed value, and hence more established bridges between two different cells will lead to stronger adhesion between cells. The adhesion strength of each bridge is mainly correlated with the parameter D_0 in Eq. (2.1) in our cell-cell interaction model. In addition, Lominadze and Dean showed the existence of fibrinogen specific binding to the RBC membrane surface and their results implied that the number of total bindings is positively correlated with the concentrations of human plasma fibrinogen within a certain range of fibrinogen concentration level. Herein, we varied the percentage of the “interactive vertices” corresponding to equivalent different fibrinogen concentration levels to describe the

different levels of rouleau adhesion strength, i.e., low, medium and high level, of rouleau adhesion strength, see Fig. 2.2(D). These RBC models were later modified to characterize patient-specific RBCs in simulations. We note that the geometry and arrangement of the microgates in the simulations followed those in companion experiments as shown in Fig. 2.2(A). The dimensions of the simulation domain is $180\ \mu\text{m}$ in length, $60\ \mu\text{m}$ in width and $12\ \mu\text{m}$ in length. Periodic boundary conditions were applied in x and y directions, whereas the flow was bounded by solid walls in z direction. In all simulations, the solid walls were modeled by freezing layers of particles with bounce-back reflection to satisfy the no-slip boundary condition [203]. An external body force was exerted on all fluid particles and RBCs along the x direction to generate a flow in the microchannel.

2.1.3 Results and discussion

In this study, we aim to establish patient-specific RBC models, and simulate the dynamics of patient-specific rouleaux at doublet and multiplet level. Specifically, we seamlessly integrate experimental data from both existing literature and our own microfluidic experiments following the flow chart shown in Fig. 2.3. At the “Input” stage, we first quantify the parameters in our cell-cell adhesive interaction model, most importantly, the coefficient D_0 in the Morse potential, through benchmark simulations mimicking AFM and OT experiments by other researchers. Second, we construct the flow field in our simulations such that the single RBC velocity in simulations matches that in our experiments; consequently, we obtain the relationship between driving pressure gradient and cell velocity. Third, we analyze the dynamics of rouleaux in our microfluidic experiments from different patients’ blood samples and build patient-specific RBC models accordingly. At the “Inference” stage, we

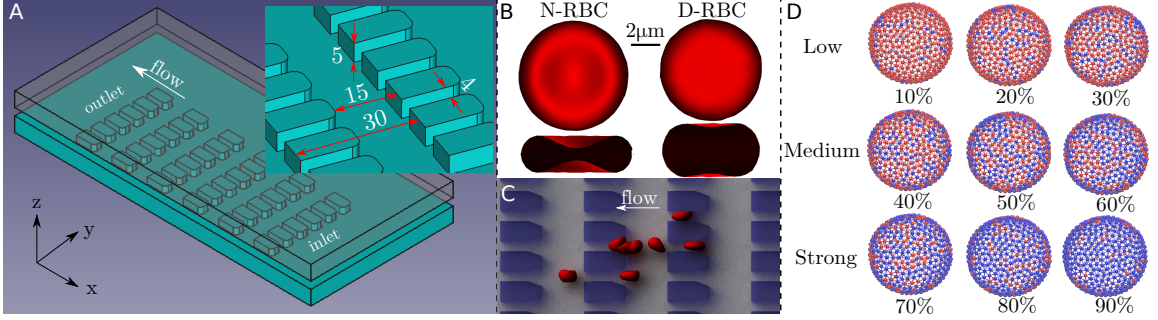


Figure 2.2: Overview of the simulation setup. (A) Schematic representation of the microfluidic device with periodic obstructions. Schematics are not drawn in scale and the dimensions are in microns. (B) Schematic of a normal (healthy) RBC (N-RBC) and type 2 diabetes mellitus RBC (D-RBC) models. N-RBC in equilibrium maintains a biconcave shape with surface to volume ratio, $S/V = 1.44$, while D-RBC maintains a more oblate shape with $S/V = 1.04$. (C) Simulation snapshot of T2DM rouleau breakup when passing through microgates under flow. (D) Cell-cell interaction model, which simulates the fibrinogen concentration dependent cell-cell interaction strength. Blue vertices denote “interactive vertices” (IVs) responsible for attractive interactions with vertices of the same type on other RBCs, while red vertices do not exhibit attractive interactions. Numbers below each cell represent the ratio (in percentage scale) of the number of IVs over the total number of vertices on the membrane. Based on the ratio, models are divided into three groups, i.e., low, medium and strong group, simulating cell-cell adhesive interactions with low, medium and strong aggregation strength, respectively, and implicitly address low, medium and high fibrinogen concentration level, respectively.

incorporate the “Model” parameters for simulations of rouleau dynamics inside the microfluidic device. First, we validate the patient-specific cell-cell interaction models at doublet level by comparing the doublet dissociation rate obtained from experiments and simulations. Second, at multiplet level, we compare the breakup patterns of two 10-cell rouleaux, where these two rouleaux travel through microgates with two different angles between the rouleau centerline and the flow direction.

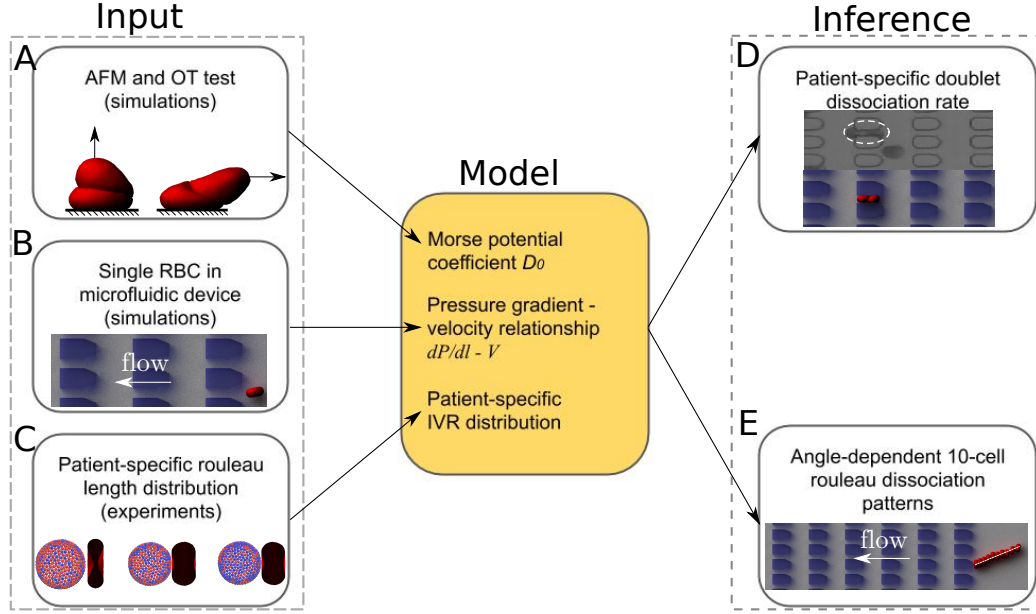


Figure 2.3: Flow chart of simulation setup for hypothesis validation. (A) Existing AFM and OT experiments were used to calibrate the parameters of the cell-cell interaction models. Based on the detaching forces, Morse potential coefficient D_0 were obtained. (B) Single-cell simulations of N-RBCs and D-RBCs (D-RBCs) were performed, passing through microgates under varying pressure-gradient values. The dependence of the single-cell velocity, V , on the pressure gradient, dP/dl , of N-RBCs and D-RBCs was obtained, respectively. (C) In-house microfluidic experiments were performed under comparable flow conditions. Higher levels of fibrinogen concentration from patient samples possessed long rouleau chains more frequently. We measured the distribution of singlets, doublets, multiplets, by taking snapshots of the rouleau within the ROI. These distributions guided the simulation scheme of the interactive vertices ratio (IVR, γ). (D) Probing the rouleau breakup dynamics under different fibrinogen concentration levels by comparing patient-specific doublet dissociation rates observed in experiments with that obtained from simulation. (E) Angle-dependent 10-cell rouleau dissociation simulations to highlight the predictive capability of our model for complex flow behaviors involving aggregatable cells.

Quantification of fibrinogen-dependent cell-cell adhesion strength at doublet level

In analogy with the experimental setups [149, 97], we perform simulations where initially one RBC is placed on top of another RBC to form a doublet, as shown in Fig. 2.4 and then the top RBC is pulled away from the bottom RBC. The RBC-wall

adhesion is simulated by keeping stationary the lower half vertices on the bottom RBC membrane. In the simulation, cell-cell adhesion between the two stacked RBCs occurs spontaneously after they approach each other (here “spontaneously” refers to the condition that no extra force is exerted on the top RBC to induce cell-cell adhesion, i.e., the top RBC is not pressed to the bottom RBC to form contact but is carefully laid on the bottom one). After sufficient contact time and the cell-cell interaction reaching an equilibrium, we impose a step-wise increasing pulling force on the top RBC until the doublet breaks up, i.e., these two RBCs are fully detached from each other. The number of pulling vertices is ϵN_v , where ϵ is the vertex fraction. In the AFM experiment, the AFM tip is positioned above the RBC center, which generates a breakup pulling force on the vertical direction normal to the RBC discoid surface, leading to a uniform cell-cell separation or a peeling breakup. In the OT experiment, the optical trap is positioned on the side of the RBC, which generates a breakup force along the horizontal direction parallel to the RBC discoid surface; hence, the two aggregated RBCs are pulled apart by sliding. Taking all these facts into consideration, we used a higher ϵ value for matching simulation with the AFM test compared to that for matching simulation with the OT test, i.e., we chose $\epsilon \approx 0.36$ for AFM (see Movie S3 in Ref. [57]) and $\epsilon \approx 0.2$ for OT test (see Movie S4 in Ref. [57]).

In addition to the simulations on the cell-cell detachment of healthy doublets under different fibrinogen concentration levels, we also carry out the simulations on the breakup of T2DM doublets, see Fig. 2.5, and record an estimation of the critical forces, i.e., the minimum force that allows the full separation of these two cells in doublets. Generally, the cell-cell detaching force increases as the interactive vertices ratio (fibrinogen concentration level) increases in both AFM and OT experiments and simulations. Also, larger D_0 introduces the condition that a higher force is required

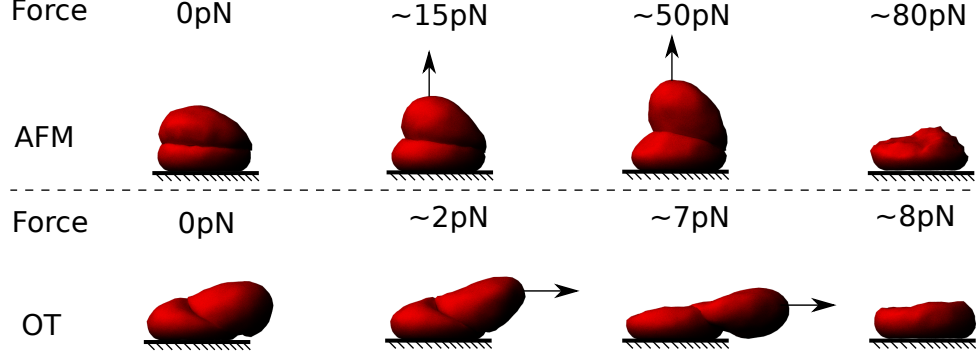


Figure 2.4: **Schematic depiction of the simulation where step-wise increasing force is exerted on the top RBC of a healthy doublet with AFM (top row) and OT test (bottom row).** RBCs with full coverage of IVs are used and the value on top of the doublets represents the force magnitude at each instant. In the last columns (last snapshots), the doublets break up hence only one RBC is shown. Video clips can be found in Movie S3 for AFM test and Movie S4 for OT test in Ref. [57].

to break up the doublets, i.e., the cases with $D_0 = 4.24 \times 10^{-25}$ J require higher detaching forces compared to those with $D_0 = 8.48 \times 10^{-26}$ J.

For the simulations mimicking OT, see Fig. 2.5(A), the critical force F of healthy doublets (black dashed line) saturates to a mean value around 10 pN, while the critical force of T2DM doublets does not saturate smoothly to a plateau value but has a further increase at high interactive vertices ratio γ . A typical simulation video clip on the cell-cell detachment of T2DM doublet with OT test is provided in Movie S5 in Ref. [57]. As shown in the video, when the top RBC of a T2DM doublet is pulled horizontally, the oblate shape of D-RBC induces a rotational motion of the top RBC around the bottom one, promotes the formation of additional binding sites during the detachment process, and hence reinforces adhesion between these two aggregated RBCs. As a result, the critical force F in T2DM doublets is higher than that in the healthy ones. Under the AFM test in Fig. 2.5(B), we found that the critical force F increases with the interactive vertex ratio γ (which is positively correlated with the fibrinogen concentration level) at low γ , whereas it smoothly approaches saturation

at high γ . However, there appears to be a gap in the critical force obtained from computation and experiment. The discrepancy could arise from the the process and analysis of experimental data in [97]. In their experiment, the maximum detachment force is about 70 pN even in the absence of fibrinogen, which is probably due to the presence of residual fibrinogen molecules coming from the plasma. If we treat it as the baseline value and perform a correction on the experimental data, we found that our predicted data fall into the range of the experimentally measured data. In addition, at the same D_0 , we found that the critical forces necessary to detach two aggregated N-RBCs are higher than those for two aggregated D-RBCs. It probably arises from the oblate shape of D-RBC, which causes less interactive vertices, leading to less possible bindings on the contact surface between two RBCs. A video clip for a typical simulation on the breakup of T2DM doublet with AFM test is provided in Movie S6 in Ref. [57]. For comparison, we also simulated the RBC suspension and studied the cell-cell detachment at a much finer MS-RBC model with $N_v = 2000$, see Fig. 2.5(B). In analogy to a previous computational study by Hoore et al. [112], the adhesion strength Γ is directly proportional to the vertex density N_v/A_0^D , i.e., $\Gamma \sim D_0 N_v/A_0^D$; hence, the value of D_0 has dropped 4 times for the DPD case with $N_v = 2000$. We found that the critical force F value decreases somewhat with finer DPD resolution. For example, for $\gamma = 0.5$, the value of critical force drops slightly from 47.6 pN with $N_v = 500$ down to 44.9 pN with $N_v = 2000$. However, since the deviation is sufficiently small, the coarse-graining level on the cell-cell aggregation does not affect our results.

Mesoscopic simulation of patient-specific single RBC dynamics

We employ a specially-designed microfluidic device as shown in Fig. 2.2(A) to study patient-specific cell-cell detachment dynamics of rouleaux. In the following, we present

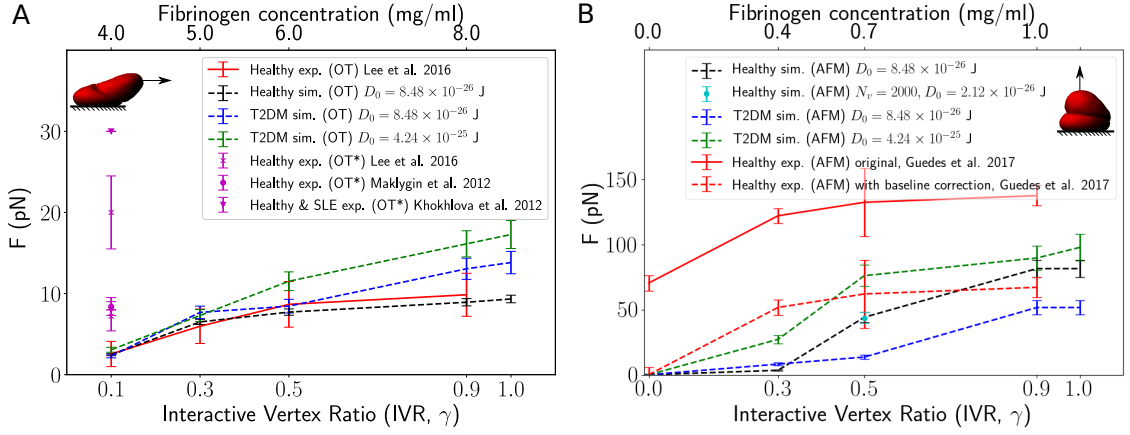


Figure 2.5: **Quantitative validation of doublet breakup forces F with simulations mimicking OT and AFM on healthy and T2DM doublets.** The top horizontal axes denote fibrinogen concentration level in experiments and the bottom horizontal axes denote the interactive vertices ratio (IVR) of the RBC models in simulation; exp. is short for experiment and sim. for simulation. (A) Result of simulation mimicking OT test with N-RBC doublets fits well with data from Lee et al. [149], hence the corresponding Morse potential coefficient $D_0 = 8.48 \times 10^{-26}$ J is applied in later simulations mimicking microfluidic experiments. Note that when IVR exceeds 0.5, T2DM doublets require a larger detaching force than healthy doublet, due to the oblate shape of D-RBC. (B) Result of simulation mimicking AFM test with N-RBC, which is quantitatively comparable to the experimental data with a baseline correction (all experimental data subtract the first experimental point at zero fibrinogen concentration) from Guedes et al. [97]. The simulations were conducted using the MS-RBC model with $N_v = 500$, except for one simulation case at $\gamma = 0.5$ (green solid circle), where we consider a finer MS-RBC model with $N_v = 2000$. Note that data points with * in the legend denote unclear fibrinogen concentration level.

the results of the blood samples from patient II, IV and V listed in Table 2.1, because they represent three different common clinical conditions of increasing severity, i.e., obesity without T2DM, obesity with good and obesity with poor control of T2DM, respectively, indicated by the HbA1c level. Here, we focus on reproducing the dynamics of rouleau in a region of interest (ROI), i.e., a zoomed-in domain where rouleau breakup occurs and from which we can infer the local fluid dynamics.

From the video clips of our microfluidic experiments, we record the time dependent

locations of single RBCs, which are close to the rouleau of interest. On the other hand, we simulate the dynamics of single N-RBC and D-RBC passing through microgates in a range of pressure gradients, see Fig. 2.6. The simulation results show that under a fixed pressure gradient the trajectory of both the single N-RBC and D-RBC maintains a periodic pattern due to the periodicity of obstacles. We fit the trajectories of the RBCs to estimate their velocities under different pressure gradient values for N-RBC in Fig. 2.6(B) and for D-RBC in Fig. 2.6(C); see also Fig. 2.6(D) for the fitted single RBC velocities under different pressure-gradient values. We find that the cell velocity is generally proportional to the pressure gradient within the simulated pressure gradient range. In addition, we find that there is a minimum pressure gradient to start the motion of RBCs inside the microchannel to overcome the resistance due to the obstacles. We also compare the simulation results against available experimental data from Bow et al. [23], where they studied the dynamics of malaria-infected RBCs inside a microfluidic device similar to ours. The shear modulus of malaria-infected RBC is much greater than N-RBC [270, 113], which prohibits a malaria-infected RBC from travelling as fast as an N-RBC under the same pressure gradient. Although not as stiff, D-RBCs also travel slower compared to N-RBCs [3, 230, 214].

Next, we monitor the trajectories of three single RBCs in the blood sample of each patient and use linear fitting to obtain the corresponding mean velocities, see Fig. 2.7(B)-(D). As shown in the figures, the velocities of three RBCs do not vary dramatically for a certain patient. Hence, we can calculate the mean velocity from these three sampled velocities and take it equal to the mean flow velocity in this small ROI. To quantify the pressure gradient required for patient-specific simulations, we use interpolation to obtain the pressure gradient required from Fig. 2.6(B)-(C) and validate the single RBC dynamics under the assumed pressure gradient, see

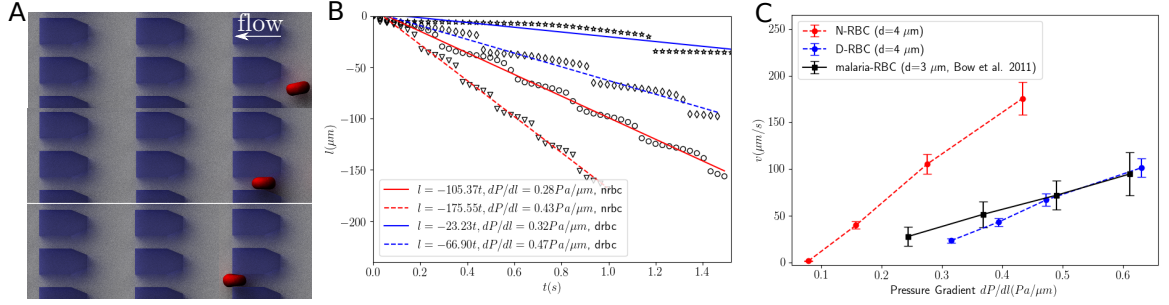


Figure 2.6: Simulation of single RBC dynamics driven by pressure gradient in the microfluidic device. (A) An example of a single D-RBC passing through microgates. Time-dependent trajectories (distance travelled l) of single (B) N-RBC and (C) D-RBC along the flow direction under different pressure gradients. (D) Functional dependence of single N-RBC (red dashed line) and D-RBC (black solid line) velocity with respect to pressure gradient with comparison to similar experimental results by Bow et al. [23] on malaria-infected RBC, which is typically stiffer than N-RBC, in a microfluidic device similar to ours. d denotes the size of the gap between neighboring microgates, which RBC can travel through. Both types of RBC require a non-zero pressure gradient for the onset of squeezing through microgates. However, to maintain a similar travelling speed, D-RBCs typically require a large pressure gradient than N-RBC given the horizontal gap between the curves mainly due to the larger shear modulus and oblate shape of D-RBC, which is also implied by the difference in the slope of the curves.

Fig. 2.7(B) for validation with N-RBC and Fig. 2.7(D) for validation with D-RBC.

Patient-specific cell-cell detachment in microfluidic device at doublet and multiplet level

To perform experiment-informed patient-specific simulations, we construct patient-specific cell-cell interaction models by learning the intrinsic relationship between the interaction model parameters and *in vitro* rouleau length distribution. In the following, our targeting patients are patient II, IV and V as in the previous section. From the experiment, we observe the microfluidic experiment videos for each patient

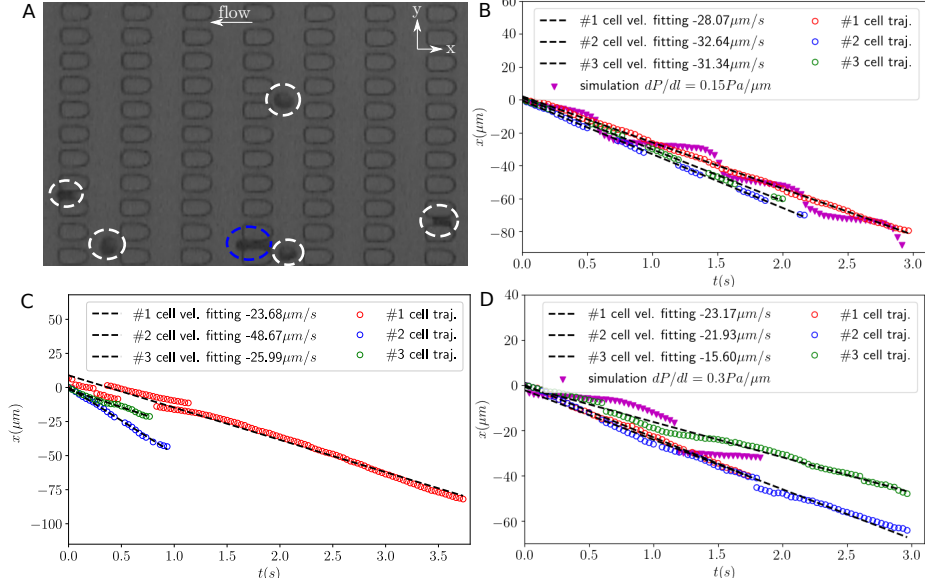


Figure 2.7: Overview for monitoring single RBC motion in the microfluidic device. (A) A typical snapshot, which is a zoomed-in figure of ROI, selected from *in vitro* experiments with single RBCs (in the white dashed circles) near a doublet (in the blue dashed circle). Trajectories of three neighbouring single RBCs in the microfluidic experiments for (B) patient II (obese without T2DM) with validation of pressure gradient at $dP/dl = 0.15 \text{ Pa}/\mu\text{m}$, (C) patient IV (well-controlled T2DM), (D) patient V (poorly-controlled T2DM) with validation of pressure gradient $dP/dl = 0.3 \text{ Pa}/\mu\text{m}$ and corresponding single cell trajectory (magenta triangles) in simulation. Magenta triangles in (B) and (D) represent the simulated cell trajectories under given pressure gradient. Red/green/blue circles represent cell trajectories at each instant measured in microfluidic experiments and black dashed lines represent a linear fitting of corresponding trajectories, see figure legends for the fitted velocity; the minus signs in the velocities imply that RBC travels along $-x$ direction.

and gather two types of statistics. First, we randomly choose 10 frames of time-independent snapshots from each patient, count the number of singlets², doublets and multiplets within the ROI. Then, we calculate the percentage of each type of rouleau for each patient, see Fig. 2.8(B). Note that the sum of these three percentages is 100% because here a rouleau is defined either as a singlet or a doublet or a multiplet. It is clear that each patient holds a share of three types of rouleau, i.e.,

²Singlet, a single RBC. We include singlet as a rouleau since it is meaningful as the most basic cell-cell adhesion element.

every patient has singlets, doublets and multiplets, despite their lab test showing distinct fibrinogen concentration levels. In addition, from the three selected patient samples, we also note that the percentage of rouleau of different lengths varies from patient to patient, which is positively correlated with their fibrinogen concentration levels. Informed by these observations, we construct patient-specific RBC models from the three groups shown in Fig. 2.2(D), i.e., the weak, medium and strong group, and assume that for each patient the percentage of weak, medium and strong adhesive dynamics is determined by their own rouleau length distributions. Although heterogeneous distribution of RBC-RBC adhesion is expected, to the best of our knowledge, there is currently no direct experimental data available about the distribution of cell-cell adhesion for RBC. Hence, our model setup here is based on the direct observations from our microfluidic experiments that the rouleau length distribution is seemingly correlated to the adhesion strength among rouleaux. To demonstrate the overall cell-cell adhesive interaction for each patient, we plot the averaged “interactive vertices ratio” of patient-specific RBC models implemented in simulations, see Fig. 2.8(B).

To validate the experiment-informed RBC model, we compare patient-specific rouleau dissociation rates at doublet level. In the experiment, we keep track of 20 doublets and record the number of doublets that are fully separated before they exit the ROI, see the unshaded bars in Fig. 2.8(C). On the other hand, for each patient we simulate 25 patient-specific doublets passing through microgates and calculate the percentage of fully separated doublets over the total amount of doublets observed, see the shaded bars in Fig. 2.8(C). The simulation and experimental results agree well with each other, confirming that the distribution of rouleau length is an important indicator in doublet breakup dynamics. Additionally, our simulation results show that under the same pressure gradient, T2DM doublets with weak cell-cell adhesion strength easily break up becoming singlets, see Movie S7 in Ref. [57], while doublets

with medium cell-cell adhesion strength mostly maintain the rouleau length, see Movie S8 in Ref. [57], and doublets with strong cell-cell adhesion strength is robust enough to maintain the adhered state and hence having higher probabilities to become a longer rouleau later, see Movie S9 in Ref. [57]. These observations, consistent with experimental records, validate our patient-specific RBC model construction. Additionally, this demonstrates that with increasing disease severity, indicated by higher HbA1c and higher fibrinogen levels, our patient-specific RBC models predict the increased formation of multiplets and decreased dissociation rates of doublets.

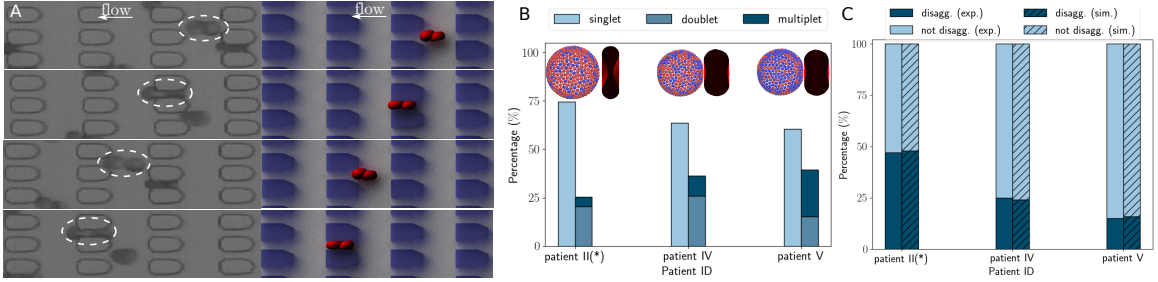


Figure 2.8: **Statistical quantification of the aggregation strength through *in vitro* experiments and simulations for selective patients.** (A) An example of a T2DM doublet (in the white dashed circles) with strong cell-cell aggregation passing through microgates in experiment (left column) and simulation (right column) without the occurrence of doublet breakup event before it exits the ROI. (B) Patient-specific experimental results on the percentage of rouleaux with different lengths, i.e., the count of singlets, doublet and multiplets divided by the total count of rouleaux, respectively. On top of each patient's rouleau length distribution, we draw a representative RBC to reflect the averaged interactive vertices coverage of those simulated RBCs for that patient. (C) Comparison between experimental and simulated patient-specific doublet dissociation rate; exp., short for experiment and sim. for simulation.

From our microfluidic experiments, we notice that the alignment of a long rouleau with respect to the flow direction plays a key role in its breakup pattern afterwards. To probe this phenomenon qualitatively, we carry out simulations on two 10-cell rouleaux (representing a long rouleau) passing through the microgates, see Fig. 2.9(A)

and Movie S10 in Ref. [57] for a rouleau entering the microchannel along the flow direction; see also Fig. 2.9(B) and Movie S11 in Ref. [57] for another rouleau entering microchannel with a 21° angle to the flow direction. Note that this type of extremely long rouleau is frequently seen in the sample of T2DM patients like patient V, therefore we adopt the D-RBC model with 100% IVR in Fig. 2.2(D). Additionally, to provide enough statistics, we run each simulation set for 5 times and obtain the rouleau length distribution at the outlet of the microchannel, see the last row in Fig. 2.9. The snapshots show that these two rouleaux experience distinct collisions with the microgates and hence exhibit different breakup patterns. The rouleau with inclined centerline breaks up into several triplets and one quadruplet while the rouleau having its centerline parallel to flow direction splits into two doublets and two triplets. This suggests that the inclination angle between rouleau centerline and flow direction can significantly affect the corresponding rouleau breakup patterns. Other studies in the literature also showed similar observations. For example, Ji et al. applied microfilters to separate white blood cells (WBCs) from RBCs within plasma and suggested that RBC aggregation will lead to filter clogging. They also compared the RBC separation and WBC trapping efficiency of microfluidic devices with weir filter, pillar filter and the cross-flow filters with slits slanted 60° and 90° , respectively. They concluded that the cross-flow design could be the filter of choice due to its convenience in fabrication and high efficiency in cell sorting [126]. We note that the slanted slits of the microfilter in their work is equivalent to the inclination angle between the centerline of rouleau and flow direction in our simulations. Therefore, our simulation of rouleau breakups at multiplet level could guide the design of microfluidic device and improve the efficiency of separating aggregatable cells.

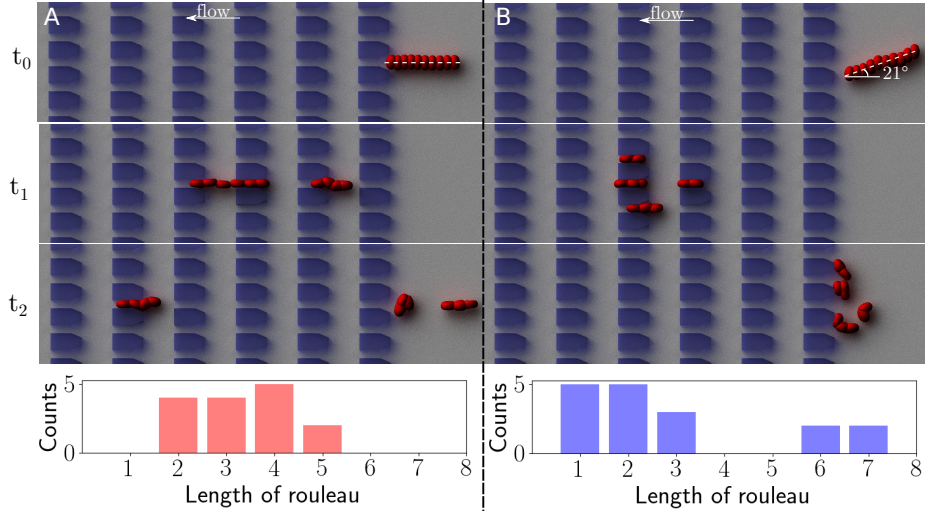


Figure 2.9: **Different breakup patterns of two 10-cell rouleaux when passing through microgates under the same pressure gradient** at $\Delta P/\Delta l = 0.4$ Pa/ μ m, where the centerline of RBCs in one rouleau is (A) parallel to and another is (B) with a 21° inclination angle to the direction of flow ($t_0 = 0s, t_1 \approx 3s, t_2 \approx 4.5s$). With successive collisions to the microgates, these 10-cell rouleaux eventually break up into rouleaux of shorter lengths. The corresponding outlet rouleau length distribution is shown in the last row. In (A), the 10-cell rouleau tends to break up into rouleaux of evenly distributed lengths suggested by the concentrated counts around 3-cell and 4-cell rouleaux, while in (B) the 10-cell rouleau breaks up to rouleaux of very different lengths. For each case, 5 different simulation tests are performed to record the lengths of shorter rouleaux produced by the rupture of 10-cell rouleau. Video clip for (A) is provided in Movie S10 in Ref. [57] and (B) in Movie S11 in Ref. [57].

2.1.4 Conclusions

Red blood cells (RBCs) in patients with type 2 diabetes mellitus (T2DM) are associated with reduced cell deformability and elevated cell aggregation, both of which make whole blood more viscous compared to healthy individuals, leading to impaired microcirculation. From the clinical point of view, it is recognized that Hb1Ac level is positively associated with microvascular complications in T2DM [16, 213, 198]. Some studies have also shown that fibrinogen level is also positively correlated with

microvascular complications [146, 64]. In this work, to enhance our understanding of fibrinogen-dependent RBC aggregation, which contributes to the abnormal microvascular complications in T2DM, we conducted microfluidic experiments with blood samples from six obese patients with and without T2DM and extract informative statistics in order to develop patient-specific RBC models. We performed experiment-informed simulations on the patient-specific cell-cell detachment process of rouleaux at doublet and multiplet level and validated the patient-specific RBC models by comparing the simulation results to data from experiments. We note here that although we simulate the RBC dynamics of two T2DM patients (patient IV and patient V) who are on different medications and represent well-controlled and poorly-controlled patients, respectively, our results on these two patients do not imply in one way or the other the effectiveness of the medications, see Table A.1 in the Appendix A.1 for details of medications.

To construct fibrinogen-dependent RBC adhesion models, we determined the model parameters through quantitatively matching the rouleau breakup forces obtained from simulations mimicking AFM and OT tests to the corresponding experimental data. Further validation of the fibrinogen-dependent RBC models was conducted by comparing the patient-specific simulation results with our *in vitro* microfluidic experiments on three selected patients (II, IV and V, representing obesity without T2D, obesity with good and with bad control of T2DM, respectively). With increasing disease severity, indicated by higher HbA1c and higher fibrinogen levels in patients' blood, our patient-specific RBC model predicts the increased formation of multiplets and decreased dissociation rates of doublets. The simulations of the microfluidic experiments match the observed patient-specific doublet breakup rates, as well as the long rouleau breakup patterns. The simulation results show that given

the same pressure gradient in the T2DM doublets with weak cell-cell adhesive interaction tend to break up easily, the T2DM doublets with medium cell-cell adhesive interaction strength mostly maintain the rouleau structure, whereas those with strong cell-cell adhesive interaction strength are extremely robust.

In addition, for poorly-controlled T2DM patients, we notice the frequent existence of extremely long rouleaux in their blood samples which is rarely seen in an obese patient without T2DM, whose plasma fibrinogen concentration level is relatively lower than that from patients with T2DM. By observing the dynamics of these extremely long rouleaux in the microfluidic device, we found that the alignment of rouleau with respect to flow direction can affect their breakup patterns after repetitive collisions with the walls of microgates. We confirmed that the observed characteristics through simulations on angle-dependent rouleau breakup dynamics at multiplet level. The angle-dependent rouleau breakup patterns captured by our simulations may help improve the design of microfluidic devices that are used to perform cell sorting or cell separation, especially involving cell-cell adhesion. More importantly, it justifies further research in patients with T2DM, who due to plaque formation and thus capillary lumen irregularities, may demonstrate higher exposure to angled rouleaux-wall collisions. Hence, our microfluidic experiments, patient-specific cell-cell interaction RBC models and experiment-informed simulations seamlessly incorporate information from patient blood samples, fluid dynamics inside the microchannel and associated hemodynamics, providing a novel way to quantify the heterogeneous patient-specific rouleau dynamics in a capillary-like microenvironment.

