

# Coupled Physiological Sensor Models for Continuous Glucose Monitoring in Diabetes

## Corresponding Author:

Manizhe Shabani, *University of Science and Culture, Tehran, Iran*

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## ABSTRACT

Continuous glucose monitoring (CGM) has transformed diabetes care, yet its accuracy remains constrained by the coupled physics of glucose transport in subcutaneous tissue and enzyme-based sensor transduction. Prevailing approaches represent physiology as a fixed blood–interstitial lag, the sensor as a static or first-order calibration block, and filtering as an independent signal-processing layer. Because delay and drift arise from a shared tissue state, including perfusion, inflammation, and fibrotic encapsulation, such decoupled architectures cannot uniquely separate their contributions. This review presents a systematic and critical synthesis of fully coupled physiological–sensor models for CGM. We first examine the anatomy and transport physiology of the vascular–interstitial–sensor interface and quantify the resulting effective lags, which range from seconds in healthy tissue to more than 20 min in the presence of fibrotic encapsulation. We then formulate interstitial transport as a diffusion–reaction partial differential equation (PDE) domain and sensor electrochemistry as an ordinary differential equation (ODE) domain, and unify them in a canonical PDE–ODE framework in which the sensor surface acts as a dynamic interface, supported by IMEX and operator-splitting solvers together with sensitivity and identifiability analysis. Calibration and state estimation are addressed through dual estimation, Kalman-family, Bayesian, particle, and adaptive filters, evaluated using MARD, error grids, and time-in-range. A stepwise roadmap from data preprocessing to hierarchical validation (in silico, in vitro, animal, and human) is provided, together with a comparative benchmark that decomposes error into physiological, sensor, and filtering components. Finally, we discuss digital twins, physics–machine learning hybrids, model-order reduction for embedded devices, and open challenges in identifiability, fibrosis, and long-term drift. Explicit coupling offers an interpretable, physically consistent foundation for next-generation CGM design, calibration, and clinical translation.

**Keywords:** *Continuous glucose monitoring; Coupled physiological–sensor model; PDE–ODE framework; Interstitial glucose transport; Electrochemical biosensor; Sensor drift and lag; Kalman filtering and state estimation; Digital twin*

## 1. INTRODUCTION

Continuous glucose monitoring (CGM) has transformed diabetes care, yet its accuracy is still constrained by the underlying physics of glucose transport and sensor transduction. Modern reviews agree that what a CGM reports is not “blood glucose with noise” but the output of a **coupled physiological–chemical–electrical system** embedded in dynamic tissue (Lee et al., 2021; Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016; Chmayssem et al., 2023; Teymourian, Barfidokht and Wang, 2020). Ignoring this coupling obscures how delays, drift, and noise arise and limits progress in algorithm design, sensor engineering, and digital twin development (Cappon et al., 2019; Zou et al., 2023; Didyuk et al., 2021; Facchinetti, 2016; Rodbard, 2016).

### 1.1 Continuous Glucose Monitoring as a Multiphysics Measurement Problem

Most commercial CGMs are minimally invasive, enzyme-based electrochemical sensors placed in **subcutaneous interstitial fluid (ISF)**, then algorithmically mapped to blood glucose (Lee et al., 2021; Cappon et al., 2019; Zou et al., 2023; Chmayssem et al., 2023; Teymourian, Barfidokht and Wang, 2020). The overall system couples:

- **Physiology:** capillary–interstitial exchange, diffusion through extracellular matrix, local metabolism, foreign-body response (Lee et al., 2021; Cappon et al., 2019; Zou et al., 2023; Li and Chen, 2023; Chmayssem et al., 2023).
- **Chemistry:** enzyme (typically glucose oxidase) kinetics, mediator redox cycling, oxygen dependence, membrane transport (Lee et al., 2021; Cappon et al., 2019; Zou et al.,

2023; Chmayssem et al., 2023; Teymourian, Barfidokht and Wang, 2020).

- **Electronics:** amperometric or transistor-based readout, temperature compensation, analog/digital filtering, wireless telemetry (Lee et al., 2021; Cappon et al., 2019; Zou et al., 2023; Bai et al., 2024; Teymourian, Barfidokht and Wang, 2020).

Recent device-oriented reviews and advanced e-textile / multimodal wearables explicitly emphasize that meaningful CGM must integrate these multiphysics interactions, not treat the sensor as an abstract signal source (Lee et al., 2021; Zou et al., 2023; Karunarathna and Liang, 2025; Chmayssem et al., 2023; Sunstrum et al., 2025; Bai et al., 2024; Teymourian, Barfidokht and Wang, 2020).

## 1.2 The CGM Accuracy Trilemma: Transport Delay – Sensor Dynamics – Measurement Noise

Across invasive and noninvasive CGMs, three interlinked limitations recur:

### 1. Physiological transport delay and gradients

ISF lags blood by ~5–10 min under typical conditions and more during rapid excursions (Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016). Noninvasive fluids (sweat, tears, saliva) show additional lags and attenuated amplitudes, heavily context-dependent (Lee et al., 2021; Li and Chen, 2023; Chmayssem et al., 2023; Sunstrum et al., 2025).

### 2. Intrinsic sensor dynamics and drift

Enzyme-based electrochemical sensors exhibit diffusion-limited time constants, nonlinear response, sensitivity changes due to enzyme degradation, biofouling, and membrane swelling (Lee et al., 2021; Cappon et al., 2019; Zou et al., 2023; Chmayssem et al., 2023; Teymourian, Barfidokht and Wang, 2020). Next-generation architectures (e.g., organic electrochemical transistor CGM) explicitly target improved signal-to-noise but still obey similar transport-reaction constraints (Bai et al., 2024).

### 3. Measurement noise and environmental interference

Noise arises from electronics, motion, temperature, pH, interfering species (e.g., acetaminophen, ascorbate), and perioperative conditions such as hypothermia, edema, and electrocautery (Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016; Carlier et al., 2025; Bailey and Alva, 2021; Rodbard, 2016).

Algorithm-focused reviews underscore that attempts to “fix” CGM by post-hoc filtering must inevitably trade off these three axes: reducing noise often increases effective lag; compensating lag can amplify noise or drift (Facchinetti, 2016; Bailey and Alva, 2021; Rodbard, 2016).

## 1.3 Evolution of CGM Modeling Paradigms – A Critical Historical Narrative

Early generations of implantable sensors (1980s–1990s) were largely engineered and evaluated empirically, with only simple transfer-function or lag-plus-noise models used to relate sensor current to

blood glucose (Didyuk et al., 2021; Rodbard, 2016; Ray, 2018). As minimally invasive needle-type CGMs became clinical tools (late 1990s–2000s), the dominant paradigm was **decoupled**:

- physiology represented implicitly as a fixed time lag;
- sensor described by static calibration and simple linear dynamics;
- filtering (e.g., smoothing, calibration algorithms) treated as an independent signal-processing problem (Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016; Bailey and Alva, 2021; Rodbard, 2016; Ray, 2018).

Around 2010–2020, several trends pushed toward more explicit modeling:

- Device reviews documented limitations from biofouling, biocompatibility, and short lifetimes, highlighting the role of tissue–sensor interactions over days (Cappon et al., 2019;; Chmayssem et al., 2023; Teymourian, Barfidokht and Wang, 2020).
- Algorithmic papers began to treat CGM data as the output of a dynamical system with state-space models and Kalman filtering, but still with rudimentary physiology (Facchinetti, 2016; Bailey and Alva, 2021; Rodbard, 2016).
- Emergence of noninvasive and multimodal wearables (optical, sweat, textiles, multi-sensor ML) made it clear that glucose cannot be inferred from any single modality without modeling the physiological mapping from blood to local signal (Lee et al., 2021; Li and Chen, 2023; Karunarathna and Liang, 2025; Sunstrum et al., 2025).

Despite this evolution, there is still no widely adopted canonical **coupled physiological–sensor model**; most commercial systems rely on proprietary, largely decoupled formulations (Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016; Bailey and Alva, 2021).

## 1.4 Limitations of the Decoupled Modeling Status Quo

In the prevailing architecture, researchers or manufacturers specify:

- a **physiology model** (often just a fixed lag or simple compartment),
- a **sensor model** (static gain + offset, sometimes a first-order dynamic),
- a **filter/calibration layer** (linear regression, Kalman filter, or ML),

and tune these blocks largely independently (Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016; Bailey and Alva, 2021; Teymourian, Barfidokht and Wang, 2020). This structure is fundamentally inconsistent with the underlying physics for several reasons:

- **Shared state, not separable effects:** tissue perfusion, local inflammation, and fibrotic encapsulation alter both ISF glucose trajectories and sensor biochemistry simultaneously, so “physiological lag” and

“sensor drift” cannot be uniquely separated without a coupled model (Cappon et al., 2019; Zou et al., 2023; Chmaysssem et al., 2023; Teymourian, Barfidokht and Wang, 2020).

- **Context-dependent lag:** blood–ISF delay depends on rate of change, tissue type, temperature, and vasoconstriction; representing it as a fixed scalar while treating sensor dynamics independently leads to systematic bias during meals, exercise, and perioperative care (Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016; Carlier et al., 2025; Rodbard, 2016).
- **Filter absorbing physics:** many algorithmic advances (e.g., adaptive calibration, prediction, deep learning like CGMformer) succeed by implicitly learning the composite mapping from blood to CGM output, but because physiology and sensor are not explicit, these models are hard to interpret, validate, or extrapolate to new conditions (Facchinetti, 2016; Karunarathna and Liang, 2025; Bailey and Alva, 2021; Lu et al., 2025).

Comprehensive technology and electrochemical reviews explicitly note that long-term drift, biofouling, and foreign-body response are major unresolved barriers that cannot be fully addressed by electronics or algorithms alone without better modeling of tissue–sensor coupling (Lee et al., 2021; Cappon et al., 2019; Zou et al., 2023; Chmaysssem et al., 2023; Bai et al., 2024; Teymourian, Barfidokht and Wang, 2020).

### 1.5 Scope, Novelty, and Contribution of This Review

Against this backdrop, the present review is positioned to:

Provide the **first systematic and critical synthesis** focused specifically on **fully coupled physiological–sensor models** for CGM, integrating insights from device engineering, electrochemistry, physiology, and algorithm design (Lee et al., 2021; Cappon et al., 2019; Zou et al., 2023; Facchinetti, 2016; Karunarathna and Liang, 2025; Chmaysssem et al., 2023; Bai et al., 2024; Teymourian, Barfidokht and Wang, 2020).

Develop a **unified taxonomy and canonical mathematical formulation** in which subcutaneous transport (PDE-like tissue domain), sensor electrochemistry (ODE-like sensor domain), and estimation/filtering are treated as a single dynamical system, rather than separable modules.

Offer a **practical methodological roadmap**: from data collection and PDE/ODE construction through coupling, numerical solution, calibration, and validation across in silico, animal, and human studies bridging engineering models and clinical metrics such as MARD, Clarke Error Grid, and time-in-range (Zou et al., 2023; Facchinetti, 2016; Carlier et al., 2025; Bailey and Alva, 2021; Rodbard, 2016; Battelino et al., 2019).

Frame CGM within a **digital twin perspective**, where individualized, physics-informed models of the tissue–sensor system can be linked to whole-body glucose–insulin models and to emerging AI/ML methods (e.g., CGMformer, multimodal wearables) for subject-specific prediction and decision support (Karunarathna and Liang, 2025; Chmaysssem et al., 2023; Lu et al., 2025; Sunstrum et al., 2025; Bai et al., 2024; Teymourian, Barfidokht and Wang, 2020).

By explicitly centering the need for coupling, this review aims to connect scattered strands of work into a coherent foundation for next-generation CGM design, evaluation, and clinical translation.

## 2. Physiology of Subcutaneous Glucose Transport

Understanding subcutaneous glucose transport requires integrating capillary microanatomy, interstitial space properties, and dynamic tissue remodeling around the sensor, especially fibrotic encapsulation (McClatchey et al., 2019; Shi et al., 2016; Novak, Yuan and Reichert, 2010; Belligoli et al., 2019; Herrón-Bedoya et al., 2021). These features jointly determine how quickly and faithfully blood glucose changes appear at the sensor location.

### 2.1 Anatomical Layers at the Vascular–Interstitial–Sensor Interface

In abdominal subcutaneous adipose tissue, glucose travels from **arterioles** → **capillaries** → **venules**, across the capillary wall into **interstitial fluid (ISF)**, then through extracellular matrix and any foreign-body capsule, to the sensor (McClatchey et al., 2019; Shi et al., 2016; Novak, Yuan and Reichert, 2010; Chadt and Al-Hasani, 2020; Belligoli et al., 2019; Herrón-Bedoya et al., 2021).

Key layers:

**Microvasculature:** Capillaries ( $\approx 200\text{--}300$  capillaries/mm<sup>2</sup> in adipose and muscle) provide diffusion radii of  $\sim 50\text{--}70$   $\mu\text{m}$  from each vessel, ensuring short diffusion paths in healthy tissue (McClatchey et al., 2019).

**Endothelial barrier and basement membrane:** Semi-permeable structures where transcapillary glucose flux follows Fick-type permeability relations and Starling–Landis fluid exchange (Shi et al., 2016; Maeda et al., 2018).

**Native interstitial matrix:** Porous collagen–elastin network with adipocytes, fibroblasts, immune cells; porosity and tortuosity control effective glucose diffusivity (Shi et al., 2016; Novak, Yuan and Reichert, 2010; Chadt and Al-Hasani, 2020; Belligoli et al., 2019).

**Foreign-body (fibrotic) capsule around sensor:** Dense collagenous tissue, relatively avascular, populated by inflammatory and fibroblast-like cells, often  $50\text{--}300$   $\mu\text{m}$  thick; this layer is now recognized as a dominant determinant of CGM delay and attenuation (McClatchey et al., 2019; Novak, Yuan and Reichert, 2010).

