# Toward a Lagrangian Framework for Biological Digital Twins: From Variational Mechanics to Organ-Scale Simulation

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**Abstract**

The Lagrangian (variational) formulation underpins all of fundamental physics: classical mechanics, field theory, fluid dynamics, and general relativity derive their equations of motion from a single scalar action functional via the principle of stationary action. Despite this universality, existing computational models of biological organs—finite-element methods, agent-based rules, pharmacokinetic compartments, and Eulerian CFD—do not employ a variational principle, forgoing the automatic conservation laws, structural couplings, and multi-scale consistency that it provides.

This paper develops the case for applying the Lagrangian framework to biological digital twins. We review the essential formalism of Lagrangian mechanics (§2) and its extension to fluid dynamics (§3), establishing the mathematical vocabulary. We then argue that biological tissue function is fundamentally *fluid-driven*—the transport of blood, bile, lymph, and interstitial fluid dictates nutrient delivery, waste clearance, mechanical signalling, and cellular fate—making the Lagrangian formulation a natural foundation for organ-scale simulation. Using the liver as the initial target organ, we outline the general form of a tissue Lagrangian, survey the existing literature to establish that, to our knowledge, no research group has proposed or implemented a Lagrangian-based biological digital twin, and present a phased research programme for pursuing this approach.

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# 1 Introduction

The concept of a *digital twin*—a computational replica of a physical system that evolves in parallel with its real counterpart— originated in aerospace engineering [Grieves, 2002], where high-fidelity models of aircraft and turbines are used for predictive maintenance and design optimisation. The extension to biology and medicine promises patient-specific models that can predict disease progression, optimise drug dosing, and simulate surgical outcomes before they are performed on a living patient.

Yet the biological digital twin faces a challenge that aerospace models do not: *the governing equations are not known from first principles.* An aircraft wing obeys the Navier–Stokes equations and linear elasticity; a liver obeys... what, exactly? The standard answer is a patchwork: mass-action kinetics for metabolism, finite-element mechanics for tissue deformation, compartment models for pharmacokinetics, agent-based rules for cell behaviour. These are stitched together with ad hoc coupling terms, each sub-model using different variables, different numerical schemes, and different assumptions about what is conserved.

This paper proposes a different starting point. We argue that:

1. Biological tissue function is *fundamentally fluid-driven*: the transport of blood, lymph, bile, and interstitial fluid is not merely a supporting service but the primary determinant of cellular behaviour, tissue structure, and organ function.
2. Because fluid dynamics has a natural variational (Lagrangian) formulation, organ-scale digital twins can be constructed from a single scalar functional—a *tissue Lagrangian*—from which all governing equations, conservation laws, and coupling terms emerge automatically via the Euler–Lagrange equations and Noether's theorem [Noether, 1918].
3. To our knowledge, this approach has not been attempted. Despite extensive literature on biological modelling, no group has proposed or implemented a Lagrangian-based digital twin of any organ.

We develop this argument using the liver as the initial target, because its architecture is dominated by fluid flow at every scale and because liver disease (cirrhosis, fatty liver disease) is a leading cause of morbidity worldwide.

# 2 The Lagrangian Framework for Physics

The variational approach to mechanics—developed over three centuries by Maupertuis, Euler, Lagrange, Hamilton, and Noether [de Maupertuis, 1744, Euler, 1744, Lagrange, 1788, Hamilton, 1834, Noether, 1918]—replaces Newton's force-by-force accounting with a single scalar functional. This section summarises the essential formalism; extended pedagogical treatments are available in standalone primers by the author.

## 2.1 Generalised Coordinates and the Action Principle

A system with $n$ degrees of freedom is described by *generalised coordinates* $q_1, q_2, \ldots, q_n$ and their time derivatives (generalised velocities) $\dot{q}_1, \dot{q}_2, \ldots, \dot{q}_n$. These can be any convenient variables: Cartesian positions, angles, distances along a track, or even abstract field amplitudes.

## 2.2 The Lagrangian

The Lagrangian is a function of the coordinates, velocities, and (optionally) time:

$$L = L(q_1, \ldots, q_n,\ \dot{q}_1, \ldots, \dot{q}_n,\ t). \tag{1}$$

For classical mechanics, $L = T - V$. For more advanced theories the form of $L$ is guided by the symmetries the theory must respect (Lorentz invariance, gauge invariance, etc.).

## 2.3 The Action

The **action** $S$ is the time integral of the Lagrangian over the system's history:

$$S[q] \;=\; \int_{t_1}^{t_2} L(q_i(t),\, \dot{q}_i(t),\, t)\; \mathrm{d}t\,. \tag{2}$$

Note that $S$ is a *functional*: it takes an entire path $q(t)$ as input and returns a single number.

## 2.4 The Principle of Stationary Action

Hamilton's principle states:

> *The physical trajectory is the one for which the action $S$ is stationary under small variations of the path, with endpoints held fixed.*

Mathematically, $\delta S = 0$. "Stationary" means neither a maximum nor a minimum in general—just a critical point—though for most mechanical systems it is indeed a minimum (hence the common but slightly inaccurate name "principle of least action").

## 2.5 The Euler–Lagrange Equations

Requiring $\delta S = 0$ and applying the calculus of variations yields one equation per degree of freedom:

$$\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial L}{\partial \dot{q}_i} \;-\; \frac{\partial L}{\partial q_i} \;=\; 0, \qquad i = 1, \ldots, n.} \tag{3}$$

These are the **Euler–Lagrange equations**. They are the Lagrangian analogue of $\mathbf{F} = m\mathbf{a}$, but they hold in *any* coordinate system and automatically incorporate all holonomic constraints.

**Example 2.1** (Free particle in one dimension)**.** *A particle of mass $m$ with no forces has $T = \tfrac{1}{2}m\dot{x}^2$ and $V = 0$, so $L = \tfrac{1}{2}m\dot{x}^2$. The Euler–Lagrange equation gives*

$$\frac{\mathrm{d}}{\mathrm{d}t} - 0 = 0 \quad\Longrightarrow\quad m\ddot{x} = 0,$$

*which is Newton's first law: constant velocity in the absence of forces.*

**Example 2.2** (Simple pendulum)**.** *Let $\theta$ be the angle from vertical and $\ell$ the length. Then $T = \tfrac{1}{2}m\ell^2\dot{\theta}^2$, $V = -mg\ell\cos\theta$, and $L = \tfrac{1}{2}m\ell^2\dot{\theta}^2 + mg\ell\cos\theta$. The Euler–Lagrange equation yields*

$$m\ell^2\ddot{\theta} + mg\ell\sin\theta = 0 \quad\Longrightarrow\quad \ddot{\theta} = -\frac{g}{\ell}\sin\theta,$$

*the exact pendulum equation—obtained without ever resolving forces along the arc or dealing with the tension in the string.*

## 2.6 Advantages of the Variational Approach

If Newton's laws and the Lagrangian method give the same answers for classical mechanics, why did physics migrate almost entirely to the Lagrangian framework? The reasons are both practical and profound.