2.2 Blood cells dynamics in coagulation cascade in normal and diabetic blood

Manuscript information

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Author contributions: A.Z., Y.D., H.L., Z.L., J.D.H., G.E.K. designed research. A.Z., Y.D., H.L., Z.L. performed computational simulations. A.Z., Y.D., H.L., E.J., Z.L., S.J., C.L., J.D.H., C.S.M., G.E.K. analyzed data. All authors contributed to writing the paper.

2.2.1 Introduction

Normal hemostasis and pathological thrombosis in a flowing bloodstream can occur on damaged vessels as well as on the surfaces of artificial internal organs [88]. A thrombus is predominantly composed of platelets, which are non-deformable ellipsoid shaped blood cells in their passive state circulating in blood with a concentration of 150,000 to 400,000 per mm^3 . The formation and growth of a thrombus at a site of injury on a blood vessel wall is a complex biological problem, involving a number of multiscale simultaneous processes including: 1) margination of the platelets from the core to the periphery of the blood vessel by red blood cells (RBCs) [206], contributing to platelets' quick activation and accumulation on the injured area of vessel

wall; 2) transport of the coagulation factors to the injured sites of the vessel; 3) a series of chemical reactions in the coagulation cascade occurring in plasma around the injured sites and on the platelet's surface; 4) activation of platelets and adherence to the thrombogenic sites [261]. Comprehensive studies involving all these processes are challenging as they occur at different spatio-temporal scales [15]. For example, platelet-wall and platelet-platelet interactions through receptor-ligand bindings occur at a sub-cellular nanoscale, whereas the blood flow dynamics in the vessel around the developing thrombus is described as a macroscopic process from several micrometers to millimeters.

Numerous computational models [252, 258, 238, 21, 270, 257, 271, 160, 228, 246, 83] have been developed to address the underlying blood clotting processes and predict thrombus growth despite making assumptions and simplifications in the models, see reviews in [253, 154]. It is worth noting that Xu et al. [254] outlined a multiscale model that included macroscale dynamics of the blood flow using the continuum Navier-Stokes (NS) equations, and microscale interactions between platelets and the wall using a stochastic discrete cellular Potts model. The enzymatic reactions of the coagulation pathway at the injured wall in plasma as well as on the platelet's surface were incorporated through coupling advection-diffusion-reaction (ADR) equations to blood flow. These numerical simulations, however, were limited to two-dimensions due to the significant cost of solving many ADR equations. Fogelson and Guy [85] used a continuum Eulerian-Lagrangian approach, where the NS equations were solved along with the ADR equations for the transport of coagulation factors, whereas an immersed boundary method was used to couple platelet (treated as rigid spherical particles) interactions with blood plasma. However, neither Tosenberger et al. [228] or Fogelson and Guy [85] simulated red blood cells (RBCs) explicitly. The effect of

RBCs on the platelet motion was not considered through enhancing platelet diffusive motion toward the wall either, in their works. Although computational models without explicit representations of RBCs and platelets can produce results in good agreement with experimental data in simple channel flows, they may not perform well in complex flow geometries such as vessels containing aneurysms or stenoses.

The high level of complexity and heterogeneity in the existing models as well as the computational cost have limited their applications in simulating a 3D physiological clotting process. In this work, we propose a multiscale numerical framework that seamlessly integrates different sub-processes involved in platelet aggregation and adhesion. This framework, which is developed based on dissipative particle dynamics (DPD) method, a mesoscopic particle-based hydrodynamics approach [65], can concurrently simulate the transport and interaction between RBCs and platelets, transport of coagulation factors involved in the coagulation, chemical reactions and adhesion of platelets to the thrombogenic sites, the four key sub-processes of blood clotting. Prior studies have demonstrated that DPD is an effective method to study cell biomechanics [71, 31], cell motions and interactions in blood flow [78, 74, 32] as well as chemical species transport [166]. The advantage of this framework is the seamless integration of hydrodynamics, cell mechanics and chemical reactions, thereby significantly reducing the computational cost induced by the unnecessary communication overhead between different solvers. To demonstrate the new capabilities, we employ the proposed framework to simulate the platelet activation and adhesion to thrombogenic sites in a 3D microchannel in normal and diabetic blood, and dissect the effects of the biomechanics and biochemistry on platelet adhesion and aggregation under physiological and pathological conditions.

The rest of the paper is organized as follows. In section 2, we introduce the methods to describe the four key components in this framework, namely blood flow

transport, coagulation kinetics, blood cell mechanics and platelet adhesion dynamics as well as how these four components are integrated in this framework. In the section 3, we implement this framework to simulate platelet adhesion to the injury sites in a micro-channel in normal and diabetic blood, respectively. In section 4, we summarize the simulation results and discuss their clinical implications.

2.2.2 Methods

The foundation of our multiscale framework is the DPD method established by [65], upon which other modules are added. The multiscale framework includes four main modules: the hemodynamics, coagulation kinetics and transport of chemical species, blood cell mechanics and platelet adhesive dynamics. Each of these modules are introduced in the following sections below.

Hemodynamics. The blood plasma in the simulation is modeled using DPD method following our previous paper [76]. Detailed information of the DPD method and model parameters can be found in Appendix A.2.

Transport of chemical species and coagulation kinetics. Transport of chemical species involved in the coagulation cascade is modeled by transport dissipative particle dynamics (tDPD), an extension of the classical DPD framework [166] with extra variables for describing concentration fields. To consider the coagulation cascade, we follow the mathematical model of Anand et al.[8], which contains a set of 21 coupled ADR equations for describing the evolution of 23 biological reactants involved in both intrinsic and extrinsic pathways of blood coagulation. Detailed information of transport of chemical species and the model of Anand et al.[8] can be found in Appendix A.2.

Cell mechanics. In this framework, we employ the DPD approach introduced in the work of Fedosov et al. [73] to represent RBCs and use its extension for platelets [255]. As shown in Fig. 2.10(A), in this study, we model a normal RBC with $N_v = 500$, shear modulus $\mu_0 = 4.73 \mu\text{N}/\text{m}$ and bending rigidity $k_0 = 2.4 \times 10^{-19}$ J. The cell surface area is selected to be $A_0^{\text{tot}} = 132.9 \mu\text{m}^2$, and cell volume $V_0^{\text{tot}} = 92.5 \mu\text{m}^3$, which give surface to volume ratio $S/V = 1.44$. All parameters used in our normal or diabetic RBCs model are calibrated based on existing experimental data and validated with simulations, from single RBC mechanics to blood flow dynamics [71, 201, 57, 165, 159, 158].

For platelets, which are nearly rigid in their passive form, we choose shear modulus and bending rigidity sufficiently large (100 times larger than the normal RBCs) to ensure its mechanical behavior as a more rigid cell. The number of vertices in the platelet's membrane network is $N_v = 48$ and the aspect ratio of the cell is $AR = 0.38$. Based on our previous analysis on the patient-specific data [31], a normal platelet has cell volume $V_0^{\text{tot}} = 6 \mu\text{m}^3$. Detailed information of the RBC and platelet model and the model parameters can be found in Appendix A.2.

Platelet adhesive dynamics. The platelet adhesive dynamics model describes the adhesive dynamics of receptors on the platelet membrane binding to their ligands. In this work, we employ the platelets adhesive dynamics model proposed by Mody and King [185]. This model utilizes the Monte Carlo method to determine each bond formation/breakage event based on specific receptor-ligand binding kinetics. We estimate the probability of bond formation P_f and probability of bond breakage

P_r using the following equations

$$P_f = 1 - \exp(-k_f \Delta t), \quad (2.3a)$$

$$P_r = 1 - \exp(-k_r \Delta t), \quad (2.3b)$$

where k_f and k_r are the rates of formation and breakage, respectively. Following the catch bond formula by Mody and King [185], the force-dependent k_f and k_r are evaluated by

$$\begin{aligned} k_f &= k_f^0 \exp\left(\frac{(\sigma_f - 0.5 |x_b - l_b|)}{k_B T}\right), \\ k_r &= k_r^0 \exp\left(\frac{\sigma_r |F_b|}{k_B T}\right), \end{aligned} \quad (2.4)$$

where k_f^0 and k_r^0 are the intrinsic bond formation and breakage rates, respectively, and σ_f and σ_r are the corresponding reactive compliance. Detailed information of the platelet adhesive dynamics model and the model parameters can be found in Appendix A.2.

Problem setup. For simplicity, we set up a 3D straight microchannel with the size of $110 \times 20 \times 20 \mu\text{m}^3$ filled with RBCs, platelets and solvent particles which carry 22 chemical species, as shown in Fig. 2.10(B). The channel is periodic in the x and z directions. The initial concentration of the species are listed in Table A.8 in Appendix A.2. The hematocrit of the blood and platelet density are selected to be 25% and $500,000 \text{ mm}^{-3}$, respectively. The platelet density is taken somewhat larger than the physiologic value such that the adhesion of platelets to vessel injury site can be more pronounced. In addition, all platelets are initially placed on the upper and lower sides of the channel to accelerate margination and the adhesion process. The wall boundaries in the simulation domain are treated as pseudo-planes, following the work of Lei et al.[151]. Specifically, particles within one cut-off distance from

the wall are reflected in a bounce-forward scheme. Further, in order to impose the no-slip condition, a predefined force that compensates for the missing particles on the opposite side of the wall is applied to the particles both in wall normal and tangential directions. Following our work in [166], we assume that coagulation occurs at the site of injury. As shown in Fig. 2.10(B), the process is initiated and sustained by imposing a boundary flux for the four species listed in Table A.10 in Appendix A.2. All the simulations were performed at Stampede2's Knights Landing (KNL) compute nodes at Texas Advanced Computing Center. Each node has 68 cores. Each simulation runs 1,000,000 timesteps (corresponding to 45 seconds in the physical time) on 5 nodes (340 CPU cores) running for 24 hours.

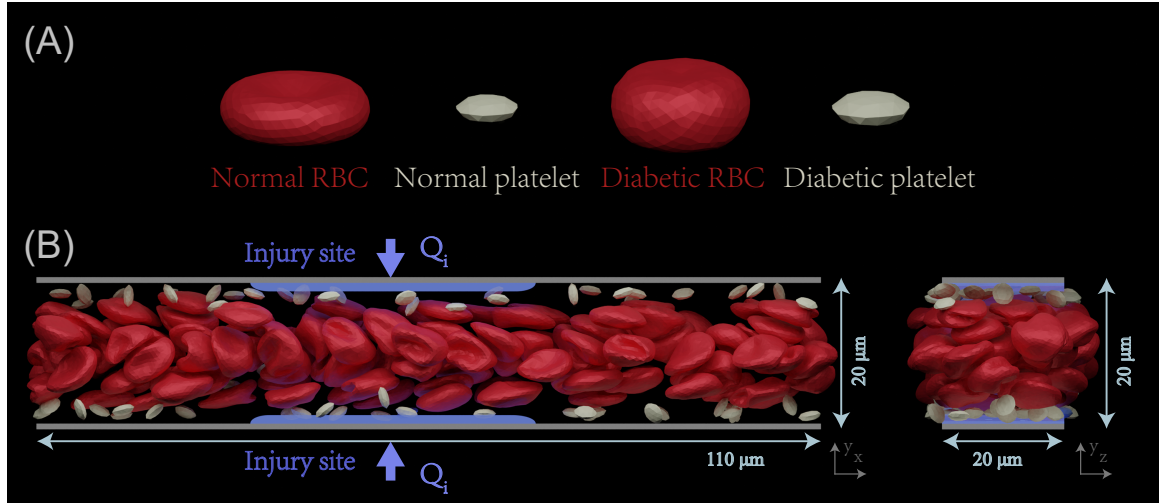


Figure 2.10: **Schematics of the simulation setup.** (A) Models for normal and diabetic RBCs and platelets. (B) A 3D rectangular microchannel with the size of $110\ \mu\text{m} \times 20\ \mu\text{m} \times 20\ \mu\text{m}$ is filled with RBCs, platelets and solvent particles which carry 22 species. Left: front view, right: side view. Solvent particles are omitted in visualization for clarity. Two injury sites (highlighted in blue) with a length of $40\ \mu\text{m}$ are located at the upper and bottom channel wall. The mass flux of four species listed in Table A.10 in Appendix A.2 are injected into the channel to initiate and drive the coagulation cascade.

People with type 2 diabetes mellitus (T2DM), the most common type of diabetes, are prone to experience thrombotic events and develop cardiovascular complications [172]. It has been determined that multiple factors induced by T2DM contribute to the prothrombotic status, such as elevated coagulation, impaired fibrinolysis, endothelial dysfunction and platelet hyperreactivity [95]. Our previous studies have demonstrated that the altered morphology and biomechanics of RBCs and platelets in diabetic blood lead to enhanced platelet margination [32] and abnormal hemorheology [31], both of which potentially aggravate the platelet aggregation and thrombus formation. In particular, diabetic RBCs, which exhibit a near-oblate shape with a reduced S/V ratio (see Table A.6 in Appendix A.2), are larger in size and less deformable than normal RBCs [265]. The reduced deformability of diabetic RBCs leads to increase in blood viscosity up to approximately 20% higher than normal samples [169]. On the other hand, clinical data have showed that the mean cell volume of platelets measured from the blood samples of diabetic patients is larger than that of the non-diabetic control, which is likely caused by osmotic swelling as a result of hyperglycemia [32].

In this work, we simulate both the normal and diabetic blood flow. Diabetic RBCs have a shear modulus of $\mu_s = 2\mu_0 = 9.46 \mu\text{N/m}$ and a reduced S/V = 1.04. A normal platelet has cell volume $V_0^{\text{tot}} = 6 \mu\text{m}^3$ whereas a diabetic platelet has $V_0^{\text{tot}} = 12 \mu\text{m}^3$. The parameters of diabetic RBCs and platelets are selected based on patient-specific data and they were validated in our previous work [31], see Table A.6 in Appendix A.2.

2.2.3 Results and discussion

Platelet adhesion in normal blood. We start the simulation without turning on the coagulation cascade and allow the blood flow first to reach equilibrium. To drive the blood flow in the microchannel, we apply a constant body force to each DPD particle, which yields a plug-like profile for blood. In Fig. 2.11(A), we plot the plug-like velocity profile and the mean blood velocity is computed as $\bar{u} = 2.05$ mm/s. The Reynolds number, $Re = \bar{u}H/\nu$, defined based on the channel width $H = 20 \mu\text{m}$, is ~ 0.015 . The characteristic shear rate is defined as the wall shear rate of a parabolic Poiseuille flow with the same mean velocity and is $\dot{\gamma}_w = 6\bar{u}/H = 615 \text{ s}^{-1}$. Furthermore, the Peclet number, a measure of ratio of advection to diffusion in transport processes, is defined by $Pe = ReSc$, which is ~ 231 for thrombin (assuming $D_{\text{IIa}} = 6.47 \times 10^{-7} \text{ cm}^2/\text{s}$) in our simulations. We also plot the average distribution of the RBCs and platelets across the channel height in Fig. 2.11(B), which shows the presence of a cell-free layer adjacent to the walls with a thickness of $\approx 3 \mu\text{m}$.

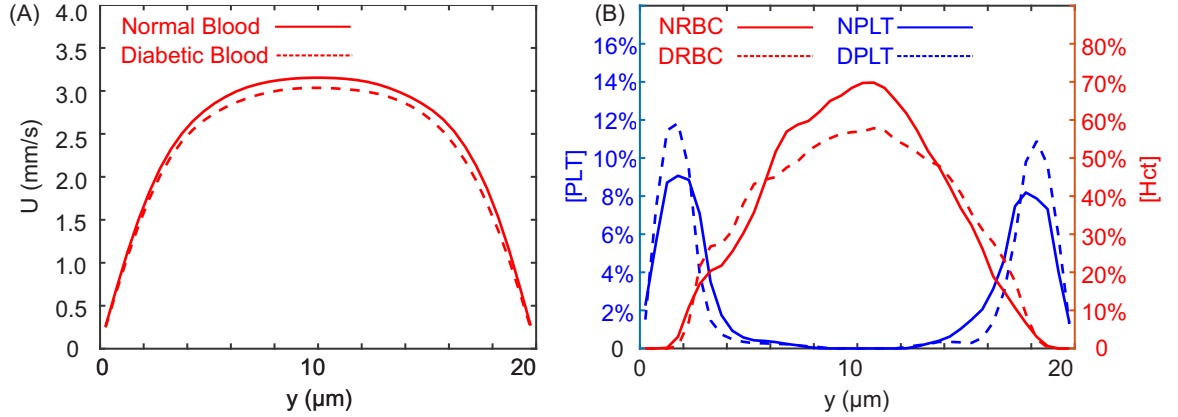


Figure 2.11: **Visualization of flow properties and platelet aggregation.** (A) Flow velocity profiles across the channel height (y direction) for normal and diabetic blood. (B) Platelet count density distribution profiles across the channel height (y direction) (blue lines) and hematocrit profiles (red lines). Solid lines represent normal blood and dashed lines represent diabetic blood. NRBC denotes normal RBCs and DRBC denotes diabetic RBCs. NPLT denotes normal platelets and DPLT denotes diabetic platelets.

Next, we initiate the coagulation cascade by injecting the four species into the blood flow from the injured wall region, as shown in Fig. 2.10(B). A sequence of snapshots of the whole blood simulation in the channel is plotted in Fig. 2.12, which shows that the concentration boundary layer has been fully developed (shown by contours of thrombin concentration $[IIa]$ in the x - y plane). We note that we set a threshold value of 1 nM for thrombin-mediated platelet activation [193] for which the platelets in the boundary layer become instantaneously activated and ready to form bonds with the particles representing vWF ligands on the site of injury. Figs. 2.12(A-C) show that platelets, after activation, are gradually adhered to the site of injury (highlighted with green particles), attempting to cover the injury sites. Meanwhile, the adhered platelets can release ADP that also contributes to the activation of passive platelets flowing the blood. The thickness of thrombin boundary layer is approximately $2 \mu\text{m}$, which is reasonable under the current flow conditions and the value of the Peclet number.

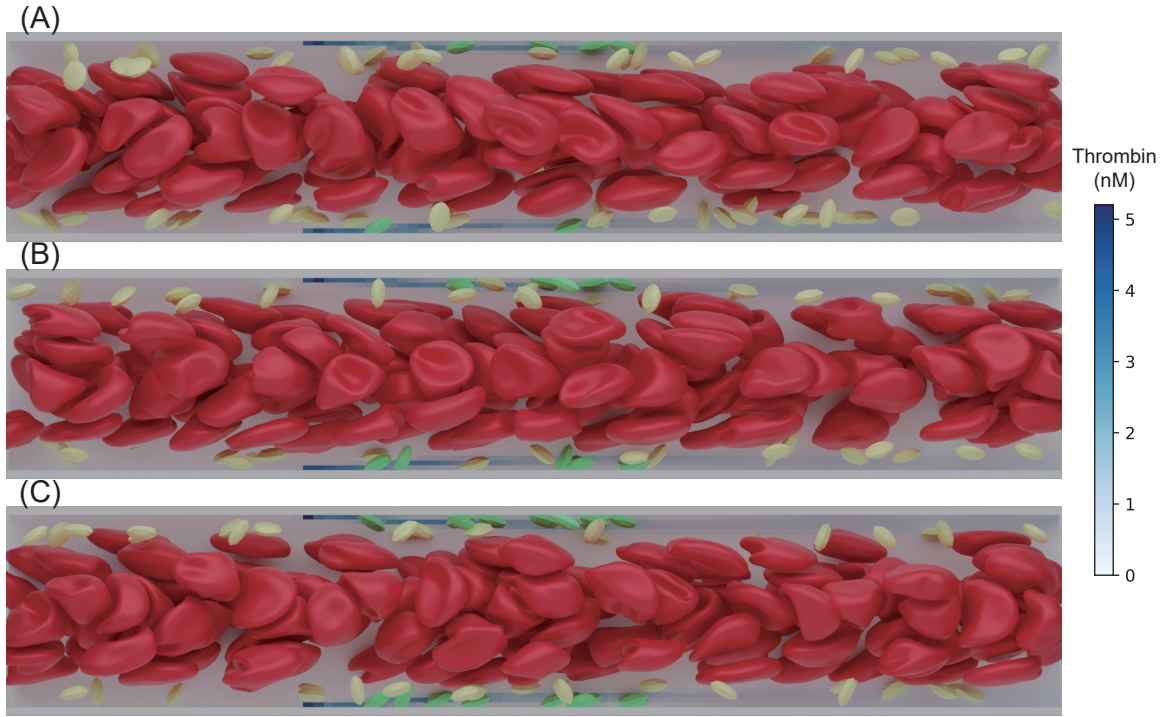


Figure 2.12: **Three sequential snapshots of normal RBCs and platelets flowing in the microchannel.** Cells adhere to the injury sites at simulation times of (A) $t = 10$ s, (B) 20 s, (C) 40 s, respectively. Coagulation reactions generate thrombin that activates passive platelets when its concentration is larger than 1 nM. An increased number of platelets are adhered to the injury sites (highlighted in green) after being activated by thrombin.

Fig. 2.13(A) presents a closer look at the time-evolution of thrombin concentration at three different axial positions, i.e., $x = 40, 50, 60 \mu\text{m}$. The results show a rapid burst of thrombin concentration occurring at $x = 40 \mu\text{m}$, followed by a gradual decrease before the concentration stabilizes. Similar variations of thrombin concentration are observed at $x = 50 \mu\text{m}$ and $x = 60 \mu\text{m}$, but with reduced magnitudes, illustrating the effect of blood flow on the transport of chemical species generated from the coagulation cascade. This effect also can be observed from Fig. 2.14 where we plot three sequential snapshots of the concentrations of three coagulation factors, including factor X, antithrombin III and fibrin. These figures show that at the early

stage of the coagulation ($t = 5$ s), the factor X and antithrombin III are consumed and the fibrin is generated around the injury sites. As the coagulation reactions continue, the coagulation factors flow in from upstream to supply the reactions whereas the generated fibrin flow downstream.

To quantify the adhesion dynamics of the platelets to the injured vessel wall, we plot the total number of bonds between activated platelets and the ligands at the injury sites in Fig. 2.15(A) with respect to time for five independent simulations under the same flow conditions. In addition, we also recorded the number of adhered platelets with time, which is shown in Fig. 2.15(C). These results show that after an initial time lag of approximately 5 seconds, the number of bonds and adhered platelets both start to rise sharply, and the growth of these numbers slows down as more platelets adhered to the injured area. We note that in our simulations platelets only form bonds with the injury sites on the wall, which leads to formation of a monolayer, but the trend of platelet aggregation is consistent with an *in vitro* study [101] and an *in vivo* measurements in mice arterioles [67], where the authors observed a time lag in the initiation of platelet aggregation followed by the increase in fluorescence intensity (i.e., number of adhered platelets) that eventually reaches a plateau.

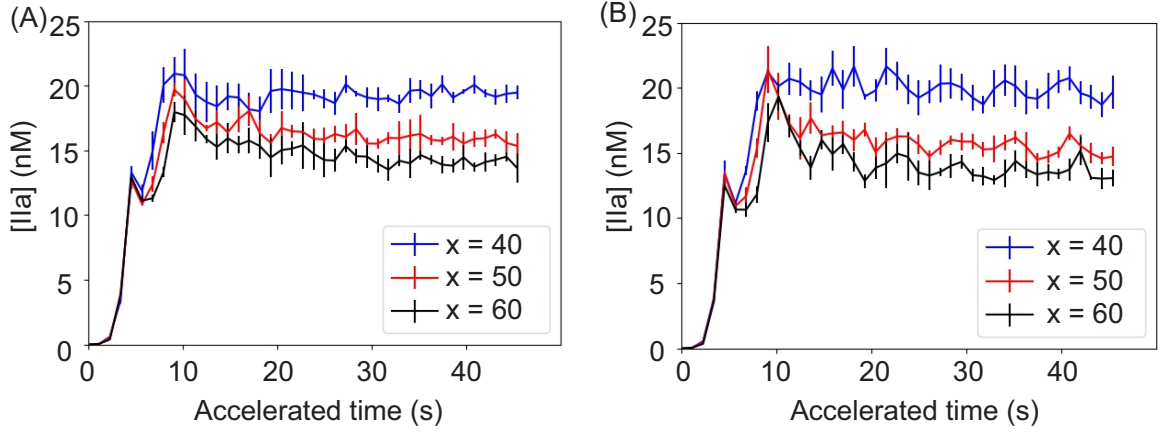


Figure 2.13: **Thrombin concentration evolution over time in the y - z cross-section.** Three axial locations of $x = 40, 50, 60 \mu\text{m}$ in case of (A) normal and (B) diabetic blood are presented. The injury sites range from $x = 25$ to $65 \mu\text{m}$. The surface concentration of TF-VIIa complex is taken as 0.25 nM for both cases and the reaction rate is accelerated 100 times. The error bars are computed based on five stochastic realizations of the simulations.

Next, we present the sensitivity of the results to several important parameters in the model, i.e., the boundary concentration level of TF-VIIa complex as well as the platelet's adhesive parameters. First, we vary the TF-VIIa concentration, which represents the extent of injury on the vessel wall, through increasing and reducing the control value by a factor of 5, respectively, and investigate how these variations affect the bond formation between the platelets and the injured vessel wall. Fig. 2.16(A) shows that as the TF-VIIa concentration is reduced to 0.05 nM , the number of formed bonds is reduced by $\sim 40\%$. On the other hand, when the TF-VIIa concentration is increased to 1.25 nM , the number of bonds is comparable to the case of $[\text{TF-VIIa}] = 0.25 \text{ nM}$. These results suggest that under our simulation conditions, decreased $[\text{TF-VIIa}]$ leads to a less pronounced platelet adhesion whereas a higher level of $[\text{TF-VIIa}]$ by a factor of 5 does not boost the platelet adhesion, which is likely attributed to the lack of other necessary species to increase the generation of thrombin.

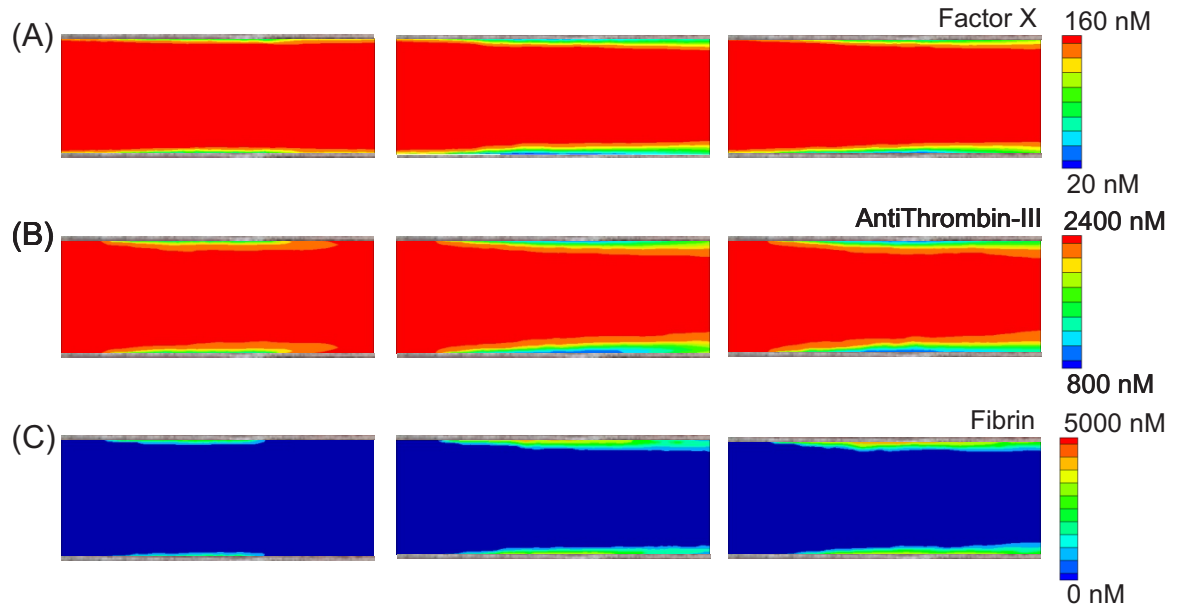


Figure 2.14: **Three sequential snapshots of the concentration boundary layers** of (A) factor X (B) antithrombin III and (C) fibrin in the x - y plane at the middle cross-section of the microchannel. Results are computed at simulation times of $t = 5s, 20s, 40s$, respectively (from left to the right).

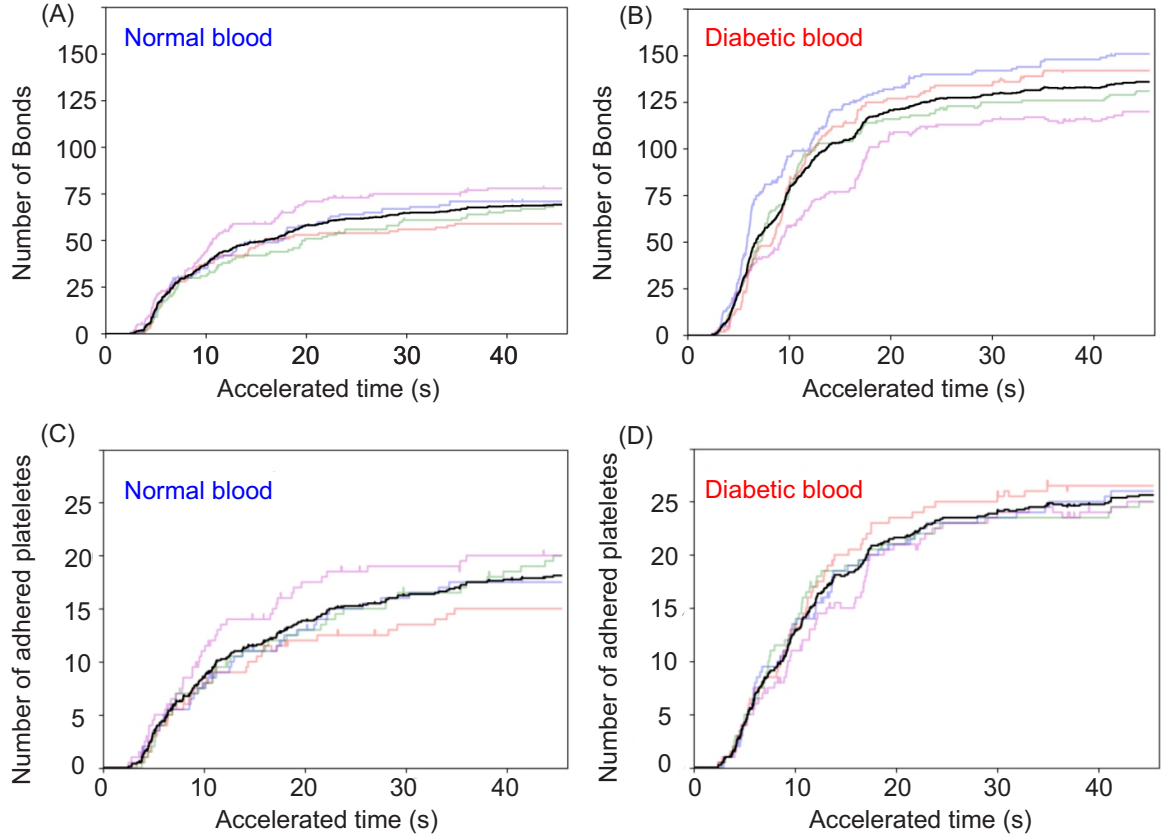


Figure 2.15: **The evolution of the number of bonds formed between platelets and injury sites** in case of (A) normal and (B) diabetic blood as well as the number of adhered platelets for (C) normal and (D) diabetic blood. The surface concentration of TF-VIIa complex is taken as 0.25 nM for both cases and the reaction rate is accelerated 100 times. Each of the plots consists of five stochastic realizations and the black curves highlight the average of the five cases.

Then, we vary the intrinsic bond breakage rate k_r^0 , which can be associated with the genetic bleeding disorder von Willebrand disease (VWD), such as 2B-type VWD or the platelet-type VWD, where the alterations in the binding kinetics allow longer bond lifetimes and enhanced bond formation rates, leading to undesired platelet and VWF binding [62]. Here, we increase and reduce the physiological value of $k_r^0 = 5 \times 10^{-7} \text{s}^{-1}$ by 10 times, respectively. Fig. 2.16(B) shows that a higher rate of breakage reduces the number of bond formations and thus diminishes the platelet adhesion whereas a lower rate of breakage promotes the bond formation. Next, we vary the

binding site density on the platelets (number of bonds can be formed on each platelet particle) and examine its effect on the bond formation. We note that although there is a significant number of GPIIb α receptors on the platelet's surface, not all of them are able to form bonds. In particular, under pathological conditions, such as in the Bernard-Soulier syndrome, a type of glycoprotein receptor deficiencies, platelets are characterized by loss-of-function mutations in GPIIb α [115]. To consider the reduced binding capability of GPIIb α in diseased states, we vary the binding site density of the platelet model from the control value of 5 to 1 and 2. As shown in Fig. 2.16(C), as the binding site density is reduced, the number of bonds formed between the platelets and injured vessel wall is decreased due to the compromised binding capacity of the GPIIb α receptors.

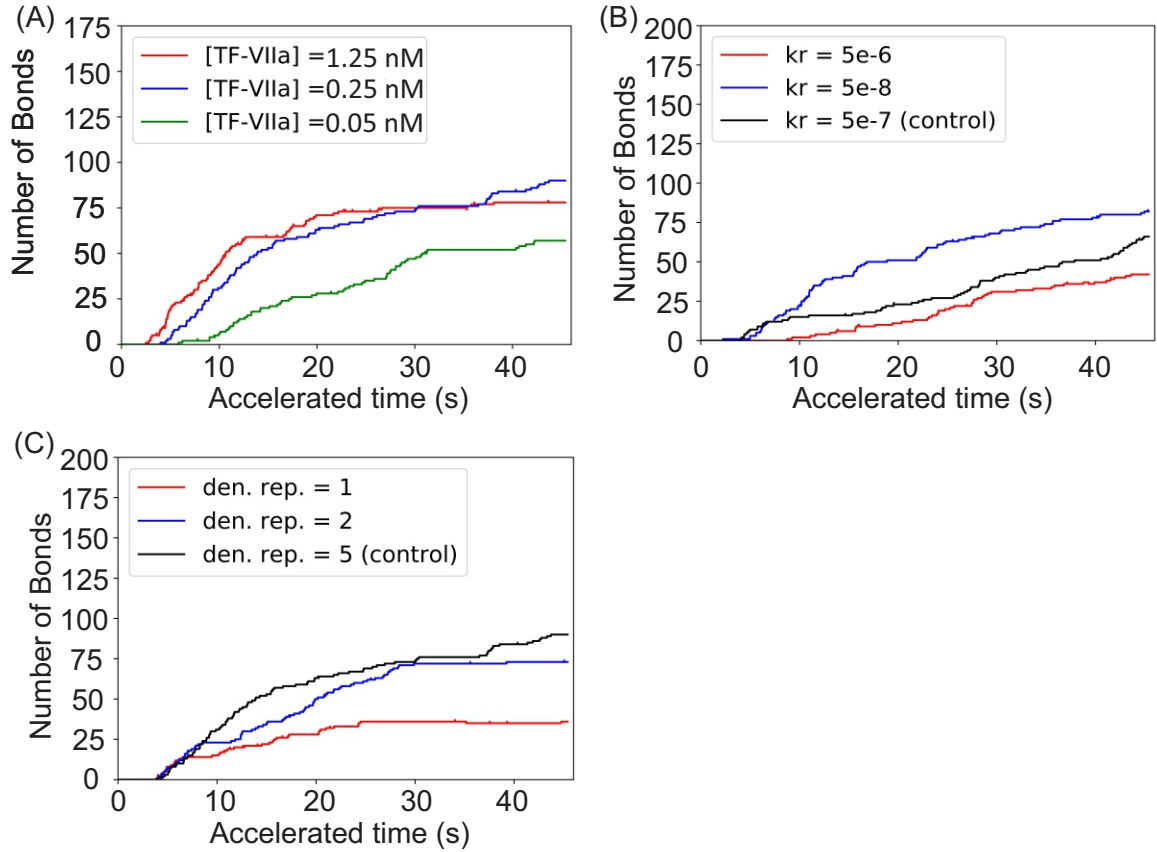


Figure 2.16: **Sensitivity analysis of TF-VIIa concentration, the bond breakage constant k_r and platelet receptor binding capacity on the number of bonds formed between platelets and injury sites.** Platelet-wall bond formation comparisons are performed at (A) three levels of TF-VIIa concentration (B) three values of k_r and (C) number of the bonds that can form on a platelet particle. den.rep. is short for density representation.