In obesity and diabetes, subcutaneous adipose tissue shows hypertrophic adipocytes, capillary rarefaction, and thickened basement membranes, especially in more metabolically impaired states, potentially worsening local transport conditions around sensors (Chadt and Al-Hasani, 2020; Belligoli et al., 2019).

## 2.2 Transport Mechanisms Governing Interstitial Glucose

### (a) Diffusion

Diffusion is the primary mechanism for glucose movement from capillaries into ISF and across tissue to the sensor. In vivo tissue diffusion coefficients for glucose are on the order of  $\sim 100 \mu\text{m}^2/\text{s}$  (McClatchey et al., 2019; Shi et al., 2016). Mathematical and experimental work shows that, given capillary spacing, such diffusivity implies **blood-ISF equilibration within seconds** in healthy, non-encapsulated tissue (McClatchey et al., 2019; Shi et al., 2016; Maeda et al., 2018). In multi-scale transport models (e.g., tumor FDG or FDG in TME), similar diffusion-reaction frameworks capture spatiotemporal gradients in interstitium (Kashkooli et al., 2022).

### (b) Convection (bulk flow)

Capillary filtration and lymphatic drainage drive **convective ISF flow**, which adds or subtracts from diffusive fluxes. Models combining Fick permeability with Starling-Landis and lymph flow show that convection is generally smaller than diffusion for glucose but can modulate gradients when capillary pressure or permeability changes (Shi et al., 2016; Maeda et al., 2018). Magnetohydrodynamic or reverse iontophoresis-based ISF extraction in noninvasive systems further introduces forced convection paths through skin or microchannels (Cheng et al., 2022; Kemp et al., 2022).

### (c) Local consumption and cellular uptake

Glucose is continuously taken up by adipocytes, fibroblasts, endothelial, and immune cells via **GLUT transporters**, especially GLUT1 and GLUT4 (Richter, Bilan and Klip, 2025; Chadt and Al-Hasani, 2020). In muscle and adipose tissue, insulin- and contraction-stimulated GLUT4 translocation critically shapes local uptake rates (Richter, Bilan and Klip, 2025; Chadt and Al-Hasani, 2020). In the foreign-body capsule, infiltrating inflammatory cells and fibroblasts may exhibit elevated metabolic rates, further depleting glucose near the sensor (McClatchey et al., 2019; Novak, Yuan and Reichert, 2010). Multi-compartment models explicitly include tissue uptake terms as reaction terms in diffusion-reaction PDEs (Shi et al., 2016; Novak, Yuan and Reichert, 2010; Maeda et al., 2018).

Collectively, effective diffusivity, porosity, vascular density, and local metabolic consumption determine the glucose concentration field at the sensor surface (McClatchey et al., 2019; Shi et al., 2016; Novak, Yuan and Reichert, 2010).

## 2.3 Blood-to-Interstitial Glucose Gradient and Temporal Lag

### 2.3.1 Physiological lag in native tissue (without capsule)

Classic human studies using subcutaneous CGM with careful blood sampling reported mean lags of  $\sim 4$ – $10$  min between venous blood and ISF, with ISF lagging in  $\sim 80\%$  of cases (Boyne et al., 2003). However, tracer-based physiological analyses and modeling suggest that true blood-ISF equilibration in normal microcirculation is much faster:

- Capillary transit time  $\sim 1$ – $3$  s (McClatchey et al., 2019).
- In vivo tissue diffusivity  $\sim 100 \mu\text{m}^2/\text{s}$  and capillary spacing  $\sim 70 \mu\text{m}$  imply equilibration in seconds (McClatchey et al., 2019).
- Lymph-based estimates of ISF dynamics yield delays from near-immediate to  $<5$  min, depending on methodology (McClatchey et al., 2019; Shi et al., 2016). Model-based in silico work shows that ISF glucose is not simply blood glucose shifted by a fixed delay; rather, it is a **time-varying, filtered version** whose shape depends on system equilibration time and the dynamic blood profile (Cobelli et al., 2016).

### 2.3.2 Contribution of sensor-tissue interface and device dynamics

In vivo experiments directly measuring CGM electrode current and a fluorescent glucose analog near the sensor show:

- In vitro sensor half-response time  $\approx 35 \pm 2$  s.
- In vivo, **time to maximum current**  $\approx 24 \pm 7$  min, while blood peaked at  $\approx 2 \pm 1$  min (McClatchey et al., 2019).
- Fluorescent analog peak at sensor  $\approx 21 \pm 7$  min vs  $\approx 6 \pm 6$  min in adjacent adipose tissue (McClatchey et al., 2019).
- Collagen content (fibrotic capsule thickness/disorganization) correlated strongly with tracer delay ( $r \approx 0.96$ ) (McClatchey et al., 2019).

A separate diffusion-reaction modeling study confirmed that increasing capsule thickness and decreasing porosity prolong sensor lag and attenuate amplitude, while low vessel density exacerbates attenuation (Novak, Yuan and Reichert, 2010). Semiphysical models that include blood transport from liver to abdominal subcutaneous tissue, capillary exchange, and ISF diffusion can reconstruct realistic transport times from central blood to sensor location when calibrated to physiological parameters (Herrón-Bedoya et al., 2021).

In vitro device testing of commercial sensors reveals **intrinsic lags of 8–40 min**, even without physiology, which are sufficient to explain a substantial portion of clinically observed delays during fast changes (Davey et al., 2010).

### 2.3.3 Net observed lags and quantitative ranges

Combining physiological transport, capsule effects, and intrinsic sensor dynamics yields a spectrum of effective lags:

- **Healthy subcutaneous tissue, minimal capsule** (preclinical or acute insertion):

True blood–ISF equilibration: seconds to  $\leq 2$ –3 min (McClatchey et al., 2019; Shi et al., 2016; Maeda et al., 2018).

- **Clinical CGM in humans (legacy systems):**

Effective lags 4–10 min on average (ISF behind blood), with large inter-sensor variability (SD  $\approx 5$  min) (Boyne et al., 2003).

- **Modern high-performance CGMs (e.g., Dexcom G7):**

Population median lag  $\approx 2$  min based on ARD minimization; some sensors lead or lag by 0–4+ min (Zhang et al., 2022).

- **Systems with pronounced fibrotic encapsulation or degraded tissue microvasculature:**

Experimental mouse data show  $\sim 20$ + min to equilibrium at sensor versus minutes in surrounding adipose tissue (McClatchey et al., 2019); models predict strong sensitivity to capsule thickness and vessel density (Novak, Yuan and Reichert, 2010).

These findings motivate treating blood-to-sensor dynamics as a **multi-stage process**: fast capillary–ISF exchange, intermediate interstitial diffusion/consumption, and slower capsule/sensor processes. For coupled CGM modeling, it is therefore insufficient to assign a single empirical lag; instead, one must explicitly represent the **gradient field** and its evolution under changing microvascular density, fibrosis, and metabolic activity (McClatchey et al., 2019; Boyne et al., 2003; Shi et al., 2016; Novak, Yuan and Reichert, 2010; Belligoli et al., 2019; Zhang et al., 2022; Herrón-Bedoya et al., 2021; Cobelli et al., 2016; Maeda et al., 2018; Dai et al., 2023).

### 3. Mathematical Modeling of Interstitial Glucose Transport (PDE Domain)

Interstitial glucose transport around a subcutaneous sensor can be described with continuum **convection–diffusion–reaction (CDR)** equations, similar to models used for capillary–tissue exchange, neurovascular units, and fixed-bed or capillary–tissue systems (Maeda et al., 2018; Nartsissov, 2022; Herrón-Bedoya et al., 2021; Wientjes et al., 1998; Kojić et al., 2017).

#### 3.1 Continuum Assumptions and Diffusion–Reaction Formulation

At the CGM scale, interstitial fluid (ISF) is treated as a continuous medium with averaged properties (porosity, tortuosity, effective diffusivity). Glucose concentration  $c(x,t)$  in porous tissue is typically modeled by:

$$\phi \frac{\partial c}{\partial t} = \nabla \cdot (D_{\text{eff}} \nabla c)$$

- $\nabla \cdot (vc)$
- $R_{\text{met}}(c)$

where  $\phi$ : is tissue porosity,  $D_{\text{eff}}$ : the effective diffusion coefficient,  $v$ : interstitial velocity, and  $R_{\text{met}}$ : local metabolic uptake (Maeda et al., 2018; Nartsissov, 2022; Wientjes et al., 1998; Kojić et al., 2017).

Maeda et al. (2018) couple capillary diffusion–convection with a tissue and lymphatic compartment, using a saturation-type uptake ( $J(C)$ ) for glucose utilization in ISF. Nartsissov formulates coupled Navier–Stokes (capillary flow) and CDR equations in capillary lumen and porous brain parenchyma to resolve spatial–temporal glucose gradients near vessels (Nartsissov, 2022). Similar CDR structures appear in phenomenological, semi-physical models of glucose transport from liver to abdominal subcutaneous adipose tissue, where subcutaneous tissue is treated as a fixed-bed tower with effective diffusion and reaction (Herrón-Bedoya et al., 2021; Herrón-Bedoya and Walteros-León, 2019).

#### 3.2 Boundary Conditions at the Capillary Wall: Dirichlet vs Neumann vs Mixed

The capillary wall forms the key boundary between blood and tissue. Different glucose transport models adopt different boundary conditions depending on time scales and vascular modeling detail:

- **Dirichlet (concentration specified)**

Capillary endothelium is assumed well mixed with blood, so wall concentration equals capillary blood glucose  $c_b(t)$ . This is common when capillary dynamics are modeled separately or treated as a forcing term for tissue PDEs (Nartsissov, 2022; Herrón-Bedoya et al., 2021; Wientjes et al., 1998; Kojić et al., 2017).

- **Neumann (flux specified)**

A specified diffusive flux across the wall, often zero at symmetry or impermeable boundaries, or a fixed flux based on global uptake (Wientjes et al., 1998; Lynch et al., 2020). In transport simulations with Neumann outflow boundaries, numerical stability and backflow can require careful treatment of total flux (Lynch et al., 2020).

- **Mixed / Robin (flux proportional to blood–tissue difference)**

Many capillary–tissue models effectively use a mixed condition:

$$-D \nabla c \cdot \mathbf{n} = P_{\text{wall}} (c_b - c_{\text{wall}})$$

is wall permeability. Nartsissov explicitly models blood–brain barrier layers and GLUT kinetics as flux functions of blood vs tissue concentration (Nartsissov, 2022). Manuela Walteros/Herrón treat capillary walls as **semipermeable membranes** with analogies to membrane mass transfer, embedding this as a transcapillary resistance in the semi-physical model (Herrón-Bedoya et al., 2021; Walteros and Herron, 2018).

On tissue outer boundaries (far from vessels), zero-flux Neumann conditions or “consistent flux” outflow conditions are often applied to avoid nonphysical loss or gain of glucose and to stabilize

advection-dominated problems (Wientjes et al., 1998; Lynch et al., 2020). Dirichlet-to-Neumann transformations can be used in FEM to impose Dirichlet data weakly while recovering accurate boundary fluxes in transport problems, reducing the need for extreme mesh refinement near boundaries (Kim et al., 2022).

### 3.3 Numerical Discretization Strategies: Finite Difference, FEM, and Compartmental Reductions Finite Difference Methods (FDM).

For simple 1D or layered geometries (e.g., glucose diffusion across capillary walls and through subcutaneous tissue modeled as a fixed bed), finite difference schemes are efficient and transparent (Herrón-Bedoya et al., 2021; Walteros and Herron, 2018). Time-delay or fractional diabetes models also use specialized finite difference schemes (e.g., Grönwald-Letnikov) for transport-like operators (Marguet, Eftimie and Lozinski, 2025; Hasan et al., 2025; Abou Hasan, 2026).

#### Finite Element Methods (FEM).

FEM is the dominant approach for complex geometries and multi-physics coupling (e.g., neurovascular units, organ-scale capillary-tissue systems, cardiovascular advection-diffusion):

- Nartsissov solves Navier-Stokes for capillary flow and CDR in both lumen and porous parenchyma using FEM on 3D neurovascular geometries (Nartsissov, 2022).
- A composite smeared finite element (CSFE) was developed to model **capillary-tissue mass transport**, smearing the capillary network into volumetric source terms while retaining separate pressure and concentration DOFs for capillary and tissue domains (Kojić et al., 2017).
- Transport-dominated PDEs use stabilized FEM, discontinuity capturing operators, and flux-consistent outflow boundary conditions to prevent oscillations and backflow instabilities at high Péclet number (Wientjes et al., 1998; Lynch et al., 2020).
- Weak imposition of Dirichlet boundary conditions (Dirichlet-to-Neumann) accelerates mesh convergence for boundary fluxes in electro-diffusive systems, a strategy transferable to glucose transport around sensors (Kim et al., 2022).

### Compartmental Reductions and Semi-physical Models.

When spatial gradients are modest or only integrated behavior is needed, spatially averaged compartment models are used:

- Wilinska et al. represent interstitial glucose in subcutaneous adipose tissue with multiple compartments and kinetic transfer terms

between plasma and ISF, without explicit spatial PDEs (Wilinska et al., 2004).

- Herrón-Bedoya and co-workers build **phenomenological-based semi-physical models (PBSM)** that condense vessel networks, capillary walls, and ISF diffusion into low-order ODE models with parameters tied to physical quantities (vessel length, wall permeability, effective diffusivity) (Herrón-Bedoya et al., 2021; Herrón-Bedoya and Walteros-León, 2019).
- Koutny reconstructs blood glucose from subcutaneous measurements by treating transcapillary transport as a dynamic linear system mapping present blood and ISF levels to future ISF levels, again in ODE form (Koutny, 2014).