## 2.7 Coordinate Freedom

The Euler–Lagrange equations have the *same form* in every coordinate system. Switching from Cartesian to spherical to curvilinear coordinates requires only rewriting $T$ and $V$; the recipe (eq. (3)) never changes. In Newtonian mechanics, each coordinate system introduces different expressions for acceleration and fictitious forces.

### 2.8 Automatic Handling of Constraints

A bead on a wire, a ball rolling on a surface, a robot arm with joints—all are systems with *constraints*. In the Newtonian approach, you must include explicit constraint forces (normal forces, tensions) and then show they cancel. In the Lagrangian approach, you simply choose coordinates that already satisfy the constraints. The constraint forces vanish from the formulation entirely.

### 2.9 Scalability

For a system of $N$ interacting particles in three dimensions, Newton gives $3N$ coupled second-order differential equations in Cartesian coordinates, plus constraint forces. The Lagrangian method reduces this to $n$ equations, where $n$ is the number of *true* degrees of freedom (often much less than $3N$).

### 2.10 Symmetry $\leftrightarrow$ Conservation (Noether)

Noether's theorem [Noether, 1918] provides a systematic, mechanical procedure for extracting conservation laws from the Lagrangian's symmetries. In the Newtonian framework, conservation laws must be discovered case by case.

### 2.11 Natural Gateway to Modern Theories

The Lagrangian formalism generalises effortlessly beyond particles:

- **Fields**: Replace the discrete coordinates $q_i(t)$ with continuous fields $\phi(x,t)$ and the Lagrangian with a *Lagrangian density* $\mathcal{L}$.
- **Relativity**: Lorentz invariance is easily enforced by requiring $\mathcal{L}$ to be a Lorentz scalar.
- **Quantum mechanics**: Feynman's path-integral formulation of quantum mechanics [Feynman and Hibbs, 1965] sums $e^{iS/\hbar}$ over *all* paths, with $S$ the classical action. The Lagrangian is the direct input.
- **Gauge theories**: The Standard Model of particle physics is specified entirely by writing down a Lagrangian density with the correct gauge symmetries.

No comparable generalisation exists for the force-based Newtonian framework.

### 2.12 From Particles to Fields: The Lagrangian Density

In particle mechanics the Lagrangian $L$ is a function of finitely many coordinates. In field theory—electromagnetism, fluid dynamics, general relativity, quantum field theory—the dynamical variable is a *field* $\phi(\mathbf{x},t)$ defined at every point in space.

The Lagrangian is replaced by a **Lagrangian density** $\mathcal{L}$:

$$L = \int \mathcal{L}(\phi,\, \partial_\mu \phi)\ \mathrm{d}^3x\,, \qquad S = \int \mathcal{L}\ \mathrm{d}^4x\,, \tag{4}$$

where $\partial_\mu\phi$ denotes the four-gradient of the field (encoding both spatial and temporal variation) and $\mathrm{d}^4x = \mathrm{d}t\ \mathrm{d}^3x$ is the spacetime volume element.

The principle $\delta S = 0$ now yields the **field-theoretic Euler–Lagrange equations**:

$$\partial_\mu \frac{\partial \mathcal{L}}{\partial(\partial_\mu \phi)} - \frac{\partial \mathcal{L}}{\partial \phi} = 0. \tag{5}$$

**Example 2.3** (Klein–Gordon field)**.** *A free scalar field of mass $m$ has*

$$\mathcal{L} = \tfrac{1}{2}(\partial_\mu\phi)(\partial^\mu\phi) - \tfrac{1}{2}m^2\phi^2.$$

*The Euler–Lagrange equation gives the Klein–Gordon equation $(\partial_\mu\partial^\mu + m^2)\phi = 0$, the relativistic wave equation for spinless particles.*

**Example 2.4** (Electromagnetism)**.** *Maxwell's equations—all four of them—follow from the Lagrangian density*

$$\mathcal{L}_{EM} = -\tfrac{1}{4} F_{\mu\nu} F^{\mu\nu} - J^\mu A_\mu,$$

*where $F_{\mu\nu} = \partial_\mu A_\nu - \partial_\nu A_\mu$ is the electromagnetic field tensor, $A_\mu$ is the four-potential, and $J^\mu$ is the four-current. Two lines of algebra encode the entirety of classical electrodynamics.*

## 2.13 General Forms of Common Lagrangians

To make the generality concrete, here are several Lagrangians spanning classical mechanics, field theory, and modern physics:

## 2.14 Classical Mechanics

$$L = \sum_{i=1}^{n} \tfrac{1}{2} m_i \dot{q}_i^2 \; - \; V(q_1, \ldots, q_n). \tag{6}$$

## 2.15 Relativistic Point Particle

$$L = -mc^2 \sqrt{1 - v^2/c^2}, \tag{7}$$

which reduces to $L \approx -mc^2 + \frac{1}{2} m v^2$ at low speeds, recovering the classical kinetic energy (up to a constant).

## 2.16 Electrodynamics

$$\mathcal{L} = -\tfrac{1}{4} F_{\mu\nu} F^{\mu\nu} - J^\mu A_\mu. \tag{8}$$

## 2.17 Scalar Field Theory

$$\mathcal{L} = \tfrac{1}{2} \partial_\mu \phi \, \partial^\mu \phi - V(\phi), \tag{9}$$

where $V(\phi)$ encodes self-interaction. The Klein–Gordon equation has $V = \frac{1}{2} m^2 \phi^2$; the Higgs potential has $V = -\mu^2 |\phi|^2 + \lambda |\phi|^4$.

## 2.18 General Relativity

$$\mathcal{L}_{\text{GR}} = \frac{1}{16\pi G} \, R \sqrt{-g}. \tag{10}$$

## 2.19 Yang–Mills Gauge Theory

$$\mathcal{L}_{\text{YM}} = -\tfrac{1}{4} F^a_{\mu\nu} F^{a\mu\nu} + \bar{\psi} (i \gamma^\mu D_\mu - m) \psi. \tag{11}$$

This is the template for QCD (the strong force) and the electroweak theory.