Platelet adhesion in diabetic blood. We simulate the platelet adhesion in diabetic blood and investigate how the altered biomechanics of diabetic RBCs and platelets as well as the changes in the amount of species involved in the coagulation affect the platelet adhesion. Following our previous work [31, 32], the structure of the diabetic RBC model is similar to the normal RBCs except that an increased shear modulus of $\mu_s = 9.46 \mu\text{N/m}$ and a reduced S/V ratio of 1.04 are employed to the diabetic RBC model, as shown in Fig. 2.10(A). On the other hand, the diabetic platelet

model has the same stiffness as the normal platelet model but with an increased volume of $12 \mu\text{m}^3$, which is twice as large as the normal one. These morphological and biomechanical changes are made based on our previous study of patient-specific data in [31, 32]. The simulation setup is the same as the case for normal RBCs shown in Fig. 2.10(B). We apply a constant body force to drive the blood flow and we allow the flow to reach equilibrium before we start the coagulation cascade, following the same approach for normal RBCs.

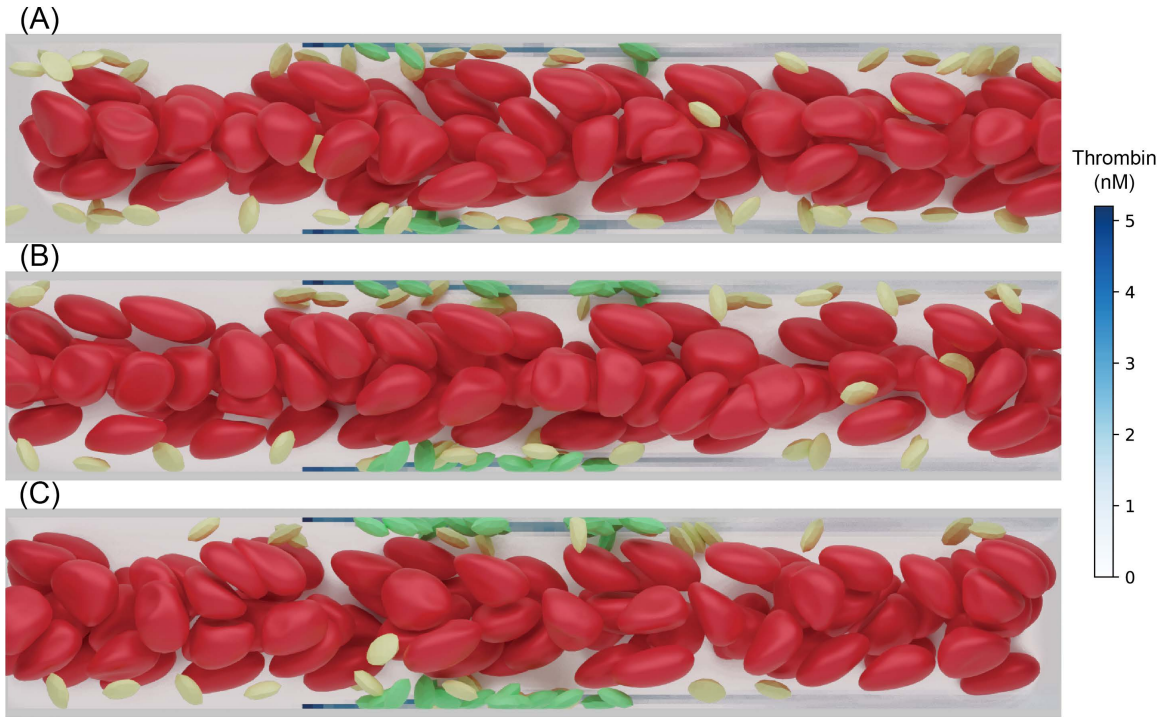


Figure 2.17: **Three sequential snapshots of diabetic RBCs and platelets flowing in the microchannel.** Cells adhered to the injury sites at simulation times of (A) $t = 10$ s, (B) 20 s, (C) 40 s, respectively. Coagulation reactions generate thrombin that activates passive platelets when its concentration is larger than 1 nM. An increased number of platelets are adhered to the injury sites (highlighted in green) after being activated by thrombin.

The velocity profile of the diabetic blood flow in Fig. 2.11(A) shows that under the same pressure drop, the maximum velocity of the diabetic blood is $\sim 15\%$ smaller

than the normal blood. This difference is caused by the increased blood viscosity as a result of increased stiffness and size of diabetic RBCs, in agreement with our previous work [31]. The average distribution of the diabetic RBCs and platelets across the channel height are plotted in Fig. 2.11(B), which shows enhanced platelet margination due to increase mean platelet volume, consistent with our previous study in [32]. A sequence of snapshots of the diabetic blood in the channel after the concentration boundary layer of thrombin has been fully developed (see Fig. 2.17) show that an increased number of platelets are adhered to the site of injury (highlighted with green particles). The number of bonds formed between activated diabetic platelets and injury sites as well as the number of the adhered diabetic platelets are shown in Figs. 2.15(B) and (D), respectively. Both of these two metrics show a rapid increase after an initial time lag of approximately 5 seconds, and then gradually slows down after platelets cover most of the injured area. We note that both the number of formed bonds and the adhered platelets for the diabetic RBCs are higher than those of normal RBCs (Figs. 2.15(A) and (C)), due to the enhanced platelet margination. Since the thickness of the thrombin boundary layer is only approximately $2\text{ }\mu\text{m}$, an increased margination of platelets can expose more platelets to the high concentration of thrombin and increase the number of activated platelets, thereby promoting platelet adhesion.

In addition to the alterations in the biomechanics of blood cells, changes in coagulation factors in the diabetic blood could promote thrombus formation in T2DM. For example, the concentration of plasma fibrinogen, a key source of fibrin, is reported to be approximately 50% higher than the normal blood samples [94]. During coagulation, fibrinogen is converted into fibrin through a thrombin-mediated proteolytic process. Fibrin molecules then form long fibrin threads and networks that trap

platelets and RBCs, building up a spongy mass that subsequently hardens and contracts to form a stable clot. Since fibrin is an essential component in a thrombus, it has been widely used to approximate the extent of a thrombus. Here, we increase the initial concentration of fibrinogen ($[I]$) in our simulation by 50% to represent the impact of elevated coagulation factors in diabetic blood and investigate how this change affects fibrin generation. Following the work of Anand et al. [8], we assume that a thrombus occurs when fibrin concentration equals or exceeds a concentration of 350 nM at the injury regions. The concentration boundary layers of fibrin ($[Ia]$) in the x - y plane at the middle cross-section of the channel are plotted in Figs. 2.18(A) and (B) for normal and diabetic blood, respectively. These results show that the excessive fibrinogen in the plasma of diabetic blood could cause increased extent and density of the thrombus formed at the injury sites of the channel wall. Quantitative results of the fibrin generation in Fig. 2.18(C) show that fibrin generated in the y - z plane at the three x -locations at the injury sites in diabetic blood is approximately 45% higher than the case of normal blood due to the increased amount of plasma fibrinogen.

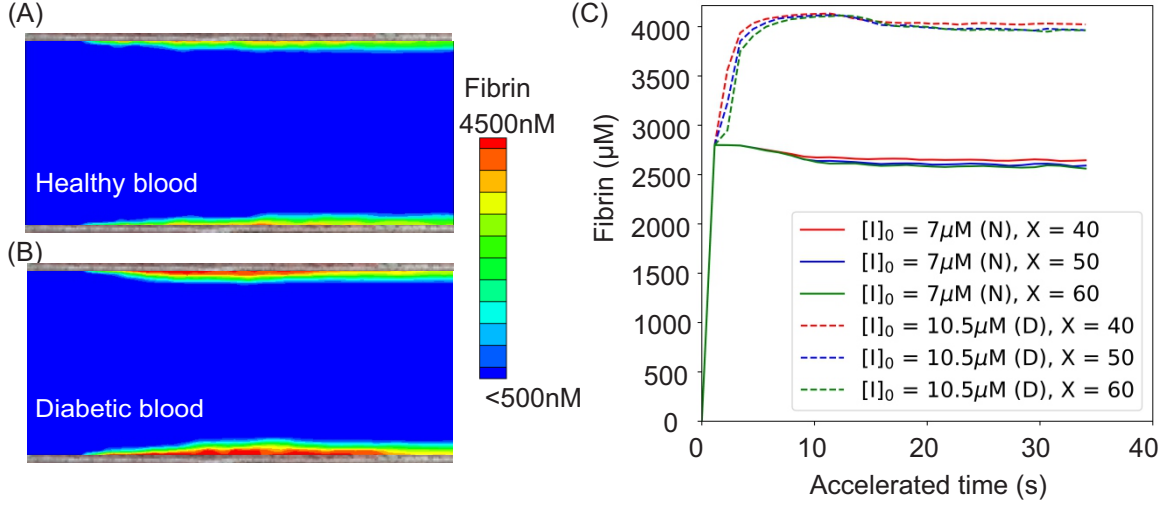


Figure 2.18: **The concentration boundary layers of fibrin ($[I_a]$) in the x - y plane in the middle cross-section of the microchannel ($z = 10 \mu\text{m}$) in case of normal (A) and (B) diabetic blood. (C) Evolution of fibrin concentration over time in the y - z cross-section at locations of $x = 40, 50, 60 \mu\text{m}$ for normal blood (solid lines) and diabetic blood (dashed lines). The injury sites range from $x = 25 \mu\text{m}$ to $x = 65 \mu\text{m}$. Initial concentration $[I]_0 = 7 \mu\text{M}$ is given in normal blood whereas $[I]_0 = 10.5 \mu\text{M}$ is given in diabetic blood. In the figure legend, (N) stands for normal blood, (D) for diabetic blood.**

2.2.4 Conclusions

Computational modeling of thrombus initiation and development at the injury sites of blood vessel wall is challenging due to the multiscale and multiphysics nature of this process, which involves chemical species and blood cell transport, coagulation cascade reactions and platelet adhesion. Diverse studies have been conducted to address this complex problem at different scales, such as cellular, mesoscopic and continuum levels or from different perspectives. In order to reduce the model complexity and increase the computational efficiency, in this work, we develop a multiscale numerical framework based on the transport DPD method that can seamlessly integrate the multiple sub-processes of thrombus formation. To demonstrate the capability of the proposed

framework, we implemented this framework to simulate platelet adhesion and aggregation triggered by exposure of tissue factor in a 3D microchannel. We show that the proposed framework can simulate thrombin-mediated platelet activation and the subsequent adhesion to the injury site of the channel wall, a key process in hemostasis. In particular, our results on transport of chemical species illustrate that the concentration boundary layers of the thrombin that is sufficient to activate the platelets in the flowing blood are very thin ($\sim 2 \mu\text{m}$), implying that platelet margination is essential for platelet activation, adhesion and subsequent clot formation in a blood vessel.

To show the versatility of the model, we simulate platelet adhesion under several pathological conditions involving different levels of vessel injury and abnormalities in the platelet adhesion, which occur in various genetic hemostasis disorders, such as VWD and the Bernard-Soulier syndrome. Our model predictions from these simulation are qualitatively consistent with prior clinical findings [115, 62]. More importantly, our model also can provide quantitative prediction of the relation between parameters obtained from experimental measurements at cellular level and the extent of thrombus formation under *in vivo* flow conditions. In addition, we simulate the platelet adhesion in diabetic blood and we find that the alterations in RBC and platelet biomechanics enhance the margination of the platelets and thus promote platelet adhesion to the injury sites on the blood vessel, whereas the changes in the amount of the species involved in the coagulation boost generation of fibrin, a key component for the thrombus growth and development after the initial platelet adherence to injury sites. These results suggest that both the elevated coagulation and altered properties of blood cells contribute to the prothrombotic status in T2DM.

In the current work, we examine the performance of the proposed model in a straight channel for simplicity as the focus of this work is to introduce this novel multiscale modeling framework. We note that different vessel geometries such as

stenosed-arteries [43, 116], curved vessels [119, 105], bends [111, 92], bifurcations [132, 117, 35, 118], could change the blood cells and coagulation factors transport and thus impact the thrombus formation. We also note that several biological assumptions have been made in this framework. In order to observe the impact of the coagulation cascade on the platelet activation and adhesion, we assume that only activated platelets can adhere to the injury sites. However, a number of studies have shown that the platelets could adhere to the injury site or growing thrombus before activation [120, 124, 123, 122, 144]. As a result, our simulation results could underestimate the number of platelets adhered to the injured vessel wall. In addition, platelets become more deformable upon activation through reordering of actin network in their membrane and undergo drastic morphological changes [90, 125]. In this work, we focus on the initial steps of thrombus formation triggered by coagulation cascade and thus did not consider the shape change of activated platelets to reduce the complexity of the model. A more sophisticated platelet model, such as [269, 270], is required to address this complex process.

Taken together, we develop a computational framework that is able to effectively address different multiscale biological processes involved in thrombosis and predict thrombus formation under physiologic and pathological conditions. An important feature of this proposed framework is that each of its components can be refined by future experimental studies to improve the accuracy and capability of the model predictions. Therefore, this framework can be potentially extended to model more complicated vascular systems and geometries and make predictions based on organ-specific flow conditions and patient-specific blood coagulation factors. As the proposed framework is capable of dissecting complex conditions when multiple factors play a role in triggering thrombosis in human circulation, it also can be potentially used to identify the key factors in thrombus formation and test the efficacy of anti-thrombosis drugs,

thereby accelerating the development of thrombosis medication.

Chapter 3

Part II: Bioinformatic Modeling

3.1 Data-driven short-term blood glucose prediction and long-term hypoglycemia detection

Manuscript information

A version of this chapter appeared in [55]: Yixiang Deng, Lu Lu, Laura Aponte, Angeliki M Angelidi, Vera Novak, George Em Karniadakis, and Christos S Mantzoros. Deep transfer learning and data augmentation improve glucose levels prediction in type 2 diabetes patients. *npj Digital Medicine*, 4(1):1–13, 2021.

The part for long-term hypoglycemia detection is in preparation.

Author contributions: G.E.K. and C.S.M. supervised the work and formulated the problem. Y.D., L.L., C.S.M., and G.E.K. developed the model. Y.D. implemented the computer code. Y.D. and L.L. performed computations. A.M.A., L.A., V.N., C.S.M., contributed the patient data analyzed herein. Y.D., L.L., C.S.M., and G.E.K. analyzed data. Y.D., L.L., A.M.A., L.A., V.N., C.S.M., and G.E.K. wrote the paper.

3.1.1 Introduction

Type 2 diabetes (T2D) is a multifactorial progressive chronic metabolic disorder, accounting for approximately 90% of all cases of diabetes [274]. The prevalence of diabetes has been increasing rapidly over the past few decades [242]. In 2019, about 463 million adults were living with diabetes, while it is estimated to be 578 and 700 million by 2030 and 2045, respectively [211]. T2D and hyperglycemia are associated with an increased risk of vascular and non-vascular complications and premature mortality [48, 224, 47]. Furthermore, emerged evidence has also emphasized the importance of avoiding fluctuations in glycemia in T2D [93]. Of note, the Advanced Technologies & Treatments for Diabetes (ATTD) consensus recommendations highlight the role of glycemic variability and the time in ranges (including the time in target range, hyperglycemia, and hypoglycemia) as key metrics for Continuous Glucose Monitoring (CGM) [52]. The available antidiabetic treatments combined with a near-to-normal glucose levels approach, indicating the efforts of reducing high glucose levels and normalizing glycated hemoglobin levels in the absence of any contraindications, may lead to a lower frequency of T2D related microvascular and macrovascular events [110, 104]. On the other hand, intensified treatment targeting towards an intensive glucose control is associated with a higher risk of therapy-induced hypoglycemia and severe hypoglycemic events, which pose a potential risk for worsening or developing major macrovascular and microvascular complications, serious neurological consequences, as well as cardiovascular and all-cause mortality [225, 275, 51, 232]. Additionally, hypoglycemia is a severe adverse outcome that may negatively impact a patient's health and psychological status, leading to poor compliance and treatment adherence [232, 51]. Hypoglycemic events are also associated with a high direct and

indirect cost for patients, healthcare systems, and society [232, 22]. Thus, the accurate prediction of blood glucose variations and, in particular, hypoglycemic events is of paramount importance to avoid potential detrimental complications and adjust the therapeutic strategy in a more optimized and personalized treatment strategy for patients with T2D. To this end, well developed predictive models with high sensitivity and accuracy, which are easy to implement, may facilitate better glycemic control, decrease the occurrence of hypoglycemic episodes or related complications and increase the quality of life in this population. Of note, due to the complexity of the blood glucose dynamics, the design of physiological models that produce an accurate prediction in every circumstance, i.e., hypo/normo/hyperglycemic events, is met with substantial restrictions.

Recently, machine learning has been shown to be very effective in solving classification and regression problems, and the ever-growing availability of already collected personal data makes the prediction of diabetic blood glucose through data-driven approaches possible [191, 131, 244]. Machine learning based data-driven approaches use the individual's recorded data, and require little understanding of the underlying physiological mechanism. Blood glucose dynamics in patients with type 2 diabetes are affected by factors such as pancreatic function, insulin levels, carbohydrate intake, history of dysglycemia and the level and extent of physical activity. Models using combinations of input parameters accounting for these factors have been previously considered [70, 49]. Many different machine learning methods have also been tested, including traditional machine learning methods, e.g., auto-regression with exogenous input (ARX) [250], support vector machines (SVM) [221], Gaussian process (GP) [226], and ensemble methods [187], as well as deep learning approaches, e.g., feed-forward neural networks (FNNs), recurrent neural networks (RNNs), and convolutional neural networks (CNNs). For more details of the studies until 2018, we refer

the readers to relevant review papers [191, 131, 244].

Due to its predictive effectiveness, deep learning has quickly become quite effective in blood glucose prediction since 2018 [4, 175, 162, 163, 70, 250, 186, 184]. Among different deep learning approaches, RNNs based on the long short-term memory (LSTM), have been designed for sequence prediction problems and are the most commonly used models [4, 175, 250, 186, 70]. However, there is no significant advantage observed by using the vanilla LSTM or convolution networks compared to a classic model (e.g., ARX), and in some cases RNNs or CNNs could showcase lower performance, as shown in a recent benchmarking study [250]. To achieve better prediction accuracy, more advanced network architectures have recently been developed, e.g., the recurrent convolutional neural network [162], which includes a multi-layer CNN followed by a RNN, and GluNet [163] based on the Wavenet architecture first presented in [190].

Deep learning usually requires a large amount of data to train the networks, therefore, they are usually trained by population level rather than individual level data [244, 162, 163]. However, due to the variability of blood glucose dynamics among different patients and the heterogeneity of patient treatment response [239], the models trained only by population level data cannot guarantee accurate prediction for each individual patient. To address the problem of *small dataset*, transfer learning [192, 241, 223, 273] can be employed, which stores knowledge gained while solving one problem (i.e., population data) and then applying it to a different but related problem (i.e., patient-specific data). Transfer learning has been employed in blood glucose prediction very recently [70, 186, 272, 54, 183], but in these studies the patient-specific model based on transfer learning performed similarly to the population-based model or other classic machine learning models.

In addition to the problem of small data, another challenge in diabetic blood glucose prediction is the *data imbalance*. In particular, the dataset of normal-level blood glucose measurements (called *majority class*) is orders-of-magnitude larger than the dataset of blood glucose measurements with specific symptom (called *minority class*), e.g., hypoglycemia. The model trained on the imbalanced dataset leads to a biased performance, i.e., the accuracy of the minority class is much worse than that of the majority class [130]. To address the data imbalance issue, various general approaches have been developed [103, 80, 130], including pre-processing approaches, algorithmic centered approaches, and hybrid approaches, but learning from imbalanced data effectively and efficiently is still an open problem [140].

In this study, we tackle both the challenge of small datasets as well as the challenge of imbalanced datasets, by leveraging recent advances in deep learning and developing new methods for patient-specific prediction of diabetic blood glucose. First, we consider three neural network architectures and compare their performance systematically. These three representative architectures are RNNs with the GRU cell [42], gated convolutional neural networks (CNN) [91], and self-attention networks (SANs) [235], all of which show their unique advantages due to the difference in architecture designs for sequence classification, especially time-dependent sequences. Given the flexible structure of neural networks, we are presented with numerous ways of fine-tuning in the transfer learning step. However, as noted in [100], the performance of each fine-tuning technique is task-specific. To the best of our knowledge, there is no established consensus on the optimal fine-tuning technique for short-term glucose prediction. Hence, we develop four transfer learning strategies for our glucose prediction task. Specifically, we examine the performance of these four transfer learning techniques by comparing the results of predicting hypoglycemia vs. normoglycemia

vs. hyperglycemia obtained from RNN, CNN and SAN models in the setting of individual-based training. In addition, we consider new pre-processing approaches to address the data imbalance issue, because they are only performed on training data and can be directly combined with any neural network algorithm. Besides the common approach of re-sampling, where the training data is augmented by repeating existing samples, we also used other data augmentation techniques to generate synthetic data, including adding random noises and employing the recent techniques of mixup [268] and time-series generative adversarial networks (TimeGAN) [266]. While mixup has been very popular in computer vision tasks [245], TimeGAN is designed specially for time series prediction tasks. In this work, we test the performance of mixup and TimeGAN for data augmentation in the short-term blood glucose prediction task. To compare the performance of our algorithms with existing literature, we evaluate the proposed algorithms using a public dataset OhioT1DM [173], documenting the CGM history and physiological metrics of several patients with type 1 diabetes. We then examine the performance of our algorithms on a private dataset recording blood glucose data for patients with type 2 diabetes. We include the details of our study design and blood glucose (BG) data collection in the Materials and Methods section. Taken together, herein we propose a model capable of predicting blood glucose variability in patients with type 2 diabetes with high sensitivity and specificity for the longest prediction horizon (time period after 30 minutes of BG collection) possible. More broadly, our combined methodology for tackling the fundamental problems of small and imbalanced datasets can be transferred to many other biomedical applications for predicting the outcomes of diseases using bio-signals and time-series data, e.g., classification of abnormal cardiac rhythms using data collected from wearable devices [227] or electrocardiogram [204], detection of seizure [2] and Alzheimer’s disease [134] using electroencephalography.

In complementary to the deep learning based algorithm for short-term blood glucose prediction in the aforementioned study, further efforts are needed to minimize the frequency and magnitude of hypoglycemia in the long-term [51]. While some researchers asserted that recurrent hospitalization due to severe hypoglycemia may reflect underlying deficiencies in patient care and diabetes management [178], others support that the occurrence of severe hypoglycemia might be seasonal and might fluctuate with temperature changes and suggested that patients should be treated more carefully during the season in which severe hypoglycemia is more common [229]. Preventing recurrence of severe hypoglycemia episodes in the long run could help preventing consequent hospitalizations and readmissions.

An apparent challenge to face with is the multi-modality of the medical records, for example, for patients with diabetes, the medical records are always a collection of comprehensive data including static information like patients' demographic data as well as dynamical information like patients' metabolism measurements during follow-ups (blood glucose levels and HbA1c levels) and initial screening. This challenge calls for sophisticated models that can handle static information and dynamical information together. Recently, with the emergence of machine learning, researchers are able to perform complicated feature extraction and hence prediction from high-dimensional data, such as the time-series, and unstructured data, like electronic medical records [184]. Using a large multi-institutional random trial dataset, namely The Action to Control Cardiovascular Risk in Diabetes (ACCORD) dataset, we develop machine learning algorithms that is capable of detecting severe hypoglycemia events one year in advance, using the past one year EHR data from patients. Specifically, by separating the unstructured data using medical domain knowledge into different groups, i.e., different views in the multi-view machine learning algorithm, we improve the accuracy and scalability of algorithms designed for unstructured data like EHR

data.

3.1.2 Methods

Short-term glucose prediction

Problem setup. The use of blood glucose (BG) history of patients with T2D in this study were approved by the institutional review board (IRB) of the Beth Israel Deaconess Medical Center. Informed consents were obtained from all human participants. The BG level was measured every 5 minutes by a Continuous Glucose Monitoring System. We analyzed data obtained from 40 outpatients with diabetes (19 males; age 65 ± 8 years; BMI at 30 ± 5 ; with a mean HbA1c level at 7.33%), who contributed a mean of 130.6 mg/dL blood glucose level through CGM (BG ranging from 40 mg/dL to 400 mg/dL). Individuals were eligible for inclusion if they were adults with a diagnosis of T2D patients using CGM. We present the blood glucose history of four selected patients in Figure A.2. 10 patients (25% of the participants) were treated with insulin while 27 (67.5% of the participants) were receiving oral or (non-insulin) injectable antidiabetic drugs. The rest of the patients (3 patients, 7.5% of the participants) were treated without oral nor insulin medications. We identified all level 1 hypoglycemic (BG level less than 80 mg/dL) and hyperglycemic (BG level greater than 180 mg/dL) episodes from the CGM recordings. To facilitate the network training, the BG levels were scaled by 0.01 [182], and we applied a smoothing step on the BG measurements to remove any large spikes that may be caused by patient movement, as suggested in [180]. An overview of the dataset used in this work can be found in Table 3.1.

The primary outcome of interest in this study is the BG values in the future, e.g., 30 min later. We take the BG measured in 30 minutes (7 BG values) as one

Demographics	N = 40
Age, years	64.5 (58.8, 70.0), 65.1 ± 8.8
Female, No. (%)	21 (52.5)
Body Compositions	
Body Mass, kg	81.0 (71.3, 94.2), 84.1 ± 18.7
Height, m	1.64 (1.59, 1.73), 1.66 ± 0.10
BMI, kg/m ²	29.7 (26.6, 33.1), 30.1 ± 5.1
Hormone Levels	
Cortisol, $\mu\text{g/dL}$	15.9 (13.0, 20.2), 16.1 ± 6.0
Leptin, ng/dL	19.8 (9.57, 31.1), 23.0 ± 17.8
Fasting Glucose, mg/dL	117.5 ± 17.9
Insulin, $\mu\text{IU/mL}$	13.33 ± 13.29
HOMA1-IR	3.51 ± 3.47
Blood Glucose Data Brief	
Data Reading Length (hours)	90 (82, 170), 117 ± 63
Model Input BG Length (minutes)	30
Hypoglycemia Threshold (mg/dL)	80
Hyperglycemia Threshold (mg/dL)	180
HbA1c (%)	7.33 ± 1.31

Table 3.1: **Baseline characteristics of the study participants and an overview of the blood glucose data.** Normally distributed variables are presented in mean $\pm$ standard deviation form, otherwise as median (first quartile, third quartile) and mean $\pm$ standard deviation form. N, the number of participants. HOMA1-IR, the homeostatic model assessment index for insulin resistance. We choose 80 mg/dL as the hypoglycemia threshold, because recent results by Farrell et al. [69] have revealed a measurement artifact, i.e., that the real-time CGM underestimates the degree of hypoglycemia by a difference of 10 mg/dL, as shown in Figure A.1.

input data segment and predict the future BG level after a prediction horizon, a time period from the most recent CGM measurement in the input BG values, as shown in Fig. 3.1.

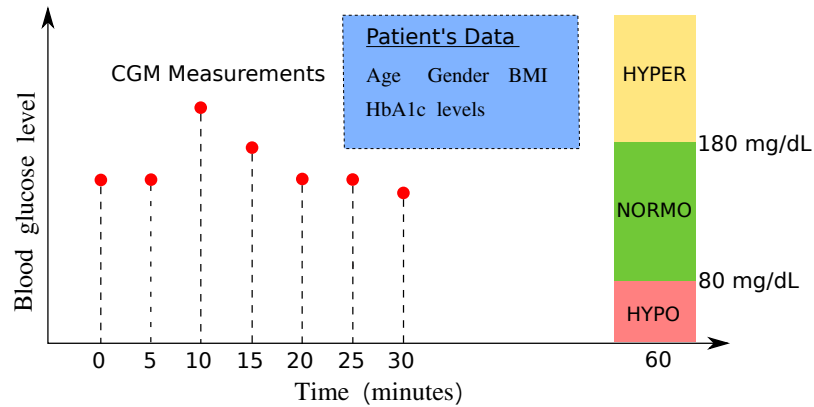


Figure 3.1: **Patient-specific prediction of diabetic blood glucose.** We use the patient’s blood glucose levels (every 5-min measurements) during several time periods in the past (e.g., 30 mins) along with key and widely available patient’s personal data to predict the patient’s blood glucose level in the future (e.g., 30 min later). In particular, we aim to detect hyperglycemia (HYPER, blood glucose level > 180 mg/dL) and hypoglycemia (HYPO, blood glucose level < 80 mg/dL). NORMO, normoglycemia, $80 \text{ mg/dL} \leq \text{blood glucose level} \leq 180 \text{ mg/dL}$.

Neural network architectures. We developed new deep learning methods for patient-specific blood glucose level prediction. We considered three different neural network architectures, including recurrent neural networks (RNN) [109, 42], gated convolutional neural networks (CNN) [91], and self-attention networks (SAN) [235] as well as three different transfer learning strategies. We also implemented Gaussian process regression (GP), fully-connected feedforward neural networks (FNN), and support vector machine (SVM) as the baseline models. We implement GP and SVM with the `sklearn` library [196]. For GP, we use a combined kernel consisting of a constant kernel, a radial basis function kernel and a white noise kernel. For SVM, we use the default hyperparameters. For FNN, we use a 10-neuron-width, 3-layer-depth

network. The detailed hyperparameters of the baseline models are optimized via grid search and can be found in the released code repository. To tackle the important issue of data imbalance, we tested four different data augmentation methods, i.e., oversampling by repeating, infusing Gaussian noises, TimeGAN and mixup, on the minority class.

The dominant deep learning method used for sequence learning is the RNN, which is a class of neural networks that allow previous outputs to be used as the inputs of the current step. The cell units in RNNs are usually chosen as long short-term memory units (LSTM) [109] and gated recurrent unit (GRU) [42], which deal with the vanishing gradient problem encountered by traditional RNNs. In addition to RNNs, CNNs and self-attention networks were proposed recently for time series forecasting, and achieved better performance than RNNs for certain tasks. In the gated CNNs, 1 dimensional (1-D) convolutional kernels create hierarchical representations over the input time series, in which nearby BG measurements interact at lower layers while distant BG measurements interact at higher layers. The mechanism of attention was first proposed in [12] for machine translation, and it has been shown that the network architecture based solely on self-attention mechanism can also be used successfully to compute a representation of the sequence [235]. Self-attention is an attention mechanism to compute a representation of the sequence by relating different positions of a sequence. In the RNNs, the input sequence is fed into the network sequentially, while in CNNs and self-attention networks, the input sequence is fed into the network simultaneously, and thus an embedding of the position of input elements is required [91]. For the hyperparameters in the networks, e.g., the depth and width, we perform a grid search to obtain an optimal set of hyperparameters, see Table 3.2 for more details. The details of the network architectures used in this study are shown in Fig. 3.2.

Transfer learning. To address the difficulty of obtaining a sufficient large dataset for each patient, we implemented transfer learning [192, 241, 223, 273] on the three aforementioned neural network architectures. In transfer learning, the training procedure of neural networks includes two steps: first, we pre-train the networks on other patients’ data by excluding the data from the target patient, and then we further fine-tune the network on one part of the target patient’s data, i.e., re-train the network on the training data of the target patient’s blood glucose history. Finally, we test the network on the rest of the data from the target patient. Two commonly-used further-training approaches are based on initialization and feature extraction [102]. In the initialization approach, the entire network is further trained, while in the feature extraction approach the last few fully-connected layers are trained from a random initialization while other layers remain unchanged. In this study, in addition to these two approaches, we consider a third approach by combining these two approaches, i.e., the last few fully-connected layers are further trained while other layers remain unchanged. The details of the four transfer learning methods can be found in Fig. 3.2 and Table 3.2.

	Models	Details
Network architecture	RNN	GRU size 10, 2 GRUs; FNN width 10, 1 FNN layer
	SAN	8 self-attention units; FNN width 10, 4 FNN layers
	CNN	1-D convolutional kernel size 4, 4 conv seq2seq units; FNN width 10, 3 FNN layers
Transfer learning method	Transfer1	Reuse weights of feature block and FNN block, retrain both blocks
	Transfer2	Reuse weights of feature block and FNN block, retrain FNN block
	Transfer3	Reuse weights of feature block, reinitialize FNN block, retrain FNN block

Table 3.2: **Details of the neural network architectures and transfer learning models.** GRU, gated recurrent unit; FNN, fully-connected neural networks; RNN, recurrent neural networks; SAN, self-attention networks; CNN, convolutional neural networks; conv seq2seq, convolutional sequence to sequence.

Imbalanced data. Imbalanced data has been an ubiquitous issue in many fields, causing most methods to yield erroneous predictions strongly biasing towards the

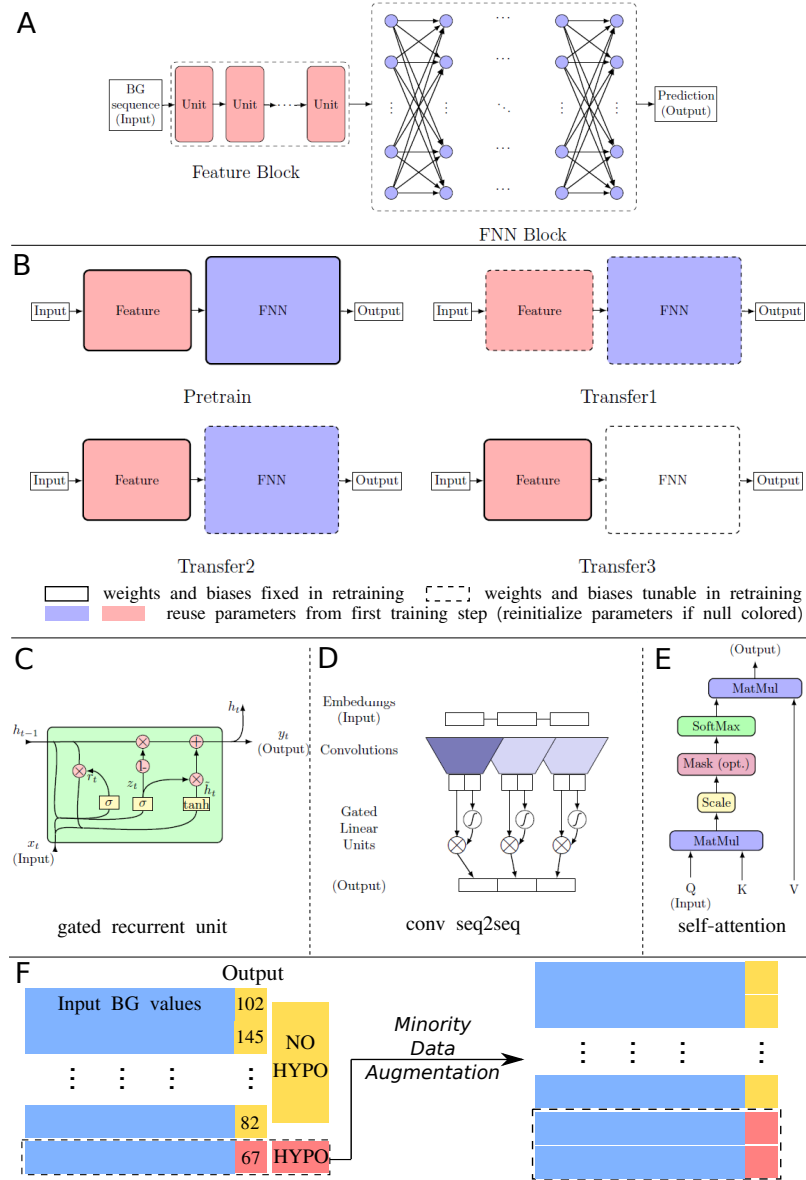


Figure 3.2: Neural network architectures, transfer learning methods and data preprocessing. (A) The general structure of the neural networks implemented, consisting of a feature block and a FNN block. The unit in the feature block is model-specific, for example, when referring to the RNN model, the units are GRUs. (B) Transfer learning methods implemented, where colored blocks represent reusing neural network parameters (weights and biases) inherited from the pre-training step, the null-colored block in Transfer3 represents re-initializing the network parameters of the FNN block. Blocks bounded with solid lines represent those blocks, of which the network parameters are frozen during retraining step. (C to E) Representations of each unit used in different types of neural networks. (C) A gated recurrent unit (GRU) used in the RNN models. (D) A convolutional sequence to sequence (conv seq2seq) unit used in the CNN models. (E) A self-attention unit used in the SAN models. More details of transfer learning can be found in Table 3.2. (F) Data pre-processing methods employed to deal with data imbalance, the minority data (sequences with hypoglycemia labels) are oversampled to increase model sensitivity for hypoglycemia detection. Output BG values greater than 80 mg/dL are labeled with “no hypoglycemia” (NO HYPO) and those smaller than 80 mg/dL are labeled with “hypoglycemia” (HYPO).

majority class. To reduce the hazardous effect of imbalanced data, we can improve the method with various techniques: (i) modifying the imbalanced data set by some mechanisms such as oversampling or undersampling or both to provide a balanced distribution; (ii) designing problem-specific cost matrices to describe the costs for misclassifying any particular data example; (iii) using boosting methods [222, 106]. Here, we tested several methods for data augmentation on the training data of the minority class only, i.e., oversampling by repeating, adding Gaussian white noises to the input data, generating synthetic minority samples using TimeGAN [266] and mixup [268]. We compared the performance of these preprocessing techniques in terms of four classification metrics, i.e., sensitivity, positive predictive value, specificity and negative predictive value.