Thus, FDM and FEM support fully spatial PDE models, whereas PBSM and multi-compartment models provide computationally cheap surrogates calibrated to reproduce PDE behavior at the sensor scale (Herrón-Bedoya et al., 2021; Walteros and Herron, 2018; Herrón-Bedoya and Walteros-León, 2019; Wilinska et al., 2004; Kojić et al., 2017; Koutny, 2014).

### 3.4 Parameterization Challenges: Diffusivity, Porosity, Metabolic Uptake

Realistic PDE models require parameters that are often heterogeneous, time-varying, or poorly measured.

#### Effective Diffusivity and Tortuosity.

Effective tissue diffusion  $D_{\text{eff}}$  reflects porosity and microstructural tortuosity. In fixed-bed and porous tissue analogies (subcutaneous adipose as a packed bed),  $D_{\text{eff}}$  is obtained from empirical correlations or fitted so that simulated blood-ISF delays (~8–9 min) match experimental CGM and microdialysis data (Herrón-Bedoya et al., 2021; Walteros and Herron, 2018; Herrón-Bedoya and Walteros-León, 2019; Wientjes et al., 1998). Capillary-tissue FE models similarly tune diffusion and permeability so that predicted gradients match PET or microdialysis measurements (Nartsissov, 2022; Kojić et al., 2017).

#### Porosity and Permeability.

Porosity enters the conservation equation as a storage factor  $\phi$  and affects Darcy permeability for interstitial flow. In neurovascular and glycocalyx flow models, Darcy's law and asymptotic analysis are used to relate microscopic structure (fiber spacing, thickness) to macroscopic hydraulic conductivity and flux (Nartsissov, 2022; Dalwadi et al., 2020). In fixed-bed analogies for subcutaneous tissue, porosity and superficial velocity strongly influence residence times and thus apparent transport delays (Herrón-Bedoya et al., 2021; Walteros and Herron, 2018; Herrón-Bedoya and Walteros-León, 2019).

#### Metabolic Uptake Kinetics.

Interstitial glucose consumption is often modeled as:

- Zero-order (constant) or first-order (linear in  $C$ ) uptake in PBSM and compartment models (Maeda et al., 2018; Herrón-Bedoya et al., 2021; Wilinska et al., 2004).
- Saturable Michaelis–Menten-type kinetics in detailed tissue models

$$J(C) = \frac{J_{\max} C}{K_m + C}$$

(Maeda et al., 2018; Nartsissov, 2022; Natale and Todeschi, 2022; Wientjes et al., 1998; Kojić et al., 2017).

Maeda et al. (2018) explicitly scale the tissue utilization rate ( $J$ ) and show how higher uptake accelerates diffusion by lowering interstitial concentration and steepening capillary–tissue gradients. In neurovascular and tumor applications, glucose uptake parameters are drawn from FDG–PET and in vitro kinetic studies, but these values are often tissue- and disease-specific, creating uncertainty for direct translation to subcutaneous adipose tissue (Nartsissov, 2022; Natale and Todeschi, 2022; Kojić et al., 2017; El-Amin and Abbdel-Naeem, 2021).

### 3.5 When Does a PDE Really Matter? Criteria for Spatial Resolution Necessity

A key modeling question is when one actually needs a **spatial PDE** instead of a lumped compartment model for interstitial glucose.

Relevant criteria include:

#### 1. Magnitude of Spatial Gradients (Damköhler Number)

If the **Damköhler number** (reaction rate / diffusion rate) is large, or if capillary wall resistance and tissue diffusional resistance dominate over systemic transport, substantial spatial gradients develop and a PDE is warranted (Maeda et al., 2018; Nartsissov, 2022; Herrón-Bedoya et al., 2021; Walteros and Herron, 2018; Kojić et al., 2017; El-Amin and Abbdel-Naeem, 2021). Semi-physical liver-to-subcutaneous models indicate that >90% of total delay arises from capillary wall and ISF diffusion, not systemic circulation, implying significant local transport limitations that can justify PDE resolution when studying sensor–tissue microenvironments (Walteros and Herron, 2018).

#### 2. Geometric Complexity and Heterogeneity

In highly heterogeneous systems—lobular liver structure, neurovascular units, dense or sparse capillary networks, composite capillary–tissue domains—smeared FE models explicitly track spatial gradients between capillaries and tissue, which cannot be captured by a single well-mixed compartment (Nartsissov, 2022; Wientjes et al., 1998; Lynch et al., 2020; Kojić et al., 2017). For whole-organ questions or average CGM delay, compartment or semi-physical models may suffice, but for understanding local sensor siting, fibrosis, or regional hypoperfusion, PDEs are needed.

### 3. Length- and Time-Scale Separation

If the diffusion equilibration time across the relevant length scale (e.g., capsule thickness, ~100–300  $\mu\text{m}$ ) is much shorter than the time scale of blood glucose changes, ISF can be approximated as spatially uniform and compartment models are adequate (Herrón-Bedoya et al., 2021; Herrón-Bedoya and Walteros-León, 2019; Wilinska et al., 2004; Koutny, 2014). If, instead, diffusion times are comparable to or exceed dynamics of interest (fast postprandial changes, exercise transients), PDE modeling becomes important.

### 4. Coupling with Detailed Hemodynamics or Boundary Layers

When the research goal includes **how changes in capillary blood flow** or boundary layer structure alter near-sensor concentration fields, fully coupled flow + CDR PDEs are essential. Nartsissov shows that different cerebral blood flow patterns change local gradients in ways that cannot be reproduced with simple transfer functions (Nartsissov, 2022). Similarly, composite FE and cardiovascular transport studies demonstrate the need for PDEs under high Péclet numbers and backflow conditions (Wientjes et al., 1998; Lynch et al., 2020; Kojić et al., 2017).

### 5. Target Outputs

If the objective is to reconstruct systemic blood glucose from CGM signals (for control algorithms), compact ODE or semi-physical models calibrated to data are often sufficient and more robust (Herrón-Bedoya et al., 2021; Herrón-Bedoya and Walteros-León, 2019; Wilinska et al., 2004; Koutny, 2014).

If the objective is to design next-generation sensors, coatings, or insertion protocols that minimize local lag and attenuation, PDEs that resolve the **spatial structure of interstitial glucose** around the sensor and across fibrotic capsules become critical (Maeda et al., 2018; Nartsissov, 2022; Walteros and Herron, 2018; Wientjes et al., 1998; Kojić et al., 2017; El-Amin and Abbdel-Naeem, 2021).

In summary, a PDE description is justified whenever spatial heterogeneity of glucose concentration, driven by local diffusion–reaction balances and complex geometry, is central to the question being asked; otherwise, carefully parameterized compartment or semi-physical models provide a practical alternative.

**Summary Table: When Is a PDE Necessary?**

| Scenario / Question                              | Expected spatial gradients | Recommended model type | Citations                                                                                                                                    |
|--------------------------------------------------|----------------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Whole-body blood–ISF delay, CGM calibration      | Mild, averaged             | Compartment / PBSM     | (Herrón-Bedoya et al., 2021; Walteros and Herron, 2018; Herrón-Bedoya and Walteros-León, 2019; Wilinska et al., 2004; Koutny, 2014)          |
| Effect of fibrotic capsule, local microstructure | Strong near sensor         | CDR PDE (FEM/FDM)      | (Maeda et al., 2018; Nartsissov, 2022; Walteros and Herron, 2018; Wientjes et al., 1998; Kojić et al., 2017; El-Amin and Abbdel-Naeem, 2021) |
| Neurovascular, liver lobule, capillary networks  | Strong, heterogeneous      | Multi-domain PDE (FEM) | (Nartsissov, 2022; Wientjes et al., 1998; Lynch et al., 2020; Kojić et al., 2017)                                                            |
| High Péclet, backflow, boundary layers           | Local fronts, layers       | Stabilized PDE         | (Kim et al., 2022; Wientjes et al., 1998; Lynch et al., 2020)                                                                                |

**Figure 1: Decision criteria for PDE vs compartment models.**

#### 4. Electrochemical Glucose Sensor Dynamics (ODE Domain): Enzyme models, dynamics, and error sources

Electrochemical glucose sensors convert local glucose concentration into current or potential via enzyme or catalytic reactions, mass transport, and electrode kinetics. These underlying physics are often reduced to low-order ODE models that describe the dynamic input–output relationship used in CGM algorithms.

##### 4.1 First-Principles Models of Enzyme-Based Sensing

Advanced models start from mass-action enzyme kinetics (typically glucose oxidase) coupled to diffusion and electrode reactions (Gao and Orazem, 2021; Gao et al, 2018; Narayanan et al, 2022; Ba et al., 2020). Gao & Orazem include: ping-pong enzyme kinetics, glucose anomerization, pH-dependent activity, buffer equilibria, and H<sub>2</sub>O<sub>2</sub> electrode reactions, all driven by tissue–sensor diffusion (Gao and Orazem, 2021; Gao et al, 2018).

For mediated systems, porous-electrode models resolve mediator and substrate concentrations in the catalyst layer and show that limiting currents are diffusion–reaction limited and depend strongly on enzyme loading and mediator regeneration (Do et al., 2015). Field-effect and ElecFET glucose biosensors are modeled by coupling Michaelis–Menten kinetics for GOx, H<sub>2</sub>O<sub>2</sub> generation, and pH change to the transistor transfer function, leading to explicit ODEs for gate potential vs. glucose (Ba et al., 2020).

Such first-principles models are then reduced to effective ODE input–output forms (e.g., nonlinear static map + first-order dynamics) for use in system identification and calibration of CGM sensors (Talukder et al, 2022).

##### 4.2 Dynamic Characteristics: Time Constants, Nonlinear Gain, Hysteresis

CGM sensor dynamics reflect both internal electrochemical time scales and external transport delays. First-order transfer functions with time

constants on the order of 10–20 min are commonly used for CGM modeling and calibration, capturing slow equilibration and filtering of blood glucose fluctuations (Talukder et al, 2022).

**Nonlinear gain** arises from enzyme saturation and mediator kinetics: sensor response is typically linear only over a limited concentration range, then saturates as described by Michaelis–Menten or more complex ping-pong kinetics (Gao and Orazem, 2021; Ba et al., 2020). For non-enzymatic metal-oxide and metal-oxide/2D-material sensors, amperometric or potentiometric responses are also strongly nonlinear functions of concentration and electrode potential due to electrocatalytic reaction mechanisms and surface coverage effects (Jin and Alam, 2019; Radhakrishnan et al., 2022; Guati et al., 2023).

**Hysteresis** in dynamic sweeps (increasing vs. decreasing glucose, or cyclic exposure) is widely reported, especially for potentiometric or non-enzymatic sensors, and is attributed to surface adsorption, redox state history, and slow drift of interfacial properties (Chou et al., 2021; Chou et al., 2016). Microfluidic dynamic tests explicitly show hysteresis loops and different forward/backward response curves for enzymatic and non-enzymatic devices (Chou et al., 2021; Chou et al., 2016; Ba et al., 2020).

##### 4.3 Error Mechanisms and Their Mathematical Representation

Multiple physical error sources can be represented in ODE-level sensor models:

**Drift and aging:** Time-dependent changes in baseline and sensitivity from enzyme deactivation, mediator loss, and electrode degradation introduce slow drifts in gain and offset. Non-enzymatic metal-oxide sensors show substantial drift in conductance/potential, which can be reduced but not eliminated by calibration circuitry (Teymourian, Barfidokht and Wang, 2020; Chou et al., 2021; Guati et al., 2023). Mathematically, this is modeled by time-varying parameters (e.g., slowly varying gain, offset, or time constant) or

random-walk processes in calibration maps (Teymourian, Barfidokht and Wang, 2020; Chou et al., 2021).

**Nonlinear transfer and limited range:** Enzyme saturation, oxygen limitation, and mediator kinetics limit linear range and produce compressive nonlinearities at high glucose (Gao and Orazem, 2021; Gao et al, 2018; Ba et al., 2020). These are captured by static nonlinear functions (e.g., sigmoid, Michaelis–Menten) cascaded with linear dynamics, as in Talukder’s CGM sensor model based on a first-order system followed by a sigmoidal nonlinearity (Talukder et al, 2022).

**Interference and selectivity:** Competing redox species, pH fluctuations, and temperature affect current or potential. Reviews document that non-enzymatic sensors in particular suffer from interference and variable sensitivity under physiological conditions (Song et al., 2024; Teymourian, Barfidokht and Wang, 2020; Li and Xiao et al., 2025; Guati et al., 2023). In ODE models, these appear as additive disturbance terms or as dependence of parameters on nuisance variables (multi-input systems).

**Transport-related lag and attenuation:** External diffusion in tissue and internal diffusion through membranes and porous layers cause low-pass filtering of true interstitial glucose, already discussed in the PDE domain; at the sensor level this is typically collapsed into additional time constants and dynamic

delays (Gao and Orazem, 2021; Gao et al, 2018; Talukder et al, 2022; Narayanan et al, 2022).

**Baseline decay and mediator charging (wired sensors):** Wired enzyme systems can show continuously decaying currents due to unintended mediator redox charging, which can mask true glucose changes (Damala, Tiuftiakov and Bakker, 2023; Juska and Pemble, 2020; Bollella and Katz, 2020). Perspective and ET-focused reviews emphasize how mediator turnover and electron-transfer rates determine apparent sensor current vs. actual substrate flux (Damala, Tiuftiakov and Bakker, 2023; Juska and Pemble, 2020; Bollella and Katz, 2020). These effects are modeled as parallel capacitive or additional kinetic states in the ODE description, giving slow exponential decays superimposed on the glucose-driven response (Gao and Orazem, 2021; Gao et al, 2018; Damala, Tiuftiakov and Bakker, 2023).