## 2.20 Why Symmetry Is the Real Story

The deepest reason physicists write Lagrangians is not computational convenience—it is that **the Lagrangian is a direct encoding of symmetry**.

When constructing a new theory, a modern physicist does not start by guessing forces. Instead, the procedure is:

1. **Identify the relevant degrees of freedom** (scalar field, spinor, gauge connection, metric, ...).
2. **Specify the symmetries** the theory must respect (Lorentz invariance, $SU(3)$ colour, $U(1)$ gauge, ...).

3. **Write the most general Lagrangian density** consistent with those symmetries and the field content, organised by mass dimension (lowest dimension = most relevant at low energies).
4. **Read off the equations of motion** via the Euler–Lagrange equations.
5. **Extract conservation laws** via Noether's theorem.
6. **Quantise** via the Feynman path integral [Feynman and Hibbs, 1965].

This algorithm is essentially what was used to construct the Standard Model, and it is the playbook for every proposed extension—supersymmetry, grand unification, string theory effective actions, and beyond.

The Lagrangian is, in this view, not just a computational shortcut. It is the **language in which nature's symmetries are most transparently expressed**.

# 3 Lagrangian Fluid Dynamics

Applying the Lagrangian framework to continuous media introduces challenges absent from particle mechanics: the configuration space becomes infinite-dimensional, and representing vorticity requires special techniques. This section summarises the essential fluid variational formalism; for a full treatment including rotating fluids, superfluids, and geophysical applications, see the companion primer by the author.

## 3.1 Lagrangian and Eulerian Descriptions

Before writing a Lagrangian, we must choose how to describe the fluid. There are two classical viewpoints, both named after the same historical figures who shaped the Lagrangian method itself.

## 3.2 The Lagrangian (Material) Description

Label each fluid parcel by its initial position $\mathbf{a}$ at time $t = 0$. The dynamical variable is the **flow map** $\mathbf{x}(\mathbf{a}, t)$: where parcel $\mathbf{a}$ ends up at time $t$.

This is the direct analogue of particle mechanics—each parcel is a "particle" with a trajectory $\mathbf{x}(t)$. The Lagrangian is straightforward:

$$L = \int \left[ \frac{1}{2} \rho_0(\mathbf{a}) \left| \frac{\partial \mathbf{x}}{\partial t} \right|^2 - \rho_0(\mathbf{a})\, \epsilon\big(\rho(\mathbf{x}, t),\, s(\mathbf{a})\big) - \rho_0(\mathbf{a})\, \Phi(\mathbf{x}) \right] \mathrm{d}^3 a \,, \tag{12}$$

where $\rho_0(\mathbf{a})$ is the initial density, $\epsilon$ is the internal energy per unit mass, $s(\mathbf{a})$ is the entropy (carried with each parcel), and $\Phi$ is any external potential (gravity). The current density is determined by volume conservation: $\rho(\mathbf{x}, t) = \rho_0(\mathbf{a})/J$, where $J = \det(\partial \mathbf{x}/\partial \mathbf{a})$ is the Jacobian of the flow map.

*Remark* 1. In this description, the Euler–Lagrange equations yield Newton's second law for each fluid element, with pressure gradients emerging naturally from the internal energy term. No constraint forces are needed.

## 3.3 The Eulerian (Spatial) Description

Fix attention on a point $\mathbf{x}$ in space and record the velocity $\mathbf{v}(\mathbf{x}, t)$, density $\rho(\mathbf{x}, t)$, and pressure $p(\mathbf{x}, t)$ as fluid streams past.

This is how we usually write fluid equations (the Navier–Stokes equations, for instance), and it is far more convenient for computation. But it creates a problem for variational principles: the velocity field $\mathbf{v}(\mathbf{x}, t)$ cannot be varied freely, because independent variations of $\mathbf{v}$ at different points would break the connection between neighbouring fluid parcels.

Resolving this tension—writing a true variational principle in Eulerian variables—is the central technical challenge of fluid Lagrangian theory, and it occupied mathematicians from the 1850s to the 1990s.

### 3.4 The Basic Fluid Lagrangian

### 3.5 Kinetic Minus Potential—For a Continuum

The fluid Lagrangian has exactly the same philosophical structure as for particles:

$$\boxed{L = \int \left[ \underbrace{\tfrac{1}{2}\rho\,|\mathbf{v}|^2}_{T\text{: kinetic energy}} - \underbrace{\rho\,\epsilon(\rho,s)}_{U\text{: internal energy}} - \underbrace{\rho\,\Phi}_{V\text{: external potential}} \right] \mathrm{d}^3x\,.} \tag{13}$$

Each term is a *density* (energy per unit volume), integrated over the entire fluid domain. The action is $S = \int_{t_1}^{t_2} L\ \mathrm{d}t$.

| Term | Symbol | Physical Meaning |
|---|---|---|
| Kinetic | $\frac{1}{2}\rho\|\mathbf{v}\|^2$ | Energy of bulk fluid motion |
| Internal | $\rho\,\epsilon(\rho,s)$ | Thermodynamic energy (pressure, temperature); encodes the equation of state |
| External | $\rho\,\Phi$ | Gravitational or other body-force potential |

### 3.6 What the Internal Energy Encodes

The function $\epsilon(\rho, s)$ is the equation of state in disguise. The pressure follows from thermodynamics:

$$p = \rho^2 \left.\frac{\partial \epsilon}{\partial \rho}\right|_s . \tag{14}$$

Different choices of $\epsilon$ give different fluids:

- **Incompressible**: $\epsilon = \text{const}$ (pressure becomes a Lagrange multiplier enforcing $\nabla \cdot \mathbf{v} = 0$).
- **Ideal gas**: $\epsilon \propto \rho^{\gamma-1}$, giving $p = K\rho^\gamma$ (polytropic).
- **Shallow water**: $\epsilon = \frac{1}{2}gh$, where $h$ is the water depth (used in oceanography).
- **Superfluid**: $\epsilon$ includes the quantum pressure $(\hbar^2/2m)\,|\nabla\sqrt{\rho}|^2/\rho$ (the quantum pressure from superfluid theory).