Model validation. For model validation, if the networks are trained on multiple patients, then we used a Leave-one-out cross-validation (LOOCV), i.e., we randomly selected the dataset of one patient to be the test dataset and used the dataset of the remaining patients to train the model. The outcome variables indicate whether or not hypoglycemia or hyperglycemia occurred. The model performance is measured in terms of the prediction accuracy, which is defined as follows,

$$\text{accuracy} = \frac{TP + TN}{TP + FN + TN + FP}, \quad (3.1)$$

and the area under the receiver operating characteristic curve (AUROC). To calibrate the data augmentation effect on the imbalanced dataset, we computed four classification metrics, sensitivity, positive predictive value (PPV), specificity and negative

predictive value (NPV) from the following formulas:

$$\begin{aligned} \text{sensitivity} &= \frac{TP}{TP + FN}, & PPV &= \frac{TP}{TP + FP}, \\ \text{specificity} &= \frac{TN}{TN + FP}, & NPV &= \frac{TN}{TN + FN}. \end{aligned} \quad (3.2)$$

where TP denotes the number of true positives, FP denotes that of false positive, TN denotes the number of true negatives and FN denotes that of false negatives.

Long-term hypoglycemia detection

Problem setup. The use of ACCORD dataset in this study were approved by the institutional review board (IRB) of the Beth Israel Deaconess Medical Center. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is a randomized, multicenter, double 2×2 factorial design study involving 10,251 middle-aged and older participants with type 2 diabetes who are at high risk for cardiovascular disease (CVD) events because of existing CVD or additional risk factors [30].

We focus on detecting 1-year severe hypoglycemia episodes, which is a binary prediction task. The positive class of the binary classification, namely severe hypoglycemia, is defined by the simultaneous occurrence of two conditions, i.e., 1) the patient had a glucose level lower than 50 mg/dL and 2) the patient either asked for medical assistance or was hospitalized within a prediction window of one-year. To build a predictive model, we use potential predictive variables hand-picked with clinical domain knowledge from the ACCORD dataset relevant to our prediction goal. A brief summary of the relevant predictive variables is given in Table 3.3. As shown in Fig. 3.3, the selected variables can be divided into static variables, such as age and race, which are not time-dependent, or dynamic variables, such as hbA1c (glycated hemoglobin) and FPG (fasting plasma glucose), measuring the glycemia of patients,

which will change over time depending on the severity of the diabetic condition of patients. We note here that though body mass index (BMI) is naturally time-varying, it is treated as a static variable in our analysis since the ACCORD dataset only provides the baseline BMI of patients.

The static variables remain in their original form in the model inputs. The dynamic variables in Table 3.3 are preprocessed as follows. Firstly, we perform forward missing data imputation, i.e., data missed at i th visit is imputed with the closest known data in the previous visits. Consequently, for each variable, we split the whole 7-year sequence into 7 subsequences and we compute the mean and standard deviation of each subsequence (one-year long sequence) and consider them all together as the model input. After data preprocessing, we finally have 1176 patients with known outcomes, where each patient has 6 years of labeled data, i.e., for each patient, we have 6 pairs of data with both the input features and the corresponding outcome. We also have the input features for the rest of the patients (9068 patients) without known outcomes, namely unlabeled data.

Variables by group	Description	Format
<i>Demographics</i>		
Gender	female or male	static, categorical (1 for female, 0 for male)
Race class	the race of patient	static, categorical value among “white, black, hispanic and other”
Baseline_age	baseline age at initial recruit	static, integer
<i>Baseline physical measurements</i>		
livealon	whether patient live alone	static, boolean (0 for no, 1 for yes)
edu	patient’s education level	static, integer from 1 to 4
yrsdiab	length of diabetes history	static, integer greater than 0
BMI	body mass index	static, float
waist_cm	waist circumference in centimeter	static, float
<i>Glycemic measurements</i>		
hbA1c	glycated hemoglobin level	dynamic, float
FPG	fasting plasma glucose level	dynamic, float
<i>Medications</i>		
Sulfonylurea	whether patient receive Sulfonylurea at visit	dynamic, boolean (0 for no, 1 for yes)
Meglitinide	whether patient receive Meglitinide at visit	dynamic, boolean (0 for no, 1 for yes)
nphl.insulin	whether patient receive Neutral Protamine Hagedorn insulin or L insulins at visit	dynamic, boolean (0 for no, 1 for yes)
lis_as insulins	whether patient receive Lispro or Aspart insulin at visit	dynamic, boolean (0 for no, 1 for yes)
pth.bol insulins	whether patient receive other bolus insulins at visit	dynamic, boolean (0 for no, 1 for yes)
premixed insulins	whether patient receive premixed insulins at visit	dynamic, boolean (0 for no, 1 for yes)
<i>Glycemic managements</i>		
g1check	average frequency of blood sugar check, times per week at visit	dynamic, integer
g1diabed	general diabetes education time (minutes)	dynamic, integer
g1nutrit	nutrition education time (minutes)	dynamic, integer
g2hwofba	frequency of insulin injection/inhalation as prescribed for basal insulin at visit	dynamic, integer
g2hwofbo	frequency of insulin injection/inhalation as prescribed for injected bolus insulin at visit	dynamic, integer
g2aveba	total basal insulin/day at visit	dynamic, float
g2avebol	total bolus insulin/day at visit	dynamic, float

Table 3.3: **Predictive variables from ACCORD dataset used in one-year severe hypoglycemia prediction.** A static variable denotes a variable not changing over time, while a dynamic variable denotes a variable being updated each time the patient visit the clinic.

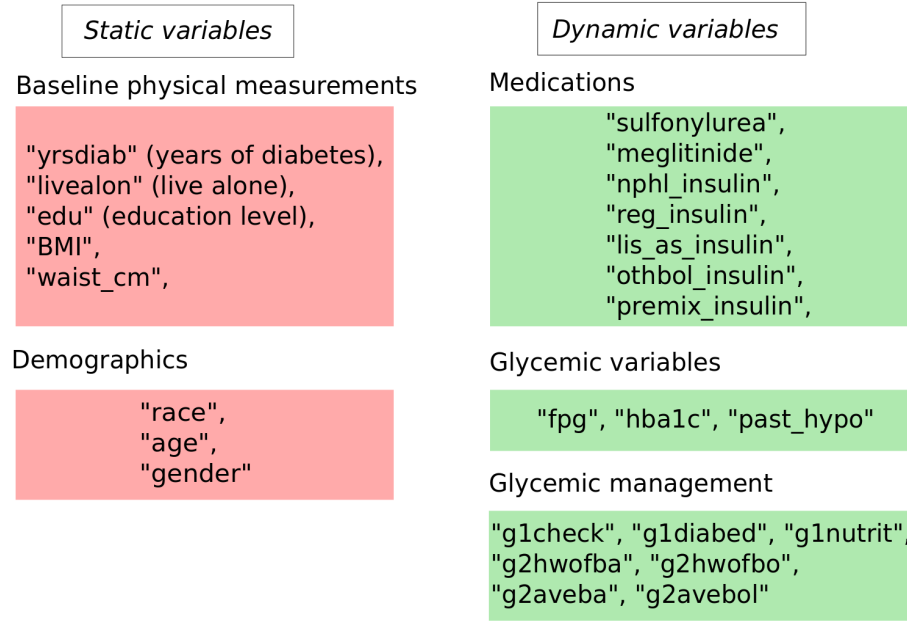


Figure 3.3: **Predictive variables categorized by time-dependency.** “yrsdiab” denotes years of diabetes history; “livealone” denotes whether the patient lives alone; “edu” denotes education level; “BMI” denotes body mass index; “waist_cm” denotes the waist circumference in centimeter; “sulfonylurea” and “meglitinide” are drugs lowering blood glucose levels; “nphl_insulin” denotes Neutral Protamine Hagedorn insulin or L insulins; “reg_insulin” denotes regular insulin; “lis_as_insulin” denotes Lispro or Aspart insulins; “othbol_insulin” denotes other bolus insulin; “premix_insulin” denotes premix insulin; “fpg” denotes fasting plasma glucose level; “hba1c” denotes glycated hemoglobin level; “past_hypo” denotes whether severe hypoglycemia occurred before the time of prediction; The full explanations of the abbreviations of glycemic management variables can be found in Table 3.3.

Multi-view learning As shown in Fig. 3.4, all available features are concatenated into one single vector as the only input vector in single-view learning, the input vector is then fed into the classifier for training. Whereas, in multi-view learning, features are separated into different groups, namely views, in order to enhance the ability of representation of all available features. In this work, we separate the selected features in Table 3.3 into different views in Fig. 3.3, according to our clinical domain knowledge. Specifically, each group of features is trained with different classifiers,

meaning that even if each group is trained with one type of classifier, for example, both using the logistic regression classifier, the hyperparameters of the classifier for view 1 and those for view 2 can be different. The final prediction of multi-view learning is then decided by ensembling the individual prediction of classifiers for each view. For multi-view learning with the unlabeled dataset, the unlabeled data is fed into the trained classifiers during the training process to create pseudo labels and the final pseudo label for each unlabeled sample is decided by the mode of the pseudo labels generated by the classifiers in different views.

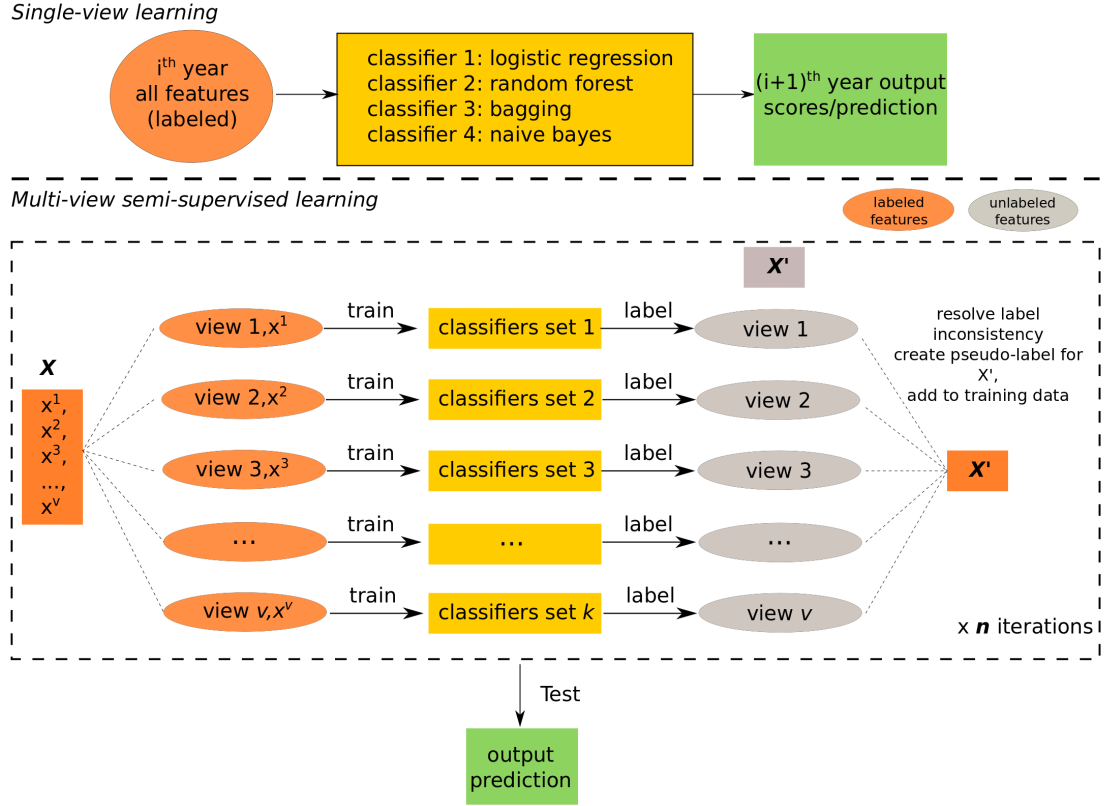


Figure 3.4: **Schematics of multi-view learning used in this work.** In single-view learning, all features of each patient are concatenated into a vector and fed into each set of classifiers. We present four classifiers as an example for a demonstration purpose. The type of classifiers can be varied in the real application. In multi-view learning, all selected features are grouped into separate vectors and then fed into different sets of classifiers.

Data imbalance Since EHR data has a highly unstructured data format, there are limited data augmentation techniques we can choose from, except for oversampling. Additionally, it is believed that complement naive bayes is particularly suited for imbalanced data sets [208]. Hence, we also try complement naive bayes to handle the problem of data imbalance.

3.1.3 Results and discussion

Short-term glucose prediction

Patient-specific prediction of blood glucose According to Cox et al. [50], severe hypoglycemia (SH) often follows a specific blood glucose fluctuation pattern that is identifiable from self-monitoring blood glucose; hence, we consider the 30-min blood glucose as the primary predictor and the future glycemia as the target prediction. In this paper, we consider the following two classification tasks of diabetic blood glucose, i.e., one classification is “hypoglycemia” vs. “no hypoglycemia” and the other is “hypoglycemia” vs. “normoglycemia” vs. “hyperglycemia”, with the setup shown in Fig. 3.1. Specifically, the threshold for hyperglycemia is set to 180 mg/dL, i.e., blood glucose levels higher than 180 mg/dL are labeled with “hyperglycemia”. On the other hand, we set the threshold for hypoglycemia to be 80 mg/dL, i.e., we label blood glucose levels lower than 80 mg/dL as “hypoglycemia”. Here, unlike the common definition for level 1 hypoglycemia based on the threshold of 70 mg/dL, we instead choose 80 mg/dL as the hypoglycemia threshold. This is because recent results by Farrell et al. [69] have revealed a measurement artifact, i.e., that the real-time Continuous Glucose Monitoring (CGM), where we would expect these algorithms to have clinical applicability, underestimates the degree of hypoglycemia by a difference of 10 mg/dL, as shown in Figure A.1.

Deep transfer learning for small patient-specific data. We compare the performance of three neural network architectures by the averaged prediction accuracy per capita for these two classification problems. The results in Fig. 3.5 suggest that as the training data size from the target patient increases, the prediction accuracy of all models generally increases. We note that CNN models are generally more accurate than RNN models and slightly outperform SAN models with higher mean and smaller standard deviation for prediction accuracy in both of the classification tasks. The results also suggest that the transfer learning models (Transfer1 and Transfer2) can sometimes outperform the pre-trained models in CNN models. We also compared our models with some existing classification methods, i.e., logistic regression, GP, SVM, and FNN in terms of 1) Predicting hypoglycemia vs. no hypoglycemia (Table A.12); 2) Predicting hypoglycemia vs. normoglycemia vs. hyperglycemia (Table A.13) over a prediction horizon of 30 minutes; 3) Predicting hypoglycemia vs. no hypoglycemia (Table A.14); 4) Predicting hypoglycemia vs. normoglycemia vs. hyperglycemia (Table A.15) over a prediction horizon of 60 minutes. In both tasks, our models showed consistent increases in accuracy and the area under the receiver operating characteristic curve (AUROC) given more training data from the target patient and, specifically, better than those by existing classification methods examined in predicting hypoglycemia vs. normoglycemia vs. hyperglycemia.

Fig. 3.6 shows the sensitivity analysis of the prediction horizon on the prediction accuracy and Fig. 3.7 shows the ROC curves (receiver operating characteristic curves) of best models among all the models tested, given the training data size from the target patient around 1000 data segments. The sensitivity between different prediction horizons is negligible in predicting hypoglycemia vs. no hypoglycemia (binary classification), while the sensitivity between different prediction horizons becomes larger when the time elapse of two prediction horizons is large in predicting hypoglycemia

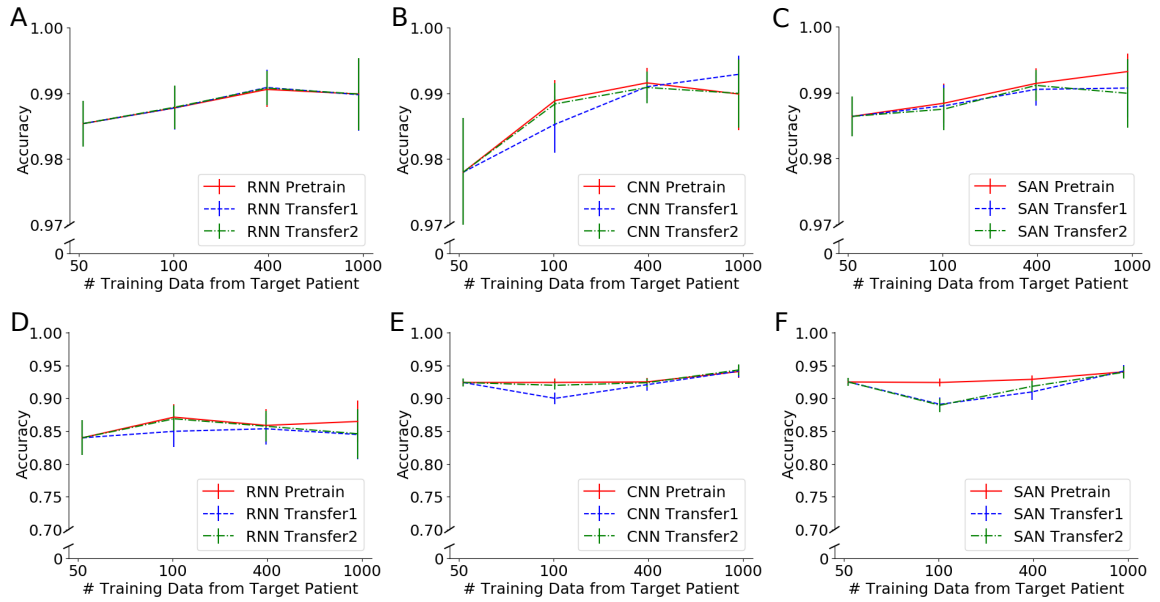


Figure 3.5: **Prediction accuracy comparison among different architectures (RNN, CNN, and SAN) with respect to the number of training data from the target patient in two classification tasks.** (A to C) Prediction accuracy of the binary classification, i.e., identifying the neural network output as hypoglycemia or no hypoglycemia, using (A) RNN, (B) CNN, and (C) SAN. (D to F) Prediction accuracy of the three-class classification, i.e., identifying the neural network output as hypoglycemia or normoglycemia or hyperglycemia, using (D) RNN, (E) CNN, and (F) SAN. The data from a target patient is divided into two parts, one is for training and the other is for testing, and the prediction horizon is fixed at 30 minutes. The accuracy of Transfer3 is lower compared to other transfer learning methods. Here, CNN Pretrain and Transfer2 as well as SAN Pretrain show the best performance.

vs. normoglycemia vs. hyperglycemia (three-class classification).

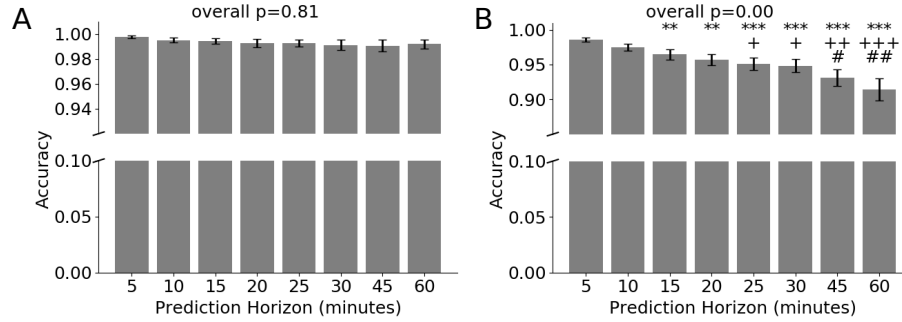


Figure 3.6: Prediction accuracy for two classification tasks given different prediction horizons using the best CNN model. Prediction accuracy for (A) binary classification, i.e., identifying the neural network output as hypoglycemia or no hypoglycemia, and (B) three-class classification, i.e., identifying the neural network output as hypoglycemia or normoglycemia or hyperglycemia, given different prediction horizons. No statistical significance is observed for binary classification. *, p-value ≤ 0.05 ; **, p-value ≤ 0.01 ; ***, p-value ≤ 0.001 , in comparison to the prediction horizon at 5 minutes; +, p-value ≤ 0.05 ; ++, p-value ≤ 0.01 ; +++, p-value ≤ 0.001 , in comparison to the prediction horizon at 10 minutes and #, p-value ≤ 0.05 ; ##, p-value ≤ 0.01 ; ###, p-value ≤ 0.001 , in comparison to the prediction horizon at 15 minutes.

We evaluate the performance of our models on the OhioT1DM dataset, a de-identified public dataset recording the glucose level, insulin dosage, exercise and other metabolism readings for 6 patients with type 1 diabetes in the 2018 version and another 6 patients with type 1 diabetes in 2020 version [173]. We demonstrate the performance of our model by evaluating it on the dataset of 6 patients in the 2020 version. Specifically, the training data is the union of all the training data of the 12 patients and the testing data of the 6 patients in the 2018 version. We discard any training sequences with one or more missing data points. The training process of our model is again two-step, i.e., in the first training step, we pretrain the model on the training data excluding the training data of the patient to be tested; in the second training step, we fine tune the model on the training data of the patient to be tested; finally we test the model on the testing data of the target patient.

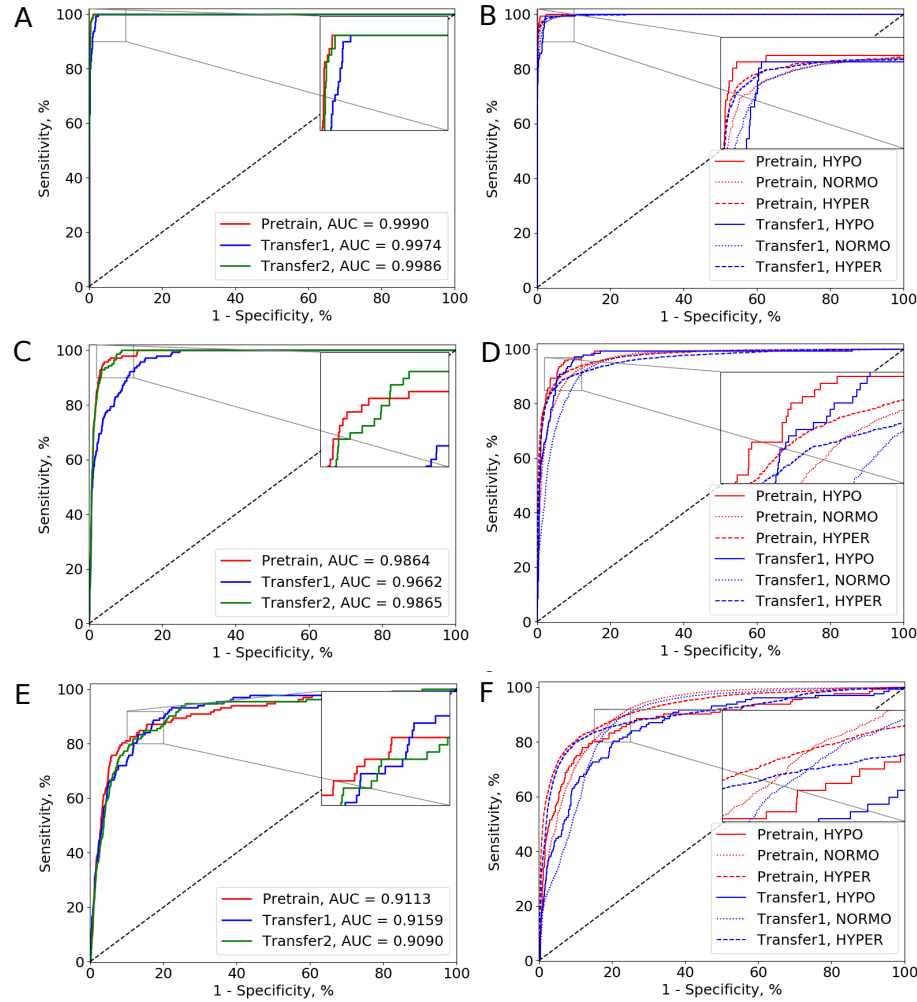


Figure 3.7: **ROC curves for two classification tasks given prediction horizons at 5 minutes, 30 minutes and 60 minutes using the best CNN model.** (A, B) Examples of the ROC curves for the prediction horizon at 5 minutes, in (A) binary classification and (B) three-class classification. (C, D) Examples of the ROC curves for the prediction horizon at 30 minutes, in (C) binary classification and (D) three-class classification. (E, F) Examples of the ROC curves for the prediction horizon at 60 minutes, in (E) binary classification and (F) three-class classification. AUC, area under the ROC curve. Binary classification denotes predicting hypoglycemia vs. no hypoglycemia. In three-class classification, we iterated over the labels (HYPO for “hypoglycemia”, NORMO for “normoglycemia” and HYPER for “hyperglycemia”) to compute the ROC curves. The results by Transfer2 are comparable to those by Pretrain while those by Transfer3 are worse than Transfer1 and Transfer2, hence we only show the results of Pretrain and Transfer1 for brevity.

To make a fair comparison, we compare our model performance with those using historical blood glucose levels as the only predictor and 30 min as the sampling horizon [133, 19, 128, 168]. Similarly, all models are evaluated on 6 patients in the 2020 dataset, see Table 3.4. The results in Table 3.4(a) suggest that our best model (CNN

Table 3.4: **Performance comparison between our best model and other models using only blood glucose levels as the model input on OhioT1DM dataset.** (A) Our model outperforms other models in terms of mean absolute error in both 30 and 60 min prediction horizon. We report the mean of the results over 5 different runs. (B) Our model for binary classification (hypoglycemia vs. no hypoglycemia) outperforms that by Bevan et al. in terms of accuracy, sensitivity and F1 score of the positive class (the hypoglycemia class). The classification results are obtained by setting a 80 mg/dL threshold to the blood glucose level, i.e., blood glucose level less than 80 mg/dL is labelled with positive class (hypoglycemia class), while those greater than 80 mg/dL with negative class (no hypoglycemia class). Our best model is CNN + Transfer2. MAE, mean absolute error; RMSE, root mean squared error; PPV, positive predictive value; NPV, negative predictive value. *, denotes the 30 min RMSE of the model by Bevan et al. [19] without imputing missing values with the mean of training dataset.

(A): Regression results for prediction horizon at 30 min and 60 min

Metrics	Ours	Bevan et al. [19]	Khadem et al. [133]	Joedicke et al. [128]	Ma et al. [168]
30 min MAE	13.53	14.37	14.14	15.50	14.52
30 min RMSE	19.08	18.23 (18.82*)	19.40	24.51	20.03
60 min MAE	24.65	25.75	25.32	24.78	26.40
60 min RMSE	33.80	31.10	33.91	38.66	34.89

(B): Binary classification results for prediction horizon at 30 min

Metrics	Ours	Bevan et al. [19]
Accuracy	95.98%	95.65%
F1 score	61.72%	57.40%
Sensitivity	59.19%	49.94%
Precision (PPV)	67.68%	69.00%
Specificity	98.15%	98.61%
NPV	97.55%	96.76%

+ Transfer2) outperforms all other models in terms of mean absolute error (MAE) in both cases of 30 min and 60 min prediction horizon. While the root mean squared error (RMSE) of our results are not the best among these five models, they are the second to the best model, i.e., the model by Bevan et al. [19], which reported RMSE

of 18.23 for 30 min prediction horizon after imputing missing value with mean value of the training dataset. Bevan et al. also reported a slightly higher RMSE at 18.82 for 30 min prediction horizon when missing data in the training sequence is discarded, which we believe is very close to our results, given the same missing data handling strategy. It is standard practice in clinical medicine to use sensitivity to evaluate the value of a test as a screening test and use specificity to evaluate the value of a test as a confirmatory test. Hence, we further examine our model performance using the regression results for binary classification of hypoglycemia class vs. no hypoglycemia class. Specifically, we set the threshold of hypoglycemia vs. no hypoglycemia to be 80 mg/dL, i.e., values less than 80 mg/dL are denoted as the positive class while greater than that as the negative class. The results of the binary classification for 30 min prediction horizon in Table 3.4(b) suggest that our model is more accurate than that by Bevan et al., i.e., higher accuracy and F1 score. Compared to the results of Bevan et al., our model shows same specificity and negative predictive value (NPV) but much better sensitivity (almost 10% higher). Hence, our model provides a better screening test (sensitivity) and equally good confirmatory test (specificity), which is an overall better test and is highly favorable in the clinical setting.

Improvement of sensitivity for imbalanced data. In this section, we show further detailed analysis with regression based models for classification, i.e., we perform regression prediction then convert the real-valued prediction into class labels, as shown in Fig. 3.1. We note that our raw BG data is innately real-valued, hence it is natural to investigate the data feature following a regression approach. Here, we aim to show the effects of different data augmentation methods mainly on the minority dataset. With our previous classification analysis, we set up the regression model with the following preconditions: the prediction horizon is 20 minutes if not

mentioned otherwise and the hypoglycemia threshold is set at 80 mg/dL. We will show results without transfer learning, i.e., we train the models on the dataset, which is the union of other patients' data except for the target patient and then directly test on the target patient's dataset. We focus on comparing the model performance in predicting hypoglycemia vs. no hypoglycemia by converting the real-valued prediction into two labels: one label is "hypoglycemia", meaning the prediction is below 80 mg/dL while the other is "no hypoglycemia", meaning the prediction is above or equal to 80 mg/dL. We also carry out the same conversion on the true BG values measured by the CGM. With the conversion, we can then compare four classification scores, sensitivity, positive predictive value, specificity and negative predictive value between different models.

Selection of loss functions. We tested the performance of four different loss functions, i.e., mean absolute error, relative mean absolute error, mean squared error and relative mean squared error using the original training dataset without data augmentation. In particular, we examined the performance of models with different loss functions using four classification metrics, i.e., sensitivity, positive predictive value (PPV), specificity and negative predictive value (NPV). To compute these four classification metrics, the real-valued blood glucose prediction is categorized into two classes, i.e., "hypoglycemia" (positive class) and "no hypoglycemia" (negative class). Fig. 3.8(a) shows the comparison of model performance using different loss functions. The result suggests that the model using *relative mean absolute error* (REL. MAE) outperforms models using the other three loss functions, because the model using the relative mean absolute error maintains a balanced high value for each of the aforementioned four metrics. Fig. 3.8(b) shows the scatter plot of true BG vs. predicted BG also suggests high prediction accuracy with the points clustering near

the diagonal black line indicating the perfect prediction. The red lines divide the whole domain into four rectangular regions, i.e., the true positive region (TP) denoting that the true BG is “hypoglycemia” and prediction is also “hypoglycemia”; the false positive region (FP) denoting that the true BG is “no hypoglycemia” but the prediction is “hypoglycemia”; the false negative region (FN) denoting that the true BG is “hypoglycemia” but the prediction is “no hypoglycemia”; the true negative region (TN) denoting that the true BG is “no hypoglycemia” and the prediction is “no hypoglycemia”.

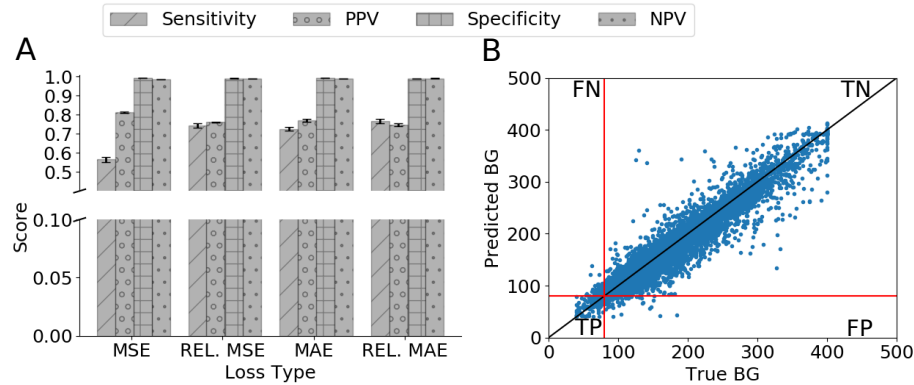


Figure 3.8: **Regression performance of the best CNN model on the original dataset (no augmentation on the training dataset), using four different loss functions.** (A) Performance comparison between four loss functions, i.e., mean squared error (MSE), relative mean squared error (REL. MSE), mean absolute error (MAE) and relative mean absolute error (REL. MAE) in terms of four prediction scores, i.e., sensitivity, positive predictive value (PPV), specificity and negative predictive value (NPV). The results suggest that the relative mean absolute error (REL. MAE) serves as the best loss function in that it maintains good and balanced performance regarding the four scores shown. Hence, we keep the REL. MAE as the loss function for the subsequent analysis. (B) True blood glucose values measured by CGM vs. the predicted blood glucose values using REL. MAE as the loss function. The blue scatter points denotes the measurement-prediction pairs. The black diagonal line denotes the perfect prediction. The red lines denote the hypoglycemia threshold 80 mg/dL.

Data augmentation. In this part, we fix the loss function in our model to be the *relative mean absolute error* (REL. MAE) and compare the performance of our model when four different data pre-processing techniques are implemented for data augmentation on the training data of the minority class.

For this data augmentation method, we repeat the minority samples (the input-output pairs where the output BG is less than 80 mg/dL) in the training dataset for k folds, i.e., for 2-fold oversampling by repeating, we duplicate the minority samples once such that the minority data is doubled in the augmented training dataset. Hence, for k -fold oversampling by repeating, we augment the training data by adding $k - 1$ copies of the training data labeled as hypoglycemia (output BG less than 80 mg/dL) to the augmented training dataset. Fig. 3.10(a) shows that oversampling by repeating only improved slightly in the sensitivity when the minority augmentation fold increases, which is different from the other three augmentation methods.

Adding Gaussian white noises to the training dataset has been proved to be an effective way of data augmentation for CNNs [162], and specifically for CNNs using wearable sensor data [231]. In this part, we tried different levels of Gaussian white noises distinguished by the variance of the noise. In particular, we infused noise with variance at 5, 10, 50 mg/dL to the input BG data of minority class, whose output BG value is below the hypoglycemia threshold, i.e., there are two copies of minority training data in the augmented dataset, one is the original copy collected by the CGMs, and the other is a copy generated by infusing Gaussian noises. Fig. 3.10(b) suggests that increasing the variance of the infused Gaussian noise will increase the sensitivity of the model.

We generated synthetic minority samples using TimeGAN [266], by training a TimeGAN using the original minority samples in our dataset. TimeGAN combines the versatility of the unsupervised GAN approach with the control over conditional

temporal dynamics afforded by supervised auto-regressive models, by leveraging the contributions of the supervised loss and jointly trained embedding network, and hence can generate realistic time-series data. Our trained TimeGAN is validated by the PCA and T-NSE plots for the original minority samples and synthetic minority samples, see Figure A.3. We then compared the performance of models when different folds of synthetic minority samples were added to augmented training dataset. Fig. 3.10(c) shows that adding more minority data generated by TimeGAN could also improve model sensitivity but not as monotonically as the other methods tested.

Zhang et al. [268] recently introduced mixup to improve the generalization of neural network architectures, by linearly interpolating between samples in the training dataset using the following formula,

$$\tilde{x} = \lambda x_i + (1 - \lambda)x_j, \quad \tilde{y} = \lambda y_i + (1 - \lambda)y_j, \quad (3.3)$$

where $\tilde{x}, \tilde{y}$ denote generated input and output, respectively; λ is a hyperparameter following the Beta distribution, $\text{Beta}(\alpha, \alpha)$; x_i, x_j denote inputs from two different samples and y_i, y_j denote the corresponding output of those two different samples. We note that in the original mixup algorithm, y_i, y_j can be of different class, while in our model we only perform mixup on the minority class, i.e., y_i, y_j satisfy the condition that $y_i < 80$ and $y_j < 80$.

There have been some attempts to perform data augmentation using mixup in time-series analysis of biosignals, such as electroencephalogram (EEG) and electrocardiogram (ECG) [34], generating virtual biosignals from real biosignals of different types [1]. To the best of our knowledge, our work may be the first to implement mixup for data augmentation on minority class only to alleviate the effect of data imbalance

as well as the first to implement k -fold mixup. By k -fold mixup, the size of the minority class is increased to k times of its original size by adding $k - 1$ copies of synthetic data using mixup for each training epoch. The original mixup algorithm does not include k as a hyperparameter, i.e., in the original mixup, the original training data is replaced by synthetic data generated by linear interpolation in the beginning of each training epoch. Fig. 3.10(d) shows that increasing the folds of minority data by mixup could help improve model sensitivity but the uncertainty in the positive predictive value is relatively larger than other augmentation methods.