Overall, electrochemical glucose sensor dynamics used in CGM can be described by compact ODE models that capture nonlinear static characteristics, one or more time constants representing transport and electrochemistry, and explicit terms for drift, hysteresis, and interference, all grounded in first-principles enzyme or catalytic mechanisms (Gao and Orazem, 2021; Jin and Alam, 2019; Song et al., 2024; Gao et al, 2018; Damala, Tiuftiakov and Bakker, 2023; Talukder et al, 2022; Chou et al., 2021; Li and Xiao et al., 2025; Narayanan et al, 2022; Guati et al., 2023; Ba et al., 2020).

#### Key Dynamic Features and Error Sources

| Feature / error                      | Typical ODE representation                         | Citations                                                                                                                            |
|--------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Enzyme saturation, mediator kinetics | Static nonlinearity (Michaelis–Menten / sigmoid)   | (Gao and Orazem, 2021; Gao et al, 2018; Narayanan et al, 2022; Do et al., 2015; Ba et al., 2020)                                     |
| Transport lag (membrane, tissue)     | First-order (or higher) low-pass, possibly delayed | (Gao and Orazem, 2021; Gao et al, 2018; Talukder et al, 2022; Narayanan et al, 2022; Ba et al., 2020)                                |
| Drift & aging                        | Time-varying gain/offset, random walk              | (Teymourian, Barfidokht and Wang, 2020; Talukder et al, 2022; Chou et al., 2021; Guati et al., 2023)                                 |
| Hysteresis & adsorption              | State-dependent parameters, bidirectional curves   | (Chou et al., 2021; Chou et al., 2016; Guati et al., 2023)                                                                           |
| Interference (pH, species)           | Additive disturbance, multi-input dependence       | (Song et al., 2024; Teymourian, Barfidokht and Wang, 2020; Li and Xiao et al., 2025; Radhakrishnan et al., 2022; Guati et al., 2023) |

Figure 2: Dynamic and error mechanisms in ODE sensor models.

## 5. Coupled PDE–ODE Frameworks for Glucose Sensing: Interfaces, canonical form, and numeric

Coupled PDE–ODE models describe spatial glucose transport (PDE) linked to lumped sensor/electronics dynamics (ODE). Similar structures appear in poroelastic–circuit models, quorum-sensing PDE–ODE systems, and ODE–PDE–ODE control problems, providing templates for glucose-sensor modeling (Gao and Orazem, 2021; Gao et al, 2018; Iyaniwura and Ward, 2021; Deutscher and Gehring, 2020; Bociu et al., 2022).

### 5.1 Conceptual Interface: Sensor Surface as Dynamic Boundary Condition

The **sensor surface** is a low-dimensional interface where tissue-scale transport meets device dynamics. In PDE–ODE language, the PDE (interstitial/tissue transport) is posed in a bulk domain, while the sensor is represented by one or more ODE states that appear as:

- a **dynamic boundary condition** (e.g., flux proportional to a sensor state), or
- a **point / small-region coupling** (cell-bulk type) (Iyaniwura and Ward, 2021).

Analogues:

- In poroelastic–circuit coupling, the PDE (Biot system) is linked to a 0D hydraulic circuit through interface conditions enforcing continuity of flux and stress (Bociu et al., 2022).
- In diffusion-sensing models, small “cells” (ODEs) exchange mass with a bulk diffusion PDE via permeable boundaries, with Robin-type coupling (Iyaniwura and Ward, 2021).
- In ODE–PDE–ODE control, actuator and sensor ODEs are bidirectionally coupled to parabolic PDEs at the boundaries, again via dynamic interface laws (Deutscher and Gehring, 2020).

These frameworks motivate treating the CGM electrode/membrane as an ODE system coupled to the tissue PDE through flux continuity and reaction–diffusion balances (Gao and Orazem, 2021; Gao et al, 2018; Mcilwaine and Gerogiorgis, 2018; Iyaniwura and Ward, 2021; Deutscher and Gehring, 2020; Bociu et al., 2022).

### 5.2 Canonical Coupled Model Formulation (New & Key)

A canonical CGM-style PDE–ODE system can be written as:

**PDE (tissue / droplet / membrane domain  $\Omega$ ):**

$$\phi \frac{\partial c}{\partial t} = \nabla \cdot (D_{\text{eff}} \nabla c) - R_{\text{met}}(c), \quad x \in \Omega$$

with suitable outer boundary conditions (e.g., capillary Dirichlet or flux) (Gao and Orazem, 2021; Gao et al, 2018; Mcilwaine and Gerogiorgis, 2018).

**Interface  $\Gamma$  (sensor surface):**

- Mass balance:

$$-D_{\text{eff}} \nabla c \cdot \mathbf{n} \Big|_{\Gamma} = J_{\text{sens}}(c_{\Gamma}, z)$$

where  $(z)$  are sensor-internal states (e.g., enzyme-substrate complexes, mediator oxidation level) (Gao and Orazem, 2021; Gao et al, 2018; Narayanan et al, 2022).

**ODEs (sensor dynamics):**

$$\begin{cases} \dot{z} = f(z, c_{\Gamma}; \theta), \\ y = g(z, c_{\Gamma}), \end{cases}$$

where  $(y)$  is measured current/impedance and  $(\theta)$  collects kinetic and transport parameters (Gao and Orazem, 2021; Gao et al, 2018; Narayanan et al, 2022).

This structure parallels:

- reactive transport + enzyme ODEs in advanced continuous glucose sensor models (Gao and Orazem, 2021; Gao et al, 2018; Narayanan et al, 2022),
- droplet-on-sensor 2D PDE with electrode-kinetics boundary at the enzyme layer (Mcilwaine and Gerogiorgis, 2018),
- PDE–ODE poroelastic–circuit couplings with nonlocal interface conditions (Bociu et al., 2022),
- multi-cell diffusion-sensing PDE–ODE systems (Iyaniwura and Ward, 2021).

### 5.3 Numerical Solution of Stiff, Multiscale Systems: IMEX and Splitting

Coupled CGM PDE–ODE models are **stiff and multiscale**: fast enzyme/electrode kinetics, slower diffusion, and very slow drift/aging. Similar stiffness appears in general stiff ODEs and PDE–ODE couplings (Gao et al, 2018; P et al., 2025; Theodosiou, Schütz and Seal, 2024; Bociu et al., 2022).

Key strategies:

**IMEX (implicit–explicit) time stepping:**

- Treat stiff diffusion/fast kinetics implicitly; non-stiff transport or nonlinearities explicitly. Modern IMEX Runge–Kutta and multiderivative IMEX schemes are designed for L-stability and high order on stiff problems (P et al., 2025; Theodosiou, Schütz and Seal, 2024).
- Preserves explicit handling of nonlinear “cheap” parts while stabilizing stiff linear operators.

**Operator splitting / staggered schemes:**

- Solve PDE and ODE subproblems sequentially within each time step, enforcing interface conditions iteratively or via energy-based operator splitting (Bociu et al., 2022).

Analysis for poroelastic–circuit coupling shows functional iterations converge under step-size and coupling conditions, while energy-based splitting can

be **unconditionally stable** with respect to  $\Delta t$  (Bociu et al., 2022).

**Specialized solvers for the PDE part:**

- 1D boundary-value formulations solved by BAND/Newman algorithms for steady and impedance-frequency response (Gao and Orazem, 2021; Gao et al, 2018).
- 2D/3D FE or FD solvers for reactive transport in droplets and porous electrodes (Mcilwaine and Gerogiorgis, 2018; Selim et al., 2025).

These techniques combine naturally: e.g., an IMEX scheme for the semi-discrete PDE–ODE system plus operator splitting across tissue and sensor submodules (Gao and Orazem, 2021; Gao et al, 2018; Mcilwaine and Gerogiorgis, 2018; P et al., 2025; Theodosiou, Schütz and Seal, 2024; Bociu et al., 2022).

**5.4 Sensitivity Analysis and Identifiability in High Dimensions**

High-dimensional parameter sets (transport, reaction, interface, circuit) require **sensitivity and identifiability analysis** to determine what can be estimated from CGM data:

- In glucose–insulin models, structural identifiability and sensitivity/Fisher Information Matrix (FIM) analyses identify parameter subsets that are both influential and estimable, guiding model reduction and parameter selection (Bachar, 2025; Lema-Perez et al., 2023; Staal et al., 2019).

- Similar Sobolev/semigroup-based sensitivity and FIM tools have been developed for delay systems in glucose regulation (Bachar, 2025).
- In UVa/Padova-type models, sensitivity + FIM analysis highlight which parameters can be reliably personalized from sparse data and how to redesign experiments for better identifiability (Staal et al., 2019).

For PDE–ODE CGM models, analogous strategies apply:

1. Compute local sensitivities (direct or adjoint, continuous or discrete) of outputs  $y_{(t)}$  to parameters in diffusion, kinetics, and interface laws (Gao and Orazem, 2021; Mcilwaine and Gerogiorgis, 2018; Iyaniwura and Ward, 2021; Bociu et al., 2022).
2. Build the **Fisher Information Matrix** to assess practical identifiability and correlation structure; reduce models or reparametrize when the FIM is ill-conditioned (Bachar, 2025; Lema-Perez et al., 2023; Staal et al., 2019).
3. Use these results to decide which physical parameters ( $D_{\text{eff}}$  enzyme loading, interface permeability) can be inferred from calibration / impedance data versus which should be fixed from independent measurements (Gao and Orazem, 2021; Gao et al, 2018; Mcilwaine and Gerogiorgis, 2018; Narayanan et al, 2022; Lema-Perez et al., 2023; Staal et al., 2019; Bociu et al., 2022).

**Canonical Coupled PDE–ODE Elements for Glucose Sensing**

| Component                                           | Role in framework                          | Example sources                                                                                                                                     |
|-----------------------------------------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Tissue / droplet diffusion PDE                      | Spatial transport, external lag            | (Gao and Orazem, 2021; Gao et al, 2018; Mcilwaine and Gerogiorgis, 2018; Selim et al., 2025; Iyaniwura and Ward, 2021; Bociu et al., 2022)          |
| Dynamic interface (flux = function of sensor state) | Couples PDE to device                      | (Gao and Orazem, 2021; Gao et al, 2018; Mcilwaine and Gerogiorgis, 2018; Iyaniwura and Ward, 2021; Deutscher and Gehring, 2020; Bociu et al., 2022) |
| Sensor ODEs (enzyme, mediator, circuitry)           | Local kinetics & signal dynamics           | (Gao and Orazem, 2021; Gao et al, 2018; Narayanan et al, 2022; Selim et al., 2025; Theodosiou, Schütz and Seal, 2024)                               |
| IMEX + operator splitting                           | Stable, efficient multiscale time stepping | (Orazem, 2018; P et al., 2025; Theodosiou, Schütz and Seal, 2024; Bociu et al., 2022)                                                               |
| Sensitivity & FIM analysis                          | Parameter selection, identifiability       | (Bachar, 2025; Lema-Perez et al., 2023; Staal et al., 2019; Bociu et al., 2022)                                                                     |

**Figure 3: Building blocks of a canonical CGM PDE–ODE model.**

In Conclusion Coupled PDE–ODE frameworks for glucose sensing treat the sensor as a dynamically active boundary/interface linking spatial transport with lumped kinetics and electronics. Canonical formulations mirror established PDE–ODE systems in biomechanics and control, and require careful IMEX/splitting schemes for stiff multiscale integration. Sensitivity and identifiability tools well developed for glucose–insulin and other physiological models are essential to reduce these high-dimensional CGM models to parameter sets that are both physiologically meaningful and practically estimable.

## 6. Calibration and State Estimation for Coupled CGM Models: Dual estimation, filters, and metrics

Coupled PDE–ODE CGM models require algorithms that estimate hidden glucose states and slowly drifting sensor parameters from noisy, delayed signals. Modern CGM calibration blends model-based estimation, Bayesian methods and performance metrics that connect algorithm design to clinical relevance.

### 6.1 Dual Estimation: States + Slowly Drifting Parameters

CGM sensors exhibit **time-varying sensitivity, baseline and lag**, so both glucose states and calibration parameters must be estimated jointly (dual estimation) (Acciaroli et al., 2018; Barceló-Rico et al., 2013). Model-based approaches use:

- a dynamic state model for BG–IG kinetics and sensor dynamics,
- **time-varying calibration functions** with priors on drift (e.g., random walk, Gaussian priors) (Acciaroli et al., 2018; Talukder et al., 2022;).

Acciaroli et al (2018) and Vettoretti et al (2019) model multi-day sensitivity drift with stochastic priors and update parameters online via Bayesian estimation, reducing calibrations from twice daily to  $\leq 2$  per week while preserving or improving accuracy. Talukder et al. treat nonlinear, time-drifting sensors via a Bayesian state-space formulation that does not assume known linear dynamics (Talukder et al, 2022).

### 6.2 Kalman Filter Family: EKF, UKF, EnKF – Strengths and Failure Modes

Kalman-based CGM calibration exploits **state-space structure and Gaussian noise assumptions**:

- **Standard / dual Kalman filters**: Separate state and parameter filters; used for noise filtering, compartment matching, and parameter tracking in commercial-grade algorithms, achieving MARD  $\approx 10$ –12% over 7 days (Singh, et al, 2021; Acciaroli et al., 2018).
- **EKF (Extended KF)**: Linearizes nonlinear BG–IG and sensor models; used to reconstruct BG, time lag, and sensitivity from CGM +

sparse SMBG (Acciaroli et al., 2017). Works well for mildly nonlinear, near-Gaussian systems but can diverge under strong nonlinearity, poor models, or large calibration errors (Acciaroli et al., 2018; Khodarahmi and Maihami, 2023).

- **UKF / cubature KF**: Propagate sigma points instead of Jacobians, improving robustness for moderately nonlinear dynamics; nonlinear cubature KF was used offline to obtain initial parameter covariances for a CGM Kalman-based algorithm (Singh et al, 2021).
- **EnKF**: Uses an ensemble to approximate covariances; attractive for **high-dimensional coupled PDE–ODE models**, but sensitive to ensemble size and inflation/localization choices (Khodarahmi and Maihami, 2023).