### 3.7 The Vorticity Problem and Its Solutions

### 3.8 The Problem

If you naively vary the Eulerian Lagrangian (eq. (13)) with respect to $\mathbf{v}$, treating $\mathbf{v}(\mathbf{x}, t)$ as an unconstrained field, you obtain only *irrotational* (curl-free) flow:

$$\mathbf{v} = \nabla\phi \quad \Longrightarrow \quad \boldsymbol{\omega} \equiv \nabla \times \mathbf{v} = 0.$$

This misses all vortical motion—tornadoes, vortex rings, turbulence, rotating storms—which is most of fluid dynamics.

The root cause is that the Eulerian velocity field has a hidden structure: not all $\mathbf{v}$ fields correspond to physically realisable flows. A legitimate velocity field must be the Eulerian image of a material flow map that preserves parcel identity. Ignoring this constraint loses vorticity.

### 3.9 Solution 1: Clebsch Variables (1859)

Alfred Clebsch [Clebsch, 1859] showed that *any* velocity field in three dimensions can be decomposed as

$$\mathbf{v} = \nabla\phi + \alpha\,\nabla\beta, \tag{15}$$

where $\phi$, $\alpha$, $\beta$ are scalar functions called **Clebsch potentials**. The vorticity is then

$$\boldsymbol{\omega} = \nabla\alpha \times \nabla\beta,$$

which is generically non-zero. The Lagrangian is varied with respect to $\phi$, $\alpha$, $\beta$ (and $\rho$, $s$) as independent fields. The Euler–Lagrange equations correctly reproduce the full Euler equations for an ideal fluid, including vortex dynamics.

*Remark* 2. The Clebsch representation is not unique and can develop singularities at vortex cores. It works beautifully for smooth flows but requires care for concentrated vortices.

### 3.10 Solution 2: Lin Constraints (1963)

Lin [1963] proposed adding Lagrange multipliers that enforce *particle conservation*—the constraint that each fluid parcel retains its identity label $\mathbf{a}$ as it moves:

$$\frac{\partial a_i}{\partial t} + \mathbf{v}\cdot\nabla a_i = 0, \qquad i = 1,2,3. \tag{16}$$

The constrained Lagrangian becomes

$$L' = L + \int \lambda_i \left( \frac{\partial a_i}{\partial t} + \mathbf{v}\cdot\nabla a_i \right) \mathrm{d}^3x\,,$$

where $\lambda_i$ are multiplier fields. Varying $\mathbf{v}$ now includes the constraint forces that maintain parcel coherence, and the full vortical Euler equations emerge.

### 3.11 Solution 3: Euler–Poincaré Reduction (1998)

The modern approach, due to Holm et al. [1998b], recognises the fluid as a dynamical system on the *group of diffeomorphisms*—the infinite-dimensional Lie group of smooth, invertible maps of space to itself. The Lagrangian is defined on the Lie algebra (velocity fields), and variations are constrained by the group structure:

$$\delta\mathbf{v} = \frac{\partial \mathbf{w}}{\partial t} + [\mathbf{v}, \mathbf{w}], \tag{17}$$

where $\mathbf{w}$ is an arbitrary vector field vanishing at the endpoints, and $[\mathbf{v},\mathbf{w}] = (\mathbf{v}\cdot\nabla)\mathbf{w} - (\mathbf{w}\cdot\nabla)\mathbf{v}$ is the Lie bracket (negative of the commutator of the flows).

This elegant formulation:

- Recovers the full Euler equations with vorticity,
- Explains Kelvin's circulation theorem [Thomson, 1869] as a Noether consequence of particle-relabeling symmetry,
- Extends naturally to magnetohydrodynamics, elasticity, complex fluids, and plasma physics.

### 3.12 Conservation Laws from Symmetry

Noether's theorem, applied to the fluid Lagrangian, yields the fundamental conservation laws of fluid dynamics automatically:

| Symmetry | Conserved Quantity | Fluid Expression |
|---|---|---|
| Time translation | Energy | $E = \int \left[\frac{1}{2}\rho|\mathbf{v}|^2 + \rho\epsilon + \rho\Phi\right] \mathrm{d}^3x$ |
| Space translation | Momentum | $\mathbf{P} = \int \rho\,\mathbf{v}\ \mathrm{d}^3x$ |
| Rotation | Angular momentum | $\mathbf{L} = \int \rho\,(\mathbf{x}\times\mathbf{v})\ \mathrm{d}^3x$ |
| Particle relabeling | Circulation | $\Gamma = \oint_C \mathbf{v}\cdot\mathrm{d}\mathbf{l}$ (Kelvin's theorem) |
| Entropy label | Entropy per parcel | $Ds/Dt = 0$ (adiabatic flow) |

### 3.13 Kelvin's Circulation Theorem

The most profound of these is the last classical entry: *particle-relabeling symmetry* (the physics doesn't depend on how we label the parcels) implies **Kelvin's circulation theorem**—the circulation $\Gamma$ around any material loop is conserved:

$$\frac{\mathrm{d}\Gamma}{\mathrm{d}t} = \frac{\mathrm{d}}{\mathrm{d}t}\oint_{C(t)} \mathbf{v}\cdot\mathrm{d}\mathbf{l} = 0. \tag{18}$$

In the Newtonian approach, Kelvin's theorem must be *proved* from the Euler equations by a calculation. In the Lagrangian approach, it is an *automatic consequence* of a symmetry—a arguably deeper and more illuminating derivation.

### 3.14 Ertel's Potential Vorticity

A related Noether consequence is the conservation of **potential vorticity**:

$$q = \frac{\boldsymbol{\omega}\cdot\nabla s}{\rho}, \qquad \frac{\mathrm{d}q}{\mathrm{d}t} = 0, \tag{19}$$

where $\boldsymbol{\omega} = \nabla\times\mathbf{v}$ is the vorticity and $s$ is the entropy. This quantity, discovered by Ertel [1942], is the single most important diagnostic in atmospheric and oceanic science. Its conservation follows from the combined particle-relabeling and entropy-label symmetries of the fluid Lagrangian [Shepherd, 1990].