The hyper-parameter α in the Beta distribution $\text{Beta}(\alpha, \alpha)$ of mixup is a very sensitive parameter controlling the diversity of the synthetic samples, i.e., higher α produces samples more resembling to the reference real data while lower α introduces samples very different from the reference real data. With $\alpha = 1$, $\text{Beta}(1, 1)$ is equivalent to a uniform random distribution. Here, we compare the performance of our model given $\alpha = 0.4$ and $\alpha = 2$ in 2-fold mixup, in terms of two classification scores, i.e., positive predictive value (PPV) and sensitivity for the positive class (the minority class, hypoglycemia samples), and examine the sensitivity of those two classification scores for different prediction horizons. The results for $\alpha = 0.4$ and $\alpha = 2$ are shown in Fig. 3.9. We note that mixup with either $\alpha = 0.4$ or $\alpha = 2$ improves the model sensitivity over different prediction horizons. Specifically, models trained on the training dataset augmented by mixup show high sensitivity within all the prediction horizons examined while the model without data pre-processing shows decreased sensitivity over longer prediction horizons. The model trained on the training dataset augmented by mixup $\alpha = 0.4$ shows different uncertainty in the predictive scores for different prediction horizons; for example, the standard deviation of sensitivity and PPV for prediction horizon at 15 minutes are much larger than those for other prediction horizons. However, the model trained on the training dataset augmented by

mixup $\alpha = 2$ shows similar uncertainty in the predictive scores among different prediction horizons, mainly because samples generated by mixup $\alpha = 0.4$ are relatively distinct from the original samples collected while those by mixup $\alpha = 2$ is similar to the original samples, hence preserves the data patterns. As the prediction horizon increases, the sensitivity of the model decreases while the PPV increases when training on the raw dataset. However, the models trained on datasets augmented by mixup show high sensitivity and a gradual drop in the PPV, regardless of the increase in the prediction horizon.

The results in Fig. 3.10 indicate that by adding more training data of minority class, either through duplication or synthesizing, will increase the model sensitivity but decrease the positive predictive value, i.e., the precision for minority class. Specifically, given the same amount of minority samples in the training data, the increase in model sensitivity and decrease in precision for minority class is more significant in those with synthetic minority samples, compared to the oversampling by repeating. These results prove a recent finding that transforms (augmentations) which preserve the labels of the data can improve estimation by enlarging the span of the training data [245]. In our case, we preserve the labels of the data by only augmenting the minority training data, which consequently increases the span of minority data, by generating synthetic data using Gaussian noise, TimeGAN or mixup. Our results also suggest that synthetic minority data (data generated by infusing Gaussian noise, TimeGAN or mixup) could increase the span of minority data much more significantly than repeating the original minority data.

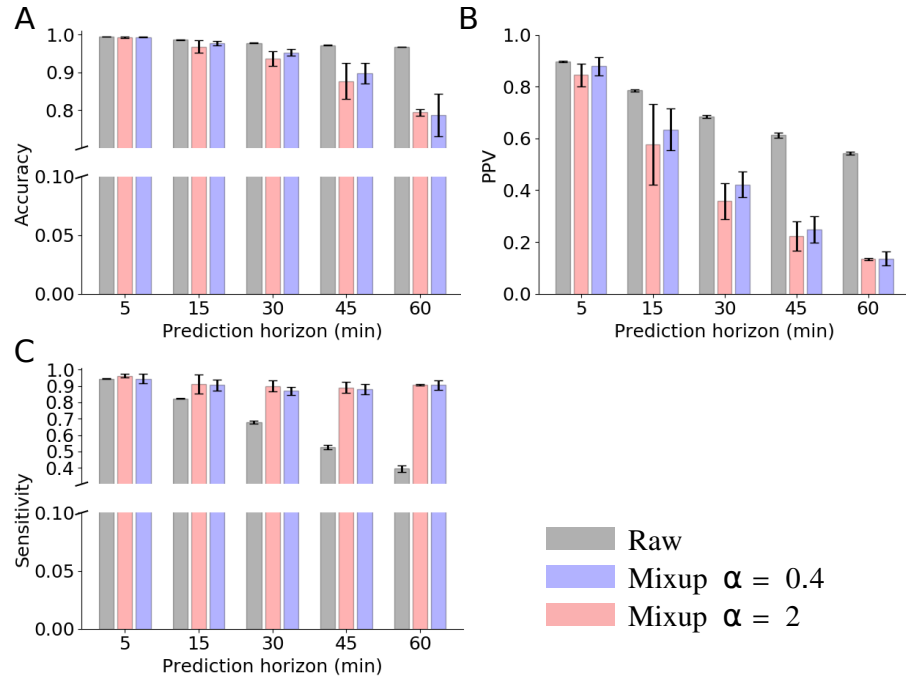


Figure 3.9: **Sensitivity analysis of the prediction horizon on three predictive scores with 2-fold mixup data augmentation on minority training data.** We compare the performance of our CNN model trained on the raw training dataset and on the training dataset augmented by two mixup models, one with $\alpha = 0.4$ and the other with $\alpha = 2$ for the Beta distribution $\text{Beta}(\alpha, \alpha)$ implemented in mixup. The performance of each model is calibrated in terms of (A) prediction accuracy, (B) positive predictive value (PPV, the precision of the positive class) and (C) sensitivity (recall of the positive class). A table for the detailed numerical results is shown in Table A.17. Hypoglycemia (the minority class, also the positive class) samples in the training data is augmented with 2-fold mixup. The purple-shaded bars denote the predictive scores by mixup ($\alpha = 0.4$), the red-shaded bars denote those by mixup ($\alpha = 2$), and the grey-shaded bars denote those by the raw training data (no data augmentation).

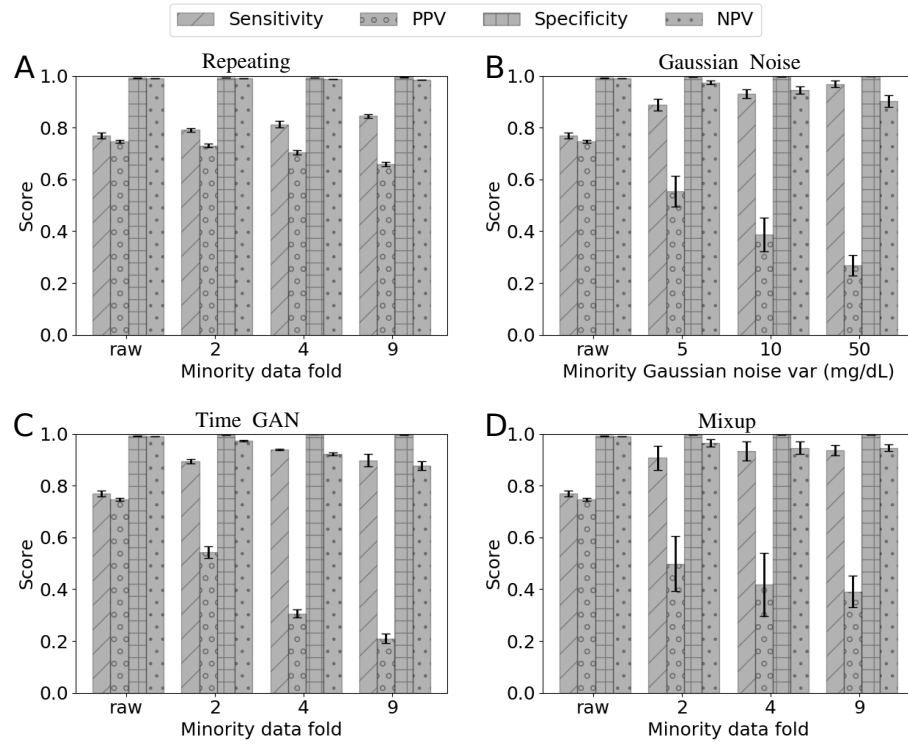


Figure 3.10: **Predictive scores by different data augmentation methods and different folds of minority data augmentation.** Hypoglycemia (the minority class, also the positive class) samples in the training data is augmented with (A) oversampling by repeating, (B) Gaussian noise infusion, i.e., the size of the minority training data is doubled by adding a copy of the raw minority data contaminated by Gaussian noises of different levels, (C) TimeGAN, and (D) mixup ($\alpha = 2$), while “no hypoglycemia” (majority class, also the negative class) samples remain intact. The minority data fold represents the number of copies of hypoglycemia samples in the training data after data augmentation. “Raw” denotes no data augmentation on the training dataset; 2-fold denotes that the raw minority data is kept in the training data and another copy of minority data is generated by either repeating or synthesizing in each training epoch. The mean and standard deviation of the classification metrics are obtained with 5 different runs. A table recording the detailed numerical results can be found in Table A.16 in the Materials.

Long-term hypoglycemia detection

Given that the data within the first two years has higher fidelity compared to data acquired later due to the possibility of patients’ withdrawal or mortality from the trial,

we show the prediction results of severe hypoglycemia (SH) in the second year using the first-year as the predictive variables. This yields a dataset with 1176 patients, from which we use 80% of the dataset for training and the rest for testing. We also perform 5-fold cross validation for each result presented below.

Single-view learning In single-view learning, we compare the SH prediction results for three different scenarios, i.e., 1) using all predictive variables (both static and dynamic variables shown in Fig. 3.3), 2) using only dynamic variables, and 3) using feature selected by Boruta algorithm [145] and oversampling. For each scenario, we test different types of machine learning algorithms, which are logistic regression, XGBoost, complement naive bayes, Gaussian naive bayes, multinomial naive bayes, bagging and random forest algorithm, implemented with the Python package `sklearn` and use default parameters, except that we use 25 estimators in bagging and 500 estimators in random forest algorithm. Table 3.5 shows the corresponding classification metrics. The results suggest that logistic regression and other ensemble methods like XGBoost, bagging and random forest show higher accuracy than other methods, while have lower sensitivity compared to naive bayes algorithms. Among the naive bayes algorithms, complement naive bayes show a good balance for those four classification metrics.

Table 3.5: **Single-view learning results.** LogisticReg denotes logistic regression, NB denotes naive bayes. NPV, negative predictive value. PPV, positive predictive value.

(a) Single-view learning using only static variables

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.8731±0.0174	0.0000±0.0000	1.0000±0.0000	0.0000±0.0000	0.8731±0.0174
XGBoost	0.8688±0.0194	0.0343±0.0430	0.9500±0.0118	0.0142±0.0178	0.8314±0.0257
ComplementNB	0.8888±0.0250	0.1477±0.0208	0.5853±0.0166	0.4994±0.0734	0.5734±0.0154
GaussianNB	0.8728±0.0176	0.0000±0.0000	0.9970±0.0041	0.0000±0.0000	0.8705±0.0186
MultinomialNB	0.8751±0.0186	0.2985±0.1711	0.9701±0.0262	0.0488±0.0185	0.8532±0.0291
Bagging	0.8718±0.0171	0.0333±0.0667	0.9820±0.0053	0.0059±0.0118	0.8584±0.0191
RandomForest	0.8728±0.0175	0.0000±0.0000	0.9970±0.0025	0.0000±0.0000	0.8705±0.0180

(b) Single-view learning using only dynamic variables

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.8726±0.0204	0.1333±0.2667	0.9951±0.0054	0.0154±0.0308	0.8690±0.0214
XGBoost	0.8755±0.0189	0.2905±0.0373	0.9806±0.0067	0.0542±0.0181	0.8614±0.0164
ComplementNB	0.8991±0.0211	0.1674±0.0308	0.6137±0.0208	0.5291±0.0823	0.6029±0.0145
GaussianNB	0.9066±0.0431	0.1372±0.0182	0.1967±0.0477	0.8681±0.0529	0.2832±0.0362
MultinomialNB	0.8885±0.0259	0.1712±0.0264	0.7468±0.0327	0.3671±0.0959	0.6964±0.0175
Bagging	0.8788±0.0180	0.4385±0.1434	0.9826±0.0104	0.0799±0.0419	0.8665±0.0123
RandomForest	0.8741±0.0179	0.6500±0.4359	0.9961±0.0057	0.0258±0.0134	0.8716±0.0184

(c) Single-view learning using all features, both static and dynamic variables

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.8754±0.0183	0.4400±0.3382	0.9930±0.0069	0.0285±0.0150	0.8705±0.0211
XGBoost	0.8783±0.0185	0.3538±0.0887	0.9831±0.0049	0.0640±0.0191	0.8662±0.0169
ComplementNB	0.8985±0.0207	0.1677±0.0188	0.6468±0.0310	0.4966±0.0788	0.6273±0.0164
GaussianNB	0.9126±0.0250	0.1395±0.0227	0.2489±0.0621	0.8341±0.0653	0.3232±0.0507
MultinomialNB	0.8891±0.0202	0.1637±0.0332	0.7278±0.0294	0.3727±0.0911	0.6820±0.0126
Bagging	0.8812±0.0153	0.4714±0.3182	0.9811±0.0136	0.0862±0.0633	0.8679±0.0138
RandomForest	0.8744±0.0162	0.4667±0.4522	0.9980±0.0024	0.0123±0.0151	0.8731±0.0158

(d) Single-view learning using Boruta selected features and apply oversampling to the training dataset.

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.9009±0.0275	0.1644±0.0151	0.6071±0.0324	0.5426±0.1085	0.5977±0.0181
XGBoost	0.8754±0.0157	0.2062±0.1206	0.9565±0.0203	0.0613±0.0230	0.8427±0.0151
ComplementNB	0.8984±0.0171	0.1665±0.0244	0.6326±0.0421	0.5058±0.0693	0.6168±0.0316
GaussianNB	0.8948±0.0232	0.1803±0.0344	0.7178±0.0392	0.4251±0.0631	0.6811±0.0421
MultinomialNB	0.8968±0.0183	0.1625±0.0245	0.6226±0.0257	0.5054±0.0618	0.6081±0.0214
Bagging	0.8781±0.0148	0.2348±0.0906	0.9612±0.0111	0.0798±0.0263	0.8497±0.0151
RandomForest	0.8795±0.0129	0.4756±0.3280	0.9881±0.0082	0.0636±0.0424	0.8714±0.0129

Multi-view learning In multi-view learning, we have the flexibility of incorporating the unlabeled dataset. Since Tables 3.5(a) and 3.5(b) for single-view learning suggest that the dynamic variables are more predictive than the static variables, we

show the results of multi-view learning using the dynamic variables categorized in three different views, see Table 3.6. In contrast to single-view learning without feature selection, algorithms in multi-view learning generally show higher accuracy. In particular, Tables 3.5(d) and 3.6(b) suggest that multi-view learning can achieve comparable results like feature selection with Boruta. Comparison between Tables 3.6(a) and 3.6(c) as well as Tables 3.6(c) and 3.6(d) suggest unlabeled dataset also improves the negative predictive value, sensitivity, and accuracy of algorithms.

Table 3.6: **Multi-view learning results.** LogisticReg denotes logistic regression, NB denotes naive bayes. NPV, negative predictive value. PPV, positive predictive value.

(a) Multi-view learning using dynamic features, 3 views, no oversampling

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.8716 $\pm$ 0.0186	0.0000 $\pm$ 0.0000	1.0000$\pm$0.0000	0.0000 $\pm$ 0.0000	0.8716 $\pm$ 0.0186
XGBoost	0.8742 $\pm$ 0.0178	0.3833 $\pm$ 0.3930	0.9903 $\pm$ 0.0085	0.0324 $\pm$ 0.0302	0.8673 $\pm$ 0.0177
ComplementNB	0.8941 $\pm$ 0.0220	0.1638 $\pm$ 0.0259	0.6220 $\pm$ 0.0339	0.5026$\pm$0.0524	0.6055 $\pm$ 0.0267
GaussianNB	0.8800 $\pm$ 0.0203	0.4726$\pm$0.1916	0.9864 $\pm$ 0.0062	0.0883 $\pm$ 0.0558	0.8707 $\pm$ 0.0181
MultinomialNB	0.8822$\pm$0.0211	0.2262 $\pm$ 0.0708	0.9038 $\pm$ 0.0257	0.1842 $\pm$ 0.0509	0.8104 $\pm$ 0.0206
Bagging	0.8729 $\pm$ 0.0177	0.2667 $\pm$ 0.2261	0.9913 $\pm$ 0.0055	0.0193 $\pm$ 0.0162	0.8665 $\pm$ 0.0145
RandomForest	0.8722 $\pm$ 0.0183	0.2000 $\pm$ 0.1400	0.9990 $\pm$ 0.0019	0.0063 $\pm$ 0.0125	0.8716$\pm$0.0176

(b) Multi-view learning using dynamic features, 3 views, with oversampling

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.9009$\pm$0.0163	0.1769 $\pm$ 0.0345	0.6392 $\pm$ 0.0346	0.5226$\pm$0.0524	0.6242 $\pm$ 0.0302
XGBoost	0.8745 $\pm$ 0.0165	0.2058 $\pm$ 0.1215	0.9727 $\pm$ 0.0106	0.0506 $\pm$ 0.0305	0.8546 $\pm$ 0.0176
ComplementNB	0.8988 $\pm$ 0.0191	0.1707 $\pm$ 0.0296	0.6219 $\pm$ 0.0275	0.5266 $\pm$ 0.0465	0.6089 $\pm$ 0.0236
GaussianNB	0.8935 $\pm$ 0.0288	0.1757 $\pm$ 0.0352	0.7075 $\pm$ 0.0403	0.4317 $\pm$ 0.1310	0.6709 $\pm$ 0.0320
MultinomialNB	0.8988 $\pm$ 0.0191	0.1707 $\pm$ 0.0296	0.6219 $\pm$ 0.0275	0.5266 $\pm$ 0.0465	0.6089 $\pm$ 0.0236
Bagging	0.8793 $\pm$ 0.0143	0.3191$\pm$0.1437	0.9669 $\pm$ 0.0120	0.0952 $\pm$ 0.0421	0.8554 $\pm$ 0.0141
RandomForest	0.8746 $\pm$ 0.0174	0.2590 $\pm$ 0.0758	0.9795$\pm$0.0063	0.0455 $\pm$ 0.0111	0.8597$\pm$0.0156

(c) Multi-view learning using dynamic features, 3 views, with unlabeled

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.8741 $\pm$ 0.0188	0.3000 $\pm$ 0.4000	0.9951 $\pm$ 0.0062	0.0264 $\pm$ 0.0368	0.8707 $\pm$ 0.0179
XGBoost	0.8726 $\pm$ 0.0168	0.2500 $\pm$ 0.2236	0.9893 $\pm$ 0.0055	0.0181 $\pm$ 0.0149	0.8648 $\pm$ 0.0142
ComplementNB	0.9018$\pm$0.0178	0.1690 $\pm$ 0.0336	0.5999 $\pm$ 0.0145	0.4667$\pm$0.4522	0.5944 $\pm$ 0.0140
GaussianNB	0.8781 $\pm$ 0.0210	0.2358 $\pm$ 0.0820	0.9543 $\pm$ 0.0168	0.1026 $\pm$ 0.0592	0.8444 $\pm$ 0.0177
MultinomialNB	0.8828 $\pm$ 0.0198	0.1571 $\pm$ 0.0331	0.7346 $\pm$ 0.0221	0.3368 $\pm$ 0.0667	0.6836 $\pm$ 0.0206
Bagging	0.8730 $\pm$ 0.0182	0.2167 $\pm$ 0.1944	0.9931 $\pm$ 0.0050	0.0193 $\pm$ 0.0162	0.8682 $\pm$ 0.0189
RandomForest	0.8737 $\pm$ 0.0179	0.5000$\pm$0.4472	0.9990$\pm$0.0019	0.0193 $\pm$ 0.0162	0.8733$\pm$0.0170

(d) Multi-view learning using dynamic features, 3 views, with oversampling and unlabeled

Algorithm	NPV	PPV	Specificity	Sensitivity	Accuracy
LogisticReg	0.9059$\pm$0.0168	0.1814 $\pm$ 0.0308	0.6277 $\pm$ 0.0283	0.5587$\pm$0.0440	0.6182 $\pm$ 0.0231
XGBoost	0.8730 $\pm$ 0.0180	0.1335 $\pm$ 0.1145	0.9650 $\pm$ 0.0147	0.0464 $\pm$ 0.0433	0.8469 $\pm$ 0.0130
ComplementNB	0.8963 $\pm$ 0.0208	0.1661 $\pm$ 0.0330	0.6124 $\pm$ 0.0361	0.5205 $\pm$ 0.0550	0.5995 $\pm$ 0.0314
GaussianNB	0.8897 $\pm$ 0.0289	0.1765 $\pm$ 0.0332	0.7377 $\pm$ 0.0426	0.3870 $\pm$ 0.1103	0.6913 $\pm$ 0.0381
MultinomialNB	0.8990 $\pm$ 0.0169	0.1708 $\pm$ 0.0356	0.6152 $\pm$ 0.0358	0.5313 $\pm$ 0.0399	0.6038 $\pm$ 0.0322
Bagging	0.8744 $\pm$ 0.0208	0.1775 $\pm$ 0.1017	0.9707 $\pm$ 0.0075	0.0561 $\pm$ 0.0396	0.8529 $\pm$ 0.0194
RandomForest	0.8739 $\pm$ 0.0181	0.2733$\pm$0.1665	0.9873$\pm$0.0040	0.0328 $\pm$ 0.0180	0.8648$\pm$0.0190

Visualization of high dimension features To analyze the difficulty of our prediction task, we visualize the high dimension data through the TSNE figure under different perplexities, see Fig. 3.11. The visualization results suggest that 1) the data

imbalance is quite severe that the positive samples overwhelm the whole figure and 2) there is barely any clear decision boundary for full separation of positive samples and negative samples, under any perplexity examined.

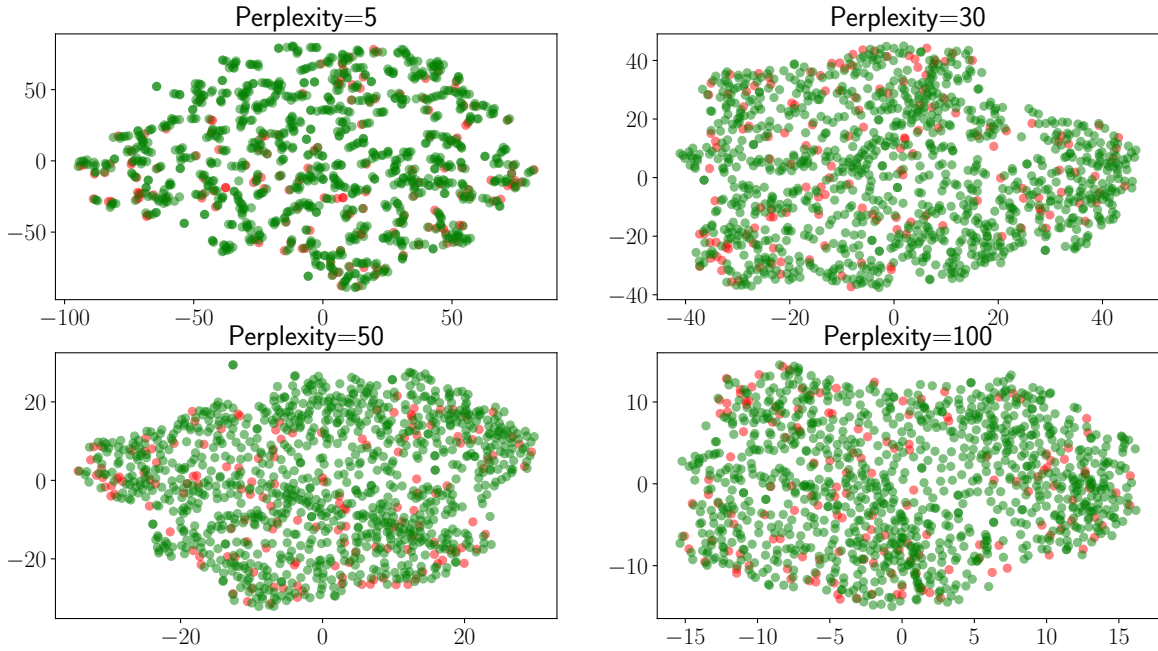


Figure 3.11: **TSNE of each sample in our dataset.** A sample (a data point) is represented by a 34-dimensional feature vector composed of the union of static variables and dynamic variables. Red circles denote positive labels (Severe hypoglycemia event occurs) and green circles denote negative labels.

3.1.4 Conclusions

Type 2 diabetes is considered an epidemic worldwide. Hyperglycemia selectively damages cells that are not able to reduce glucose transport into the cell, such as capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and neurons and Schwann cells in peripheral nerves. High intracellular glucose concentration leads to the exhaustion of the antioxidant pathways, altered regulation of gene transcription, and increased expression of pro-inflammatory molecules resulting in cellular dysfunction and death [26]. On a clinical level, these cellular changes translate into

micro and macrovascular complications of diabetes associated with poor outcomes and increased mortality [86]. Current diabetes treatment regimens may decrease the occurrence of complications associated with hyperglycemia, however, they also suppose a risk of extremely low glucose levels. Hypoglycemia can lead to permanent neurological damages if not treated promptly and increased mortality [51]. The prediction of blood glucose variations helps to adjust acute therapeutic measures and food intake in patients with type 2 diabetes.

We developed transfer learning methods to predict “hypoglycemia” vs. “no hypoglycemia” or “hypoglycemia” vs. “normoglycemia” vs. “hyperglycemia” for patients with type 2 diabetes. We obtained state-of-the-art results by tackling two major challenges associated with the small data size for individual patients as well as the imbalanced datasets, i.e., small samples for hypoglycemia. To deal with small datasets, we considered three neural network models, including recurrent neural networks (RNNs), convolutional neural networks (CNNs), and self-attention networks (SAs). We also examined four transfer learning strategies, which enabled us to train the neural networks with a small amount of the individual patient’s recorded data. We demonstrated the performance of our methods on the data obtained from 40 patients. We achieved high prediction accuracy for the task of predicting hypoglycemia vs. no hypoglycemia with accuracy no less than 98% and AUROC greater than 0.9 for all the prediction horizons examined. For the task of predicting hypoglycemia vs. normoglycemia vs. hyperglycemia, the best model among all tested models achieved high accuracy greater than 89% and AUROC greater than 0.86, for all the prediction horizons examined (up to one hour). Our results suggest that as the prediction horizon prolongs, the prediction accuracy, as well as the AUROC, decreases, as expected, in both classification tasks. When comparing the model performance on predicting hypoglycemia vs. no hypoglycemia and predicting hypoglycemia vs. normoglycemia vs.

hyperglycemia, our results suggest that the overall prediction accuracy and AUROC in the task of predicting hypoglycemia vs. no hypoglycemia are always higher than those in the task of predicting hypoglycemia vs. normoglycemia vs. hyperglycemia.

More specifically, statistical significance was observed between two short prediction horizons (5 mins and 10 mins) and the largest prediction horizon (60 mins) in the task of predicting hypoglycemia vs. normoglycemia vs. hyperglycemia. We note that despite the statistical differences observed among different prediction horizons, the model always maintained high accuracy.

However, a closer examination of our dataset reveals that most of the blood glucose levels are labeled as either normoglycemia or hyperglycemia, and hence only very few blood glucose levels are labeled as hypoglycemia, making hypoglycemia the definite minority class, resulting in models with sensitivity around 77% and positive predictive value around 75% for a prediction horizon of 20 minutes. Given the need to detect hypoglycemia more accurately and robustly, data augmentation on the minority class, i.e., augment the hypoglycemia samples in our training dataset, is an effective way of enforcing the neural network to learn the underlying patterns of the hypoglycemia data at a finer scale compared to learning on the dataset without data augmentation. Our tests suggest that data augmentation on the minority class using synthetic data (not oversampling by repeating) increases the model sensitivity in detecting hypoglycemia, from less than 80% to more than 96% depending on the specific augmentation method for a prediction horizon of 20 minutes. This allows early treatment intervention and prevention of potential hypoglycemic events and hence is a significant improvement preferred in clinical diagnosis given the fatal consequences of hypoglycemia for patients with serious complications caused by type 2 diabetes. However, given the imbalanced nature of our dataset, the increased sensitivity, i.e., the recall of the minority class, observed from models trained on the

augmented dataset also comes with a decrease in the positive predictive value, i.e., the precision of the minority class. Although the trade-off between the precision and recall for imbalanced datasets is a commonly observed dilemma, with minority data augmentation of different folds, we could still achieve a good balance between those two metrics such that they are acceptable in practical scenarios.

Despite the high accuracy and a few training data demanded by our method, there are some limitations to current work. Different from other physiologically derived approaches, this method is purely data-driven with no physiological knowledge and performs prediction merely based on the blood glucose history. It is recognized that data-driven methods are double-edged swords. On one side, data-driven methods relieve physicians from exhausting all possible combinations of physiological inputs given large samples or data. On the other side, it is not an easy task to incorporate domain knowledge into data-driven methods, especially in neural networks-based models. In our study, we identify nutritional intake, exercise, or stress conditions in dysglycemia prediction as the domain knowledge, the appropriate incorporation of which could possibly improve the model accuracy. Hence, we will propose the development of physiologic-informed neural network models in our future work. This and similar methods in the future are expected to have important clinical implications in terms of preventing and avoiding this potentially lethal complication, e.g., through alerts generated directly to the patient or by linking the prediction algorithms to the programmable insulin pumps.

To summarize, we proposed a new method for predicting hypoglycemia vs. no hypoglycemia and predicting hypoglycemia vs. normoglycemia vs. hyperglycemia, and the method shows remarkable performance characterized by high prediction accuracy and AUROC as well as other metrics, including specificity and sensitivity. In particular, a combined approach of transfer learning and data augmentation for

imbalanced data can be proved a very powerful new framework for short-term predictions for type 2 diabetes. Here, we focused on time periods up to 60 minutes, with notable sensitivity and positive predictive value of the model observed during the first 15 and 30 minutes. We believe that accurate hypoglycemia prediction over this period of time offers the most in terms of having potential warning signs and preventing adverse events by hypoglycemia. By incorporating transfer learning, this method could provide patient-specific results in both predicting hypoglycemia vs. no hypoglycemia and predicting hypoglycemia vs. normoglycemia vs. hyperglycemia with relatively few blood glucose samples. Similarly, in the long-term severe hypoglycemia, we are also faced with the challenges of small data and data imbalance. Due to the high-dimensional and unstructured format of the electronic medical record, we have limited choices in terms of data augmentation and dimension reduction. We attempt to handle these problems through multi-view learning algorithms with oversampling, which demand less data for an accurate prediction. We also test the performance of an algorithm specially designed for the imbalanced dataset, i.e., complement naive bayes. Our visualization of the latent space of the high dimensional data suggests that the decision boundary is straightforward enough for accurate classification.

3.2 Artificial pancreas design using offline reinforcement learning

Manuscript information

A version of this chapter is in preparation.

3.2.1 Introduction

Type 1 diabetes is a chronic autoimmune disease characterized by insulin deficiency and resultant hyperglycemia [61]. Patients with type 1 diabetes mellitus (T1DM) are frequently suffering from complications associated with unstable glucose levels when the blood glucose (BG) regulation is not well controlled. According to the Diabetes Control and Complications Trial, better BG control leads to lower HbA1c levels, which finally leads to better outcomes in terms of both microvascular and macrovascular complications [188]. Combining a glucose sensor, a control algorithm, and an insulin infusion device, artificial pancreas (AP) is a closed-loop system designed for patients with T1DM to improve their BG regulation, and consequently, decrease the risk of diabetic complications [45, 205, 240]. It is believed that appropriate insulin treatment requires frequent dosing adjustments for carbohydrates intakes, physical exercises, and illness or stress [61], which makes it a challenging problem to design an effective artificial pancreas that is capable of providing accurate and automated insulin dosages in time.

Before evaluating the performance of control algorithms and insulin infusion routes, the primary step of AP design is to provide a metabolic environment for the algorithm to interact with. Although in vitro experiments provide the most authentic environment to evaluate the performance of a control algorithm, it is also very expensive and

risky. Hence, many *in silico* models have been proposed as a safe surrogate to evaluate the control algorithms of APs [17, 220, 150, 138, 171]. However, these models either only simulate average population dynamics or consider patients in the ambulatory setting, where patients barely move, rather than those in an outpatient setting. This gives rise to other challenging problems in the design of modern artificial pancreas, one is that the AP must be able to handle inter- and intra-patient variability, and the other is that the AP in an outpatient setting should also be able to cope with the daily lifestyle of patients, not only meal intakes but also exercise, medication and stress.

To build an AP at the patient-specific level, it is also fundamental to build a simulator equipped with a cohort of *in silico* subjects that spans sufficiently well the observed inter-person variability of key metabolic parameters in the T1DM population. Recently, Marling and Bunesu curated the OhioT1DM dataset, a publicly available dataset including continuous glucose monitoring, insulin, physiological sensor, and self-reported life-event data for 12 people with type 1 diabetes [174, 173]. Furthermore, it is confirmed that regular physical activity can enhance a number of aspects of diabetes management, including but not limited to, improving insulin sensitivity, controlling body weight, reducing diabetes-related inflammation, and optimize long-term protection against cardiovascular diseases [89, 37, 46]. Hence, APs should also consider the influence of physical exercise on patient's glucose-insulin dynamics. Roy et al. developed a set of differential equations to include the major effects of exercise on plasma glucose and insulin levels [209]. Through validation with literature data, they showed the exercise model successfully captured the glucose and insulin dynamics during short- and long-term exercise. In this work, by combining real patients' data from the OhioT1DM dataset, we use system biology informed neural networks (SBINNs) [260] to learn patient-specific ODE parameters in the Roy

model and hence obtain a personalized simulator for each patient in the OhioT1DM dataset.

Being the decision-making component of the AP, the control algorithm is undoubtedly considered to be the brain demanding high accuracy and high robustness. Popular control algorithms in the AP design, like model predictive control (MPC) [170] and proportional integral derivative (PID) control algorithms [195], are mostly derived theoretically and parameterized by the average value of the population distribution. Recently, with the rapid development of machine learning, the reinforcement learning framework establishes a mathematical formalization of intelligent decision-making that is powerful and widely applicable in control problems. Unlike supervised learning where a direct input and output mapping is given explicitly, reinforcement learning algorithms define the control problem as a Markov decision process, and train an agent which collects a step-by-step reward through interactions with the environment of interest. The goal of the agent is to respond to the environment changes such that the total reward of the series of responses, namely actions, is maximized by the end of training.

Furthermore, the data-driven machine learning based on deep neural networks provides a more general representation of nonlinear dynamics for the control environments, which naturally leads to the improved performance of reinforcement learning in control tasks, from autonomous driving to personalized recommendations. However, one significant drawback of reinforcement learning, especially deep reinforcement learning, is that the training/learning process requires a large training dataset, and more importantly, the agent must be able to constantly interact with the environment in order to improve the policy iteratively. Besides the disadvantage of cost when collecting data in a large-scale system, the huge demand for agent-environment interaction also puts much pressure on the safety of data collecting in reinforcement learning

when the human subject is involved, for example in healthcare-related problems and autonomous driving. Utilizing only previously collected offline data without additional online interaction with the environment, offline reinforcement learning resolves the potentially high expense and danger in online reinforcement learning. However, the benefits of offline reinforcement learning also come with some disadvantages, for example, the distributional shift, i.e., while the function approximations might be trained under one distribution, it will be evaluated on a different distribution. Efforts to address this challenge can be generally grouped into two categories: policy constraint methods, which constrain the learned policy to lie close to the behavior policy, which was used to collect the offline dataset, and uncertainty based methods, which attempt to estimate the epistemic uncertainty of value functions, and then utilize this uncertainty to detect the distributional shift. A detailed review of offline reinforcement learning algorithms could be found in [157].

In summary, we develop a novel framework for designing the patient-specific artificial pancreas using offline reinforcement learning algorithms. We first build a patient-specific simulator using the model developed by Roy et al. [209], where the parameters are inferred with system biology informed neural networks (SBINNs) [260] and patient-specific data from the OhioT1DM dataset [174, 173]. We believe the proposed framework is also beneficial to other similar clinical control problems, where some patient-specific data and clinically verified physiological models are available. By using these patient-specific data and physiological models, we can first construct patient-specific physiological models and then use the same data for the offline training of reinforcement learning, which optimizes the desired control problem.

3.2.2 Methods

Problem setup. In this work, we develop a framework to design a patient-specific automated insulin delivery system for six patients with type 1 diabetes using patient-specific metabolic data, namely the OhioT1DM dataset. The OhioT1DM dataset contains eight weeks' worth of continuous glucose monitoring, insulin, physiological sensor, and self-reported life-event data for each of 12 people with type 1 diabetes, in which 6 patients appear in the 2018 version and the other 6 patients in the 2020 version of the dataset [173]. A workflow of this work is shown in Fig. 3.12. On the one hand, the OhioT1DM dataset is used for parameter inference of the patient-specific ODE model [209], providing required records of total exogenous insulin (bolus insulin+basal insulin), carbohydrate intakes, heart rate, CGM measured glucose level. On the other hand, to build the automated insulin delivery system, we use the OhioT1DM dataset to train the offline reinforcement learning algorithm. The final optimized agent powered by the deep neural networks will serve as the patient-specific artificial pancreas.

OhioT1DM dataset. All data contributors in the OhioT1DM were on insulin pump therapy with continuous glucose monitoring (CGM), throughout the 8-week data collection period. In these 8 weeks of monitoring, the patients also reported life-event data via a custom smartphone app and provided physiological data from a fitness band. Based on the Roy model, we select a subset of the data including 1) the CGM blood glucose level measure every 5 minutes, 2) insulin doses, both bolus insulin and basal insulin, 3) self-reported meal times with carbohydrate estimates, and 4) the heart rate measured every 5 min. We note here that only the data of those 6 patients in the 2018 version is used in our analysis, given the data of patients in the 2020 version does not include heart rate monitoring.