In CGM, failures typically appear as filter drift with sensor aging, mis-tracking during rapid glucose excursions (BG–IG lag), and bias when noise and drift are non-Gaussian or poorly modeled (Singh et al, 2021; Acciaroli et al., 2017; Talukder et al, 2022; Acciaroli et al., 218; Khodarahmi and Maihami, 2023).

### 6.3 Bayesian and Particle Filtering: Handling Non-Gaussian Drift

When **sensor drift, outliers, and nonlinearities** violate Gaussian assumptions, fully Bayesian methods and particle filters (PFs) are more appropriate.

- **Bayesian calibration with time-varying functions**: Vettoretti et al (2019) and Acciaroli et al (2018) use priors on multi-day sensitivity and baseline parameters and update them via Bayesian estimation from sparse SMBG, outperforming manufacturer calibration at far lower calibration frequency.
- **Dynamic Bayesian calibration for nonlinear, drifting sensors**: Talukder et al (2022) estimate glucose as a posterior conditional mean given finite sensor-measurement windows and time, with an online update of the learned calibration map; validated on optical CGM data and virtual patients
- **Particle filters**: PFs approximate arbitrary non-Gaussian posteriors via weighted samples and can naturally represent multimodal parameter distributions and heavy-tailed noise (Arulampalam et al., 2002). They are especially suitable for cyber-physical systems with missing data, saturations and complex sensor effects (Li et al., 2025).

Compared to EKF/UKF, PFs are more flexible but **computationally heavier**, can suffer from particle degeneracy, and need careful design of proposal distributions and resampling strategies (Talukder et al, 2022; Arulampalam et al., 2002; Li et al., 2025).

### 6.4 Adaptive and Moving-Window Calibration

Adaptive calibration algorithms explicitly track **slow drift** and re-tune parameters:

- **Adaptive normalization / local models:** Barceló-Rico et al. adapt normalization parameters in real time (with a forgetting window) to minimize mean absolute relative deviation at calibration points, improving performance, especially over multi-day simulations (Barceló-Rico et al., 2013).
- **Bayesian multiday frameworks:** Time-varying sensitivity/baseline with statistical priors are updated from infrequent SMBG; effective with as few as 0.25 calibrations/day (Acciaroli et al., 2018).
- **Dynamic calibration functions correcting drift:** Microfluidic cell-based platforms incorporate a calibration function to compensate enzyme decay and maintain accurate glucose prediction over  $\geq 20$  h (Chen et al., 2025). Dual-mode optical sensors use redundant signals (absorbance + fluorescence) and recalibrate internally when drift is detected, avoiding external calibration (Wang et al., 2024).
- **Moving-window / forgetting strategies:** Time-windowed updates prevent old, drift-corrupted data from dominating the calibration parameters (Acciaroli et al., 2017; Talukder et al., 2022; Acciaroli et al., 2018; Barceló-Rico et al., 2013).

Factory-calibrated systems embed **population-level calibration and error models** at the manufacturing stage, then apply limited or optional user recalibrations (Shah et al., 2018; Sabatini et al., 2024; Wadwa et al., 2018).

## 6.5 Performance Metrics: MARD, Error Grids, Time-in-Range

Algorithm quality is evaluated by both **analytical accuracy** and **clinical impact**:

### Classical sensor-accuracy metrics

- **MARD** (Mean Absolute Relative Difference): Widely reported as average  $|\text{CGM} - \text{reference}| / \text{reference}$ ; e.g., Kalman-based CGM calibration achieves  $\text{MARD} \approx 10\text{--}12\%$  (Singh,

et al., 2021; Shah et al., 2018; Sabatini et al., 2024; Wadwa et al., 2018).

- $\%15/15$ ,  $\%20/20$ ,  $\%30/30$ : Percentage of pairs within  $\pm 15\%$ ,  $\pm 20\%$ ,  $\pm 30\%$  (or fixed mg/dL if  $\leq 100$  mg/dL) (Shah et al., 2018; Sabatini et al., 2024; Wadwa et al., 2018).
- **MAD** (Mean Absolute Difference) in hypoglycemia range (Wadwa et al., 2018).

Recent critiques emphasize that MARD is sensitive to study design, glucose distribution, and population and does not directly reflect clinical risk (Vigersky and Shin, 2024; Acanfora et al., 2025).

### Clinically oriented metrics

- **Error grids:** Clarke / Parkes or Surveillance Error Grid (SEG) classify CGM–reference pairs into zones A–E with graded clinical risk; used in physiological BG reconstruction and CGM evaluation (Wadwa et al., 2018; Koutny, 2022; Acanfora et al., 2025).
- **Time-in-Range (TIR):** Percentage of time within a target range (e.g., 70–180 mg/dL); strongly linked to long-term complications and widely used in CGM outcome studies (Acanfora et al., 2025).
- **Other indices:** Glycemic Risk Index (GRI), Precision Absolute Relative Difference (PARD), hypoglycemia detection rates and predictive-alert performance provide richer views of safety and performance, especially for automated insulin delivery (Vigersky and Shin, 2024; Acanfora et al., 2025).

### Metrics in practice

Dexcom G6 studies report **MARD  $\approx 9\text{--}10\%$** ,  **$\%20/20 \approx 92\text{--}94\%$**  and robust performance over 10 days in adults and youth (Shah et al., 2018; Sabatini et al., 2024; Wadwa et al., 2018). Emerging editorials argue for a **multi-dimensional framework** combining safety, performance, usability and equity, with MARD as only one component (Vigersky and Shin, 2024; Acanfora et al., 2025).

### Summary Table: Estimation / Calibration Approaches

| Topic               | Key idea for coupled CGM models                                                             | Citations                                                                                                                                            |
|---------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dual estimation     | Joint tracking of glucose states + drifting sensitivity/baseline                            | (Singh et al, 2021; Acciaroli et al., 2017; Talukder et al, 2022; Acciaroli et al., 2018; Barceló-Rico et al., 2013)                                 |
| Kalman family       | Model-based Gaussian filters; efficient but sensitive to nonlinearity/mismodelling          | (Singh et al, 2021; Acciaroli et al., 2018; Khodarahmi and Maihami, 2023; Tuveri et al., 2021)                                                       |
| Bayesian / PF       | Fully Bayesian, handle non-Gaussian drift and complex noise                                 | (Talukder et al, 2022; Acciaroli et al., 2018; Arulampalam et al., 2002; Li et al., 2025)                                                            |
| Adaptive / windowed | Real-time parameter adaptation with forgetting, multiday priors, or dual-mode recalibration | (Acciaroli et al., 2017; Talukder et al 2022; Chen et al., 2025; Wang et al., 2024; Acciaroli et al., 2018; Barceló-Rico et al., 2013)               |
| Metrics             | MARD, $\%20/20$ , error grids, TIR and newer safety-focused indices                         | (Acciaroli et al., 2017; Shah et al., 2018; Sabatini et al., 2024; Wadwa et al., 2018; Vigersky and Shin, 2024; Koutny, 2022; Acanfora et al., 2025) |

**Figure 4: Overview of estimation, calibration, and evaluation tools for CGM.**

## 7. From CGM Data to a Validated Coupled PDE–ODE Model: A stepwise roadmap

This roadmap links real CGM / lab data to a mechanistic, numerically robust PDE–ODE sensor model and its validation across in silico, preclinical, and clinical stages. Examples are drawn from advanced electrochemical sensor modeling, CGM error models, and practical data pipelines.

### 7.1 Data Sources and Preprocessing

#### Sources

- CGM + reference BG: factory-calibrated and user-calibrated sensors (Dexcom G6, FreeStyle Navigator) with parallel YSI/BGM references (Breton and Kovatchev, 2008; Abdolbaghi, Tabatabaei and Keyanpour, 2025; Vettoretti et al., 2019).
- In vitro / in silico: benchtop impedance and steady-state polarization curves for sensor layers (Gao and Orazem, 2021; Singh et al., 2023; Buckland et al., 2024); UVa/Padova simulators and synthetic drift datasets (Breton and Kovatchev, 2008; Sabatini et al., 2024; Buckland et al., 2024).
- Wearables / multimodal: accelerometer, HR, EDA, skin temperature for non-invasive or adjunct prediction (Matabuena et al., 2020; Karunarathna and Liang, 2025; Rajeswari and Vijayakumar, 2024).

#### Preprocessing steps

- Time alignment, removal of duplicated/missing timestamps, interpolation to a common grid (Matabuena et al., 2020; Vettoretti et al., 2019; Karunarathna and Liang, 2025).
- Outlier detection, smoothing or ARMA-based noise modeling of sensor error (Facchinetti et al., 2013; Breton and Kovatchev, 2008; Vettoretti et al., 2019).
- Feature construction (e.g., BG rate of change, glucodensities, circadian features) for exploration and later validation (Matabuena et al., 2020; Boiroux et al., 2016; Karunarathna and Liang, 2025; Rajeswari and Vijayakumar, 2024).

### 7.2 Step 1: PDE Domain Construction

Use physiology and device geometry to build the **transport domain**:

- Tissue / vasculature: PBSM models of volumetric flow + diffusion from liver to abdominal subcutaneous tissue, including capillary–interstitium exchange and needle coating (Herrón-Bedoya et al., 2021).
- Sensor stack: multi-layer diffusion–reaction in membranes, enzyme layer, and electrolyte using effective diffusion and partition coefficients (Gao and Orazem, 2021; Buckland et al., 2024).
- Error/lag models: 1st-order or fractional diffusion models linking blood to interstitial

glucose to capture delay and hysteresis in CGM error simulators (Breton and Kovatchev, 2008; Vettoretti et al., 2019; Gaetano et al., 2021).

### 7.3 Step 2: Sensor ODE Identification

Identify **lumped sensor dynamics** from in vitro / impedance data:

- Enzyme/electrochemistry: ping-pong enzyme kinetics, mediator redox, pH and buffer equilibria represented by ODEs embedded in the sensor domain (Gao and Orazem, 2021; Singh et al., 2023; Buckland et al., 2024).
- Electrical/macroscale dynamics: ARMAX or transfer-function models relating glucose steps or CV/impedance inputs to current, matched to equivalent circuits to infer electrical parameters (Singh et al., 2023).
- Phenomenological CGM/physiology ODE or FDE models for systemic glucose trends when needed (stomach, gut, blood, tissue) (Aliffi et al., 2023; Gaetano et al., 2021).
- Parameter estimation via least squares, ML with EKF/UKF, or global optimizers (e.g., particle swarm) using CGM or lab data (Aliffi et al., 2023; Singh et al., 2023; Boiroux et al., 2016; Vettoretti et al., 2019; Ozaslan et al., 2025).

### 7.4 Step 3: Coupling and Solver Architecture

Form the **PDE–ODE coupled system** and choose a solver stack:

- Couple tissue/blood PDEs to sensor ODEs through flux/Robin conditions at the sensor surface; include blood–to–ISF delay/proxy models where full vasculature is not resolved (Gao and Orazem, 2021; Breton and Kovatchev, 2008; Vettoretti et al., 2019; Herrón-Bedoya et al., 2021; Buckland et al., 2024).
- Discretize PDE (FD/FE) and assemble a semi-discrete ODE system; add sensor and possibly controller/observer ODEs (Gao and Orazem, 2021; Breton and Kovatchev, 2008; Abdolbaghi, Tabatabaei and Keyanpour, 2025).
- Use stiff-aware solvers: IMEX, operator splitting, or adaptive time-stepping with ARMA noise layers for realistic error simulation (Facchinetti et al., 2014; Breton and Kovatchev, 2008; Sabatini et al., 2024; Vettoretti et al., 2019; Buckland et al., 2024).
- For observers/controllers of coupled systems, consider neural-operator or adaptive-observer architectures as higher-level alternatives (Abdolbaghi, Tabatabaei and Keyanpour, 2025; Guo, Tan and Zhao, 2025; Zheng et al., 2025).

## 7.5 Step 4: Calibration Filter Implementation

Embed **state and parameter estimation** on top of the mechanistic model:

- Choose filter family: ML-EKF/UKF for nonlinear state-space identification (Boiroux et al., 2016; Vettoretti et al., 2019); dual/extended Kalman filters for CGM error/stochastic drift models (Vettoretti et al., 2019); Bayesian and learning-based approaches for non-Gaussian, drifting sensors (Gaitán-Guerrero et al., 2024; Sabatini et al., 2024).
- Explicitly model calibration error and drift (time-varying polynomial or stochastic processes) jointly with BG-ISF kinetics and sensor noise (Breton and Kovatchev, 2008; Sabatini et al., 2024; Vettoretti et al., 2019).
- Use synthetic data (UVa/Padova, stress-generation models) for stress-testing filters across populations, drift scenarios, and missing data (Breton and Kovatchev, 2008; Sabatini et al., 2024; Buckland et al., 2024).

## 7.6 Step 5: Validation Hierarchy

Progressively validate from controlled to real-world data:

1. **In silico**
  - Validate PDE-ODE + error + filter stack against CGM error simulators and virtual patient platforms (UVa/Padova, sensor-error simulators, stress-generation tools) (Breton and Kovatchev, 2008; Sabatini et al., 2024; Buckland et al., 2024).
2. **In vitro / benchtop**
  - Compare PDE-ODE predictions with stepped glucose, impedance spectra, and stability tests in droplet/microfluidic or

electrochemical cells (Gao and Orazem, 2021; Facchinetti et al., 2013; Singh et al., 2023; Buckland et al., 2024).

### 3. Animal studies

- Use implantable/non-invasive prototypes with reference BG (YSI) in controlled protocols; fit and refine kinetics and drift models (Gaitán-Guerrero et al., 2024; Sabatini et al., 2024).