### 3.15 Summary of Fluid Lagrangians

| System | Lagrangian (density) | Key Feature |
|---|---|---|
| Ideal fluid (material) | $\frac{1}{2}\rho_0\lvert\dot{\mathbf{x}}\rvert^2 - \rho_0\epsilon(\rho_0/J, s)$ | Direct particle analogy; Jacobian $J$ tracks volume |
| Ideal fluid (Eulerian) | $\frac{1}{2}\rho\lvert\mathbf{v}\rvert^2 - \rho\epsilon(\rho, s)$ | Requires Clebsch / Lin / Euler–Poincaré for vorticity |
| Rotating fluid | $\frac{1}{2}\rho\lvert\mathbf{v}'\rvert^2 + \rho\mathbf{v}'\cdot(\boldsymbol{\Omega}\times\mathbf{x}) + \frac{1}{2}\rho\lvert\boldsymbol{\Omega}\times\mathbf{x}\rvert^2 - \rho\epsilon$ | Coriolis is 1st-order in $\mathbf{v}'$; centrifugal modifies potential |
| Shallow water (rotating) | $\frac{1}{2}\rho h\lvert\mathbf{v}\rvert^2 + \rho h\mathbf{v}\cdot(\boldsymbol{\Omega}\times\mathbf{x}) - \frac{1}{2}\rho g h^2$ | Rossby waves, tsunamis, ocean gyres |
| Superfluid (Gross–Pitaevskii) | $i\hbar\psi^*\partial_t\psi - \frac{\hbar^2}{2m}\lvert\nabla\psi\rvert^2 - \frac{g}{2}\lvert\psi\rvert^4$ | Velocity $= (\hbar/m)\nabla\theta$; quantised vortices |
| Two-fluid (Khalatnikov) | $\frac{1}{2}\rho_s\lvert\mathbf{v}_s\rvert^2 + \frac{1}{2}\rho_n\lvert\mathbf{v}_n\rvert^2 - \epsilon(\rho, s)$ | Second sound; fountain effect; mutual friction |

## 4 Current Approaches to Biological Digital Twins

A survey of the computational physiology literature reveals four dominant modelling paradigms for organ-scale digital twins. None employs a variational principle.

### 4.1 Finite-Element Methods (FEM)

FEM discretises the organ into small elements and solves partial differential equations (typically elasticity, diffusion, or Navier–Stokes) on the resulting mesh. Major efforts include the *Virtual Physiological Human* (VPH) initiative in Europe, the *Living Heart Project* (Dassault Systèmes), and various cardiac electromechanics models.

**Limitation**: FEM solves equations that are written down *before* the simulation begins. The equations are not derived from a unifying principle; they are postulated for each sub-domain (mechanics, electrics, perfusion) and coupled via boundary conditions. Conservation laws must be manually enforced.

### 4.2 Agent-Based Models (ABM)

ABMs represent cells as discrete agents with rule-based behaviours: "if TGF-$\beta$ exceeds threshold $X$, activate and produce collagen at rate $Y$." This approach has been applied to tumour growth, wound healing, and liver fibrosis.

**Limitation**: The rules are phenomenological, not derived from any principle. There is no guarantee that the model conserves mass, energy, or momentum. Changing one rule can have unpredictable cascading effects on others, making calibration fragile.

### 4.3 Pharmacokinetic / Compartment Models

These treat the organ as a set of well-mixed compartments connected by flow rates, described by ordinary differential equations (ODEs). They are the workhorse of drug development and pharmacology.

**Limitation**: Compartment models have no spatial resolution. They cannot capture the gradients, flow patterns, and structural remodelling that define organ pathology. A compartment model of the liver cannot distinguish periportal from pericentral hepatocytes—a distinction that is central to metabolic zonation and disease.

### 4.4 Eulerian Computational Fluid Dynamics (CFD)

Several groups have applied Navier–Stokes-based CFD to hepatic blood flow, including studies of portal vein haemodynamics and sinusoidal perfusion. These models solve the Eulerian fluid equations directly, often coupled to passive scalar transport for nutrients or drugs.

**Limitation**: Eulerian CFD solves the equations of motion but does not derive them from a variational principle. As discussed in the companion paper on fluid Lagrangians, the Eulerian Navier–Stokes equations *can* be obtained from a Lagrangian, but standard CFD practice does not exploit this structure. Conservation laws are enforced numerically rather than structurally.

### 4.5 Summary

| **Approach** | **Spatial** | **Multi-scale** | **Conservation** | **Variational** | **Coupling** |
|---|---|---|---|---|---|
| FEM | ✓ | Partial | Manual | No | Ad hoc |
| ABM | ✓ | ✓ | None | No | Rules |
| Compartment | No | No | Mass | No | ODEs |
| Eulerian CFD | ✓ | No | Numerical | No | BCs |
| **Lagrangian (proposed)** | ✓ | ✓ | **Automatic** | **Yes** | **Structural** |

# 5 The Fluid Nature of Biological Tissue

The central thesis of this paper is that biological tissue function is *fluid-driven* in a deep, not merely supportive, sense. We argue this at three levels.

## 5.1 Nutrient Transport and Metabolic Zonation

Every cell in the body depends on convective and diffusive transport of oxygen, glucose, hormones, and signalling molecules delivered by blood flow. In the liver, this dependence is extreme: hepatocytes are arranged in lobules around a central vein, and their metabolic programme depends on their position along the *porto-central axis*—a gradient established entirely by sinusoidal blood flow.

Periportal hepatocytes (near the portal triad, receiving oxygen-rich blood) specialise in oxidative metabolism, gluconeogenesis, and urea synthesis. Pericentral hepatocytes (near the central vein, receiving oxygen-depleted blood) specialise in glycolysis, lipogenesis, and drug metabolism via cytochrome P450 enzymes. This *metabolic zonation* is not genetically hard-wired; it is dynamically maintained by the oxygen and morphogen gradients established by flow. Reverse the flow direction experimentally, and the zonation pattern reverses with it.

## 5.2 Mechanotransduction and Structural Remodelling

Fluid flow exerts shear stress on the cells lining blood vessels and sinusoids. These endothelial cells are not passive pipes; they are mechanosensors that transduce shear stress into biochemical signals:

- **Liver sinusoidal endothelial cells (LSECs)** maintain fenestrations (nanopores) that allow plasma to filter through to hepatocytes. Fenestration is regulated by shear stress and nitric oxide, both flow-dependent quantities.
- **Hepatic stellate cells (HSCs)** reside in the space of Disse and respond to flow-mediated signals (TGF-$\beta$, PDGF) by either remaining quiescent or activating into myofibroblasts that produce collagen—the key driver of fibrosis [Friedman, 2008].
- **Portal pressure** (measured clinically as the hepatic venous pressure gradient, HVPG) is a direct fluid-mechanical quantity: the pressure drop across the hepatic vascular bed. It is the single most important prognostic marker in chronic liver disease.