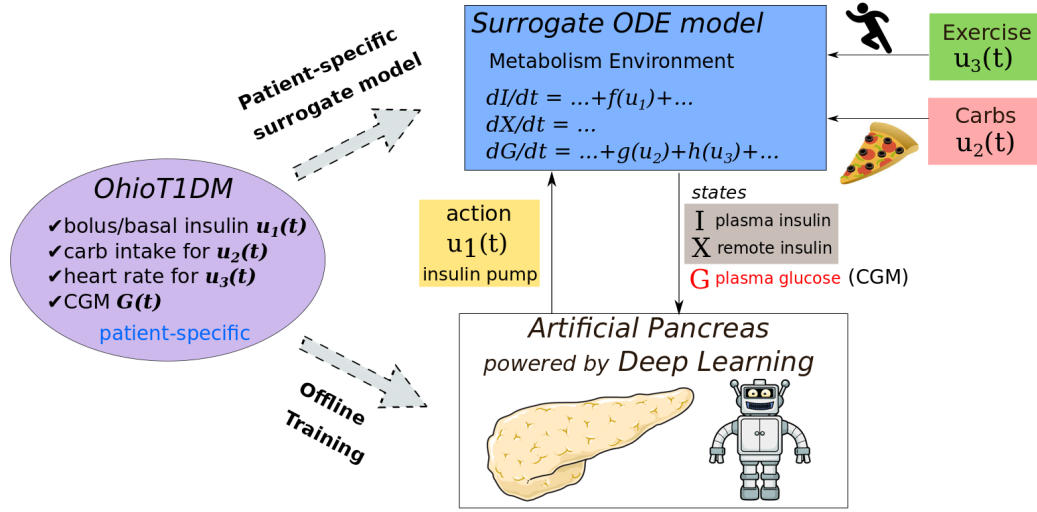


Figure 3.12: **Overview of patient-specific offline reinforcement learning.** Exogenous insulin (bolus insulin+basal insulin, $u_1(t)$), carbohydrate intake, $u_2(t)$; heart rate, $u_3(t)$; CGM measured glucose level $G(t)$.

Roy model. We adopt a slightly simplified version of the ODE system in Roy et al. [209], by omitting the $G_{gly}(t)$ term representing the decline of the glycogenolysis rate during prolonged exercise due to the depletion of liver glycogen stores, since the patients we consider only perform sporadic and light physical activities. The resulting ODE system for the 7 state variables $X_{1,\dots,7} = [I, X, G, G_{prod}, G_{up}, I_e, PVO_{max}^2]$, shown in Eqs. (3.4)-(3.10), captures the exercise-induced dynamics of plasma insulin clearance and the elevation of glucose uptake and hepatic glucose production rates.

$$\frac{dI}{dt} = -nI(t) + p_4u_1(t) - I_e(t); \quad I(0) = I_b = \frac{p_4}{n}u_{1b} \quad (3.4)$$

$$\frac{dX}{dt} = -p_2X(t) + p_3[I(t) - I_b]; \quad X(0) = 0 \quad (3.5)$$

$$\frac{dG}{dt} = -p_1[G(t) - G_b] - X(t)G(t) + \frac{W}{Vol_G}G_{prod}(t) - \frac{W}{Vol_G}G_{up}(t) + \frac{u_2(t)}{Vol_G}; \quad G(0) = G_b \quad (3.6)$$

$$\frac{dG_{prod}}{dt} = a_1PVO_2^{\max}(t) - a_2G_{prod}(t); \quad G_{prod}(0) = 0 \quad (3.7)$$

$$\frac{dG_{up}}{dt} = a_3PVO_2^{\max}(t) - a_4G_{up}(t); \quad G_{up}(0) = 0 \quad (3.8)$$

$$\frac{dI_e}{dt} = a_5PVO_2^{\max}(t) - a_6I_e(t); \quad I_e(0) = 0 \quad (3.9)$$

$$\frac{dPVO_2^{\max}}{dt} = -0.8PVO_2^{\max}(t) + 0.8u_3(t); \quad PVO_2^{\max}(0) = 0 \quad (3.10)$$

Data preprocessing. The exogenous insulin is calculated as the sum of basal insulin and bolus insulin at each minute. According to the user manual of the insulin pumps, i.e., Medtronic 530G and 630G, while the basal insulin is given at a rate and is provided explicitly, bolus insulin is a one-time dose and can be released into the bloodstream using different modes, i.e., “normal”, “normal dual”, “square” and “square dual”. Given limited information for the exact releasing process of these different modes in the OhioT1DM dataset, we manually define the conversions through literature [107] and the user guides for the insulin pump [60, 59]. In the “normal” type, the single x mU dose bolus insulin is converted to a constant pseudo basal insulin at a rate of $x/10$ mU lasting for 10 minutes. In the “square” type, the single x mU dose bolus insulin is converted to a constant pseudo basal insulin at a rate of x/t mU lasting for t minutes, where t denotes the time elapsed between two adjacent boluses. In “normal dual” and “square dual”, the single dose is divided evenly into two identical half doses. These two half doses are released sequentially by “normal”

and “square” type in “normal dual”, while by “square” and “normal” type in “square dual”, respectively. Additionally, we also consider “temp basal” insulin to override the basal insulin set previously. The glucose infusion rate is computed by the meal carb intakes using an exponential decay function [260] as follows,

$$I_G(t) = 0.0083 \sum_{j=1}^N m_j \exp(0.0083(t_j - t)), \quad (3.11)$$

where m_j gram of carb intake is recorded at t_j . The percentage of $\text{VO}_{\max}^2$ ($\text{PVO}_{\max}^2$) denoting the exercise intensity is approximated by the heart rate as follows [155],

$$\begin{aligned} \text{PVO}_2^{\max}(t) &= 0.888\text{HR} - 71.91, \\ u_3(t) &= \text{PVO}_2^{\max}(t) - 8, \text{ if } u_3(t) > 0 \text{ else } 0 \end{aligned} \quad (3.12)$$

where 8 denotes basal $\text{VO}_{\max}^2$ at 8%, HR denotes heart rate.

System biology informed neural networks (SBINNs). Yazdani et al. developed a new systems-biology-informed deep learning framework, namely system biology informed neural networks (SBINNs), which successfully incorporates the system of ordinary differential equations (ODE) into the neural networks [260]. Inspired by the physics-informed neural networks, SBINNs is sequentially composed of an input-scaling layer to allow input normalization for the robust performance of the neural networks, a feature layer marking different patterns of state variables in the ODE system, and the output-scaling layer to convert normalized state variables back to physical units. By effectively adding constraints derived from the ODE system to the optimization procedure, SBINNs is able to simultaneously infer the dynamics of unobserved species, external forcing, and the unknown model parameters.

Given the measurements of $y_1, y_2, \dots, y_M$ at the time $t_1, t_2, \dots, t_{Ndata}$, SBINNs

enforce the network to satisfy the ODE system at the time point $\tau_1, \tau_2, \dots, \tau_{N^{ode}}$. The total loss is defined as a function of both the parameters of the neural networks, denoted by $\boldsymbol{\theta}$ and parameters of the ODE system, denoted by $\boldsymbol{p}$.

$$\mathcal{L}(\boldsymbol{\theta}, \boldsymbol{p}) = \mathcal{L}^{data}(\boldsymbol{\theta}) + \mathcal{L}^{ode}(\boldsymbol{\theta}, \boldsymbol{p}) + \mathcal{L}^{aux}(\boldsymbol{\theta}) \quad (3.13)$$

where $\mathcal{L}^{data}$ is associated with the M sets of observations of the state variables $\boldsymbol{y}$ in the ODE system; $\mathcal{L}^{ode}$ enforces the structure imposed by the system of ODEs; $\mathcal{L}^{aux}$ is introduced as an additional source of information for the system identification. We recommend Ref. [260] for the details of the loss functions. The final step of SBINNs is to infer the neural network parameters $\boldsymbol{\theta}$ as well as the unknown ODE parameters $\boldsymbol{p}$ simultaneously by minimizing the aforementioned loss function via gradient-based optimizers.

In this work, the known observed state variable y is the CGM measured glucose record in the OhioT1DM dataset, i.e., $G(t)$, which is used for minimizing the data loss, $\mathcal{L}^{data}$. We use $\mathcal{L}^{ode}$ to minimize the residue of the ODE system in the Roy model, shown in Eqs. (3.4)-(3.10). Following Yazdani et al. [260], we impose the sum of the initial condition at time $t = 0$.

Offline reinforcement learning. While (online) reinforcement learning is the problem faced by an agent that must learn behavior through trial-and-error interactions with a dynamic environment, offline reinforcement learning algorithms utilize previously collected data, without additional online data collection through interacting with the environment [129, 157]. As shown in Fig. 3.13, in online reinforcement learning, the policy π_k is updated with streaming data collected by π_k . In offline reinforcement learning, a buffer dataset is collected by some behavior policy π_β . The

dataset is collected once and is not altered during training. Finally, the policy is only deployed after being fully trained. In this work, we generate a buffer by sampling the states like glucose level, carb intake, and exercise, the action denoted by total exogenous insulin, i.e., the sum of bolus insulin and basal insulin, and the corresponding returns.

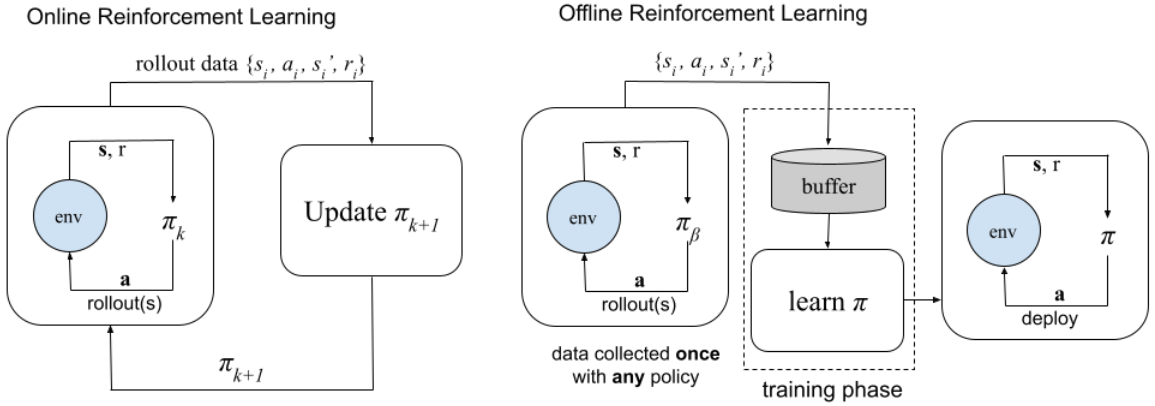


Figure 3.13: **Pictorial illustration of classic online reinforcement learning and offline reinforcement learning.** The figure is adapted from Levine et al. [157]. s denotes the states of the environment; r denotes the return which is the sum of the value of each state in the past. π denotes the policy which is a function of state s and action a . π_k denotes the policy at k -th iteration. π_β denotes a behavioral policy used for one-time data collection.

In this work, we implement the batch constrained Q-learning (BCQ) algorithm, which is one of the most popular offline reinforcement learning algorithms [87]. By restricting the action space to force the agent towards behaving close to a subset of the given data, BCQ can learn successfully without interacting with the environment by considering extrapolation error. The details of BCQ algorithm are shown in Algorithm 1. Similar to those in Fujimoto et al. [87], we use fully connected feed-forward neural networks for the Q-networks and the variational autoencoders (VAE). The hyper-parameters used in this work can be found in Table A.18.

Algorithm 1 Batch constrained Q-learning algorithm.

Require: Batch $\mathcal{B}$, horizon T , target network update rate τ , mini-batch size N , max perturbation Φ , number of sampled actions n , minimum weighting λ .

Initialize Q-networks $Q_{\theta_1}, Q_{\theta_2}$, perturbation network ϵ_ϕ , and VAE $G_\omega = \{E_{\omega_1}, D_{\omega_2}\}$, with random parameters $\theta_1, \theta_2, \phi, \omega$, and target networks $Q_{\theta'_1}, Q_{\theta'_2}, \epsilon_{\phi'}$, with $\theta'_1 \leftarrow \theta_1, \theta'_2 \leftarrow \theta_2, \phi' \leftarrow \phi$. $t \leftarrow 0$.

while $t < T$ **do**

 Sample mini-batch of N transitions (s, a, r, s') from $\mathcal{B}$

$\mu, \sigma = E_{\omega_1}(s, a), \tilde{a} = D_{\omega_2}(s, z), z \sim \mathcal{N}(\mu, \sigma)$

$\omega \leftarrow \operatorname{argmin}_\omega \sum (a - \tilde{a})^2 + D_{KL}(\mathcal{N}(\mu, \sigma) || \mathcal{N}(0, 1))$

 Sample n actions: $\{a_i \sim G_\omega(s')\}_{i=1}^n$

 Perturb each action: $\{a_i = a_i + \epsilon_\phi(s', a, \Phi)\}_{i=1}^n$

 State value target y

$\theta \leftarrow \operatorname{argmin}_\theta \sum (y - Q_\theta(s, a))^2$

$\phi \leftarrow \operatorname{argmax}_\phi \sum Q_{\theta_1}(s, a + \epsilon_\phi(s, a, \Phi)), a \sim G_\omega(s)$

 Update target networks: $\theta'_i \leftarrow \tau\theta + (1 - \tau)\theta'_i$

$\phi' \leftarrow \tau\phi + (1 - \tau)\phi'$

$t \leftarrow t + 1$.

end while

3.2.3 Results and discussion

Patient-specific Roy model using SBINNs

To build a surrogate environment for our agent to interact with, we perform parameter inference using system biology informed neural networks (SBINNs) on the Roy model. We first perform structural identification on the ODEs the set of parameters $\{n, \text{Vol}_G, p_1, p_2, p_3, p_4, a_1, a_2, a_3, a_4, a_5, a_6, W, I_b\}$ in Eqs. (3.4)-(3.10). Despite that most of the ODE parameters are not readily available in the OhioT1DM dataset, there are several parameters that are practically available for patients in future applications. For example, the patient's body weight (W) can be measured practically but is not available in OhioT1DM. While the basal plasma insulin (I_b) is not available in the OhioT1DM, but it can be obtained using a blood test. We consider the identifiability of the aforementioned parameters under different scenarios

depending on whether W and I_b are known for the given patient. Table 3.7 suggests that when W and I_b are both known, other parameters are either globally identifiable or locally identifiable. We adopt this scenario in the following analysis by assuming $W = 60 \text{ kg}$, and construct patient-specific model by inferring the set of parameters $\{n, \text{Vol}_G, p_1, p_2, p_3, p_4, a_1, a_2, a_3, a_4, a_5, a_6\}$ using patient-specific plasma glucose record in one day.

Parameter	W and I_b unknown	Identifiability		
		W known, I_b unknown	W unknown, I_b known	W and I_b known
n	locally	locally	locally	locally
Vol_G	globally	globally	globally	globally
p_1	nonidentifiable	globally	globally	globally
p_2	locally	locally	locally	locally
p_3	nonidentifiable	nonidentifiable	locally	locally
p_4	nonidentifiable	nonidentifiable	locally	locally
a_1	nonidentifiable	locally	nonidentifiable	locally
a_2	locally	locally	locally	locally
a_3	nonidentifiable	locally	nonidentifiable	locally
a_4	locally	locally	locally	locally
a_5	nonidentifiable	nonidentifiable	locally	locally
a_6	globally	globally	globally	globally
I_b	nonidentifiable	nonidentifiable	-	-
W	nonidentifiable	-	nonidentifiable	-

Table 3.7: **Parameter identifiability in Roy model under four different scenarios.** W denotes the bodyweight of the patient, I_b denotes the basal plasma insulin level. Details of other parameters can be found in [209].

Parameter inference using synthetic data. In this toy model, we assume the weight of a virtual patient to be $W = 60 \text{ kg}$ and generate synthetic data by solving an initial value problem, where the forcing terms in the ODE system are given by Eqs. (3.14)-(3.16); the model parameters are given by the nominal value in [209], see Table 3.8); and the initial condition of the ODE system is given by $[I, X, G,$

$$G_{prod}, G_{up}, I_e, PVO_{max}^2]_{t=0} = [20, 0, 120, 0, 0, 0, 0].$$

$$\text{exogenous insulin infusion } u_1(t) = 20 + 2 \sin(0.001t - 1) \quad (3.14)$$

$$\text{meal intake } u_2(t) = 2 + 5 \cos(0.002t) \quad (3.15)$$

$$\text{exercise intensity } u_3(t) = 3 \sin(0.002t) \quad (3.16)$$

As required by SBINNs, we take the one-day glucose record, the only state variable available in the OhioT1DM dataset among those 7 variables in the Roy model, to be the known state variable. Hence, the data loss L_{data} denotes the mean squared error (MSE) between the known one-day glucose record and the model predicted glucose dynamics. For the auxiliary loss L_{aux} , we impose the sum of the MSE between the synthetic data and the model prediction of the state variables at the initial moment and the MSE between them at the terminal moment. Table 3.8 and Fig. 3.14 show the parameters and the time-dependent dynamics of the state variables, both the known state G and the other hidden states, inferred by SBINNs, respectively. These results suggest SBINNs is capable of inferring the model parameters as well as the hidden dynamics of unobserved states, i.e., $[I, X, G_{prod}, G_{up}, I_e, PVO_{max}^2]$ with high accuracy.

Parameter	Nominal value	Inferred value
n	0.142	0.116
Vol_G	117	101
p_1	0.035	0.035
p_2	0.05	0.042
p_3	0.000028	0.000024
p_4	0.098	0.082
a_1	0.00158	0.00149
a_2	0.056	0.053
a_3	0.00195	0.00174
a_4	0.0485	0.0441
a_5	0.00125	0.0012
a_6	0.075	0.073

Table 3.8: **Parameter inference by SBINNs for the modified Roy model using the data from a synthetic case.** In this case, the parameters are set to be the nominal values given in Roy [\[209\]](#).

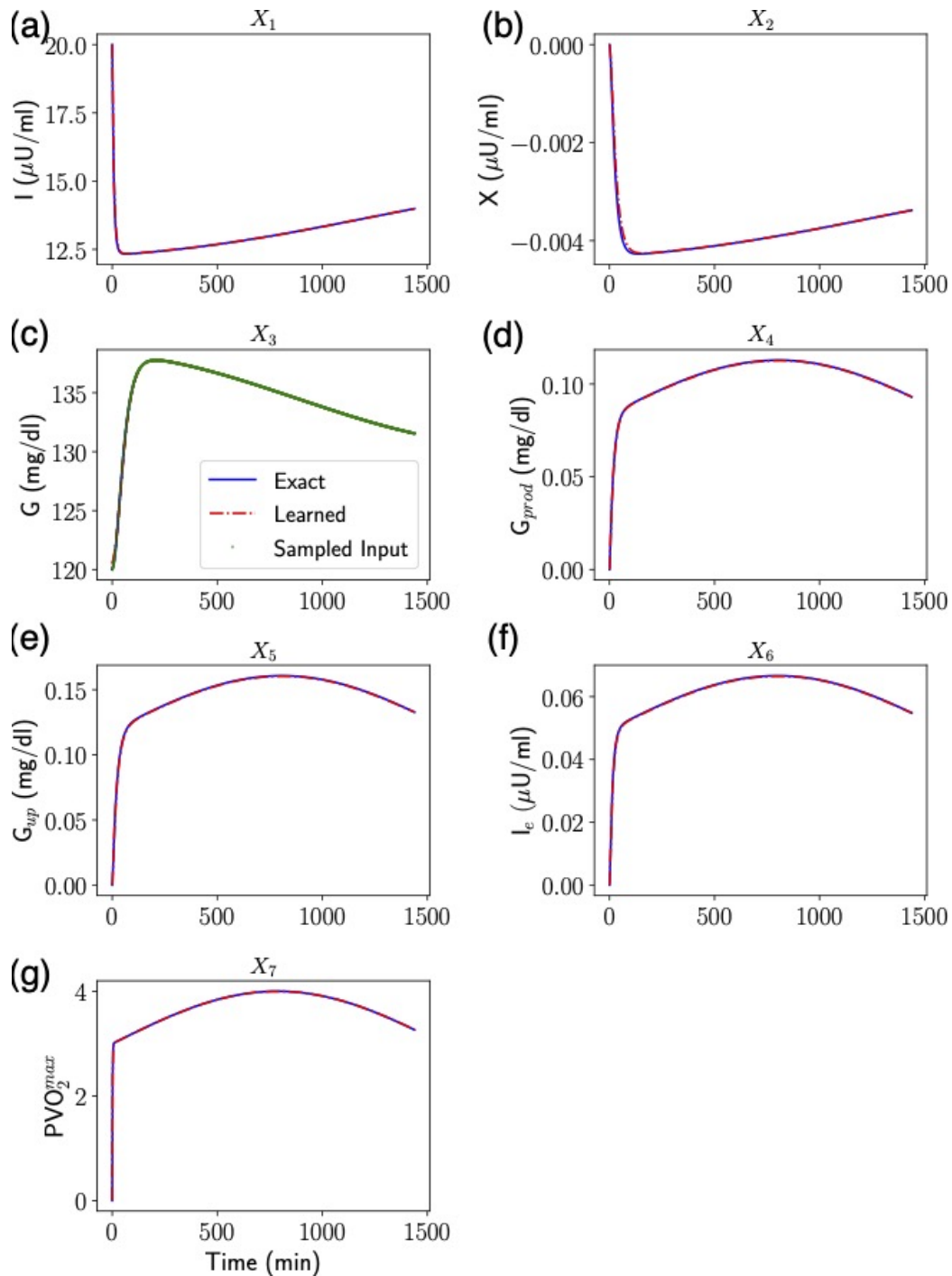


Figure 3.14: **Prediction of 7 state variables in the Roy model using SBINNs for a synthetic case.** In this case, the one-day glucose record (green points in (c)) is given. The blue solid line denotes the numerical solution of the system of ODEs. The red dash line denotes the prediction by SBINNs. SBINNs can infer all state variables correctly both the observed state variable (X_3) and hidden state variables, ($X_1, X_2, X_4, X_5, X_6, X_7$).

Patient-specific parameter inference using OhioT1DM. In the OhioT1DM dataset, we assume the patient’s weight is 60 kg, i.e., $W = 60$ kg. The initial condition of the ODE system is given by $[I, X, G, G_{prod}, G_{up}, I_e]_{t=0} = [I_b, 0, G_b, 0, 0, 0]$, where I_b is approximated from the basal insulin rate and G_b is given by the CGM recording. In contrast to the toy case, we only impose the initial condition for the auxiliary loss in this real-world case. We also impose smoothing using a moving window of 30 data points on the model inputs to speed up the convergence of parameter inference. Fig. 3.15 shows the model inputs for the real-world case. We also make Vol_G (glucose distribution space) and p_1 (glucose removal rate from the plasma) time-dependent to improve inference accuracy. Fig. 3.16 shows the inferred time-dependent Vol_G and p_1 and Table A.19 shows other inferred parameters. Fig. 3.17 shows the corresponding prediction of the 6 state variables in the Roy model using SBINNs, which suggests SBINNs is capable of inferring the model parameters as well as the hidden dynamics of unobserved states. In addition, Fig. 3.17(c) implies that the results of the forward solver using ODEs with inferred parameters also match the observed plasma glucose level.

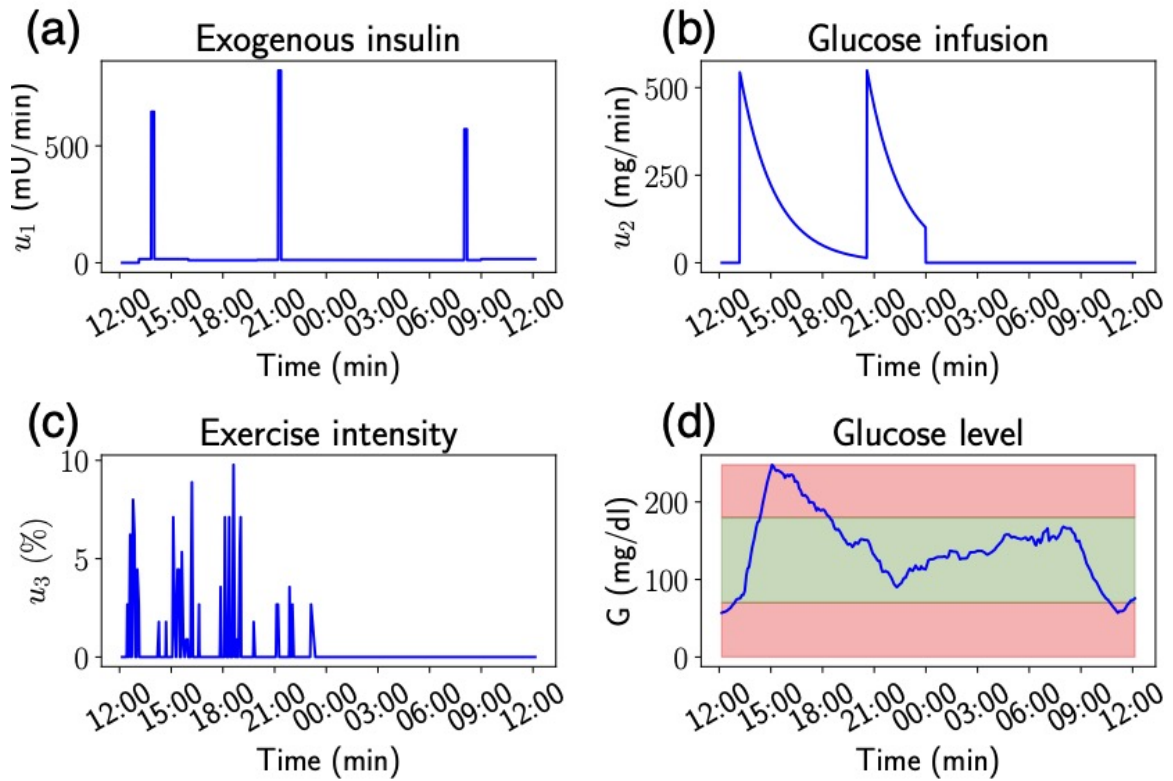


Figure 3.15: **Model inputs required for the Roy model in a real-world case.** (a) exogenous insulin infusion rate, (b) glucose infusion/uptake rate, (c) exercise intensity, and (d) plasma glucose level. The green region denotes normoglycemia, i.e., glucose levels within 70 mg/dl and 180 mg/dl, while the red region denotes either hypoglycemia or hyperglycemia, i.e., glucose levels below 70 mg/dl or above 180 mg/dl, respectively.

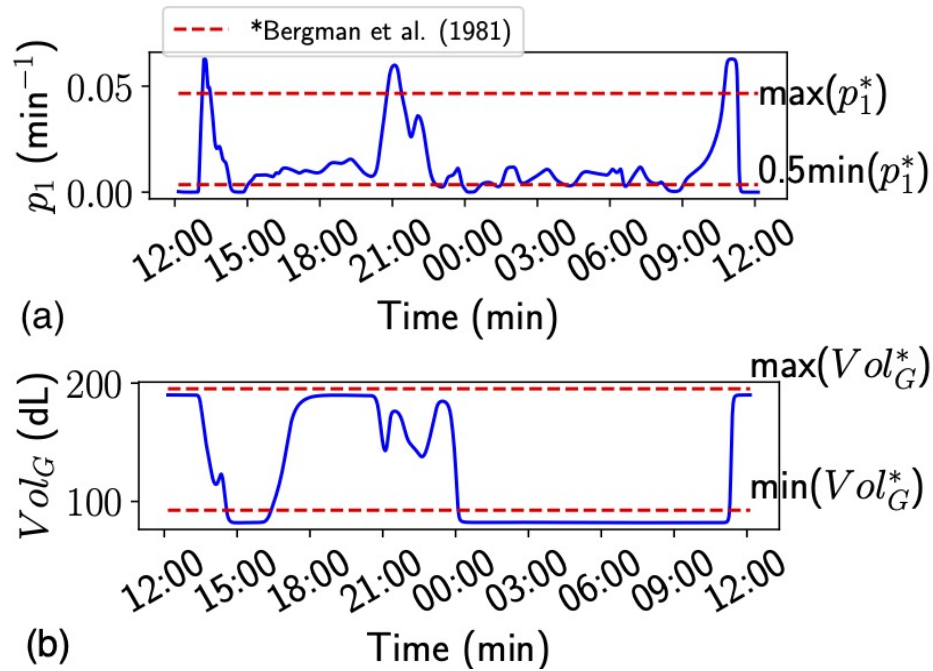


Figure 3.16: **Inferred time-dependent parameters for a real-world case.** (a) glucose depletion rate from plasma p_1 , (b) glucose distribution space Vol_G . Red dashed lines denote the thresholds calculated from 18 human subjects (8 lean and 10 obese) in Bergman et al. [18].

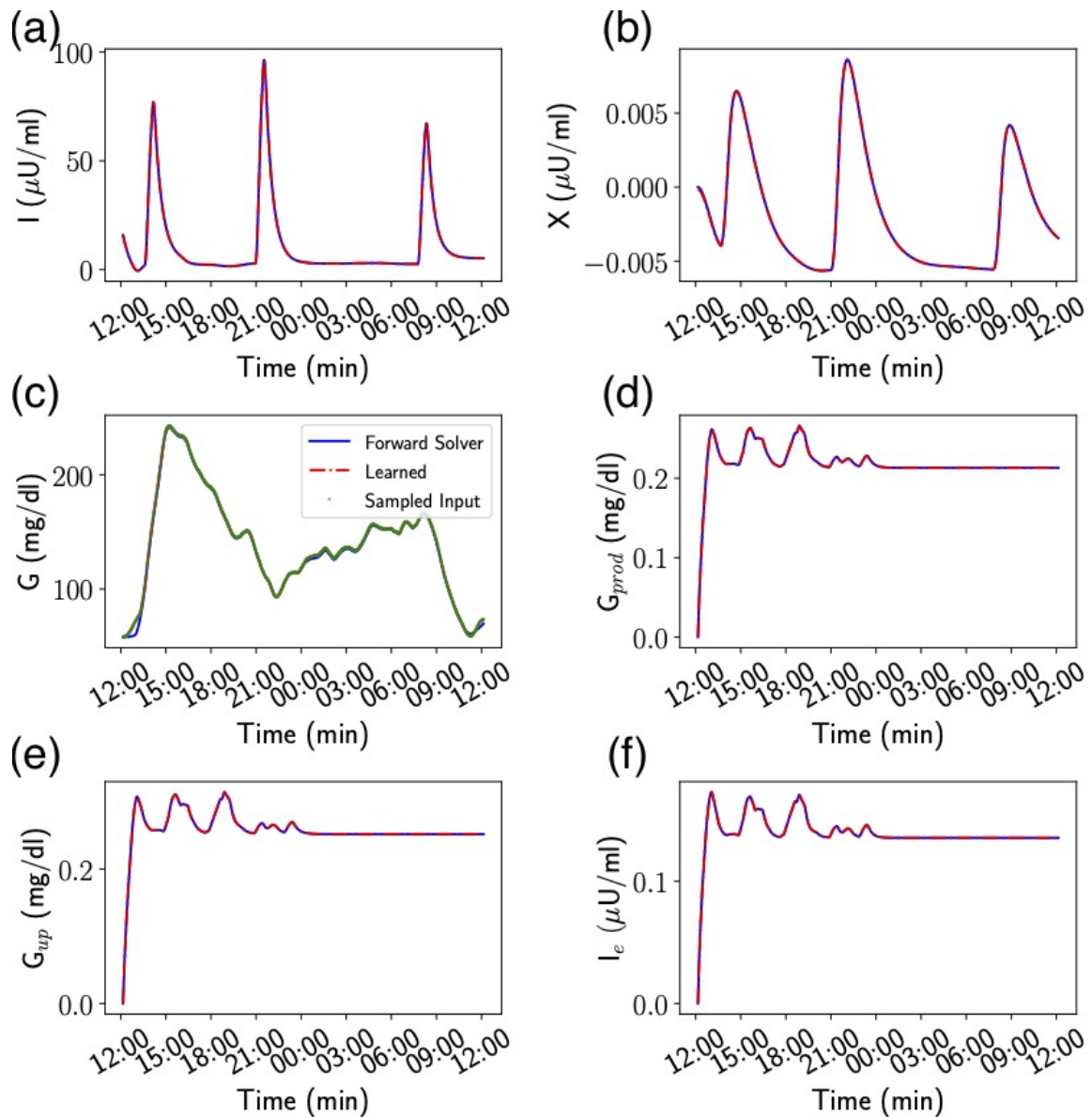


Figure 3.17: **Prediction of 6 state variables in the Roy model using SBINNs for a real-world case.** In this case, the one-day glucose record (blue points in subfigure $X_3 = G$) is given. The blue solid line denotes the numerical solution of the system of ODEs, using inferred parameters. The red dash line denotes the prediction by SBINNs. SBINNs can infer all state variables correctly both the observed state variable (X_3) and hidden state variables, ($X_1, X_2, X_4, X_5, X_6, X_7$).

Offline reinforcement learning using OhioT1DM

In this part, we build a simplified patient-specific model, using the parameters inferred with SBINNs, see Table A.19 in Appendix A.4. For the time-dependent parameters, p_1 and Vol_G , we use the corresponding mean values to simplify the parameterization of the simulation. In this case, the forcing terms required by the Roy model, i.e., the exogenous insulin infusion rate u_1 , glucose infusion rate u_2 and the exercise intensity u_3 are shown in Fig. 3.18. The consequent glucose dynamics due to the change of time-dependent parameters (black dashed curve in Fig. 3.19(b)) is smoother than the original glucose trajectory (black solid curve in Fig. 3.19(b)).

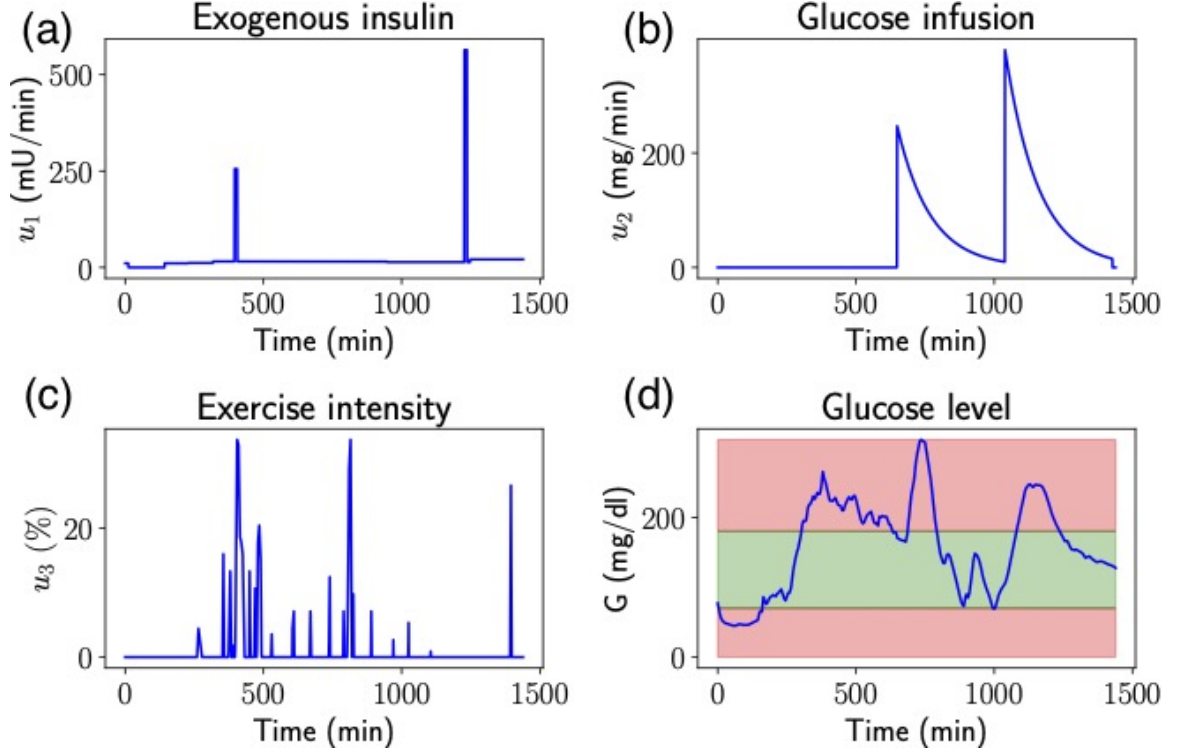


Figure 3.18: **Model inputs required for the Roy model in a real-world case with violent glucose levels ranging from hypoglycemia, normoglycemia, and hyperglycemia.** (a) exogenous insulin infusion rate, (b) glucose infusion/uptake rate, (c) exercise intensity, and (d) plasma glucose level. The green region denotes normoglycemia, i.e., glucose levels within 70 mg/dl and 180 mg/dl, while the red region denotes either hypoglycemia or hyperglycemia, i.e., glucose levels below 70 mg/dl or above 180 mg/dl, respectively.