### 4. Retrospective human data

- Fit error and transport models to large CGM + BG datasets (Navigator, Dexcom, etc.), evaluate error structure versus BG rate of change and over sensor lifetime (Facchinetti et al., 2013; Breton and Kovatchev, 2008; Abdolbaghi, Tabatabaei and Keyanpour, 2025; Vettoretti et al., 2019).
- Analyze higher-level endpoints such as glucodensities and time-in-range distributions (Matabuena et al., 2020; Boiroux et al., 2016; Rajeswari and Vijayakumar, 2024).

### 5. Prospective human studies

- Embed the full model + calibration filter in real-time or near-real-time systems; evaluate MARD, error-grid zones, time-in-range, and robustness across populations and free-living conditions (Matabuena et al., 2020; Abdolbaghi, Tabatabaei and Keyanpour, 2025; Boiroux et al., 2016; Karunarathna and Liang, 2025; Rajeswari and Vijayakumar, 2024; Ozaslan et al., 2025).

## Roadmap Snapshot

| Step                 | Main goal                        | Typical data / tools          | Citations                                                                                                                                                                                                             |
|----------------------|----------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data & preprocessing | Clean, aligned CGM/BG & lab data | CGM traces, YSI, wearables    | (Facchinetti et al., 2013; Breton and Kovatchev, 2008; Matabuena et al., 2020; Abdolbaghi, Tabatabaei and Keyanpour, 2025; Vettoretti et al., 2019; Karunarathna and Liang, 2025; Rajeswari and Vijayakumar, 2024)    |
| PDE domain           | Geometry + transport physics     | PBSM, diffusion / flow models | (Gao and Orazem, 2021; Breton and Kovatchev, 2008; Vettoretti et al., 2019; Gaetano et al., 2021; Herrón-Bedoya et al., 2021; Buckland et al., 2024)                                                                  |
| Sensor ODEs          | Local kinetics & circuitry       | Impedance, CV, CGM trends     | (Gao and Orazem, 2021; Aliffi et al., 2023; Singh et al., 2023; Boiroux et al., 2016; Gaetano et al., 2021; Buckland et al., 2024)                                                                                    |
| Coupling & solver    | Stable PDE-ODE numerics          | FD/FE, ARMA noise, observers  | (Gao and Orazem, 2021; Facchinetti et al., 2013; Breton and Kovatchev, 2008; Abdolbaghi, Tabatabaei and Keyanpour, 2025; Vettoretti et al., 2019; Guo, Tan and Zhao, 2025; Buckland et al., 2024; Zheng et al., 2025) |
| Calibration filter   | Online state + drift estimation  | EKF/UKF, Bayesian, TinyML     | (Gaitán-Guerrero et al., 2024; Facchinetti et al., 2013; Breton and Kovatchev, 2008; Sabatini et al., 2024; Boiroux et al., 2016; Vettoretti et al., 2019; Buckland et al., 2024)                                     |
| Validation           | From virtual to                  | Simulators, in                | (Facchinetti et al., 2013; Breton and Kovatchev, 2008;                                                                                                                                                                |

|        |          |               |                                                                                                                                                                          |
|--------|----------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ladder | clinical | vitro, trials | Matabuena et al., 2020; Sabatini et al., 2024; Abdolbaghi, Tabatabaei and Keyanpour, 2025; Boiroux et al., 2016; Rajeswari and Vijayakumar, 2024; Buckland et al., 2024) |
|--------|----------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Figure 5: End-to-end pathway from CGM data to validated mechanistic model.

8.Comparative Analysis and Applications of Coupled CGM Models

This section contrasts published coupled physiology sensor–filter models, decomposes error sources, and links them to digital-twin platforms, sensor design, and benchmarking. Focus is on models that explicitly or implicitly capture physiology, sensor technology, and signal processing for CGM.

8.1 Critical Review of Published Coupled Models

**Diffusion + ARMA noise simulators:** Blood–interstitial diffusion PDE/ODE plus ARMA noise form the backbone of the UVA/Padova CGM error simulator, widely used for in silico AP testing and FDA-cleared as part of a virtual platform (Facchinetti, 2016; Kovatchev et al., 2015; Breton and Kovatchev, 2008).

**Multi-component error models from parallel CGMs:** Facchinetti et al. decompose error into diffusion, calibration/drift, and noise using multiple simultaneous Dexcom sensors, effectively coupling physiology and technology in a stochastic framework (Facchinetti, 2016; Facchinetti et al., 2014).

**Drift-focused AR models:** Zhou et al. separately identify drift and random error for an intravascular sensor using autoregressive models, enabling realistic Monte-Carlo simulation of sensor behavior (Zhou, Dickson and Chase, 2017).

**Wearable multimodal ML models:** Tree-based and XGBoost regressors using multi-sensor wearable data act as “data-driven observers” on top of CGM physiology, with MARD ≈7% and >99% points in Clarke A/B (Karunarathna and Liang, 2025; Xue et al., 2022).

**Hybrid/digital-twin frameworks:** Physiologically constrained neural ODE/NN digital twins align to ODE glucoregulatory models while individualizing to real-world T1D data, enabling patient-specific in silico trials (Roquemen-Echeverri et al., 2025).

8.2 Error Source Decomposition: Physiology vs Sensor vs Filtering

- Key works explicitly separate **three error layers**:
1. **Physiology (BG→ISF transport, lags, ROC dependence)**
    - Diffusion / compartment models reproduce non-linear error vs BG rate of change; errors become positive on falling BG and negative on rising BG (Facchinetti, 2016; Kovatchev et al., 2015; Breton and Kovatchev, 2008).
  2. **Sensor technology (calibration, drift, interferents, gaps)**
    - Time-varying calibration gain/offset and slow drift are modeled as linear time-varying or AR components

- (Facchinetti, 2016; Zhou, Dickson and Chase, 2017; Facchinetti et al., 2013).
  - Interfering substances and biofouling are major technology-driven biases; mitigated by membranes, mediators, or optical designs (Zou et al., 2023; Lee et al., 2021; Setford, 2025).
  - Data gaps and disconnections can be modeled with Markov switching processes (Sabatini et al., 2024).
3. **Filtering / algorithms (denoising, prediction, ML)**
- Digital filters and ARMA-based denoising improve precision and reduce random noise impact (Facchinetti, 2016; Zhou, Dickson and Chase, 2017; Breton and Kovatchev, 2008).
  - Kalman-type or Bayesian filters and post-processing / ML predictors (RNN, XGBoost) further reduce effective MARD and improve time-in-range (Karunarathna and Liang, 2025; Zou et al., 2023; Cappon et al., 2019; Teymourian, Barfidokht and Wang, 2020; Xue et al., 2022).
  - Stress-generation / TinyML drift-compensation models explicitly target algorithmic correction of long-term drift at the edge (Sabatini et al., 2024).

8.3 Digital Twin Platforms for CGM Algorithm Testing

Digital-twin and in silico platforms combine the above components to test CGM algorithms safely:

**UVA/Padova + CGM error models:** Physiological virtual patients coupled with sensor-error simulators (diffusion + ARMA + calibration variability) form a standard platform for closed-loop controller and alarm testing, including accuracy thresholds for non-adjunct use (Facchinetti, 2016; Kovatchev et al., 2015; Breton and Kovatchev, 2008).

**Physiologically constrained NN twins:** ODE-aligned NN digital twins simulate individual glucose profiles and endpoints (time-in-range, hypo/hyper) with clinical equivalence, enabling personalized in silico evaluation of therapies and algorithms (Roquemen-Echeverri et al., 2025).

**Synthetic stress/dataset generators:** Stress-generation models produce large, realistic multi-sensor CGM datasets with embedded drift and interference for training and benchmarking TinyML filters and calibration strategies (Sabatini et al., 2024).

8.4 Implications for Sensor Design and Insertion Strategy

Coupled analyses have direct impact on hardware and insertion:

**Interference and membrane design:** Reviews of electrochemical sensors highlight optimization of enzyme layers, mediators, and protective membranes to limit interferent flux and biofouling, reducing systematic bias and drift (Zou et al., 2023; Lee et al., 2021; Teymourian, Barfidokht and Wang, 2020; Setford, 2025).

**Minimally invasive vs non-invasive trade-offs:** Minimally invasive electrochemical CGMs currently deliver superior accuracy (MARD ≈9–12%) but at the cost of invasiveness; nanomaterial-assisted and optical/non-invasive designs aim to reduce insertion trauma while maintaining acceptable error grids (Zou et al., 2023; Safarkhani et al., 2024; Teymourian, Barfidokht and Wang, 2020; Litvinova et al., 2023).

**Insertion site/tissue heterogeneity:** Patent and clinical reviews emphasize that tissue perfusion,

edema, and local blood flow strongly affect BG–ISF kinetics and thus the physiological component of error, motivating site-specific modeling and possibly adaptive insertion strategies (Zou et al., 2023; Litvinova et al., 2023).

**Wear duration and lifetime:** Error-decomposition models show worsening calibration/drift over sensor life; this informs maximum wear times and need for on-board drift-compensation filters or factory calibration strategies (Facchinetti, 2016; Zou et al., 2023; Sabatini et al., 2024; Eichenlaub et al., 2025).

8.5 Comparative Benchmark Table (PDE/ODE/Filter/Real-Time/MARD/Gain)

The table below conceptually compares representative model/algorithm classes (not individual brands) using typical reported accuracies and properties.

Comparative Benchmark of Modeling/Filtering Approaches

| Model / Platform Class                                 | Physiology Model (PDE/ODE)                                                                 | Sensor/Error Model                                                                                                           | Filter Algorithm Layer                                   | Real-time capable?                 | Typical MARD / Error Performance                                                                                                                               | Main “Gain” vs Raw CGM                                           | Citations                                                                                           |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Classical CGM error simulator (UVA/Padova + Navigator) | Compartment / diffusion ODE/PDE for BG→ISF (Facchinetti, 2016; Breton and Kovatchev, 2008) | Diffusion lag + ARMA noise + calibration variability (Facchinetti, 2016; Kovatchev et al., 2015; Breton and Kovatchev, 2008) | Offline / real-time capable denoisers and AP controllers | Yes (basis for closed-loop trials) | Simulated to match Navigator clinical MARD (~14–16%) (Facchinetti, 2016; Breton and Kovatchev, 2008; Facchinetti et al., 2013)                                 | Provides realistic error for safe AP in silico testing           | (Facchinetti, 2016; Kovatchev et al., 2015; Breton and Kovatchev, 2008; Facchinetti et al., 2013)   |
| Multi-sensor error decomposition (Dexcom SEVEN Plus)   | BG→ISF diffusion, first-order / compartment (Facchinetti, 2016; Facchinetti et al., 2013)  | Time-varying calibration + AR noise separated using 4 parallel CGMs (Facchinetti et al., 2013)                               | Can inform design of tailored digital filters            | Conceptually yes                   | Global MARD ≈14.2% with explicit contributions: ~3.5% diffusion, 12.8% calibration, 5.6% noise (overlapping) (Facchinetti et al., 2014; Sabatini et al., 2024) | Clear attribution of error sources for sensor & algorithm design | (Facchinetti, 2016; Zhou, Dickson and Chase, 2017; Sabatini et al., 2024; Facchinetti et al., 2013) |
| AR-based                                               | BG as                                                                                      | Separate                                                                                                                     | Monte-Carlo                                              | Yes (for                           | Simulated                                                                                                                                                      | Enables                                                          | (Zhou,                                                                                              |

|                                                              |                                                                                                          |                                                                                                                     |                                                                                                 |                                        |                                                                                                                                                                 |                                                                            |                                                                                                                                                  |
|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| intravascular drift/noise model (GlySure)                    | external input (no explicit PDE) (Zhou, Dickson and Chase, 2017)                                         | AR drift and noise processes from clinical ICU data (Zhou, Dickson and Chase, 2017)                                 | simulation, supports filter design                                                              | protocol design, not embedded )        | vs clinical MARD 9.6% vs 9.9% (Zhou, Dickson and Chase, 2017)                                                                                                   | protocol-level assessment of impact of drift vs noise                      | Dickson and Chase, 2017)                                                                                                                         |
| Advanced post-processing ML on commercial CGM / non-invasive | Often implicit physiology ; sometimes simple BG dynamics (Karunaratna and Liang, 2025; Xue et al., 2022) | Empirical error from CGM or alternative sensing (microwave, fusion) (Karunaratna and Liang, 2025; Xue et al., 2022) | XGBoost, RNN, GE, etc. for denoising/prediction (Karunaratna and Liang, 2025; Xue et al., 2022) | Yes (designed for near real-time)      | Frequently achieve >90–100% in Clarke A/B, MARD down to ~7–10% in some datasets (Karunaratna and Liang, 2025; Xue et al., 2022)                                 | Significant reduction in apparent error & improved trend prediction        | (Karunaratna and Liang, 2025; Williamson, Lee and Gaynanova, 2025; Cappon et al., 2019; Teymourian, Barfidokht and Wang, 2020; Xue et al., 2022) |
| Multimodal wearable ML (non-invasive adjunct prediction)     | No explicit PDE/ODE; physiology encoded via features (Karunaratna and Liang, 2025)                       | Implicit in regression residuals                                                                                    | Tree-based ML (RF, XGBoost)                                                                     | Yes                                    | $R^2 \approx 0.73$ , RMSE 11.9 mg/dL, MARD 7.1%; 99.4% in Clarke A/B (Karunaratna and Liang, 2025)                                                              | Adjunct prediction & redundancy, potentially reducing need for calibration | (Karunaratna and Liang, 2025; Safarkhani et al., 2024; Xue et al., 2022)                                                                         |
| Digital twin (physiologically constrained NN)                | ODE-aligned NN state-space model for glucose–insulin (Roquemen-Echeverri et al., 2025)                   | Implicit sensor model (or assumes CGM as noisy observation)                                                         | NN-based state estimation; potential filters on top                                             | Designed for near real-time simulation | Endpoints (TIR, TBR, TAR) statistically equivalent to real data; not reported as MARD but clinically equivalent distributions (Roquemen-Echeverri et al., 2025) | Patient-specific in silico testing of therapies/algorithms                 | (De Jong et al., 2024; Roquemen-Echeverri et al., 2025)                                                                                          |

|                                                                 |                                                                                  |                                                                                |                                             |                                |                                                                                                        |                                                               |                                                                    |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------|
| Factory-calibrated CGM error & drift stress generators (TinyML) | Physiological patterns from virtual patients + real data (Sabatini et al., 2024) | Explicit drift, calibration, and interference patterns (Sabatini et al., 2024) | TinyML random forest/SVR drift compensators | Intended for embedded edge use | MAE around 16 mg/dL in stressed conditions; baseline models $\approx 11$ mg/dL (Sabatini et al., 2024) | Framework to stress-test and improve edge calibration filters | (Facchinetti, 2016; Kovatchev et al., 2015; Sabatini et al., 2024) |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------|

Figure 6: Comparison of major CGM modeling and filtering approaches.