## 5.3 Disease as Disrupted Flow

In this view, liver disease is fundamentally a *fluid dynamics pathology*:

- **Fibrosis**: Collagen deposition increases flow resistance $\rightarrow$ portal pressure rises $\rightarrow$ sinusoidal shear stress changes $\rightarrow$ LSEC defenestration and HSC activation $\rightarrow$ more collagen. This is a positive feedback loop mediated entirely by fluid mechanics.
- **Cirrhosis**: Advanced fibrosis restructures the vascular architecture, creating regenerative nodules with abnormal flow $\rightarrow$ metabolic dysfunction, ascites, variceal bleeding.
- **Steatosis (fatty liver)**: Fat accumulation in hepatocytes compresses sinusoids $\rightarrow$ reduced flow $\rightarrow$ hypoxia $\rightarrow$ inflammation $\rightarrow$ further fat accumulation and eventual fibrosis.

In each case, the disease trajectory is governed by the interplay between fluid flow, mechanical forces, and cellular response—exactly the kind of multi-physics coupling that a Lagrangian formulation handles naturally.

# 6 Why the Lagrangian Formalism Is Appropriate

Given that tissue function is fluid-driven, and that fluid dynamics has a natural variational formulation (as developed in the companion paper), the application of Lagrangian methods to

biological tissue becomes not just possible but arguably *natural*. The specific advantages are:

### 6.1 Automatic Conservation Laws

A Lagrangian formulation guarantees, via Noether's theorem [Noether, 1918], that the model automatically conserves the quantities mandated by its symmetries. For a tissue model, these include:

| **Symmetry** | **Conservation Law** | **Biological Meaning** |
|---|---|---|
| Time translation | Energy | Metabolic energy balance |
| Space translation | Momentum | Force balance in tissue |
| Particle relabeling | Circulation | Vascular flow topology |
| Mass-phase symmetry | Mass | Cell & fluid mass conservation |

In current ABM and FEM approaches, these conservation laws must be enforced explicitly and may be violated at insufficient resolution or by modelling inconsistency.

### 6.2 Structural Coupling

In a Lagrangian formulation, different physical processes are not coupled via ad hoc terms; they are coupled *structurally* through the action principle. Adding a new physics (e.g., bile transport, immune cell migration) means adding terms to the Lagrangian, and all cross-couplings emerge automatically from the variational principle. This eliminates the "integration tax" that plagues multi-physics models.

### 6.3 Multi-Scale Consistency

The Lagrangian formalism scales naturally from microscopic to macroscopic. A coarse-grained Lagrangian can be derived from a fine-grained one by integrating out fast degrees of freedom—a procedure well-established in condensed matter physics (the Wilsonian renormalisation group) [Wilson and Kogut, 1974]. This provides a principled way to connect molecular-scale processes (receptor binding, enzyme kinetics) to tissue-scale observables (portal pressure, fibrosis score) without ad hoc scale-bridging assumptions.

### 6.4 Natural Treatment of Dissipation

Biological systems are dissipative: energy is continuously consumed and entropy produced. The Lagrangian framework handles dissipation through the Rayleigh dissipation function or, more fundamentally, through the inclusion of irreversible entropy production terms. The resulting equations are thermodynamically consistent by construction—a property difficult to guarantee in ad hoc models.

### 6.5 Approximation Preserves Structure

Following Salmon's principle [Salmon, 1998] (discussed in the companion paper), approximating the Lagrangian *before* deriving equations of motion ensures that the approximate model inherits correct (approximate) conservation laws. This is critical for long-time simulations of disease progression, where accumulated conservation violations in conventional models can produce unphysical drift.

# 7 General Form of a Tissue Lagrangian

We now sketch the general form of a Lagrangian density for a fluid-perfused biological tissue. This is presented as a research framework, not a final model; the specific functional forms must be determined by calibration against experimental data.

## 7.1 Degrees of Freedom

The dynamical fields of a perfused tissue include:

- $\mathbf{v}(\mathbf{x}, t)$: blood (sinusoidal) velocity field
- $\rho(\mathbf{x}, t)$: blood density (effectively incompressible)
- $c_i(\mathbf{x}, t)$: concentrations of key solutes (oxygen, glucose, TGF-$\beta$, etc.)
- $f(\mathbf{x}, t)$: fibrosis (collagen) fraction
- $\phi(\mathbf{x}, t)$: porosity / fenestration density
- $s(\mathbf{x}, t)$: entropy density (thermodynamic state)

## 7.2 Proposed Structure

The tissue Lagrangian density takes the general form:

$$\boxed{\mathcal{L}_{\text{tissue}} = \underbrace{\mathcal{L}_{\text{flow}}}_{\text{fluid kinetics}} + \underbrace{\mathcal{L}_{\text{transport}}}_{\text{solute dynamics}} + \underbrace{\mathcal{L}_{\text{matrix}}}_{\text{structural remodelling}} + \underbrace{\mathcal{L}_{\text{cell}}}_{\text{cellular energetics}} + \underbrace{\mathcal{L}_{\text{dissipation}}}_{\text{entropy production}}} \tag{20}$$

Each term has a clear physical interpretation:

### 7.2.1 Flow term $\mathcal{L}_{\text{flow}}$

This is the fluid Lagrangian of sinusoidal blood flow, modified by the tissue microstructure:

$$\mathcal{L}_{\text{flow}} = \frac{1}{2}\rho\,\phi\,|\mathbf{v}|^2 - p_{\text{eff}}(\rho, f, \phi) - \rho\,\Phi_{\text{grav}}, \tag{21}$$

where $\phi$ (porosity) modulates the effective flow volume and $p_{\text{eff}}$ is an effective pressure that depends on both fluid density and tissue structure (fibrosis narrows sinusoids, increasing flow resistance).

### 7.2.2 Transport term $\mathcal{L}_{\text{transport}}$

Solute transport along the sinusoid is described by advection-diffusion-reaction terms:

$$\mathcal{L}_{\text{transport}} = \sum_i \left[\frac{1}{2}D_i\,|\nabla c_i|^2 + c_i\,(\mathbf{v}\cdot\nabla\mu_i) - U_i(c_i, f, \phi)\right], \tag{22}$$

where $D_i$ are diffusion coefficients, $\mu_i$ are chemical potentials, and $U_i$ encodes reaction terms (oxygen consumption, growth factor binding, etc.).

### 7.2.3 Matrix term $\mathcal{L}_{\text{matrix}}$

The extracellular matrix (collagen) has both elastic energy and a remodelling potential:

$$\mathcal{L}_{\text{matrix}} = \frac{1}{2}\kappa\,|\nabla f|^2 - V_{\text{matrix}}(f, c_{\text{TGF}}, c_{\text{MMP}}), \tag{23}$$

where the gradient term penalises sharp fibrosis boundaries (surface tension of fibrotic fronts), and $V_{\text{matrix}}$ encodes the balance between collagen deposition (driven by TGF-$\beta$) and degradation (driven by matrix metalloproteinases, MMPs).