We formulate the reinforcement learning problem for glucose regulation using the glucose infusion rate u_2 and exercise intensity u_3 from the OhioT1DM dataset, and we train the agent to provide the optimal exogenous insulin infusion rate u_1 for a full day period. The observed states $\mathbf{s}_t$ at time t is the glucose levels in the past 30 minutes, i.e., $\mathbf{s}_t = [G_{t-29}, G_{t-28}, \dots, G_t]$. The action a_t at time t is a value within the range $[0, 740]$ mU/min. Informed by the prior knowledge of the danger due to hyperglycemia and hypoglycemia, we design the reward function such that the reward penalties much more on actions leading to glucose levels falling into hypoglycemia or

hyperglycemia. The reward function at time t is given by Eq. 3.17 and the final return function is given by Eq. 3.18.

$$r_t(G_t) = \begin{cases} -(\frac{G_t - G_{target}}{G_{target}})^2, & 70 \leq G \leq 180; \\ -10, & \text{otherwise.} \end{cases} \quad (3.17)$$

$$R = \sum_{i=0}^{T_{end}} \gamma^i r_i \quad (3.18)$$

where we set the target glucose level to be 120 mg/dl and terminal time T_{end} to be 1439 min, for a total 1440-min episode. The history of return for the training of 5 different runs is shown in Fig. A.5 in Appendix, which suggests the BCQ is capable of outperforming the patient’s self-operated insulin infusion resulting in a baseline return -2238.14. The performance of the best agent is given by the solid blue curve in Fig. 3.19 (a), which results in a total return of -1263.36, much higher than the baseline return -2238.14. However, we do notice that the agent-prescribed insulin tends to be a constant value in the example we show here. A potential cause for this phenomenon is that insulin dosages in the offline dataset are mostly continuous constants due to overwhelmed constant basal insulin required for patients with type 1 diabetes. Possible improvements for this drawback can be multiple aspects, including increasing the dimensionality of the actor network so as to have a more expressive agent for a dynamic insulin dosage. We could also modify the observed states from pure glucose levels to a combination of glucose levels and glucose infusion rate as well as exercise intensity such that the actor network learns better with those additional information. For now, we defer these improvements to our future work.

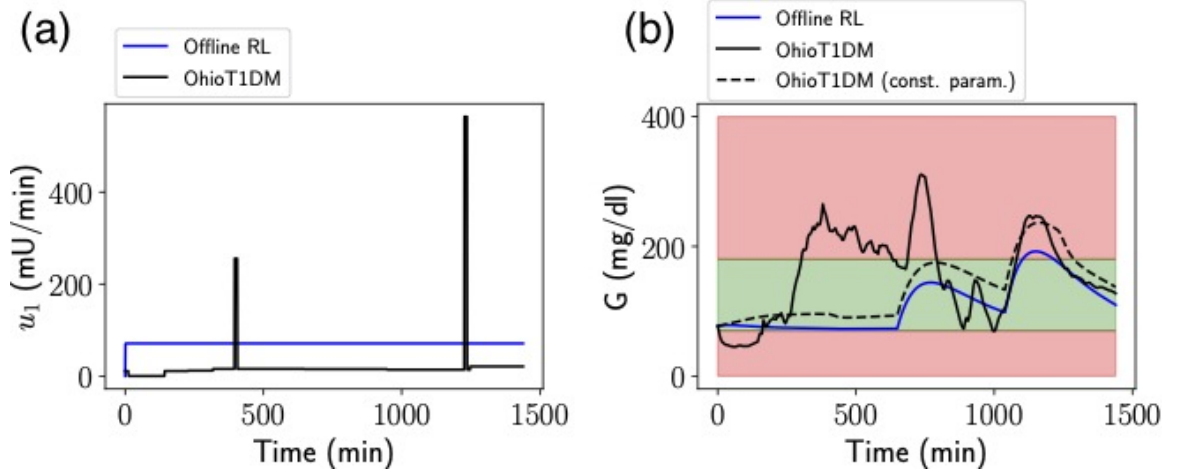


Figure 3.19: **Performance comparison between offline data and the trained agent.** (a) The solid blue curve denotes the insulin infusion rate over time provided by the trained agent, and the solid black curve denotes the patient’s self-operated insulin infusion rate recorded in the offline dataset. (b) The solid blue curve denotes the glucose trajectory solved by the patient-specific Roy model using the insulin infusion rate provided by the trained agent. The solid black curve denotes the glucose trajectory recorded in the offline dataset. The dashed black curve denotes the glucose trajectory solved by the patient-specific Roy model using the patient’s self-operated insulin infusion rate.

3.2.4 Conclusions

Insulin is the mainstay of treatment for patients with type 1 diabetes mellitus and long-standing type 2 diabetes mellitus to achieve good glycemic control [215]. Over-estimation in the necessary insulin dosage can be extremely dangerous and leading to fatally low blood glucose levels below 70 mg/dl, namely, hypoglycemia, while under-estimated insulin leaving blood glucose above 180 mg/dl, resulting in a state called hyperglycemia, is believed to be responsible for micro- and macrovascular diseases in the long run. In modern medicine, the use of insulin pumps along with continuous glucose monitors has made it easier but requires significant resources and patient education. Hence, designing a closed-loop control system, also called the artificial pancreas, which automates insulin infusion so as to maintain a consistently stable

blood glucose level is undoubtedly one of the best treatments relieving the burden of both patients and doctors, as well as saving medical costs.

Formidable challenges remain before an ideal artificial pancreas can be safely used in free-living situations in T1D. These include personalization of algorithms based on changes in physiological parameters (e.g., insulin sensitivity, glucagon sensitivity) related to multiple natural perturbations induced by physical activity, meals, inter-current illness, stress, circadian variability, and biological factors (puberty, menstrual cycles, pregnancy, menopause) [142]. In this work, we attempt to address a few of the challenges with a novel framework that effectively combines three key components to build a patient-specific artificial pancreas. These important components are 1) a real-world historical medical dataset, namely OhioT1DM dataset, containing patient-specific glucose, insulin, meal intake, and exercise intensity, 2) a flexible ODEs model defining glucose-insulin dynamics by systematically prioritizing two significant external factors, i.e., meal intake and physical activities, and 3) an offline reinforcement learning algorithm, namely batch constraint Q-learning, which is capable of developing an efficient agent with no need of interacting with the target environment. We firstly employ system biology informed neural networks (SBINNs) to infer patient-specific parameters of the ODEs model using patient-specific data, i.e., glucose trajectory, glucose infusion rate, exogenous insulin infusion rate, and exercise intensity. After validating the parameters inferred by SBINNs, we train an agent to automate insulin infusion and evaluate the performance of the agent on the patient-specific ODE model. The evaluation results suggest that the best trained agent has a better performance in terms of maintaining blood glucose levels within the safe range, i.e., within 70 mg/dl and 180 mg/dl, compared to the self-operated insulin infusion on the patient’s own.

Despite the improved glycemic control provided by our offline agent compared to

that by the patient and minimal human intervention demanded by our framework, we could still identify possible improvements to the proposed framework. Although we correctly identify the patient-specific parameters required in the Roy model from one-day glucose data, we may still need to address the variability of the parameters in practice. One possible solution to this practical problem is to adapt the constant parameters to stochastic parameters represented by neural networks. Since the current model considers only patients with type 1 diabetes, i.e., the β cell of the patient's pancreas secrete very little insulin, we must adjust the ODEs model to consider insulin resistance, to build models for patients with type 2 diabetes. Sturis et al. suggest that the occurrence of sustained insulin and glucose oscillation is dependent on 1) a time delay of 30-45 min for the effect of insulin on glucose production and 2) a sluggish effect of insulin on glucose utilization, because insulin acts from a compartment remote from plasma [220]. To incorporate these characteristics into the numerical model, we need to modify the ODEs system accordingly to address the time delay between insulin and glucose.

Chapter 4

Conclusion

4.1 Summary

In summary, I have presented biomechanistic and bioinformatic models with applications to real-world data to address the fundamental problems, i.e., the mechanisms of hemodynamics changes and glycemic controls in patients with diabetes.

Fibrinogen-dependent red cell aggregation. Fibrinogen is regarded as the main glycoprotein in the aggregation of red blood cells (RBCs), a normally occurring phenomenon that has a major impact on blood rheology and hemodynamics, especially under pathological conditions including type 2 diabetes mellitus (T2DM). In this study, we investigate the fibrinogen-dependent aggregation dynamics of T2DM RBCs through patient-specific predictive computational simulations that invoke key parameters derived from microfluidic experiments. We first calibrate our model parameters at doublet (rouleau consisting of two aggregated RBCs) level for healthy

blood samples, by matching the detaching force required to fully separate RBC doublets with the measurements using atomic force microscopy (AFM) and optical tweezers (OT). Using results from companion microfluidic experiments that also provide *in vitro* quantitative information on cell-cell adhesive dynamics, we then quantify the rouleau dissociation dynamics at doublet and multiplet (rouleau consisting of three or more aggregated RBCs) levels for obese patients with or without T2DM. Specifically, we examine the rouleau breakup rate when it passes through microgates at doublet level and investigate the effect of rouleau alignment in altering its breakup pattern at multiplet level. This study seamlessly integrates *in vitro* experiments and simulations, and consequently enhances our understanding of the complex cell-cell interaction highlighting the importance of the aggregation and disaggregation dynamics of RBCs in patients at increased risk of microvascular complications.

Blood cells dynamics in coagulation cascade. Normal hemostasis is an important physiological mechanism that prevents excessive bleeding during trauma whereas the pathological thrombosis especially in diabetics leads to increased incidence of heart attacks and strokes as well as peripheral vascular events. In this work, we propose a new multiscale framework that integrates seamlessly four key components of blood clotting, namely transport of coagulation factors, coagulation kinetics, blood cell mechanics and platelet adhesive dynamics, to model the development of thrombi under physiological and pathological conditions. We implement this framework to simulate platelet adhesion due to the exposure of tissue factor in a 3D microchannel. Our results show that our model can simulate thrombin-mediated platelet activation in the flowing blood, resulting in platelet adhesion to the injury site of the channel wall. Furthermore, we simulate platelet adhesion in diabetic blood, and our results show that both the pathological alterations in the biomechanics of blood cells and

changes in the amount of coagulation factors contribute to the excessive platelet adhesion and aggregation in diabetic blood. Taken together, this new framework can be used to probe synergistic mechanisms of thrombus formation under physiological and pathological conditions, and open new directions in modeling complex biological problems that involve several multiscale processes.

Short-term and long-term hypoglycemia detection. Accurate prediction of blood glucose variations in type 2 diabetes (T2D) will facilitate better glycemic control and decrease the occurrence of hypoglycemic episodes as well as the morbidity and mortality associated with T2D, hence increasing the quality of life of patients. Due to the complexity of the blood glucose dynamics, it is difficult to design accurate predictive models in every circumstance, i.e., hypo/normo/hyperglycemic events. We developed deep learning methods to predict patient-specific blood glucose during various time horizons in the immediate future using patient-specific every 30-min long glucose measurements by the continuous glucose monitoring (CGM) to predict future glucose levels in 5 minutes to 1 hour. In general, the major challenges to address are (1) the dataset of each patient is often too small to train a patient-specific deep learning model, and (2) the dataset is usually highly imbalanced given that hypo- and hyperglycemic episodes are usually much less common than normoglycemia. We tackle these two challenges using transfer learning and data augmentation, respectively. We systematically examined 3 neural network architectures, different loss functions, 4 transfer learning strategies, and 4 data augmentation techniques, including mixup and generative models. Taken together, utilizing these methodologies we achieved over 95% prediction accuracy and 90% sensitivity for a time period within the clinically useful one-hour prediction horizon that would allow a patient to react

and correct either hypoglycemia and/or hyperglycemia within a clinically useful time-frame. Using a large multi-institutional random trial dataset, namely The Action to Control Cardiovascular Risk in Diabetes (ACCORD) dataset, we develop multi-view learning based machine learning algorithms that are capable of detecting severe hypoglycemia events one year in advance, using the past one year electronic health data from patients.

Artificial pancreas design. Insulin is one of the most popular treatments for patients with diabetes mellitus to achieve good glycemic control. Overestimation on the necessary insulin dosage can be extremely dangerous and leading to fatally low blood glucose levels below 70 mg/dl, namely hypoglycemia, while underestimated insulin leaving blood glucose above 180 mg/dl, resulting a state called hyperglycemia, is believed to be responsible for micro- and macrovascular diseases in the long run. In modern medicine, the use of insulin pumps along with continuous glucose monitors has made it easier but requires significant resources and patient education. Hence, designing a closed-loop control system, also called artificial pancreas, which automates insulin infusion so as to maintain a consistently stable blood glucose level is undoubtedly one of the best treatments relieving the burden of both patients and doctors, as well as saving medical costs.

Formidable challenges remain before an ideal artificial pancreas can be safely used in free-living situations in T1D. These include personalization of algorithms based on changes in physiological parameters, for example, physical activity, meals, illness, stress, and so on. In this work, we attempt to address a few of the challenges with a novel framework that effectively combines three key components to build a patient-specific artificial pancreas. These important components are 1) a real-world historical medical dataset, namely OhioT1DM dataset, containing patient-specific

glucose, insulin, meal intake, and exercise intensity, 2) a flexible ODEs model defining glucose-insulin dynamics by systematically prioritizing two significant external factors, i.e., meal intake and physical activities, and 3) an offline reinforcement learning algorithm, which is capable of developing an efficient agent with no need of interacting with the target environment. We firstly employ system biology informed neural networks (SBINNs) to infer patient-specific parameters of the ODEs model using patient-specific data, i.e., glucose trajectory, glucose infusion rate, exogenous insulin infusion rate, and exercise intensity. After validating the parameters inferred by SBINNs, we train an agent to automate insulin infusion and evaluate the performance of the agent on the patient-specific ODE model. The evaluation results suggest that the best trained agent has a better performance in terms of maintaining blood glucose levels within the safe range, i.e., within the range between 70 mg/dl and 180 mg/dl, compared to the self-modulated insulin infusion on the patient's own.

4.2 Future work

Although we have already introduced several successful efforts in two approaches of diabetes management, namely the biomechanistic approach and bioinformatic approach, respectively, the most significant part remain is to join these efforts together to create a patient-specific digital surrogate, thoroughly mimicking the patient's metabolism. By carrying out computational simulations on this surrogate, we aim to provide a prognostic diagnosis for the patient, as shown in Fig. 4.1.

Specifically, we aim to exploit the power of big data to first learn the general patterns of the diabetic patients, and then fine-tune the learnt models with a small amount of patient's own data. By performing the multi-step learning, we can quickly

provide *patient-specific model inputs* for the biomechanistic models developed beforehand. For example, in modeling the blood coagulation cascade, we can first build data-driven models that connect a small subset of measurable concentration levels of co-factor and factors with the other factors or co-factors that are difficult to measure/calibrate through existing experimental equipments. With necessary concentration levels of co-factors and factors set up, we could then carry out simulations with high fidelity to provide forecasting on the patient's metabolic evolution.

By integrating simulations at multiple scales we can eventually *build* a digital twin which can provide patient-specific prognostic simulation at the corresponding levels. The prognostic simulations for patients' digital twins again produce a large quantity of data, i.e., big prognostic data from the digital twin, which we will be able to identify the potential risk factors distinguishing patients with good diabetes outcomes from those with poor outcomes. By improving every step in this cycle, we will eventually *improve* the quality of life for patients with diabetes.

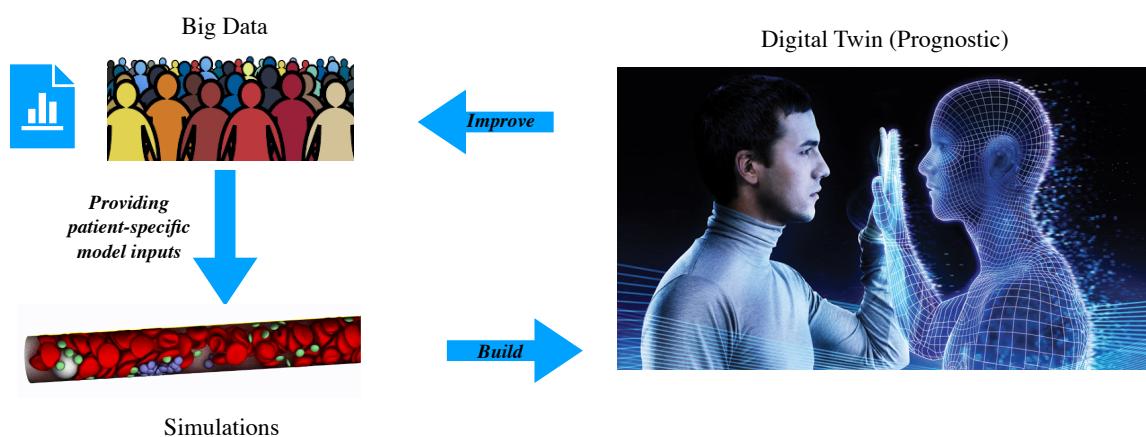


Figure 4.1: Schematic view of future works joining the best of both the biomechanistic approach and the bioinformatic approach.

Appendix A

Appendix

A.1 Fibrinogen-dependent red blood cell aggregation in type 2 diabetes

A.1.1 Summary of patient metabolism indices and medication history

To substantiate our claims in this work, we measure and summarize the metabolism indices and medication history of patients in Table [A.1](#). In particular, we confirm that patients are all obese, indicated from their BMIs ($\text{BMI} \geq 25$). More importantly, the selected patient II, IV and V for simulations are representatives from healthy, well-controlled T2DM and poorly-controlled T2DM patients, respectively, indicated by their Hb1Ac levels in Table [2.1](#) in the main text.

Patient ID	I	II	III	IV	V	VI
Age (y)	57	65	64	46	60	61
Weight (kg)	127.1	99.8	103.3	137.8	116.9	105.4
Height (cm)	170.7	170.5	176.2	166.3	192.9	179.1
BMI (kg/m ²)	43.62	34.33	33.27	49.83	31.42	32.86
Medications	No	No	Aspirin, Statin, HCT	Metformin	Metformin, ACE-inhibitor	Aspirin, Amlodipin, ACE-inhibitor, Statin
Glucose (mg/dl)	105	82	105	94	141	109
BUN (mg/dl)	9	10	18	13	11	9
Creatinine, Serum (mg/dl)	0.64	1.03	0.75	0.7	0.91	0.92
Sodium, Serum (mmol/l)	137	142	142	139	142	136
Potassium, Serum (mmol/l)	4.1	5.8	4.2	4.4	4.6	3.9
Chloride, Serum (mmol/l)	96	105	103	100	102	101
Carbon Dioxide, Total (mmol/L)	26	22	23	25	25	23

Table A.1: **Measurement of Patients' Metabolic Characteristics.** HCT, Hydrochlorothiazide; BUN, blood urea nitrogen.

A.1.2 RBC models

We construct the following potential to represent the elastic energy of the RBC models,

$$V_s = \sum_{j \in 1, \dots, N_s} \left[\frac{k_B T l_m (3x_j^2 - 2x_j^3)}{4p(1 - x_j)} + \frac{k_p}{(n - 1)l_j^{n-1}} \right], \quad (\text{A.1})$$

where p denotes the persistence length, l_i denotes the length of i th spring, l_0 denotes equilibrium spring length, l_m denotes maximal spring extension and $k_B T$ is the energy unit. The bending resistance of the RBC membrane is achieved using the following potential,

$$V_b = \sum_{\alpha, \beta \text{ pair}} k_b [1 - \cos(\theta_{\alpha\beta} - \theta_0)], \quad (\text{A.2})$$

where k_b is constant denoting the bending modulus, $\theta_{\alpha\beta}$ is the instantaneous angle between two adjacent triangles sharing a common edge and θ_0 is the spontaneous angle. Additionally, to impose area and volume conservation of RBC models due to the area conservation of the lipid bilayer and the incompressibility of the cytoplasm, we apply the following combined potentials,

$$V_{a+v} = \sum_{j \in 1, \dots, N_t} \frac{k_d (A_j - A_0)^2}{2A_0} + \frac{k_a (A - A_0^{\text{tot}})^2}{2A_0^{\text{tot}}} + \frac{k_v (V - V_0^{\text{tot}})^2}{2V_0^{\text{tot}}}, \quad (\text{A.3})$$

where k_a and k_v are area and volume constraint constants, and A is the instantaneous area of RBC during simulations.

A.1.3 Simulation model parameters

In all simulations presented in the main text, the parameters were calibrated based on experimental results then kept consistent unless otherwise noted in the main text.

Cell-cell interaction potentials

Detailed parameter values of the Morse potential and the Lennard-Jones potential are listed in Table A.2.

Table A.2: **Model parameters for Morse potential and LJ potential.**

Parameter	Simulation	Physical
r_0	1.0	1 μm
β	1.5	1.5 (scaling factor for distance, dimensionless)
σ	0.3	0.3 μm
ϵ	0.4	$3.392 \times 10^{-25} \text{ J}$
r_{LJ}	0.25	0.25 μm

Cell-fluid and fluid-fluid interaction

Under the DPD framework, the force F between a pair of atoms, for example, atom i and atom j , at a distance $r = |r_{ij}|$ within cutoff distance r_c , is given as a sum of three terms as follows,

$$F = (F^C + F^D + F^R)r_{ij}$$

$$F^C = Aw(r)$$

$$F^D = -\gamma w^2(r)(r_{ij} \cdot v_{ij})$$

$$F^R = \sigma w(r)\alpha(\Delta t)^{-1/2}$$

$$w(r) = (1 - r/r_c)^m$$

where F^C is a conservative force, F^D is a dissipative force, and F^R is a random force. r_{ij} is a unit vector in the direction $r_i - r_j$, v_{ij} is the vector difference in velocities of atom i and atom j , α is a Gaussian random number with zero mean and unit variance, Δt is the timestep size; m is an exponential factor and by setting it to 1 our DPD framework reduces to the standard DPD framework. We applied the same set of DPD parameters for cell-fluid and fluid-fluid interactions, as listed in Table A.3.

n	r_c	a_C	γ	k	η
4	1.58	5.0	20.0	0.2	117.6

Table A.4: **DPD fluid parameters used in current study.** n is the fluid’s number density, a_c is the conservative force coefficient, γ is the dissipative force coefficient, k is the weight function exponent, and η is the fluid’s dynamic viscosity. In all simulations, we set the particle mass $m = 1$, and the thermal energy $k_B T = 0.1$ in DPD units.

Parameter	Value
A	2.5
γ	10
σ	1.414
m	0.25

Table A.3: **Model parameters for cell-cell and cell-fluid interactions.**

A.2 Blood cells dynamics in coagulation cascade in normal and diabetic blood

A.2.1 Hydrodynamics and blood cell models

We employ a dissipative particle dynamics (DPD) to model blood flow, i.e., plasma, red blood cells (RBCs) and platelets, in the microfluidic channels. The background flow (blood plasma) in the simulation is described using the standard DPD method.

The DPD method is a mesoscopic particle-based simulation technique, where each DPD particle represents a lump of molecules and interacts with other particles through soft pairwise forces. Since these interactions depend only on the relative positions and velocities, the resulting DPD fluids are Galilean invariant. Therefore, DPD can provide the correct hydrodynamic behavior of fluids at the mesoscale, and it has been successfully applied to study complex fluids [76, 262]. The equation of

motion for each particle i is governed by the sum of pair interactions $\mathbf{f}_i$ with the surrounding particles j and integrated using a velocity-Verlet algorithm. The time evolution of velocity ($\mathbf{v}_i$) and position ($\mathbf{r}_i$) of a particle i with mass m_i is determined by Newton's second law of motion:

$$d\mathbf{r}_i = \mathbf{v}_i dt; \quad d\mathbf{v}_i = \mathbf{f}_i/m_i dt. \quad (\text{A.4})$$

In the classical DPD method, the total force $\mathbf{f}_i$ exerted on particle i by particle j is composed of a conservative force ($\mathbf{F}_{ij}^C$), a dissipative force ($\mathbf{F}_{ij}^D$), and a random force ($\mathbf{F}_{ij}^R$) given by

$$\mathbf{F}_{ij}^C = a_{ij}(1 - \frac{r_{ij}}{r_c})\hat{\mathbf{r}}_{ij} \quad \text{for } r_{ij} \leq r_c; \quad \mathbf{F}_{ij}^C = 0 \quad \text{for } r_{ij} > r_c, \quad (\text{A.5})$$

$$\mathbf{F}_{ij}^D = \gamma\omega_d(r_{ij})(\hat{\mathbf{r}}_{ij} \cdot \hat{\mathbf{v}}_{ij})\hat{\mathbf{r}}_{ij}, \quad (\text{A.6})$$

$$\mathbf{F}_{ij}^R = \sigma\omega_r(r_{ij})\frac{\zeta_{ij}}{\sqrt{dt}}\hat{\mathbf{r}}_{ij}, \quad (\text{A.7})$$

where r_c is a cut-off radius, and a_{ij} , γ , σ are the conservative, dissipative, random coefficients, respectively, r_{ij} is the distance with the corresponding unit vector $\hat{\mathbf{r}}_{ij}$, $\hat{\mathbf{v}}_{ij}$ is the difference between the two velocities, ζ_{ij} is a Gaussian random number with zero mean and unit variance, and dt is the simulation timestep size. The parameters γ and σ and the weight functions coupled through the fluctuation-dissipation theorem and are related by $\omega_d = \omega_r^2$ and $\sigma^2 = 2\gamma k_B T$, where k_B is the Boltzmann constant and T is the temperature of the system. The weight function $\omega_r(r_{ij}) = (1 - r_{ij}/r_c)^k$ with $k = 1$ in the standard DPD method, whereas other values of k have been used to increase the fluid viscosity [68]. Table A.4 presents the DPD parameters used for

the fluid particles following our previous studies in [78]. More detailed description of DPD method can be found elsewhere [66, 96]; see also [256] for RBC and platelet modeling.

In addition to blood plasma modeled by collections of free DPD particles, the membrane of suspending cells including RBCs and platelets is constructed by a 2D triangulated network with N_v vertices (DPD particles). The vertices are connected by N_s elastic bonds to impose proper membrane mechanics. These DPD representations of RBCs and platelets were extensively used and validated in the previous studies for both healthy and diseased cells [72, 202, 256, 153]. For a single cell, the free energy (V_{cell}) is given by

$$V_{cell} = V_s + V_b + V_{a+v}. \quad (\text{A.8})$$

The elastic energy V_s representing the elastic interactions of the cell membrane is defined by

$$V_s = \sum_{j \in 1 \dots N_s} \left[\frac{k_B T l_m (3x_j^2 - 2x_j^3)}{4p(1 - x_j)} + \frac{k_p}{l_j} \right], \quad (\text{A.9})$$

where p is the persistence length, k_p is the spring constant, $k_B T$ is the energy unit, l_j is the length of the spring j , l_m is the maximum spring extension, and $x_j = l_j/l_m$. p and k_p are computed by balancing the forces at equilibrium and from their relation to the macroscopic shear modulus, μ_s :

$$\mu_s = \frac{\sqrt{3}k_B T}{4pl_m x_0} \left(\frac{x_0}{2(1 - x_0)^3} - \frac{1}{4(1 - x_0)^2} + \frac{1}{4} \right) + \frac{3\sqrt{3}k_p}{4l_0^3}, \quad (\text{A.10})$$

where l_0 is the equilibrium spring length and $x_0 = l_0/l_m$. The bending resistance V_b of the cell membrane is modeled by

$$V_b = \sum_{j \in 1 \dots N_s} k_b [1 - \cos(\theta_j - \theta_0)], \quad (\text{A.11})$$

where k_b is the bending constant, and it is related to the macroscopic bending rigidity k_c with the expression $k_b = 2k_c/\sqrt{3}$, θ_j is the instantaneous angle between two adjacent triangles having the common edge j , and θ_0 is the spontaneous angle. In addition, the area and volume constraints V_{a+v} are imposed to mimic the area-preserving lipid bilayer and the incompressible interior fluid. The corresponding energy is given by

$$V_{a+v} = \sum_{j \in 1 \dots N_t} \frac{k_d(A_j - A_0)^2}{2A_0} + \frac{k_a(A_{\text{cell}} - A_0^{\text{tot}})^2}{2A_0^{\text{tot}}} + \frac{k_v(V_{\text{cell}} - V_0^{\text{tot}})^2}{2V_0^{\text{tot}}}, \quad (\text{A.12})$$

where N_t is the number of triangles in the membrane network, A_0 is the equilibrium value of a triangle area, and k_d , k_a and k_v are the local area, global area and volume constraint coefficients, respectively. The terms A_0^{tot} and V_0^{tot} are targeted cell area and volume.

In this study, we model a normal RBC with $N_v = 500$, shear modulus $\mu_0 = 4.73 \mu\text{N/m}$ and bending rigidity $k_0 = 2.4 \times 10^{-19} \text{ J}$. The cell surface area is selected to be $A_0^{\text{tot}} = 132.9 \mu\text{m}^2$, and cell volume $V_0^{\text{tot}} = 92.5 \mu\text{m}^3$, which give surface to volume ratio $S/V = 1.44$. All parameters used in our normal or diabetic RBCs model are calibrated based on existing experimental data and validated with simulations, from single RBC mechanics to blood flow dynamics [31, 57].

In the case of platelets, which are nearly rigid in their passive form, we choose shear modulus and bending rigidity sufficiently large (100 times larger than the normal RBCs) to ensure its rigid behavior. The number of vertices in the platelet's membrane network is $N_v = 48$ and the aspect ratio of the cell is $AR = 0.38$. Based on our previous analysis on the patient-specific data [31], a normal platelet has cell volume $V_0^{\text{tot}} = 6 \mu\text{m}^3$. The DPD parameters used in eqn (A.5)-(A.7) for all types of DPD particles and the cell membrane parameters used in eqn (A.9)-(A.12) for all blood cell models are given in Tables A.5 and A.6, respectively.

Table A.5: **DPD parameters used in simulations.** r_c is a cut-off radius, a_{ij} is the conservative coefficient, γ is the dissipative coefficient, and k is the weight function exponent. In all simulations, we set the particle mass $m = 1$, and the thermal energy $k_B T = 0.10$ in DPD units. Note that S stands for solvent (representing plasma), R stands for RBC and P stands for platelet.

type	r_c	a_{ij}	γ	k
S-S	1.58	5.0	20.0	0.20
S-R	1.5	0.0	45.0	0.20
S-P	1.5	0.0	10.0	0.20
R-R	1.0	10.0	10.0	0.20
R-P	1.0	10.0	10.0	0.20
P-P	1.0	10.0	10.0	0.20

In order to prevent cell overlap we also employ a Morse potential between cell membrane particles in the form of

$$V_M(r) = D_e [e^{2\beta(r_0-r)} - 2e^{\beta(r_0-r)}], \quad (\text{A.13})$$

where r is the separation distance, r_0 is the zero force distance, D_e is the well depth of the potential, and β characterizes the interaction range. By properly setting the parameters, we can ensure sufficiently strong repulsive forces between cell membrane particles and prevent their overlap. We present the Morse potential parameters used for cell-cell interactions in Table A.7. Note that the cutoff radius $r_{cM} = 1$ for all the Morse interactions is given.

Table A.6: **Cell membrane parameters** for normal RBCs (NRBCs), diabetic RBCs (DRBCs), platelets with mean platelet volume (MPV)= 6 fL (PLTs) and platelets with MPV= 12 fL (PLT*). N_v is the number of DPD particles on the membrane, l_m is the maximum bond extension, l_0 is the equilibrium bond length, k_b is the bending constant, μ_s is the shear modulus, A_0^{tot} and V_0^{tot} are the specified cell area and volume, respectively, $k_d + k_a$ is the combined area constraint coefficient, and k_v is the volume constraint coefficient.

cell	N_v	l_m/l_0	k_b	μ_s	$A_0^{\text{tot}} (V_0^{\text{tot}})$	$k_d + k_a (k_v)$
NRBC	500	1.8	6.025	100.0	132.87 (92.45)	5000 (5000)
DRBC	500	1.8	6.025	200.0	132.87 (127.45)	5000 (5000)
PLT	48	1.8	100.0	10^4	19.63 (6.02)	5000 (10^4)
PLT*	48	1.8	100.0	10^4	31.16 (12.01)	5000 (10^4)

type	D_e	β	r_0
R-R	5.0	2.0	0.95
R-P	10.0	2.0	1.0
P-P	10.0	2.0	1.0

Table A.7: **Morse potential parameters for cell-cell interactions.** D_e is the well depth of the potential, r_0 is the zero force distance, and β characterizes the interaction range. Note that R= RBC and P= platelet

A.2.2 Conversion from DPD units to physcial units

In order to relate the DPD parameters with the physical values, we need to first define length and time scales. The RBC membrane shear modulus imposes the time scale for the DPD system, which follows

$$[t] = [L] \frac{\eta^P \mu_s^M}{\eta^M \mu_s^P} \quad (\text{A.14a})$$

$$[F] = [L] \eta^M \frac{\mu_s^P}{\mu_s^M} \quad (\text{A.14b})$$

where μ_s is the RBC membrane shear modulus, η is the plasma viscosity, and superscripts M and P denote the model (DPD) and physical units, respectively. The length scale is taken as $[L] = 1 \times 10^{-6}m$, whereas the time scale is evaluated by Eq. (8) $[t] = 2.27 \times 10^{-4}s$ (using membrane shear modulus of healthy RBCs $\mu_s^p = 4.73 \times 10^{-6}N/m$ and plasma viscosity $\eta^p = 1.2 \times 10^{-3}Pa \cdot s$). Further, chemical concentrations are scaled by $[C_0] = 1.0nM \cdot [L]^3/n$ where n is the DPD particles density.

A.2.3 Coagulation factor transport and chemical kinetics model

Index	Species	Name	c_i^0 (nM)	$D_i \times 10^{-7}$ (cm ² /s)
1	IXa	enzyme IXa	90×10^{-5}	6.25
2	IX	zymogen IX	90	5.63
3	VIIIa	enzyme VIIIa	0.7×10^{-5}	3.92
4	VIII	zymogen VIII	0.7	3.12
5	Va	enzyme Va	20×10^{-5}	3.82
6	V	zymogen V	20	3.12
7	Xa	enzyme Xa	170×10^{-5}	7.37
8	X	zymogen X	170	5.63
9	IIa	thrombin	1400×10^{-5}	6.47
10	II	prothrombin	1400	5.21
11	Ia	fibrin	7000×10^{-5}	2.47
12	I	fibrinogen	7000	3.1
13	XIa	enzyme XIa	30×10^{-5}	5.0
14	XI	zymogen XI	30	3.97
15	ATIII	anti-thrombin-III	2410	5.57
16	TFPI	tissue factor pathway inhibitor	2.5	6.30
17	APC	active protein C	60×10^{-5}	5.50
18	PC	protein C	60	5.44
19	α_1 AT	α_1 -AntiTrypsin	45000	5.82
20	tPA	Tissue plasminogen activator	0.08	5.28
21	ADP	adenosine diphosphate	0.0	25.70
22	Z	tenase	1.125×10^{-4}	—
23	W	prothrombinase	0.034	—

Table A.8: **List of reactants in the coagulation cascade along with their initial concentrations c_i^0 and diffusion constants D_i .**[8]

The equations of motion and concentration for each particle of mass m_i are denoted by $dr_i = v_i dt$; $dv_i = f_i/m_i dt$; $dC_i = Q_i/m_i dt$ and integrated using a velocity-Verlet algorithm, where C_i represents the concentration of a species per unit mass carried by a particle, and $Q_i = \sum_{i \neq j} (Q_{ij}^D + Q_{ij}^R) + Q_i^S$ is the corresponding concentration flux. We note that C_i can be a vector C_i containing N components, i.e., $C_1, C_2, \dots, C_N$, when N chemical species are considered. In the tDPD model, the total concentration flux accounts for the Fickian flux Q_{ij}^D and random flux Q_{ij}^R , which are given by

$$Q_{ij}^D = -k_{ij}\omega_{DC}(r_{ij})(C_i - C_j), \quad (\text{A.15})$$

$$Q_{ij}^R = \epsilon_{ij}\omega_{RC}(\xi_{ij})(\Delta t^{-1/2}), \quad (\text{A.16})$$

where k_{ij} and ϵ_{ij} determine the strength of the Fickian and random fluxes, and Q_i^S represents the source term for the concentration due to chemical reactions. Further, the fluctuation-dissipation theorem is employed to relate the random terms to the dissipative terms, i.e., $\omega_{DC} = \omega_{RC}^2$, and the contribution of the random flux Q_{ij}^R to the total flux is negligible [166]. More detailed information about the tDPD model can be found in our previous work [166].