**In Summary** Published CGM modeling work spans rigorous diffusion+ARMA simulators, multi-sensor error decomposition, AR drift models, ML post-processing, multimodal wearables, and physiologically constrained digital twins (Facchinetti, 2016; Karunarathna and Liang, 2025; Zhou, Dickson and Chase, 2017; Breton and Kovatchev, 2008; Roquemen-Echeverri et al., 2025; Facchinetti et al., 2013). Decomposing error into **physiology, sensor, and filtering** clarifies where improvements are most effective: membranes and chemistries for interferents and drift, insertion strategies for BG-ISF kinetics, and advanced filters/ML for noise and prediction (Facchinetti, 2016; Zou et al., 2023; Lee et al., 2021; Teymourian, Barfidokht and Wang, 2020; Sabatini et al., 2024; Setford, 2025; Facchinetti et al., 2013). Digital-twin platforms built on these coupled models underpin safer in silico testing of CGM algorithms and guide next-generation sensor design and benchmarking.

9. Future Directions & Converging Frontiers

9.1 Subject-Specific Personalization via Bayesian Inference

Bayesian frameworks enable real-time adaptation to individual physiology/sensor characteristics using prior/posterior updating on streaming data (Koutny, 2022; Lu et al., 2025).

9.2 Physics–Machine Learning Hybrids (PINNs): Critical Limitations Highlighted

Physics-informed neural networks promise flexible personalization but face challenges in interpretability/data requirements/model identifiability when applied to Multiphysics systems like CGM (Lu et al., 2025).

9.3 Model Order Reduction for Embedded Devices

Reduced-order surrogates retain essential dynamics while enabling real-time execution on wearable hardware a key step toward practical deployment.

9.4 Towards a Unified Digital Patient Integration with Whole-body Glucose Metabolism

Integrating local CGM models into whole-body digital twins will support comprehensive simulation/prediction across organ systems/disease states.

9.5 Open Challenges: Identifiability, Fibrosis, Long-term Drift

Long-term foreign body response/fibrosis alters local transport properties unpredictably; identifiability remains difficult when multiple error sources overlap temporally/spatially.

10.Conclusion and Roadmap

Coupled physiological–sensor modeling represents a paradigm shift in continuous glucose monitoring research enabling more accurate prediction/calibration by unifying physical processes across domains previously treated separately. Future work should focus on robust parameter identification under real-world variability/fibrosis/drift conditions, integration with machine learning surrogates, and translation into embedded digital twin platforms supporting closed-loop therapy.

DISCUSSION

The evidence strongly supports that treating continuous glucose monitoring as a tightly coupled Multiphysics problem yields superior accuracy, robustness, and interpretability compared to traditional decoupled approaches ((Gao and Orazem, 2021; Facchinetti et al., 2013)). Fully integrated PDE–ODE frameworks allow explicit attribution/decomposition of error sources; they also provide a principled basis for advanced calibration/filtering algorithms essential for long-term reliability. However, practical challenges remain regarding parameter identifiability under variable physiology/fibrosis/drift; the need for large-scale personalized datasets; and computational constraints on embedded devices.

| Claim                                                                              | Evidence Strength                | Reasoning                                                                     | Papers                                           |
|------------------------------------------------------------------------------------|----------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------|
| Coupled physiological-sensor models improve CGM accuracy over decoupled approaches | Evidence strength: Strong (9/10) | Multiple studies show reduced bias/error during rapid excursions/interference | (Gao and Orazem, 2021; Facchinetti et al., 2013) |
| Ignoring coupling leads to systematic bias/drift                                   | Evidence strength: Strong        | Error decomposition reveals overlapping/confounded error sources              | (Facchinetti et al., 2013)                       |

|                                                                     |                                    |                                                                               |                         |
|---------------------------------------------------------------------|------------------------------------|-------------------------------------------------------------------------------|-------------------------|
|                                                                     | (8/10)                             |                                                                               |                         |
| Digital twins enable robust preclinical algorithm testing           | Evidence strength: Moderate (7/10) | In silico platforms validated against animal/human data                       | (Buckland et al., 2024) |
| Machine learning hybrids require large datasets/high-quality priors | Evidence strength: Moderate (6/10) | PINNs/personalized ML show promise but face generalizability/data limitations | (Lu et al., 2025)       |
| Parameter identifiability remains challenging under fibrosis/drift  | Evidence strength: Moderate (4/10) | Foreign body response alters local transport unpredictably                    | (Koutny, 2022)          |

Figure 7: Key claims/support evidence identified among included papers.

### CONCLUSION

Coupled physiological sensor modeling marks a critical advance toward reliable, personalized continuous glucose monitoring. By unifying physical processes across domains previously treated separately, these frameworks support improved calibration, error attribution, algorithm development, and ultimately safer closed-loop diabetes management.

### Research Gaps

Despite progress, gaps remain regarding long-term validation under fibrosis/drift; scalable personalization; real-time implementation on embedded devices; and integration into whole-body digital twins.

| Topic/Outcome                      | Animal Validation | Human Validation | Digital Simulation | Twin |
|------------------------------------|-------------------|------------------|--------------------|------|
| Coupled PDE–ODE model              | 7                 | 11               | 16                 |      |
| Calibration/filtering algorithms   | 6                 | 13               | 14                 |      |
| Noninvasive modalities             | 4                 | 10               | 7                  |      |
| Personalization/Bayesian inference | GAP               | 6                | 11                 |      |

Figure 8: Research gaps matrix showing study types vs outcomes/topics.

### REFERENCES

1. Abdolbaghi, M., Tabatabaei, S., & Keyanpour, M., 2025. Neural operator for observer gains and output-feedback control of coupled PDE–ODE systems. *Scientific Reports*, 15(1), p.29479. <https://doi.org/10.1038/s41598-025-14090-0>

2. Acanfora, M., Pedone, E., Presciuttini, B., Ré, F. and Acanfora, L., 2025. Beyond Mean Absolute Relative Difference (MARD): Rethinking Continuous Glucose Monitoring (CGM) Evaluation for Real-World Diabetes Care. *Cureus*, 17(9), p.e91427.<https://doi.org/10.7759/cureus.91427>

3. Acciaroli, G., Vettoretti, M., Facchinetti, A., & Sparacino, G., 2018. Calibration of Minimally Invasive Continuous Glucose Monitoring Sensors: State-of-The-Art and Current Perspectives. *Biosensors*, 8(1), p24. <https://doi.org/10.3390/bios8010024>

4. Acciaroli, G., Vettoretti, M., Facchinetti, A., Sparacino, G., & Cobelli, C., 2017. Reduction of Blood Glucose Measurements to Calibrate Subcutaneous Glucose Sensors: A Bayesian Multiday Framework. *IEEE Transactions on Biomedical Engineering*, 65(3), pp. 587-595. <https://doi.org/10.1109/tbme.2017.2706974>

5. Aliffi, G., Nastasi, G., Romano, V., Pitocco, D., Rizzi, A., Moore, E., & De Gaetano, A., 2023. A system of ODEs for representing trends of CGM signals. *Journal of Mathematics in Industry*, 14(1), p. 23. <https://doi.org/10.1186/s13362-024-00161-w>

6. Arulampalam, M., Maskell, S., Gordon, N., & Clapp, T., 2002. A tutorial on particle filters for online nonlinear/non-Gaussian Bayesian tracking. *IEEE Trans. Signal Process.*, 50(2), pp. 174-188. <https://doi.org/10.1109/78.978374>

7. Bachar, M., 2025. Sensitivity analysis for a delay mathematical model: the glucose-insulin model. *Frontiers in Applied Mathematics and Statistics*, 11. <https://doi.org/10.3389/fams.2025.1562636>

8. Barceló-Rico, F., Díez, J., Rossetti, P., Vehí, J., & Bondia, J., 2013. Adaptive Calibration Algorithm for Plasma Glucose Estimation in Continuous Glucose Monitoring. *IEEE Journal of Biomedical and Health Informatics*, 17(3), pp. 530-538. <https://doi.org/10.1109/jbhi.2013.2253325>

9. Bociu, L., Guidoboni, G., Sacco, R., & Prada, D., 2022. Numerical simulation and analysis of multiscale interface coupling between a poroelastic medium and a lumped hydraulic circuit: Comparison between functional iteration and operator splitting methods. *J. Comput. Phys.*,

- 466, pp. 111379.  
<https://doi.org/10.1016/j.jcp.2022.111379>
10. Boiroux, D., Hagdrup, M., Mahmoudi, Z., Poulsen, N., Madsen, H., & Jørgensen, J., 2016. Model Identification using Continuous Glucose Monitoring Data for Type 1 Diabetes. *IFAC-PapersOnLine*, 49, pp. 759-764.  
<https://doi.org/10.1016/j.ifacol.2016.07.279>
11. Breton, M., & Kovatchev, B., 2008. Analysis, Modeling, and Simulation of the Accuracy of Continuous Glucose Sensors. *Journal of Diabetes Science and Technology*, 2(5), pp. 853 - 862.  
<https://doi.org/10.1177/193229680800200517>
12. Buckland, J., Tarotin, I., Meredith, S., Goode, P., Thrower, J., & Tapsak, M., 2024. 1021-P: In Silico Modeling of a Long-Term Implantable Continuous Blood Glucose Monitor—A Joint Investigation by Glucotrack Inc. and TTP. *Diabetes*. American Diabetes Association, 73(Supplement\_1):1021-P  
<https://doi.org/10.2337/db24-1021-p>
13. Chen, L., Shinha, K., Nakamura, H., Komori, K., & Kimura, H., 2025. A Microfluidic Device Integrating a Glucose Sensor and Calibration Function for Cell-Based Assays. *Biosensors*, 15(5), p.307.  
<https://doi.org/10.3390/bios15050307>
14. De Jong, L., Li, X., Emamipour, S., Van Der Werf, S., Postma, M., Van Dijk, P., & Feenstra, T., 2024. Evaluating the Cost-Utility of Continuous Glucose Monitoring in Individuals with Type 1 Diabetes: A Systematic Review of the Methods and Quality of Studies Using Decision Models or Empirical Data. *Pharmacoeconomics*, 42(9), pp. 929 - 953.  
<https://doi.org/10.1007/s40273-024-01388-6>
15. Deutscher, J. and Gehring, N., 2020. Output feedback control of coupled linear parabolic ODE–PDE–ODE systems. *IEEE Transactions on Automatic Control*, 66(10), pp.4668-4683.  
<https://doi.org/10.1109/tac.2020.3030763>
16. Eichenlaub, M., Waldenmaier, D., Wehrstedt, S., Pleus, S., Link, M., Jendrike, N., Öter, S., Haug, C., Schinz, M., Braunack-Mayer, V., Schneider, R., Brandt, D., & Freckmann, G., 2025. Performance of Three Continuous Glucose Monitoring Systems in Adults With Type 1 Diabetes.. *Journal of diabetes science and technology*, pp. 19322968251315459.  
<https://doi.org/10.1177/19322968251315459>
17. Facchinetti, A., 2016. Continuous Glucose Monitoring Sensors: Past, Present and Future Algorithmic Challenges. *Sensors (Basel, Switzerland)*, 16.  
<https://doi.org/10.3390/s16122093>
18. Facchinetti, A., Del Favero, S., Sparacino, G., Castle, J., Ward, W., & Cobelli, C., 2013. Modeling the Glucose Sensor Error. *IEEE Transactions on Biomedical Engineering*, 61(3), pp. 620-629.  
<https://doi.org/10.1109/tbme.2013.2284023>
19. Gaetano, A., Sakulrang, S., Borri, A., Pitocco, D., Sungnul, S., & Moore, E., 2021. Modeling Continuous Glucose Monitoring with Fractional Differential Equations Subject to Shocks.. *Journal of theoretical biology*, pp. 110776.  
<https://doi.org/10.1016/j.jtbi.2021.110776>
20. Gaitán-Guerrero, J., Ruiz, J., Espinilla, M., & Martínez-Cruz, C., 2024. Toward an Interpretable Continuous Glucose Monitoring Data Modeling. *IEEE Internet of Things Journal*, 11(19), (, pp. 31080-31094.  
<https://doi.org/10.1109/jiot.2024.3419260>
21. Gao, M., & Orazem, M., 2021. The development of advanced mathematical models for continuous glucose sensors. *Electrochimica Acta*, pp. 138226.  
<https://doi.org/10.1016/j.electacta.2021.138226>
22. Guo, B., Tan, Z., & Zhao, R., 2025. Adaptive observer for a coupled ODE-wave PDE system. *International Journal of Systems Science*, 56, pp. 2945 - 2957.  
<https://doi.org/10.1080/00207721.2025.2466051>
23. Herrón-Bedoya, A., Walteros-León, M., Lema-Perez, L., & Alvarez, H., 2021. Phenomenological-Based Model of Glucose Transport from Liver to Abdominal Subcutaneous Adipose Tissue.. *Journal of theoretical biology*, pp. 110883.  
<https://doi.org/10.1016/j.jtbi.2021.110883>
24. Iyaniwura, S.A. and Ward, M.J., 2021. Synchrony and oscillatory dynamics for a 2-D PDE-ODE model of diffusion-mediated communication between small signaling compartments. *SIAM Journal on Applied Dynamical Systems*, 20(1), pp.438-499.
25. Juska, V.B. and Pemble, M.E., 2020. A critical review of electrochemical glucose sensing: Evolution of biosensor platforms based on advanced nanosystems. *Sensors*, 20(21), p.6013.  
<https://doi.org/10.3390/s20216013>
26. Karunarathna, T., & Liang, Z., 2025. Development of Non-Invasive Continuous Glucose Prediction Models Using Multi-Modal Wearable Sensors in Free-Living Conditions. *Sensors (Basel, Switzerland)*, 25 (10), p.3207.  
<https://doi.org/10.3390/s25103207>
27. Karunarathna, T., & Liang, Z., 2025. Development of Non-Invasive Continuous Glucose Prediction Models Using Multi-Modal Wearable Sensors in Free-Living Conditions. *Sensors (Basel,*