#### 7.2.4 Cellular energetics $\mathcal{L}_{\text{cell}}$

Hepatocyte and stellate cell behaviour is encoded as an effective potential landscape:

$$\mathcal{L}_{\text{cell}} = -W(\phi, f, c_{\text{O}_2}, c_{\text{TGF}}), \tag{24}$$

where $W$ captures stellate cell activation, hepatocyte viability, fenestration regulation, and the feedback loops that drive disease progression. The specific form of $W$ is where biological knowledge enters the model.

#### 7.2.5 Dissipation $\mathcal{L}_{\text{dissipation}}$

Viscous dissipation and irreversible processes are included via a Rayleigh-type dissipation function:

$$\mathcal{R} = \frac{1}{2}\eta(\phi, f)\,|\nabla \mathbf{v}|^2 + \sum_i \frac{1}{2}\gamma_i\,\dot{c}_i^2, \tag{25}$$

where $\eta$ is the effective viscosity (which increases with fibrosis as sinusoids narrow) and $\gamma_i$ are relaxation coefficients for solute dynamics. The dissipation function modifies the Euler–Lagrange equations via $\frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial L}{\partial \dot{q}} - \frac{\partial L}{\partial q} = -\frac{\partial \mathcal{R}}{\partial \dot{q}}$.

## 8 The Liver as Initial Target

The liver is an ideal first target for a Lagrangian digital twin for several reasons:

### 8.1 Flow-Dominated Architecture

The liver receives approximately 25% of cardiac output—about 1.5 litres of blood per minute through both the portal vein (75%) and hepatic artery (25%). This dual blood supply perfuses a vast sinusoidal network with a total endothelial surface area estimated at 100–200 $\text{m}^2$ in the adult human. No other solid organ has such an intimate coupling between blood flow and parenchymal cell function.

### 8.2 Measurable Fluid-Mechanical Endpoints

Liver disease progression has well-validated fluid-mechanical biomarkers:

| **Biomarker** | **Measurement** | **Clinical Threshold** |
|---|---|---|
| HVPG | Catheterisation (mmHg) | $\geq 10$: clinically significant |
| Liver stiffness | Elastography (kPa) | $\geq 12.5$: cirrhosis |
| Flow velocity | Doppler ultrasound (cm/s) | Reversal = decompensation |

These are direct outputs of a fluid-mechanical model, providing natural validation targets for a Lagrangian digital twin.

### 8.3 Well-Characterised Disease Progression

Chronic liver disease follows a stereotyped trajectory (F0 $\rightarrow$ F1 $\rightarrow$ F2 $\rightarrow$ F3 $\rightarrow$ F4 $\rightarrow$ decompensation) with well-studied intermediate biomarkers. The METAVIR fibrosis scoring system, HVPG thresholds, and Child–Pugh/MELD scores provide a rich validation framework.

### 8.4 Clinical Urgency

Chronic liver disease affects over 1.5 billion people worldwide. Non-alcoholic fatty liver disease (now termed metabolic dysfunction- associated steatotic liver disease, MASLD) alone affects approximately 25% of the global population. A predictive digital twin could guide drug development (e.g., resmetirom, semaglutide) and personalise treatment decisions.

## 9 Literature Survey: Novelty of the Approach

To substantiate the claim that a Lagrangian-based biological digital twin is novel, we surveyed the literature across several relevant domains. Our conclusion is that, **to our knowledge, no research group has proposed or implemented a digital twin of any biological organ based on a variational (Lagrangian) principle**.

### 9.1 Liver-Specific Digital Twins

The most advanced liver modelling efforts include:

- The **Virtual Liver Network** [Gille et al., 2010] (Germany, 2010–2016): Multi-scale modelling of liver metabolism using coupled ODEs and agent-based models. No variational formulation.
- **HepatoNet1** [Gille et al., 2010]: A genome-scale metabolic network model solved by flux balance analysis. Algebraic constraint-based, not dynamical.
- **Ricken et al.** [Ricken et al., 2015]: FEM models of liver perfusion and lobule mechanics using porous media theory (Biot equations). Continuum mechanics, not variational.
- **Debbaut et al.** [Debbaut et al., 2012]: CFD modelling of hepatic blood flow using patient-specific vascular geometries from CT scans. Eulerian Navier–Stokes, not variational.
- **Ashworth et al.** [Ashworth et al., 2016]: Computational model of zonated hepatic energy metabolism, used to study steatosis in NAFLD. ODE-based compartmental approach—no variational formulation.

### 9.2 Cardiac Digital Twins

The most mature organ digital twin field is cardiac modelling:

- **Living Heart Project** (Dassault, 2014–present): FEM-based electromechanical model. Uses constitutive laws, not a Lagrangian.
- **Niederer et al.** [Niederer et al., 2019]: Review of cardiac digital twins. Discusses FEM, lumped-parameter, and electrophysiology models. No variational formulation mentioned.
- **Corral-Acero et al.** [Corral-Acero et al., 2020]: "The 'Digital Twin' to enable the vision of precision cardiology." Surveys imaging-based models and machine learning. No Lagrangian framework.

### 9.3 Variational Methods in Biology

Variational principles have been applied to specific biological sub-problems, but never as a unifying framework for organ-scale digital twins:

- **Helfrich free energy** [Helfrich, 1973]: A variational formulation for cell membrane shape. Widely used in biophysics but describes equilibrium membrane geometry, not organ-scale dynamics.
- **Murray's law** [Murray, 1926]: Minimisation of total power dissipation to predict vascular branching ratios. A static optimality principle, not a dynamical Lagrangian.
- **Prigogine's minimum entropy production** [Prigogine, 1955]: A variational principle for near-equilibrium thermodynamics applied to biological systems. Controversial and limited to linear irreversible thermodynamics; not used for spatially-resolved tissue models.

- **Mori et al.** [Mori et al., 2008]: Variational formulations for cell motility using phase-field models. Single-cell scale, not organ-scale.
- **Onsager variational principle** [Doi, 2011]: Application to soft matter dynamics including gels and polymers. Relevant to extracellular matrix mechanics but not applied to organ-scale modelling.