The ADR equations are in the form of

$$\frac{d[i]}{dt} = \Delta(D_i \Delta[i]) + Q_i^S \quad (\text{A.17})$$

where $[i]$ denotes the concentration of i^{th} reactant and D_i is the corresponding diffusion coefficient. Here, Q_i^S are the nonlinear source terms representing the production or consumption of $[i]$ due to the enzymatic reactions. See Table A.8 for the list of the 23 biological reactants, their diffusion coefficients and expressions to calculate the source terms for each reactants. We note that the typical timescale of blood

coagulation reactions is in the order of minutes and this makes the long-time tDPD computation very expensive. Therefore, following our previous work in [166], we keep the same Peclet number in our simulation to capture the correct flow physics, while we accelerate the reaction processes by 100 times to reduce the computational cost.

Here, we focus only on the coagulation cascade initiated by the tissue factor (TF) or extrinsic pathway to isolate and analyze the effect of TF-VIIa complex on the rate of thrombin production. Following the work of Anand et al. [8], the initial concentration of Fibrinogen (I), zymogens (II, V, VIII, IX, X, XI), inhibitors (ATIII, TFPI), and protein C (PC) are determined based on normal human physiological values which can be found the Table A.8, whereas concentrations of the enzymes (IIa, Va, VIIIa, IXa, Xa, XIa), fibrin and APC in plasma are initially zero or very small number. To initiate the coagulation, a spatially varied concentration level of subendothelium-bound TF-VIIa complex is prescribed at the site of injury, as shown in Fig. 2.10(B) in the main text. This TF-VIIa complex drives four reactions at the wall (represented by flux conditions in Table A.10) that generate enzymes IXa and Xa which, in turn, initiate the extrinsic pathway. The concentration of $[TF-VIIa]_0$ was initially set at 0.25 nM for venous flows, in the range of concentration levels a in former study [143] (estimated to be initially $O(1)$ nM at a shear rate of 500 s^{-1}). The concentration of $[TF-VIIa]$ complex decreases with the increased concentration of fibrin as the fiber network could cover the injury sites and block the $[TF-VIIa]$ complex. However, the exact correlation for the variation of $[TF-VIIa]$ with $[Ia]$ is not known. Here, we assume a cubic function in the form of $[TF-VIIa] = [TF-VIIa]_0(1 - ([Ia]/[Ia]_{thr})^3)$, following our prior work [258]. $[Ia]_{thr}$ is selected to be 5,000 nM, which is the threshold concentration at the core of the clot causing the lowest clot permeability $k_P = 8 \times 10^{-12} \text{ m}^2$ [136].

As mentioned in the main text, we use the coagulation model from Anand et al. [8].

The list of reactants and their normal initial concentration along with their diffusion coefficients in blood plasma are given in Table A.8. The equations governing the generation and depletion of the species (S_i) are formulated based on experimental data for the reaction kinetics, and are listed in Table A.9. The kinetic constants, also obtained from experimental data, are given in the table's caption. Further, concentrations of two other chemical species tenase (Z) and prothrombinase (W) are computed through the relations $[Z]=[VIIIa][IXa]/K_{dZ}$ and $[W]=[Va][Xa]/K_{dW}$, respectively [8].

At the site of injury, we assume that the subendothelium-bound TF-VIIa complex drives the extrinsic pathway of the coagulation cascade through the subendothelium reactions that are represented by Neumann boundary conditions in the form of $-D_j \partial c_j / \partial n = Q_j$. Surface reactions Q_j along with their kinetic constants are given in Table A.10.

A.2.4 Platelet adhesion dynamics model

In this work, we consider the platelet adhesion triggered by the interaction between the platelet receptor GPIb α and A1 domains of immobilized von Willebrand factor (vWF) on the vessel wall injury as we are simulating platelet adhesion in blood flow in a channel with a shear rate of $\sim 600 \text{ s}^{-1}$, where only the binding between the GPIb α and vWF has a sufficiently fast on-rate to initiate platelet adhesion [210]. Assuming a harmonic GPIb α -vWF bond with stiffness k_b , the force F_b in the bond can be calculated as $F_b = -k_b(x_b - l_b)$, where x_b is the receptor-ligand distance and l_b is the equilibrium bond length. The values of the parameters in the platelet adhesive dynamics model are listed in Table A.11. Passive platelets can become activated by exposure to sufficiently high concentrations of thrombin, TxA2 and ADP. We define

an activation function $\omega(x, t) = [\text{IIa}]/[\text{IIa}]_{thr} + [\text{ADP}]/[\text{ADP}]_{thr} + [\text{TxA2}]/[\text{TxA2}]_{thr}$, where the subscript ‘thr’ corresponds to the threshold concentration that activates the platelets. Platelets transporting through the regions with values of $\omega > 1$ will become activated. In this study, we assume a negligible activating effect for TxA2, and the threshold values of $[\text{IIa}]_{thr} = 1 \text{ nM}$ [217] and $[\text{ADP}]_{thr} = 1000 \text{ nM}$ [114]. Experimental measurements show that platelets release approximately $3 \times 10^{-8} \text{ nM}$ ADP to the blood stream within 5 seconds following activation [114, 207]. Here, we assign a normal distribution for the release function $R(t) = \exp[-(t - \mu)^2/\sigma^2]/\sqrt{2\pi\sigma^2}$ with the mean release time of $\mu = 3 \text{ s}$ (seconds) and variance of $\sigma^2 = 2 \text{ s}^2$ (second²). We also assume that once the platelets become activated, they are ready to form bonds with the particles representing vWF ligands on the site of injury.

Parameter (unit)	Physical Value	DPD Value	Reference
$k_f^0 (\text{s}^{-1})$	40	9.1×10^{-3}	[135]
$k_r^0 (\text{s}^{-1})$	0.0022	5.0×10^{-7}	[135]
$\sigma_f (\text{nm})$	1.8	1.8×10^{-3}	[135]
$\sigma_r (\text{nm})$	1.62	1.62×10^{-3}	[135]
$k_b (\text{pN/nm})$	10	2.222×10^5	[185]
$l_b (\text{nm})$	128	0.128	[185]

Table A.11: **Values for bond formation and breakage kinetics in physical and DPD units.** DPD values are estimated based on $[L] = 1 \times 10^{-6} \text{ m}$, $[t] = 2.27 \times 10^{-4} \text{ s}$, and $[F] = 4.5 \times 10^{-14} \text{ N}$.

$$\begin{aligned}
S_1 &= (k_9[\text{XIa}][\text{IX}])/(K_{9M} + [\text{IX}]) - h_9[\text{IXa}][\text{ATIII}] \\
S_2 &= -(k_9[\text{XIa}][\text{IX}])/(K_{9M} + [\text{IX}]) \\
S_3 &= (k_8[\text{IIa}][\text{VIII}])/(K_{8M} + [\text{VIII}]) - h_8[\text{VIIIa}] - (h_{C8}[\text{APC}][\text{VIIIa}])/(H_{C8M} + [\text{VIIIa}]) \\
S_4 &= (k_8[\text{IIa}][\text{VIII}])/(K_{8M} + [\text{VIII}]) \\
S_5 &= (k_5[\text{IIa}][\text{V}])/(K_{5M} + [\text{V}]) - h_5[\text{Va}] - (h_{C5}[\text{APC}][\text{Va}])/(H_{C5M} + [\text{Va}]) \\
S_6 &= -(k_5[\text{IIa}][\text{V}])/(K_{5M} + [\text{V}]) \\
S_7 &= (k_{10}[\text{Z}][\text{X}])/(K_{10M} + [\text{X}]) - h_{10}[\text{Xa}][\text{ATIII}] - h_{TFPI}[\text{TFPI}][\text{Xa}] \\
S_8 &= -(k_{10}[\text{Z}][\text{X}])/(K_{10M} + [\text{X}]) \\
S_9 &= (k_2[\text{W}][\text{II}])/(K_{2M} + [\text{II}]) - h_2[\text{IIa}][\text{ATIII}] \\
S_{10} &= -(k_2[\text{W}][\text{II}])/(K_{2M} + [\text{II}]) \\
S_{11} &= (k_1[\text{IIa}][\text{I}])/(K_{1M} + [\text{I}]) \\
S_{12} &= -(k_1[\text{IIa}][\text{I}])/(K_{1M} + [\text{I}]) \\
S_{13} &= (k_{11}[\text{IIa}][\text{XI}])/(K_{11M} + [\text{XI}]) - h_{11}^{A3}[\text{XIa}][\text{ATIII}] - h_{11}^{L1}[\text{XIa}][\alpha_1\text{AT}] \\
S_{14} &= -(k_{11}[\text{IIa}][\text{XI}])/(K_{11M} + [\text{XI}]) \\
S_{15} &= -(h_9[\text{IXa}] + h_{10}[\text{Xa}] + h_2[\text{IIa}] + h_{11}^{A3}[\text{XIa}])[\text{ATIII}] \\
S_{16} &= -h_{TFPI}[\text{TFPI}][\text{Xa}] \\
S_{17} &= (k_{PC}[\text{IIa}][\text{PC}])/(K_{PCM} + [\text{PC}]) - h_{PC}[\text{APC}][\alpha_1\text{AT}] \\
S_{18} &= -(k_{PC}[\text{IIa}][\text{PC}])/(K_{PCM} + [\text{PC}]) \\
S_{19} &= -h_{PC}[\text{APC}][\alpha_1\text{AT}] - h_{11}^{L1}[\text{XIa}][\alpha_1\text{AT}] \\
S_{20} &= 0 \\
S_{21} &= [\text{ADP}]_{plt} \exp[-(t - \mu)^2/\sigma^2]/\sqrt{2\pi\sigma^2}
\end{aligned}$$

Table A.9: **Reaction equations for source terms.** The parameters are given as $k_9 = 2.54 \times 10^{-2}$, $K_{9M} = 160$, $h_9 = 3.74 \times 10^{-5}$, $k_8 = 0.449$, $K_{8M} = 1.12 \times 10^5$, $h_8 = 5.13 \times 10^{-4}$, $h_{C8} = 2.36 \times 10^{-2}$, $H_{C8M} = 14.6$, $k_5 = 6.24 \times 10^{-2}$, $K_{5M} = 140.5$, $h_5 = 3.93 \times 10^{-4}$, $h_{C5} = 2.36 \times 10^{-2}$, $H_{C5M} = 14.6$, $k_{10} = 5.523$, $K_{10M} = 160$, $h_{10} = 8.01 \times 10^{-4}$, $h_{TFPI} = 1.11 \times 10^{-3}$, $k_2 = 3.105$, $K_{2M} = 1060$, $h_2 = 1.65 \times 10^{-3}$, $k_1 = 8.177$, $K_{1M} = 3160$, $h_1 = 3.456$, $H_{1M} = 2.50 \times 10^5$, $k_{11} = 1.80 \times 10^{-5}$, $K_{11M} = 50$, $h_{11}^{A3} = 3.70 \times 10^{-6}$, $h_{11}^{L1} = 3.00 \times 10^{-8}$, $k_{PC} = 9.01 \times 10^{-2}$, $K_{PCM} = 3190$, $h_{PC} = 1.52 \times 10^{-9}$, $k_{PLA} = 2.77 \times 10^{-2}$, $K_{PLAM} = 18$, $h_{PLA} = 2.22 \times 10^{-4}$, $[\text{ADP}]_{plt} = 3 \times 10^{-8} \text{ nM}$, $\mu = 3 \text{ s}$, $\sigma^2 = 2 \text{ s}^2$.

Index j	Boundary flux terms Q_j
1	$(k_{7,9}[2]^W[\text{TF-VIIa}]^W)/(K_{7,9M} + [2]^W)L$
2	$-(k_{7,9}[2]^W[\text{TF-VIIa}]^W)/(K_{7,9M} + [2]^W)L$
7	$(k_{7,10}[8]^W[\text{TF-VIIa}]^W)/(K_{7,10M} + [8]^W)L$
8	$-(k_{7,10}[8]^W[\text{TF-VIIa}]^W)/(K_{7,10M} + [8]^W)L$

Table A.10: **Flux boundary conditions at the injured vessel wall region.** The parameters are given as $k_{7,9} = 7.48 \times 10^{-2}$, $K_{7,9M} = 24$, $k_{7,10} = 0.238$, $K_{7,10M} = 240$.

A.3 Short-term and long-term blood glucose prediction using machine learning

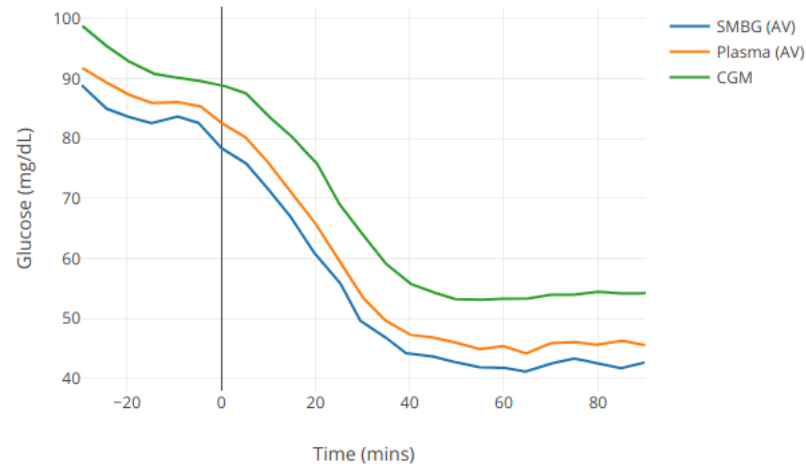


Figure A.1: **Glucose data (mean) during hyperinsulinemic hypoglycemic clamps.** Orange curve represents AV plasma glucose; blue curve, AV blood tested via SMBG; green curve, CGM. AV, arterialized venous. SMBG, self-monitoring of blood glucose. Figure reproduced from Farrell et al. [69].

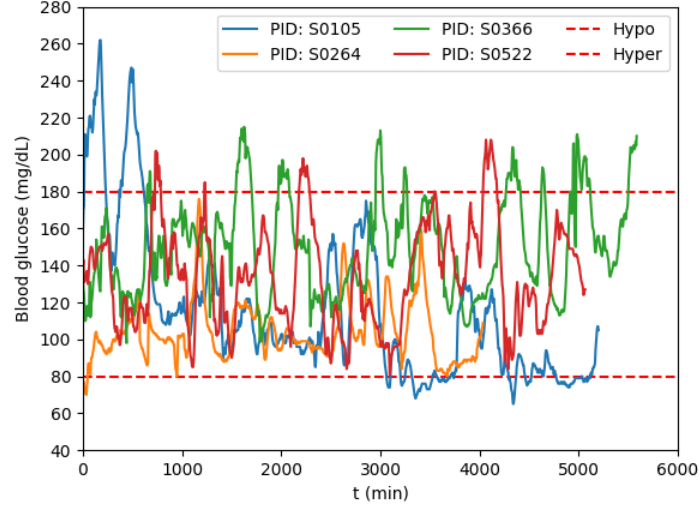


Figure A.2: **Blood glucose (BG) history measured by CGM of four selected patients.** Each colored solid line represents the blood glucose history of one patient, the ID of which is marked in the figure caption. The red dash lines denote the critical threshold of hypoglycemia (BG = 80 mg/dL) and hyperglycemia (BG = 180 mg/dL), respectively. PID, patient's ID.

# Training Data from Target Patient	Logistic Regression	GP	SVM	FNN	Our Best
50	0.990 $\pm$ 0.003	0.988 $\pm$ 0.003	0.990 $\pm$ 0.003	0.990 $\pm$ 0.003	0.988 $\pm$ 0.003
100	0.990 $\pm$ 0.003	0.989 $\pm$ 0.003	0.990 $\pm$ 0.003	0.991 $\pm$ 0.002	0.990 $\pm$ 0.003
400	0.992 $\pm$ 0.003	0.991 $\pm$ 0.003	0.991 $\pm$ 0.003	0.992 $\pm$ 0.002	0.992 $\pm$ 0.002
1000	0.973 $\pm$ 0.015	0.971 $\pm$ 0.016	0.973 $\pm$ 0.015	0.973 $\pm$ 0.016	0.993 $\pm$ 0.002

Table A.12: **Hypoglycemia detection (binary classification, hypoglycemia vs. no hypoglycemia) accuracy (mean $\pm$ standard error) of different methods with different numbers of training data from the target patient, for prediction horizon at 30 minutes and training models on the cohort (patients participated in this study) data.** GP, Gaussian Process; SVM, supporting vector machine; FNN, the best fully-connected neural networks; Our Best, the best model among the combinations of three proposed architectures (RNN, CNN and SAN) and four transfer learning methods (Pretrain, Transfer1, Transfer2 and Transfer3). Details of the network architectures and transfer learning methods can be found in Fig. 3.2 and Table 3.2.

# Training Data from Target Patient	Logistic Regression	GPC	SVC	FNN	Our Best
50	0.924±0.007	0.919±0.007	0.924±0.006	0.926±0.006	0.929±0.006
100	0.924±0.007	0.919±0.008	0.924±0.007	0.927±0.007	0.926±0.007
400	0.929±0.007	0.926±0.007	0.927±0.007	0.931±0.006	0.930±0.007
1000	0.939±0.011	0.938±0.012	0.938±0.011	0.941±0.011	0.948±0.010

Table A.13: **Hypoglycemia and hyperglycemia detection (three-class classification) accuracy** (mean $\pm$ standard error) of different methods with different numbers of training data from the target patient, for prediction horizon at 30 minutes and training models on the cohort (patients participated in this study) data. In *three-class classification*, the output label of prediction is one out of three labels, “hypoglycemia”, “normoglycemia” and “hyperglycemia”, at any given time. GP, Gaussian Process; SVM, supporting vector machine; FNN, the best fully-connected neural networks. Our Best, the best model among the combinations of three proposed architectures (RNN, CNN and SAN) and four transfer learning methods (Pretrain, Transfer1, Transfer2 and Transfer3). Details of the network architectures and transfer learning methods can be found in Fig. 3.2 and Table 3.2.

# Training Data from Target Patient	Logistic Regression	GP	SVM	FNN	Our Best
50	0.990±0.003	0.988±0.003	0.990±0.003	0.990±0.002	0.988±0.003
100	0.990±0.003	0.988±0.003	0.990±0.003	0.990±0.003	0.990±0.003
400	0.992±0.003	0.992±0.003	0.991±0.003	0.992±0.002	0.992±0.002
1000	0.988±0.006	0.988±0.006	0.988±0.006	0.988±0.006	0.992±0.003

Table A.14: **Hypoglycemia detection (binary classification) accuracy** (mean $\pm$ standard error) of different methods with different numbers of training data from the target patient, for prediction horizon at 60 minutes. GP, Gaussian Process; SVM, supporting vector machine; FNN, the best fully-connected neural networks; Our Best, the best model among the combinations of three proposed architectures (RNN, CNN and SAN) and four transfer learning methods (Pretrain, Transfer1, Transfer2 and Transfer3). Details of the network architectures and transfer learning methods can be found in Fig. 3.2 and Table 3.2.

# Training Data from Target Patient	Logistic Regression	GPC	SVC	FNN	Our Best
50	0.924 $\pm$ 0.007	0.918 $\pm$ 0.007	0.924 $\pm$ 0.006	0.927 $\pm$ 0.006	0.929 $\pm$ 0.006
100	0.924 $\pm$ 0.007	0.919 $\pm$ 0.007	0.924 $\pm$ 0.007	0.925 $\pm$ 0.007	0.926 $\pm$ 0.007
400	0.929 $\pm$ 0.007	0.926 $\pm$ 0.007	0.927 $\pm$ 0.007	0.929 $\pm$ 0.006	0.930 $\pm$ 0.007
1000	0.939 $\pm$ 0.011	0.940 $\pm$ 0.010	0.938 $\pm$ 0.011	0.940 $\pm$ 0.010	0.944 $\pm$ 0.010

Table A.15: **Hypoglycemia and hyperglycemia detection (three-class classification) accuracy** (mean $\pm$ standard error) **of different methods with different numbers of training data from the target patient, for prediction horizon at 60 minutes.** GP, Gaussian Process; SVM, supporting vector machine; FNN, the best fully-connected neural networks; Our Best, the best model among the combinations of three proposed architectures (RNN, CNN and SAN) and four transfer learning methods (Pretrain, Transfer1, Transfer2 and Transfer3). Details of the network architectures and transfer learning methods can be found in Fig. 3.2 and Table 3.2.

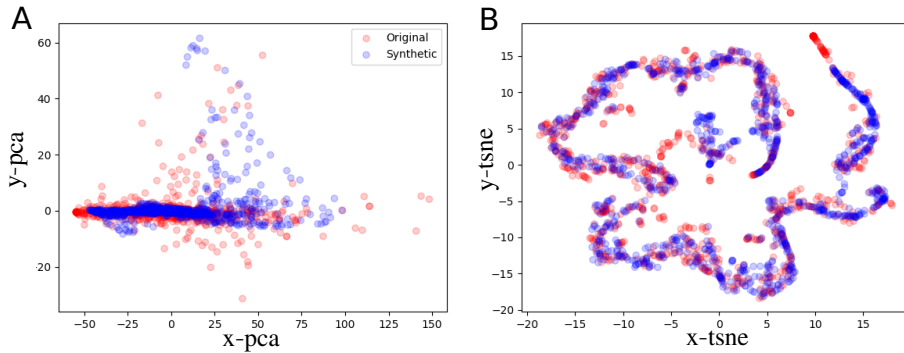


Figure A.3: **The visualization results of the hypoglycemia samples generated by TimeGAN.** (A) PCA (principle component analysis) and (B) T-SNE. The discriminative score output from our trained TimeGAN is around 0.10.

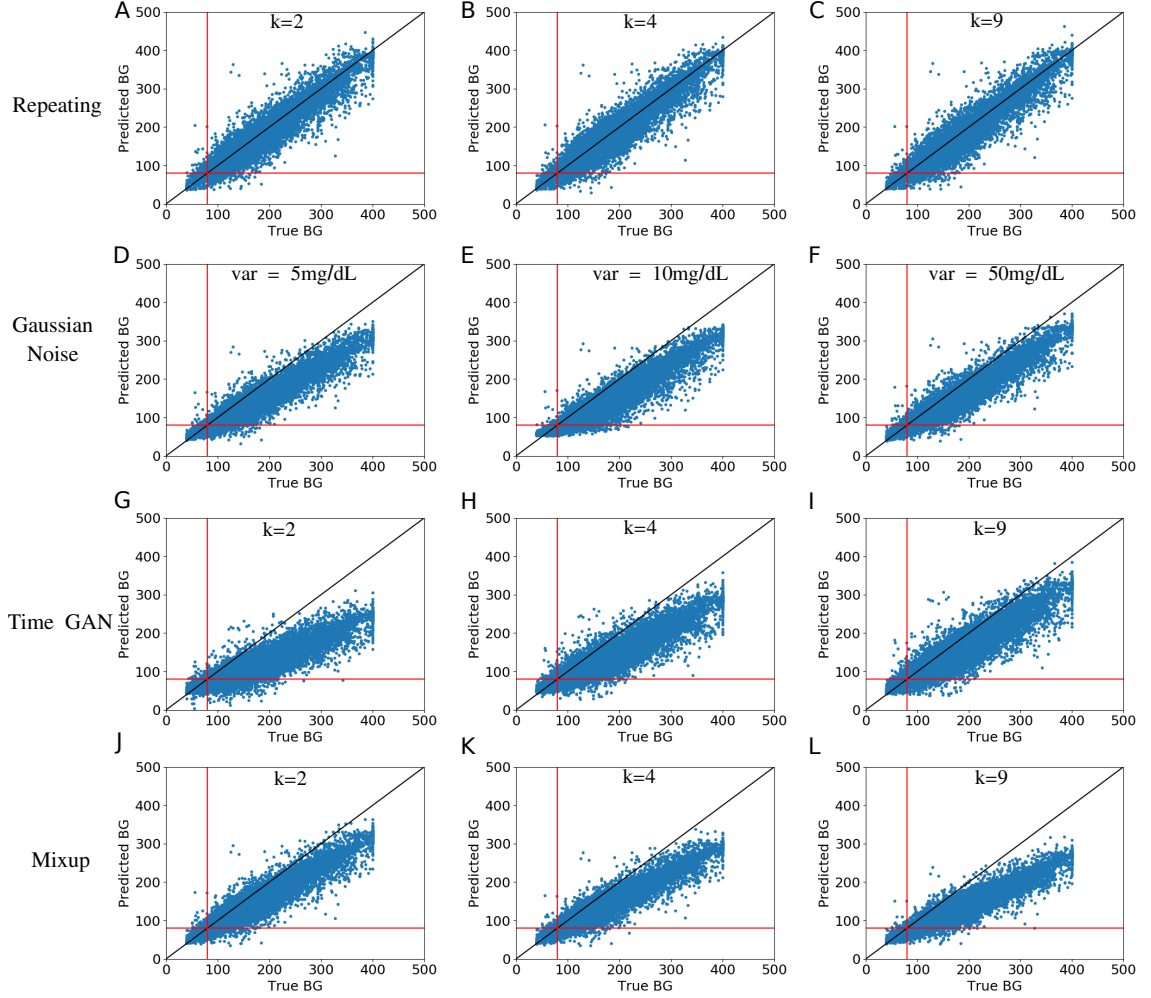


Figure A.4: **True BG measured by CGM vs. BG prediction from our model trained with data augmentation on the minority training data, given different data augmentation/preprocessing methods.** Minority training data is augmented with (A to C) oversampling by repeating, (D to F) Gaussian white noise infusion to a copy of minority training data, (G to I) TimeGAN [266] and (J to L) mixup [268]. Minority training data size is (A, G, J) doubled or (B, E, K) becomes 4 times or (C, I, L) becomes 9 times of its original size after data augmentation. Minority training data size is doubled in (D to F), but different noise level is considered in each figure, i.e., the new copy of minority data is generated by infusing Gaussian white noise with (D) variance 5mg/dL, (E) variance 10 mg/dL and (F) variance 50 mg/dL to the original minority training data. We note that with data augmentation methods, such as Gaussian noise, TimeGAN and mixup, which introduce synthetic data, the model sensitivity increases to more than 90%. Specifically, for TimeGAN and mixup, increasing the minority data fold k , further increases the model sensitivity. However, the increase in sensitivity sacrifices the precision of the minority class (hypoglycemia), as indicated by the inclination of the scattering points, i.e., the (True BG, Predicted BG) pairs, towards x axis shown in the figure.

Table A.16: **Comparison of four classification scores using four different data augmentation methods on minority class.** Classification scores for model trained on dataset with (A) repeating, (B) Gaussian noise, (C) TimeGAN (D) mixup ($\alpha = 2$). PPV, positive predictive value. “raw”, model without data augmentation. NPV, negative predictive value. Noise Var, noise variance. Positive class is the class of samples labeled with hypoglycemia, which is also the minority class.

(A): Repeating

Fold	Sensitivity	PPV	Specificity	NPV
raw	$0.7688 \pm 1.12 \times 10^{-2}$	$0.7466 \pm 5.50 \times 10^{-3}$	$0.9917 \pm 4.00 \times 10^{-4}$	$0.9906 \pm 4.00 \times 10^{-4}$
2	$0.7907 \pm 7.10 \times 10^{-3}$	$0.7309 \pm 7.10 \times 10^{-3}$	$0.9925 \pm 3.00 \times 10^{-4}$	$0.9895 \pm 5.00 \times 10^{-4}$
4	$0.8123 \pm 1.26 \times 10^{-2}$	$0.7038 \pm 8.80 \times 10^{-3}$	$0.9932 \pm 4.00 \times 10^{-4}$	$0.9877 \pm 7.00 \times 10^{-4}$
9	$0.8443 \pm 7.40 \times 10^{-3}$	$0.6583 \pm 8.60 \times 10^{-3}$	$0.9944 \pm 3.00 \times 10^{-4}$	$0.9843 \pm 7.00 \times 10^{-4}$

(B): Gaussian Noise

Noise var	Sensitivity	PPV	Specificity	NPV
raw	$0.7688 \pm 1.12 \times 10^{-2}$	$0.7466 \pm 5.50 \times 10^{-3}$	$0.9917 \pm 4.00 \times 10^{-4}$	$0.9906 \pm 4.00 \times 10^{-4}$
5	$0.8878 \pm 2.22 \times 10^{-2}$	$0.5539 \pm 5.85 \times 10^{-2}$	$0.9959 \pm 8.00 \times 10^{-4}$	$0.9735 \pm 6.80 \times 10^{-3}$
10	$0.9312 \pm 1.75 \times 10^{-2}$	$0.3859 \pm 6.53 \times 10^{-2}$	$0.9974 \pm 6.00 \times 10^{-4}$	$0.9443 \pm 1.41 \times 10^{-2}$
50	$0.9679 \pm 1.26 \times 10^{-2}$	$0.2688 \pm 3.95 \times 10^{-2}$	$0.9987 \pm 5.00 \times 10^{-4}$	$0.9022 \pm 2.18 \times 10^{-2}$

(C): TimeGAN

Fold	Sensitivity	PPV	Specificity	NPV
raw	$0.7688 \pm 1.12 \times 10^{-2}$	$0.7466 \pm 5.50 \times 10^{-3}$	$0.9917 \pm 4.00 \times 10^{-4}$	$0.9906 \pm 4.00 \times 10^{-4}$
2	$0.8947 \pm 8.90 \times 10^{-3}$	$0.5433 \pm 2.34 \times 10^{-2}$	$0.9961 \pm 3.00 \times 10^{-4}$	$0.9729 \pm 2.80 \times 10^{-3}$
4	$0.9386 \pm 3.60 \times 10^{-3}$	$0.3061 \pm 1.57 \times 10^{-2}$	$0.9976 \pm 1.00 \times 10^{-4}$	$0.9233 \pm 5.70 \times 10^{-3}$
9	$0.8976 \pm 2.49 \times 10^{-2}$	$0.2096 \pm 1.89 \times 10^{-2}$	$0.9958 \pm 9.00 \times 10^{-4}$	$0.8769 \pm 1.72 \times 10^{-2}$

(D): mixup, $\alpha = 2$

Fold	Sensitivity	PPV	Specificity	NPV
raw	$0.7688 \pm 1.12 \times 10^{-2}$	$0.7466 \pm 5.50 \times 10^{-3}$	$0.9917 \pm 4.00 \times 10^{-4}$	$0.9906 \pm 4.00 \times 10^{-4}$
2	$0.9068 \pm 4.74 \times 10^{-2}$	$0.4987 \pm 1.07 \times 10^{-1}$	$0.9966 \pm 1.70 \times 10^{-3}$	$0.9639 \pm 1.40 \times 10^{-2}$
4	$0.9339 \pm 3.65 \times 10^{-2}$	$0.4181 \pm 1.22 \times 10^{-1}$	$0.9975 \pm 1.30 \times 10^{-3}$	$0.9459 \pm 2.46 \times 10^{-2}$
9	$0.9366 \pm 1.94 \times 10^{-2}$	$0.3905 \pm 6.10 \times 10^{-2}$	$0.9976 \pm 7.00 \times 10^{-4}$	$0.9454 \pm 1.32 \times 10^{-2}$

Table A.17: **Comparison of three classification scores for minority class between two mixup models and the original dataset.** Classification scores for model trained on dataset with **(A)** no data augmentation, **(B)** minority data augmentation by mixup ($\alpha = 0.4$) and **(C)** minority data augmentation by mixup ($\alpha = 2$). PPV, positive predictive value. NPV, negative predictive value. Positive class is the class of samples labeled with hypoglycemia, which is also the minority class.

(A): No data augmentation

Prediction horizon (min)	Sensitivity	PPV	Specificity	NPV	Accuracy
5	0.9437 $\pm$ 2.40e-3	0.8972 $\pm$ 2.40e-3	0.9961 $\pm$ 1.00e-4	0.9980 $\pm$ 1.00e-4	0.9943 $\pm$ 1.00e-4
15	0.8236 $\pm$ 2.70e-3	0.7855 $\pm$ 4.00e-3	0.9919 $\pm$ 2.00e-4	0.9937 $\pm$ 1.00e-4	0.9861 $\pm$ 2.00e-4
30	0.6777 $\pm$ 8.60e-3	0.6843 $\pm$ 5.60e-3	0.9888 $\pm$ 4.00e-4	0.9884 $\pm$ 3.00e-4	0.9780 $\pm$ 2.00e-4
45	0.5269 $\pm$ 1.21e-2	0.6126 $\pm$ 1.02e-2	0.9881 $\pm$ 6.00e-4	0.9832 $\pm$ 4.00e-4	0.9721 $\pm$ 5.00e-4
60	0.3942 $\pm$ 1.84e-2	0.5423 $\pm$ 6.00e-3	0.9881 $\pm$ 4.00e-4	0.9786 $\pm$ 6.00e-4	0.9676 $\pm$ 4.00e-4

(B): Minority data augmentation by mixup: $\alpha = 0.4$

Prediction horizon (min)	Sensitivity	PPV	Specificity	NPV	Accuracy
5	0.9633 $\pm$ 1.08e-2	0.8455 $\pm$ 4.38e-2	0.9935 $\pm$ 2.30e-3	0.9987 $\pm$ 4.00e-4	0.9925 $\pm$ 1.80e-3
15	0.9121 $\pm$ 5.75e-2	0.5767 $\pm$ 1.56e-1	0.9704 $\pm$ 1.85e-2	0.9968 $\pm$ 2.00e-3	0.9684 $\pm$ 1.60e-2
30	0.8996 $\pm$ 3.27e-2	0.3576 $\pm$ 6.91e-2	0.9378 $\pm$ 2.15e-2	0.9962 $\pm$ 1.20e-3	0.9365 $\pm$ 1.97e-2
45	0.8911 $\pm$ 3.51e-2	0.2234 $\pm$ 5.67e-2	0.8763 $\pm$ 5.05e-2	0.9956 $\pm$ 1.20e-3	0.8768 $\pm$ 4.76e-2
60	0.9086 $\pm$ 5.10e-3	0.1342 $\pm$ 5.00e-3	0.7902 $\pm$ 9.20e-3	0.9959 $\pm$ 2.00e-4	0.7942 $\pm$ 8.80e-3

(C): Minority data augmentation by mixup: $\alpha = 2$

Prediction horizon (min)	Sensitivity	PPV	Specificity	NPV	Accuracy
5	0.9447 $\pm$ 3.05e-2	0.8794 $\pm$ 3.53e-2	0.9952 $\pm$ 1.70e-3	0.9980 $\pm$ 1.10e-3	0.9935 $\pm$ 7.00e-4
15	0.9056 $\pm$ 3.33e-2	0.6341 $\pm$ 8.00e-2	0.9801 $\pm$ 7.50e-3	0.9966 $\pm$ 1.20e-3	0.9776 $\pm$ 6.10e-3
30	0.8695 $\pm$ 2.55e-2	0.4216 $\pm$ 4.92e-2	0.9559 $\pm$ 1.05e-2	0.9951 $\pm$ 9.00e-4	0.9529 $\pm$ 9.30e-3
45	0.8808 $\pm$ 3.00e-2	0.2478 $\pm$ 5.17e-2	0.8982 $\pm$ 2.87e-2	0.9953 $\pm$ 1.00e-3	0.8976 $\pm$ 2.68e-2
60	0.9053 $\pm$ 2.74e-2	0.1363 $\pm$ 2.76e-2	0.7828 $\pm$ 5.99e-2	0.9958 $\pm$ 9.00e-4	0.7871 $\pm$ 5.70e-2

A.4 Artificial pancreas design using offline reinforcement learning

Hyper-parameter	Value
Optimizer	Adam [137]
Learning Rate	10^{-3}
Batch Size	512
Normalized Observations	Yes
Gradient Clipping	No
Discount Factor	0.99
Target Update Rate (τ)	0.005
Exploration Policy	$\mathcal{N}(0, 0.1)$

Table A.18: **Hyper-parameters used in BCQ learning for glucose regulation.**

Parameter	Inferred value
n	0.036
Vol_G^*	156
p_1^*	0.0069
p_2	0.09
p_3	0.0000056
p_4	0.0196
a_1	0.0013
a_2	0.068
a_3	0.0015
a_4	0.061
a_5	0.001
a_6	0.091

Table A.19: **Parameter inference by SBINNs for the modified Roy model using the data from a real case.** * denote the mean value of the corresponding time dependent parameters, p_1 and Vol_G .

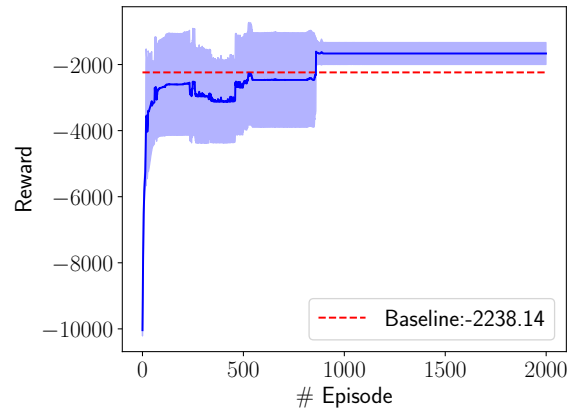


Figure A.5: **Training curve using offline dataset.** The mean and standard deviation are computed using 5 different runs. The baseline reward corresponds to the return of the glucose trajectory using constant parameters, i.e., the black dashed curve in Fig. 3.19.

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