- Switzerland),  
<https://doi.org/10.3390/s25103207>
28. Khodarahmi, M., & Maihami, V., 2023. A Review on Kalman Filter Models. *Archives of Computational Methods in Engineering*, 30(1), pp. 727-747. <https://doi.org/10.1007/s11831-022-09815-7>
  29. Koutny, T., 2022. Physiological reconstruction of blood glucose level using CGMS-signals only. *Scientific Reports*, 12(1). <https://doi.org/10.1038/s41598-022-09884-5>
  30. Kovatchev, B., Patek, S., Ortiz, E., & Breton, M., 2015. Assessing Sensor Accuracy for Non-Adjunct Use of Continuous Glucose Monitoring. *Diabetes Technology & Therapeutics*, 17(3), pp. 177 - 186. <https://doi.org/10.1089/dia.2014.0272>
  31. Lee, I., Probst, D., Klonoff, D., & Sode, K., 2021. Continuous glucose monitoring systems - Current status and future perspectives of the flagship technologies in biosensor research.. *Biosensors & bioelectronics*, 181. p. 113054. <https://doi.org/10.1016/j.bios.2021.113054>
  32. Lema-Perez, L., Aguirre-Zapata, E., Fougner, A., Amicarelli, A., & Alvarez, H., 2023. Connecting sensitivity, identifiability and interpretability of a glucose minimal model. In *2023 XX Workshop on Information Processing and Control (RPIC)*, pp. 1-7. <https://doi.org/10.1109/rpic59053.2023.10530857>
  33. Li, B., Li, J., Lou, P., Rong, L., Wang, Z., & Xiong, H., 2025. Particle filtering for nonlinear cyber-physical systems under Round-Robin protocol: Handling complex sensor issues and non-Gaussian noise. *Journal of the Franklin Institute*, 362(3), p.107507. <https://doi.org/10.1016/j.jfranklin.2025.107507>
  34. Lin, S., Li, Y., Yang, Z., Li, Q., Pang, B., Feng, Y., Fu, J., , G., & Long, Y., 2025. Photopolymerization 3D-Printed Dual-Modal Flexible Sensor for Glucose and pH Monitoring. *Sensors (Basel, Switzerland)*, 25(17). <https://doi.org/10.3390/s25175358>
  35. Litvinova, O., Eitenberger, M., Bilir, A., Yeung, A., Parvanov, E., MohanaSundaram, A., Horbańczuk, J., Atanasov, A., & Willschke, H., 2023. Patent analysis of digital sensors for continuous glucose monitoring. *Frontiers in Public Health*, 11. <https://doi.org/10.3389/fpubh.2023.1205903>
  36. Lu, Y., Liu, D., Liang, Z., Liu, R., Chen, P., Liu, Y., Li, J., Feng, Z., Li, L., Sheng, B., Jia, W., Chen, L., Li, H., & Wang, Y., 2025. A pretrained transformer model for decoding individual glucose dynamics from continuous glucose monitoring data. *National Science Review*, 12. <https://doi.org/10.1093/nsr/nwaf039>
  37. Matabuena, M., Petersen, A., Vidal, J., & Gudé, F., 2020. Glucodensities: A new representation of glucose profiles using distributional data analysis. *Statistical Methods in Medical Research*, 30, pp. 1445 - 1464. <https://doi.org/10.1177/0962280221998064>
  38. McIlwaine, F. and Gerogiorgis, D.I., 2018. Dynamic modelling and simulation of reactive transport phenomena in an amperometric blood glucose biosensor. In *Computer Aided Chemical Engineering* (Vol. 43, pp. 1649-1654). Elsevier. <https://doi.org/10.1016/b978-0-444-64235-6.50287-4>
  39. Ozaslan, B., Aiello, E., Fushimi, E., Doyle, F., & Dassau, E., 2025. Personalized Model Identification for Glucose Dynamics From Clinical Data With Incomplete Inputs. *IEEE Transactions on Biomedical Engineering*, 72(6), pp. 2001-2012. <https://doi.org/10.1109/tbme.2025.3530711>
  40. P., Reshma K. , Prasad, Shashikant , Sharma, Chetan Kumar , Deshpande, Abhijeet , Bagal, Sahebrao Bhaurao & Tejaswi, K. (2025) High-accuracy Runge&ndash;Kutta methods for stiff ODE systems, *Journal of Interdisciplinary Mathematics*, 28:6, PP, 2217–2225. <https://doi.org/10.47974/jim-2363>
  41. Radhakrishnan, S., Lakshmy, S., Santhosh, S., Kalarikkal, N., Chakraborty, B. and Rout, C.S., 2022. Recent developments and future perspective on electrochemical glucose sensors based on 2D materials. *Biosensors*, 12(7), p.467. <https://doi.org/10.3390/bios12070467>
  42. Rajeswari, S., & Vijayakumar, P., 2024. Development of sensor system and data analytic framework for non-invasive blood glucose prediction. *Scientific Reports*, 14(1). p.9206. <https://doi.org/10.1038/s41598-024-59744-7>
  43. Roquemen-Echeverri, V., Kushner, T., Jacobs, P., & Lopez, C., 2025. A Physiologically-Constrained Neural Network Digital Twin Framework for Replicating Glucose Dynamics in Type 1 Diabetes. *ArXiv*, abs/2508.05705. <https://doi.org/10.48550/arxiv.2508.05705>
  44. Sabatini, A., Cenerini, C., Vollero, L., & Pau, D., 2024. Calibrating Glucose Sensors at the Edge: A Stress Generation Model for Tiny ML Drift Compensation. *BioMedInformatics*. 4(2), pp.1519-1530. <https://doi.org/10.3390/biomedinformatics4020083>
  45. Sabatini, A., Cenerini, C., Vollero, L., & Pau, D., 2024. Calibrating Glucose Sensors at the Edge: A Stress Generation Model for Tiny ML Drift Compensation. *BioMedInformatics*. <https://doi.org/10.3390/biomedinformatics4020083>

46. Sabatini, A., Cenerini, C., Vollero, L., & Pau, D., 2024. Calibrating Glucose Sensors at the Edge: A Stress Generation Model for Tiny ML Drift Compensation. *BioMedInformatics*, 4(2), pp.1519-1530. <https://doi.org/10.3390/biomedinformatics4020083>
47. Safarkhani, M., Aldhaher, A., Heidari, G., Zare, E.N., Warkiani, M.E., Akhavan, O., Huh, Y. and Rabiee, N., 2024. Nanomaterial-assisted wearable glucose biosensors for noninvasive real-time monitoring: Pioneering point-of-care and beyond. *Nano Materials Science*, 6(3), pp.263-283. <https://doi.org/10.1016/j.nanoms.2023.11.009>
48. Selim, K., Khalifa, Z., Ali, A., & Abdellatif, S., 2025. Experimentally Driven Numerical Model of Carbon/Polyaniline-Based Glucose Monitoring Sensors: An Evaluation Using a New Figure of Merit. *IEEE Sensors Journal*, 25, pp. 24473-24484. <https://doi.org/10.1109/jsen.2025.3570069>
49. Setford, S., 2025. The Impact of Interfering Substances on Continuous Glucose Monitors: Part 2: Marketed CGM Designs, Labeled Interfering Substances, and Design Mitigations.. *Journal of diabetes science and technology*, pp. 19322968251377008. <https://doi.org/10.1177/19322968251377008>
50. Shah, V., Laffel, L., Wadwa, R., & Garg, S., 2018. Performance of a Factory-Calibrated Real-Time Continuous Glucose Monitoring System Utilizing an Automated Sensor Applicator. *Diabetes Technology & Therapeutics*, 20(6), pp. 428 - 433. <https://doi.org/10.1089/dia.2018.0143>
51. Singh, A., Bhuyan, M., Hazarika, A., & Dutta, L., 2023. Model-Based Derivation of Electrical Parameters and Impedance Study of Two-Electrode Copper Nanoparticle-Based Pencil-Drawn Glucose Sensor. *IEEE Transactions on Industrial Informatics*, 20(2), pp. 2897-2906. <https://doi.org/10.1109/tii.2023.3297628>
52. Singh, A., Rebec, M., & Haidar, A., 2020. Kalman-Based Calibration Algorithm for AgaMatrix Continuous Glucose Monitoring System. *IEEE Transactions on Control Systems Technology*, 29(3), pp. 1257-1267. <https://doi.org/10.1109/tcst.2020.3003450>
53. Staal, O., Fougner, A., Saelid, S., & Stavadahl, Ø., 2019. Glucose-insulin metabolism model reduction and parameter selection using sensitivity analysis. *2019 American Control Conference (ACC)*, pp. 4104-4111. <https://doi.org/10.23919/acc.2019.8814949>
54. Stefanovski, D., Pacini, G., & Boston, R., 2021. Editorial: Mathematical Modeling of Endocrine Systems. *Frontiers in Endocrinology*, 12. <https://doi.org/10.3389/fendo.2021.789386>
55. Talukder, S., Kundu, S. and Kumar, R., 2022. Dynamic calibration of nonlinear sensors with time-drifts and delays by bayesian inference. arXiv preprint arXiv:2208.13819.
56. Teymourian, H., Barfidokht, A., & Wang, J., 2020. Electrochemical glucose sensors in diabetes management: an updated review (2010-2020). *Chemical Society reviews*. 49(21), pp.7671-7709. <https://doi.org/10.1039/d0cs00304b>
57. Theodosiou, E., Schütz, J., & Seal, D., 2024. An explicitness-preserving IMEX-split multiderivative method. *Comput. Math. Appl.*, 158, pp. 139-149. <https://doi.org/10.1016/j.camwa.2023.12.040>
58. Tuveri, A., Perez-Garcia, F., Lira-Parada, P.A., Imsland, L. and Bar, N., 2021. Sensor fusion based on Extended and Unscented Kalman Filter for bioprocess monitoring. *Journal of process control*, 106, pp.195-207. <https://doi.org/10.1016/j.jprocont.2021.09.005>
59. Vettoretti, M., Battocchio, C., Sparacino, G., & Facchinetti, A., 2019. Development of an Error Model for a Factory-Calibrated Continuous Glucose Monitoring Sensor with 10-Day Lifetime. *Sensors (Basel, Switzerland)*, 19. <https://doi.org/10.3390/s19235320>
60. Vigersky, R., & Shin, J., 2024. The Myth of MARD (Mean Absolute Relative Difference): Limitations of MARD in the Clinical Assessment of Continuous Glucose Monitoring Data. *Diabetes Technology & Therapeutics*, 26(S3), pp. 38 - 44. <https://doi.org/10.1089/dia.2023.0435>
61. Wadwa, R., Laffel, L., Shah, V., & Garg, S., 2018. Accuracy of a Factory-Calibrated, Real-Time Continuous Glucose Monitoring System During 10 Days of Use in Youth and Adults with Diabetes. *Diabetes Technology & Therapeutics*, 20(6), pp. 395 - 402. <https://doi.org/10.1089/dia.2018.0150>
62. Wang, B., Eden, A., Chen, Y., Kim, H., Queenan, B., Bazan, G., & Pennathur, S., 2024. Auto recalibration based on dual-mode sensing for robust optical continuous glucose monitoring. *Sensors and Actuators B: Chemical*. 418, p.136277. <https://doi.org/10.1016/j.snb.2024.136277>
63. Williamson, W., Lee, J., & Gaynanova, I., 2025. A Processing Algorithm to Address Real-World Data Quality Issues With Continuous Glucose Monitoring Data.. *Journal of diabetes science and technology*, pp. 19322968251319801. <https://doi.org/10.1177/19322968251319801>
64. Xue, Y., Thalmayer, A., Zeising, S., Fischer, G., & Lübke, M., 2022. Commercial and Scientific

- Solutions for Blood Glucose Monitoring—A Review. *Sensors (Basel, Switzerland)*, 22(2), p.425. <https://doi.org/10.3390/s22020425>
65. Zheng, J.Y., Bo, D.J., Wang, Z.P., Wang, J.W. and Qiao, J.F., 2025. Intermittent Sampled-Data Control for Coupled PDE-ODE Systems. *IFAC-PapersOnLine*, 59(8), pp.220-225. <https://doi.org/10.1016/j.ifacol.2025.08.094>
66. Zhou, T., Dickson, J., & Chase, G., 2017. Autoregressive Modeling of Drift and Random Error to Characterize a Continuous Intravascular Glucose Monitoring Sensor. *Journal of Diabetes Science and Technology*, 12(1), pp. 90 - 104. <https://doi.org/10.1177/1932296817719089>