### 9.4 Assessment

The gap is clear: variational principles are established in fluid mechanics, well-explored at the molecular and cellular scale in biophysics, and extensively theorised in non-equilibrium thermodynamics—but **no group has assembled these ingredients into a Lagrangian-based digital twin of a biological organ**. The approach proposed here is, to our knowledge, **without precedent** in the literature.

## 10 Advantages Over Existing Approaches

1. **Principled multi-physics coupling.** Adding a new biological process (e.g., immune cell infiltration, bile transport, lymphatic drainage) requires only adding a term to $\mathcal{L}_{\text{tissue}}$. All cross-couplings emerge from the Euler–Lagrange equations. In FEM or ABM, each new process requires hand-crafted coupling code.

2. **Conservation by construction.** Mass, momentum, energy, and topological invariants (vascular connectivity) are automatically conserved. In multi-year disease simulations, this prevents unphysical drift.

3. **Structural testability.** The tissue Lagrangian makes explicit predictions about conservation laws and symmetries. If the model predicts that a certain quantity is conserved and experiment shows it is not, the Lagrangian must be modified—providing a clear falsification pathway.

4. **Approximation hierarchy.** Coarse-grained models (lobule-scale $\to$ organ-scale $\to$ whole-body) can be derived systematically by averaging the Lagrangian over fast/small-scale degrees of freedom.

5. **Natural interface with control theory.** Drug interventions and clinical decisions can be formulated as optimal control problems on the action functional, leveraging well-developed mathematical tools (Pontryagin's maximum principle, Hamilton–Jacobi–Bellman equations).

6. **Connection to fundamental physics.** Because the tissue Lagrangian has the same mathematical structure as field-theoretic Lagrangians in physics [Arnold, 1966, Holm et al., 1998a], the entire apparatus of modern theoretical physics—symmetry analysis, perturbation theory, renormalisation, topological methods—becomes available for biological modelling.

## 11 Research Programme

We propose a phased research programme to develop and validate the Lagrangian digital twin approach:

### 11.1 Phase 1: Proof of Concept

- Implement a minimal tissue Lagrangian for a single liver sinusoid, coupling blood flow, oxygen transport, and collagen dynamics.
- Validate against known sinusoidal haemodynamics and fibrosis progression rates.
- Demonstrate that conservation laws (mass, momentum) are maintained over long simulation times without explicit enforcement.

### 11.2 Phase 2: Multi-Scale Extension

- Extend from single sinusoid to lobule scale using coarse-graining of the Lagrangian.
- Incorporate hepatocyte metabolic zonation as a flow-dependent field.
- Validate against HVPG measurements and elastography data at different fibrosis stages.

### 11.3 Phase 3: Disease Trajectory Prediction

- Simulate full F0 $\rightarrow$ F4 disease progression for alcohol-associated liver disease (ALD) and MASLD.
- Introduce drug intervention as perturbations to the Lagrangian and predict treatment response.
- Compare with clinical trial data (e.g., MAESTRO-NASH for resmetirom).

### 11.4 Phase 4: Generalisation

- Adapt the framework to other flow-dominated organs: kidney (glomerular filtration), lung (alveolar ventilation/ perfusion), brain (cerebrovascular coupling).
- Develop a general-purpose "tissue Lagrangian toolkit" for the computational physiology community.

## 12 Discussion: Challenges and Limitations

We acknowledge several open challenges:

1. **Choosing the right Lagrangian.** Unlike fundamental physics, where symmetries strongly constrain the Lagrangian, biology has many possible terms and the "correct" Lagrangian is not known a priori. It must be determined by a combination of physical reasoning and empirical calibration.

2. **Dissipation.** Biological tissues are far from equilibrium. While the Rayleigh dissipation function and GENERIC (General Equation for Non-Equilibrium Reversible- Irreversible Coupling) framework provide tools, the treatment of strong dissipation within a variational framework remains an active research area.

3. **Biological complexity.** The liver contains dozens of cell types, hundreds of signalling molecules, and feedback loops at every scale. Any tractable Lagrangian must represent a radical simplification, retaining only the fields that dominate the dynamics. The claim is not that a Lagrangian captures everything, but that it captures the essential fluid-mechanical backbone on which the rest is scaffolded.

4. **Computational cost.** Solving the full Euler–Lagrange equations on a 3D tissue domain with multiple coupled fields is computationally demanding. However, GPU acceleration and the inherent parallelism of lattice-based Lagrangian methods make this increasingly tractable.

# 13 Conclusion

We have argued that:

1. Biological tissue function is fundamentally fluid-driven, with blood flow, shear stress, and pressure gradients governing cellular behaviour, tissue structure, and organ function.

2. The Lagrangian (variational) formulation of fluid dynamics—which encodes conservation laws, symmetries, and multi-scale structure in a single scalar functional—is a natural and potentially superior foundation for biological digital twins.

3. The liver is an ideal initial target due to its flow-dominated architecture, measurable fluid-mechanical biomarkers, well-characterised disease progression, and enormous clinical need.

4. No research group has, to our knowledge, proposed or implemented a Lagrangian-based digital twin of any biological organ. This approach is novel and fills a structural gap in the computational physiology landscape.

The tissue Lagrangian proposed here is a *framework*, not a finished model. Its value lies in providing a principled starting point from which all governing equations, conservation laws, and coupling terms emerge from a single variational principle—replacing the ad hoc integration of disparate sub-models that characterises current practice.

We believe this approach has the potential to transform biological digital twins from primarily empirical constructions toward more theoretically grounded physical models, bringing to biology the same clarity that the Lagrangian formulation brought to physics over the past two and a half centuries.

> *"If the Lagrangian can describe the Standard Model, general relativity, and electromagnetism, why not a liver? The blood already knows the variational principle—it follows the path of least resistance through every sinusoid, every capillary, every day of our lives. We need only write down what it already knows."*

# Disclosures

## Related Intellectual Property

This work is related to U.S. Provisional Patent Application No. 64/100,396, *"Systems and Methods for Computational Prediction of Hepatic Fibrosis Progression, Irreversibility Detection, and Treatment Management,"* filed June 27, 2026; and U.S. Provisional Patent Application No. 64/101,014, *"Method for Resolution-Invariant Computational Simulation of Biological Tissue Using Variational Lagrangian Discretization,"* filed June 29, 2026. The author has a financial interest in the commercialisation of this technology.

## Use of AI Tools

Portions of this manuscript were drafted with the assistance of large language models (Google Gemini, Anthropic Claude). The author reviewed, verified, and takes full responsibility for all content, including all mathematical derivations, citations, and factual claims.

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